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Tetrahedron

Tetrahedron Vol. 62, No. 33, 2006

Contents

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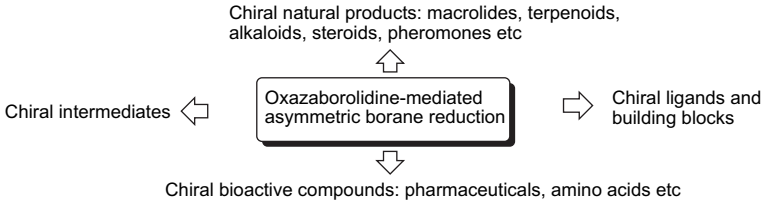

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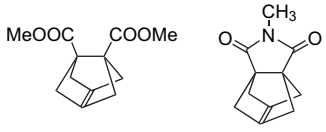
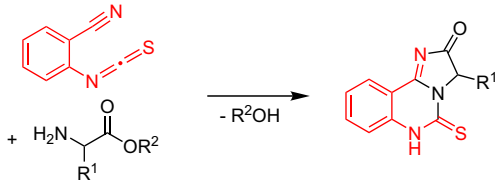
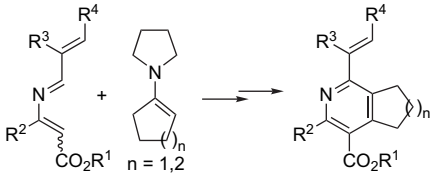
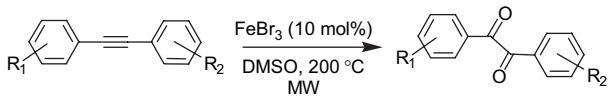
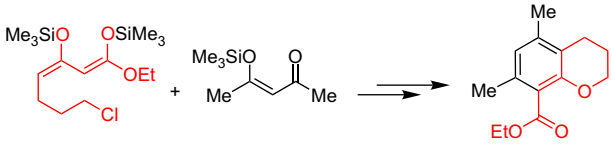
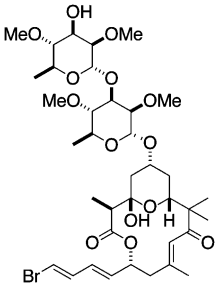


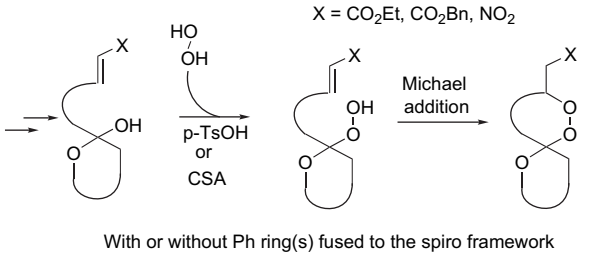


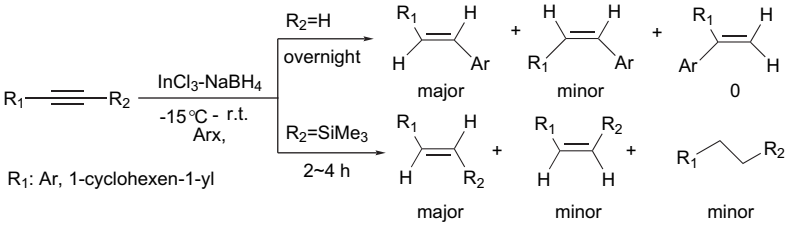


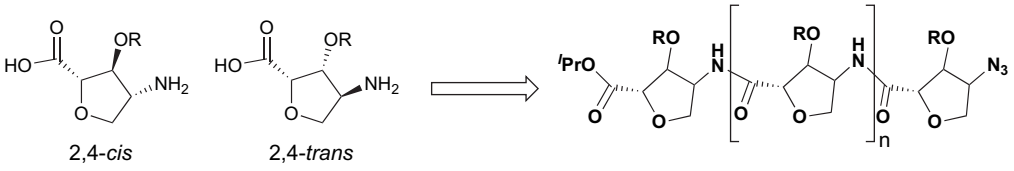


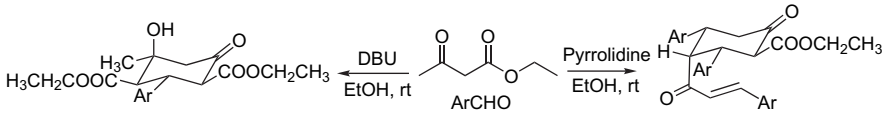


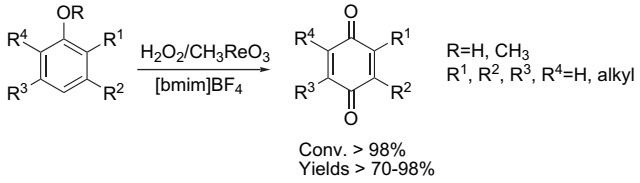




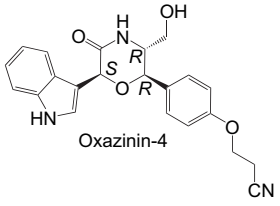


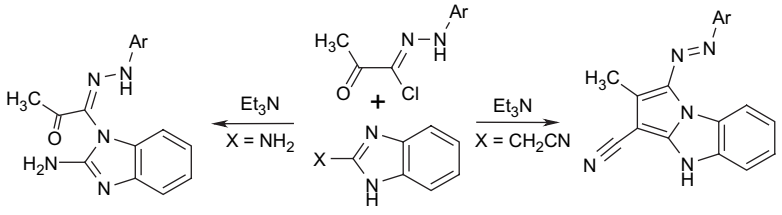


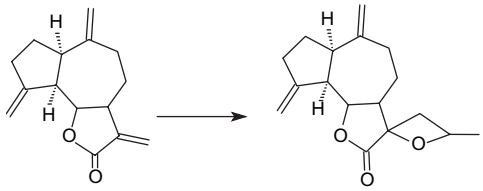


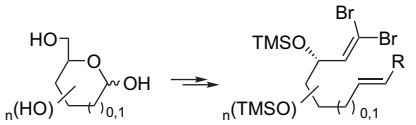


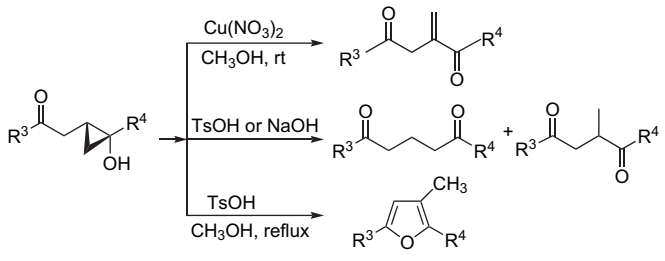
1,4-Benzoquinones were selectively obtained in good yields starting with alkylated phenol and methoxytoluene derivatives by oxidation with a hydrogen peroxide/methyltrioxorhenium catalytic system in 1-butyl-3-methylimidazolium tetrafluoroborate, a neutral ionic liquid. The antifungal activity of some 1,4-benzoquinones was tested in vitro.

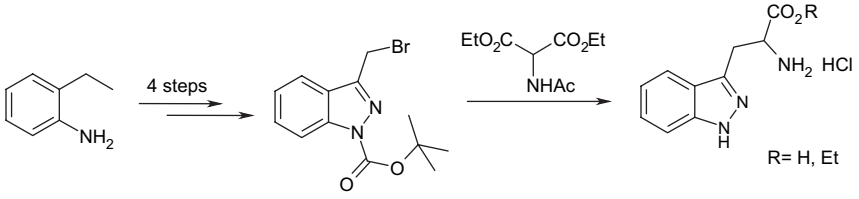


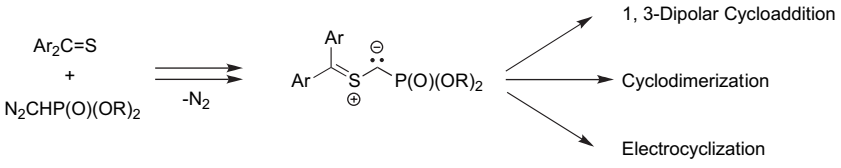


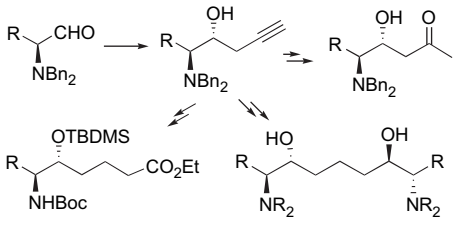


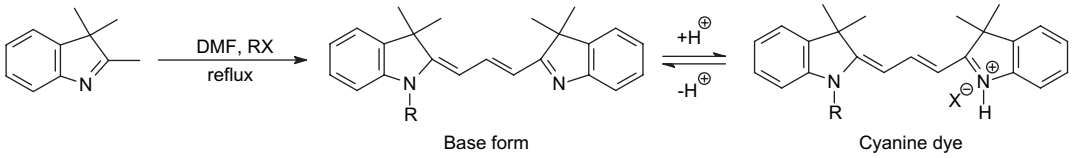


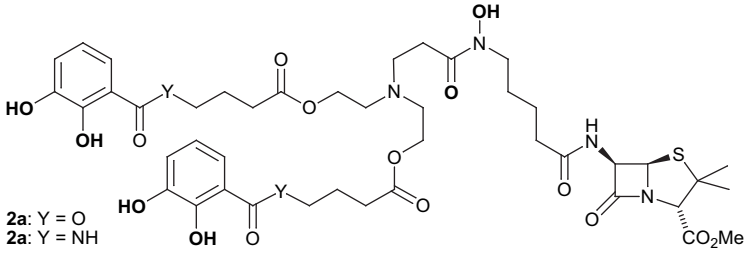


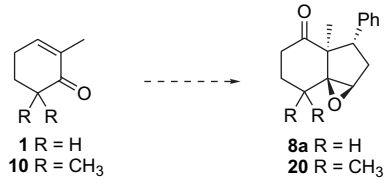


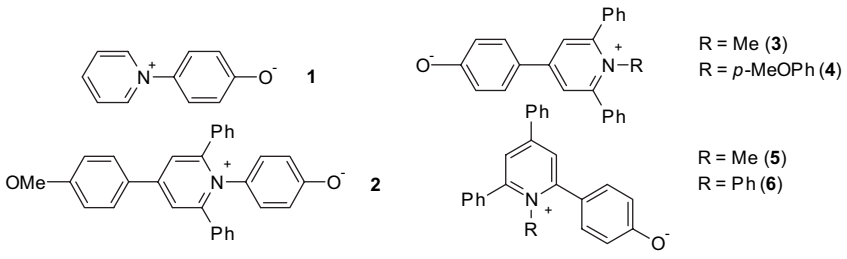


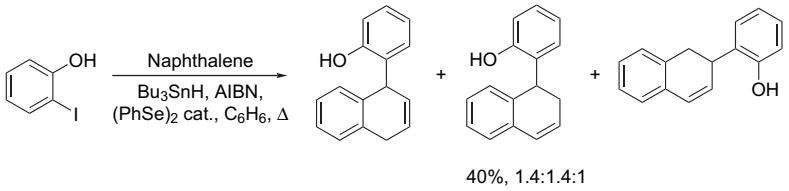


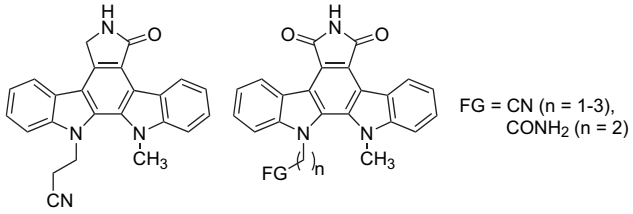




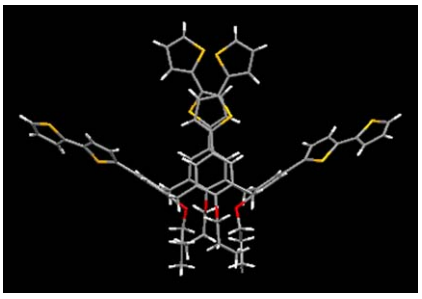


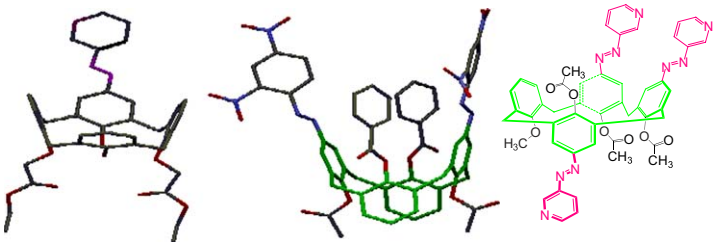


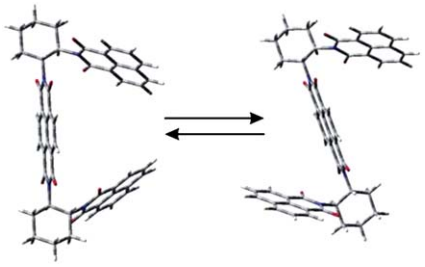


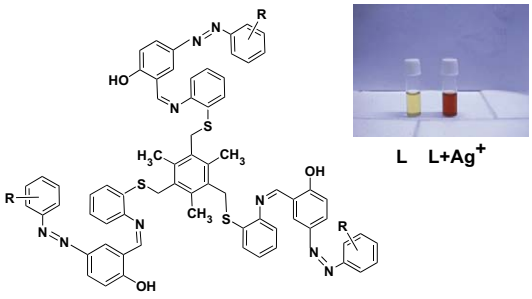


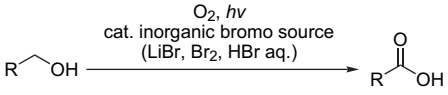
In addition to peak/band broadening, spectral shifting, and fluorescence quantum yield quenching, the close proximity of the tetra-oligothiophenes constructed within a calix[4]arene assembly lowers the first ionization potential, stabilizes the formation of resulting radical cation, and results in the occurrence of higher oxidation states.

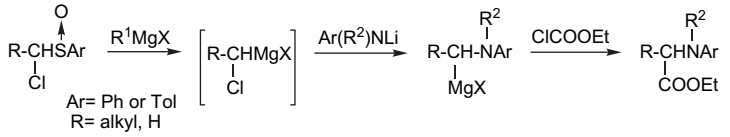


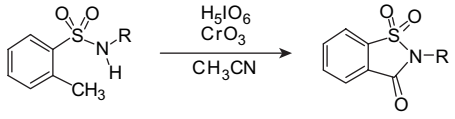


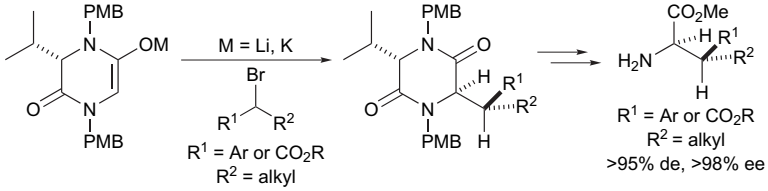




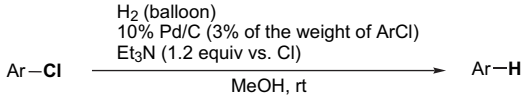


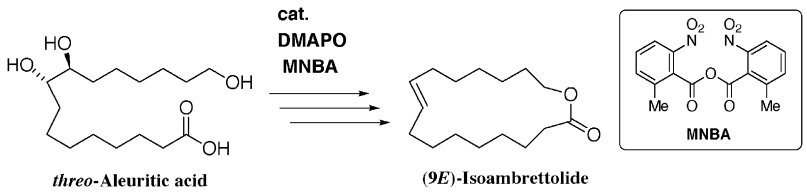






Enolates of (*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-*iso*-propylpiperazine-2,5-dione exhibit high levels of enantiodiscrimination in alkylations with (*RS*)-1-aryl-1-bromoethanes and (*RS*)-2-bromoesters affording, after *N*-deprotection and hydrolysis, methyl 2-amino-3-aryl-butanoates and 3-methyl-aspartates in high de and ee.





threo-Aleuritic acid (9*E*)-Isoambrettolide

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 7621–7643

Tetrahedron report number 763

Recent advances in the synthetic applications of the oxazaborolidine-mediated asymmetric reduction

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Received 5 May 2006
Available online 5 June 2006

Contents

1. Introduction

Optically active alcohols and amines are important compounds utilized widely as starting materials, intermediates, and chiral auxiliaries for preparing biologically active substances including natural products. One of the simplest and most useful methods for the preparation of such compounds is the asymmetric reduction of prochiral ketones and ketimines. Since Itsuno[1] and Corey[2] reported the first oxazaborolidine (OAB; **1** and **2**)-catalyzed borane reduction (Fig. 1), a number of such reductions have been extensively studied.[3] For prochiral ketones, these reductions are very effective not only for most of aryl alkyl ketones, but also for various functionalized ketones, such as heterocyclic ketones, α-halo- and sulfonyloxy ketones, α-hydroxy ketones, diketones, α-keto acetals or thioketals, α,β-enones and ynones, α-azido ketones, *meso*-imides, keto esters, keto phosphates, β-keto sulfides and sulfones, and biaryl ketones and lactones, to furnish high enantioselectivity

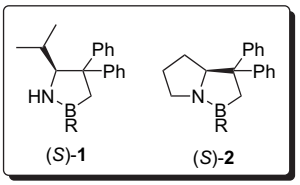

Figure 1.

Keywords: Chiral oxazaborolidine; Asymmetric reduction; Chiral natural products; Chiral bioactive compounds.
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0040–4020/$ - see front matter
doi:10.1016/j.tet.2006.05.036

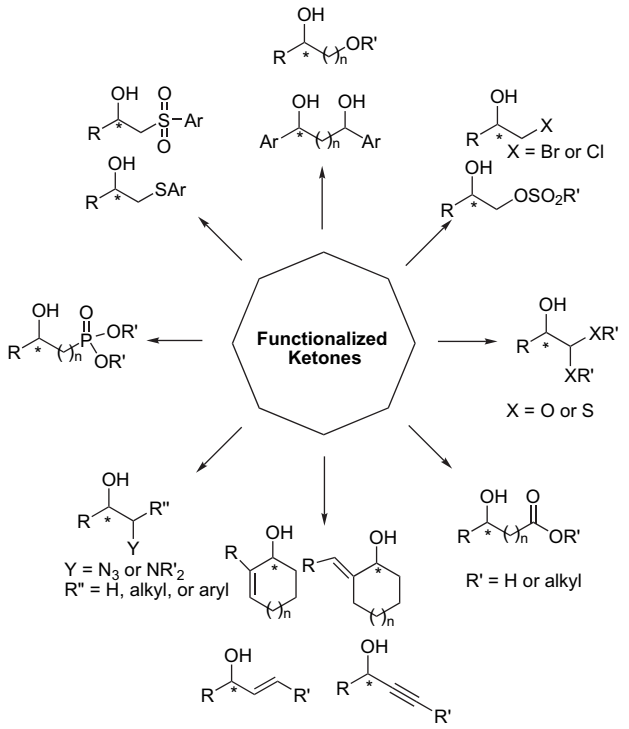


Figure 2.

with predictable configurations, even in the presence of only 2 mol % of OAB (Figs. 2 and 3). Many applications of this methodology for the synthesis of nonracemic natural products, bioactive compounds including chiral drugs and/or their intermediates have therefore been reported.[3] This review will cover only recent advances for the applications published during the years from 1998 through to mid-2005, since such applications reported until 1997 have been adequately reviewed.[3d] On the other hand, the reduction of ketimines using OABs as asymmetric inducers afforded only limited success, in contrast to the enormous progress made in the reduction of ketones. This is attributable to the low electrophilicity of the imine carbon and the rapid equilibration between the *E* and *Z* isomers. In addition, most of the chiral Lewis acids including OABs are trapped by the basic nitrogen atoms of imines and/or product amines, leading to less effective catalytic reactions.[3b] In order to illustrate the methodology, this review will begin with a brief description of the OAB-mediated asymmetric borane reduction.

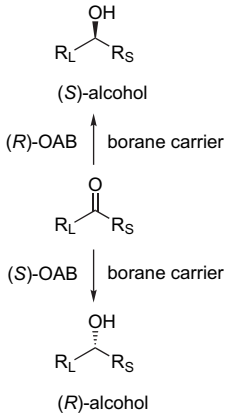


Figure 3.

2. Oxazaborolidine-mediated asymmetric borane reduction

In the OAB-mediated asymmetric borane reduction of ketones and ketimines, OABs play a role as Lewis acid–Lewis base bifunctional asymmetric inducer, which would activate both ketone or imine and borane, respectively, at the defined positions.[4] The dual activation mechanism involves the enantiofacial addition of boron–hydrogen bond to the activated ketone or imine (Fig. 4).[3e] In this reduction, OABs are used as both catalyst and stoichiometric reagent for asymmetric induction. Most of the OABs reported were prepared from chiral 1,2-amino alcohols with boron reagents, such as borane carriers, alkyl- or aryl-boronic acids, trimethylboroxine or trialkyl borate. Among these, CBS[5] reagents and their derivatives **2a**–**e** have been widely applied as some of the most effective asymmetric inducers (or catalysts) for the reduction. These reagents have been prepared from (*R*)- or (*S*)-2,2-diphenylhydroxymethylpyrrolidine (DPP, **3**) with borane–THF (BH_3–THF) or borane-dimethyl sulfide (BMS), trimethylboroxine, *n*-butylboronic acid, 4-*t*-butylphenylboronic acid, and trimethyl (or isopropyl) borate, respectively (Scheme 1).[2,6] Of these, **2a** and **2e** were usually used as themselves after in situ generation from **3** with borane and trimethyl or triisopropyl borate, respectively. The reagent **2b** is commercially available. The OAB-mediated borane reductions are generally performed by the

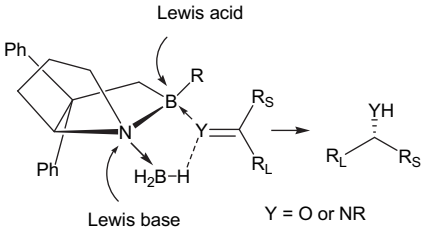
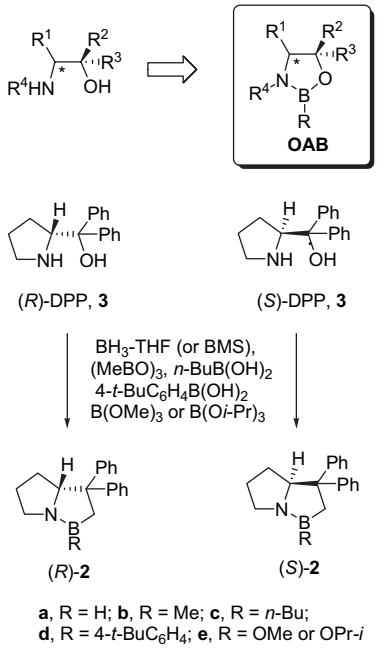


Figure 4.



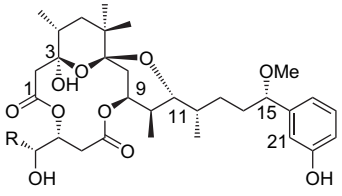
Scheme 1.

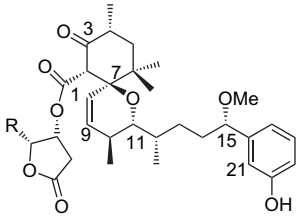
addition of prochiral ketones (or imines) to a mixture of OABs and borane carriers in an appropriate solvent at ambient temperature. As borane carriers, BH_3–THF, BMS, catecholborane (CB), and phenylamine–borane complexes, such as *N*,*N*-diethylaniline-borane (DIANB) and *N*-ethyl-*N*-isopropylaniline-borane (EIANB), are commonly used.

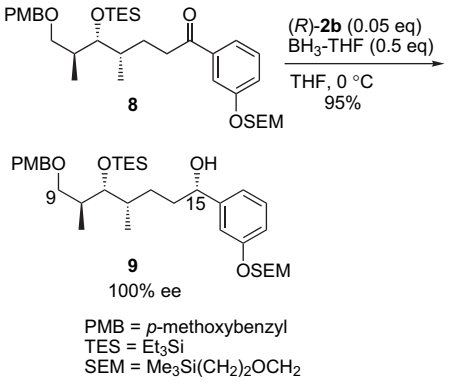
3. Applications

3.1. Synthesis of natural products and related compounds

3.1.1. Lactones and macrolides. Aplysiatoxin and oscillatoxin derivatives are a class of natural macrolide products, which are metabolites of some species of tropical marine blue-green algae. Of these, it has been known that the toxic debromoaplysiatoxin (**4**) and oscillatoxin A (**5**) are significant tumor promoters, whereas the nontoxic oscillatoxin D (**6**) and 30-methyloscillatoxin D (**7**) possess antileukemic activity. An approach to the synthesis of a chiral alcohol **9**, which comprises a selectively protected C_9–C_{21} portion of these compounds, using the catalytic CBS reduction has been investigated. The reduction of an aromatic ketone **8** using (*R*)-**2b** and BH_3–THF as catalyst and borane carrier, respectively, provided **9** in 95% yield as a single stereoisomer (Scheme 2).[7]

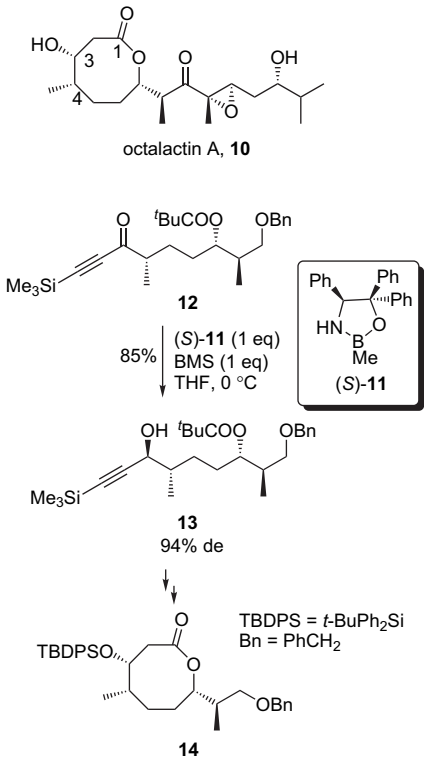






Scheme 2.

A stoichiometric OAB-mediated borane reduction of an acetylenic ketone **12** using (*S*)-**11** derived from (*S*)-phenylglycine as asymmetric inducer was applied to the synthesis of C_1–C_4 fragment of the lactone ring of a marine actinomycete, octalactin A (**10**), a potent cytotoxin against some human tumor cell lines. The reduction provided the acetylenic alcohol **13** in 85% yield and 94% diastereomeric excess (de). The chiral alcohol **13** obtained has been used as a precursor for the synthesis of the octalactin lactone ring (**14**) (Scheme 3).[8]

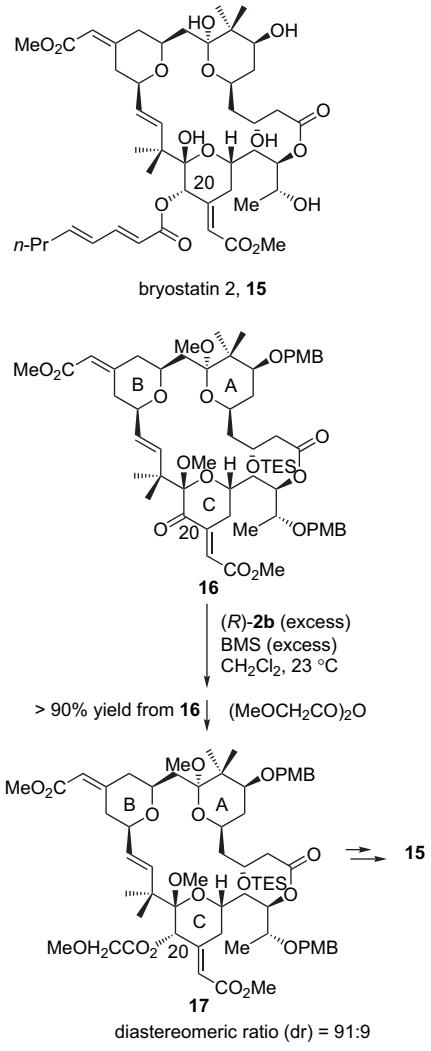


Scheme 3.

For the synthesis of a marine natural macrolide, bryostatin 2 (**15**), exhibiting potent antitumor activity, the stoichiometric CBS reduction of an exocyclic α,β-enone **16** to give the required allylic alcohol functionality at the C_{20} position of the C-ring (**17**) in a 91:9 selectivity has been utilized (Scheme 4).[9]

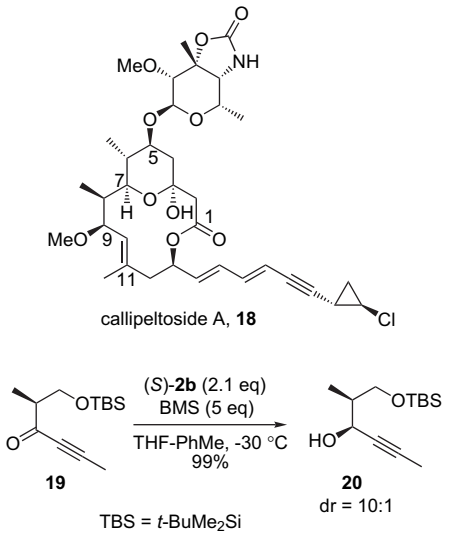
Similarly, the stoichiometric CBS reduction of the acetylenic ketone **19** using 2.1 equiv of (*S*)-**2b** and 5 equiv of BMS at −30 °C afforded the desired propargylic alcohol **20** with a 10:1 diastereoselectivity. This alcohol can be used as a starting material for the synthesis of C_7 to C_{11} fragment of callipeltoside A (**18**), a marine sponge possessing antitumor activity (Scheme 5).[10]

11-Desmethyllaulimalide (**22**), an analogue of the antitumor active laulimalide (**21**) isolated from a marine sponge, has been prepared by the CBS reduction of an acyclic enone **23**, followed by Sharpless epoxidation. The reduction afforded the required (20*S*)-allylic alcohol **24** with very high diastereoselectivity (diastereomeric ratio (dr) = 56.6:1). In contrast, the use of other reducing agents, such as lithium *tert*-butoxyaluminum hydride and L-Selectride, proved to be less effective (Scheme 6).[11]

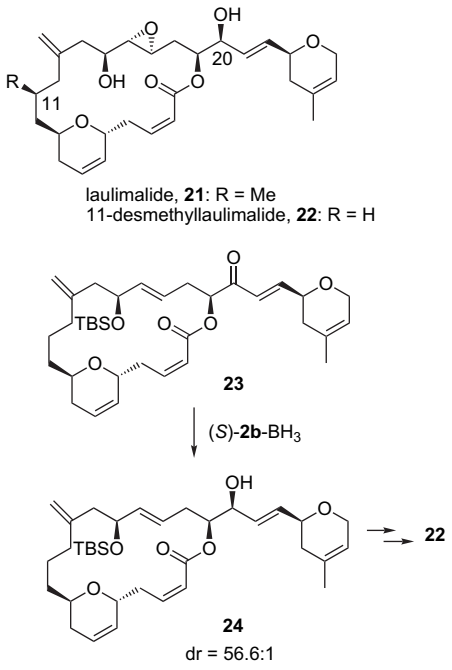


Scheme 4.

Starting from the CBS reduction of 2-methylcyclopentenone **26** using 1 equiv of (*S*)-**2b**·BH_3, a tricyclic spirobutenolide precursor **30**, which can serve as a common intermediate

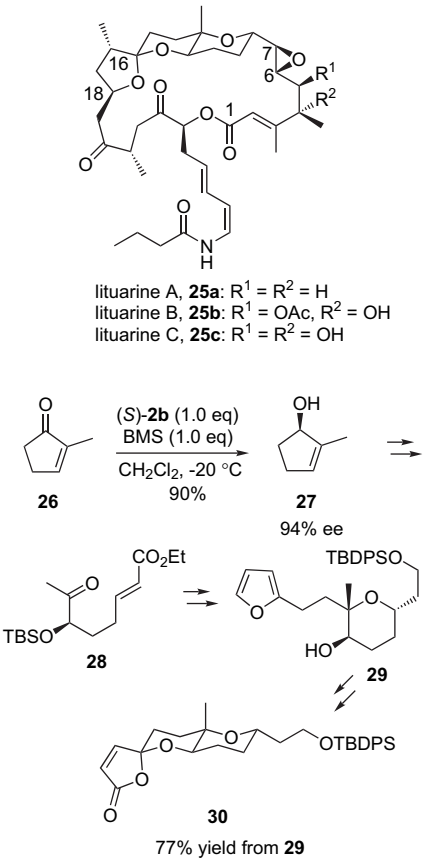


Scheme 5.



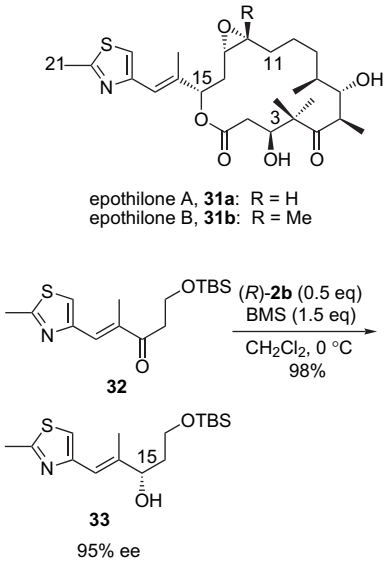
Scheme 6.

for the synthesis of C_7–C_{18} fragment of the antifungal marine natural products, lituarines A–C (**25a**–**c**), has been prepared. The reduction afforded a chiral enol **27** with 94% ee, which was converted into the desired precursor **30** via intermediates **28** and **29** (Scheme 7).[12]



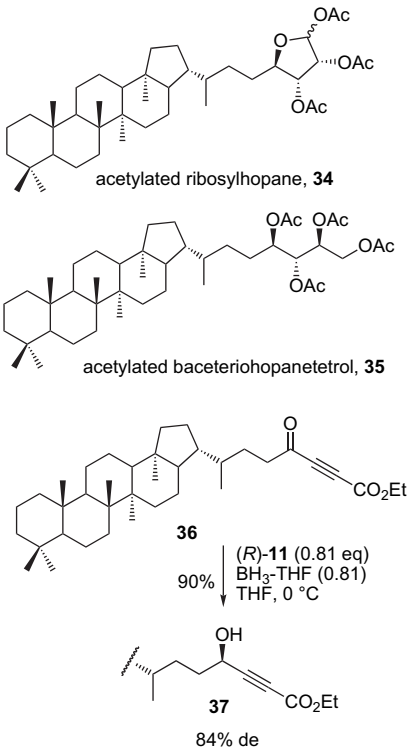
Scheme 7.

A (15*S*)-allylic alcohol **33**, which is the C_{13}–C_{21} fragment of epothilones A and B (**31a** and **31b**) isolated from myxobacteria exhibiting antimitotic activity against multidrug resistant cancer cell lines, has been prepared in 98% yield and 95% ee from the CBS reduction of the enone **32** using 0.5 equiv of (*R*)-**2b** and 1.5 equiv of BMS (Scheme 8).[13]



Scheme 8.

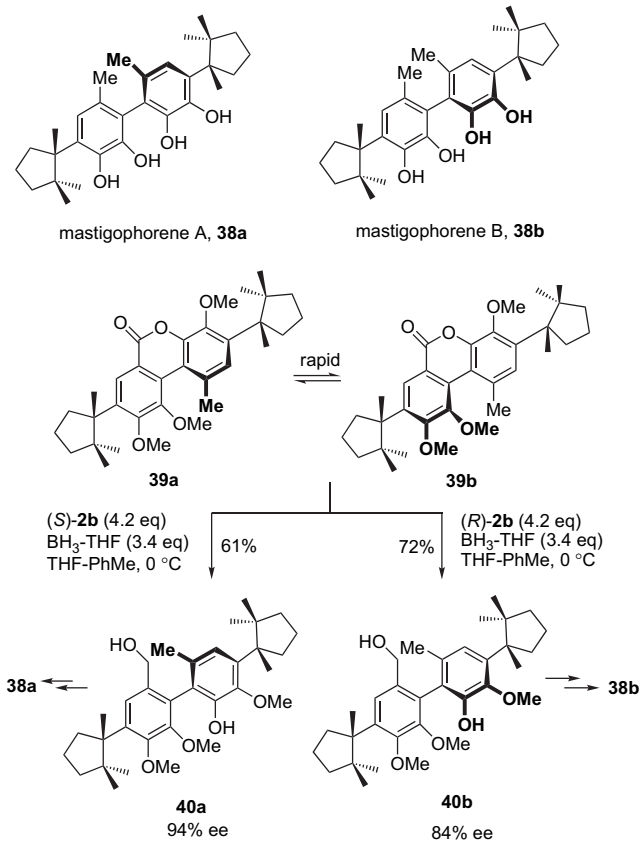
3.1.2. Terpenoids. Hopanoids, a class of triterpenoids, are widely distributed in bacteria and blue-green algae, where they are important cell membrane constituents. Acetylated ribosylhopane **34** and acetylated bacteriohopanetetrol **35** are the putative biosynthetic precursors of bacterial triterpenoids. An OAB-mediated reduction of an acetylenic ketone **36** using (*R*)-**11** as asymmetric inducer has been applied to the synthesis of the desired propargylic alcohol **37** with 90% yield and 84% de, which can serve as a precursor for the synthesis of these hopanoid compounds (Scheme 9).[14]



Scheme 9.

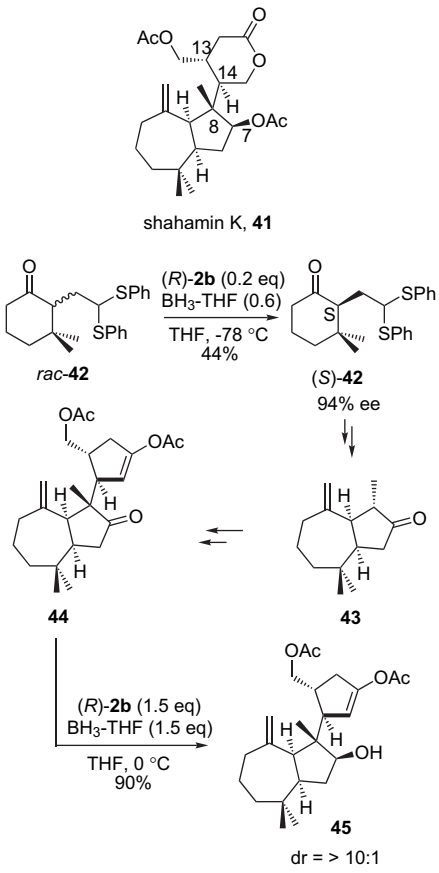
A dynamic kinetic resolution of two rapidly interconverting atropodiastereomeric lactones, **39a** and **39b**, by CBS reduction was utilized for the synthesis of the natural products, mastigophorene A and B (**38a** and **38b**), which are regarded as therapeutic agents for degenerative diseases of the central nervous system such as Parkinson's disease and Alzheimer's disease. These compounds have a C_2-symmetric structure involving elements of both axial and centro chirality. When the reduction of an equilibrium mixture of **39a** and **39b** using a large excess of BH_3–THF in the presence of each of (*S*)-**2b** and (*R*)-**2b** was carried out at 0 °C, the reactions provided **40a** in 61% yield and 94% ee and **40b** in 72% yield and 84% ee, respectively. The chiral products obtained have been converted into **38a** and **38b** by a reductive benzylic deoxygenation and demethylation (Scheme 10).[15]

Shahamin K (**41**) is a marine natural product having a *cis*-hydroazulene unit. This compound has been synthesized starting from an enol acetate alcohol **45**. The CBS reductions were applied to the synthesis of the chiral hydroazulenone **43** and the alcohol **45**, which were used as key intermediates for the synthesis of **41**. A chiral ketone (*S*)-**42** obtained from the kinetic resolution of a racemic ketone *rac*-**42** with (*R*)-**2b**-catalyzed reduction was converted into **43** and a chiral keto enol acetate **44** through multiconversion steps. Finally, a stoichiometric CBS reduction of **44** with (*R*)-**2b**



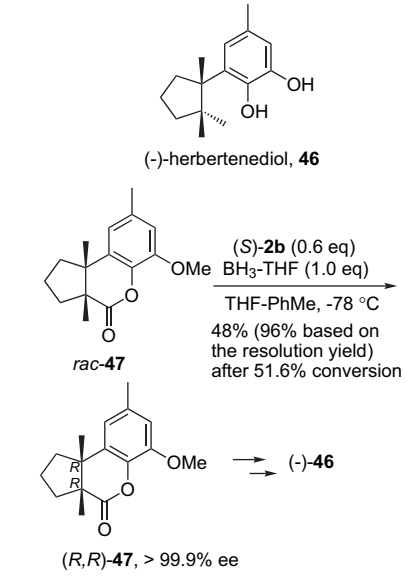
Scheme 10.

gave the desired alcohol **45** in 90% yield with high diastereoselectivity (dr >10:1) (Scheme 11).[16]

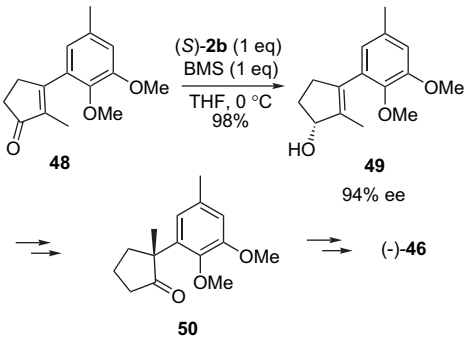


Scheme 11.

(−)-Herbetenediol (**46**) is a sesquiterpene isolated from liverwort exhibiting anti-lipid peroxidation activity. For the synthesis of this compound, two different methods using CBS reduction have been reported. Scheme 12 shows the synthesis of **46** starting from a chiral lactone, (*R*,*R*)-**47**, obtained from the enantiomer-differentiating reduction of *rac*-**47** by CBS reduction under a kinetic resolution condition.[15] The other method begins with a stoichiometric CBS reduction of α,β-enone **48** to give a chiral enol **49** in 94% ee. The enol **49** obtained has been converted into **46** via a chiral cyclopentanone **50** (Scheme 13).[17]

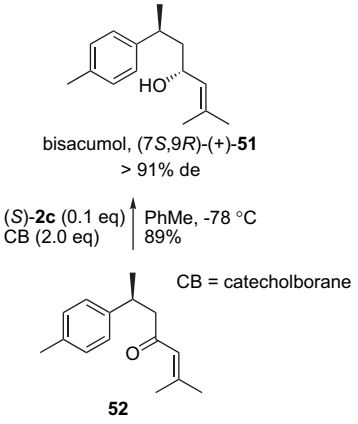


Scheme 12.



Scheme 13.

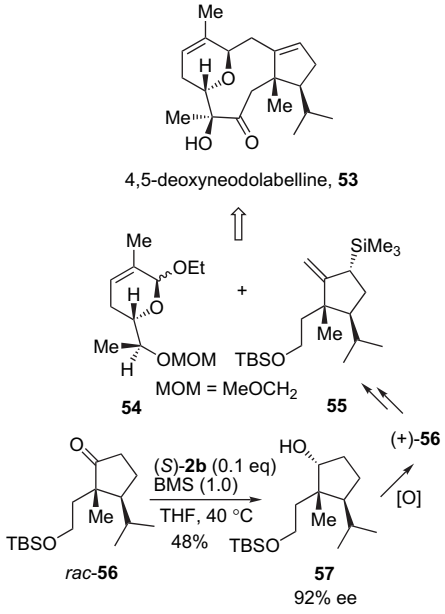
Scheme 14 outlines the (*S*)-**2c**-catalyzed CBS reduction of α,β-enone **52** to provide an antitumor aromatic bisabolane sesquiterpene, (+)-bisacumol **51**, in 89% yield and >91% de.[18]



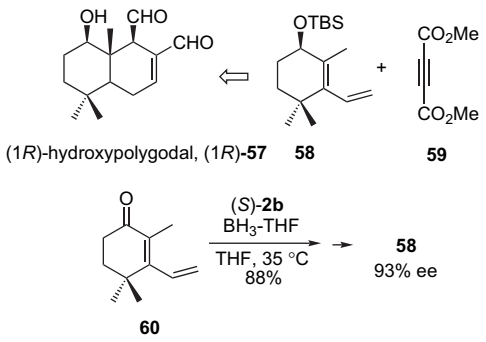
Scheme 14.

4,5-Deoxyneodolabelline (**53**) isolated from a marine bicyclic diterpene is an analogue of dolabellanes showing cytotoxic, antibacterial, and antiviral activity. This compound has been prepared by a reductive coupling of nonracemic dihydropyran **54** and cyclopentenylsilane **55**. Of these intermediates, **55** was prepared via a multistep route, starting from a chiral ketone (+)-**56** obtained from the catalytic CBS reduction of *rac*-**56**, followed by a chromatographic separation of the desired alcohol **57** and subsequent oxidation (Scheme 15).[19]

(1*R*)-Hydroxypolygodal (**57**) is an analogue of polygodal isolated from terrestrial and marine sources possessing a pungent sensation on the human tongue. This compound has been synthesized by Diels–Alder reaction of a chiral protected hydroxydiene derivative **58** and dimethyl acetylenedicarboxylate **59**. Of these, **58** has been prepared in 88% yield and 93% ee by CBS reduction of dienone **60** using (*S*)-**2b** (Scheme 16).[20]



Scheme 15.

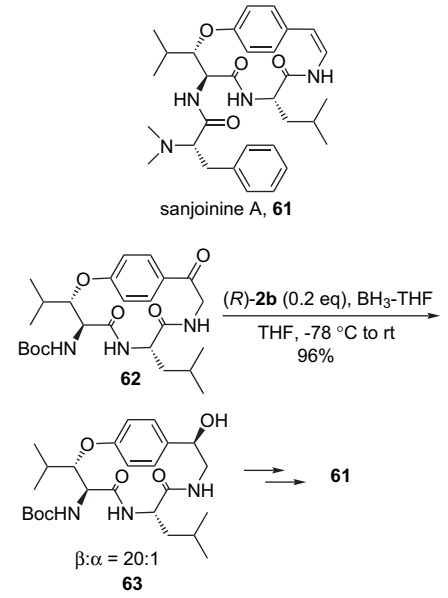


Scheme 16.

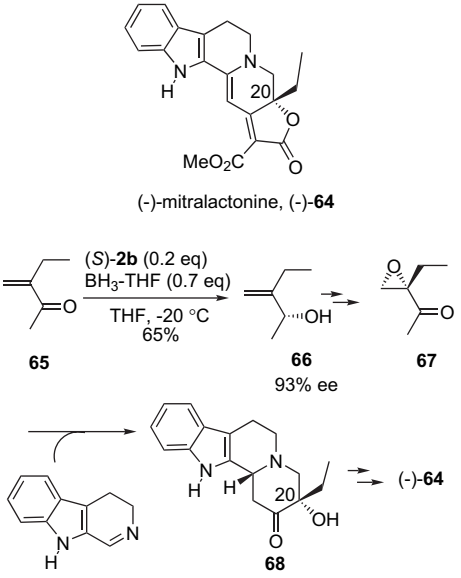
3.1.3. Alkaloids. Sanjoinine A (frangufoline, **61**) is a natural alkaloid used as a sedative herbal medicine in the Orient. A key intermediate, β-hydroxy isomer **63** required for constructing the *cis*-enamine of **61**, has been prepared in 96% yield and 20:1 (β:α) stereoselectivity by a (*R*)-**2b**-catalyzed borane reduction of amido ketone **62** (Scheme 17).[21]

(−)-Mitralactonine (**64**) is a monoterpenoid indole alkaloid, which is known to exhibit narcotic-like actions, such as opioid agonistic properties. The catalytic CBS reduction of α,β-enone **65** provided a chiral allylic alcohol **66** in 65% yield and 93% ee. This alcohol was subjected to Sharpless epoxidation under the kinetic resolution conditions and subsequent oxidation to give a chiral α-epoxy ketone **67** with >99% ee, possessing the desired configuration at the C_{20} position of **64**. The stereoselective condensation of **67** with dihydro-β-carboline gave a chiral hydroxyl ketone **68**. The target compound **64** has been prepared in 46% yield from **67** by Knoevenagel condensation of **68** with dimethyl malonate, followed by elimination (Scheme 18).[22]

The atropoenantioselective ring cleavage reaction of an equilibrium mixture of racemic lactones, **70a** and **70b**, using a stoichiometric CBS reduction in the presence of each of



Scheme 17.

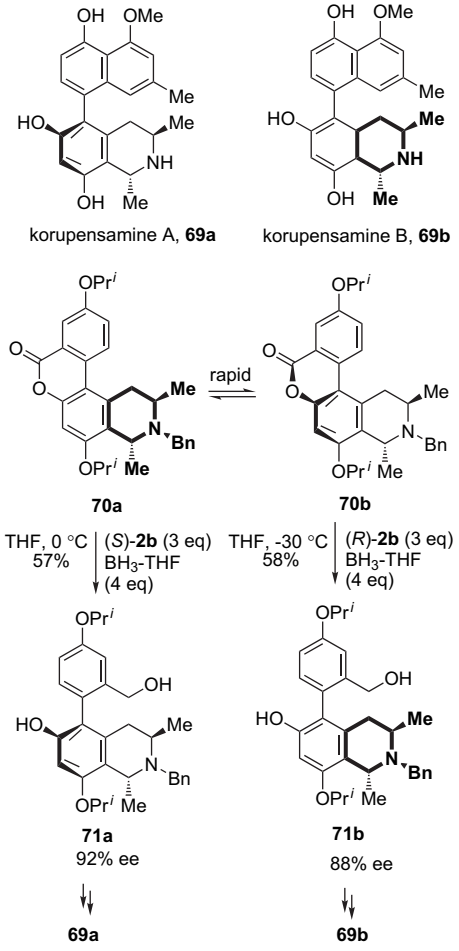


Scheme 18.

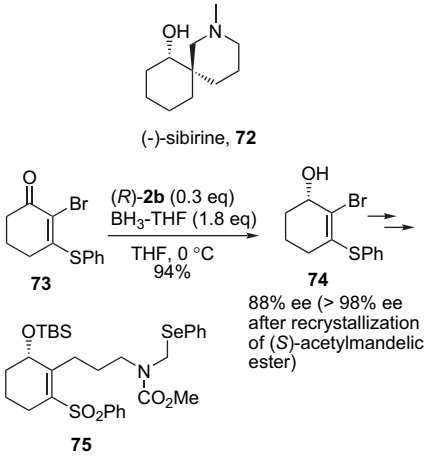
(*S*)- and (*R*)-**2b**, provided **71a** and **71b** with 92 and 88% ee, respectively. From these latter products, the synthesis of dimeric naphthylisoquinoline alkaloids, korupensamines A and B (**69a** and **69b**), which exhibit good antimalarial activities in vitro and in vivo, has been reported (Scheme 19).[23]

The catalytic CBS reduction of α-bromo α,β-enone **73** gave a chiral 2-bromoallylic alcohol **74** in 94% yield and 88% ee. Starting from this alcohol, a natural spiropiperidine alkaloid, (−)-sibirine (**72**), has been prepared via the precursor **75** (Scheme 20).[24]

Compound (+)-*trans*-195A (**76**) is an alkaloid having decahydroquinoline structure isolated from amphibian skin, which shows noncompetitive blocking activity of nicotinic receptor channels and an inhibitory effect against sodium and potassium transport. This compound has been prepared

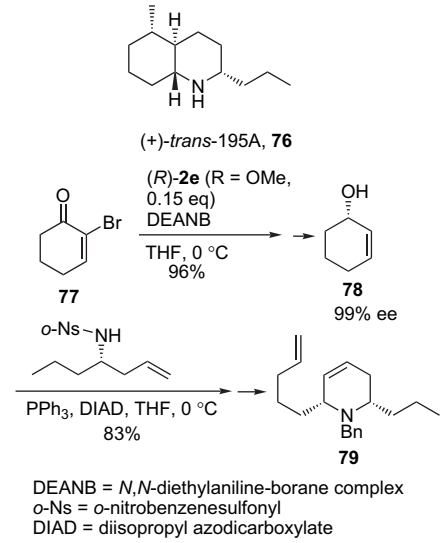


Scheme 19.



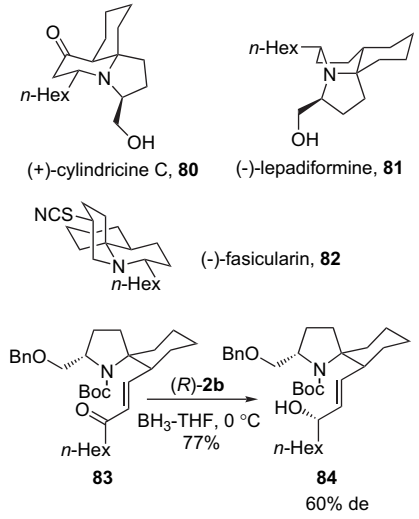
Scheme 20.

by a stereoselective ring-closure reaction of **79**, prepared from (*S*)-cyclohex-2-ol **78**. CBS reduction of 2-bromocyclohex-2-one **77** using (*R*)-**2e** (R=OMe) as catalyst, followed by debromination, provided (*S*)-**78** in 96% yield and 99% ee (Scheme 21).[25]



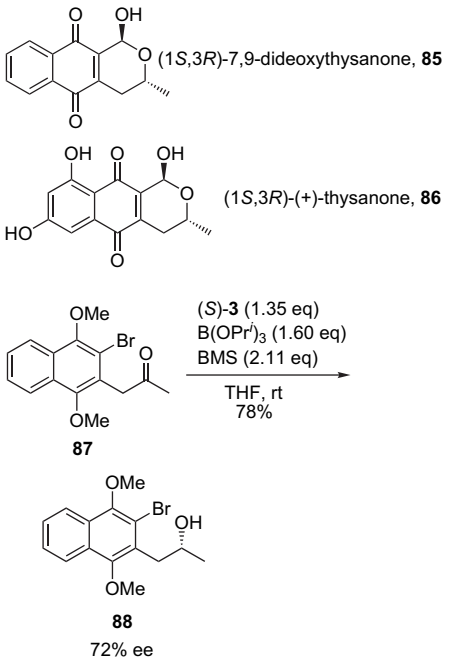
Scheme 21.

Very recently, a total synthesis of the tricyclic marine alkaloids (+)-cylindricine C (**80**), (−)-lepadiformine (**81**), and (−)-fasicularin (**82**), using CBS reduction as a key step have been reported. These compounds were prepared from an intramolecular conjugate azaspirocyclization of a chiral common intermediate **84**, obtained from the CBS reduction of an α,β-enone **83** (Scheme 22).[26]



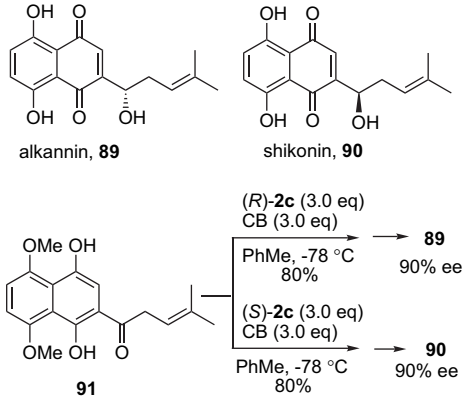
Scheme 22.

3.1.4. Phenolics and propargylic alcohols. (1*S*,3*R*)-7,9-Dideoxythysanone (**85**) is an analogue of (1*S*,3*R*)-(+)-thysanone (**86**), which is a fungal benzoisochromanquinone with potent human rhinovirus 3C protease inhibitory activity, and can be used as a chemotherapeutic agent for the control of common cold. The stoichiometric CBS reduction of bromoketone **87**, using BMS in the presence of an excess of triisopropyl borate and (*S*)-**3**, provided a chiral bromoalcohol **88** in 78% yield and 72% ee, which can serve as a key intermediate for the synthesis of **85** (Scheme 23).[27]



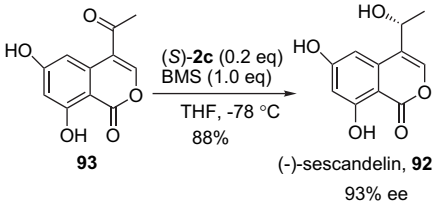
Scheme 23.

Starting from a stoichiometric CBS reduction of **91** with (*R*)-**2c** and (*S*)-**2c**, the natural products, alkannin (**89**) and shikonin (**90**), in 90% ee have been prepared (Scheme 24).[28] These compounds exhibit a very wide spectrum of biological activities including anti-inflammatory, antibacterial, antifungal, anticancer, analgesic, antipyretic, antithrombotic, immunostimulatory, angiostatic, and wound-healing properties.



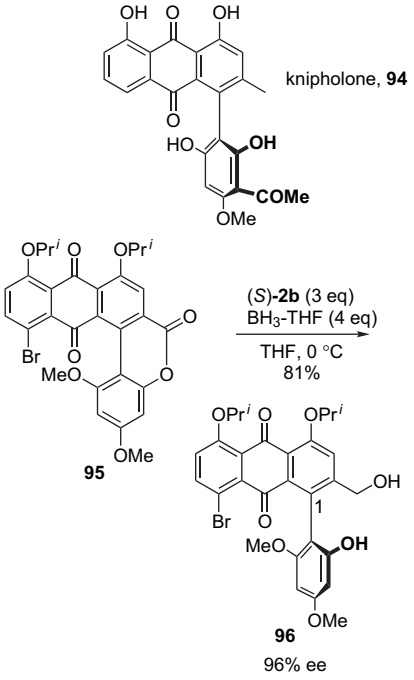
Scheme 24.

CBS reduction of acetylisocoumarin **93**, using (*S*)-**2c** as catalyst, afforded (−)-sescandelin (**92**), a fungal natural product having anti-angiogenic activities, in 88% yield and 93% ee (Scheme 25).[29]



Scheme 25.

Knipholone (**94**) is a natural phenylanthraquinone possessing high antiplasmodial activity in vitro against *Plasmodium falciparum*, the carrier of the most lethal malaria tropica. The enantioselective ring cleavage of a racemic biaryl lactone **95** using stoichiometric CBS reduction gave the desired alcohol **96** with high optical purity, which can serve as a key intermediate for the synthesis of **94** (Scheme 26).[30]

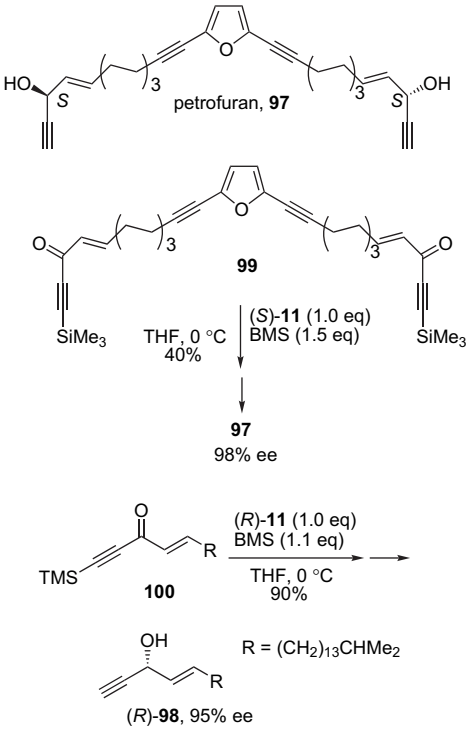


Scheme 26.

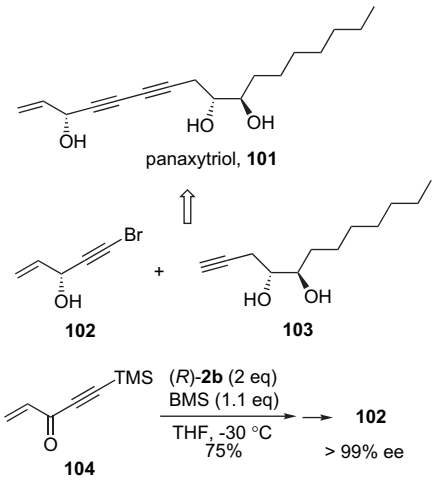
Some long-chain chiral propargylic alcohols, such as petrofuran (**97**)[31a] and (*R*)-**98**,[31b] isolated from marine sponges, exhibit antimicrobial, cytotoxic, immunosuppressive, and antitumor properties. A stoichiometric OAB-mediated reduction of enynones, **99** and **100**, using (*S*)- and (*R*)-**11** as asymmetric inducers, respectively, followed by desilylation, provided **97** in 98% ee and (*R*)-**98** in 95% ee (Scheme 27).

Panaxytriol **101**, isolated from red ginseng widely used as a folk medicine in Oriental regions, is known to have inhibitory activity against a human breast carcinoma cell line and to enhance the cytotoxicity of mitomycin C against human gastric adenocarcinoma cell lines. This compound has been synthesized by a cross-coupling reaction of two chiral alcohols **102** and **103**. Among these, the chiral alcohol **102** with >99% ee has been prepared by a stoichiometric CBS reduction of enynone **104**, followed by bromination (Scheme 28).[32]

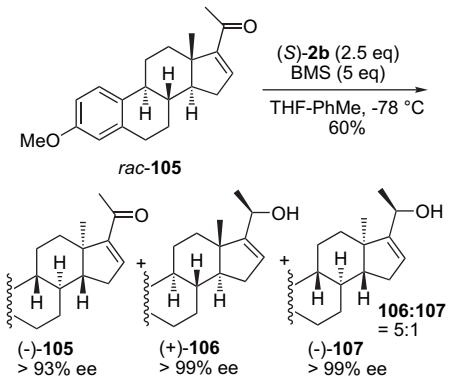
3.1.5. Steroids, lignans, and pheromones. A stoichiometric CBS reduction has been successfully applied to a kinetic resolution of a racemic steroidal ketone *rac*-**105** to give (−)-**105** with high enantiopurity. When the reduction of *rac*-**105** with BMS in the presence of (*S*)-**2b** at −78 °C was quenched at approximately 60% completion, (−)-**105** was isolated in 40% yield with >93% ee, along with a 5:1 mixture of diastereomeric alcohols (+)-**106** and (−)-**107**, each with >99% ee (Scheme 29).[33]



Scheme 27.

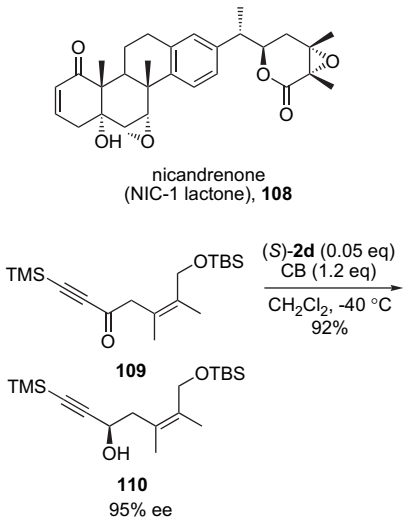


Scheme 28.



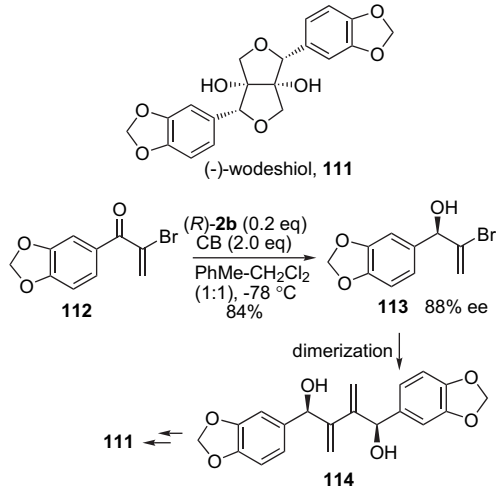
Scheme 29.

Nicandrenone (NIC-1 lactone, **108**) is a steroid-derived natural product, which exhibits insect repellent and antifeedant properties. CBS reduction of acetylenic ketone **109**, using (*S*)-**2d** as catalyst, provided the desired chiral alcohol **110** in 95% ee, which can be utilized as a precursor for the synthesis of the lactone ring component in the side chain (Scheme 30).[34]



Scheme 30.

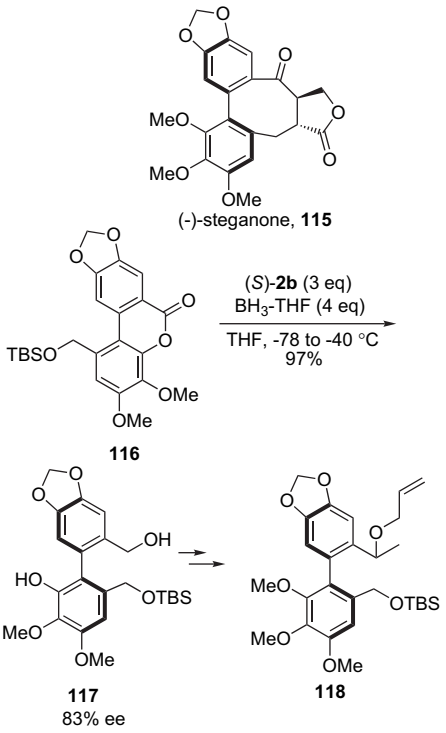
The catalytic CBS reduction of α,β-enone **112**, using (*R*)-**2b** and CB as catalyst and borane carrier, respectively, provided a chiral allylic alcohol **113** in 84% yield and 88% ee. Using **114** obtained from dimerization of **113** as a key intermediate, a natural lignan-containing furan ring, (−)-wodeshiol (**111**), has been prepared (Scheme 31).[35]



Scheme 31.

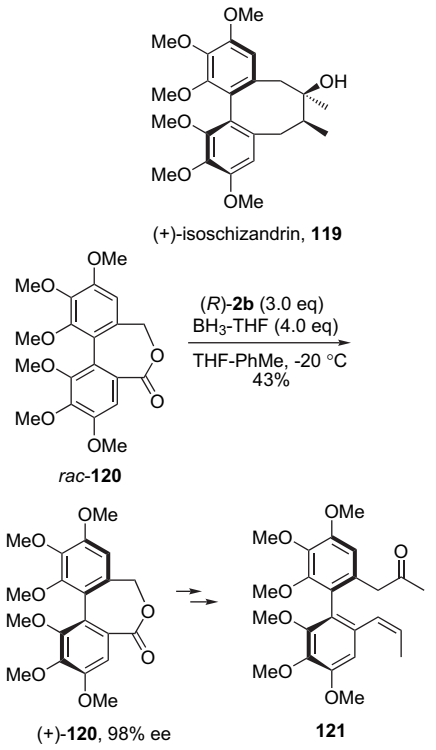
(−)-Steganone (**115**) is a natural lignan bearing an asymmetrical 2,2′-disubstituted biphenyl moiety with an axial chirality. This compound is known to have antileukemic activity. The stoichiometric CBS reduction was utilized for enantioselective construction of the biaryl part of this compound.

The reductive asymmetric lactone ring-opening reaction of racemic lactone **116** based on dynamic optical resolution afforded a chiral biaryl alcohol **117** in 97% yield and 83% ee. From this alcohol, a chiral homoallyl ether **118**, which can be used as a key intermediate for the synthesis of **115**, has been prepared (Scheme 32).[36]



Scheme 32.

A kinetic resolution of a racemic biaryl lactone *rac*-**120**, using the stoichiometric CBS reduction using (*R*)-**2b**, provided a chiral lactone (+)-**120** in 43% yield and 98% ee. Using a chiral keto (*Z*)-olefin **121**, obtained from (+)-**120** as a key intermediate, a dibenzocyclooctadiene lignan, (+)-isoschizandrin (**119**), displaying antirheumatic, antihepatotoxic, and antiulcer activities, has been prepared (Scheme 33).[37]

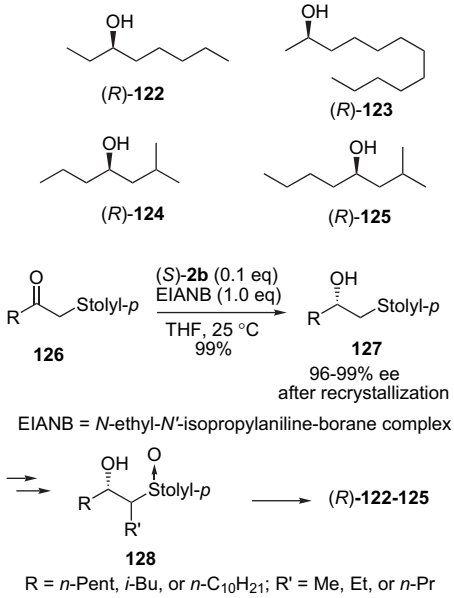


Scheme 33.

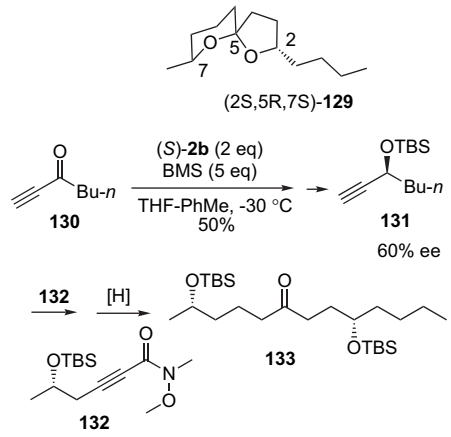
Chiral aliphatic alcohols (*R*)-**122**–**125** are pheromones found in various classes of insects, showing a variety of biological activities. As shown in Scheme 34, these compounds have been prepared by using chiral β-hydroxy sulfides **127** as key intermediates. The catalytic CBS reduction of β-keto sulfides **126** afforded chiral β-hydroxy sulfides **127**, which were converted into (*R*)-**122**–**125** by desulfurization of alkylated sulfoxides **128** obtained from selective oxidation of **126**, followed by alkylation.[38] Although the reduction of **126** initially provided **127** with 74–71% ee, their optical purities were improved to 96–99% ee by recrystallization of their nitrobenzoates.

Scheme 35 illustrates the synthesis of an optically active spiroacetal insect pheromone **129** via intramolecular ketal formation of chiral dihydroxy ketone **133**, prepared from a cross-coupling reaction of two chiral propargylic alcohols **131** and **132**, followed by catalytic hydrogenation. Of these alcohols, **131** was obtained from the stoichiometric CBS reduction of acetylenic ketone **130** (Scheme 35).[39]

3.1.6. Prostanoids, sphinganines, and biotins. The catalytic CBS reduction was applied to the synthesis of a chiral iodoallylic alcohol **136**, which is a precursor for the synthesis of an ω-side chain of prostaglandin E_1 (**134**). The reduction of γ-iodovinyl ketone **135** with CB in the presence of

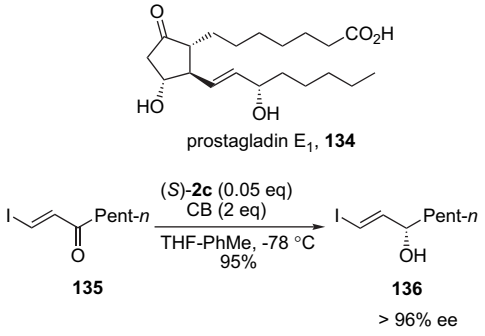


Scheme 34.



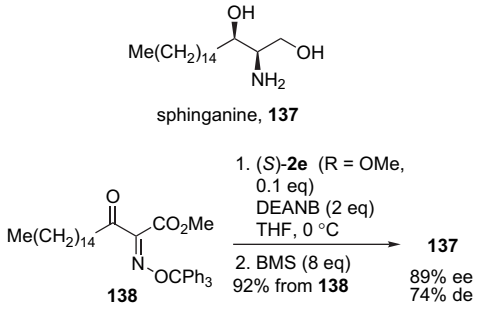
Scheme 35.

0.05 equiv of (*S*)-**2c** at −78 °C provided **136** in 95% yield and >96% ee (Scheme 36).[40]



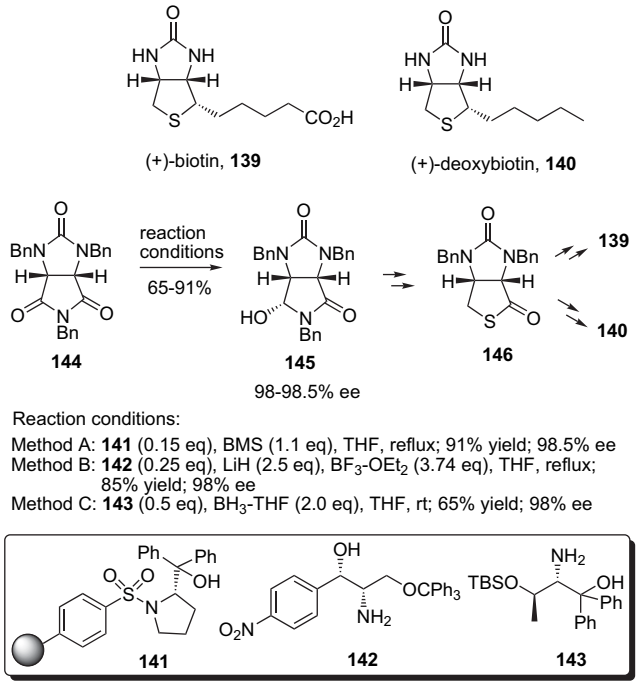
Scheme 36.

Sphinganine (**137**) is an intermediate in the biosynthesis of sphingolipids, which play important roles in cell regulation and signal transduction. The synthesis of this compound was achieved by the catalytic CBS reduction of an α-imino ketone derivative **138** using 2 equiv of DEANB in the presence of 0.1 equiv of (*S*)-**2e** (R=OMe) in situ generated from (*S*)-**3** with $B(OMe)_3$, followed by further reduction with an excess of BMS (Scheme 37).[41]



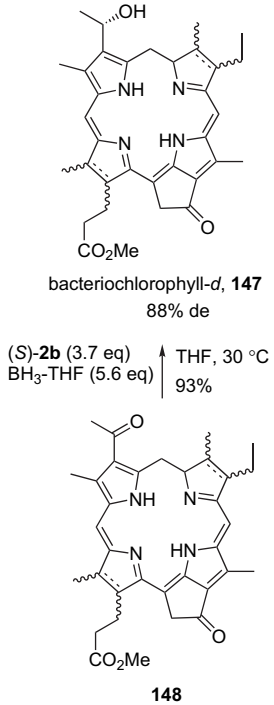
Scheme 37.

(+)-Biotin (**139**) is a water-soluble vitamin showing a significant biological activity for human nutrition and animal health. On the other hand (+)-deoxybiotin **140** is important as a precursor of **139**. The catalytic borane reduction of *meso*-imide **144** using OABs derived from each of **141**,[42a] **142**,[42b] and **143**[42c] as asymmetric inducers provided a chiral hydroxylactam **145** with 98–98.5% ee, which can be then converted into the chiral thiolactone **146**, a common intermediate for the synthesis of **139** and **140** (Scheme 38).[42]



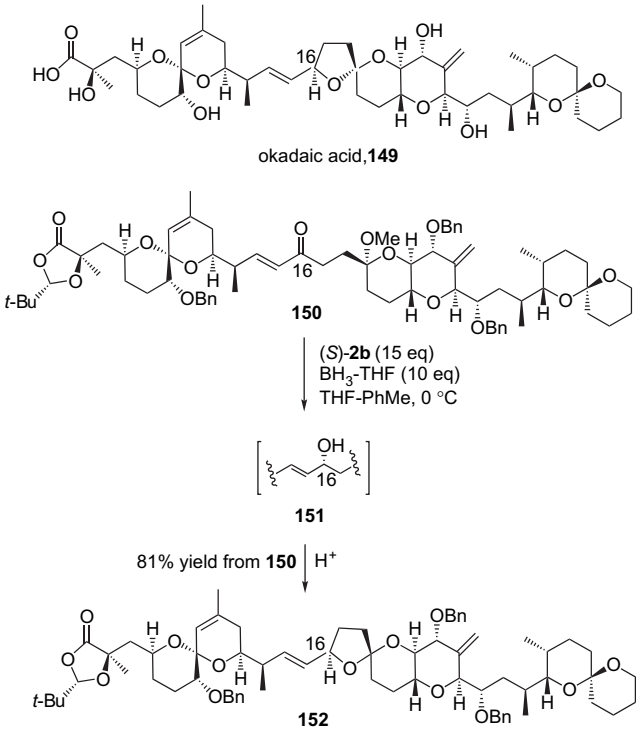
Scheme 38.

3.1.7. Other natural products. The stoichiometric CBS reduction of the corresponding ketone **148** using a large excess of (*S*)-**2b** and borane provided chiral bacteriochlorophyll-*d* (**147**), which is a natural pigment in light-harvesting antennae of green photosynthetic bacteria (Scheme 39).[43]



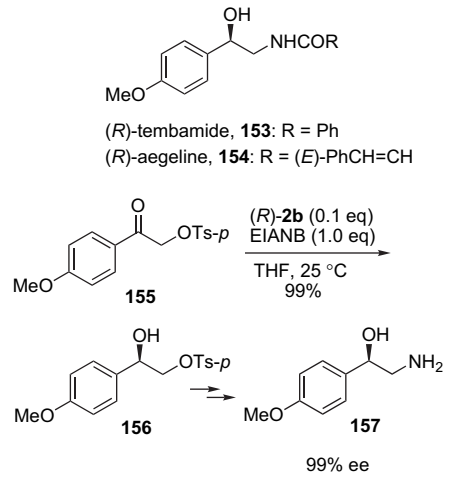
Scheme 39.

Okadaic acid (**149**) is a marine natural product with a rich modern history and is known as a potential anticancer agent. CBS reduction was applied to the introduction of (*R*)-configuration at C_{16} of this compound. The borane reduction of (*E*)-enone **150** in the presence of a large excess of (*S*)-**2b** provided the corresponding enol **151**. This alcohol was converted into the spiroketal **152** by spiroketalization and then **149** was obtained through hydrolysis and debenzylation of **152** (Scheme 40).[44]

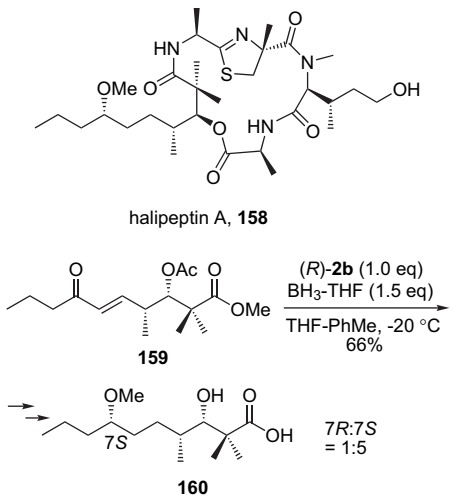


Scheme 40.

The catalytic CBS reduction was successfully utilized for the synthesis of (*R*)-tembamide (**153**) and (*R*)-aegeline (**154**), naturally occurring bioactive substances, which are used in traditional Indian medicine and have been shown to have hypoglycemic activity. The catalytic CBS reduction of α-*p*-tosyloxyketone **155** using (*R*)-**2b** as catalyst provided the chiral 1,2-diol monotosylate **156** with high enantiomeric purity. The target compounds, **153** and **154**, have been prepared from acylation of a chiral amino alcohol **157**, obtained by the reaction of **156** with sodium azide, followed by a catalytic hydrogenation (Scheme 41).[45]



Scheme 41.

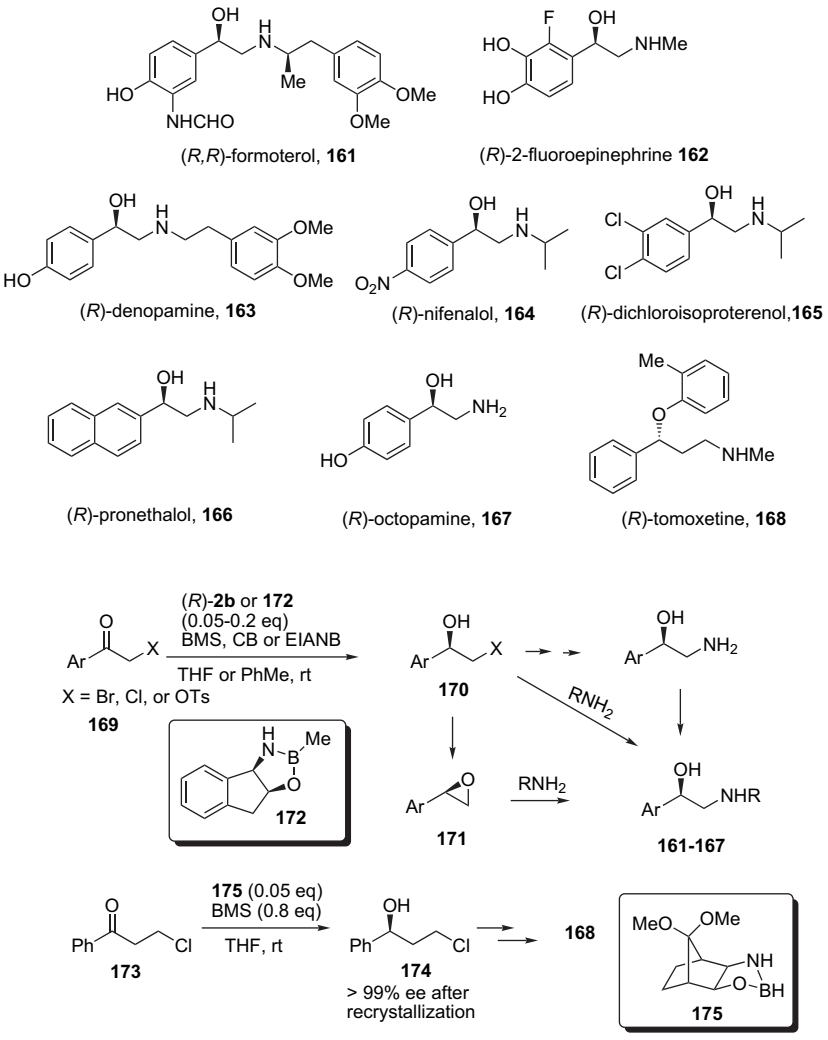


Scheme 42.

Halipeptin A (**158**) is a potent anti-inflammatory cyclic depsipeptide isolated from a marine sponge. The stoichiometric CBS reduction of enone **159** using (*R*)-**2b** as an asymmetric inducer, followed by a catalytic hydrogenation and methylation, was applied for the introduction of (*S*)-configuration at C_7 of a polyketide fragment **160** of this compound (Scheme 42).[46]

3.2. Synthesis of unnatural bioactive compounds

3.2.1. β-Adrenergic agonists. Pharmaceuticals **161–168** having a structural unit of 2-amino-1-arylethanol are of great importance as β-adrenergic agonists in the therapy of asthma, bronchitis, and congestive heart failure. In general, the (*R*)-isomers of these drugs show more potent pharmacological activity than their racemates. The OAB-catalyzed reductions have been effectively applied to the synthesis of these chiral drugs with high optical purity. Scheme 43 shows the synthesis of these drugs from 1,2-diol monotosylates (or halohydrins) **170** or chiral styrene oxides **171** obtained from the asymmetric reduction of α-*p*-tosyloxyketones (or α-halo ketones) **169**. (*R*,*R*)-Formoterol **161** was prepared by amination of the corresponding chiral epoxide obtained from OAB (**172**)-catalyzed reduction of the α-bromo ketone.[47a–c] (*R*)-2-Fluoroepinephrine (**162**),[48] (*R*)-denopamine (**163**), (*R*)-nifenalol (**164**), (*R*)-dichloroisoproterenol (**165**), and (*R*)-pronethalol (**166**) were prepared by direct amination of the corresponding chiral iodohydrin or 1,2-diol monotosylates **170** obtained from (*R*)-**2b**-catalyzed reduction of **169**.[49] (*R*)-Octopamine (**167**) was prepared by azidation of the corresponding 1,2-diol monotosylate, followed by catalytic hydrogenation.[45] The OAB (**175**)-catalyzed reduction of 3-chloropropiophenone **173** provided the (*S*)-chloro alcohol **174** with >99% ee after a single recrystallization, and this was subjected to Mitsunobu inversion with *o*-cresol, followed by amination, to give (*R*)-tomoxetine (**168**).[47d]



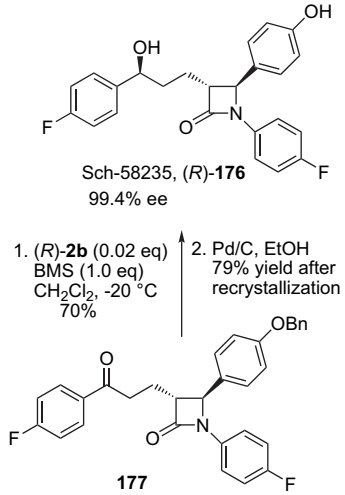
Scheme 43.

3.2.2. Other bioactive compounds. A chiral *trans*-azetidinone (Sch-58235, (*R*)-**176**) is known to be a potent cholesterol absorption inhibitor, which has shown efficacy in clinical trials for reducing cholesterol levels. CBS reduction of a ketone **177**, using (*R*)-**2b** as catalyst, followed by debenzylation, provided (*R*)-**176** in 56% yield and 99.4% ee (Scheme 44).[50]

Scheme 45 illustrates the catalytic CBS reduction of a diaryl ketone–chromium complex **179** to give the desired chiral alcohol **180** in 91% ee. The alcohol **180** can serve as a key intermediate for the synthesis of a selective opioid receptor agonist, (*S*)-diarylmethylamine derivative **178**, via **181**.[51]

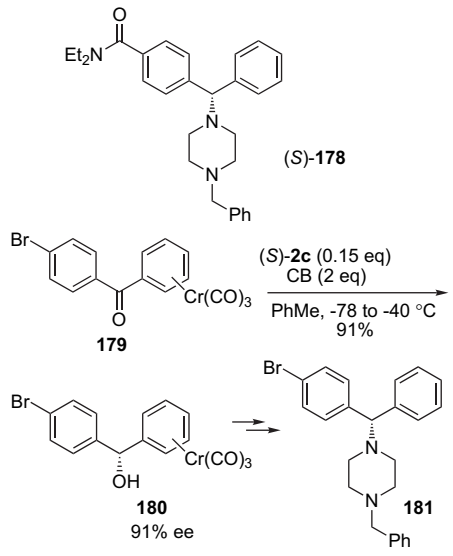
Using the catalytic CBS reduction of a heterocyclic ketone **183** to give a chiral alcohol **184** in 83% yield and 98% ee, the synthesis of an analgesic, (*R*)-cizolirtine **182**, has been reported (Scheme 46).[52]

An enantiopure spiro[(2*S*)-hydroxyindane-1,4′-piperidine] (*S*)-**185** is known as a component of growth hormone secretagogues and also as one of the key constituents of a tachykinin receptor antagonist. The (2*S*)-configuration has been shown to be an essential requirement for more potent binding

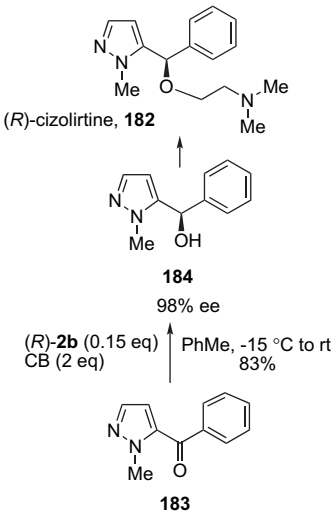


Scheme 44.

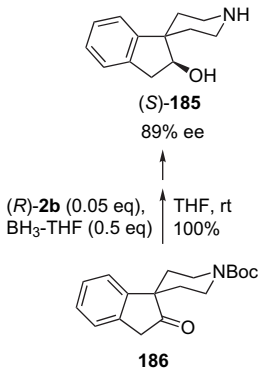
affinities of the tachykinin receptor. This compound has been prepared by the catalytic CBS reduction of a Boc-amino ketone **186** using (*R*)-**2b** as a catalyst (Scheme 47).[53]



Scheme 45.

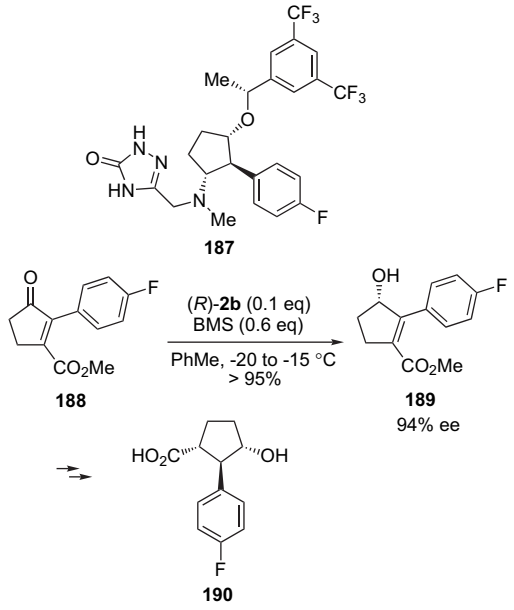


Scheme 46.



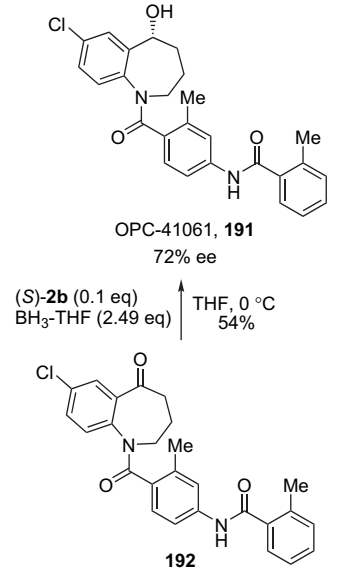
Scheme 47.

Using the catalytic CBS reduction of cyclopentenone derivative **188** as a key step to give the corresponding enol **189** with 94% ee, the synthesis of a cyclopentane-based nonpeptide antagonist (**187**) of human neurokinin-1 receptor, which is under development as an antidepressant has been reported. The chiral enol **189** obtained was used as a starting material for the synthesis of hydroxyacid intermediate **190** bearing the *trans*,*trans*-cyclopentyl structure, which served as the core synthetic intermediate for **187** (Scheme 48).[54]



Scheme 48.

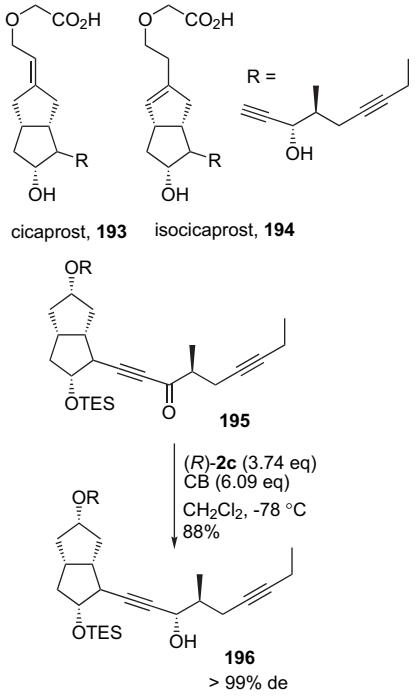
The racemic benzodiazepine derivative, 7-chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (OPC-41061, **191**), is a new vasopressin V receptor antagonist under clinical trial as an aquaretic agent. The catalytic CBS reduction of ketone **192** using (*S*)-**2b** as catalyst provided **191** in 54% yield and 72% ee (Scheme 49).[55]



Scheme 49.

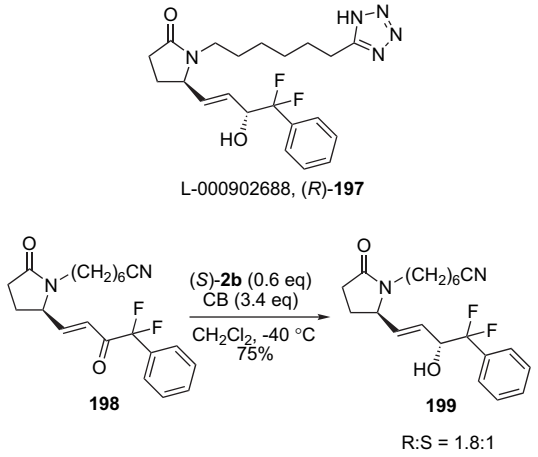
Similarly, the stoichiometric CBS reduction of a diynone **195** using (*R*)-**2c** as an asymmetric inducer was utilized for the synthesis of a key intermediate **196** for cicaprost

(**193**) and isocicaprost (**194**) (Scheme 50).[56] These compounds are known to be attractive drugs for the therapy of solid tumor metastasis and cardiovascular diseases.



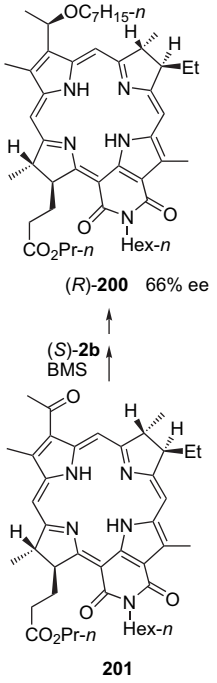
Scheme 50.

Compound L-000902688, **197** is a prostaglandin E_2 analogue, which is an orally bioavailable EP4 receptor agonist exhibiting bone-growth activity in animals. It is known that its (*R*)-isomer shows more potent biological activity than the corresponding (*S*)-isomer. CBS reduction of (*E*)-enone **198** using (*S*)-**2b** as catalyst was applied to the preparation of a key intermediate **199** for the synthesis of **197** (Scheme 51).[57]



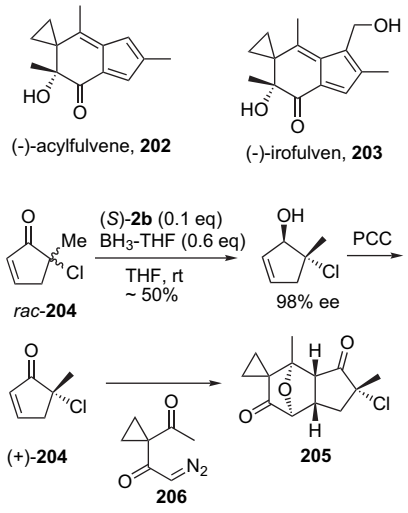
Scheme 51.

The stoichiometric CBS reduction of 3-acetylbacteriopurpurimide **201** using (*S*)-**2b** as an asymmetric inducer, followed by O-alkylation, afforded a bacteriopurpurimide derivative (*R*)-**200**, which is a photosensitizer exhibiting long-wavelength absorption near 800 nm, which can be used for photodynamic therapy in the treatment of various types of tumors. The efficacy of its (*R*)-isomer is greater than that of the (*S*)-isomer (Scheme 52).[58]



Scheme 52.

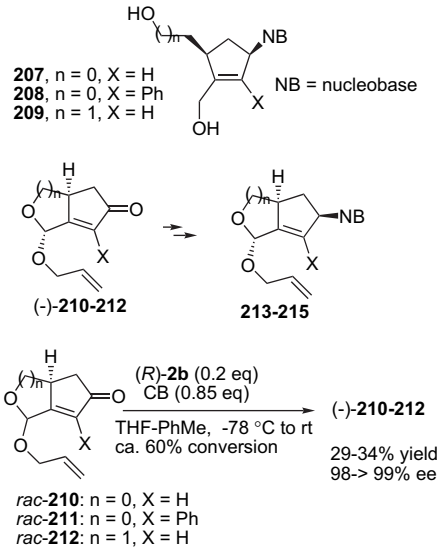
Scheme 53 outlines the synthesis of optically active (−)-acylfulvene (**202**) and (−)-irofulven (**203**) possessing antitumor activity using kinetic resolution of racemic cyclopentenone *rac*-**204** by employing CBS reduction as a key step. The reduction of *rac*-**204** using (*S*)-**2b** as catalyst, followed by oxidation, provided a chiral enone (+)-**204** in 98% ee.[59a] The chiral ketone obtained was reacted with diazoketone **206** to give a chiral diketone **205**, which could be used as a key intermediate for the synthesis of both **202** and **203**.[59b]



Scheme 53.

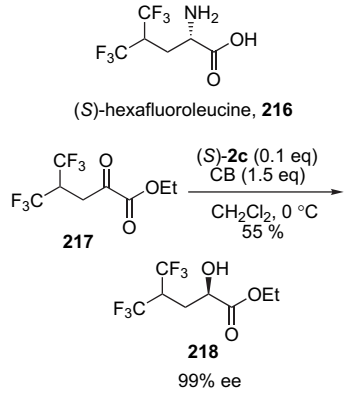
Carbocyclic nucleosides, where the furanose oxygen atom of the normal nucleoside is replaced by a methylene group,

play important roles as antiviral or antitumor drugs. The monoprotected, 2′,3′-unsaturated carbocyclic nucleoside analogues **207**–**209** were prepared via the precursors **213**–**215**, starting from chiral bicyclic enones (−)-**210**–**212**. The kinetic resolution of *rac*-**210**–**212** by CBS reduction using (*R*)-**2b** as catalyst provided (−)-**210**–**212** in 29–34% yields and 98–99% ee. The precursors **213**–**215** have been prepared by stereoselective reduction and subsequent introduction of various pyrimidine and purine nucleobases by means of Pd-catalyzed allylic substitution of (−)-**210**–**212** (Scheme 54).[60]



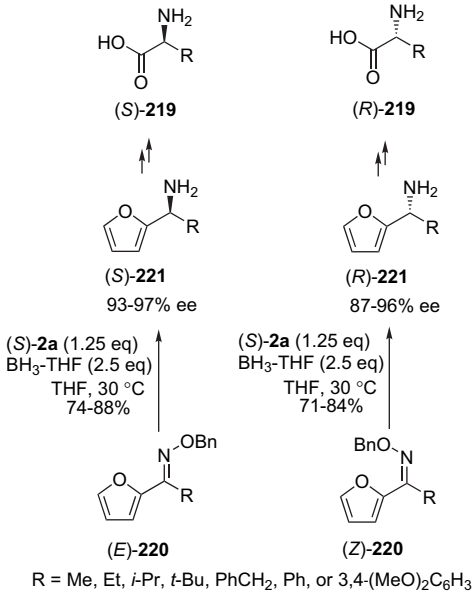
Scheme 54.

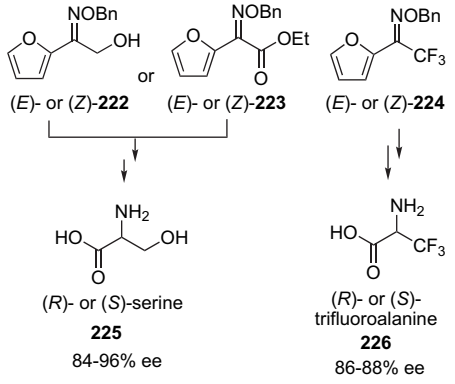
3.2.3. Amino acid derivatives. CBS reduction of an α-keto ester **217** using (*S*)-**2c** as catalyst provided a chiral hydroxyl ester **218** in 55% yield and 99% ee. This alcohol was converted into an *F*-containing α-amino acid, (*S*)-hexafluoroleucine **216**, by a S_N2 reaction with an amine (Scheme 55).[61]



Scheme 55.

Scheme 56 shows an asymmetric synthesis of α-amino acids **219** using a stoichiometric CBS reduction of (*E*)- or (*Z*)-2-furyl alkyl ketone oxime ethers **220**. The reduction using 1.25 equiv of (*S*)-**2a** provided optically active 2-furyl amines **221** in 87–97% ee, which could be converted into (*R*)- or (*S*)-**219** by oxidative cleavage of the furan ring. In this reduction, the absolute configurations of **221** formed depend upon the geometry of **220**: (*E*)-oximes led to the (*S*)-amines, while (*Z*)-oximes gave rise to the (*R*)-amines.[62a] Using the same methodology (*R*)- or (*S*)-serine **225** and trifluoroalanine **226** were obtained from the oxime ethers of furyl hydroxymethyl ketone **222** or α-imino ester **223**[62b] and furyl trifluoromethyl ketone oxime **224**,[62c] respectively.

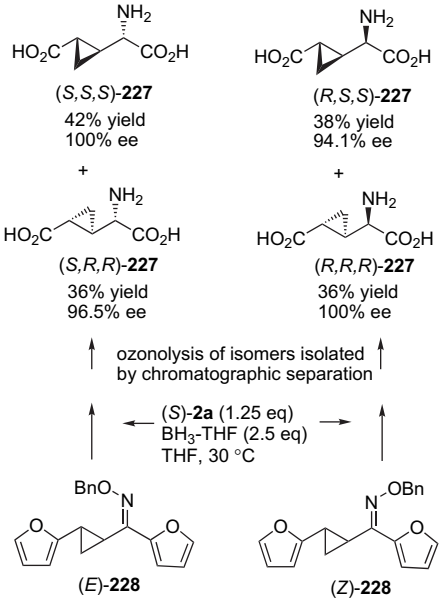




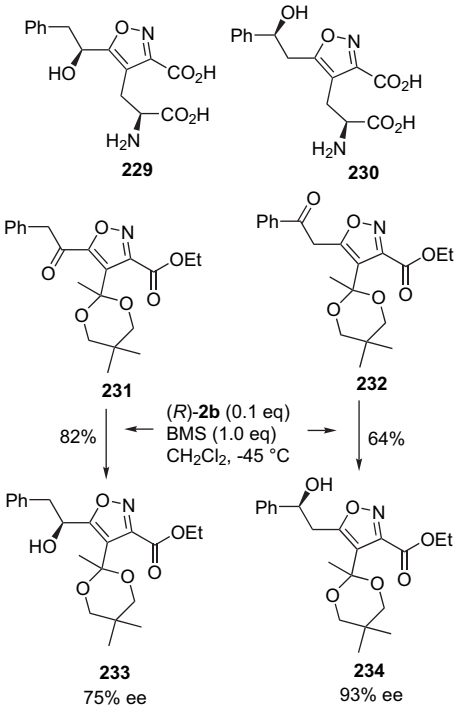
Scheme 56.

The same methodology has been applied to the synthesis of optically active α-amino acids **227** containing a cyclopropyl ring, which are conformationally constrained L-glutamate analogues, from the reduction of oxime ethers **228** (Scheme 57).[63]

L-Glutamate analogues having an isoxazole ring, **229** and **230**, play important roles as neurotransmitters in the human CNS. The catalytic CBS reduction of ketones **231** and **232** provided the corresponding alcohols, **233** with 75% ee and **234** with 93% ee, respectively. These alcohols obtained were converted into **229** and **230** through further steps including hydrolysis of ketal groups and asymmetric Strecker synthesis (Scheme 58).[64]

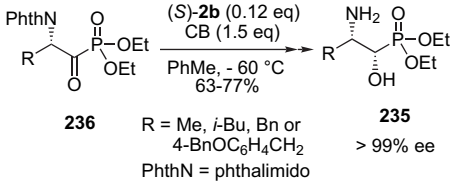


Scheme 57.



Scheme 58.

CBS reduction has been utilized for the synthesis of chiral 2-amino-1-alkylhydroxyphosphonic acids **235**, known as inhibitors of proteolytic enzymes such as renin and HIV protease. The diastereoselective reduction of chiral phthalimido keto phosphonates **236** using (*S*)-**2b** as the catalyst and CB as reductant, followed by deprotection of phthalimido group, provided **235** with >99% ee. In this reduction, however, the use of BMS instead of CB as the borane source gave diastereoisomeric mixtures of **235** (Scheme 59).[65]



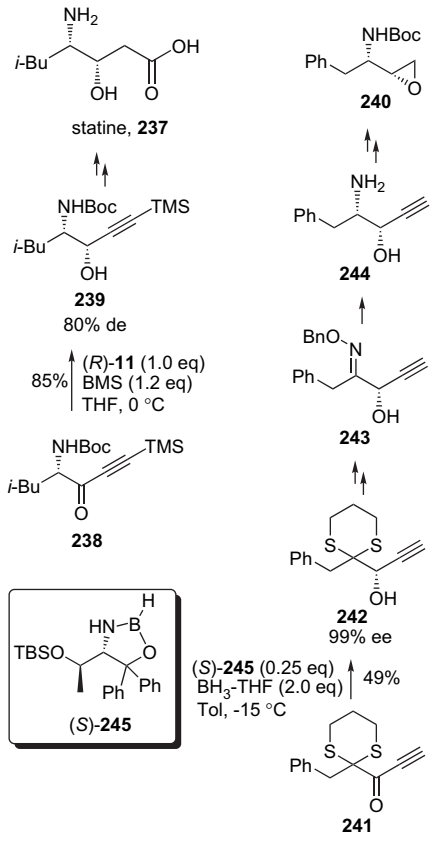
Scheme 59.

3.3. Synthesis of chiral intermediates, ligands, and building blocks

The chiral *syn*-3-hydroxy-4-amino acid moiety has been the focus of much attention in connection with the development of new pharmaceuticals based on protease inhibitors e.g., statine **237** is an essential component of pepstatine, a natural hexapeptide antibiotic, which acts as an inhibitor of aspartic acid protease. Starting from a stoichiometric OAB-mediated reduction of chiral α-amido acetylenic ketone **238** using (*R*)-**11** as asymmetric inducer, **237** has been prepared.[66a] The reduction gave **239** in 85% yield and 80% de, which was converted into **237** by transformation of the acetylenic group to a carboxylic acid group using hydroboration and subsequent oxidation. On the other hand, the chiral amino epoxide **240** is a key intermediate for the synthesis of HIV protease inhibitors, such as saquinavir and palinavir. This compound has also been prepared by using OAB-catalyzed reduction as a key step. The reduction of an acetylenic ketone **241**, using (*S*)-**245** derived from (*S*)-threonine as asymmetric inducer, provided a chiral propargylic alcohol **242** with 99% ee. After conversion of **242** into a chiral imino alcohol **243** by deprotection of the 1,3-dithianyl group and subsequent benzyloxyimination, diastereoselective reduction of **243** gives a *syn*-amino alcohol **244**, which can be used as a key intermediate for the synthesis of **240** (Scheme 60).[66b]

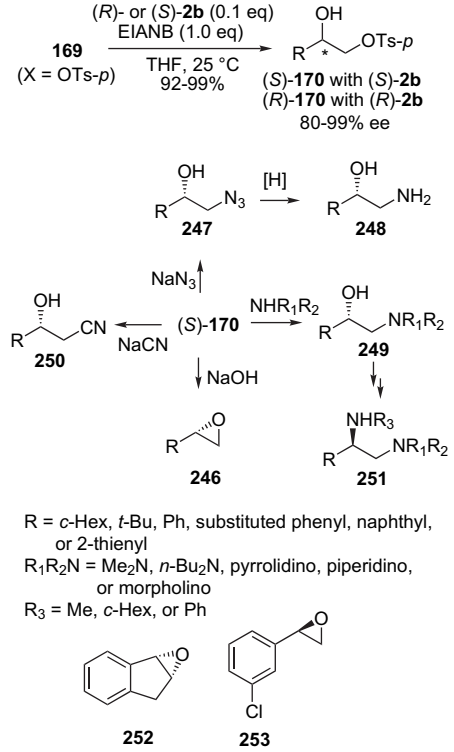
Chiral 1,2-diol monotosylates **170** prepared by the catalytic CBS reduction of **169** have been widely utilized for the synthesis of a variety of chiral intermediates such as chiral epoxides **246**,[67a] β-azido and amino alcohols **247**–**249**,[45] β-hydroxy cyanides **250**,[67b] and 1,2-diamines **251**[67c] (Scheme 61). This methodology has also been applied to the synthesis of enantiopure (1*S*,2*R*)-indene oxide **252**[67d] and (*R*)-3-chlorostyrene oxide **253**,[67e] which can be used as essential intermediates for the synthesis of an HIV protease inhibitor, indinavir, and β_3-agonists possessing antiobesity and antidiabetic activities, respectively.

Scheme 62 outlines the synthesis of other synthetically useful chiral β-functionalized alcohols, such as 1,2-diols **254**,[68] α-hydroxy acetals **255**,[69] β-azido alcohols **247**,[70] β-hydroxy sulfides **127**,[71a,b] β-hydroxy sulfones **256**,[72] and β-amido alcohols **257**,[73] via the catalytic CBS reduction of the corresponding ketones. Among these, chiral β-hydroxy sulfides **127** were successfully used as starting materials for the synthesis of chiral epoxides,[71c] diols,[71c] and unhindered aliphatic alcohols.[71d] In particular, the successful application of **127** for the synthesis of near-enantiopure unhindered aliphatic alcohols **258** possessing a similar steric bias between the two alkyl groups adjacent to the carbinyl group is noteworthy.

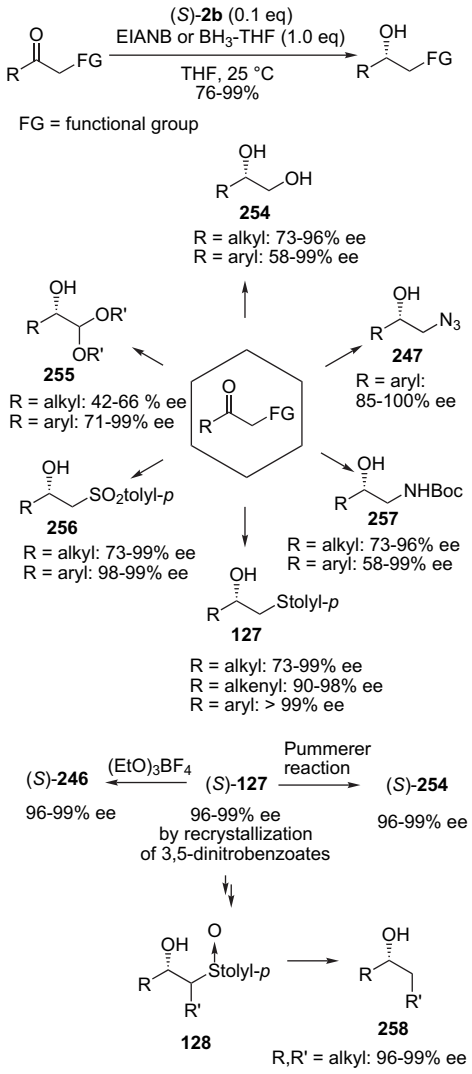


Scheme 60.

Homochiral 2-amino-1,2-diarylethanols **259** and 1,2-diaryl-1,2-ethanediols **262** are widely used as chiral building blocks and ligands for organic synthesis. When α-keto oxime ethers



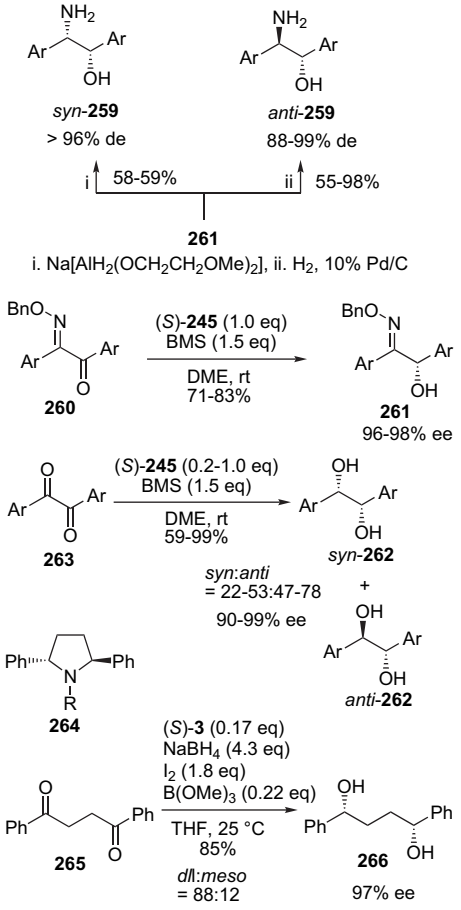
Scheme 61.



Scheme 62.

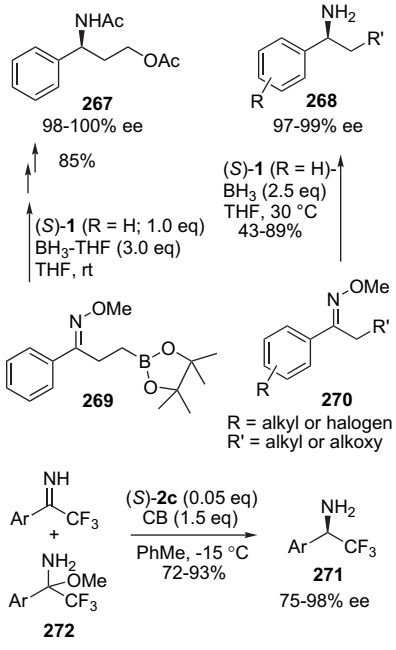
260 were reacted with 1.5 equiv of BMS using 1.0 equiv of (*S*)-**245** as asymmetric inducer in DME at room temperature, the carbonyl group was reduced much faster than the imine to give the chiral imino alcohols **261** in 73–83% yield and 96–98% ee. Further reduction of **261** using $Na[AlH_2(OCH_2CH_2OMe)_2]$ produced *syn*-**259** in >96% de, whereas the reduction with catalytic hydrogenation on Pd/C gave the *anti*-isomers with 88–99% de. The asymmetric reduction of 1,2-diketones **263** using the same methodology provided the chiral 1,2-diols *syn*-**262** with 90–99% ee. This reduction, however, afforded a low diastereoselectivity.[74] Similarly, CBS reduction was applied to the synthesis of chiral *trans*-2,5-diphenylpyrrolidines **264**, which is utilized as C_2-symmetric chiral auxiliaries or ligands for asymmetric synthesis. When the reduction of 1,4-diketone **265** was carried out in the presence of trimethyl borate, the reduction provided (*S*,*S*)-diol **266** in 85% yield and 97% ee with *dl*/*meso* ratio of 88:12, and this diol is easily converted into **264** by dimesylation, followed by a S_N2 reaction with an amine.[75] These results are summarized in Scheme 63.

Scheme 64 illustrates the stoichiometric OAB-mediated reduction of oxime ethers **269** and **270** using Itsuno's reagent,



Scheme 63.

(*S*)-**1** (R=H), derived from (*S*)-valine as asymmetric inducer to give the chiral benzylic amine derivatives **267** and **268** with high enantiopurity.[76] Very recently, the asymmetric synthesis of chiral trifluoromethylated amines **271** with good enantiopurity by the catalytic CBS reduction has been reported. The reduction of a mixture **272** obtained from the methanolysis of *N*-silylimines of the corresponding ketones using 1.5 equiv of CB in the presence of 0.05 equiv of (*R*)-**2c** at −15 °C in toluene afforded **271** in 72–95% yields and 75–98% ee.[77]



Scheme 64.

4. Summary and outlook

Chiral OAB-mediated borane reductions of prochiral ketones and ketimines have been very widely utilized for the highly effective asymmetric synthesis of a broad range of chiral natural products, bioactive compounds, intermediates, ligands, and building blocks, which include a chiral alcohol or amine functionality in their structures. Such applications of this methodology continue to increase rapidly in number. The effective asymmetric reduction of ketimine derivatives using this methodology, however, remains a challenging target, since only a few examples of the successful asymmetric reduction of prochiral ketimine derivatives in contrast to those for ketones have been reported.

Acknowledgements

This work was supported by Hallym University Research Fund, 2006 (HRF-2006-024).

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Biographical sketch

Byung Tae Cho was born in Seoul and grew up in Kang Nung, Republic of Korea. He received his B.S. degree in pharmacy from Seoul National University in 1967, MSc degree in 1971 and PhD degree in 1982 from Sogang University. After his military service for 3 years, he worked in the Korea Institute of Science and Engineering (KIST) for 4 years and in Dong Wha Pharmaceutical Company for 8 years. In 1982, he joined Hallym University as an assistant professor of chemistry. From 1985 to 1987, he undertook a postdoctoral fellowship with Professor Herbert C. Brown at Purdue University, where he worked on the development of new chiral borohydrides and their applications to the asymmetric reduction of ketones. Since 1993, he has been working at Hallym University as a full professor. His research interests include the catalytic asymmetric reductions, enantioselective carbonyl alkylations, and the synthesis of chiral drugs.

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Tetrahedron 62 (2006) 7645–7652

Generation and trapping of tricyclo[3.3.0.0^{3,7}]oct-1(5)-ene derivatives containing carbonyl functionalities

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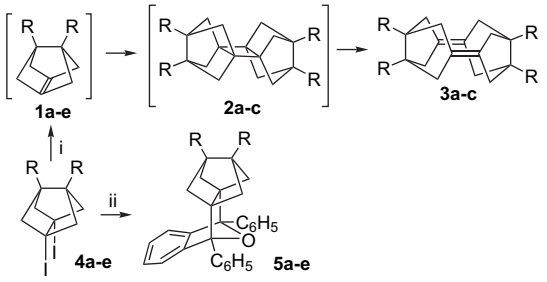
Received 11 May 2006; accepted 30 May 2006
Available online 16 June 2006

Abstract—Two new functionalized highly pyramidalized tricyclo[3.3.0.0^{3,7}]oct-1(5)-ene derivatives containing carbonyl functionalities have been trapped as Diels–Alder adducts, although they failed to dimerize. An interesting fragmentation of the bisnoradamantane skeleton to norbornane derivatives has also been observed.

1. Introduction

Some time ago, we published the synthesis, chemical trapping, and dimerization of two *non-functionalized* highly pyramidalized tricyclo[3.3.0.0^{3,7}]oct-1(5)-ene derivatives (**1a**,**b**).[1] In our continuing efforts for expanding the usefulness of pyramidalized alkenes,[2] more recently, we described the generation of *functionalized* derivatives **1c–e**. While derivatives **1c–e** were trapped as Diels–Alder adducts, only dimer **3c** was formed.[3a] Probably the sulfonyldioxy group of **1d** is not compatible with the conditions normally used to generate and dimerize highly pyramidalized alkenes (molten sodium or sodium amalgam).[3b] The lack of dimerization of **1e** is not evident because this alkene gave in medium yield a cross-coupling product with **1b** (Scheme 1).[3b]



Scheme 1. Reactivity of highly pyramidalized alkenes **1a–e**. **a**, R=H; **b**, R=Me; **c**, R=–OC(CH$_3$)$_2$O–; **d**, R=–OS(O)$_2$O–; **e**, R=–*o*,*o*′-biphenylene–. (i) Molten sodium, 1,4-dioxane, reflux; (ii) *t*-BuLi, 1,3-diphenylisobenzofuran, THF, −78 °C.

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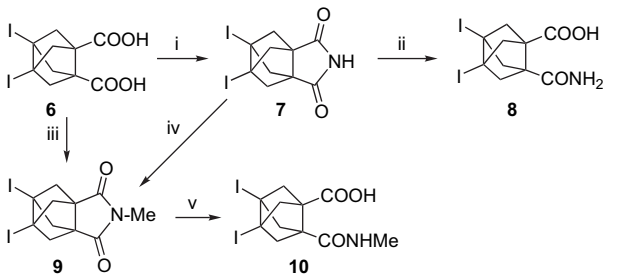
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.05.074

Owing to the rich reactivity of the carbonyl group, we considered of much interest the generation of highly pyramidalized alkenes of the type of **1** bearing carbonyl functionalities, and its possible dimerization to compounds of general structure **3**, because they may give access to new polycyclic cage compounds of theoretical interest. In this article we describe the successful generation and trapping of two new highly pyramidalized tricyclo[3.3.0.0^{3,7}]oct-1(5)-ene (**1f** and **1i** in Scheme 3) derivatives containing carbonyl functionalities. However, no dimers were obtained from these pyramidalized alkenes under the different reaction conditions studied. An interesting, unprecedented fragmentation of the bisnoradamantane skeleton to norbornane derivatives was observed instead when pyramidalized alkene **1i** was generated by reaction of its diiodo precursor with *t*-butyllithium (*t*-BuLi).

2. Results and discussion

Considering our previous experience with derivatives **1a–e**, we considered that compounds **9** and **12** could be suitable precursors for the pyramidalized alkenes **1f** and **1i**, respectively. In fact, in a related, parallel study, we had described the preparation of diester **12** and diacid **6**.[4] As shown in Scheme 2, conversion of diacid **6** into imide **9** was carried out by two alternative procedures. Reaction of diacid **6** with urea gave imide **7** in 74% yield. Alkylation of **7** with methyl iodide led to the desired *N*-methylated imide, **9** in 72% isolated yield. More conveniently, reaction of diacid **6** with acetic anhydride followed by reaction of the corresponding anhydride (not isolated) with aqueous methylamine and a second treatment with acetic anhydride led to **9** in 98% overall yield.

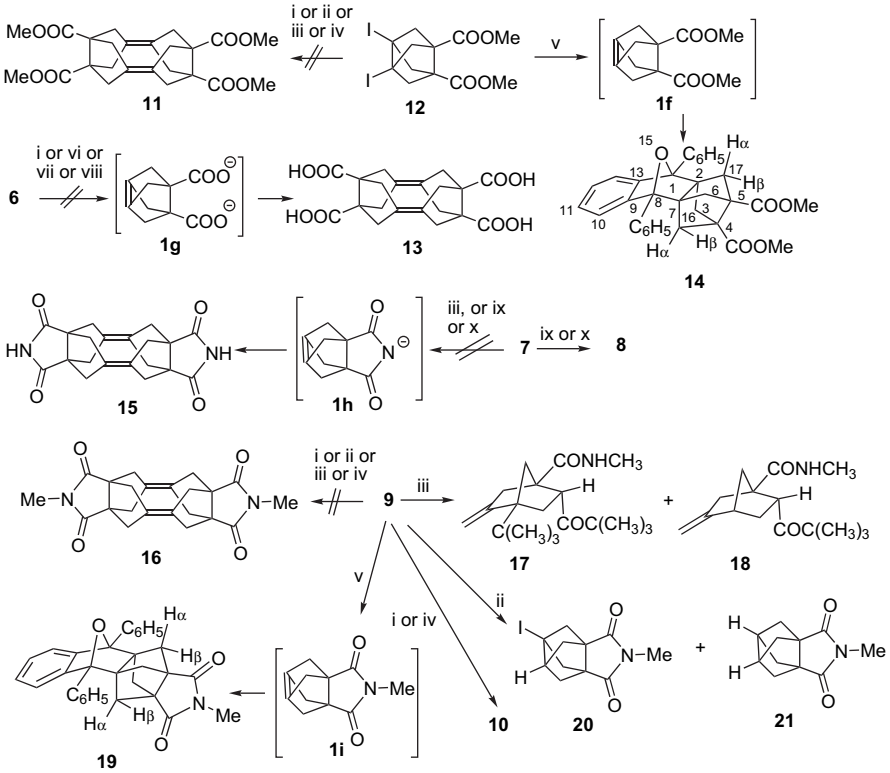


Scheme 2. Synthesis of the bisnoradamantane derivatives **7**–**10**. (i) Urea, 180 °C, 30 min, 74%; (ii) (a) aqueous 1 N NaOH, 50 °C, 1 h; (b) aqueous 10% HCl, 79%; (iii) (a) Ac_2O, reflux; (b) toluene, aqueous 40% $MeNH_2$, rt, 2.5 h; (c) Ac_2O, reflux, 1 h, 98%; (iv) NaH, MeI, anhydrous THF, rt, 16 h, 72%; (v) (a) aqueous 1 N NaOH, reflux, 1 h; (b) aqueous 10% HCl, 85%.

With diiodides **6**, **7**, **9**, and **12** in our hands, we first studied the generation of highly pyramidalized alkene **1f** from diester **12**. As shown in Scheme 3, reaction of **12** with *t*-BuLi in the presence of 1,3-diphenylisobenzofuran led to the isolation, in 46% yield, of **14**, presumably arising from the Diels–Alder reaction of the starting diene with the pyramidalized alkene **1f**.

Although we succeeded in generating and trapping the pyramidalized alkene **1f**, all our efforts directed toward its dimerization were fruitless. Thus, reaction of diester **12** with molten sodium in boiling 1,4-dioxane or with 0.45% Na(Hg) in 1,4-dioxane at room temperature, led to very complex mixtures of products, with important losses of material. We also used the radical anion derived from 4,4′-di-*t*-butylbiphenyl and lithium as the reducing agent[5] in this reaction but, again, a complex mixture of products, not containing the expected dimer **11**, was obtained. Taking into account that we successfully generated **1f** from **12** on reaction with *t*-butyllithium and that Borden and coworkers had previously used organolithium reagents to generate and dimerize highly pyramidalized alkenes,[6] we considered of interest to study the possible dimerization of **1f** generated by reaction of diiodide **12** with *t*-BuLi. However, owing to the well-known reactivity of these kind of highly pyramidalized alkenes with nucleophiles, a low yield of the dimer was to be expected.[7] Unfortunately, reaction of **12** with *t*-BuLi in THF at −78 °C led to a very complex mixture of products where no cyclobutane or diene dimers were detected.

Considering that the methoxycarbonyl groups were not compatible with the aggressive conditions used, we next tried the generation of highly pyramidalized alkene **1g** from diacid **6**. Unfortunately, reaction of diacid **6** with molten sodium or lithium led to the recovery of the starting material. During these reactions the formation of a precipitate was observed, so we reasoned that **6** reacted with the metal to give the disodium or dilithium salt that precipitated, thus preventing further reaction of the metals with the substrate. In order to improve the solubility we carried out the reaction of the preformed disodium salt of **6** with molten sodium in the presence of 2 equiv of the crown ether 18-crown-6.[8] However, as



Scheme 3. Generation and trapping of highly pyramidalized tricyclo[3.3.0.0^{3,7}]oct-1(5)-ene derivatives containing carbonyl functions, **1f** and **1i**. (i) Molten sodium in boiling 1,4-dioxane; (ii) 0.45% Na(Hg), 1,4-dioxane; (iii) 0.7 M *t*-BuLi in pentane, anhydrous THF, −78 °C; (iv) 4,4′-di-*t*-butylbiphenyl, Li, anhydrous THF; (v) 1,3-diphenylisobenzofuran (DPIBF), 0.7 M *t*-BuLi in pentane, anhydrous THF, −78 °C; (vi) lithium in boiling THF; (vii) preformed disodium salt of **6** plus 18-crown-6 (2 equiv) in hot 1,4-dioxane added to molten sodium in boiling 1,4-dioxane; (viii) preformed bis-tetrabutylammonium salt of **6** in 1,4-dioxane added to molten sodium in boiling 1,4-dioxane; (ix) 18-crown-6 (3 equiv) plus molten sodium in boiling 1,4-dioxane; (x) preformed sodium salt of **7** plus 18-crown-6 (3 equiv) in 1,4-dioxane added to molten sodium in boiling 1,4-dioxane.

before, a precipitate was formed, no dimers were observed, and the starting compound was mainly recovered. Similarly, when the preformed bis-tetrabutylammonium salt of **6** was reacted with molten sodium, diacid **6** was the only isolated product.

Since the solubility of disodium salts of dicarboxylic acids in 1,4-dioxane in the presence of crown ethers was low, we planned the use of the monosodium salt of imide **7** for the dimerization reaction. The preformed sodium salt of **7**, from imide **7** and NaH, was dissolved in anhydrous 1,4-dioxane in the presence of 3 equiv of 18-crown-6 and this solution was added to molten sodium in boiling 1,4-dioxane. However, the only isolated compound from this reaction was the amido acid **10**, probably formed by hydrolysis of imide **7** during the work-up. A similar result was obtained on reaction of **7** with molten sodium in boiling 1,4-dioxane in the presence of 3 equiv of 18-crown-6. The reaction of **7** with *t*-BuLi in ratios (**7**/*t*-BuLi) 1:2 or 1:3 gave complex mixtures of products where the expected cyclobutane or diene dimers were not observed.

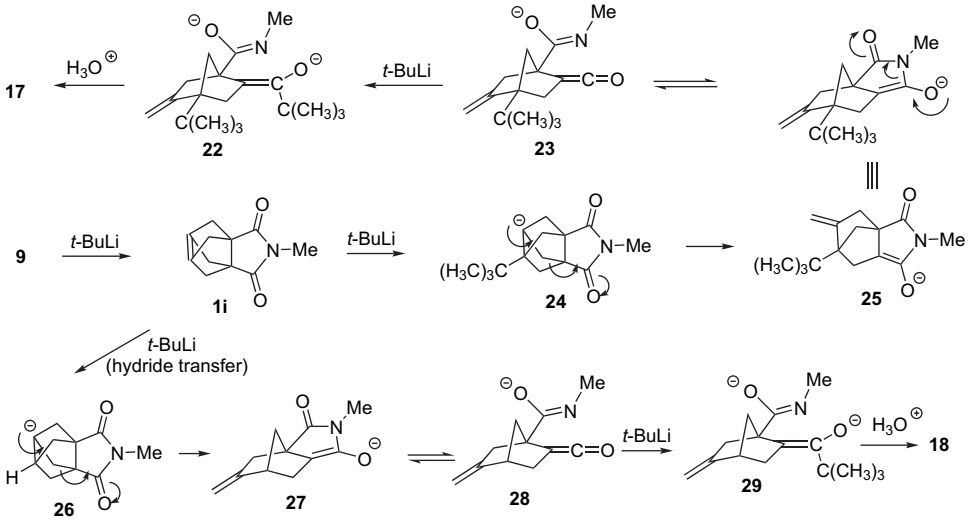
Finally, to prevent salt formation during the generation of the pyramidalized alkene we used imide **9** as the substrate, whose carbonyl functions are less reactive than the ester functions of diester **12**. Reaction of **9** with molten sodium in boiling 1,4-dioxane gave in good yield, amido acid **10** from hydrolysis of **9**, as the only detected product. A similar result was obtained when **9** was reacted with the radical anion derived from 4,4′-di-*t*-butylbiphenyl and lithium. Reaction of **9** with 0.45% sodium amalgam for 3.5 h gave a mixture containing mainly two compounds whose molecular ions in GC–MS suggest them to be the monodeiodinated and the bisdeiodinated derivatives **20** and **21**, respectively, as observed in related cases,[3b] plus a small amount of starting **9**.

However, reaction of **9** with *t*-BuLi in the presence of 1,3-diphenylisobenzofuran gave the expected compound **19**, the Diels–Alder adduct of the pyramidalized alkene **1i**, and the diene, in medium yield. Since formation of the pyramidalized alkene appeared to be possible by reaction with *t*-BuLi, we tried the reaction of **9** with *t*-BuLi in the absence of a trapping agent with the aim of favoring the dimer formation. From this reaction we obtained a complex mixture, which analyzed by GC–MS showed to contain two main components (rt, 14.84 and 17.92 min, 21 and 37% relative areas, respectively). These compounds could be isolated in low yield by column chromatography and were fully characterized by spectroscopic means, showing that they were compounds **18** (rt, 14.84 min) and **17** (rt, 17.92 min), respectively.

The formation of these compounds may be explained as shown in Scheme 4 via the intermediate formation of the pyramidalized alkene **1i**. Nucleophilic addition of *t*-BuLi to **1i** would give carbanion **24**, which could experience the shown fragmentation giving rise to the enolate **25**, containing the norbornane framework, thus releasing the strain of the tricyclo[3.3.0.0^{3,7}]octane skeleton. Enolate **25** might be in equilibrium with the ketene anion **23**, which on reaction with *t*-BuLi could give dianion **22**. Protonation of this dianion during the quenching of the reaction mixture would give **17**, in which the *endo*-arrangement of the pivaloyl group could be due to the kinetically controlled protonation of the corresponding ketone enolate by the less hindered *exo*-side. In a similar way, *t*-BuLi could transfer a hydride to the pyramidalized alkene **1i**, the formed anion **26** could rearrange to enolate **27**, which might be in equilibrium with ketene anion **28**. Addition of *t*-BuLi to the ketene function as before would give dianion **29**, which, on protonation, would give **18** with the pivaloyl group in an *endo*-arrangement, as for **17**.

All of the new compounds herein described were fully characterized by spectroscopic means (IR, ^{1}H and ^{13}C NMR, MS) and elemental analysis or accurate mass measurement. Assignments given for the NMR spectra are based on DEPT, COSY ^{1}H/^{1}H, HETCOR ^{1}H/^{13}C (HSQC and HMBC sequences for one bond and long range heterocorrelations, respectively), and NOESY experiments for selected compounds.

Also, we have performed DFT calculations [B3LYP/6-31G(d)] on pyramidalized alkenes **1f** and **1i** (Fig. 1). All



Scheme 4. Possible mechanisms for the formation of compounds **17** and **18** in the reaction of **9** with *t*-BuLi.

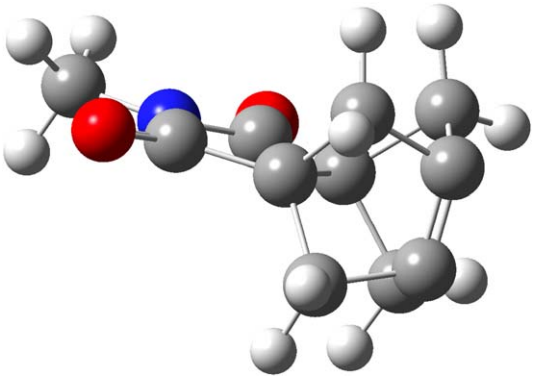


Figure 1. Minimum energy conformation [B3LYP/6-31G(d)] of highly pyramidalized alkene **1i**.

the calculated parameters compare very well with those previously calculated for related pyramidalized alkenes. Thus, the pyramidalization angles of **1f** and **1i** (Φ=61.5 and 61.7°, respectively) and the carbon–carbon double bond length (1.380 and 1.381 Å, respectively) are quite similar to those previously calculated for **1a–e**.[2a] Also, the distance between the α-ester carbon atoms in diester **1f** (1.703 Å) is comparable to that previously calculated between the methyl-bearing carbon atoms in **1b** (1.704 Å). In the pyramidalized alkene **1i**, the distance between the α-carbonyl carbon atoms is shorter (1.636 Å) as in the related cases **1c** (1.625 Å) or **1d** (1.645 Å), where the substituents on C1 and C5 are connected through a five-membered ring.

3. Conclusions

In conclusion, two new highly pyramidalized alkenes containing carbonyl groups (**1f** and **1i**) have been generated and trapped as Diels–Alder adducts. Several attempts to carry out the dimerization of these alkenes were unsuccessful, probably due in part to the lability of the carbonyl groups. We failed to generate the pyramidalized alkenes **1g** and **1h**, derived from diacid **6** and imide **7**, respectively, probably due to the formation of insoluble salts under the reaction conditions, in spite of using 18-crown-6 to increase the solubility of these salts. Interestingly, the reaction of the *N*-methylated imide **9** with *t*-BuLi led to a mixture of two norbornane derivatives as a result of an unprecedented anion-induced fragmentation of the bisnoradamantane skeleton followed by reaction of *t*-BuLi with the intermediate ketene, thus formed, and protonation of the enolate from the less hindered exo face during the work up.

4. Computational details

All quantum-mechanical calculations were carried out at Becke's three-parameter hybrid functional with the Lee, Yang, and Parr correlation functional (B3LYP) level,[9] using the 6-31G(d) basis set,[10] as implemented in Gaussian 03 on a Compaq HPC320 computer.[11] Geometry optimizations were undertaken using appropriate symmetry constraints and default convergence limits. The minimum energy nature of the optimized structures was verified from vibrational frequency analysis.

5. Experimental

5.1. General

Melting points were determined with a MFB 595010 M Gallenkamp melting point apparatus. Unless otherwise stated, NMR spectra were recorded in $CDCl_3$ in the following spectrometers: ^{1}H NMR (500 MHz, Varian VXR 500), ^{13}C NMR (75.4 MHz, Varian Gemini 300). ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in parts per million with respect to internal tetramethylsilane (TMS). The multiplicity of the signals is: s, singlet; d, doublet; t, triplet, q, quartet, m, multiplet; or their combinations. Assignments given for the NMR spectra are based on DEPT, COSY ^{1}H/^{1}H, HETCOR ^{1}H/^{13}C (HSQC and HMBC sequences for one bond and long range heterocorrelations, respectively), and NOESY experiments for selected compounds. Diastereotopic methylene protons in tricyclo[3.3.0.0^{3,7}]octane derivatives are referred as H_α/H_β as shown in the corresponding structures. IR spectra were recorded on a FT/IR Perkin–Elmer spectrometer, model 1600; only the more intense absorption bands are given. Routine MS spectra were taken on a Hewlett–Packard 5988A spectrometer, the sample was introduced directly or through a gas chromatograph, Hewlett–Packard model 5890 Series II, equipped with a 30-meter HP-5 (5% diphenyl/95% dimethyl-polysiloxane) column [conditions: 10 psi, initial temperature: 35 °C (2 min), then heating at a rate of 8 °C/min then isothermic at 300 °C] and the electron impact technique (70 eV). Only significant ions are given: those with higher relative abundance, except for the ions with higher *m*/*z* values. HRMS were performed on a Micromass Autospec spectrometer. Neutral aluminum oxide (MN), Brockmann activity 1 or silica gel SDS 60 (35–70 μm) was utilized for the standard and flash column chromatography, respectively. NMR and routine MS spectra were performed at the *Serveis Científico-Tècnics* of the University of Barcelona, while high resolution mass spectra and elemental analyses were carried out at the Mass Spectrometry Laboratory of the University of Santiago de Compostela (Spain) and at the Microanalysis Service of the IIQAB (C.S.I.C, Barcelona, Spain), respectively.

5.2. 3,7-Diiodotricyclo[3.3.0.0^{3,7}]octane-1,5-dicarboximide (7)

A mixture of diacid **6** (237 mg, 0.53 mmol) and urea (160 mg, 2.64 mmol) was melted at about 130 °C and then heated to 180 °C for 30 min. The black residue was taken in water (20 mL) and the mixture was extracted with diethyl ether (6×10 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo to dryness to give imide **7** (167 mg, 74% yield) as a white solid. The analytical sample was obtained by crystallization from diethyl ether, mp>219 °C (dec). IR (KBr): ν 3400–2700 (max. at 3200, 3074, 2996, 2946), 1768 and 1706 (C=O, st), 1475, 1381, 1341, 1311, 1273, 1143, 1097, 1069, 1055, 961, 835, 775, 731, 707, 617 cm^{-1}. ^{1}H NMR (300 MHz): δ 2.42 (d, J=8.0 Hz, 4H) and 2.68 (d, J=8.0 Hz, 4H) [2(4,6,8)-H_α and 2(4,6,8)-H_β], 7.60–7.80 (br s, 1H, NH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.50 [s, 8H, 2(4,6,8)-H_α and 2(4,6,8)-H_β], 11.15 (1H, NH). ^{13}C NMR (DMSO-d_6): δ 44.0 [C, C3(7)], 58.5 [C, C1(5)], 58.8 [CH_2, C2(4,6,8)], 173.4 (C, imide CO). MS (EI), *m*/*z* (%): 429 ($M^{\bullet+}$, 2), 358

[(M−CONHCO)$^{\bullet+}$, 2], 302 [(M−I)$^+$, 8], 259 [(M−I−CONH)$^+$, 10], 231 [(M−I−CONHCO)$^+$, 97], 105 (12), 104 [(M−2I−CONHCO)$^+$, 100], 103 (33), 78 (28), 77 (30), 63 (20). MS (ESI−), *m/z* (%): 429 (9), 428 [(M−H)$^-$, 100]. Accurate mass measurement: calcd for $C_{10}H_8I_2NO_2$ [(M−H)$^-$]: 427.8639; found: 427.8647.

5.3. 5-Carbamoyl-3,7-diiodotricyclo[3.3.0.0^{3,7}]octane-1-carboxylic acid (8)

A mixture of imide **7** (89 mg, 0.21 mmol) and aqueous 1 N NaOH (0.75 mL) was heated at about 50 °C for 1 h. The obtained solution was diluted with water (2 mL) and made acidic with aqueous 10% HCl (1 mL). The precipitated solid was filtered in vacuo, thoroughly washed with water, and dried in vacuo in the presence of P_2O_5 to give amide acid **8** (74 mg, 79% yield) as a white solid, mp>236 °C (dec). IR (KBr): ν 3500–2150 (max. at 3477, 3344, 3000, 2925, 2581), 1702 and 1630 (C=O, st), 1594, 1477, 1406, 1310, 1276, 1238, 1216, 1172, 1097, 994, 963 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.28–2.42 (complex signal, 8H, 2(8)-H_2 and 4(6)-H_2], 7.10 (s, 1H) and 7.14 (s, 1H, $CONH_2$), 12.48 (br s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ 42.9 [C, C3(7)], 58.0 (C) and 59.9 [C, (C1 and C5)], 60.7 (CH_2) and 60.8 (CH_2) [C2(8) and C4(6)], 169.5 (C, $CONH_2$), 170.1 (C, COOH). MS (EI), *m/z* (%): 447 (M$^{\bullet+}$, 1), 430 [(M−OH)$^+$, 1], 320 [(M−I)$^+$, 7], 302 [(M−I−H_2O)$^+$, 9], 280 (57), 262 (11), 231 (20), 153 (60), 148 (21), 147 (21), 136 (22), 135 (27), 127 (17), 105 (42), 104 (90), 103 (77), 78 (53), 77 (100), 65 (34), 63 (37), 51 (75). MS (ESI−), *m/z* (%): 915 [(2M−2H+Na)$^-$, 15]. 447 (15), 446 [(M−H)$^-$, 100], 402 [(M−H−CO_2)$^-$, 36]. Accurate mass measurement: calcd for $C_{10}H_{10}I_2NO_3$ [(M−H)$^-$]: 445.8745; found: 445.8742.

5.4. 3,7-Diiodo-*N*-methyltricyclo[3.3.0.0^{3,7}]octane-1,5-dicarboximide (9)

5.4.1. From diacid 6. A mixture of diacid **6** (100 mg, 0.22 mmol) and acetic anhydride (2 mL) was heated under reflux for 1 h. The excess acetic anhydride and the formed acetic acid were distilled off in vacuo and the residue (97 mg) was dissolved in toluene (0.5 mL), 40% aqueous methylamine solution (20 μL, 0.24 mmol) was added and the mixture stirred for 2.5 h at room temperature. Concentration of the mixture in vacuo gave a yellowish residue (111 mg), acetic anhydride (2 mL) was added and the mixture was heated under reflux for 1 h. Evaporation of the volatile compounds in vacuo gave a yellowish residue (108 mg), which was submitted to column chromatography [neutral aluminum oxide (1.2 g), heptane/ethyl acetate mixtures]. On elution with a mixture heptane/ethyl acetate in the ratio of 9:1, imide **9** was obtained as a white solid (97 mg, 98% global yield). The analytical sample was obtained by crystallization from ethyl acetate/*n*-pentane (1:1), mp 176–177 °C. IR (KBr): ν 2995, 2946, 2907, 1764 and 1699 (C=O, st), 1419, 1372, 1318, 1266, 1126, 1114, 1012, 964, 836, 795, 735 cm^{-1}. ^{1}H NMR (300 MHz): δ 2.34 (d, J=8.1 Hz, 4H) and 2.69 (d, J=8.1 Hz, 4H) [2(4,6,8)-H_α and 2(4,6,8)-H_β], 3.01 (s, 3H, N-CH_3). ^{13}C NMR ($CDCl_3$): δ 25.3 (CH_3, N-CH_3), 42.1 [C, C3(7)], 57.8 [C, C1(5)], 60.1 [CH_2, C2(4,6,8)], 171.8 (C, imide CO). MS (EI), *m/z* (%): 443 (M$^{\bullet+}$, 2), 316 [(M−I)$^+$, 39], 231 [(M−I−CONMeCO)$^+$, 85], 132 (11), 105 (10), 104 [(M−2I−CONMeCO)$^{\bullet+}$, 100], 103 (20). Elemental analysis: calcd for $C_{11}H_{11}I_2NO_2$ (443.02): C 29.82, H 2.50, N 3.16, I 57.29. Found: C 29.88, H 2.32, N 3.13, I 56.95.

5.4.2. From imide 7. A mixture of imide **7** (160 mg, 0.37 mmol) and NaH (24 mg of a 45–55% suspension in mineral oil, about 0.5 mmol) in anhydrous THF (2 mL) was magnetically stirred under an argon atmosphere for 30 min. Then, methyl iodide (0.4 mL, 0.91 g, 6.4 mmol) was added and the mixture was stirred for 1 h. More methyl iodide (0.4 mL, 6.4 mmol) was added and the mixture was stirred for 15 h more. The reaction mixture was concentrated in vacuo and the solid residue was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were filtered and concentrated in vacuo to give imide **9** (119 mg, 72% yield) as a yellowish solid.

5.5. 3,7-Diiodo-5-(*N*-methylcarbamoyl)tricyclo[3.3.0.0^{3,7}]-octane-1-carboxylic acid (10)

A mixture of imide **9** (100 mg, 0.23 mmol) and aqueous 0.5 N NaOH (0.7 mL) was heated under reflux for 1 h. The obtained solution was diluted with water (2 mL) and made acidic with aqueous 10% HCl. The precipitated solid was filtered in vacuo, thoroughly washed with water and dried in vacuo in the presence of P_2O_5 to give amide acid **10** (88 mg, 85% yield) as a white solid, mp 223.5–226 °C (dec). IR (KBr): ν 3400–2200 (max. at 3373, 2943, 2624), 1696 and 1627 (C=O, st), 1612, 1549, 1474, 1420, 1330, 1292, 1248, 1219, 1160, 1110, 1072, 991, 960, 743, 710, 640 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ 2.39–2.49 (complex signal, 8H, 2(8)-H_2 and 4(6)-H_2], 2.70 (s, 3H, $NHCH_3$), 4.85 (s, mobile H, COOH and CONHMe). ^{13}C NMR (DMSO-d_6): δ 26.1 (CH_3, $NHCH_3$), 42.8 [C, C3(7)], 58.2 (C) and 60.0 [C, C1 and C5], 60.6 (CH_2) and 60.7 [CH_2, C2(8) and C4(6)], 167.9 (C, CON), 170.1 (C, COOH). MS (EI), *m/z* (%): 461 (M$^{\bullet+}$, 1), 443 [(M−H_2O)$^{\bullet+}$, 1], 334 [(M−I)$^+$, 14], 316 [(M−I−H_2O)$^+$, 44], 294 (97), 231 [(M−I−CONHMe−COOH)$^+$, 83], 167 (97), 149 (77), 127 (23), 105 (35), 104 [(M−2I−CONHMe−COOH)$^{\bullet+}$, 100], 103 (57), 78 (21), 77 (35). Elemental analysis: calcd for $C_{11}H_{13}I_2NO_3$ (461.04): C 28.66, H 2.84, N 3.04, I 55.05. Found: C 28.95, H 2.64, N 2.83, I 55.02.

5.6. Reaction of the sodium salt of imide 7 with molten sodium in boiling 1,4-dioxane in the presence of 18-crown-6

A solution of imide **7** (100 mg, 0.23 mmol) in anhydrous 1,4-dioxane (1.5 mL) was added to a suspension of NaH (9 mg, 55–65% in mineral oil, 0.23 mmol, previously washed with the above solvent) in the same solvent (1 mL), and the mixture was heated under reflux for 10 min, with formation of a white precipitate. Then, 18-crown-6 (186 mg, 0.7 mmol) was added until the precipitate was completely dissolved. The above solution was added to molten sodium (54 mg, 2.4 mmol) in boiling 1,4-dioxane (1 mL) and the mixture was heated under reflux for 3 h under an argon atmosphere. The mixture was allowed to cool to room temperature and was filtered by washing the solid with diethyl ether (3×10 mL). The combined filtrate and washings were concentrated to dryness in vacuo to give a solid residue (145 mg), which showed to be mainly 18-crown-6 (^{1}H NMR). The excess sodium from the

filter was destroyed by careful addition to water, and then the filter was washed with more water (10 mL). The combined aqueous phases were made acidic with 2 N HCl and were extracted with AcOEt (3×10 mL). The combined organic extracts were dried (anhydrous Na_2SO_4), filtered, and concentrated to dryness in vacuo to give a solid residue (59 mg), which showed to be **8** (^{1}H NMR).

5.7. Dimethyl 1,8-diphenyl-15-oxahexacyclo-[6.6.1.1^{2,5}.1^{4,7}.0^{2,7}.0^{9,14}]heptadeca-9,11,13-triene-4,5-dicarboxylate (14)

To a cold (−78 °C) solution of diiodide **12** (100 mg, 0.21 mmol) and 1,3-diphenylisobenzofuran (DPIBF, 63 mg, 0.23 mmol) in anhydrous THF (3.2 mL) under an argon atmosphere, a solution of *t*-BuLi (1.5 M in *n*-pentane, 0.3 mL, 0.45 mmol) was added dropwise. After 30 min at −78 °C, the mixture was allowed to heat to room temperature, methanol (1.3 mL) and water (4 mL) were added and it was extracted with diethyl ether (3×5 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a yellowish solid (114 mg), which was submitted to column chromatography [neutral aluminum oxide (11 g), column diameter: 1.5 cm, hexane/AcOEt mixtures]. On elution with a mixture hexane/AcOEt in the ratio of 96:4, compound **14** (47 mg, 46% yield) was isolated. An analytical sample of **14** (21 mg, 21% yield) was obtained as a white crystalline solid, mp 220–221 °C, by crystallization of the above product from diethyl ether (4.5 mL). IR (KBr): ν 3025, 2983, 2942, 2891, 1731 (C=O, st), 1603, 1477, 1457, 1448, 1432, 1351, 1302, 1272, 1236, 1217, 1186, 1113, 979, 765, 744, 734, 699, 660 cm^{-1}. ^{1}H NMR: δ 1.34 [dd, J=8.5 Hz, J'=3.5 Hz, 2H, 3(16)-H$_\beta$], 1.92 [dd, J=8.5 Hz, J'=3.5 Hz, 2H, 6(17)-H$_\beta$], 2.06 [d, J=8.5 Hz, 2H, 6(17)-H$_\alpha$], 2.22 [d, J=8.5 Hz, 2H, 3(16)-H$_\alpha$], 3.57 (s, 3H, 5COOCH$_3$), 3.60 (s, 3H, 4COOCH$_3$), 6.98 [m, 2H, 10(13)-H], 7.11 [m, 2H, 11(12)-H], 7.36 (tt, J=7.5 Hz, J'=1.5 Hz, 2H, ArH$_{para}$), 7.44 (m, 4H, ArH$_{meta}$), 7.58 (m, 4H, ArH$_{ortho}$). ^{13}C NMR: δ 50.0 [CH$_2$, C3(16)], 50.1 [CH$_2$, C6(17)], 51.69 [CH$_3$, 5COO*C*H$_3$)], 51.75 [CH$_3$, 4COO*C*H$_3$)], 60.6 (C, C4), 61.1 (C, C5), 66.4 [C, C2(7)], 87.5 [C, C1(8)], 120.2 [CH, C10(13)], 125.6 (CH, ArC$_{ortho}$), 127.0 [CH, C11(12)], 127.8 (CH, ArC$_{para}$), 128.5 (CH, ArC$_{meta}$), 137.1 (C, ArC$_{ipso}$), 147.2 [C, C9(14)], 171.6 [C, C4*C*OOCH$_3$)], 171.7 [C, C5*C*OOCH$_3$)]. MS (EI), *m*/*z* (%): 492 (M$^{\bullet+}$, 10), 388 (25), 387 (94), 271 (25), 270 [(C$_{20}$H$_{14}$O)$^{\bullet+}$, 59], 241 (24), 239 (20), 165 (25), 105 (C$_6$H$_5$CO$^+$, 100), 103 (39), 77 (83), 59 (60). Elemental analysis: calcd for C$_{32}$H$_{28}$O$_5$·0.4H$_2$O (499.78): C 76.90, H 5.81. Found: C 76.69, H 5.71.

5.8. Reaction of imide 7 with molten sodium in boiling 1,4-dioxane in the presence of 18-crown-6

Solid imide **7** (155 mg, 0.36 mmol) was added to molten sodium (83 mg, 3.6 mmol) in a boiling solution of 18-crown-6 (289 mg, 1.09 mmol) in 1,4-dioxane (3.6 mL) and the mixture was heated under reflux for 2.5 h under an argon atmosphere. The mixture was allowed to cool to room temperature and was filtered by washing the solid with diethyl ether (3×10 mL). The combined filtrate and washings were concentrated to dryness in vacuo to give a brown oily residue (318 mg), which showed to be mainly the crown ether. The sodium from the filter was destroyed by careful addition to water, then the filter was washed with water (5 mL), and the combined aqueous phases were made acidic with 2 N HCl and were extracted with AcOEt (3×10 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a yellowish solid residue (65 mg) which, after being washed with *n*-pentane (3×0.5 mL) and CH_2Cl_2 (3×0.2 mL), gave amide acid **8** (58 mg, 36%).

5.9. Reaction of imide 9 with *t*-butyllithium: 4-*t*-butyl-*endo*-2-(2,2-dimethylpropionyl)-*N*-methyl-5-methylenebicyclo[2.2.1]heptane-1-carboxamide (17) and *endo*-2-(2,2-dimethylpropionyl)-*N*-methyl-5-methylenebicyclo-[2.2.1]heptane-1-carboxamide (18)

To a cold (−78 °C) solution of diiodide **9** (100 mg, 0.23 mmol) in anhydrous THF (1.2 mL), kept under an argon atmosphere, a solution of *t*-BuLi (0.7 M in *n*-pentane, 0.6 mL, 0.42 mmol) was added dropwise. After 45 min at −78 °C, the mixture was allowed to heat to room temperature, methanol (0.4 mL) and water (2 mL) were added and the mixture was extracted with diethyl ether (4×5 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a residue (34 mg), which was analyzed by GC–MS showing the presence of two main components, **18** (rt 14.84 min, 21% relative area, molecular ion *m*/*z*=249) and **17** (rt 17.92 min, 37% relative area, molecular ion *m*/*z*=305), the rest of components showing relative areas below 6%. The above residue was submitted to column chromatography [flash silica gel (3.4 g), column diameter: 1 cm, heptane/AcOEt mixtures in ratios from 6:4 to 4:6]. In order of elution, slightly impure compound **17** (7 mg) and pure **18** (8 mg, 14% yield) were isolated as colorless oils.

When this reaction was carried out as before but using 0.21 mmol *t*-BuLi, instead of 0.42 mmol, a residue (37 mg) containing mainly **18** (17% relative area), **17** (50% relative area), and other components showing relative areas below 10%, was obtained. Column chromatography of the above residue [flash silica gel (6 g), column diameter: 1 cm, heptane/AcOEt mixtures] allowed us to isolate pure **17** (8 mg, 11% yield) as a colorless oil. Spectroscopic and analytic data of **17**: IR (KBr): ν 3409, 3088, 2970, 2871, 1693 and 1661 (C=O, st), 1533, 1478, 1464, 1412, 1366, 1092, 1078, 894 cm^{-1}; ^{1}H NMR: δ 1.07 [s, 9H, 4-C(C*H*$_3$)$_3$], 1.09 [s, 9H, 2-COC(C*H*$_3$)$_3$], 1.36 (ddd, $J_{3\text{-H}_{endo}/3\text{-H}_{exo}}$=12.0 Hz, $J_{2\text{-H}/3\text{-H}_{endo}}$=7.0 Hz, $J_{3\text{-H}_{endo}/7\text{-H}_{anti}}$=2.5 Hz, 1H, 3-H$_{endo}$), 1.69 (dd, $J_{7\text{-H}_{anti}/7\text{-H}_{syn}}$=10.0 Hz, $J_{3\text{-H}_{endo}/7\text{-H}_{anti}}$=2.5 Hz, 1H, 7-H$_{anti}$), 1.95 (ddd, $J_{7\text{-H}_{anti}/7\text{-H}_{syn}}$=10.0 Hz, $J_{6\text{-H}_{endo}/7\text{-H}_{syn}}$= 2.0 Hz, 1H, 7-H$_{syn}$), 2.33 (t, $J_{3\text{-H}_{endo}/3\text{-H}_{exo}}$=12.0 Hz, $J_{2\text{-H}/3\text{-H}_{exo}}$=12.0 Hz, 1H, 3-H$_{exo}$), 2.37 (dq, $J_{6\text{-H}_{exo}/6\text{-H}_{endo}}$= 15.0 Hz, $J_{2\text{-H}/6\text{-H}_{exo}}$=2.0 Hz, $J_{6\text{-H}_{exo}/5=\text{CH}(Z)}$=2.0 Hz, $J_{6\text{-H}_{exo}/5=\text{CH}(E)}$=2.0 Hz, 1H, 6-H$_{exo}$), 2.75 (d, $J_{\text{NH}/\text{NHC}H_3}$= 5.0 Hz, 3H, NHC*H*$_3$), 3.45 (ddt, $J_{6\text{-H}_{exo}/6\text{-H}_{endo}}$=15.0 Hz, $J_{6\text{-H}_{endo}/7\text{-H}_{syn}}$=2.0 Hz, $J_{6\text{-H}_{endo}/5=\text{CH}(Z)}$=3.0 Hz, $J_{6\text{-H}_{endo}/5=\text{CH}(E)}$= 2.0 Hz, 1H, 6-H$_{endo}$), 3.59 (ddd, $J_{2\text{-H}/3\text{-H}_{exo}}$=12.0 Hz, $J_{2\text{-H}/3\text{-H}_{endo}}$=7.0 Hz, $J_{2\text{-H}/6\text{-H}_{exo}}$=2.0 Hz, 1H, 2-H), 4.84 (t, $J_{5=\text{CH}(E)/6\text{-H}_{exo}}$=2.0 Hz, $J_{5=\text{CH}(E)/6\text{-H}_{endo}}$=2.0 Hz, 1H, 5=CH(*E*)), 4.97 (t, $J_{5=\text{CH}(Z)/6\text{-H}_{exo}}$=2.0 Hz, $J_{5=\text{CH}(Z)/6\text{-H}_{endo}}$= 3.0 Hz, 1H, 5=CH(*Z*)), 5.66 (br s, 1H, N*H*CH$_3$). ^{13}C NMR (100.6 MHz): δ 26.0 [CH$_3$, 2-COC(*C*H$_3$)$_3$], 26.2 (CH$_3$,

NH*C*H$_3$), 27.2 [CH$_3$, 4-C(*C*H$_3$)$_3$], 32.4 [C, 4-*C*(CH$_3$)$_3$], 37.7 (CH$_2$, C3), 38.3 (CH$_2$, C6), 44.8 [C, 2-CO*C*(CH$_3$)$_3$], 45.8 (CH$_2$, C7), 49.3 (CH, C2), 55.0 (C, C1), 60.6 (C, C4), 104.4 (CH$_2$, 5=CH$_2$), 152.4 (C, C5), 174.1 (C, *C*ONHMe), 218.8 [C, 2-*C*OC(CH$_3$)$_3$]. MS (EI), *m/z* (%): 305 (M$^{\bullet+}$, 3), 248 [(M−*t*-Bu)$^+$, 31], 193 (8), 164 [(M−*t*-BuCO)$^+$, 9], 136 (40), 58 (29), 57 (100). MS (ESI+), *m/z* (%): 634 (19), 633 [(2M+Na)$^+$, 30], 344 [(M+K)$^+$, 10], 329 (31), 328 [(M+Na)$^+$, 100], 325 (13), 306 [(M+H)$^+$, 32], 275 [(M−NHCH$_3$)$^+$, 22]. Accurate mass measurement (ESI+): calcd for $C_{19}H_{32}NO_2$ [(M+H)$^+$]: 306.2428; found: 306.2424. Spectroscopic and analytic data of **18**: IR (KBr): ν 3343, 3072, 2963, 2872, 1698, 1643 (C=O, st), 1538, 1479, 1467, 1409, 1366, 1270, 1086, 902, 873 cm^{-1}. ^{1}H NMR: δ 1.09 [s, 9H, 2-COC(C*H*$_3$)$_3$], 1.38 (ddd, $J_{3\text{-H}_{endo}/3\text{-H}_{exo}}$= 12.0 Hz, $J_{2\text{-H}/3\text{-H}_{endo}}$=6.0 Hz, $J_{3\text{-H}_{endo}/7\text{-H}_{anti}}$=2.0 Hz, 1H, 3-H$_{endo}$), 1.71 (dt, $J_{7\text{-H}_{anti}/7\text{-H}_{syn}}$=10.0 Hz, $J_{3\text{-H}_{endo}/7\text{-H}_{anti}}$=2.0 Hz, $J_{4\text{-H}/7\text{-H}_{anti}}$=2.0 Hz, 1H, 7-H$_{anti}$), 1.93 (ddd, $J_{7\text{-H}_{anti}/7\text{-H}_{syn}}$= 10.0 Hz, $J_{6\text{-H}_{endo}/7\text{-H}_{syn}}$=3.0 Hz, $J_{4\text{-H}/7\text{-H}_{syn}}$=2.0 Hz, 1H, 7-H$_{syn}$), 2.24 (dt, $J_{3\text{-H}_{endo}/3\text{-H}_{exo}}$=12.0 Hz, $J_{2\text{-H}/3\text{-H}_{exo}}$=12.0 Hz, $J_{3\text{-H}_{exo}/4\text{-H}}$=5.0 Hz, 1H, 3-H$_{exo}$), 2.25 (dm, $J_{6\text{-H}_{exo}/6\text{-H}_{endo}}$= 15.0 Hz, 1H, 6-H$_{exo}$), 2.77 (d, $J_{\text{NH/NHC}H_3}$=5.0 Hz, 3H, NHC*H*$_3$), 2.81 (br d, $J_{3\text{-H}_{exo}/4\text{-H}}$=5.0 Hz, 1H, 4-H), 3.37 (ddt, $J_{6\text{-H}_{exo}/6\text{-H}_{endo}}$=15.0 Hz, $J_{6\text{-H}_{endo}/7\text{-H}_{syn}}$=2.0 Hz, $J_{6\text{-H}_{endo}/5=\text{CH}(Z)}$= 2.0 Hz, $J_{6\text{-H}_{endo}/5=\text{CH}(E)}$=3.0 Hz, 1H, 6-H$_{endo}$), 3.55 (ddd, $J_{2\text{-H}/3\text{-H}_{exo}}$=12.0 Hz, $J_{2\text{-H}/3\text{-H}_{endo}}$=6.0 Hz, $J_{2\text{-H}/6\text{-H}_{exo}}$=2.0 Hz, 1H, 2-H), 4.65 (br s, 1H, 5=C*H*(*E*), 4.84 (t, $J_{5=\text{CH}(Z)/6\text{-H}_{exo}}$= 2.0 Hz, $J_{5=\text{CH}(Z)/6\text{-H}_{endo}}$=2.0 Hz, 1H, 5=CH(*Z*)), 5.72 (br s, 1H, N*H*CH$_3$). ^{13}C NMR (100.6 MHz): δ 26.1 [CH$_3$, 2-COC(*C*H$_3$)$_3$], 26.3 (CH$_3$, NHC*H*$_3$), 34.4 (CH$_2$, C6), 36.5 (CH$_2$, C3), 44.4 (CH$_2$, C7), 44.8 [C, 2-CO*C*(CH$_3$)$_3$], 46.4 (CH, C4), 48.5 (CH, C2), 57.9 (C, C1), 102.7 (CH$_2$, 5=CH$_2$), 152.7 (C, C5), 174.1 (C, *C*ONHMe), 219.0 [C, 2-*C*OC(CH$_3$)$_3$]. MS (EI), *m/z* (%): 249 (M$^{\bullet+}$, 19), 192 [(M−*t*-Bu)$^+$, 20], 164 [(M−*t*-BuCO)$^+$, 18], 137 (63), 107 (18), 105 (21), 91 (20), 86 (20), 79 (31), 77 (25), 58 (77), 57 (100). MS (ESI+), *m/z* (%): 273 (17), 272 [(M+Na)$^+$, 100], 250 [(M+H)$^+$, 4]. Accurate mass measurement (ESI+): calcd for $C_{15}H_{24}NO_2$ [(M+H)$^+$]: 250.1802; found: 250.1797.

5.10. Reaction of imide 9 with molten sodium in boiling 1,4-dioxane

Solid imide **9** (100 mg, 0.23 mmol) was added to molten sodium (52 mg, 2.25 mmol) in boiling 1,4-dioxane (2.2 mL) and the mixture was heated under reflux for 4 h under an argon atmosphere. The mixture was allowed to cool to room temperature and was filtered by washing the solid with diethyl ether (3×10 mL) and 1,4-dioxane (10 mL). The combined filtrate and washings were concentrated to dryness in vacuo to give a solid residue (52 mg), which showed to be partially insoluble in CD_3OD. This solid was taken in water (5 mL), acidified with 2 N HCl, and extracted with AcOEt (3×10 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a solid residue (16 mg), which showed to be amide acid **10**. The sodium from the filter was destroyed by careful addition to water, and then the filter was washed with water (5 mL). The combined aqueous phases were made acidic with 2 N HCl and were extracted with AcOEt (3×6 mL). The combined organic extracts were treated as before to give more **10** (83 mg, total yield 95%).

5.11. Reaction of imide 9 with the radical anion from lithium and 4,4′-di-*t*-butylbiphenyl

A solution of 4,4′-di-*t*-butylbiphenyl (141 mg, 0.53 mmol) in anhydrous THF (1.5 mL) was placed in a Schlenk tube and kept under an argon atmosphere. Lithium in small pieces (4 mg, 0.58 mmol) was added and the mixture sonicated for 1.75 h keeping the temperature of the bath at 6–8 °C. After 5 min the solution took a green color that remained all the time. Then, the above solution cooled to 0 °C was added to a cold (ice-bath) solution of imide **9** (100 mg, 0.23 mmol) in anhydrous THF (0.5 mL) and the brown solution was reacted at this temperature for 1 h and at room temperature for 12 h. Water (4 mL) was added and the mixture was extracted with CH_2Cl_2 (4×4 mL). The combined organic phases were dried (anhydrous Na_2SO_4) and concentrated to dryness in vacuo to give a solid residue (166 mg), which analyzed by GC–MS showed to be mainly 4,4′-di-*t*-butylbiphenyl and reduction products derived from it. The aqueous phase was made acidic with 2 N HCl and extracted with AcOEt (3×4 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a solid residue, consisting mainly of **10** (56 mg).

5.12. 1,8-Diphenyl-*N*-methyl-15-oxahexacyclo-[6.6.1.1^{2,5}.1^{4,7}.0^{2,7}.0^{9,14}]heptadeca-9,11,13-triene-4,5-dicarboximide (19)

To a cold (−78 °C) solution of diiodide **9** (100 mg, 0.23 mmol) and 1,3-diphenylisobenzofuran (DPIBF, 73 mg, 0.27 mmol) in anhydrous THF (3 mL), a solution of *t*-BuLi (0.7 M in *n*-pentane, 0.3 mL, 0.21 mmol) was added dropwise. After 30 min at −78 °C, the mixture was allowed to heat to room temperature, methanol (1 mL) and water (5 mL) were added and it was extracted with diethyl ether (3×10 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a yellowish solid (162 mg), which was submitted to column chromatography [neutral aluminum oxide (16 g), column diameter: 1.5 cm, heptane/AcOEt mixtures]. On elution with a mixture heptane/AcOEt in the ratio of 97:3, slightly impure compound **19** (83 mg) was isolated. An analytical sample of **19** (30 mg, 29% yield) was obtained as a white crystalline solid, mp 246–247 °C, by crystallization of the above product from isopropanol (3 mL). IR (KBr): ν 3033, 2997, 2939, 1764, 1700 (C=O st), 1601, 1497, 1473, 1448, 1426, 1370, 1347, 1318, 1261, 1129, 1009, 981, 753, 700, 684 cm^{-1}. ^{1}H NMR: δ 1.62 [dd, J=8.7 Hz, J'=3.5 Hz, 2H, 3(16)-H$_\alpha$], 1.95 [dm, J=8.7 Hz, 2H, 6(17)-H$_\beta$], 2.09 [dm, J=8.7 Hz, 2H, 3(16)-H$_\beta$], 2.18 [dd, J=8.7 Hz, J'=3.5 Hz, 2H, 6(17)-H$_\alpha$], 2.92 (s, 3H, N-CH$_3$), 7.03 [m, 2H, 10(13)-H], 7.16 [m, 2H, 11(12)-H], 7.39 (tm, J=7.5 Hz, 2H, ArH$_{para}$), 7.47 (m, 4H, ArH$_{meta}$), 7.59 (dm, J=8.0 Hz, 4H, ArH$_{ortho}$). ^{13}C NMR (100.6 MHz): δ 24.6 (CH$_3$, N-*C*H$_3$), 49.3 [CH$_2$, C3(16)], 49.4 [CH$_2$, C6(17)], 57.8 (C, C4), 58.1 (C, C5), 70.1 [C, C2(7)], 87.3 [C, C1(8)], 120.3 [CH, C10(13)], 125.5 (CH, ArC$_{ortho}$), 127.3 [CH, C11(12)], 127.9 (CH, ArC$_{para}$), 128.6 (CH, ArC$_{meta}$), 136.7 (C, ArC$_{ipso}$), 146.8 [C, C9(14)], 174.5 [C, 4*C*ON)], 174.8 [C, 5*C*ON)]. MS (EI), *m/z* (%): 460 (13), 459 (M$^{\bullet+}$, 35), 355 (29), 354 (92), 270 [(C$_{20}$H$_{14}$O)$^{\bullet+}$, 48], 269 (23), 253 (20), 252 (31), 241 (32), 239 (43), 226 (31), 217 (24), 215 (25), 202 (30), 189 [(M−C$_{20}$H$_{14}$O)$^{\bullet+}$, 26], 165 (46), 105

($C_6H_5CO^+$, 100), 77 (51). Elemental analysis: calcd for $C_{31}H_{25}NO_3 \cdot 0.25H_2O$ (464.05): C 80.24, H 5.54, N 3.02. Found: C 80.24, H 5.65, N 2.77.

5.13. Reaction of imide 9 with 0.45% sodium amalgam

Imide **9** (100 mg, 0.23 mmol) and 1,4-dioxane (2.2 mL) were added to 0.45% sodium amalgam, previously prepared from sodium (63 mg, 2.9 mmol) and mercury (13.9 g), and the mixture was vigorously stirred for 3.5 h under an argon atmosphere. The mixture was filtered through a pad of Celite® under reduced pressure washing the solid with diethyl ether (3×10 mL) and CH_2Cl_2 (5 mL). The combined filtrate and washings were concentrated to dryness in vacuo to give a solid residue (37 mg), which by GC–MS showed the presence of three main components (14, 55, and 9% relative areas), whose MS spectra suggest them to be **21**, **20**, and starting **9**. MS spectrum of **21**: (EI), m/z (%): 191 ($M^{\bullet+}$, 8), 134 [(M−CONMe)$^{\bullet+}$, 26], 106 [(M−CONMeCO)$^{\bullet+}$, 100], 105 (18), 93(19), 92(28), 91(39), 78(25), 65(21). MS spectrum of **20**: (EI), m/z (%): 317 (M^+, 20), 232 [(M−CONMeCO)$^{\bullet+}$, 31], 190 [(M−I)$^+$, 34], 133 (23), 105 [(M−CONMeCO−I)$^+$, 100], 93 (21).

Acknowledgements

Financial support from *Ministerio de Ciencia y Tecnología* (Project CTQ2005-02192) and *Comissionat per a Universitats i Recerca* (Project 2005-SGR-00180) is gratefully acknowledged. We thank the *Centre de Supercomputació de Catalunya* (CESCA) for computational facilities, the *Serveis Científico-Tècnics* of the University of Barcelona for the NMR and MS facilities, and Ms. P. Domènech from the II-QAB (CSIC, Barcelona, Spain) for carrying out the elemental analyses.

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Synthesis of 2-oxo-2,3,5,6-tetrahydro-5-thioxoimidazo[1,2-*c*]-quinazolines by one-pot cyclization of α-aminocarboxylic esters with 2-(isothiocyanato)benzonitrile (ITCB)

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Received 3 May 2006; revised 25 May 2006; accepted 29 May 2006
Available online 19 June 2006

Abstract—The cyclization of 2-(isothiocyanato)benzonitrile with α-aminocarboxylic esters and acids afforded a variety of 2-oxo-2,3,5,6-tetrahydro-5-thioxo-imidazo[1,2-*c*]quinazolines with very good regioselectivity.

1. Introduction

2-(Isothiocyanato)benzonitrile (ITCB) represents a versatile synthetic building block.[1] In recent years, one-pot cyclizations of ITCB with a number of nucleophiles have been reported. Recently, we and others have reported one-pot cyclizations of ITCB with hydrazine,[2] carboxylic hydrazides,[3,4] α-aminoketones,[5] and carbon nucleophiles.[6] In addition, one-pot cyclizations of ITCB-derived dichloroisocyanides have been reported.[7,8] Recently, we reported the synthesis of 2-oxo-2,3,5,6-tetrahydro-5-thioxo-imidazo[1,2-*c*]quinazolines by one-pot cyclization of ITCB with α-aminocarboxylic esters.[9] Herein, we report full details of this work and studies related to the preparative scope. Notably, functionalized quinazolines are of pharmacological relevance and show antihypertonic, antirheumatic, antianaphylactic, antiasthmatic, tranquilizing, neuro-stimulating, and benzodiazepine binding activity.[10] In addition, they represent useful synthetic building blocks.

2. Mechanism and optimization

The reaction of ethyl glycinate (**2a**) with ITCB (**1a**) afforded—based on MS data and elemental analysis—a tricyclic cyclization product. The formation of 2-oxo-2,3,5,6-tetrahydro-5-thioxoimidazo[1,2-*c*]quinazoline **3a** or its isomer *iso*-**3a** can be discussed. The formation of **3a** can be explained by attack of the amino group onto the isothiocyanate (intermediate **A**), attack of the amino group onto the nitrile (intermediate **B**), and subsequent attack of the imino group onto the ester group (Scheme 1). The formation of *iso*-**3a** may proceed by attack of the amino group onto the isothiocyanate, attack of the sulfur atom onto the nitrile (intermediate **C**), Dimroth rearrangement (intermediate **D**), and subsequent attack of the amino group onto the ester. Based on structural investigations (vide infra), we believe that **3a** is formed in the reaction, although the structure *iso*-**3a** cannot be completely ruled out.

The best yields were obtained when a two phase system of a CH_2Cl_2 solution of the starting materials and of an aqueous solution of Na_2CO_3 was stirred for 10 min at 20 °C (formation of **A**) and subsequently refluxed for 20 min (formation of **B**). After aqueous work-up, an *i*PrOH solution of **B** was refluxed (formation of **3a**). The yield of **3a** decreased when the CH_2Cl_2 solution was refluxed immediately without stirring at 20 °C. In contrast, intermediate **A** was isolated when the reaction was carried out at 20 °C without reflux. The yield of **3a** dropped and intermediate **B** was isolated when the *i*PrOH solution was not refluxed for sufficient time. The reaction could be also carried out as a one-pot reaction without isolation of **B**. However, the yield dropped (36%) compared to the sequential procedure (58%).

Keywords: Amino acids; Cyclizations; Domino reactions; Isothiocyanates; Regioselectivity.
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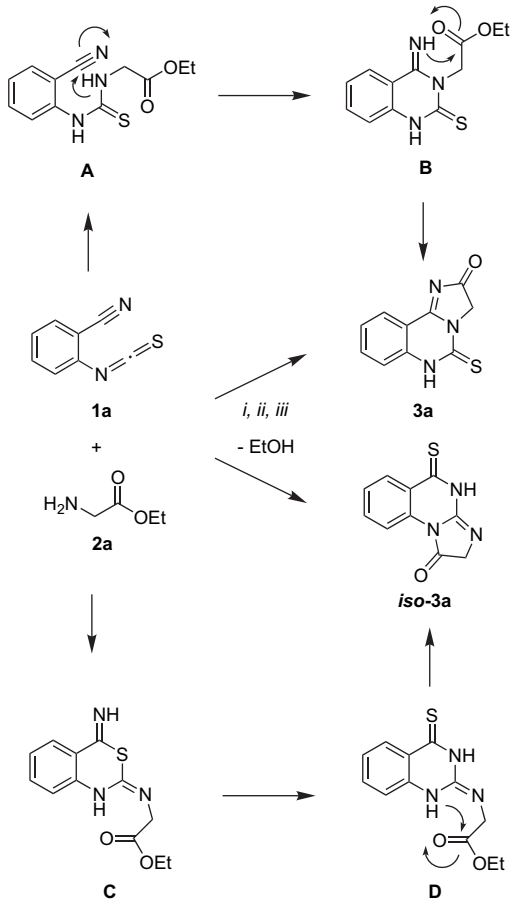
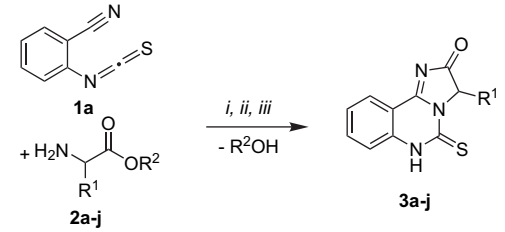
doi:10.1016/j.tet.2006.05.075



Scheme 1. Possible mechanistic pathways of the cyclization of ITCB (**1a**) with ethyl glycinate: (i) Na_2CO_3, H_2O, CH_2Cl_2, 20 °C, 10 min; (ii) reflux, 20 min, isolation of crude intermediate **B**; (iii) *i*PrOH, reflux, 10 h.

3. Scope and limitations

The reaction of ITCB with ethyl alanate furnished the 2-oxo-2,3,5,6-tetrahydro-5-thioxoimidazo[1,2-*c*]quinazoline **3b**, albeit in only 21% yield (Scheme 2, Table 1). The cyclization of ITCB with the amino acid alanine gave **3b** in 45% yield. The cyclization of ITCB with methyl 2-aminobutyrate afforded **3c**. The cyclization of ITCB with ethyl valinate and valine afforded **3d** in 77 and 43% yield, respectively. 5-Thioxoimidazo[1,2-*c*]quinazoline **3e** was prepared from methyl leucinate. The cyclization of ITCB with ethyl 2-amino-4-cyclohexylbutyrate gave the quinazoline **3f**. Heterocycles **3g** and **3h** were prepared from methyl phenylalanate ester and ethyl 2-phenylglycinate, respectively. The reaction of



Scheme 2. Synthesis of **3a–j**: (i) Na_2CO_3, H_2O, CH_2Cl_2, 20 °C, 10 min; (ii) reflux, 20 min, isolation of crude **B**; (iii) *i*PrOH, reflux, 10 h.

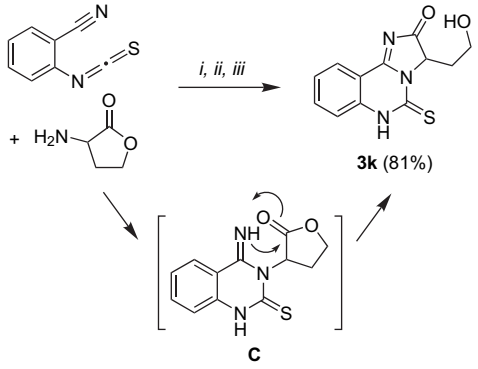
Table 1. Products and yields

3	R^1	R^2	% (3)[a]
a	H	Et	58
b	Me	Et	21
b	Me	H	45
c	Et	Me	20
d	*i*Pr	Et	77
d	*i*Pr	H	43
e	*i*Bu	Me	86
f	$(CH_2)_2$(*c*Hex)	Et	81
g	Bn	Me	35
h	Ph	Et	62
i	CO_2Et	Et	60
j	CH_2CO_2Bn	Bn	84

[a] Yields of isolated products.

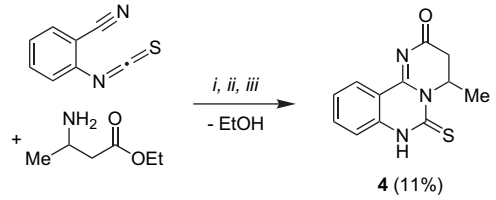
ITCB with diethyl 2-aminomalonate and dibenzyl aspartate gave the ester substituted quinazolines **3i** and **3j**, respectively. Notably, racemic products were isolated when enantiomerically pure starting materials were used, due to racemization.

The reaction of α-amino-γ-butyrolactone with ITCB afforded 3-(2-hydroxyethyl)-5-thioxoimidazo[1,2-*c*]quinazolin-2-one **3k**. The formation of **3k** can be explained by attack of the amino group onto the isothiocyanate, subsequent cyclization by attack of the amino group onto the nitrile (intermediate **C**), and subsequent nucleophilic attack of the imino group onto the lactone ring and cleavage of the latter (Scheme 3).



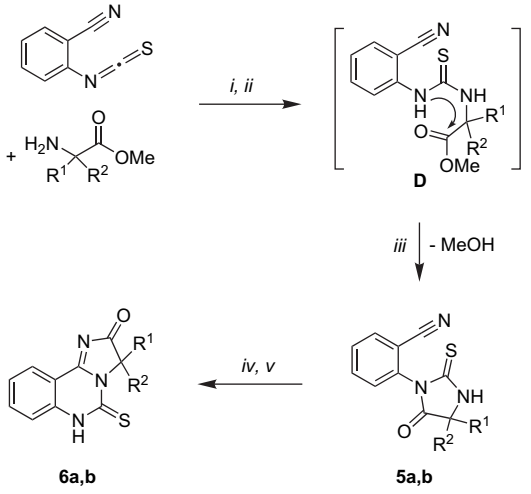
Scheme 3. Synthesis of **3k**: (i) Na_2CO_3, H_2O, CH_2Cl_2, 20 °C, 10 min; (ii) reflux, 20 min, isolation of crude **C**; (iii) *i*PrOH, reflux, 10 h.

The reaction of ITCB with racemic ethyl 3-aminobutyrate (**4**) afforded the racemic pyrimidinone **5**, albeit, in only 11% yield (Scheme 4). The final cyclization step (attack of the imino group onto the ester group) proved to be problematic. The yield could *not* be improved by extension of the reaction time or by variation of the concentration.



Scheme 4. Synthesis of **4**, conditions: (i) Na_2CO_3, H_2O, CH_2Cl_2, 20 °C, 10 min; (ii) reflux, 20 min; (iii) *i*PrOH, reflux, 10 h.

The reaction of ITCB with methyl 2-amino-2-methylpropionate and methyl 1-aminocyclohexylcarboxylate afforded 2-thioxoimidazolidinones **5a** and **5b** (Scheme 5, Table 2). The formation of **5a**,**b** can be explained by attack of the amino group onto the isothiocyanate and subsequent cyclization by attack of the ITCB-derived amino group onto the ester. The change in the mechanism can be explained by (a) the steric hindrance of the 2-amino-2-methylpropionate and (b) Thorpe–Ingold effect. Treatment of **5a**,**b** with an aqueous solution of sodium hydroxide afforded 2-oxoimidazo[1,2-*c*]-quinazolines **6a**,**b** by ring cleavage to give a carboxylic acid, attack of the amino group onto the nitrile, and subsequent attack of the imino group onto the carboxylic acid.



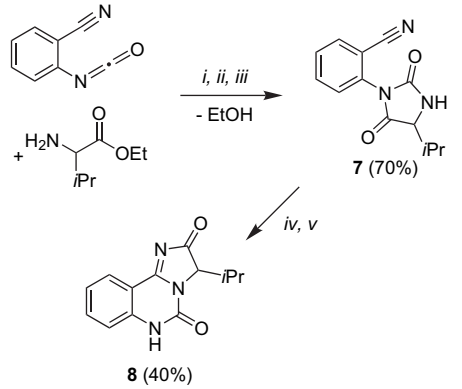
Scheme 5. Synthesis of **5a**,**b** and **6a**,**b**: (i) Na_2CO_3, H_2O, CH_2Cl_2, 20 °C, 10 min; (ii) reflux, 20 min, isolation of **D**; (iii) *i*PrOH, reflux, 10 h; (iv) NaOH, H_2O (4%), 20 °C, 24 h; (v) H_2O, HCl.

Table 2. Products and yields

5,6	R^1	R^2	% (**5**)[a]	% (**6**)[a]
a	Me	Me	40	80
b	–$(CH_2)_5$–		40	35

[a] Isolated yields.

The reaction of ethyl valinate with 2-isocyanatobenzonitrile—the oxa-analog of ITCB—afforded the imidazolidine-2,5-dione **7** (Scheme 6). Treatment of **7** with an aqueous solution of NaOH afforded the 2,5-dioxo-imidazo[1,2-*c*]quinazoline **8**. The formation of **7** and **8** follows the mechanism as discussed for the formation of **5a**,**b** and **6a**,**b**.



Scheme 6. Synthesis of **8**: (i) NEt_3, CH_2Cl_2, 20 °C, 10 min; (ii) reflux, 40 min, isolation of intermediate; (iii) *i*PrOH, NH_4OH, reflux, 48 h; (iv) NaOH, H_2O (4%), 20 °C, 24 h; (v) HCl, H_2O.

4. Structure elucidation

The structures of products **3a–j** were assigned based on the similarity of their NMR spectroscopic data, on a detailed structural analysis of **3g** and **6a**, and on an X-ray crystal structure analysis of **6a** (vide infra). The NMR signals of **3g** were assigned by DEPT and two-dimensional ^{1}H–^{1}H COSY, ^{1}H–^{1}H NOESY, and ^{1}H–^{13}C correlation spectra (HSQC, HMBC). In the HMBC spectrum cross peaks were found for C-11 with H-3, H-7, and H-10; as well as NH with CS and C-10a, which confirm the given structure. The alternative structure given in Figure 1 can be excluded based on the HMBC spectrum in which a correlation was found between the NH proton and the signal for the quaternary aromatic carbon atom C-10a at δ=110.7. Furthermore, the NMR data of **3g** are in best agreement with those assigned for compound **6a**. All derivatives **3a–k** exhibit very similar IR absorptions (C=O), ^{13}C NMR data (C=O and C=S groups and carbon atoms C-6a, C-8, C-9, C-7, C-10a, and C-3 of the quinazoline moiety), and ^{1}H NMR data (protons 3-H and NH) (Fig. 1, Table 3).

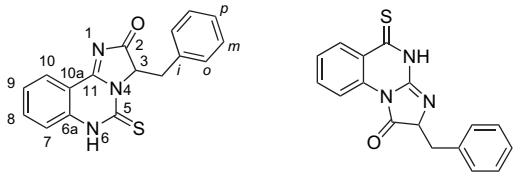


Figure 1. Atom numbering of **3g** for NMR signal assignment.

The structures of products **6a**,**b** were assigned based on the similarity of their NMR spectroscopic data, on a detailed structural analysis of **6a**, and on an X-ray crystal structure analysis of **6a**. The NMR signals of **6a** were assigned by DEPT and two-dimensional ^{1}H–^{1}H COSY, ^{1}H–^{1}H NOESY, and ^{1}H–^{13}C correlation spectra (HSQC, HMBC). In the HMBC spectrum cross peaks were found for NH with C=S, C-7, C-10a, and C-6a; C-11 with H-10 and H-7 (^4J); and Me (protons) with C-2 and C-3 (Fig. 2). In the NOESY spectrum cross peaks were found for the NH proton with H-7. No other correlations besides this for the aromatic protons were observed. The structure of **6a** was independently confirmed by X-ray crystal structure analysis (Fig. 3).[11]

In conclusion, we have reported the synthesis of 2-oxo-2,3,5,6-tetrahydro-5-thioxoimidazo[1,2-*c*]quinazolines based on the cyclization reactions of 2-(isothiocyanato)benzonitrile with α-aminocarboxylic esters.

5. Experimental

5.1. General

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^{1}H and ^{13}C

Table 3. Characteristic spectroscopic features of **3a–k**, **6a**, and **8**

Nr.	$\tilde{\nu}$(C=O) (cm^{-1})	δ (ppm) 3-H	δ (ppm) NH	δ (ppm) C-3	δ (ppm) C=O	δ (ppm) C=S	δ (ppm) C-6a	δ (ppm) C-8	δ (ppm) C-9	δ (ppm) C-7	δ (ppm) C-10a
3a	1746, 1627	4.48	13.85	53.6	184.4	168.3	139.8	137.0	125.6	116.3	111.0
3b	1743, 1624	4.57	13.24	59.7	188.4	168.5	139.6	137.0	125.0	115.9	111.2
3c	1741, 1624	4.64	13.20	64.4	187.6	168.8	139.7	137.1	125.1	116.0	110.8
3d	1733, 1627	4.51	13.25	67.9	186.5	168.5	139.7	137.1	125.2	116.1	110.9
3e	1746, 1627	4.62	13.25	62.4	187.9	168.5	139.6	137.0	125.1	115.9	110.9
3f	1752, 1624	4.63	13.25	63.8	187.7	168.6	139.6	137.1	125.1	116.0	110.8
3g	1736, 1624	4.89	13.30	64.8	187.2	169.1	139.6	137.5	125.5	116.2	110.7
3h	1743	5.64	13.28	67.2	185.1	169.4	139.9	137.3	125.1	116.0	111.0
3i	1752, 1625	5.38	13.65	66.2	179.1	169.1	139.9	138.1	125.7	116.4	110.2
3j	1744, 1625	4.83	13.26	60.0	186.6	168.8	139.5	137.1	125.2	116.0	111.0
3k	1717, 1624	4.64	13.18	61.7	187.8	168.7	139.5	136.9	125.0	115.8	111.0
6a	1729, 1627	—	13.13	67.4	191.6	169.0	139.8	136.8	125.3	115.9	111.7
8	1745/1728, 1628	4.39	13.79	64.7	187.2	171.9	141.2	136.7	123.3	115.8	109.1

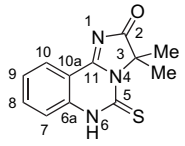


Figure 2. Atom numbering of **6a** for NMR signal assignment.

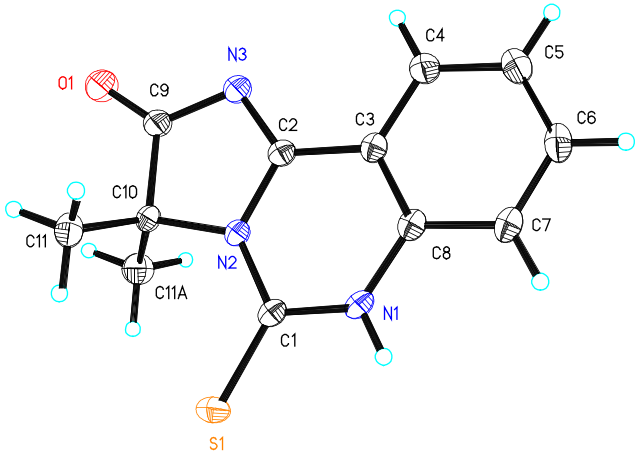


Figure 3. ORTEP plot of **6a**. The thermal ellipsoids of 50% probability are shown for the non-hydrogen atoms.

NMR, the deuterated solvents indicated were used. The ^{1}H NMR (300.13 MHz) and ^{13}C NMR (75.9 MHz) were recorded on a Bruker spectrometer ARX 300. In addition to the routine measurements, spectra of **3g** and **6a** were measured on a Bruker Spectrometer AVANCE 500 (^{1}H: 500.13 MHz and ^{13}C: 125.8 MHz). Calibration of spectra was carried out on the solvent signals (DMSO-d_6: δ ^{1}H=2.50, δ ^{13}C=39.7). Mass spectrometric data (MS) were obtained by electron ionization (70 eV), chemical ionization (CI, H_2O), or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

5.1.1. 5-Thioxo-5,6-dihydroimidazo[1,2-*c*]quinazolin-2-one (3a). 2-(Isothiocyanato)benzonitrile (1.00 g, 6.4 mmol) and ethyl glycinate hydrochloride (1.21 g, 6.4 mmol) were suspended in dichloromethane (40 ml). A solution of sodium carbonate (1.83 g in 12 ml water) was added and the mixture was stirred for 10 min at ambient temperature and for 10 min under reflux. After cooling to room temperature, a colorless precipitate was formed. The latter was filtered off, the organic and the aqueous layer were separated, and the latter was extracted with dichloromethane (2×20 ml). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent of the filtrate was removed at reduced pressure. The residue and the precipitate were suspended in isopropanol (200 ml) and the mixture was refluxed for 12 h. The product was crystallized after cooling. Concentration of the mother liquor at reduced pressure gave a further amount of the product. Yield: 0.80 g (58%), brown roods (acetone), mp 320–323 °C (decomp.). IR (KBr): $\tilde{\nu}$=3105, 3071 (w), 3013, 2993, 2928, 2922, 2847 (m), 1746, 1636, 1627, 1601, 1554, 1529, 1479, 1424, 1342, 1306, 1255, 1226, 1175, 1067 (s), 945 (w), 756, 543 (s) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ=4.48 (s, 2H, CH_2), 7.41–7.48 (m, 2H, Ar), 7.84–8.07 (m, 2H, Ar), 13.85 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=53.6 (CH_2), 111.0 (C), 116.3, 125.6, 127.5, 137.0 (CH), 139.8, 168.1, 168.3 (C), 184.4 (C=O). MS (EI, 70 eV): *m/z* (%)=218 (13), 217 (M^+, 100), 171 (23), 161 (11), 160 (13), 143 (19), 129 (12), 102 (21). UV–vis (CH_3CN): λ_{max} (log ε)=246 (4.22), 249 (4.22), 267 (4.45), 292 (4.48), 350 (3.68). Anal. Calcd for $C_{10}H_7N_3OS$ (217.25): C, 55.29; H, 3.25; N, 19.34; found: C, 55.35; H, 3.33; N, 19.32.

5.1.2. 3-Methyl-5-thioxo-5,6-dihydroimidazo[1,2-*c*]-quinazolin-2-one (3b). Method A: from alanine (285 mg, 3.2 mmol), 2-(isothiocyanato)benzonitrile (500 mg, 3.2 mmol), TEA (1 ml) in ethanol/water (50 ml/5 ml), and 15 h reflux. Yield: 330 mg (45%). Method B: from ethyl alaninate hydrochloride (0.98 g, 6.4 mmol) and 2-(isothiocyanato)-benzonitrile (1.000 g, 6.4 mmol). Yield: 0.300 g (21%), yellow prisms (ethanol), mp 314 °C (decomp.). IR (KBr): $\tilde{\nu}$=3016, 2982, 2938, 2912 (w), 1743, 1633, 1624 (s), 1600 (m), 1560, 1536, 1533, 1530, 1527, 1478 (s), 1459 (m), 1405, 1351, 1331, 1304 (s), 1284 (m), 1252, 1213, 1161, 1152 (s) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ=1.69 (d, J=7.1 Hz, 3H, CH_3), 4.57 (q, J=7.1 Hz, 1H, 3-H), 7.41–8.09 (m, 4H, Ar), 13.24 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=14.9 (CH_3), 59.7 (C-3), 111.2 (C), 115.9, 125.0, 127.4, 137.0 (CH), 139.6, 168.0, 168.5 (C), 188.4 (C=O). MS (EI, 70 eV): *m/z* (%)=232 (16), 231 (M^+, 100), 216 (17), 198 (39), 171 (22), 161 (20), 160 (18), 143 (24), 102 (18). UV–vis (CH_3CN): λ_{max} (log ε)=251 (4.18), 268 (4.42), 295 (4.49), 352 (3.60). Anal. Calcd for

$C_{11}H_9N_3OS$ (231.28): C, 57.13; H, 3.92; N, 18.17; found: C, 57.02; H, 4.12; N, 17.73.

5.1.3. 3-Ethyl-5-thioxo-5,6-dihydroimidazo[1,2-*c*]quinazolin-2-one (3c). Method B: from methyl 2-aminobutyrate hydrochloride (0.49 g, 3.2 mmol) and 2-(isothiocyanato)-benzonitrile (0.500 g, 3.2 mmol). Yield: 0.15 g (20%), colorless prisms (ethanol), mp 260–264 °C (decomp.). IR (KBr): $\tilde{\nu}$=3075, 3017 (w), 2965, 2938, 2918, 2879 (m), 1741, 1624 (s), 1602 (m), 1526, 1477 (s), 1465 (m), 1405 (s), 1351, 1338 (m), 1280 (s), 1257 (m), 1234 (w), 1210 (s), 1154 (m), 1078 (w) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=0.67 (t, J=7.4 Hz, 3H, CH_3), 2.11 (m, 1H, CH_2), 2.71 (m, 1H, CH_2), 4.64 (dd, J=6.3, 2.7 Hz, 1H, 3-H), 7.43–7.48 (m, 2H, Ar), 7.85–8.09 (m, 2H, Ar), 13.20 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=6.6 (CH_3), 21.0 (CH_2), 64.4 (C-3), 110.8 (C), 116.0, 125.1, 127.5, 137.1 (CH), 139.7, 168.5, 168.8 (C), 187.6 (C=O). MS (EI, 70 eV): *m*/*z* (%)=246 (16), 245 (M^+, 100), 230 ([M−CH_3]$^+$, 50), 217 (71), 216 ([M−C_2H_5]$^+$, 32), 212 (42), 204 (20), 203 (27), 171 (22), 161 (51), 145 (10), 144 (13), 143 (26), 134 (13), 129 (17), 102 (20). UV–vis (CH_3CN): λ_{max} (log ε)=209 (4.38), 252 (4.20), 269 (4.44), 295 (4.51), 352 (3.63). Anal. Calcd for $C_{12}H_{11}N_3OS$ (245.30): C, 58.76; H, 4.52; N, 17.13; found: C, 58.84; H, 4.91; N, 17.07.

5.1.4. 3-Isopropyl-5-thioxo-5,6-dihydroimidazo[1,2-*c*]-quinazolin-2-one (3d). Method A: from valine (375 mg, 3.2 mmol), 2-(isothiocyanato)benzonitrile (500 mg, 3.2 mmol), TEA (1 ml) in ethanol/water (50 ml/5 ml), and 16 h reflux. Yield: 357 mg (43%). Method B: from ethyl valinate hydrochloride (1.16 g) and 2-(isothiocyanato)benzonitrile (1.000 g, 6.4 mmol). Yield: 1.28 g (77%), colorless prisms (isopropanol), mp 278–288 °C (decomp.). IR (KBr): $\tilde{\nu}$=3171, 3113, 3079, 3027, 2968 (m), 1733, 1627, 1557, 1529, 1476 (s), 1413 (m), 1348 (s), 1295 (m), 1260, 1207, 1149 (s), 1067, 969, 762 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=0.63 (d, J=6.8 Hz, 3H, CH_3), 1.20 (d, J=7.1 Hz, 3H, CH_3), 3.34–3.38 (m, 1H, C*H*(CH_3)$_2$), 4.51 (d, J=3.3 Hz, 1H, 3-H), 7.41–7.48 (m, 2H, Ar), 7.84–8.07 (m, 2H, Ar), 13.25 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=14.9 (CH_3), 16.9 (CH_3), 25.9 (*C*H(CH_3)$_2$), 67.9 (C-3), 110.9 (C), 116.1, 125.2, 127.6, 137.1 (CH), 139.7, 168.51, 168.52 (C), 186.5 (C=O). MS (EI, 70 eV): *m*/*z* (%)=260 (18), 259 (M^+, 100), 244 (38), 226 (23), 218 (11), 217 (70), 216 (55), 204 (36), 203 (82), 178 (36), 177 (15), 171 (11), 162 (25), 161 (59), 160 (10), 145 (19), 144 (15), 134 (14), 129 (15), 102 (25), 39 (10). UV–vis (CH_3CN): λ_{max} (log ε)=210 (4.52), 248 (4.20), 253 (4.21), 269 (4.44), 296 (4.51), 352 (3.63). Anal. Calcd for $C_{13}H_{13}N_3OS$ (259.33): C, 60.21; H, 5.05; N, 16.20; found: C, 60.61; H, 5.48; N, 16.46.

5.1.5. 3-Isobutyl-5-thioxo-5,6-dihydroimidazo[1,2-*c*]-quinazolin-2-one (3e). Method B: from methyl leucinate hydrochloride (1.16 g, 6.4 mmol) and 2-(isothiocyanato)-benzonitrile (1 g, 6.4 mmol). Yield: 1.51 g (86%), colorless prisms (isopropanol), mp 250–264 °C (decomp.). IR (KBr): $\tilde{\nu}$=3176, 3108, 3022 (w), 2960 (m), 1746, 1627 (s), 1601 (m), 1550, 1520, 1474 (s), 1402, 1346, 1334, 1221, 1195 (m), 1151 (s) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=0.82 (d, J=6.7 Hz, 3H, CH_3), 0.89 (d, J=6.5 Hz, 3H, CH_3), 1.86 (m, 1H, C*H*(CH_3)$_2$), 2.10–2.26 (m, 2H, CH_2), 4.62 (dd, J=8.2, 3.4 Hz, 1H, 3-H), 7.42–7.47 (m, 2H, Ar), 7.84–8.09 (m, 2H, Ar), 13.25 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=21.8, 23.21 (CH_3), 23.22 (CH), 36.1 (CH_2), 62.4 (C-3), 110.9 (C), 115.9, 125.1, 127.4, 137.0 (CH), 139.6, 168.2, 168.5 (C), 187.9 (C=O). MS (EI, 70 eV): *m*/*z* (%)=273 (M^+, 5), 230 (34), 217 (100), 161 (22), 102 (11), 71 (13). UV–vis (CH_3CN): λ_{max} (log ε)=247 (4.21), 252 (4.21), 269 (4.44), 296 (4.50), 353 (3.63). Anal. Calcd for $C_{14}H_{15}N_3OS$ (273.36): C, 61.51; H, 5.53; N, 15.37; found: C, 61.47; H, 5.70; N, 15.47.

5.1.6. 3-(2-Cyclohexylethyl)-5-thioxo-5,6-dihydroimidazo[1,2-*c*]quinazolin-2-one (3f). Method B: from ethyl 2-amino-4-cyclohexylbutyrate hydrochloride (1.60 g) and 2-(isothiocyanato)benzonitrile (1.000 g, 6.4 mmol). Yield: 1.69 g (81%), colorless prisms (ethanol), mp 278–295 °C (decomp.). IR (KBr): $\tilde{\nu}$=3105, 3016 (w), 2921, 2850, 1752, 1629, 1624 (s), 1602 (m), 1527, 1478 (s), 1449 (m), 1405, 1350 (s), 1336, 1289, 1264 (m), 1215, 1199 (s), 1153, 1072, 756 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=0.78–1.16 (m, 8H, CH_2), 1.59–1.63 (m, 5H, 2CH_2, CH), 2.11 (m, 1H, CH_2 ethyl), 2.65 (m, 1H, CH_2 ethyl), 4.63 (dd, J=6.5, 2.7 Hz, 1H, 3-H), 7.42–7.48 (m, 2H, Ar), 7.85–8.08 (m, 2H, Ar), 13.25 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=25.1, 25.6, 25.6, 25.9, 29.2, 32.4, 32.6 (CH_2), 36.6 (CH), 63.8 (C-3), 110.8 (C), 116.0, 125.1, 127.4, 137.1 (CH), 139.6, 168.5, 168.6 (C), 187.7 (C=O). MS (EI, 70 eV): *m*/*z* (%)=327 (M^+, 25), 295 (21), 294 (100), 232 (12), 230 (44), 219 (13), 218 (24), 217 (96), 204 (21), 203 (21), 198 (12), 178 (13), 161 (26), 55 (17), 41 (20). UV–vis (CH_3CN): λ_{max} (log ε)=247 (4.22), 252 (4.22), 269 (4.44), 295 (4.50), 352 (3.64). Anal. Calcd for $C_{18}H_{21}N_3OS$ (327.45): C, 66.03; H, 6.46; N, 12.83; found: C, 66.22; H, 6.45; N, 12.45.

5.1.7. 3-Benzyl-5-thioxo-5,6-dihydroimidazo[1,2-*c*]-quinazolin-2-one (3g). Method B: from methyl phenyl alaninate hydrochloride (1.38 g, 6.4 mmol) and 2-(isothiocyanato)benzonitrile (1.000 g, 6.4 mmol). Yield: 0.68 g (35%), yellow prisms (ethanol), mp 246–252 °C (decomp.). IR (KBr): $\tilde{\nu}$=3185, 3145, 3111, 3095, 3071, 3027, 2934 (w), 1736, 1624, 1550, 1521, 1478, 1404, 1342, 1216 (s), 1153 cm^{-1}. The atom numbering for NMR signal assignment is given in Figure 1. ^1H NMR (DMSO-d_6, 500 MHz): δ=3.28 (dd, $^2J_{CH_{2(a)},CH_{2(b)}}$=13.6 Hz, $^3J_{3,CH_{2(b)}}$= 2.5 Hz, 1H, $CH_{2(b)}$), 4.15 (dd, $^2J_{CH_{2(a)},CH_{2(b)}}$=13.6 Hz, $^3J_{3,CH_{2(a)}}$=6.3 Hz, 1H, $CH_{2(a)}$), 4.89 (dd, $^3J_{3,CH_{2(a)}}$= 6.3 Hz, $^3J_{3,CH_{2(b)}}$=2.5 Hz, 1H, 3-H), 7.03–7.15 (m, 5H, Ph), 7.34 (ddd, $^3J_{9,10}$=8.0 Hz, $^3J_{8,9}$=7.2 Hz, $^4J_{7,9}$=1.0 Hz, 1H, H-9), 7.41 (br d, $^3J_{7,8}$=8.2 Hz, 1H, H-7), 7.81 (ddd, $^3J_{7,8}$=8.2 Hz, $^3J_{8,9}$=7.2 Hz, $^4J_{8,10}$=1.5 Hz, 1H, H-8), 7.83 (dd, $^3J_{9,10}$=8.0 Hz, $^4J_{8,10}$=1.5 Hz, 1H, H-10), 13.30 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125.8 MHz): δ=33.3 (CH_2), 64.8 (C-3), 110.7 (C-10a), 116.2 (C-7), 125.5 (C-9), 127.3 (*p*-Ph), 127.7 (C-10), 128.4 (*m*-Ph), 129.3 (*o*-Ph), 134.5 (*i*-Ph), 137.5 (C-8), 139.6 (C-6a), 168.8 (C-11), 169.1 (C=S), 187.2 (C-2). MS (EI, 70 eV): *m*/*z* (%)=308 (21), 307 (M^+, 100), 274 (17), 216 (71), 204 (20), 203 (61), 161 (20), 143 (12), 103 (19), 102 (18), 91 (31), 77 (15). UV–vis (CH_3CN): λ_{max} (log ε)=252 (4.20), 270 (4.42), 296 (4.46), 354 (3.60). Anal. Calcd for $C_{17}H_{13}N_3OS$ (307.36): C, 66.43; H, 4.26; N, 13.67; found: C, 66.19; H, 4.29; N, 13.98.

5.1.8. 3-Phenyl-5-thioxo-5,6-dihydroimidazo[1,2-*c*]quinazolin-2-one (3h). Method B: from ethyl phenyl glycinate hydrochloride (1.29 g, 6.4 mmol) and 2-(isothiocyanato)-benzonitrile (1.000 g, 6.4 mmol). Yield: 1.16 g (62%), colorless prisms (isopropanol), mp 295 °C (decomp.). IR (KBr): $\tilde{\nu}$=3164, 3109, 3073, 3026, 2962, 2956, 2922 (w), 1743, 1677, 1602, 1558, 1526, 1479 (s), 1455 (w), 1403, 1345, 1325 (m), 1296 (s), 1254, 1236 (w), 1210, 1186 (s), 1152 (s), 1061 (w) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=5.64 (s, 1H, 3-H), 7.23–7.51 (m, 7H, Ar), 7.89–8.17 (m, 2H, Ar), 13.28 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=67.2 (C-3), 111.0 (C), 116.0, 125.1, 126.5, 127.7, 127.8, 128.5 (CH), 133.4 (C), 137.3 (CH), 139.9, 168.2, 169.4 (C), 185.1 (C=O). MS (EI, 70 eV): *m/z* (%)=294 (19), 293 (M^+, 100), 261 (13), 260 (63), 171 (15), 143 (21), 129 (10), 104 (12), 102 (15), 91 (11), 77 (13). UV–vis (CH_3CN): λ_{max} (log ε)=247 (4.28), 269 (4.47), 295 (4.50), 357 (3.66). Anal. Calcd for $C_{16}H_{11}N_3OS$ (293.35): C, 65.51; H, 3.78; N, 14.32; found: C, 65.82; H, 4.11; N, 14.34.

5.1.9. Ethyl 2-oxo-5-thioxo-2,3,5,6-tetrahydroimidazo[1,2-*c*]quinazolin-3-carboxylate (3i). Method B: from diethyl 2-aminomalonate hydrochloride (1.35 g, 6.4 mmol) and 2-(isothiocyanato)benzonitrile (1.000 g, 6.4 mmol). Yield: 1.11 g (60%), colorless prisms (isopropanol), mp 229–239 °C (decomp.). IR (KBr): $\tilde{\nu}$=3185 (m), 3121, 3081, 3022, 2982, 2959, 2934 (w), 1752, 1724, 1625 (s), 1598 (m), 1549, 1518 (s), 1479, 1409, 1345 (m), 1301 (s), 1241 (m), 1202, 1143 (s), 1078, 1023, 762, 565 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=1.22 (t, J=7.2 Hz, 3H, CH_3), 4.23 (q, J=7.2 Hz, 2H, CH_2), 5.38 (s, 1H, 3-H), 7.48–7.53 (m, 2H, Ar), 7.93–8.12 (m, 2H, Ar), 13.65 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=13.8 (CH_3), 62.1 (CH_2), 66.2 (C-3), 110.2 (C), 116.4, 125.7, 127.8, 138.1 (CH), 139.9, 162.4, 167.7 (C), 169.1, 179.1 (C=O). MS (EI, 70 eV): *m/z* (%)=290 (17), 289 (M^+, 100), 243 ([M−C_2H_6O]$^+$, 31), 217 (41), 216 ([M−$COOC_2H_5$]$^+$, 93), 215 (39), 171 (14), 160 (28), 143 (15), 134 (13), 129 (18), 103 (13), 102 (57), 90 (16), 76 (31), 65 (11), 64 (12). UV–vis (CH_3CN): λ_{max} (log ε)=209 (4.29), 247 (4.18), 269 (4.50), 294 (4.46), 358 (3.62). Anal. Calcd for $C_{13}H_{11}N_3O_3S$ (289.31): C, 53.97; H, 3.83; N, 14.52; found: C, 54.02; H, 4.26; N, 14.64.

5.1.10. Benzyl (2-oxo-5-thioxo-2,3,5,6-tetrahydroimidazo[1,2-*c*]quinazolin-3-yl)acetate (3j). Method A: from dibenzyl aspartate (714 mg, 3.2 mmol), 2-(isothiocyanato)-benzonitrile (500 mg, 3.2 mmol), TEA (1 ml) in ethanol/water (50 ml/5 ml), and 15 h reflux. Yield: 350 mg (30%). Method B: from dibenzyl aspartate toluenesulfonate (3.10 g, 6.4 mmol) and 2-(isothiocyanato)benzonitrile (1.000 g, 6.4 mmol). Yield: 1.97 g (84%), colorless platelets (ethanol), mp 233–234 °C (decomp.). ^1H NMR (DMSO-d_6, 300 MHz): δ=3.35–3.52 (m, 1H, CH_2COO), 3.90 (m, J=17.3, 5.9 Hz, 1H, CH_2COO), 4.83 (m, J=5.9, 3.3 Hz, 1H, 3-H), 4.95–5.07 (q(AB), J=12.4 Hz, 2H, OCH_2), 7.22–7.25 (m, 5H, phenyl), 7.43–7.48 (m, 2H, CH), 7.85–8.05 (m, 2H, CH), 13.26 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=32.9 (CH_2), 60.0 (C-3), 65.9 (OCH_2), 111.0 (C), 116.0, 125.2, 127.5, 127.7, 127.9, 128.2 (Ar–H), 135.4 (C), 137.1 (Ar–H), 139.5, 168.6, 168.8 (C), 169.0, 186.6 (C=O). IR (KBr): $\tilde{\nu}$=3175, 3116, 3082, 3031, 2979, 2953 (w), 1744, 1625 (s), 1603 (m), 1558, 1554, 1526 (s), 1479, 1406, 1355 (m), 1333 (s), 1283, 1254 (m), 1220, 1176 (s), 1146 (m), 1073 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%)=365 (M^+, 17), 274 (70), 260 (14), 259 (93), 257 (13), 256 (49), 232 (11), 231 (56), 230 (94), 229 (13), 228 (14), 217 (40), 204 (11), 203 (12), 202 (13), 198 (11), 161 (42), 143 (10), 102 (18), 91 (100), 71 (21), 66 (19), 43 (11). UV–vis (CH_3CN): λ_{max} (log ε)=269 (4.45), 295 (4.48), 354 (4.44). Anal. Calcd for $C_{19}H_{15}N_3O_3S$ (365.41): C, 62.45; H, 4.14; N, 11.50; found: C, 62.38; H, 4.29; N, 11.28.

5.1.11. 3-(2-Hydroxyethyl)-5-thioxo-5,6-dihydroimidazo[1,2-*c*]quinazolin-2-one (3k). Method B: from α-amino-γ-butyrolactone hydrobromide (1.16 g, 6.4 mmol) and 2-(isothiocyanato)benzonitrile (1.000 g, 6.4 mmol). Yield: 1.69 g (81%), colorless prisms (ethanol), mp 263–265 °C (decomp.). IR (KBr): $\tilde{\nu}$=3410, 3254, 3018 (w), 2962, 2940, 2918, 2860 (m), 1717, 1624 (s), 1602 (m), 1533 (s), 1480, 1426, 1405 (m), 1329 (s), 1286, 1238, 1221, 1201, 1156, 1084, 752 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=2.27–2.38 (m, 1H, CH_2), 2.70–2.81 (m, 1H, CH_2), 3.36–3.44 (m, 1H, CH_2), 4.47–4.50 (m, 1H, CH_2), 4.64 (dd, J=7.1, 2.6 Hz, 1H, 3-H), 7.41–7.47 (m, 2H, Ar–H), 7.83–8.08 (m, 2H, Ar–H), 13.18 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=30.6, 56.0 (CH_2), 61.7 (C-3), 111.0 (C), 115.8, 125.0, 127.5, 136.9 (CH), 139.5, 168.4, 168.7 (C), 187.8 (C=O). MS (EI, 70 eV): *m/z* (%)=261 ([M]$^+$, 1), 243 ([M−H_2O]$^+$, 4), 230 ([M−CH_2OH]$^+$, 6), 217 ([M−C_2H_3OH]$^+$, 25), 143 (2), 129 (3). UV–vis (CH_3CN): λ_{max} (log ε)=207 (4.33), 231 (4.07), 248 (4.18), 251 (4.18), 269 (4.37), 295 (4.40), 349 (3.64). Anal. Calcd for $C_{12}H_{11}N_3O_2S$ (261.30): C, 55.16; H, 4.24; N, 16.08; found: C, 55.35; H, 4.48; N, 15.79.

5.1.12. 4-Methyl-6-thioxo-3,4,5,6-tetrahydropyrimidino[2,3-*c*]quinazolin-2-one (4). Method B: from ethyl 3-aminobutyrate hydrochloride (0.84 g, 6.4 mmol) and 2-(isothiocyanato)benzonitrile (1.000 g, 6.4 mmol). Yield: 0.18 g (11%), colorless prisms (ethanol), mp 290–307 °C (decomp.). IR (KBr): $\tilde{\nu}$=3243, 3209, 3129, 3073, 3033, 2978, 2962 (w), 1687, 1621, 1606, 1549, 1528, 1510, 1486 (s), 1447 (m), 1403 (s), 1311, 1278 (m), 1261, 1175, 1155 (s), 1125, 1095 (m), 1081 (w), 1005 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=1.26 (d, J=6.6 Hz, 3H, CH_3), 2.45 (dd, J=15.0, 1.6 Hz, 1H, CH_2), 2.93 (dd, J=15.0, 6.6 Hz, 1H, CH_2), 5.78 (dq, J=6.6, 1.6 Hz, 1H, C*H*CH_3), 7.34–7.40 (m, 2H, Ar), 7.74–7.79 (m, 1H, Ar), 8.17–8.20 (m, 1H, Ar), 13.25 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=15.8 (CH_3), 35.8 (CH_2), 51.5 (*C*HCH_3), 115.5, 124.9 (CH), 127.0 (C), 127.2, 135.7 (CH), 138.6, 153.2, 172.2 (C), 175.8 (C=O). MS (EI, 70 eV): *m/z* (%)=246 (12), 245 ([M]$^+$, 87), 230 ([M−CH_3]$^+$, 7), 212 (21), 204 (30), 203 (100), 161 (30), 145 (26), 144 (14), 143 (12). UV–vis (CH_3CN): λ_{max} (log ε)=209 (4.44), 231 (3.82), 252 (4.14), 271 (4.35), 298 (4.54), 349 (3.74). Anal. Calcd for $C_{12}H_{11}N_3OS$ (245.30): C, 58.76; H, 4.52; N, 17.13; found: C, 58.82; H, 4.88; N, 17.53.

5.1.13. 2-(4,4-Dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-benzonitrile (5a). Method B: from methyl 2-amino-isobutyrate hydrochloride (0.49 g, 3.2 mmol) and 2-(isothiocyanato)benzonitrile (0.50 g, 3.2 mmol). Yield: 0.31 g (39%), colorless prisms (ethanol), mp 260–264 °C

(decomp.). IR (KBr): $\tilde{\nu}$=3304 (s), 3114 (w), 2237 (m), 1764 (s), 1600 (w), 1517, 1460 (s), 1402 (m), 1278, 1183 (s), 1131, 766 (m), 634 (w), 599 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=1.46 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 7.65–8.06 (m, 4H, Ar), 10.91 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=22.9 (CH_3), 24.1 (CH_3), 61.4 ($C(CH_3)_2$), 112.4 (CN), 115.4 (C), 130.2, 131.2, 133.1, 134.1 (CH), 135.7, 176.4 (C), 179.2 (C=O). MS (EI, 70 eV): *m/z* (%)=246 (12), 245 (M^+, 100), 161 (48), 160 (80), 143 (8), 129 (11), 115 (10), 102 (24), 100 (16). Anal. Calcd for $C_{12}H_{11}N_3OS$ (245.30): C, 58.76; H, 4.52; N, 17.13; found: C, 58.71; H, 4.62; N, 17.18.

5.1.14. 3,3-Dimethyl-5-thioxo-5,6-dihydroimidazo[1,2-*c*]-quinazolin-2-one (6a). Compound **5a** (100 mg, 0.4 mmol) was dissolved in a mixture of an aqueous solution of sodium hydroxide (2%, 30 ml) and isopropanol (2 ml). The mixture was stirred for 12 h at room temperature, diluted with water, and acidified with concd hydrochloric acid. The solid precipitate was collected and dried. Yield: 65 mg (65%), colorless prisms (ethanol), mp 320–327 °C (decomp.). IR (KBr): $\tilde{\nu}$=3437 (w), 3246 (s), 3124, 2978 (w), 1729, 1627, 1601, 1543, 1510 (s), 1474, 1392, 1374, 1348 (m), 1303 (s), 1273, 1245 (m), 1210 (s), 1157 (m), 1135 (s), 1100 (m) cm^{-1}. The atom numbering for NMR signal assignment is given in Figure 2. ^1H NMR (DMSO-d_6, 500 MHz): δ=1.74 (s, 6H, 2Me), 7.42 (dt, $^3J_{9,10}$=8.0 Hz, $^3J_{8,9}$=7.2 Hz, $^4J_{7,9}$= 1.0 Hz, 1H, H-9), 7.43 (d, $^3J_{7,8}$=8.2 Hz, 1H, H-7), 7.84 (ddd, $^3J_{7,8}$=8.2 Hz, $^3J_{8,9}$=7.2 Hz, $^4J_{8,10}$=1.5 Hz, 1H, H-8), 8.11 (dd, $^3J_{9,10}$=8.0 Hz, $^4J_{8,10}$=1.5 Hz, 1H, H-10), 13.13 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125.8 MHz): δ=21.1 (2Me), 67.4 (C-3), 111.7 (C-10a), 115.9 (C-7), 125.3 (C-9), 128.0 (C-10), 137.3 (C-8), 139.8 (C-6a), 168.1 (C-11), 169.0 (C=S), 191.6 (C-2). MS (EI, 70 eV): *m/z* (%)=246 (12), 245 (M^+, 100), 230 ([M−CH_3]$^+$, 32), 213 (13), 212 (84), 204 (14), 171 (39), 161 (31), 160 (11), 143 (32), 102 (21). UV–vis (CH_3CN): λ_{max} (log ε)=209 (4.44), 252 (4.18), 269 (4.40), 299 (4.51), 354 (3.60). $C_{12}H_{11}N_3OS$ (245.30).

5.1.15. 3-(2-Cyanophenyl)-2-thioxo-1,3-diazaspiro[4,5]-decan-4-one (5b). Method A: from 1-aminocyclohexanoic acid (460 mg, 3.2 mmol), 2-(isothiocyanato)benzonitrile (500 mg, 3.2 mmol), TEA (320 mg) in ethanol/water (50 ml/5 ml), and 16 h reflux. Yield: 0.32 g (35%), colorless prisms (isopropanol), mp 302–312 °C (decomp.). IR (KBr): $\tilde{\nu}$=3293, 3179, 2941, 2859, 2234 (w), 1767, 1513 (s), 1457, 1401, 1262 (m), 1225 (s), 1074 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=1.38–1.83 (m, 10H, 5CH_2), 7.64–7.72 (m, 2H, Ar), 7.86–8.05 (m, 2H, Ar), 11.21 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=20.4 (2CH_2), 24.2 (CH_2), 32.0 (CH_2), 33.3 (CH_2), 64.6 (C-3), 112.5 (CN), 115.6 (C), 130.3, 131.4, 133.3, 134.2 (CH), 135.8, 175.9 (C), 179.7 (C=O). MS (EI, 70 eV): *m/z* (%)=286 (17), 285 ([M]$^+$, 100), 256 (16), 230 (53), 229 (13), 161 (52), 160 (18), 143 (12), 129 (16), 102 (22), 97 (18), 96 (11). Anal. Calcd for $C_{15}H_{15}N_3OS$ (285.37): C, 63.13; H, 5.30; N, 14.73; found: C, 62.80; H, 5.72; N, 14.35.

5.1.16. Spirocyclohexan-1,3′-2-oxo-2-thioxo-4,5-dihydroimidazo[1,2-*c*]quinazoline (6b). Compound **5b** (100 mg, 0.35 mmol) was dissolved in a mixture of an aqueous solution of sodium hydroxide (2%, 50 ml) and of isopropanol (5 ml). The solution was stirred for 12 h at room temperature, diluted with water, and acidified with concd hydrochloric acid. The solid precipitate was collected and dried. Yield: 0.40 g (40%), colorless prisms (ethanol), mp 363–370 °C (decomp.). IR (KBr): $\tilde{\nu}$=3244, 3230 (m), 2930, 2863 (w), 1724, 1626, 1544, 1517 (s), 1482, 1454, 1391, 1354, 1323 (m), 1276, 1207, 1167, 1141, 1082 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=1.24–1.29 (m, 1H, CH_2), 1.54–1.71 (m, 5H, CH_2), 2.07–2.11 (m, 2H, CH_2), 3.52–3.60 (m, 2H, CH_2), 7.37–7.42 (m, 2H, Ar), 7.80–7.84 (m, 1H, Ar), 8.06–8.09 (m, 1H, Ar), 13.06 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=19.5 (2CH_2), 23.8 (CH_2), 25.7 (2CH_2), 68.8 (C-3), 111.5, 115.7 (C), 125.0, 127.6, 130.5, 136.9 (CH), 167.5 (C=N), 168.7 (C), 190.3 (C=O). MS (EI, 70 eV): *m/z* (%)=285 ([M]$^+$, 4), 198 (13), 118 (100), 91 (38). UV–vis (CH_3CN): λ_{max} (log ε)=211 (4.36), 254 (4.14), 270 (4.34), 301 (4.47), 354 (3.57). $C_{15}H_{15}N_3OS$ (285.37).

5.1.17. 2-(4-Isopropyl-2,5-dioxoimidazolidin-1-yl)benzonitrile (7). 2-(Isocyanato)benzonitrile (1.44 g, 10.0 mmol) and ethyl valinate hydrochloride (1.81 g 10.0 mmol) were suspended in 40 ml of dry dichloromethane. A dichloromethane solution (20 ml) of TEA (1.01 g, 10.0 mmol) was dropwise added with stirring. The mixture was stirred for 10 min at 20 °C and for 1 h under reflux. The solvent was removed in vacuo and the residue was washed with water (100 ml) and dried by exposure to air. Yield of noncyclized intermediate: 2.07 g (79%), colorless solid. IR (KBr): $\tilde{\nu}$=3329 (m), 2969, 2876 (w), 2219 (w, CN), 1739 (s), 1708 (m), 1655 (s), 1608, 1582 (m), 1555 (s), 1474, 1451, 1301, 1238, 1208, 1157 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=0.91 (d, J=7.2 Hz, 3H, CH_3), 0.93 (d, J=7.1 Hz, 3H, CH_3), 1.22 (t, J=7.1 Hz, 3H, CH_3 ester), 2.07–2.13 (m, 1H, CH), 4.11–4.20 (m, 3H, CH_2 ester, CH), 7.09–7.14 (m, 1H, Ar), 7.44 (d, J=8.3 Hz, 1H, NH), 7.56–7.71 (m, 2H, Ar), 8.09–8.11 (m, 1H, Ar), 8.72 (s, 1H, NH). An isopropanol solution (100 ml) of the open-chained product (1.200 g, 4.6 mmol) and TEA (3 ml) was refluxed for 24 h. The solvent was removed in vacuo. A few drops of methanol were added to the residue to give product **7** as a precipitate, which was filtered off. Yield: 0.78 g (70%), colorless prisms (isopropanol), mp 129.0–133.0 °C (decomp.). IR (KBr): $\tilde{\nu}$=3243, 3129, 2968 (m), 2233 (w, CN), 1778 (m), 1727 (s), 1497, 1459 (m), 1415 (s), 1350, 1297, 1237, 1177 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=0.95 (d, J=6.8 Hz, 3H, CH_3), 1.09 (d, J=7.0 Hz, 3H, CH_3), 2.11–2.19 (m, 1H, CH), 4.25 (m, 1H, CH), 7.55–7.69 (m, 2H, Ar), 7.84–7.89 (m, 1H, Ar), 8.00–8.03 (m, 1H, Ar), 8.74 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=15.9 (CH_3), 18.4 (CH_3), 29.8, 61.9 (CH), 111.4 (CN), 115.8 (C), 129.5, 129.8, 133.4, 134.1 (CH), 134.3 (C), 154.8, 172.1 (C, C=O). MS (EI, 70 eV): *m/z* (%)=243 ([M]$^+$, 9), 202 (11), 201 (100), 145 (32), 144 (17). UV–vis (CH_3CN): λ_{max} (log ε)=242 (4.62), 249 (4.60), 273 (4.30), 312 (4.11), 324 (4.19). Anal. Calcd for $C_{13}H_{13}N_3O_2$ (243.26): C, 64.19; H, 5.39; N, 17.27; found: C, 64.58; H, 5.48; N, 17.14.

5.1.18. 3-Isopropyl-2,5-dioxo-5,6-dihydroimidazo[1,2-*c*]quinazoline (8). Compound **7** (0.500 g, 2.0 mmol) was dissolved in a mixture of an aqueous solution of sodium hydroxide (4%, 100 ml) and isopropanol (5 ml). The mixture was stirred over night at room temperature, diluted with water, and acidified with concd hydrochloric acid. The solid

precipitate was collected and dried. Yield: 0.34 g (68%), colorless prisms (isopropanol), mp 258–265 °C (decomp.). IR (KBr): $\tilde{\nu}$=3211, 3154 (w), 3101, 3085, 3058, 3019, 2966, 2907, 2882 (m), 1745, 1728, 1705, 1628, 1601, 1562, 1519, 1487, 1449 (s), 1353 (m), 1317 (s), 1258 (w), 1189, 1147 (m) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ=0.74 (d, J=6.9 Hz, 3H, CH_3), 1.15 (d, J=7.1 Hz, 3H, CH_3), 2.74–2.80 (m, 1H, CH), 4.39 (d, J=3.3 Hz, 1H, 3-H), 7.26–7.35 (m, 2H, Ar), 7.76–7.82 (m, 1H, Ar), 8.01–8.04 (m, 1H, Ar), 11.79 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=16.0 (CH_3), 17.0 (CH_3), 27.4 ($CH(CH_3)_2$), 64.7 (CH, C-3), 109.1 (C), 115.8, 123.3, 127.7, 136.7 (CH), 141.2, 145.6 (C), 171.9, 187.2 (C=O). MS (EI, 70 eV): m/z (%)=243 (M^+, 0.4), 228 (12), 201 (75), 188 (14), 145 (15). UV–vis (CH_3CN): λ_{max} (log ε)= 231 (4.70), 252 (3.93), 262 (3.98), 277 (3.99), 290 (3.85), 335 (3.69). Anal. Calcd for $C_{13}H_{13}N_3O_2$ (243.26): C, 64.15; H, 5.35; N, 17.28; found: C, 64.29; H, 5.37; N, 17.46.

Acknowledgements

Financial support by the state of Mecklenburg-Vorpommern (scholarship for A.B.) and by the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

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11. Crystallographic data (excluding structure factors) for the structure in this paper (**6a**) have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-603359. Copies of these 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 or via www.ccdc.cam.ac.uk/conts/retrieving.html.

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Tetrahedron 62 (2006) 7661–7666
Tetrahedron

Regioselective cycloaddition of 3-azatrienes with enamines. Synthesis of pyridines derived from β-aminoacids

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Received 2 May 2006; revised 25 May 2006; accepted 29 May 2006
Available online 21 June 2006

Abstract—Aza-Wittig reaction of *N*-vinylic phosphazenes with α,β-unsaturated aldehydes leads to the formation of 3-azatrienes through a [2+2]-cycloaddition–cycloreversion process. Subsequent, regioselective [4+2]-cycloaddition of 3-azatrienes with pyrrolidinocycloalkanone affords bicyclic dihydropyridines and pyridines in a regioselective fashion. 2-Heterodiene moiety of azatriene is involved in the formation of the six-membered ring skeleton of pyridine derivatives.

1. Introduction

Aza-Wittig reaction of *N*-vinylic phosphazenes with carbonyl compounds represents an easy method for the preparation of 2-azadienes. Therefore, *N*-vinylic phosphazenes[1] have proved to be useful building blocks for the synthesis of functionalized imine compounds such as electronically neutral-2-azadienes **I** (Fig. 1),[2] electron-poor 2-azadienes derived from aminophosphorus derivatives,[3] electron-poor 2-azadienes **II** (Fig. 1) derived from α-[4] or β-aminoacids,[5] and 3-fluoroalkyl-2-azadienes **III** (Fig. 1).[6] *N*-vinylic phosphazenes have also been used as key intermediates in the preparation of glycosides[7] and cyclic compounds[8–11] as well as in the construction of the framework of pharmacologically active alkaloids.[12]

Functionalized 2-azabutadienes have proved to be efficient key intermediates in organic synthesis for the preparation of heterocycles although the great majority of 2-azadienes studied are substituted with electron-donating groups being excellent reagents in aza-Diels–Alder (ADA) reactions with electron-poor dienophiles.[13–15]

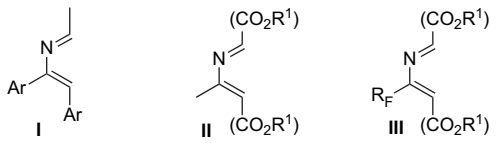
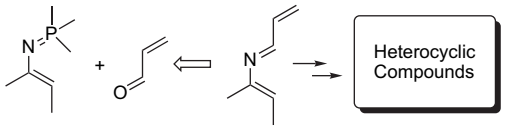


Figure 1.

In this context, we have described new methods for the preparation of nitrogen heterocyclic compounds by the use of 2-azabutadiene systems.[2,5,6] Therefore, we report here the preparation of 3-azatrienes by aza-Wittig reaction of *N*-vinylic phosphazenes with α,β-unsaturated aldehydes. Moreover, we report that 3-azatrienes can be used as key intermediates in the synthesis of dihydropyridine and pyridine compounds derived from β-aminoacids (Scheme 1) through [4+2] cycloaddition processes. It is known that 3-azatriene systems give heterocyclic compounds through electrocyclic ring closure.[16,17] However, as far as we know no examples of aza-Diels–Alder (ADA) reaction of 3-azatrienes have been reported.



Scheme 1.

2. Results and discussion

2.1. Aza-Wittig reaction of phosphazenes 1 with α,β-unsaturated aldehydes 2. Synthesis of 3-azatrienes

Reaction of *N*-vinylic phosphazenes **1a** (R=Ph, R^1=Et, R^2=H) and **1b** (R=Ph, R^1=Me, R^2=CO_2Me) with cinnamaldehyde **2a** (R^3=H, R^4=Ph), crotonaldehyde **2b** (R^3=H, R^4=Me) or methacrolein **2c** (R^3=Me, R^4=H) at room temperature, gave the [2+2]-aza-Wittig[18] products **3a–d** in excellent yields (Scheme 2, Table 1, entries 1–4). However, these azatrienes **3** were unstable during distillation

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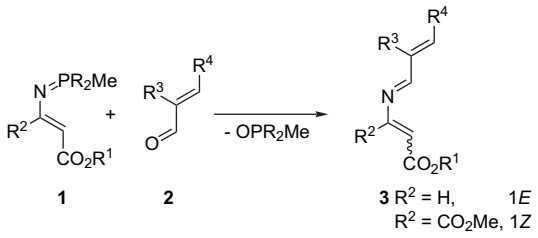
doi:10.1016/j.tet.2006.05.073

Table 1. Azatrienes **3** obtained

Entry	Starting materials		Product	R^1	R^2	R^3	R^4	Reaction conditions		Yield (%)[a]
	Phosphazene	Aldehyde						*T* (°C)	Time (h)	
1	**1a/1c**	**2a**	**3a**	Et	H	H	Ph	rt	7/1	75/98
2	**1a/1c**	**2b**	**3b**	Et	H	H	Me	rt	24/5	65/90
3	**1a/1c**	**2c**	**3c**	Et	H	Me	H	rt	30/4	90/62
4	**1b**	**2a**	**3d**	Me	CO_2Me	H	Ph	70	30	85

[a] Yield calculated by ^1H NMR.

and/or chromatography and were used without purification.[19] The use of conjugated phosphazenes **1c** derived from trimethylphosphine (R=Me, R^1=Et, R^2=H) was more favorable because the formation of azatrienes **3** took place in shorter periods of time and the elimination of trimethylphosphine oxide from the reaction mixture was easier (Table 1, entries 1–3). Next, we explored the synthetic utility of these 3-azatrienes **3** and whether new azatrienes **3** could be used as versatile tools for the construction of nitrogen-containing heterocycles through their cycloaddition reaction.

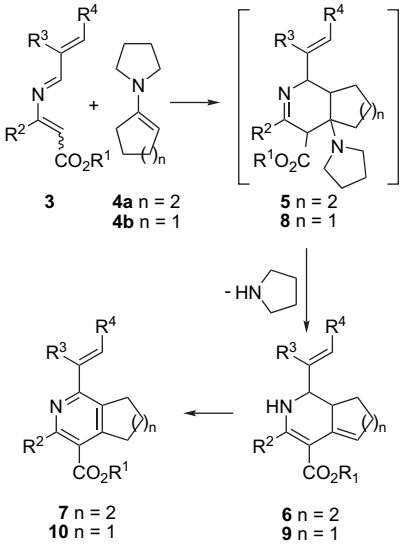


Scheme 2.

2.2. Cycloaddition reaction of azatrienes 3 with enamines

The presence of a third double bond in 3-azatrienes conjugated with 2-azadiene may have influence in the reactivity of the new systems. As it has been reported previously, 3-azatrienes through a thermal electrocyclic ring closure afford the corresponding heterocyclic compounds.[16,17,20] Therefore, we studied the synthetic usefulness of these new azatrienes **3** as heterodienes for heterocyclic synthesis.[13,20] At this point, it is noteworthy that these substrates would be an interesting starting material for the preparation of pipecolic acid derivatives.[21]

We then turned our attention to study the cycloaddition reaction of electron-deficient 3-azatrienes **3** with enamines (Scheme 3). Pyrrolidinecyclohexanone **4a** (*n*=2) reacted with heterodienes **3a**,**b** (R^2=H) at room temperature affording 1,2,6,7,8,8a-hexahydroisoquinoline compounds **6** (Table 2, entries 1 and 2). Spectral data were in agreement with the enamine structure of a bicyclic heterocycle.



Scheme 3.

The formation of these hexahydroisoquinolines **6** can be explained through a [4+2] cycloaddition reaction of 3-azatriene **3** with enamine **4a**, formation of a cycloadduct **5** followed by the loss of pyrrolidine and prototropic tautomerization under the reaction conditions. Oxidation of bicyclic heterocycles **6** with quinone or $Mn(AcO)_3$[22] led to the formation of 5,6,7,8-tetrahydroisoquinoline **7** derived from β-aminoacids (Table 2, entries 3 and 4).

Then, we tried to extend the process to other enamine, pyrrolidinecyclopentanone **4b**. Thus, 3-azatriene **3c** (R^2=H) reacted with *N*-cyclopent-1-enylpyrrolidine **4b** (*n*=1) at room temperature until disappearance of starting material, affording bicyclic compound **9** (Table 2, entry 5). Similarly,

Table 2. Bicyclic heterocycles **5**–**8** obtained

Entry	Starting material	Products	R^1	R^2	R^3	R^4	Reaction conditions		Yield (%)[a]
							T (°C)	Time (h)	
1	**3a**	**6a**	Et	H	H	Ph	rt	18	42
2	**3b**	**6b**	Et	H	H	Me	rt	18	42
3	**6a**	**7a**	Et	H	H	H	100	24	84[b]
4	**6b**	**7b**	Et	H	H	Me	rt	0.5	83[c]
5	**3c**	**9**	Et	H	Me	H	rt	14	35
6	**3d**	**10**	Me	CO_2Me	H	Ph	rt	20	40

[a] Purified by chromatography.
[b] Obtained by oxidation with *p*-benzoquinone.
[c] Obtained by oxidation with $Mn(AcO)_3$.

3-methoxycarbonyl-substituted azatriene **3d** also reacted with pyrrolidinecyclopentanone **4b** (n=1). However in this case, completely aromatized bicyclic pyridine **10** (Table 2, entry 6) was obtained. Formation of compounds **9** and **10** could be explained, as before, by formation of a [4+2]-cycloadduct **8** followed by the loss of pyrrolidine to give dihydropyridine **9** and oxidation to yield bicyclic compound **10** (Scheme 3).

In summary, we conclude that aza-Wittig reaction of *N*-vinylic phosphazenes with the carbonyl group of unsaturated aldehydes gives 3-azatrienes **3**. Hetero-Diels–Alder reaction of azatrienes **3** with enamines leads to the formation of bicyclic pyridine compounds derived from β-aminoacids. It is worth noting that pyridine compounds derived from β-aminoacids are useful heterocycles not only for their biological activities[23] but also because the pyridine nucleus is a structural unit appearing in many natural products.[24]

3. Experimental

3.1. General

Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with silica gel 60 F_{254} and aluminum oxide N/UV_{254} plates. Visualization was accomplished by UV light. Flash chromatography was carried out using silica gel 60 (230–400 mesh ASTM) and aluminum oxide 90 active neutre (70–230 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^{1}H NMR (300 MHz, 250 MHz), ^{13}C NMR (75 MHz), and ^{31}P NMR (120 MHz) spectra were recorded on a Varian VXR 300 MHz spectrometer using $CDCl_3$ or CD_3OD solutions with TMS as an internal reference (δ=0.00 ppm) for ^{1}H and ^{13}C NMR spectra, and phosphoric acid (85%) (δ=0.0 ppm) for ^{31}P NMR spectra. Chemical shifts (δ) are reported in parts per million. Coupling constants (J) are reported in hertz. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on a Hewlett Packard 5971 or 5973 spectrometer. Data are reported in the form m/z (intensity relative to base = 100). Infrared spectra (IR) were taken on a Nicolet IRFT Magna 550 spectrometer, and were obtained as solids in KBr or as neat oils. Peaks are reported in cm^{-1}. Elemental analyses were performed in a LECO CHNS-932 apparatus. Phosphazenes **1a** and **1b** were prepared according to literature processes.[5]

3.2. 4-(Ethoxycarbonyl)-1,1,1-trimethyl-2-aza-1-λ^5-phosphabuta-1,3-diene (1c)

A solution of 0.705 g (5 mmol) of ethyl 3-azidoacrylate in anhydrous CH_2Cl_2 (3 mL) was added dropwise to a 0 °C solution of 5 mL (5 mmol) of trimethylphosphine (1.0 M solution in hexane) in anhydrous CH_2Cl_2 (8 mL), and the mixture was stirred for 30 min at 0 °C. Phosphazene **1c** is unstable during distillation and/or chromatography and was used without purification for the following reactions. It was obtained as a 85:15 diastereomeric mixture of *E*/*Z* isomers of **1c**. ^{1}H NMR (300 MHz, $CDCl_3$) of crude reaction mixture δ 1.14–1.22 (m, 6H), 1.61 (d, $^2J_{PH}$=12.8 Hz, 9H) for isomer *E*, 1.81 (d, $^2J_{PH}$=12.8 Hz, 9H) for isomer *Z*, 3.98–4.09 (m, 4H), 4.59 (dd, $^3J_{HH}$=7.6 Hz, $^4J_{PH}$=3.1 Hz, 1H) for isomer *Z*, 4.99 (d, $^3J_{PH}$=12.4 Hz, 1H) for isomer *E*, 6.97 (dd, $^3J_{HH}$=7.6 Hz, $^3J_{PH}$=35.5 Hz, 1H) for isomer *Z*, 7.86 (dd, $^3J_{HH}$=12.4 Hz, $^3J_{PH}$=33.3 Hz, 1H) for isomer *E* ppm; ^{13}C NMR (75 MHz, $CDCl_3$) of crude reaction mixture δ 13.4 (d, $^2J_{PC}$=66 Hz) for isomer *Z*, 13.5 (d, $^2J_{PC}$=66 Hz) for isomer *E*, 14.3 for isomer *E*, 14.5 for isomer *Z*, 56.7 for isomer *E*, 57.2 for isomer *Z*, 92.2 (d, $^3J_{PC}$=27 Hz) for isomer *E*, 95.5 (d, $^3J_{PC}$=29 Hz) for isomer *Z*, 153.7 (d, $^2J_{PC}$=5 Hz) for isomer *Z*, 156.2 (d, $^2J_{PC}$=4 Hz) for isomer *E*, 166.1 for isomer *E*, 169.4 for isomer *Z* ppm; ^{31}P NMR (120 MHz, $CDCl_3$) δ 27.41 for isomer *Z*, 28.12 for isomer *E* ppm.

3.3. General procedure A for the preparation of 3-azatrienes 3

Unsaturated aldehyde **2** (4 mmol) was added to a 0–10 °C solution of phosphazene **1** (4 mmol) in $CHCl_3$ (10 mL) under N_2, and the mixture was stirred at room temperature or warmed at 70 °C until ^{1}H NMR indicated the disappearance of phosphazene. 3-Azatrienes **3** are unstable during distillation and/or chromatography and were used without purification for the following reactions.

3.4. General procedure B for the preparation of 3-azatrienes 3

Unsaturated aldehyde **2** (4 mmol) was added to a 0–10 °C solution of phosphazene **1** (4 mmol), prepared 'in situ' in $CHCl_3$ (10 mL) under N_2, and the mixture was stirred at room temperature until ^{1}H NMR indicated the disappearance of phosphazene. 3-Azatrienes **3** are unstable during distillation and/or chromatography and were used without purification for the following reactions.

3.4.1. 1-(Ethoxycarbonyl)-6-phenyl-3-azahexa-1,3,5-triene (3a). The general procedure A was followed using phosphazene **1a** (1.252 g, 4 mmol) and cinnamaldehyde **2a** (0.504 mL, 4 mmol) (room temperature/7 h). ^{1}H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**3a**+Ph_2MePO) δ 1.25 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.96 (d, $^2J_{PH}$=13.0 Hz, 3H), 4.17 (q, $^3J_{HH}$=7.2 Hz, 2H), 6.08 (d, $^3J_{HH}$=13.1 Hz, 1H), 6.98 (dd, $^3J_{HH}$=9.0, 16.0 Hz, 1H), 7.14 (d, $^3J_{HH}$=16.0 Hz, 1H), 7.31–7.70 (m, 15H), 7.77 (d, $^3J_{HH}$=13.1 Hz, 1H), 8.14 (d, $^3J_{HH}$=9.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) of crude reaction mixture (**3a**+Ph_2MePO) δ 14.2, 16.5 (d, $^1J_{PC}$=74.0 Hz), 60.3, 118.6, 126.3–131.7, 147.1, 152.6, 155.5, 167.5, 169.4 ppm. The general procedure B was followed using phosphazene **1c** (4 mmol), prepared 'in situ', and 0.504 mL (4 mmol) of cinnamaldehyde **2a** (room temperature/1 h). ^{1}H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**3a**+Me_3PO) δ 1.25 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.47 (d, $^2J_{PH}$=12.8 Hz, 9H), 4.17 (q, $^3J_{HH}$=7.2 Hz, 2H), 6.08 (d, $^3J_{HH}$=13.1 Hz, 1H), 6.98 (dd, $^3J_{HH}$=9.0, 16.0 Hz, 1H), 7.14 (d, $^3J_{HH}$=16.0 Hz, 1H), 7.30–7.51 (m, 5H), 7.77 (d, $^3J_{HH}$=13.1 Hz, 1H), 8.14 (d, $^3J_{HH}$=9.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$)

of crude reaction mixture (**3a**+Me_3PO) δ 14.2, 17.8 (d, $^1J_{PC}$=70.0 Hz), 60.3, 118.6, 126.3–131.7, 147.1, 152.6, 155.5, 167.5, 169.4 ppm.

3.4.2. 1-(Ethoxycarbonyl)-3-azahepta-1,3,5-triene (3b). The general procedure A was followed using phosphazene **1a** (1.252 g, 4 mmol) and crotonaldehyde **2b** (0.328 mL, 4 mmol) (room temperature/24 h). ^{1}H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**3b**+Ph_2MePO) δ 1.23 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.92 (dd, $^4J_{HH}$=1.2 Hz, $^3J_{HH}$=6.7 Hz, 3H), 1.96 (d, $^2J_{PH}$=13.0 Hz, 3H), 4.15 (q, $^3J_{HH}$=7.2 Hz, 2H), 6.00 (d, $^3J_{HH}$=13.1 Hz, 1H), 6.33 (ddd, $^4J_{HH}$= 1.2 Hz, $^3J_{HH}$=15.3, 9.0 Hz, 1H), 6.48 (dq, $^3J_{HH}$=6.7, 15.3 Hz, 1H), 7.36–7.74 (m, 11H), 7.95 (d, $^3J_{HH}$=9.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) of crude reaction mixture (**3b**+Ph_2MePO) δ 14.0, 16.5 (d, $^1J_{PC}$=74.0 Hz), 18.8, 60.0, 117.8, 128.3–134.5, 147.4, 153.7, 155.5, 166.8, 169.4 ppm. The general procedure B was followed using phosphazene **1c** (4 mmol), prepared 'in situ', and 0.328 mL (4 mmol) of crotonaldehyde **2b** (room temperature/5 h). ^{1}H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**3b**+Me_3PO) δ 1.23 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.47 (d, $^2J_{PH}$=12.8 Hz, 9H), 1.92 (dd, $^4J_{HH}$=1.2 Hz, $^3J_{HH}$=6.7 Hz, 3H), 4.15 (q, $^3J_{HH}$=7.2 Hz, 2H), 6.00 (d, $^3J_{HH}$=13.1 Hz, 1H), 6.33 (ddd, $^4J_{HH}$=1.2 Hz, $^3J_{HH}$=15.3, 9.0 Hz, 1H), 6.48 (dq, $^3J_{HH}$=6.7, 15.3 Hz, 1H), 7.68 (d, $^3J_{HH}$=13.1 Hz), 7.95 (d, $^3J_{HH}$=9.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) of crude reaction mixture (**3b**+Me_3PO) δ 14.0, 17.8 (d, $^1J_{PC}$=70.0 Hz), 18.8, 60.0, 117.8, 147.4, 153.7, 155.5, 166.8, 169.4 ppm.

3.4.3. 1-(Ethoxycarbonyl)-5-methyl-3-azahexa-1,3,5-triene (3c). The general procedure A was followed using phosphazene **1a** (1.252 g, 4 mmol) and methacrolein **2c** (0.238 mL, 4 mmol) (room temperature/30 h). ^{1}H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**3c**+Ph_2MePO) δ 1.23 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.91 (s, 3H), 1.96 (d, $^2J_{PH}$=13.0 Hz, 3H), 4.15 (q, $^3J_{HH}$=7.2 Hz, 2H), 5.58 (s, 1H), 5.77 (s, 1H), 6.03 (d, $^3J_{HH}$=13.3 Hz, 1H), 7.27–7.09 (m, 10H), 7.76 (d, $^3J_{HH}$=13.3 Hz, 1H), 7.99 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) of crude reaction mixture (**3c**+Ph_2MePO) δ 14.1, 16.4, 16.5 (d, $^1J_{PC}$=74.0 Hz), 60.1, 118.1, 128.4–132.4, 133.2, 155.1, 166.8, 170.1 ppm. The general procedure B was followed using phosphazene **1c** (4 mmol), prepared 'in situ', and 0.238 mL (4 mmol) of methacrolein **2c** (room temperature/4 h). ^{1}H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**3c**+Me_3PO) δ 1.23 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.47 (d, $^2J_{PH}$=12.8 Hz, 9H), 1.91 (s, 3H), 4.15 (q, $^3J_{HH}$=7.2 Hz, 2H), 5.58 (s, 1H), 5.77 (s, 1H), 6.03 (d, $^3J_{HH}$=13.3 Hz, 1H), 7.76 (d, $^3J_{HH}$= 13.3 Hz, 1H), 7.99 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) of crude reaction mixture (**3c**+Me_3PO) δ 14.1, 16.4, 17.8 (d, $^1J_{PC}$=70.0 Hz), 60.1, 118.1, 129.4, 133.2, 155.1, 166.8, 170.1 ppm.

3.4.4. 1,2-(Dimethoxycarbonyl)-6-phenyl-3-azahexa-1,3,5-triene (3d). The general procedure A was followed using phosphazene **1b** (1.428 g, 4 mmol) and cinnamaldehyde **2a** (0.504 mL, 4 mmol) (70 °C/30 h). ^{1}H NMR (300 MHz, $CDCl_3$) of crude reaction mixture (**3d**+Ph_2MePO) δ 1.96 (d, $^2J_{PH}$=13.0 Hz, 3H), 3.59 (s, 3H), 3.73 (s, 3H), 6.22 (s, 1H), 6.91–7.87 (m, 17H), 7.95 (d, $^3J_{HH}$= 8.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) of crude reaction mixture (**3d**+Ph_2MePO) δ 16.5 (d, $^1J_{PC}$=74.0 Hz), 51.2, 52.7, 108.4, 124.9–134.6, 146.2, 152.3, 163.7, 165.0 ppm.

3.5. General procedure for [4+2] cycloaddition reaction of 3-azatrienes 3 with cyclic enamines 4a,b

Cyclic enamine **4** (4 mmol) was added to a 0–10 °C solution of 3-azatriene **3** (4 mmol), prepared 'in situ', in $CHCl_3$ (10 mL) under N_2, and the mixture was stirred at room temperature until ^{1}H NMR indicated the disappearance of 3-azatriene. Evaporation of solvent under reduced pressure afforded an oil that was chromatographed on silica gel to give the compounds **6**, **9**, and **10**.

3.5.1. Ethyl 1-(2-phenylethenyl)-1,2,6,7,8,8a-hexahydro-4-isoquinolinecarboxylate (6a). The general procedure was followed using 3-azatriene **3a** and 1-pyrrolidine-1-cyclohexene **4a** (0.605 g, 4 mmol) for 18 h at room temperature. The crude oil was chromatographed on silica gel (10:1 hexane/AcOEt) to give 0.381 g (42%) of **6a** as a white solid: mp 169–170 °C (recrystallized from hexane/AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02–1.19 (m, 1H), 1.21 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.48–2.21 (m, 6H), 3.45–3.51 (m, 1H), 4.04–4.15 (m, 2H), 4.23 (d, $^3J_{HH}$=6.1 Hz, 1H), 6.01 (dd, $^3J_{HH}$=8.6, 15.7 Hz, 1H), 6.47 (s, 1H), 6.55 (d, $^3J_{HH}$= 15.7 Hz, 1H), 7.18–7.34 (m, 5H), 7.44 (d, $^3J_{HH}$=6.1 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 21.8, 25.9, 27.2, 38.4, 59.1, 60.4, 99.1, 120.6, 126.5, 128.0, 128.7, 128.8, 134.2, 136.1, 142.0, 142.1, 167.3 ppm; IR (KBr) 3423, 1656; MS (EI) *m*/*z* 309 (M^+, 14). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.68; H, 7.48; N, 4.52.

3.5.2. Ethyl 1-(1-propenyl)-1,2,6,7,8,8a-hexahydro-4-isoquinolinecarboxylate (6b). The general procedure was followed using 3-azatriene **3b** and 1-pyrrolidine-1-cyclohexene **4a** (0.605 g, 4 mmol) for 18 h at room temperature. The crude oil was chromatographed on silica gel (10:1 hexane/AcOEt) to give 0.594 g (42%) of **6b** as a white solid: mp 134–135 °C (recrystallized from hexane/AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89–1.00 (m, 1H), 1.20 (t, $^3J_{HH}$= 7.1 Hz, 3H), 1.26–2.21 (m, 9H), 3.23–3.29 (m, 1H), 4.02–4.17 (m, 2H), 4.35 (s, 1H), 5.28 (dd, $^3J_{HH}$=8.7, 15.3 Hz, 1H), 5.61–5.72 (m, 1H), 6.43 (s, 1H), 7.40 (d, $^3J_{HH}$=6.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 17.7, 21.8, 25.9, 27.1, 38.1, 59.0, 60.2, 98.5, 120.1, 130.5, 130.7, 142.2, 142.3, 167.4 ppm; IR (KBr) 3320, 1690; MS (EI) *m*/*z* 247 (M^+, 31). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.87; H, 8.57; N, 5.65.

3.5.3. Ethyl 6-(1-methylethenyl)-5,4-(1-propanyl-3-yliden)-1,4,5,6-tetrahydro-3-pyridinecarboxylate (9). The general procedure was followed using 3-azatriene **3c** (4 mmol), prepared 'in situ', and 1-pyrrolidine-1-cyclopentene **4b** (0.496 g, 4 mmol) for 14 h at room temperature. The crude oil was chromatographed on silica gel (7:1 hexane/AcOEt) to give 0.594 g (35%) of **9** as a white solid: mp 120–121 °C (recrystallized from hexane/AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17–1.31 (m, 4H), 1.72 (s, 3H), 1.90–1.99 (m, 1H), 2.36–2.38 (m, 2H), 2.66–2.72 (m, 1H), 3.39 (d, $^3J_{HH}$=10.5 Hz, 1H), 4.09–4.18 (m, 2H), 4.50 (s, 1H), 4.91 (s, 1H), 4.95 (s, 1H), 5.97 (s, 1H), 7.46

(d, $^3J_{HH}$=6.4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 17.7, 28.4, 31.8, 46.3, 59.2, 65.2, 97.3, 115.0, 120.5, 133.7, 143.2, 144.1, 167.3 ppm; IR (KBr) 3325, 1700; MS (EI) *m/z* 233 (M^+, 100). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.03; H, 8.19; N, 6.01.

3.5.4. Dimethyl 6-(phenylethenyl)-4,5-trimethylene-2,3-pyridinedicarboxylate (10). The general procedure was followed using 3-azatriene **3d** (4 mmol), prepared 'in situ', and 1-pyrrolidine-1-cyclopentene **4b** (0.496 g, 4 mmol) for 20 h at room temperature. The crude oil was chromatographed on silica gel (10:1 hexane/AcOEt) to give 0.540 g (40%) of **10** as a white solid: mp 145–146 °C (recrystallized from hexane/AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09–2.19 (m, 2H), 3.03–3.13 (m, 4H), 3.85 (s, 3H), 3.93 (s, 3H), 7.11 (d, $^3J_{HH}$=15.8 Hz, 1H), 7.23–7.56 (m, 5H), 7.82 (d, $^3J_{HH}$=15.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 30.7, 33.0, 52.5, 52.9, 122.2, 123.7, 127.5, 128.7, 128.9, 136.4, 136.6, 140.0, 147.9, 152.1, 155.6, 166.8, 167.3 ppm; IR (KBr) 1751, 1707; MS (EI) *m/z* 337 (M^+, 100). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.18; H, 5.70; N, 4.14.

3.6. Oxidation with *p*-benzoquinone. Synthesis of ethyl 1-(2-phenylethenyl)-5,6,7,8-tetrahydro-4-isoquinolinecarboxylate (7a)

To a solution of bicyclic compound **6a** (0.619 g, 2 mmol) in dioxane (8 mL) was added 0.212 g (2 mmol) of *p*-benzoquinone, and the mixture was stirred for 24 h at 100 °C under N_2. The solvent was evaporated under reduced pressure, and the resulting oil was purified by silica gel column chromatography (10:1 hexane/AcOEt) to give 0.515 g (84%) of **7a** as a white solid: mp 126–127 °C (recrystallized from hexane/AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, $^3J_{HH}$=7.0 Hz, 3H), 1.74–1.81 (m, 4H), 2.82–2.86 (m, 2H), 3.03–3.07 (m, 2H), 4.30 (q, $^3J_{HH}$=7.0 Hz, 2H), 7.22–7.56 (m, 6H), 7.81 (d, $^3J_{HH}$=15.4 Hz, 1H), 8.82 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 21.8, 22.1, 28.1, 29.7, 60.9, 123.3–128.7, 130.2, 136.2, 136.9, 148.2, 148.6, 150.1, 166.3 ppm; IR (KBr) 1705; MS (EI) *m/z* 307 (M^+, 100). Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.18; H, 6.90; N, 4.57.

3.7. Oxidation with manganese triacetate. Ethyl 1-(1-propenyl)-5,6,7,8-tetrahydro-4-isoquinolinecarboxylate (7b)[22]

To a solution of manganese triacetate (0.536 g, 2 mmol) in acetic acid (5 mL) was added the bicyclic compound **6b** (0.247 g, 1 mmol). The reaction mixture was stirred at room temperature for 30 min. After completion of the reaction, as indicated by TLC examination, manganese diacetate was filtered off and the reaction mixture poured into water. The contents were then neutralized by $NaHCO_3$, extracted with dichloromethane (2×10 mL) of **7b** and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting crude product was purified by silica gel column chromatography (20:1 hexane/AcOEt) to give 0.204 g (83%) of **7b** as a white solid: mp 51–52 °C (recrystallized from hexane/AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, $^3J_{HH}$=7.2 Hz, 3H), 1.63–1.83 (m, 4H), 1.90 (dd, $^3J_{HH}$=6.9 Hz, $^4J_{HH}$=1.7 Hz, 3H), 2.68 (t, $^3J_{HH}$=6.1 Hz, 2H), 3.01 (t, $^3J_{HH}$=6.1 Hz, 2H), 4.28 (q, $^3J_{HH}$=7.2 Hz, 2H), 6.59 (dd, $^3J_{HH}$=15.1 Hz, $^4J_{HH}$=1.7 Hz, 1H), 6.91 (dd, $^3J_{HH}$=15.1, 6.9 Hz, 1H), 8.73 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.7, 21.6, 22.0, 25.9, 27.9, 60.6, 123.5, 126.8, 128.9, 134.6, 147.9, 148.2, 156.2, 166.5 ppm; IR (KBr) 1725; MS (EI) *m/z* 245 (M^+, 99). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.48; H, 7.79; N, 5.70.

Acknowledgements

The present work has been supported by the *Dirección General de Investigación del Ministerio de Ciencia y Tecnología* (MCYT, Madrid DGI, PPQ2003-0910) and by the *Universidad del País Vasco* (UPV, GC/2002). E.H. thanks the *Departamento de Educación, Universidades e Investigación del Gobierno Vasco* for a Predoctoral Fellowship.

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Tetrahedron 62 (2006) 7667–7673

Microwave-assisted efficient synthesis of 1,2-diaryldiketones: a novel oxidation reaction of diarylalkynes with DMSO promoted by $FeBr_3$

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Received 19 April 2006; accepted 29 May 2006
Available online 22 June 2006

Abstract—This paper reports the oxidation of functionalized diarylalkynes with DMSO in the presence of the environmentally friendly $FeBr_3$ catalyst. This non-toxic procedure is general and has been applied successfully under microwave irradiation leading rapidly to benzil derivatives in good yields.

1. Introduction

Benzil derivatives are an important class of compounds, which have been reported for their application as inhibitors of the acid corrosion of mild steel,[1] as photosensitive agents in photocurable coatings,[2] and also as natural compounds.[3] Moreover, benzil substrates constitute useful intermediates in organic synthesis as precursors of various heterocyclic compounds such as, for example, imidazoles[4] or quinoxalines.[5] Conventionally, benzil derivatives are obtained by oxidation of benzoins[6] or hydrobenzoins.[7] However, the access to functionalized benzoins is not easy and their oxidation very often required the use of toxic and/or expensive reagents (e.g., thallium nitrate,[6d] ammonium chlorochromate–alumina,[6e] RuO_4[6g] and *N*-hydroxyphthalimide–$Co(acac)_3$).[7c] Besides other methodologies,[8,6g] by far the most important procedure for the preparation of benzils is the oxidation of diarylalkynes, which are easily prepared by Sonogashira–Linstrumelle coupling. Thus, a large number of oxidizing systems have been utilized including $Co(OAc)_2$/$Mn(OAc)_2$/NaBr,[9] $ZnCr_2O_7 \cdot 3H_2O$,[10] SO_3–dioxane complex,[11] H_5IO_6[12] and CH_3ReO_3/H_2O_2.[13] However, these reagents have several drawbacks in terms of toxicity, difficult reaction conditions, long reaction times and/or low yields. DMSO as an oxidant in the presence of an excess of NBS[14] has been successfully reported to transform diphenylacetylene into benzil. Similarly, an attractive protocol using DMSO as oxidant in the presence of $PdCl_2$ has been described by a Russian team.[15] While this transformation is a suitable method, its success was influenced by the electronic nature of the aryl substituents.[16] A recent work concerning the oxidation of alkynes into α-diketones with DMSO and $CH_3SO_3H/HCO_2H/HBr$[17] prompted us to report the results of our study. With respect to the environmental concerns, there is a strong demand for a clean, safe and highly efficient catalytic methodology for the conversion of arylalkynes to benzil derivatives.

2. Results and discussion

As a part of our programme aimed at the development of new, soft and selective oxidizing methodologies,[18] we have investigated the oxidation of various internal arylalkynes **1** with DMSO in the presence of catalytic amounts of friendly transition-metal salts. Herein, we report a simple and convenient procedure for the synthesis of a range of functionalized benzil derivatives promoted by the non-toxic and cheap $FeBr_3$.

At the outset of this work, we began our approach by screening a variety of catalysts using diarylalkyne **1a** as a model substrate in DMSO.

The results described in Table 1 showed clearly that transition-metal catalysts promoted the oxidation of **1a** while no reaction occurred without catalyst (entry 1). Whereas all studied metal salts (bromides or chlorides) were effective in a surprising way, $MnCl_2$ (two attempts) did not catalyze the oxidation reaction (entry 8) and starting alkyne **1a** was recovered unchanged. Examination of Table 1 indicates that transition-metal salt bromide catalysts were superiors

Keywords: Benzils; DMSO; Iron bromide; Alkynes; Microwave irradiation.
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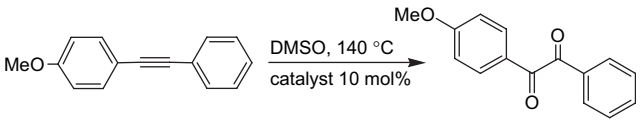
doi:10.1016/j.tet.2006.05.072

Table 1. Oxidation of diarylalkyne **1a** to benzil **2a**



1a **2a**

Entry	Catalyst	Time (h)	Yield[a] (%)
1	—	72	0
2	CuCl	72	65
3	CuBr	72	66
4	$InCl_3$	16	65
5	$InBr_3$	14	70
6	$NiCl_2$	40	72
7	$NiBr_2$	24	76
8	$MnCl_2$	36	0[b]
9	$MnBr_2$	14	75[b]
10	$Fe(acac)_3$	40	68
11	$FeCl_3$	36	73
12	$FeBr_3$	10	80
13	$FeBr_3$[c]	10	78

[a] Isolated yield.
[b] Two reproducible attempts.
[c] 1 equiv of $FeBr_3$ was used.

to the corresponding chlorides in terms of increasing yields and reducing reaction times. In all studied cases, no traces of arylalkyne **1a** were found at the end of the reaction and then purifications were easy. Of the transition-metal salts examined, $FeBr_3$ was the most efficient catalyst delivering benzil **2a** in high yield (10 h, 80%, entry 12) whereas, under the same conditions $FeCl_3$ and $Fe(acac)_3$ gave similar yields but with longer reaction times (entries 10 and 11). With CuBr, $InBr_3$, $NiBr_2$ and $MnBr_2$, the oxidation reaction was also successful but with lower yields and longer reaction times (entries 3, 5, 7 and 9). Finally, increasing the amount of the iron bromide catalyst was not efficient to observe neither a reduced reaction time nor a better yield (entry 13).

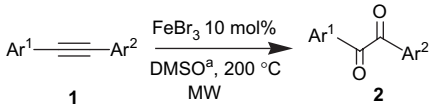
In our current work to develop rapid and efficient methods for oxidation reactions, we thought to speed up the synthesis of various benzils using microwave-assisted irradiation.[18d]

Our first efforts were focused on the optimization of the reaction temperature. When the reaction of **1a** is carried out at 140 °C (as base line control to evaluate the microwaves contribution) for 20 min, one notes that 20% of the starting product **1a** was transformed into its corresponding benzil **2a**, while only traces of **2a** (<5%, indicated by GC) were obtained by conventional thermal conditions. By increasing gradually the reaction temperature, we were pleased to observe that, using microwave irradiation at 200 °C, diarylalkyne **1a** was totally transformed into **2a** in only 20 min and with a satisfactory yield (75%).[19] It should be noted that under convention thermal heating (200 °C, 20 min, sealed tube) the reaction occurred smoothly and 50% of the starting material was recovered unchanged. $InBr_3$ (10 mol %) and $MnBr_2$ (10 mol %) were also tested, but longer reaction times, by comparison with $FeBr_3$, were required to oxidize **1a** completely (75%, 40 min and 68%, 45 min, respectively).

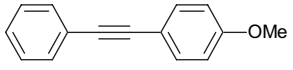
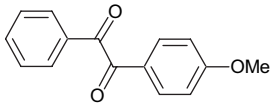
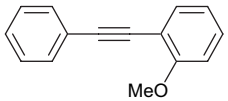
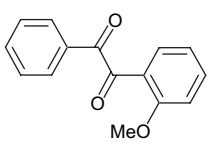
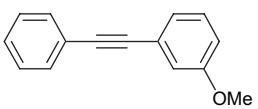
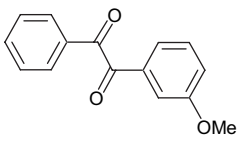
Next, we investigated the oxidizing species. When using stoichiometric amounts or slight excess (5 equiv) of DMSO, no traces of **2a** were detected even after a prolongated reaction time (48 h). A similar result was obtained when DMSO was replaced by sulfolane (tetramethylene sulfone); the oxidation reaction failed and starting alkyne **1a** was recovered unchanged. We are presently examining alternatives to DMSO for the oxygen transfer step.

To demonstrate the scope of the reaction, a series of acetylenic substrates **1a–o** were synthesized by Sonogashira–Linstrumelle coupling[20] and subjected to oxidation by the DMSO–$FeBr_3$ couple under microwave irradiation. The results of this study are summarized in Table 2.

Table 2. Oxidation of diarylalkynes **1** to benzyl derivatives **2** under microwave irradiation

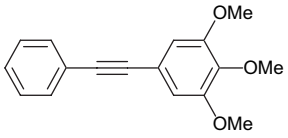
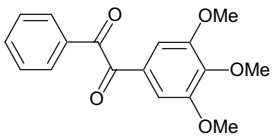
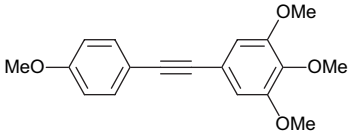
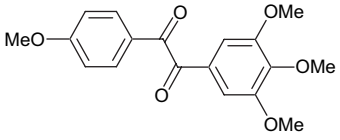
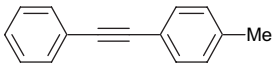
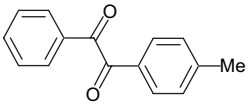
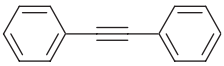
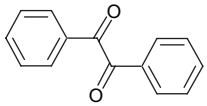
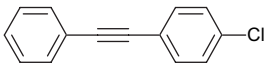
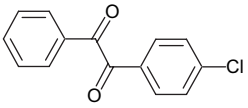
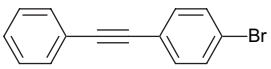
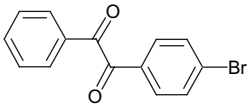
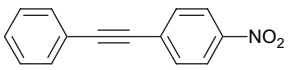
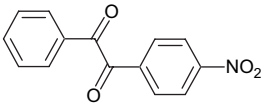
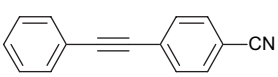
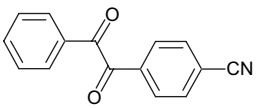
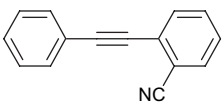
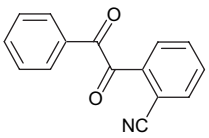
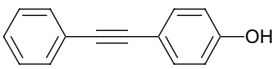
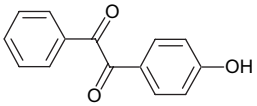
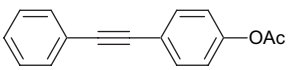
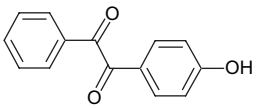
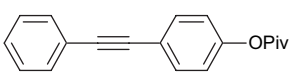
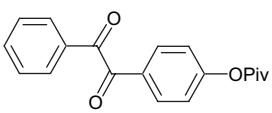


1 **2**

Entry	Alkynes	1	Benzils	2	Time (min)	Yield[b] (%)
1		**1a**		**2a**	20	75[c]
2		**1b**		**2b**	40	70
3		**1c**		**2c**	9	75

(*continued*)

Table 2. (*continued*)

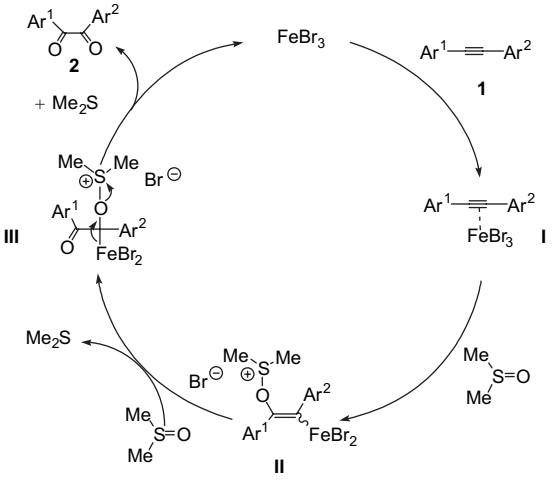
Entry	Alkynes	1	Benzils	2	Time (min)	Yield[b] (%)
4		**1d**		**2d**	25	64
5		**1e**		**2e**	30	65
6		**1f**		**2f**	11	61
7		**1g**		**2g**	20	73
8		**1h**		**2h**	9	75
9		**1i**		**2i**	9	72
10		**1j**		**2j**	15	72
11		**1k**		**2k**	21	46
12		**1l**		**2l**	16	43
13		**1m**		**2m**	120	0
14		**1n**		**2m**	9	51
15		**1o**		**2o**	8	59

[a] During this study, we did not observe a notable degradation of the DMSO[21] under microwave irradiation.
[b] Isolated yield. All compounds exhibited satisfactory spectral properties and microanalyses.
[c] No oxidation was observed when reactions were conducted without $FeBr_3$ in DMSO at 200 °C under MWI.

Arylalkynes substituted with an electron-donating group (Me, OMe) have been transformed into benzil derivatives in good yields (from 61% to 76%) and with reduced reaction times (<1 h). It should be noted that the position of the substituent (*o*, *m*, *p*) on the aromatic ring had no influence on the oxidation yield, although the *meta* benzil **2c** was obtained in a shorter reaction time (compare entry 3 with entries 1 and 2). We were also pleased to observe that halogenated substituted arylalkynes **1h** and **1i** afforded the expected benzils with reduced times and good yields (<10 min, 72–75%, entries 8 and 9). Moreover, the presence of an electron-withdrawing group on the aryl ring such as NO_2 did not affect the yield as well as the reaction time of the oxidizing process and provides benzil **2j** in 72% yield (entry 10). However, by using arylalkynes **1k** and **1l** substituted with an *ortho* or a *para* cyano group, respectively, the desired corresponding benzil derivatives **2k** and **2l** were obtained in moderate yields although totally disappearance of starting material was observed. It seems that under these conditions, the cyano group interferes with the outcome of the present reaction (non-identified hydrolyzed by-products were observed in the crude reaction mixture). One can note that the phenolic arylalkyne **1m** did not give its corresponding benzil **2m**, even after a prolongated reaction time under MW irradiation. However, when the hydroxy substituent of **1m** was protected as an acetate (**1n**), we observed the formation of **2m**, after oxidation of the triple bond followed by cleavage of the acetoxyester group. A similar result (oxidation and cleavage) has been obtained with conventional heating (70%, 7 h). On the contrary, pivaloyl substituted ester **1o** was successfully transformed into its corresponding benzil **2o**, but without removal of the bulky protecting group (entry 15). It is important to note that this new oxidation process with $FeBr_3$–DMSO is not sensitive to the electronic nature of the acetylenic substrates, unlike some others methodologies.[11]

3. Mechanistic consideration

At first, an experiment was performed in which the DMSO solution was degassed. Without O_2, oxidation of **1a** was still observed with comparable yields and reaction times, implying that DMSO constitutes the oxidizing species. When **1a** was heated in DMSO without any catalysts, the oxidation occurred slowly (stirring for 72 h at 140 °C, starting alkyne **1a** (10%) was still recovered). In the plausible proposed mechanism (Scheme 1) concerning the oxidation of arylalkynes **1**, the Fe(III), acting as a Lewis acid, may activate the triple bond to generate **I** and allowed successive additions of DMSO. After a first addition, a vinyl iron species **II** (or its cationic equivalent) would be formed and then trapped by a second molecule of DMSO. The species **III** formed would evolve to afford the desired benzyl **2** together with Me_2S and regenerated the catalyst.



Scheme 1. Proposed pathway for the oxidation of arylalkynes **1**.

In order to activate better the alkyne function, the Lewis acidity of the Fe(III) catalyst should be increased. For that purpose, an additional experiment was achieved by introducing 30 mol % of trifluoromethanesulfonic acid (TfOH) to the reaction mixture (**1a**, 10 mol % of $FeBr_3$, DMSO). We were pleased to observe that under classical thermal conditions (140 °C), the oxidation proceeded in only 1 h and with a good yield (71%). In order to determine the positive influence of TfOH associated with $FeBr_3$, we performed the oxidation without $FeBr_3$, as control. Total disappearance of **1a** was observed but after 10 h of reaction. It is reasonable to think that the catalytic species formed $Fe(OTf)_3$,[22] which is a stronger Lewis acid than $FeBr_3$, activates considerably the triple bond. Other attempts were achieved with various iodine salts in the place of TfOH but unfortunately failed to give **2a** in shorter reaction times. This latest oxidation reaction involving the synergetic couple TfOH and $FeBr_3$ is currently under investigation in our laboratory.

4. Conclusion

In conclusion, we have developed a simple and efficient process for oxidation of arylalkynes using DMSO and catalytic $FeBr_3$. The use of friendly non-toxic catalytic $FeBr_3$, short reaction times, high to excellent yields, low cost and easy preparation are the obvious advantages of the present method. Under classical thermal conditions, we have demonstrated that the tandem $FeBr_3$–DMSO can be used to prepare benzil derivatives in reasonable reaction times and satisfactory yields. The microwave-assisted procedure allows for the rapid synthesis of various benzils, 20 min compared to 10 h by conventional methods. The experimental microwaves experiments described in this paper are well established and controlled and can be safely and beneficially reproduced.

5. Experimental

5.1. Materials

All glasswares were oven-dried at 140 °C and all reactions were conducted under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl. Triethylamine (TEA) was distilled from potassium hydroxide under argon prior to use.

5.2. Instrumentation

All microwave experiments were performed using an Emrys Optimizer in 2–5 mL Pyrex reaction vessels. Each contained a Teflon stir bar and Teflon coated reaction vessel cap.

The compounds were all identified by usual physical methods, i.e., ^{1}H NMR, ^{13}C NMR, IR and elemental analysis. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with a Bruker AC 200 or Bruker ARX 400. ^{1}H NMR chemical shifts are reported in parts per million from an internal standard TMS or of residual chloroform (7.27 ppm). The following abbreviations are used: m (multiplet), s (singlet), d (doublet), t (triplet), dd (doublet of doublet), tt (triplet of triplet). ^{13}C NMR chemical shifts are reported in parts per million from the central peak of deuteriochloroform (77.14). IR spectra were measured on a Bruker Vector 22 spectrophotometer (neat, cm^{-1}). Elemental analyses were performed with a Perkin–Elmer 240 analyzer. Mass spectra were obtained with a LCT Micromass spectrometer. Analytical TLC were performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Melting points (mp) were recorded on a Büchi B-450 apparatus and were uncorrected.

5.3. General procedure for the preparation of arylalkynes from aryl halides

All arylalkynes except **1o** were known compounds and have been prepared according to the following procedure.

5.3.1. 2,2-Diethyl-propionic acid-4-phenylethynyl-phenyl ester 1o. To a mixture of 2,2 dimethyl-propionic acid-4-iodo-phenyl ester (303 mg; 1 mmol), $PdCl_2(PPh_3)_2$ (35.1 mg; 0.05 mmol), CuI (19.1 mg; 0.1 mmol) and TEA (404.8 mg; 4.0 mmol) in THF (10 mL), a solution of phenylacetylene (132.6 mg; 1.2 mmol) was added dropwise under an argon atmosphere. The mixture was stirred at room temperature for overnight. Then Et_2O (20 mL) was added to the crude and the mixture was filtered over a short pad of Celite. The organic layer was washed twice with brine (5 mL), separated, dried over $MgSO_4$, filtered and concentrated. Resulting residue was further purified by flash chromatography.

Yield: 95%; mp: 92 °C; TLC: R_f 0.61 (cyclohexane/EtOAc, 90/10, SiO_2). Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52%. Found: C, 81.87; H, 6.47. IR (neat) ν_{max}/cm^{-1}: 2971, 1743, 1593, 1506, 1479, 1445, 1396, 1369, 1275, 1235, 1197, 1160, 1140, 1115, 1033, 1013, 954, 919, 897, 859, 842, 801. ^{1}H NMR for **1o** ($CDCl_3$, 200 MHz, 298 K): δ, ppm 7.62–7.51 (m, 4H), 7.36–7.33 (m, 3H), 7.06 (d, 2H, J=8.7 Hz), 1.37 (s, 9H). ^{13}C NMR for **1o** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 176.7 (CO), 151.0 (C), 132.7 (2CH), 131.6 (2CH), 128.3 (2CH), 128.3 (CH), 123.2 (C), 121.6 (2CH), 120.7 (C), 89.3 (C), 88.6 (C), 39.1 (C), 27.1 ($3CH_3$).

5.4. General procedure for the preparation of benzils 2a–o from alkynes under microwave irradiation

To an Emrys Optimizer 2–5 mL Pyrex reaction vessel were added alkyne (0.5 mmol), $FeBr_3$ (15 mg; 0.05 mmol), in DMSO (2.5 mL). The reaction vessel was then placed in the Emrys Optimizer and exposed to microwave irradiation according to the following specifications: temperature: 200 °C, time (see Table 2), fixed hold time: on, sample absorption: high, pre-stirring: 60 s. After cooling to room temperature, H_2O (3 mL) was added to the crude and the mixture was extracted with EtOAc (3×2 mL). Organic layers were then washed with an aqueous saturated NH_4Cl solution, dried and concentrated. The crude mixture was then purified by column chromatography on silica gel.

5.4.1. 1-(4-Methoxyphenyl)-2-phenyl-ethane-1,2-dione 2a. Yield: 75%; mp: 65 °C; TLC: R_f 0.40 (cyclohexane/EtOAc, 80/20, SiO_2). Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03%. Found: C, 74.81; H, 5.21. IR (neat) ν_{max}/cm^{-1}: 2938, 2842, 1666, 1649, 1594, 1569, 1509, 1450, 1422, 1320, 1303, 1268, 1214, 1182, 1162, 1110, 1020, 973, 931, 877, 841, 818, 803. ^{1}H NMR for **2a** ($CDCl_3$, 200 MHz, 298 K): δ, ppm 7.98–7.92 (m, 4H), 7.69–7.66 (m, 1H), 7.52–7.44 (m, 2H), 6.96 (d, 2H, J=9 Hz), 3.87 (s, 3H). ^{13}C NMR for **2a** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 194.7 (CO), 193.0 (CO), 164.9 (C), 134.6 (CH), 133.7 (C), 132.2 (2CH), 129.7 (2CH), 128.8 (2CH), 125.9 (C), 114.2 (2CH), 55.5 (CH_3). m/z MS (ES+) 263.1 ($M+Na^+$).

5.4.2. 1-(2-Methoxyphenyl)-2-phenyl-ethane-1,2-dione 2b. Yield: 70%; TLC: R_f 0.63 (cyclohexane/EtOAc, 85/15, SiO_2). Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03%. Found: C, 74.58; H, 4.95. IR (neat) ν_{max}/cm^{-1}: 2945, 1676, 1654, 1596, 1580, 1483, 1466, 1450, 1435, 1306, 1271, 1246, 1202, 1162, 1114, 1017, 875. ^{1}H NMR for **2b** ($CDCl_3$, 400 MHz, 298 K): δ, ppm 8.06 (d, 1H, J=8.0 Hz), 7.95 (d, 2H, J=8.0 Hz), 7.64–7.60 (m, 2H), 7.56 (t, 2H, J=8.0 Hz), 7.16 (t, 1H, J=8.0 Hz), 6.97 (t, 1H, J=8.0 Hz), 3.59 (s, 3H). ^{13}C NMR for **2b** ($CDCl_3$, 100 MHz, 298 K): δ, ppm 194.6 (CO), 193.5 (CO), 160.4 (C), 136.4 (CH), 133.7 (CH), 133.0 (C), 130.6 (CH), 129.3 (2CH), 128.7 (2CH), 124.0 (CH), 121.6 (CH), 112.4 (CH), 55.6 (CH_3). m/z MS (ES+) 263.0 ($M+Na^+$).

5.4.3. 1-(3-Methoxyphenyl)-2-phenyl-ethane-1,2-dione 2c. Yield: 75%; TLC: R_f 0.54 (cyclohexane/EtOAc, 80/20, SiO_2). Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03%. Found: C, 74.88; H, 4.99. IR (neat) ν_{max}/cm^{-1}: 3074, 3010, 2838, 1658, 1592, 1484, 1467, 1453, 1429, 1337, 1321, 1298, 1259, 1203, 1174, 1157, 1079, 1033, 994, 932, 903, 874, 832, 803. ^{1}H NMR for **2c** ($CDCl_3$, 200 MHz, 298 K): δ, ppm 7.87 (d, 1H, J=7.0 Hz), 7.58–7.49 (m, 1H), 7.40–7.22 (m, 5H), 7.13 (s, 1H), 7.10–7.04 (m, 1H), 3.74 (s, 3H). ^{13}C NMR for **2c** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 194.4 (2CO), 160.0 (C), 134.8 (CH), 134.2 (C), 133.0 (C), 130.0 (CH), 129.8 (2CH), 128.9 (2CH), 123.1 (CH), 121.8 (CH), 112.9 (CH), 55.4 (CH_3).

5.4.4. 1-Phenyl-2-(3,4,5-trimethoxyphenyl)-ethane-1,2-dione 2d. Yield: 64%; mp: 102 °C; TLC: R_f 0.48 (cyclohexane/EtOAc, 70/30, SiO_2). Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37%. Found: C, 67.91; H, 5.30. IR (neat) ν_{max}/cm^{-1}: 2932, 2834, 1664, 1581, 1504, 1460, 1450, 1413, 1343, 1317, 1283, 1233, 1180, 1157, 1129, 1076, 993, 947, 859, 819. ^{1}H NMR for **2d** ($CDCl_3$, 200 MHz, 298 K): δ, ppm 7.95 (d, 2H, J=7.4 Hz), 7.66 (t, 1H, J=7.4 Hz), 7.49 (t, 2H, J=7.4 Hz), 7.11 (s, 2H), 3.93 (s, 3H), 3.85 (s, 6H). ^{13}C NMR for **2d** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 194.2 (CO), 193.2 (CO), 153.4 (2C), 144.2 (C), 134.7 (CH), 133.1 (C), 129.8 (2CH), 128.9 (2CH), 127.9 (C), 107.2 (2CH), 60.9 (CH_3), 56.3 ($2CH_3$). m/z MS (ES+) 323.1 ($M+Na^+$).

5.4.5. 1-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-ethane-1,2-dione 2e. Yield: 65%; mp: 140 °C; TLC: R_f

0.37 (cyclohexane/EtOAc, 80/20, SiO_2). Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49%. Found: C, 65.46; H, 5.59. IR (neat) ν_{max}/cm^{-1}: 2982, 1651, 1598, 1571, 1502, 1448, 1427, 1412, 1342, 1273, 1245, 1180, 1155, 1125, 1017, 998, 948, 854. ^1H NMR for **2e** ($CDCl_3$, 200 MHz, 298 K): δ, ppm 7.95 (d, 2H, J=9.0 Hz), 7.23 (s, 2H), 6.98 (d, 2H, J=9.0 Hz), 3.94 (s, 3H), 3.89 (s, 3H), 3.88 (s, 6H). ^{13}C NMR for **2e** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 193.5 (CO), 192.8 (CO), 164.9 (C), 153.2 (2C), 144.1 (C), 132.3 (2CH), 128.1 (C), 126.1 (C), 114.3 (2CH), 107.2 (2CH), 60.9 (CH_3), 56.3 ($2CH_3$), 55.5 (CH_3). *m/z* MS (ES+) 353.1 ($M+Na^+$).

5.4.6. 1-Phenyl-2-*p*-tolyl-ethane-1,2-dione 2f. Yield: 61%; mp: 96 °C; TLC: R_f 0.51 (cyclohexane/EtOAc, 90/10, SiO_2). Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79%. Found: C, 79.92; H, 4.81. IR (neat) ν_{max}/cm^{-1}: 1665, 1591, 1578, 1449, 1325, 1209, 1173, 998, 874. ^1H NMR for **2f** ($CDCl_3$, 200 MHz, 298 K): δ, ppm 7.97 (d, 4H, J=8.0 Hz), 7.67 (m, 2H), 7.52 (d, 4H, J=8.0 Hz). ^{13}C NMR for **2f** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 194.0 (2CO), 134.7 (2CH), 132.9 (2CH), 129.8 (4CH), 128.9 (4CH). *m/z* MS (ES+) 233.0 ($M+Na^+$).

5.4.7. 1,2-Diphenyl-ethane-1,2-dione (benzil) 2g. Yield: 73%; TLC: R_f 0.27 (cyclohexane/EtOAc, 90/10, SiO_2). Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39%. Found: C, 80.26; H, 5.31. IR (neat) ν_{max}/cm^{-1}: 1667, 1603, 1572, 1475, 1449, 1410, 1324, 1287, 1208, 1173, 1120, 1019, 879, 828. ^1H NMR for **2g** ($CDCl_3$, 200 MHz, 298 K): δ, ppm 7.96 (d, 2H, J=7.3 Hz), 7.86 (d, 2H, J=8.0 Hz), 7.64 (t, 1H, J=7.3 Hz), 7.49 (t, 2H, J=7.3 Hz), 7.30 (d, 2H, J=8.0 Hz), 2.42 (s, 3H). ^{13}C NMR for **2g** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 194.7 (CO), 194.2 (CO), 146.1 (C), 134.7 (CH), 133.1 (C), 130.6 (C), 129.9 (2CH), 129.8 (2CH), 129.7 (2CH), 128.9 (2CH), 21.8 (CH_3).

5.4.8. 1-(4-Chlorophenyl)-2-phenyl-ethane-1,2-dione 2h. Yield: 75%; mp: 77 °C; TLC: R_f 0.35 (cyclohexane/EtOAc, 70/30, SiO_2). Anal. Calcd for $C_{14}H_9ClO_2$: C, 68.72; H, 3.71%. Found: C, 69.01; H, 3.75. IR (neat) ν_{max}/cm^{-1}: 1663, 1584, 1487, 1450, 1402, 1321, 1208, 1172, 1113, 1093, 1013, 873, 833. ^1H NMR for **2h** ($CDCl_3$, 200 MHz, 298 K): δ, ppm 7.98–7.90 (m, 3H), 7.70–7.63 (m, 2H), 7.55–7.40 (m, 4H). ^{13}C NMR for **2h** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 193.8 (CO), 193.0 (CO), 141.5 (C), 135.0 (CH), 132.8 (C), 131.4 (C), 131.2 (2CH), 129.9 (2CH), 129.4 (2CH), 129.0 (2CH).

5.4.9. 1-(4-Bromophenyl)-2-phenyl-ethane-1,2-dione 2i. Yield: 72%; mp: 87 °C; TLC: R_f 0.61 (cyclohexane/EtOAc, 94/6, SiO_2). Anal. Calcd for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14%. Found: C, 58.02; H, 3.03. IR (neat) ν_{max}/cm^{-1}: 1662, 1578, 1483, 1450, 1398, 1321, 1204, 1172, 1113, 1069, 1024, 1009, 870, 829. ^1H NMR for **2i** ($CDCl_3$, 200 MHz, 298 K): δ, ppm 7.96 (d, 2H, J=7.4 Hz), 7.84 (d, 2H, J=8.6 Hz), 7.68–7.64 (m, 3H), 7.52 (t, 2H, J=7.4 Hz). ^{13}C NMR for **2i** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 193.8 (CO), 193.2 (CO), 135.0 (CH), 132.8 (C), 132.4 (2CH), 131.8 (C), 131.2 (2CH), 130.4 (C), 129.9 (2CH), 129.0 (2CH).

5.4.10. 1-(4-Nitrophenyl)-2-phenyl-ethane-1,2-dione 2j. Yield: 72%; mp: 141 °C; TLC: R_f 0.27 (cyclohexane/EtOAc, 50/50, SiO_2). Anal. Calcd for $C_{14}H_9NO_4$: C, 65.88; H, 3.55; N, 5.49%. Found: C, 65.81; H, 3.54; N, 5.48. IR (neat) ν_{max}/cm^{-1}: 1660, 1594, 1523, 1450, 1344, 1200, 1170, 1110, 883, 859, 839. ^1H NMR for **2j** ($CDCl_3$, 200 MHz, 298 K): δ, ppm 8.36 (d, 2H, J=8.7 Hz), 8.17 (d, 2H, J=8.7 Hz), 7.99 (dd, 2H, J=7.9, 1.0 Hz), 7.71 (tt, 1H, J=7.9, 1.0 Hz), 7.55 (t, 2H, J=7.9 Hz). ^{13}C NMR for **2j** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 192.8 (CO), 192.0 (CO), 151.1 (C), 137.3 (C), 135.4 (CH), 132.4 (C), 130.9 (2CH), 130.0 (2CH), 129.2 (2CH), 129.0 (2CH).

5.4.11. 1-(4-Cyanophenyl)-2-phenyl-ethane-1,2-dione 2k. Yield: 46%; mp: 111.5 °C; TLC: R_f 0.42 (cyclohexane/EtOAc, 90/10, SiO_2). Anal. Calcd for $C_{15}H_9NO_2$: C, 76.59; H, 3.86; N, 5.95%. Found: C, 76.38; H, 3.61; N, 5.85. IR (neat) ν_{max}/cm^{-1}: 3072, 2226, 1679, 1658, 1593, 1579, 1450, 1405, 1321, 1297, 1206, 1171, 1116, 999, 971, 879, 843, 800. ^1H NMR for **2k** ($CDCl_3$, 200 MHz, 298 K): δ, ppm 8.08 (d, 2H, J=8.0 Hz), 7.96 (d, 2H, J=8.6 Hz), 7.80 (d, 2H, J=8.6 Hz), 7.69 (t, 1H, J=8.0 Hz), 7.53 (t, 2H, J=8.0 Hz). ^{13}C NMR for **2k** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 193.0 (CO), 192.4 (CO), 135.9 (C), 135.3 (CH), 132.7 (C), 132.5 (2CH), 130.2 (2CH), 130.0 (2CH), 129.2 (2CH), 117.9 (C), 117.5 (C).

5.4.12. 2-(2-Oxo-2-phenylacetyl)-benzonitrile 2l. Yield: 43%; mp: 67.5 °C; TLC: R_f 0.36 (cyclohexane/EtOAc, 70/30, SiO_2). Anal. Calcd for $C_{15}H_9NO_2$: C, 76.59; H, 3.86; N, 5.95%. Found: C, 76.47; H, 3.79; N, 5.92. IR (neat) ν_{max}/cm^{-1}: 3067, 2926, 2227, 1668, 1592, 1570, 1489, 1451, 1367, 1318, 1212, 1180, 1124, 1017, 951, 888, 869. ^1H NMR for **2l** ($CDCl_3$, 400 MHz, 298 K): δ, ppm 8.05 (d, 2H, J=8.4 Hz), 7.96–7.92 (m, 2H), 7.82–7.71 (m, 3H), 7.58 (t, 2H, J=8.4 Hz). ^{13}C NMR for **2l** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 192.1 (CO), 191.2 (CO), 135.6 (CH), 135.3 (CH), 135.1 (C), 134.0 (CH), 132.7 (CH), 132.4 (C), 132.3 (CH), 130.1 (2CH), 129.1 (2CH), 117.0 (C), 117.9 (CN), 112.0 (C).

5.4.13. 1-(4-Hydroxyphenyl)-2-phenyl-ethane-1,2-dione 2m. Yield: 51%; mp: 125 °C; TLC: R_f 0.50 (cyclohexane/EtOAc, 70/30, SiO_2). Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46%. Found: C, 74.18; H, 4.32. IR (neat) ν_{max}/cm^{-1}: 3385, 1672, 1648, 1595, 1562, 1515, 1449, 1302, 1204, 1157, 1047, 998, 878, 845. ^1H NMR for **2m** ($CDCl_3$, 400 MHz, 298 K): δ, ppm 7.88 (d, 2H, J=7.3 Hz), 7.80 (d, 2H, J=8.6 Hz), 7.57 (t, 1H, J=7.3 Hz), 7.42 (t, 2H, J=7.3 Hz), 6.82 (d, 2H, J=8.6 Hz), 6.80–6.10 (m, 1H). ^{13}C NMR for **2m** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 195.4 (CO), 193.6 (CO), 162.5 (C), 135.0 (CH), 133.0 (C), 132.7 (2CH), 129.9 (2CH), 129.0 (2CH), 125.6 (C), 116.1 (2CH).

5.4.14. 2,2-Dimethyl-propionic acid-4-(2-oxo-2-phenyl-acetyl)-phenyl ester 2o. Yield: 59%; mp: 87 °C; TLC: R_f 0.47 (cyclohexane/EtOAc, 90/10, SiO_2). Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85%. Found: C, 73.41; H, 5.79. IR (neat) ν_{max}/cm^{-1}: 2978, 1742, 1662, 1594, 1505, 1479, 1454, 1400, 1366, 1326, 1296, 1280, 1231, 1207, 1174, 1157, 1116, 1032, 1012, 997, 974, 904, 873, 804. ^1H NMR for **2o** ($CDCl_3$, 400 MHz, 298 K): δ, ppm 8.05–7.94 (m, 4H), 7.65 (tt, 1H, J=7.7, 1.4 Hz), 7.54–7.46 (m, 2H), 7.26–7.16 (m, 2H). ^{13}C NMR for **2o** ($CDCl_3$, 50 MHz, 298 K): δ, ppm 194.2 (CO), 193.2 (CO), 176.2 (OCO), 156.3

(C), 134.9 (CH), 132.9 (C), 131.5 (2CH), 130.3 (C), 129.9 (2CH), 129.0 (2CH), 122.2 (2CH), 93.2 (C), 27.0 ($3CH_3$).

Acknowledgements

The CNRS is gratefully acknowledged for support of this research and the MNSER for a doctoral fellowship to A.G. The authors wish also to thank Pr. T. Besson for fruitful discussions concerning the use of DMSO under MW irradiations.

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Synthesis of chromanes by sequential '[3+3]-cyclization/Williamson' reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes

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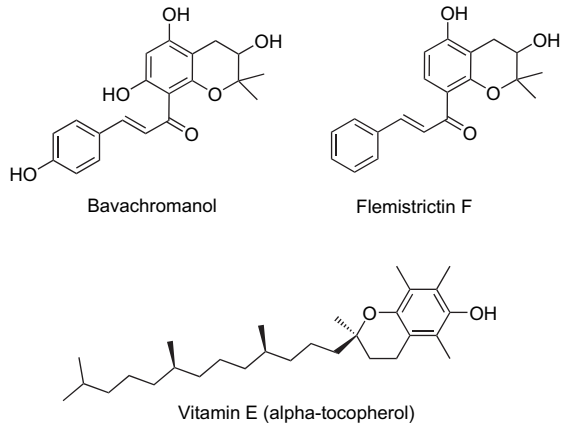
Received 17 April 2006; revised 24 May 2006; accepted 29 May 2006
Available online 16 June 2006

Abstract—Functionalized chromanes were prepared by sequential '[3+3]-cyclization/Williamson' reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes with 1,1,3,3-tetramethoxypropane, 3-silyloxyalk-2-en-1-ones, and 1,1-diacetylcyclopropane. The first step of the sequence involves [3+3] cyclizations of the starting materials to give 2-(3-chloropropyl)phenols. The subsequent cyclization proceeds by intramolecular nucleophilic substitution. 6-(2-Hydroxybenzoyl)chromanes were prepared based on sequential '[3+3]-cyclization/Williamson' reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes with 3-formylchromones.

1. Introduction

3,4-Dihydro-2*H*-chromenes (chromanes) represent pharmacologically relevant heterocycles, which occur in a variety of natural products (Scheme 1).[1,2] For example, bavachromanol has been isolated from leaves of *Maclura tinctoria* L. (Venezuela).[2a] The chromanol moiety of vitamin E (α-tocopherol) exhibits anti-androgen properties. Many synthetic approaches to 3,4-dihydro-2*H*-chromenes are based on intramolecular Friedel–Crafts alkylations.[2] Finn et al. have prepared chromanes from salicylic aldehydes and vinylboronic acids in the presence of catalytic amounts of dibenzylamine.[3] Jones et al. reported the synthesis of chromanes by Diels–Alder reactions of *o*-quinone methides, which were generated from salicylic aldehydes and alcohols.[4]



Scheme 1. Chromane natural products.

Chan and co-workers reported an efficient one-pot synthesis of salicylates based on [3+3] cyclizations of 1,3-bis-silyl enol ethers[5] with 3-silyloxyalk-2-en-1-ones or 1,1,3,3-tetramethoxypropane.[6] Recently, we have reported[7] an extension of this method by the first use of 1,3-bis-(trimethylsilyloxy)-7-chlorohepta-1,3-dienes (chloro-substituted 1,3-bis-silyl enol ethers)[8] in [3+3] cyclizations. The combination of these [3+3] cyclizations with subsequent intramolecular Williamson reactions allows for the synthesis of functionalized chromanes. Herein, we report full details of these studies. With regard to our preliminary communication in this field,[7] we herein report, for the first time, the synthesis of 6-(2-hydroxybenzoyl)-3,4-dihydro-2*H*-chromenes based on sequential '[3+3]-cyclization/Williamson' reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes with 3-formylchromones. The general strategy reported herein allows for a convenient synthesis of a variety functionalized chromanes. Notably, the substitution patterns of these products are not readily available by other methods.

Keywords: Benzopyrans; Cyclizations; Ethers; Lewis acids; Silyl enol ethers.
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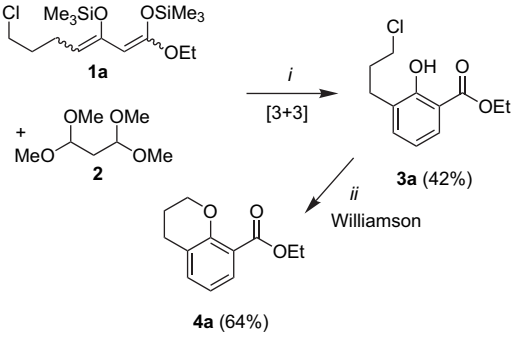
doi:10.1016/j.tet.2006.05.076

2. Results and discussion

2.1. [3+3] Cyclization of 1,1,3,3-tetramethoxypropane

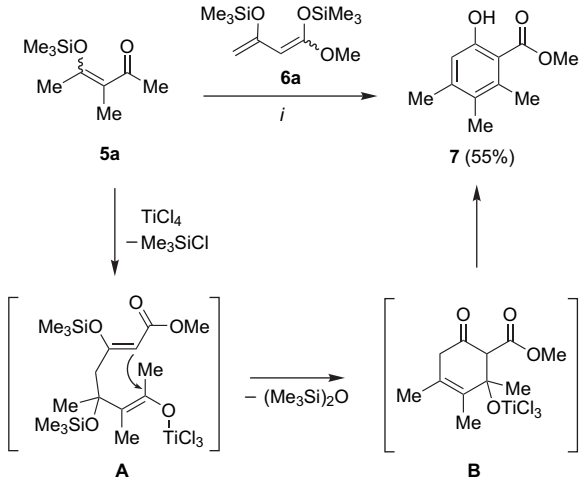
The key substrates of this study—1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes **1a**,**b**—were prepared in three steps from ethyl acetoacetate as previously reported.[7,9] The $TiCl_4$-mediated [3+3] cyclization of **1a** with 1,1,3,3-tetramethoxypropane (**2**) afforded the 2-(3-chloropropyl)phenol **3a**. The formation of **3a** proceeds by attack of carbon atom C-4 of **1a** onto **2**, cyclization via carbon C-2, and finally aromatization. Notably, the chloride functionality remained unattacked during the reaction. Treatment of a THF solution of **3a** with sodium hydride (NaH), in the presence of tetrabutylammonium iodide (TBAI), afforded chromane **4a** (Scheme 2).



Scheme 2. Synthesis of chromane **4a**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C; (ii) NaH, TBAI, THF, 20 °C.

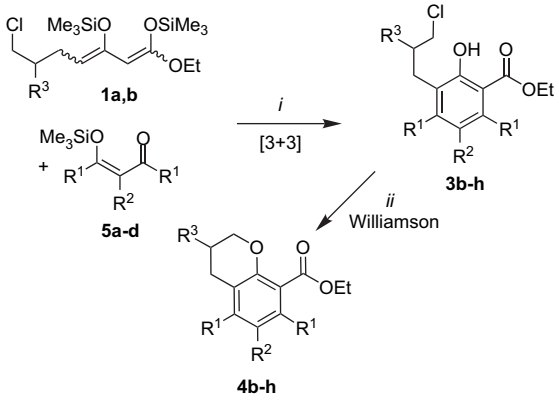
2.2. [3+3] Cyclizations of 3-silyloxyalk-2-en-1-ones

The [3+3] cyclization of 1,3-bis-silyl enol ether **6a** with 3-silyloxyalk-2-en-1-one **5a** has been reported to give salicylate **7**.[6] The cyclization proceeds by $TiCl_4$-mediated conjugate addition of the terminal carbon atom of the bis-silyl enol ether onto **5a**, cyclization, extrusion of siloxane, and aromatization (Scheme 3).



Scheme 3. Synthesis of salicylate **7** by Chan et al. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C.

The [3+3] cyclization of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes **1a**,**b** with 3-silyloxyalk-2-en-1-ones **5a–d** afforded the 2-(3-chloropropyl)phenols **3b–h**. The latter were transformed (by NaH and TBAI) into chromanes **4b–h** (Scheme 4, Table 1). The formation of **3b–h** can be explained, following the mechanism proposed by Chan,[6] by initial attack of carbon atom C-4 of **1a**,**b** onto the carbon atom attached to the silyloxy group of **5a–d**, cyclization by attack of carbon C-2 onto the carbonyl group and subsequent aromatization.



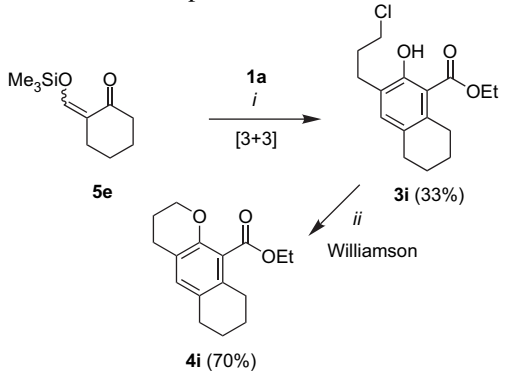
Scheme 4. Synthesis of chromanes **4b–h**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C; (ii) NaH, TBAI, THF, 20 °C.

Table 1. Synthesis of chromanes **4b–h**

5	3,4	R^1	R^2	R^3	% (3)[a]	% (4)[a]
a	**b**	Me	Me	H	52	90
b	**c**	Me	H	H	46	70
c	**d**	Me	Et	H	43	82
d	**e**	Et	H	H	42	65
a	**f**	Me	Me	Me	44	94
b	**g**	Me	H	Me	46	80
c	**h**	Et	H	Me	53	97

[a] Yields of isolated products.

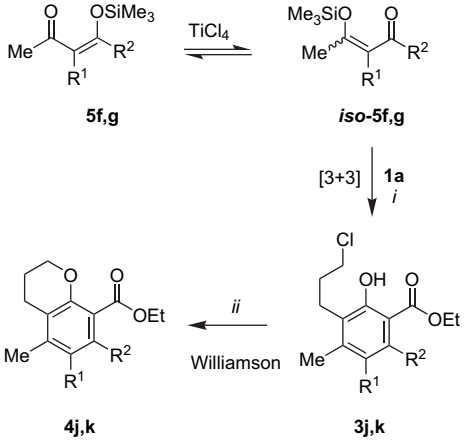
The [3+3] cyclization of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-diene **1a** with 3-silyloxyalk-2-en-1-one **5e**, prepared from 2-(hydroxymethylidene)cyclohexan-1-one, furnished tetrahydronaphthalene **3i** (Scheme 5). In contrast to **3b–h**, the formation of regioisomers is theoretically possible in case of **3i**. The regioselective formation of **3i** can be explained by the same mechanism as described for **3b–h**, i.e. by initial attack of carbon atom C-4 of **1a** onto the carbon attached to the silyloxy group of **5e**. Treatment of **3i** with NaH/TBAI afforded the tricyclic benzopyran **4i**. The structure of **4i** was established by H,H-COSY, C,H-COSY, HMBC, and NOESY experiments.



Scheme 5. Synthesis of chromane **4i**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C; (ii) NaH, TBAI, THF, 20 °C.

The [3+3] cyclization of **1a** with 3-silyloxyalk-2-en-1-one **5f**, available by silylation of 2-acetylcyclohexanone,

regioselectively afforded **3j**, which was transformed into the tricyclic chromane **4j** (Scheme 6, Table 2). The formation of **3j** can be explained by $TiCl_4$-mediated isomerization of **5f** into *iso*-**5f** and subsequent attack of carbon C-4 of **1a** onto the carbon attached to the silyloxy group of *iso*-**5e**. The structure of **4j** was established by H,H-COSY, C,H-COSY, HMBC, and NOESY experiments. The cyclization of **1a** with 3-silyloxyalk-2-en-1-one **5g**, prepared from 2-acetyltetralone, regioselectively afforded **3k**, which was transformed into the tetracyclic chromane **4k**. The formation of **3k** presumably follows the mechanism as discussed for **3j**. The structure of **4k** was established by H,H-COSY, C,H-COSY, HMBC, and NOESY experiments. Notably, the structures of **3j**,**k** and **4j**,**k** have to be revised with respect to our preliminary communication.



Scheme 6. Synthesis of chromanes **4j**,**k**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C; (ii) NaH, TBAI, THF, 20 °C.

Table 2. Products and yields

3,4	R^1	R^2	% (3)[a]	% (4)[a]
j	$-(CH_2)_4-$		34	87
k	$-(CH_2)_2C_6H_4-$		27	88

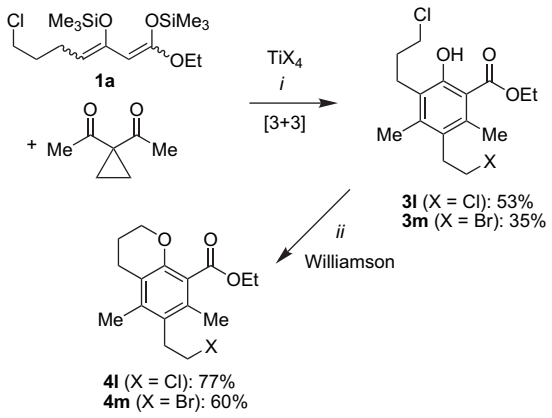
[a] Isolated yields.

2.3. [3+3] Cyclizations of 1,1-diacetylcyclopropane

We have recently reported[9] the synthesis of 2-(3-chloropropyl)-4-(2-chloroethyl)phenol **3l** by $TiCl_4$-mediated cyclization of **1a** with 1,1-diacetylcyclopropane (**6**) (Scheme 7). The formation of **3l** can be explained by initial [3+3] cyclization to give a spirocyclopropane, which is cleaved by attack of $TiCl_4$ (homo-Michael reaction).[10] Likewise, the $TiBr_4$-mediated cyclization of **1a** with **6** furnished 2-(3-chloropropyl)-4-(2-bromoethyl)phenol **3m**. Treatment of **3l**,**m** with NaH/TBAI afforded the novel functionalized chromanes **4l**,**m**.

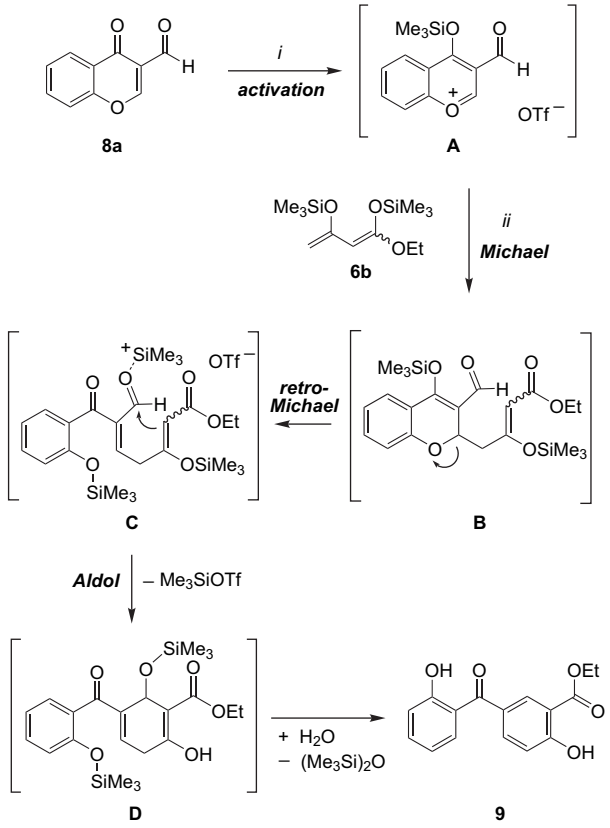
2.4. [3+3] Cyclizations of 3-formylchromones

We have recently reported the reaction of 1,3-bis-silyl enol ethers with 3-formylchromones to give functionalized benzophenones.[11] The formation of the products can be explained by a domino 'Michael/Retro-Michael/Aldol' reaction following the mechanism as given in Scheme 8. The reaction can be formally regarded as a [3+3] cyclization of an activated enal and resemble the [3+3] cyclizations of 1,3-bis-silyl enol ethers with 3-silyloxyalk-2-en-1-ones discussed above. Herein, we



Scheme 7. Synthesis of chromanes **4l**,**m**. Reagents and conditions: (i) TiX_4 (X=Cl, Br, 2 equiv), CH_2Cl_2, −78→20 °C; (ii) NaH, TBAI, THF, 20 °C.

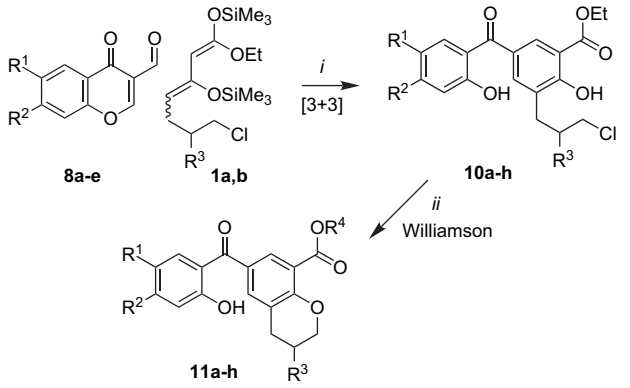
report the reaction of formylchromones with 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes, which allow for an efficient synthesis of 6-(2-hydroxybenzoyl)-3,4-chromanes.



Scheme 8. Mechanism of the cyclization of 1,3-bis-silyl enol ethers with 3-formylchromones (Ref. 11). Reagents and conditions: (i) Me_3SiOTf (0.3 equiv), 20 °C, 10 min; (ii) (1) **2a** (1.3 equiv), CH_2Cl_2, 0→20 °C, 12 h; (2) HCl (10%).

The TMSOTf catalyzed reaction of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes **1a**,**b** with 3-formylchromones **8a–e** afforded the 4-(2-hydroxybenzoyl)salicylates **10a–h** containing a remote chloride group (Scheme 9, Table 3). The mechanism of these reactions can be explained analogously to the formation of **9** (Scheme 8). Treatment of **10a–h** with NaH/TBAI afforded the 6-(2-hydroxybenzoyl)-3,4-dihydro-2*H*-chromenes **11a**,**b**,**e–h** by intramolecular Williamson reaction. These products were isolated in the

form of their carboxylic acids (except for **11a**); the hydrolysis of the ester group presumably occurred during the aqueous work-up using hydrochloric acid (10%). Notably, the employment of the latter proved to be mandatory for a successful isolation of any type of product of this reaction.



Scheme 9. Synthesis of **11a–h**. Reagents and conditions: (i) (1) Me_3SiOTf (0.3 equiv), 0 °C, 10 min; (2) **1a**,**b** (1.3 equiv), CH_2Cl_2, 20 °C, 12 h; (3) HCl (10%); (ii) NaH (1.5 equiv), TBAI (2.0 equiv), THF, 20 °C, 20 h; for **11b**,**e–h**: HCl (10%).

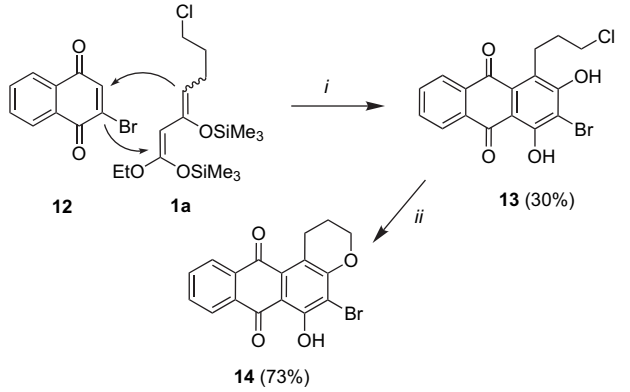
Table 3. Products and yields

8	1	10/11	R^1	R^2	R^3	R^4	% (**10**)	% (**11**)[a]
a	**a**	**a**	H	H	H	Et	41	68
b	**a**	**b**	Me	H	H	H	54	94
c	**a**	**c**	Et	H	H	H	48	—[b]
d	**a**	**d**	Cl	H	H	H	51	—[b]
e	**a**	**e**	Cl	Me	H	H	47	70
a	**b**	**f**	H	H	Me	H	43	71
b	**b**	**g**	Me	H	Me	H	41	86
d	**b**	**h**	Cl	H	Me	H	38	73

[a] Isolated yields.
[b] Experiment not carried out.

2.5. [4+2] Cyclization of 2-bromonaphthalene-1,4-dione

Some years ago, Brassard et al. reported the [4+2] cycloaddition of 1,3-bis-silyl enol ethers with bromoquinones to give anthraquinones.[12] The reaction of **1a** with 2-bromonaphthalene-1,4-dione (**12**) afforded the functionalized anthraquinone **13**. Surprisingly, the product contained a bromide group located at the benzene moiety formed during the reaction. Treatment of **13** with NaH/TBAI afforded chromane **14** (Scheme 10). The formation of **13** can be explained by a radical mechanism.



Scheme 10. Synthesis of **14**. Reagents and conditions: (i) (1) THF, 1 h, −78 °C, (2) 14 h, −78→20 °C, (3) HCl (10%); (ii) NaH, TBAI, THF, 20 °C.

3. Conclusions

We have reported the synthesis of functionalized chromanes by double-annulation reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes with 1,1,3,3-tetramethoxypropane, 3-silyloxyalk-2-en-1-ones, and 1,1-diacetylcyclopropane. The products were formed by [3+3] cyclization of the starting materials to give 2-(3-chloropropyl)phenols and subsequent cyclization by intramolecular nucleophilic substitution. 6-(2-Hydroxybenzoyl)chromanes were prepared based on double-annulation reactions of 3-formylchromones; an anthraquinone derived chromane was prepared from 2-bromonaphthoquinone. The general strategy reported herein allows for a convenient synthesis of a variety of functionalized chromanes. Notably, the substitution patterns of these products are not readily available by other methods.

4. Experimental

4.1. General

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra, the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O), or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

4.2. General procedure for the synthesis of salicylates 3a–k

To a CH_2Cl_2 solution of **1a**,**b** and **2** or **5a–g** was dropwise added $TiCl_4$ at −78 °C under argon atmosphere. The solution was stirred at −78 °C for 30 min and was subsequently warmed to 20 °C within 18 h. To the solution was added a saturated aqueous solution of $NaHCO_3$. The organic and the aqueous layer were separated and the latter was extracted with ether. The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane/EtOAc).

4.2.1. Ethyl 3-(3-chloropropyl)-2-hydroxybenzoate (3a). Starting with **1a** (1.75 g, 5.0 mmol), **2** (0.8 g, 5.0 mmol), and $TiCl_4$ (0.94 g, 5.0 mmol) in CH_2Cl_2 (15 mL), **3a** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 30:1) as a colorless oil (0.5 g, 42%). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.41 (t, J=7.1 Hz, 3H, CH_3), 2.11 (quint, J=6.5 Hz, 2H, CH_2), 2.82 (t, J=7.1 Hz, 2H, CH_2), 3.54 (t, J=6.6 Hz, 2H, CH_2–Cl), 4.41 (q, J=7.1 Hz, 2H, OCH_2), 6.18 (m, 1H, CH of Ar), 7.32–7.35 (m, 1H, CH of Ar), 7.75 (d, 1H, CH of Ar), 11.13 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.2 (CH_3), 21.2, 31.9, 44.6, 61.4 (CH_2), 112.3, 118.6, 128.0, 128.9 (C), 135.9 (CH), 159.9, 170.6 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3140 (m), 2986 (m), 1671 (s), 1615 (s), 1449 (s), 1401 (s), 1374 (s), 1297 (s), 1249 (s), 1178 (s), 1152 (s), 1087 (m), 1026 (m), 761 (s), 725 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=212 (4.42), 242 (3.92), 310 (3.55) nm. MS (EI, 70 eV): m/z (%)=244 ($M^+[^{37}Cl]$, 11), 242 ($M^+[^{35}Cl]$, 34), 196 (19), 161 (100),

134 (44), 105 (21), 77 (24), 51 (9), 27 (10). HRMS (ESI): calcd for $C_{12}H_{16}ClO_3$ ([M+1]$^+$): 245.07584 [^{37}Cl], 243.07879 [^{35}Cl]; found: 245.07565 [^{37}Cl], 243.0787 [^{35}Cl]. Anal. Calcd for $C_{12}H_{15}ClO_3$ (242.699): C, 59.39; H, 6.23. Found: C, 60.88; H, 6.36.

4.2.2. Ethyl 3-(3-chloropropyl)-2-hydroxy-4,5,6-trimethylbenzoate (3b). The synthesis of **3b** has been previously reported.[9] Starting with **1a** (1.23 g, 3.5 mmol), **5a** (0.61 g, 3.5 mmol), and $TiCl_4$ (0.66 g, 3.5 mmol) in CH_2Cl_2 (10 mL), **3b** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 30:1) as a colorless oil (0.516 g, 52%).

4.2.3. Ethyl 3-(3-chloropropyl)-2-hydroxy-4,6-dimethylbenzoate (3c). Starting with **1a** (2.90 g, 8.2 mmol), **5b** (1.42 g, 8.2 mmol), and $TiCl_4$ (1.55 g, 8.2 mmol) in CH_2Cl_2 (15 mL), **3c** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 30:1) as a colorless oil (1.02 g, 46%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.42 (t, J=7.1 Hz, 3H, CH_3), 2.00 (quint, J=6.6 Hz, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.78 (t, J=7.7 Hz, 2H, CH_2), 3.61 (t, J=6.7 Hz, 2H, CH_2–Cl), 4.42 (q, J=7.1 Hz, 2H, OCH_2), 6.54 (s, 1H, CH), 11.76 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.2, 19.8 (CH_3), 23.6, 23.9, 31.8, 45.3, 61.4 (CH_2), 109.7 (C), 124.8 (CH), 125.2, 138.4, 143.1, 161.1, 172.2 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2977 (s), 2937 (s), 1938 (w), 1653 (s), 1563 (m), 1447 (s), 1396 (s), 1376 (s), 1349 (s), 1311 (s), 1273 (s), 1232 (s), 1175 (s), 1037 (s), 848 (s), 811 (s). UV–vis (CH_3CN, nm): λ_{max} (log ε)= 216 (4.45), 253 (4.00), 316 (3.60) nm. MS (EI, 70 eV): *m*/*z* (%)=272 (M$^+$[^{37}Cl], 6), 270 (M$^+$[^{35}Cl], 21), 224 (20), 189 (100), 162 (25), 133 (7), 105 (5), 91 (10), 27 (5.3). HRMS (ESI): calcd for $C_{14}H_{20}ClO_3$ ([M+1]$^+$): 273.10714 [^{37}Cl], 271.11009 [^{35}Cl]; found: 273.10647 [^{37}Cl], 271.10950 [^{35}Cl]. Anal. Calcd for $C_{14}H_{19}ClO_3$ (270.752): C, 62.11; H, 7.10. Found: C, 61.20; H, 7.80.

4.2.4. Ethyl 3-(3-chloropropyl)-5-ethyl-2-hydroxy-4,6-dimethylbenzoate (3d). Starting with **1a** (1.75 g, 5.0 mmol), **5c** (1.42 g, 5.0 mmol), and $TiCl_4$ (0.94 g, 5.0 mmol) in CH_2Cl_2 (15 mL), **3d** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 30:1) as a colorless oil (0.630 g, 43%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ_C=1.10 (t, J=7.2 Hz, 3H, CH_3), 1.39 (t, J=7.1 Hz, 3H, CH_3), 1.99 (quint, J=6.7 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.65 (q, J=7.5 Hz, 2H, CH_2), 2.85 (m, J=6.0 Hz, 2H, CH_2), 3.61 (t, J=6.7 Hz, 2H, CH_2–Cl), 4.43 (q, J=7.1 Hz, 2H, OCH_2), 10.83 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=13.7, 14.2, 15.9, 18.3 (CH_3), 22.8, 24.1, 30.1, 45.3, 61.4 (CH_2), 111.5, 125.3, 133.1, 135.1, 141.3, 157.3, 172.1 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2967 (s), 2874 (m), 1726 (m), 1651 (s), 1599 (s), 1448 (s), 1701 (s), 1375 (s), 1322 (s), 1269 (s), 1195 (s), 1090 (s), 1037 (s), 806 (s), 768 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=218 (4.42), 256 (3.95), 320 (3.58) nm. MS (EI, 70 eV): *m*/*z* (%)=300 (M$^+$[^{37}Cl], 3), 298 (M$^+$[^{35}Cl], 14), 252 (20), 217 (100), 189 (16), 176 (40), 161 (30), 91 (8), 28 (44). Anal. Calcd for $C_{16}H_{23}ClO_3$ (298.805): C, 64.31; H, 7.76. Found: C, 64.35; H, 8.10.

4.2.5. Ethyl 3-(3-chloropropyl)-4,6-diethyl-2-hydroxybenzoate (3e). Starting with **1a** (1.75 g, 5.0 mmol), **5d** (1.00 g, 5.0 mmol), and $TiCl_4$ (0.94 g, 5.0 mmol) in CH_2Cl_2 (15 mL), **3e** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 30:1) as a colorless oil (0.62 g, 41%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.21 (t, J=7.5 Hz, 6H, 2×CH_3), 1.42 (t, J=7.2 Hz, 3H, CH_3), 2.02 (quint, J=7.2 Hz, 2H, CH_2), 2.62 (q, J=7.6 Hz, 2H, CH_2), 2.79 (m, J=6.0 Hz, 2H, CH_2), 2.91 (q, J=7.5 Hz, 2H, CH_2), 3.61 (t, J=6.6 Hz, 2H, CH_2–Cl), 4.44 (q, J=7.2 Hz, 2H, OCH_2), 6.58 (s, 1H, CH), 11.68 (s, 1H, OH). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2969 (m), 1654 (s), 1614 (m), 1453 (m), 1401 (s), 1317 (m), 1264 (s), 1171 (s), 1073 (m), 1024 (m), 816 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=217 (4.44), 254 (4.04), 316 (3.64) nm. MS (EI, 70 eV): *m*/*z* (%)=300 (M$^+$[^{37}Cl], 3), 298 (M$^+$[^{35}Cl], 11), 252 (15), 217 (100), 189 (14), 133 (9), 70 (10), 28 (29). Anal. Calcd for $C_{16}H_{23}ClO_3$ (298.805): C, 64.31; H, 7.76. Found: C, 64.24; H, 9.30.

4.2.6. Ethyl 3-(3′-chloroisobutyl)-2-hydroxy-4,5,6-trimethylbenzoate (3f). The synthesis of **3f** has been previously reported.[9] Starting with **1b** (1.09 g, 3.0 mmol), **5a** (0.56 g, 3.0 mmol), and $TiCl_4$ (0.56 g, 3.0 mmol) in CH_2Cl_2 (10 mL), **3f** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 30:1) as a colorless oil (0.398 g, 44%).

4.2.7. Ethyl 3-(3-chloro-2-methylpropyl)-2-hydroxy-4,6-dimethylbenzoate (3g). Starting with **1b** (1.46 g, 4.0 mmol), $TiCl_4$ (0.75 g, 4.0 mmol), and **5b** (0.69 g, 4.0 mmol) in CH_2Cl_2 (10 mL), **3g** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 30:1) as a colorless oil (520 mg, 46%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.05 (d, J=6.7 Hz, 3H, CH_3), 1.42 (t, J=7.1 Hz, 3H, CH_3), 2.23 (m, 1H, CH), 2.27 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.59–2.79 (m, J=24, 6.9 Hz, 2H, CH_2), 3.42–3.56 (dq, J=7.0 Hz, 2H, CH_2–Cl), 4.43 (q, J=7.2 Hz, 2H, OCH_2), 6.55 (s, 1H, CH), 11.78 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=15.3, 18.9, 21.2, 24.9 (CH_3), 31.8, 36.8 (CH), 52.5, 62.5 (CH_2), 109.8, 124.6 (C), 125.9 (CH), 138.4, 143.6, 161.4, 172.3 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2959 (m), 2933 (m), 1654 (s), 1618 (m), 1449 (m), 1397 (m), 1268 (s), 1174 (m), 1097 (m), 1042 (m), 846 (m), 808 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=216 (4.45), 254 (4.02), 315 (3.62) nm. MS (EI, 70 eV): *m*/*z* (%)=286 (M$^+$[^{37}Cl], 1.4), 284 (M$^+$[^{35}Cl], 8), 203 (57), 194 (22), 161 (40), 148 (32), 147 (76), 120 (20), 91 (20), 32 (23), 28 (100). Anal. Calcd for $C_{15}H_{21}ClO_3$ (284.778): C, 63.25; H, 7.14. Found: C, 62.62; H, 7.49.

4.2.8. Ethyl 3-(3-chloro-2-methylpropyl)-4,6-diethyl-2-hydroxybenzoate (3h). Starting with **1b** (1.82 g, 5.0 mmol), $TiCl_4$ (0.95 g, 5.0 mmol), and **5d** (1.0 g, 5.0 mmol) in CH_2Cl_2 (10 mL), **3h** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 30:1) as a colorless oil (0.820 g, 53%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.07 (d, J=6.8 Hz, 3H, CH_3), 1.19 (m, J=7.1 Hz, 6H, 2×CH_3), 1.45 (t, J= 7.1 Hz, 3H, CH_3), 2.28 (m, J=4.5 Hz, 1H, CH), 2.62 (m, J=7.0 Hz, 2H, CH_2), 2.75 (q, J=7.0 Hz, 2H, CH_2), 2.91 (q, J=7.3 Hz, 2H, CH_2), 3.51 (dq, J=6.8, 5.0 Hz, 2H, CH_2–Cl), 4.44 (q, J=7.1 Hz, 2H, OCH_2), 10.77 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.4, 15.5, 16.7, 18.3 (CH_3), 26.6, 30.1, 31.8 (CH_2), 36.5 (CH), 51.9, 61.8 (CH_2), 109.1 (C), 121.9 (CH), 123.9, 144.9, 149.7, 161.3, 172.1 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2972 (s), 2877 (s), 1654 (s), 1613 (m), 1564 (m), 1460 (s), 1399 (s), 1376 (s), 1315 (s), 1267 (s),

1171 (s), 1071 (m), 946 (m), 867 (m), 813 (m), 725 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=217 (4.48), 255 (4.05), 317 (3.64) nm. MS (EI, 70 eV): *m/z* (%)=314 ($M^+[^{37}Cl]$, 2), 312 ($M^+[^{35}Cl]$, 9), 232 (43), 231 (100), 190 (12), 189 (51), 176 (29), 133 (13), 28 (25). HRMS (ESI): calcd for $C_{17}H_{25}ClO_3$ ($[M+1]^+$): 315.15410 [^{37}Cl], 313.15705 [^{35}Cl]; found: 315.15432 [^{37}Cl], 313.15664 [^{35}Cl].

4.2.9. Ethyl 3-(3-chloropropyl)-5,6,7,8-tetrahydro-2-hydroxynaphthalene-1-carboxylate (3i). Starting with **1a** (2.8 g, 8.0 mmol), $TiCl_4$ (1.5 g, 8.0 mmol), and **5e** (1.59 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **3i** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless solid (0.72 g, 33%). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.42 (t, *J*=7.1 Hz, 3H, CH_3), 1.74 (m, *J*=3.3 Hz, 4H, 2×CH_2), 2.11 (quint, *J*=6.9 Hz, 2H, CH_2), 2.69 (m, 2H, CH_2), 2.75 (m, *J*=7.0 Hz, 2H, CH_2), 2.97 (m, 2H, CH_2), 3.55 (t, *J*=6.7 Hz, 2H, CH_2–Cl), 4.43 (q, *J*=7.1 Hz, 2H, OCH_2), 7.01 (s, 1H, CH), 11.18 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.4 (CH_3), 22.5, 23.6, 27.5, 29.6, 29.9, 32.2, 44.9, 61.6 (CH_2), 115.3, 126.2, 128.0 (C), 136.4 (CH), 137.2, 155.3, 172.2 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2934 (s), 2860 (m), 1653 (s), 1431 (s), 1373 (s), 1316 (s), 1283 (s), 1159 (m), 1023 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=213 (4.41), 252 (3.99), 324 (3.80) nm. MS (EI, 70 eV): *m/z* (%)=298 ($M^+[^{37}Cl]$, 7), 296 ($M^+[^{35}Cl]$, 25), 250 (56), 215 (100), 188 (42), 160 (10), 114 (9), 91 (10), 28 (7). HRMS (ESI): calcd for $C_{16}H_{22}ClO_3$ ($[M+1]^+$): 299.12279 [^{37}Cl], 297.12574 [^{35}Cl]; found: 299.12179 [^{37}Cl], 297.12495 [^{35}Cl]. Anal. Calcd for $C_{16}H_{22}ClO_3$ (297.797): C, 64.85; H, 7.14. Found: C, 64.58; H, 7.35.

4.2.10. Ethyl 3-(3-chloropropyl)-5,6,7,8-tetrahydro-2-hydroxy-4-methylnaphthalene-1-carboxylate (3j). Starting with **1a** (1.40 g, 4.0 mmol), $TiCl_4$ (0.72 g, 4.0 mmol), and **5f** (0.85 g, 4.0 mmol) in CH_2Cl_2 (15 mL), **3j** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 30:1) as a colorless oil (0.42 g, 34%). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.41 (t, *J*=7.1 Hz, 3H, CH_3), 1.68 (m, *J*=2.5 Hz, 2H, CH_2), 1.76 (m, *J*=2.0 Hz, 2H, CH_2), 1.98 (quint, *J*=6.8 Hz, 2H, CH_2), 2.21 (s, 3H, CH_3), 2.58 (t, *J*=6.5 Hz, 2H, CH_2), 2.86 (m, *J*=7.0 Hz, 2H, CH_2), 2.98 (t, *J*=6.2 Hz, 2H, CH_2), 3.61 (t, *J*=6.7 Hz, 2H, CH_2–Cl), 4.42 (q, *J*=7.1 Hz, 2H, OCH_2), 11.23 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.2, 15.7 (CH_3), 22.8, 23.0, 23.9, 27.9, 30.3, 32.2, 45.3, 61.4 (CH_2), 110.2, 125.2, 127.4, 136.9, 142.4, 158.1, 172.2 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3416 (w), 2931 (s), 2863 (m), 1650 (s), 1598 (m), 1434 (s), 1401 (s), 1375 (s), 1316 (s), 1275 (s), 1241 (s), 1202 (s), 1149 (m), 1035 (m), 804 (m), 651 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=216.5 (4.36), 257.9 (3.98), 320.7 (3.59) nm. MS (EI, 70 eV): *m/z* (%)=312 ($M^+[^{37}Cl]$, 5), 310 ($M^+[^{35}Cl]$, 17), 264 (27), 230 (16), 229 (100), 202 (15), 28 (13). Anal. Calcd for $C_{17}H_{23}ClO_3$ (310.816): C, 65.69; H, 7.46. Found: C, 65.39; H, 7.78.

4.2.11. Ethyl-2-(3-chloropropyl)-9,10-dihydro-3-hydroxy-1-methylphenanthrene-4-carboxylate (3k). Starting with **1a** (2.8 g, 8.0 mmol), **5g** (2.08 g, 8.0 mmol), and $TiCl_4$ (1.52 g, 8.0 mmol) in CH_2Cl_2 (20 mL), **3k** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 30:1) as a colorless oil (0.78 g, 27%). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.00 (t, *J*=7.1 Hz, 3H, CH_3), 2.03 (quint, 7.5 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.65 (t, *J*=5.6 Hz, 2H, CH_2), 2.81 (t, *J*=6.7 Hz, 2H, CH_2), 2.92 (t, *J*=6.2 Hz, 2H, CH_2), 3.64 (t, *J*=7.7 Hz, 2H, CH_2–Cl), 4.16 (q, *J*=7.1 Hz, 2H, OCH_2), 7.06–7.09 (dd, 1H, CH of Ar), 7.12–7.18 (m, 2H, 2×CH of Ar), 7.21–7.24 (dd, 1H, CH of Ar), 9.95 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=13.4, 15.7 (CH_3), 24.2, 25.7, 29.2, 31.1, 45.2, 61.3 (CH_2), 109.0 (C), 125.4 (CH), 126.7 (C), 126.8, 126.9, 129.2 (CH), 130.6, 134.6 (C), 137.6 (2C), 139.7, 156.5, 172.2 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3293 (w), 2956 (m), 1662 (s), 1592 (m), 1443 (m), 1397 (m), 1373 (m), 1313 (s), 1246 (s), 1188 (s), 1162 (m), 1071 (m), 1029 (m), 765 (s). UV–vis (CH_3CN, nm): λ_{max} (log ε)=204 (4.48), 232 (4.40), 280 (3.94), 341 (3.89) nm. MS (EI, 70 eV): *m/z* (%)=358 ($M^+[^{35}Cl]$, 6), 344 (6), 312 (5), 277 (16), 263 (32), 242 (24), 196 (13), 161 (100), 134 (41), 105 (19), 77 (22), 28 (39). Anal. Calcd for $C_{21}H_{23}ClO_3$ (358.859): C, 70.28; H, 6.46. Found: C, 70.44; H, 6.11.

4.3. General procedure for the preparation of salicylates (3l,m)

The synthesis of **3l**,**m** has been previously reported.[9] To a stirred CH_2Cl_2 solution (100 mL) of 1,1-diacetylcyclopropane (**6**) (1.1 mmol) and 1,3-bis-silyl enol ether **1a** (1.6 mmol) was added $TiCl_4$ (2.0 mmol in 2 mL CH_2Cl_2) at −78 °C under argon atmosphere in the presence of molecular sieves (4 Å, 1.0 g). The temperature of the reaction mixture was allowed to rise to 20 °C during 6 h. The solution was stirred for additional 6 h at 20 °C. The reaction mixture was filtered and the filtrate was poured into an aqueous solution of HCl (10%, 100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3× 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc) to give **3l**,**m**.

4.3.1. Ethyl 5-(2-chloroethyl)-3-(3-chloropropyl)-2-hydroxy-4,6-dimethylbenzoate (3l). The synthesis of **3l** has been previously reported.[9] Starting with CH_2Cl_2 (250 mL), **6** (0.48 g, 3.8 mmol), **1a** (2.0 g, 5.7 mmol), and $TiCl_4$ (2.16 g, 11.4 mmol), **3l** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 25:1) as a colorless solid (0.672 g, 53%).

4.3.2. Ethyl 5-(2-bromoethyl)-3-(3-chloropropyl)-2-hydroxy-4,6-dimethylbenzoate (3m). The synthesis of **3m** has been previously reported.[9] Starting with **1a** (1.58 g, 4.5 mmol), **6** (0.38 g, 3.0 mmol), $TiBr_4$ (2.21 g, 6.0 mmol), and CH_2Cl_2 (200 mL), **3m** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless solid (0.397 g, 35%).

4.4. General procedure for the synthesis of 5-(2-hydroxybenzoyl)salicylates (10a–h)

To the 3-formylchromone **8a–e** (1.0 equiv) was added Me_3SiOTf (0.3 equiv) at 20 °C. After stirring for 10 min, CH_2Cl_2 (8 mL) was added, the solution was cooled to 0 °C and the 1,3-bis-silyl enol ether **1a**,**b** (1.3 equiv) was added. The mixture was stirred for 12 h at 20 °C and was

subsequently poured into an aqueous solution of hydrochloric acid (10%). The organic and the aqueous layer were separated and the latter was extracted with Et_2O (3×80 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc = 10:1→3:1).

4.4.1. Ethyl 3-(3-chloropropyl)-5-(2-hydroxybenzoyl)-salicylate (10a). Starting with **8a** (268 mg, 1.54 mmol), Me_3SiOTf (103 mg, 0.46 mmol), and 1,3-bis-silyl enol ether **1a** (703 mg, 2.00 mmol), **10a** was isolated as a yellow solid (229 mg, 41%), mp=107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.41 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 2.15 (m, 2H, $CH_2CH_2CH_2$), 2.90 (t, *J*=7.1 Hz, 2H, $ArCH_2$), 3.58 (t, *J*=6.5 Hz, 2H, CH_2–Cl), 4.44 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 6.92 (m, 1H, Ar), 7.09 (dd, *J*=8.4, 1.0 Hz, 1H, Ar), 7.53 (m, 1H, Ar), 7.59 (dd, *J*=8.0, 1.5 Hz, 1H, Ar), 7.40 (d, *J*=2.3 Hz, 1H, Ar), 8.18 (d, *J*=2.3 Hz, 1H, Ar), 11.65 (s, 1H, OH), 11.88 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=14.1 (CH_3), 27.2, 31.6 (CH_2), 44.4 (CH_2Cl), 62.1 (OCH_2CH_3), 111.9 (C), 118.5, 118.7 (CH), 119.0, 128.4, 129.5 (C), 130.5, 132.9, 136.1, 136.6 (CH), 162.9, 163.0 (C-OH), 169.9, 199.2 (C=O). IR (KBr): $\tilde{\nu}$ = 3329 (m), 3095 (m), 3070 (m), 2991 (m), 2963 (m), 2938 (m), 1675 (s), 1624 (s), 1590 (s), 1483 (s), 1450 (s), 1407 (s), 1381 (s), 1348 (s), 1328 (s), 1289 (s), 1264 (s), 1237 (s), 1192 (s), 1158 (s), 1134 (w), 1023 (m), 807 (w), 770 (s), 738 (m), 706 (m), 659 (w) cm^{-1}. UV–vis (CH_3CN): λ_{max} (log ε): 316 (3.93), 289 (3.99), 240 (4.28), 214 (4.47) nm. MS (EI, 70 eV): *m*/*z* (%)=362 (M^+, 64), 317 (4), 281 (67), 252 (19), 242 (24), 197 (6), 161 (10), 121 (100), 93 (9). HRMS (FT-ICR): calcd for $C_{19}H_{19}O_5Cl$ ([M+1]$^+$): 363.09938; found: 363.09970. Anal. Calcd for $C_{19}H_{19}ClO_5$: C, 62.90; H, 5.28. Found: C, 62.72; H, 5.51.

4.4.2. Ethyl 3-(3-chloropropyl)-2-hydroxy-5-(2-hydroxy-5-methylbenzoyl)benzoate (10b). Starting with **8b** (376 mg, 2.00 mmol), Me_3SiOTf (133 mg, 0.60 mmol), and 1,3-bis-silyl enol ether **1a** (917 mg, 2.60 mmol), **10b** was isolated as a yellow solid by column chromatography with *n*-hexane/EtOAc = 25:1 (410 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.43 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 2.16 (m, *J*=6.6 Hz, 2H, $CH_2CH_2CH_2Cl$), 2.28 (s, 3H, CH_3), 2.90 (t, *J*=7.1 Hz, 2H, $ClCH_2CH_2CH_2$), 3.58 (t, *J*=6.5 Hz, 2H, $CH_2CH_2CH_2Cl$), 4.46 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 7.00 (d, *J*=2.3 Hz, 1H, Ar), 7.26 (d, *J*=2.0 Hz, 1H, Ar), 7.36 (dd, *J*=1, 2 Hz, 1H, Ar), 7.74 (d, *J*=2.0 Hz, 1H, Ar), 8.19 (d, *J*=2.3 Hz, 1H, Ar), 11.63 (s, 1H, OH), 11.68 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=14.2, 20.5 (CH_3), 27.2, 31.5, 44.3, 62.0 (CH_2), 112.1 (C), 118.3 (CH), 118.8, 127.9, 128.6, 129.4 (C), 130.6, 132.7, 136.7, 137.2 (CH), 160.0, 163.0, 170.1, 199.2 (C). MS (EI, 70 eV): *m*/*z* (%)=378 (M^+[^{37}Cl ^{35}Cl], 18), 376 (M^+[^{35}Cl ^{35}Cl], 55), 340 (34), 295 (55), 206 (31), 135 (100), 44 (72). IR (KBr): $\tilde{\nu}$ = 2990 (w), 1674 (s), 1631 (s), 1583 (s), 1484 (m), 1406 (s), 1378 (s), 1348 (s), 1290 (s), 1236 (s), 1177 (s), 1023 (m), 786 (m), 705 (m) cm^{-1}. UV–vis (CH_3CN): λ_{max} (log ε)=214.9 (4.45), 240.3 (4.29), 285.3 (3.99), 343.5 (3.74) nm. Anal. Calcd for $C_{20}H_{21}O_5Cl$: C, 63.74; H, 5.62. Found: C, 63.60; H, 5.72.

4.4.3. Ethyl 3-(3-chloropropyl)-2-hydroxy-5-(2-hydroxy-5-ethylbenzoyl)benzoate (10c). Starting with **8c** (505 mg, 2.50 mmol), Me_3SiOTf (167 mg, 0.75 mmol), and 1,3-bis-silyl enol ether **1a** (1.147 mg, 3.25 mmol), **10c** was isolated as a yellow solid by column chromatography with *n*-hexane/EtOAc = 25:1 (472 mg, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.20 (t, *J*=7.6 Hz, 3H, CH_3CH_2), 1.42 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 2.15 (m, *J*=6.4 Hz, 2H, $CH_2CH_2CH_2Cl$), 2.57 (q, *J*=7.5 Hz, 2H, CH_3CH_2), 2.89 (t, *J*=7.2 Hz, 2H, $ClCH_2CH_2CH_2$), 3.59 (t, *J*=6.5 Hz, 2H, $CH_2CH_2CH_2Cl$), 4.45 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 7.02 (d, *J*=8.4 Hz, 1H, Ar), 7.35–7.41 (m, *J*=2.1 Hz, 2H, Ar), 7.77 (t, *J*=1.5 Hz, 1H, Ar), 8.19 (d, *J*=2.3 Hz, 1H, Ar), 11.64 (s, 1H, OH), 11.68 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=14.1, 15.9 (CH_3), 27.2, 27.9, 31.7, 44.4, 62.0 (CH_2), 111.9 (C), 118.3, 118.8 (CH), 128.5, 129.6 (C), 130.8, 131.6 (CH), 134.4 (C), 136.1, 136.7 (CH), 161.1, 163.1, 170.1, 199.1 (C). IR (KBr): $\tilde{\nu}$ = 3167 (br), 2961 (m), 1675 (s), 1629 (m), 1588 (s), 1476 (m), 1342 (m), 1290 (m), 1254 (s), 1200 (s), 1166 (m), 1023 (m), 841 (m) cm^{-1}. UV–vis (CH_3CN): λ_{max} (log ε)=251.0 (4.42), 239.6 (4.26), 287.9 (3.96), 344.5 (3.71) nm. MS (EI, 70 eV): *m*/*z* (%)=392 (M^+[^{37}Cl], 8), 390 (M^+[^{35}Cl], 29), 310 (45), 226 (38), 225 (100), 148 (61), 147 (51), 133 (19), 74 (17), 28 (71). HRMS (ESI): calcd for $C_{21}H_{23}O_5Cl$: 390.12340; found: 390.12216.

4.4.4. Ethyl 3-(3-chloropropyl)-2-hydroxy-5-(2-hydroxy-5-chlorobenzoyl)benzoate (10d). Starting with **8d** (522 mg, 2.50 mmol), Me_3SiOTf (167 mg, 0.75 mmol), and 1,3-bis-silyl enol ether **1a** (1.147 g, 3.25 mmol), **10d** was isolated as yellow solid by column chromatography with *n*-hexane/EtOAc = 25:1 (507 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.42 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 2.16 (m, *J*=6.5 Hz, 2H, $CH_2CH_2CH_2Cl$), 2.92 (t, *J*=7.0 Hz, 2H, $ClCH_2CH_2CH_2$), 3.59 (t, *J*=6.5 Hz, 2H, $CH_2CH_2CH_2Cl$), 4.48 (q, *J*=7.2 Hz, 2H, OCH_2CH_3), 7.05 (d, *J*=8.5 Hz, 1H, Ar), 7.35–7.41 (dd, *J*=2.6 Hz, 6.2 Hz, 1H, Ar), 7.58 (d, *J*=2.6 Hz, 1H, Ar), 7.75 (t, *J*=1 Hz, 1H, Ar), 8.18 (d, *J*=2.3 Hz, 1H, Ar), 11.70 (s, 1H, OH), 11.74 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=14.1 (CH_3), 27.3, 31.6, 44.3, 62.2 (CH_2), 112.1, 119.7 (C), 120.1 (CH), 123.5, 127.8, 130.0 (C), 130.7, 131.9, 135.9, 136.4 (CH), 161.4, 163.5, 169.9, 198.2 (C). IR (KBr): $\tilde{\nu}$ = 3089 (br), 2956 (w), 1675 (m), 1630 (m), 1464 (m), 1335 (m), 1256 (m), 1206 (m), 1017 (w), 843 (m) cm^{-1}. UV–vis (CH_3CN): λ_{max} (log ε)=218.9 (4.39), 293.1 (3.84) nm. MS (EI, 70 eV): *m*/*z* (%)=398 (M^+[^{37}Cl ^{35}Cl], 4), 390 (M^+[^{35}Cl ^{35}Cl], 10), 363 (4), 320 (8), 291 (40), 275 (19), 219 (33), 217 (31), 203 (18), 146 (20), 129 (29), 74 (100), 28 (59). Anal. Calcd for $C_{19}H_{18}O_5Cl_2$: C, 57.63; H, 4.58. Found: C, 56.75; H, 5.43.

4.4.5. Ethyl 3-(3-chloropropyl)-2-hydroxy-5-(2-hydroxy-5-chloro-3-methylbenzoyl)benzoate (10e). Starting with **8e** (556 mg, 2.50 mmol), Me_3SiOTf (167 mg, 0.75 mmol), and 1,3-bis-silyl enol ether **1a** (1.147 mg, 3.25 mmol), **10e** was isolated as yellow solid by column chromatography with *n*-hexane/EtOAc = 25:1 (482 mg, 47%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.43 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 2.16 (m, *J*=6.5 Hz, 2H, $CH_2CH_2CH_2Cl$), 2.42 (s, 3H, CH_3), 2.92 (t, *J*=7.3 Hz, 2H, $ClCH_2CH_2CH_2$), 3.59 (t, *J*=6.5 Hz, 2H, $CH_2CH_2CH_2Cl$), 4.48 (q, *J*=7.1 Hz, 2H,

OCH_2CH_3), 6.99 (d, J=1.0 Hz, 1H, Ar), 7.56 (s, 1H, Ar), 7.73 (dd, J=1, 2 Hz, 1H, Ar), 8.17 (d, J=2.3 Hz, 1H, Ar), 11.67 (s, 1H, OH), 11.77 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=14.1, 20.8 (CH_3), 27.3, 31.6, 44.3, 62.1 (CH_2), 112.1, 117.9 (C), 120.5 (CH), 124.1, 127.9, 129.9 (C), 130.5, 132.3, 136.4 (CH), 145.4, 161.4, 163.3, 169.9, 197.9 (C). IR (KBr): $\tilde{\nu}$ = 3110 (br), 2957 (m), 1678 (s), 1626 (m), 1587 (s), 1471 (m), 1381 (m), 1340 (s), 1264 (s), 1242 (s), 1181 (s), 1022 (m), 843 (s) cm^{-1}. UV–vis (CH_3CN): λ_{max} (log ε)=218.9 (4.39), 293.1 (3.84) nm. MS (EI, 70 eV): m/z (%)=413 (M^+[^{37}Cl ^{35}Cl], 20), 411 (M^+[^{35}Cl ^{35}Cl], 36), 371 (11), 329 (26), 219 (35), 217 (39), 169 (49), 129 (24), 74 (100), 29 (19). HRMS (ESI): calcd for $C_{20}H_{20}O_5Cl_2$: 410.06878; found: 410.06721.

4.4.6. Ethyl 3-(3-chloro-2-methylpropyl)-2-hydroxy-5-(2-hydroxybenzoyl)benzoate (10f). Starting with formylchromone **8a** (348 mg, 2.0 mmol), Me_3SiOTf (133 mg, 0.60 mmol), and 1,3-bis-silyl enol ether **1b** (949 mg, 2.6 mmol), **10f** was isolated by column chromatography (silica gel, *n*-hexane/EtOAc = 25:1) as a yellow solid (324 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.08 (d, J=6.7 Hz, 3H, CH_3(CH)CH_2), 1.42 (t, J=7.2 Hz, 3H, OCH_2CH_3), 2.38 (m, J=5.7 Hz, 1H, CH_3(CH)CH_2), 2.69 (q, J=7.2 Hz, 1H, CH_3(CH)CH_2), 2.87 (q, J=7.1 Hz, 1H, CH_3(CH)CH_2), 3.43–3.57 (qq, J=5.4, 9.2 Hz, 2H, CH_3(CH)CH_2Cl), 4.46 (q, J=7.1 Hz, 2H, OCH_2CH_3), 6.89–6.94 (td, J=6.3, 1.0 Hz, 1H, Ar), 7.08–7.10 (dd, J=7.6, 1.0 Hz, 1H, Ar), 7.49–7.56 (td, J=7.0, 2.0 Hz, 1H, Ar), 7.59–7.62 (dd, J=6.3, 2.0 Hz, 1H, Ar), 7.72 (d, J=2.2 Hz, 1H, Ar), 8.20 (d, 2.2 Hz, 1H, Ar), 11.66 (s, 1H, OH), 11.89 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=14.2, 17.7 (CH_3), 34.4 (CH_2), 34.9 (CH), 50.6, 62.1 (CH_2), 112.1 (C), 118.5, 118.7 (CH), 119.1, 128.4, 128.8 (C), 130.6, 132.9, 136.2, 137.4 (CH), 163.0, 163.2, 170.1, 199.3 (C). UV–vis (CH_3CN): λ_{max} (log ε)=214.9 (4.46), 240.2 (4.28), 289.6 (3.99), 317.2 (3.94) nm. IR (KBr): $\tilde{\nu}$ = 3418 (br), 2960 (w), 1675 (s), 1624 (s), 1587 (s), 1482 (m), 1458 (m), 1348 (s), 1296 (s), 1263 (s), 1240 (s), 1180 (s), 766 (m) cm^{-1}. MS (EI, 70 eV): m/z (%)=378 (M^+[^{37}Cl], 1), 376 (M^+[^{35}Cl], 5), 295 (8), 253 (8), 121 (14), 32 (24), 28 (100). Anal. Calcd for $C_{20}H_{21}O_5Cl$: C, 63.75; H, 5.62. Found: C, 63.52; H, 5.65.

4.4.7. Ethyl 3-(3-chloro-2-methylpropyl)-2-hydroxy-5-(2-hydroxy-5-methylbenzoyl)benzoate (10g). Starting with **8b** (376 mg, 2.0 mmol), Me_3SiOTf (133 mg, 0.60 mmol), and 1,3-bis-silyl enol ether **1b** (948 mg, 2.60 mmol), **10g** was isolated as yellow solid by column chromatography with *n*-hexane/EtOAc = 25:1 (320 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.09 (d, J=6.7 Hz, 3H, CH_3(CH)CH_2), 1.44 (t, J=7.2 Hz, 3H, CH_3CH_2O), 2.28 (s, 3H, CH_3), 2.38 (m, J=5.5 Hz, 1H, CH_3(CH)CH_2), 2.69 (q, J=6.2 Hz, 1H, CH_3(CH)CH_2), 2.87 (q, J=6.5 Hz, 1H, CH_3(CH)CH_2), 3.45–3.58 (qq, J=5.2, 9.0 Hz, 2H, CH_3(CH)CH_2Cl), 4.46 (q, J=7.1 Hz, 2H, CH_3CH_2O), 7.00 (d, J=8.3 Hz, 1H, Ar), 7.31–7.38 (m, J=1.0, 2.0 Hz, 2H, Ar), 7.71 (d, J=2.2 Hz, 1H, Ar), 7.74 (d, J=2.0 Hz, 1H, Ar), 8.21 (d, J=2.3 Hz, 1H, Ar), 11.63 (s, 1H, OH), 11.68 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=14.2, 17.8, 20.5 (CH_3), 30.3 (CH), 34.4 (CH_2), 34.9 (CH_3), 50.6, 62.1 (CH_2), 112.1 (C), 118.3 (CH), 118.8, 127.9, 128.5 (C), 130.6, 132.7, 137.2, 137.5 (CH), 160.9, 163.1, 170.1, 199.3 (C). IR (KBr): $\tilde{\nu}$ = 2962 (w), 1676 (s), 1630 (s), 1586 (s), 1482 (m), 1349 (s), 1291 (s), 1265 (s), 1204 (s), 1173 (m), 791 (m) cm^{-1}. UV–vis (CH_3CN): λ_{max} (log ε)=213.3 (4.47), 240.6 (4.29), 287.8 (3.98), 345.1 (3.73) nm. MS (EI, 70 eV): m/z (%)=326 (M^+, 90), 175 (100), 134 (91), 77 (15), 28 (29). HRMS (ESI): calcd for $C_{21}H_{23}O_5Cl$: 390.12340; found: 390.12286.

4.4.8. Ethyl 3-(3-chloro-2-methylpropyl)-2-hydroxy-5-(2-hydroxy-5-chlorobenzoyl)benzoate (10h). Starting with **8d** (417 mg, 2.00 mmol), Me_3SiOTf (133 mg, 0.60 mmol), and 1,3-bis-silyl enol ether **1b** (948 mg, 2.6 mmol), **10h** was isolated as yellow solid by column chromatography with *n*-hexane/EtOAc=25:1 (410 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.08 (d, J=6.7 Hz, 3H, CH_3(CH)CH_2), 1.43 (t, J=7.1 Hz, 3H, OCH_2CH_3), 2.37 (m, J=5.4 Hz, 1H, CH_3(CH)CH_2), 2.69 (q, J=7.0 Hz, 1H, CH_3(CH)CH_2), 2.88 (q, J=7.0 Hz, 1H, CH_3(CH)CH_2), 3.44–3.57 (qq, J=5.4, 8.0 Hz, 2H, CH_3(CH)CH_2Cl), 4.47 (q, J=7.2 Hz, 2H, OCH_2CH_3), 7.06 (d, J=8.9 Hz, 1H, Ar), 7.44–7.48 (m, J=2.5, 6.3 Hz, 1H, Ar), 7.57 (d, J=2.0 Hz, 1H, Ar), 7.71 (d, J=2.2 Hz, 1H, Ar), 8.19 (d, J=2.2 Hz, 1H, Ar), 11.69 (s, 1H, OH), 11.73 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=14.1, 17.7 (CH_3), 34.4 (CH_2), 34.9 (CH), 50.6, 62.2 (CH_2), 112.2, 119.7 (C), 120.1 (CH), 123.4, 127.5, 129.1 (C), 130.7, 131.9, 135.9, 137.2 (CH), 161.4, 163.5, 169.9, 198.1 (C). IR (KBr): $\tilde{\nu}$ = 3109 (br), 2970 (w), 1674 (s), 1629 (s), 1593 (s), 1464 (s), 1378 (m), 1347 (s), 1320 (s), 1287 (s), 1254 (s), 1231 (s), 1177 (s), 737 (m) cm^{-1}. UV–vis (CH_3CN): λ_{max} (log ε)=218.6 (4.52), 294.2 (3.95), 343.1 (3.78) nm. MS (EI, 70 eV): m/z (%)=413 (M^+[^{37}Cl ^{35}Cl], 7), 412 (31), 411 (M^+[^{35}Cl ^{35}Cl], 11), 410 (47), 374 (34), 287 (12), 220 (100), 155 (49). HRMS (ESI): calcd for $C_{20}H_{20}O_5Cl_2$: 410.06878; found: 410.06794. Anal. Calcd for $C_{20}H_{20}O_5Cl_2$: C, 58.41; H, 4.90. Found: C, 58.45; H, 4.89.

4.4.9. 2-Bromo-4-(3-chloropropyl)-1,3-dihydroxyanthracene-9,10-dione (13). A THF solution (50 mL) of **1a** (2.81 g, 8.0 mmol) and 2-bromonaphthalene-1,4-dione (**12**) (0.95 g, 4.0 mmol) was stirred at −78 °C for 1 h. The solution was allowed to warm to 20 °C during 14 h. To the solution was added hydrochloric acid (10 mL, 6 M). The THF was removed in vacuo and the residue was washed with water and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc = 20:1) to give **13** as a yellowish solid (0.375 g, 30%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.14 (m, J=6.9, 1.5 Hz, 2H, CH_2), 3.36 (m, J=5.7 Hz, 2H, CH_2), 3.74 (t, J=6.8 Hz, 2H, CH_2–Cl), 6.59 (s, 1H, OH), 7.71–7.83 (m, 2H, 2×CH of Ar), 8.22–8.29 (m, 2H, 2×CH of Ar), 14.44 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=25.1, 31.9, 45.3 (CH_2), 105.4, 110.6 (C), 126.3, 127.3 (CH), 127.5, 130.4, 132.1 (C), 134.5 (CH), 134.6 (C), 135.2 (CH), 160.5, 161.1, 184.2, 187.1 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3435 (s), 1667 (s), 1626 (s), 1586 (s), 1439 (s), 1393 (s), 1358 (s), 1279 (s), 1183 (s), 1150 (s), 1013 (m), 838 (m), 732 (s), 628 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=206.7 (4.32), 248.9 (4.37), 272.5 (4.37), 338.6 (3.51), 408.4 (3.77) nm. MS (EI, 70 eV): m/z (%)=398 (M^+[^{81}Br ^{37}Cl], 20), 397 (12), 396 (M^+[^{81}Br ^{35}Cl],

M^+[^{79}Br ^{37}Cl], 100), 395 (8), 394 (M^+[^{79}Br ^{35}Cl], 73), 331 (85), 264 (8), 210 (14), 139 (34), 105 (6), 77 (13), 28 (40). HRMS (ESI): calcd for $C_{17}H_{12}BrClO_4$ ([M+1]$^+$): 396.96562 [^{81}Br ^{35}Cl], 394.96857 [^{79}Br ^{35}Cl]; found: 396.94806 [^{81}Br ^{35}Cl], 394.95052 [^{79}Br ^{35}Cl]. Anal. Calcd for $C_{17}H_{12}BrClO_4$ (395.632): C, 51.59; H, 3.06. Found: C, 51.86; H, 3.60.

4.5. General procedure for the synthesis of chromanes (4a–m), (11a–h), and (14)

To a THF solution of **3a**–**m**, **10a**–**h**, or **13** and of NaH was added TBAI. After stirring at 20 °C for 20 h, the mixture was concentrated in vacuo and the residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc) to give the product.

4.5.1. Ethyl 3,4-dihydro-2*H*-chromene-8-carboxylate (4a). Starting with **3a** (0.329 g, 1.36 mmol), NaH (0.040 g, 1.66 mmol), and TBAI (0.721 g, 2.21 mmol) in THF (22 mL), **4a** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless oil (0.230 g, 64%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.37 (t, J=7.1 Hz, 3H, CH_3), 2.04 (m, J=5.3 Hz, 2H, CH_2), 2.82 (t, J=6.5 Hz, 2H, CH_2), 4.29 (t, J=5.3 Hz, 2H, CH_2), 4.35 (q, J=7.1 Hz, 2H, OCH_2), 6.83 (t, J=7.6 Hz, 1H, CH of Ar), 7.17 (m, J=6.5, 1 Hz, 1H, CH of Ar), 7.61 (dt, J=7.8, 1 Hz, 1H, CH of Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.3 (CH_3), 21.7, 25.1, 60.6, 66.9 (CH_2), 111.1 (CH), 119.6, 123.4 (C), 129.3, 133.7 (CH), 154.9, 166.2 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2979 (m), 2937 (m), 1726 (s), 1595 (s), 1473 (s), 1454 (s), 1367 (m), 1298 (s), 1265 (s), 1238 (s), 1176 (s), 1138 (s), 1094 (s), 1055 (s), 958 (m), 878 (m), 761 (s). UV–vis (CH_3CN, nm): λ_{max} (log ε)=209 (4.43), 298 (3.51) nm. MS (EI, 70 eV): *m*/*z* (%)=207 ([M+1]$^+$, 6), 206 (M^+, 46), 161 (100), 133 (34), 105 (31), 77 (27), 51 (18), 29 (8). HRMS (FT-ICR): calcd for $C_{12}H_{14}O_3$ ([M+1]$^+$): 207.10212; found: 207.10165. Anal. Calcd for $C_{12}H_{14}O_3$ (206.238): C, 69.89; H, 6.84. Found: C, 69.18; H, 6.75.

4.5.2. Ethyl 3,4-dihydro-5,6,7-trimethyl-2*H*-chromene-8-carboxylate (4b). Starting with **3b** (0.307 g, 1.09 mmol), NaH (0.039 g, 1.63 mmol), and TBAI (0.771 g, 2.18 mmol) in THF (20 mL), **4b** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless solid (0.235 g, 90%), mp=76 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.36 (t, J=7.1 Hz, 3H, CH_3), 2.00 (m, 2H, CH_2), 2.13 (s, 6H, 2×CH_3), 2.17 (s, 3H, CH_3), 2.65 (t, J=6.5 Hz, 2H, CH_2), 4.11 (t, J=5.2 Hz, 2H, CH_2), 4.39 (q, J=7.1 Hz, 2H, OCH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.3, 15.3, 15.5 (CH_3), 17.2, 22.5, 23.2, 60.9, 65.8 (CH_2), 118.6, 121.6, 126.8, 130.9, 136.8, 149.3, 169.4 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2983 (m), 2936 (m), 1724 (s), 1581 (m), 1455 (m), 1312 (m), 1277 (s), 1184 (s), 1114 (s), 1084 (m), 1046 (s), 964 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=205 (4.49), 289 (3.43) nm. MS (EI, 70 eV): *m*/*z* (%)=249 ([M+1]$^+$, 14), 248 (M^+, 100), 203 (66), 202 (22), 174 (25), 161 (40), 133 (13), 105 (11), 77 (16), 51 (5), 29 (8). HRMS (ESI): calcd for $C_{15}H_{20}O_3$ ([M+1]$^+$): 249.14910; found: 249.14908.

4.5.3. Ethyl 5,7-dimethyl-3,4-dihydro-2*H*-chromene-8-carboxylate (4c). Starting with **3c** (0.059 g, 0.22 mmol), NaH (0.008 g, 0.33 mmol), and TBAI (0.144 g, 0.44 mmol) in THF (5 mL), **4c** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless oil (0.036 g, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.36 (t, J=7.1 Hz, 3H, CH_3), 2.02 (m, J=4.2, 1.2 Hz, 2H, CH_2), 2.16 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.59 (t, J=6.6 Hz, 2H, CH_2), 4.14 (t, J=5.2 Hz, 2H, CH_2), 4.38 (q, J=7.1 Hz, 2H, OCH_2), 6.75 (s, 1H, CH of Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.3, 18.9, 19.0 (CH_3), 22.0, 22.2, 60.9, 66.1 (CH_2), 118.6, 120.9 (C), 123.1 (CH), 133.1, 138.6, 151.9, 168.7 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3414 (m), 2977 (s), 2938 (s), 1716 (s), 1612 (m), 1574 (m), 1457 (s), 1369 (m), 1303 (s), 1273 (s), 1151 (s), 1106 (s), 1056 (s), 959 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=207 (4.48), 285 (3.34) nm. MS (EI, 70 eV): *m*/*z* (%)=236 ([M+2]$^+$, 1), 235.1 ([M+1]$^+$, 12), 234 (M^+, 87), 189 (100), 161 (31), 132 (20), 103 (7), 77 (12), 28 (17). HRMS (ESI): calcd for $C_{14}H_{19}O_3$ ([M+1]$^+$): 235.13342; found: 235.13286. Anal. Calcd for $C_{14}H_{18}O_3$ (234.291): C, 71.77; H, 7.74. Found: C, 70.94; H, 7.37.

4.5.4. Ethyl-3,4-dihydro-5,7-dimethyl-6-ethyl-2*H*-chromene-8-carboxylate (4d). Starting with **3d** (0.274 g, 0.92 mmol), NaH (0.033 g, 1.37 mmol), and TBAI (0.600 g, 1.84 mmol) in THF (20 mL), **4d** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless oil (0.198 g, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.06 (t, J=7.5 Hz, 3H, CH_3), 1.36 (t, J=7.2 Hz, 3H, CH_3), 2.01 (m, J=6.5 Hz, 2H, CH_2), 2.15 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.56–2.64 (m, J=7.4 Hz, 4H, 2×CH_2), 4.09 (t, J=5.2 Hz, 2H, CH_2), 4.37 (q, J=7.1 Hz, 2H, OCH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=13.7, 14.1, 14.6, 16.0 (CH_3), 22.2, 22.3, 23.0, 60.8, 65.7 (CH_2), 118.8, 121.8, 130.2, 132.6, 136.1, 149.2, 169.3 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3435 (w), 2968 (s), 2934 (s), 2872 (s), 1728 (s), 1583 (s), 1451 (s), 1372 (m), 1275 (s), 1187 (s), 1115 (s), 1087 (s), 1043 (s), 956 (m), 735 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=207 (4.48), 289 (3.36) nm. MS (EI, 70 eV): *m*/*z* (%)=263 ([M+1]$^+$, 7), 262 (M^+, 50), 247 (66), 217 (32), 201 (28), 188 (20), 84 (56), 32 (25), 28 (100).

4.5.5. Ethyl 5,7-diethyl-3,4-dihydro-2*H*-chromene-8-carboxylate (4e). Starting with **3** (0.330 g, 1.10 mmol), NaH (0.040 g, 1.66 mmol), TBAI (0.721 g, 2.21 mmol) in THF (20 mL), **4e** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless oil (0.230 g, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.19 (t, J=7.5 Hz, 6H, 2×CH_3), 1.36 (t, J=7.1 Hz, 3H, CH_3), 2.03 (m, J=4.4 Hz, 2H, CH_2), 2.53 (m, J=7.5 Hz, 4H, 2×CH_2), 2.67 (t, J=6.5 Hz, 2H, CH_2), 4.15 (t, J=5.2 Hz, 2H, CH_2), 4.38 (q, J=7.1 Hz, 2H, OCH_2), 6.61 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.1, 14.2, 15.6 (CH_3), 21.6, 22.0, 25.4, 26.3, 60.8, 66.0 (CH_2), 117.8 (C), 119.8 (CH), 120.5, 139.5, 144.4, 151.6, 168.7 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2969 (s), 2937 (s), 2874 (s), 1728 (s), 1609 (s), 1571 (s), 1463 (s), 1442 (s), 1417 (s), 1370 (m), 1276 (s), 1248 (s), 1150 (s), 1113 (s), 1066 (s), 868 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=207 (4.53), 284 (3.38) nm. MS (EI, 70 eV): *m*/*z* (%)=263 ([M+1]$^+$, 6), 262 (M^+, 50), 217 (73), 216 (100), 215 (34), 189 (15), 188 (15), 187 (17), 159 (9), 91 (13), 28 (36). Anal. Calcd for $C_{16}H_{22}O_3$ (262.344): C, 73.53; H, 8.10. Found: C, 73.49; H, 8.94.

4.5.6. Ethyl 3,4-dihydro-3,5,6,7-tetramethyl-2*H*-chromene-8-carboxylate (4f). Starting with **3f** (0.230 g, 0.77 mmol), NaH (0.028 g, 1.15 mmol), and TBAI (0.503 g, 1.54 mmol) in THF (12 mL), **4f** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless solid (0.190 g, 94%), mp=111 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.05 (d, J=6.5 Hz, 3H, CH_3), 1.34 (t, J=7.1 Hz, 3H, CH_3), 2.09 (m, 1H, CH), 2.13 (s, 6H, 2×CH_3), 2.17 (s, 3H, CH_3), 2.22 (m, 1H, CH_2), 2.74 (dq, J=10.1, 1.8 Hz, 1H, CH_2), 3.57 (m, J=10 Hz, 1H, CH_2), 4.12 (m, J=5.3, 1.8 Hz, 1H, CH_2), 4.39 (q, J=7.1 Hz, 2H, OCH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.3, 15.3, 15.5, 17.1, 17.3 (CH_3), 27.3 (CH), 31.9, 60.9, 71.2 (CH_2), 118.4, 121.4, 126.9, 130.9, 136.6, 148.8, 169.4 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2983 (m), 1726 (s), 1464 (m), 1268 (s), 1185 (s), 1123 (m), 1042 (s). UV–vis (CH_3CN, nm): λ_{max} (log ε)=203 (4.57), 288 (3.43) nm. MS (EI, 70 eV): m/z (%)=263 ([M+1]$^+$, 16), 262 (M$^+$, 100), 217 (89), 216 (40), 188 (39), 175 (21), 146 (11), 91 (12), 32 (17), 28 (80). Anal. Calcd for $C_{16}H_{22}O_3$ (262.344): C, 73.25; H, 8.45. Found: C, 72.85; H, 7.98.

4.5.7. Ethyl 3,4-dihydro-3,5,7-trimethyl-2*H*-chromene-8-carboxylate (4g). Starting with **3g** (0.176 g, 0.62 mmol), NaH (0.039 g, 1.63 mmol), and TBAI (0.771 g, 2.18 mmol) in THF (12 mL), **4g** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless solid (0.123 g, 80%), mp=71 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.05 (d, J=6.3 Hz, 3H, CH_3), 1.36 (t, J=7.1 Hz, 3H, CH_3), 2.10 (m, 1H, CH), 2.16 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.18 (m, 1H, CH_2), 2.68 (m, 1H, CH_2), 3.61 (m, J=12 Hz, 1H, CH_2), 4.15 (m, J=5.5 Hz, 1H, CH_2), 4.38 (q, J=7.1 Hz, 2H, OCH_2), 6.57 (s, 1H, CH of Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.3, 17.2, 18.9, 19.0 (CH_3), 26.9 (CH), 30.9, 60.9, 71.5 (CH_2), 110.9, 118.4, 120.7 (C), 123.2 (CH), 133.2, 138.5, 151.4, 168.7 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3442 (m), 2978 (s), 1728 (s), 1612 (m), 1574 (m), 1452 (m), 1282 (s), 1265 (s), 1151 (s), 1056 (s), 1042 (s), 862 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=206 (4.52), 284 (3.39) nm. MS (EI, 70 eV): m/z (%)=249 ([M+1]$^+$, 8), 248 (M$^+$, 100), 202 (66), 161 (21), 32 (22), 28 (100). Anal. Calcd for $C_{15}H_{20}O_3$ (248.318): C, 72.55; H, 8.12. Found: C, 72.10; H, 8.43.

4.5.8. Ethyl 5,7-diethyl-3,4-dihydro-3-methyl-2*H*-chromene-8-carboxylate (4h). Starting with **3h** (0.450 g, 1.44 mmol), NaH (0.052 g, 2.16 mmol), and TBAI (0.941 g, 2.88 mmol) in THF (24 mL), **4h** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless solid (0.385 g, 97%), mp=42 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.05 (d, J=6.5 Hz, 3H, CH_3), 1.20 (q, J=7.0 Hz, 6H, 2×CH_3), 1.36 (t, J=7.1 Hz, 3H, CH_3), 2.14 (m, 1H, CH_2), 2.24 (m, 1H, CH_2), 2.53 (m, 4H, 2×CH_2), 2.75–2.79 (m, 1H, CH), 3.62 (dd, J=10 Hz, 1H, OCH_2), 4.15–4.19 (dd, J=2.4 Hz, 1H, OCH_2), 4.38 (q, J=7.1 Hz, 2H, OCH_2), 6.61 (s, 1H, CH of Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.6, 14.7, 16.1, 17.7 (CH_3), 25.9, 26.7 (CH_2), 27.3 (CH), 30.7, 61.3, 71.9 (CH_2), 117.7, 119.9 (C), 120.4 (CH), 139.6, 144.4, 151.2, 168.8 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2967 (s), 2933 (s), 2875 (s), 1728 (s), 1610 (m), 1571 (s), 1462 (s), 1417 (s), 1274 (s), 1242 (s), 1150 (s), 1261 (s), 1044 (s), 866 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=208 (4.53), 284 (3.39) nm. MS (EI, 70 eV): m/z (%)=277.6 ([M+1]$^+$, 21), 276.7 (M$^+$, 100), 231 (39), 230 (64), 229 (16), 189 (8), 188 (7), 29 (6). HRMS (ESI): calcd for $C_{17}H_{24}O_3$ ([M+1]$^+$): 277.18037, found: 277.18035.

4.5.9. Ethyl 3,4,6,7,8,9-hexahydro-2*H*-benzo[*g*]chromene-10-carboxylate (4i). Starting with **3i** (311 mg, 1.05 mmol), NaH (38 mg, 1.58 mmol), and TBAI (685 mg, 2.10 mmol) in THF (20 mL), **4i** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless oil (0.189 g, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.36 (t, J=7.2 Hz, 3H, CH_3), 1.71–1.76 (m, J=3.3 Hz, 4H, 2×CH_2), 1.97 (m, J=4.3 Hz, 2H, CH_2), 2.65 (m, 6H, 3×CH_2), 2.71 (t, J=6.5 Hz, 2H, CH_2), 4.16 (t, J=5.2 Hz, 2H, CH_2), 4.36 (q, J=7.1 Hz, 2H, OCH_2), 6.77 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.3 (CH_3), 22.2, 22.8, 22.9, 24.5, 26.2, 28.8, 60.9, 66.6 (CH_2), 111.9, 122.4, 128.7, 131.1, 132.3, 149.4, 168.7 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2977 (s), 2931 (s), 2858 (s), 1729 (s), 1582 (s), 1476 (s), 1446 (s), 1367 (s), 1285 (s), 1249 (s), 1179 (s), 1164 (s), 1108 (s), 1061 (s), 961 (s), 866 (s), 724 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=204 (4.41), 294 (3.55) nm. MS (EI, 70 eV): m/z (%)=261 ([M+1]$^+$, 6), 260 (M$^+$, 50), 214 (64), 186 (23), 168 (12), 153 (16), 128 (6), 114 (6), 91 (9), 28 (100). HRMS (ESI): calcd for $C_{16}H_{20}O_3$ ([M+1]$^+$): 261.14907; found: 261.14928. Anal. Calcd for $C_{16}H_{20}O_3$ (260.328): C, 73.81; H, 7.74. Found: C, 73.51; H, 8.02.

4.5.10. Ethyl 3,4,6,7,8,9-hexahydro-5-methyl-2*H*-benzo[*g*]chromene-10-carboxylate (4j). Starting with **3j** (0.305 g, 0.98 mmol), NaH (0.035 g, 1.47 mmol), and TBAI (0.640 g, 1.96 mmol) in THF (18 mL), **4j** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless solid (0.234 g, 87%), mp=74 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.38 (t, J=7.2 Hz, 3H, CH_3), 1.69–1.79 (m, 4H, 2×CH_2), 2.00–2.06 (m, 2H, CH_2), 2.10 (s, 3H, CH_3), 2.58 (t, J=6.5 Hz, 2H, CH_2), 2.64 (m, 4H, 2 CH_2), 4.13 (t, J=5.2 Hz, 2H, CH_2), 4.36 (q, J=7.1 Hz, 2H, OCH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.2, 14.3 (CH_3), 22.4 (2 CH_2), 22.9, 23.1, 23.2, 26.9, 60.8, 65.8 (CH_2), 118.7, 120.6, 127.1, 131.9, 136.9, 149.3, 168.9 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3430 (w), 2931 (s), 1725 (s), 1579 (m), 1445 (m), 1272 (s), 1188 (s), 1076 (m), 1034 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=206 (4.51), 290 (4.47) nm. MS (EI, 70 eV): m/z (%)=275 ([M+1]$^+$, 3), 274 (M$^+$, 20), 229 (17), 228 (21), 174 (29), 114 (4), 91 (4), 32 (25), 28 (100). Anal. Calcd for $C_{17}H_{22}O_3$ (274.355): C, 74.42; H, 8.09. Found: C, 74.31; H, 8.18.

4.5.11. Ethyl 6,8,9,10-tetrahydro-7-methyl-5*H*-naphtho[2,1-*g*]chromene-12-carboxylate (4k). Starting with **3k** (0.353 g, 0.984 mmol), NaH (0.035 g, 1.48 mmol), and TBAI (0.643 g, 1.97 mmol) in THF (18 mL), **4k** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless solid (0.280 g, 88%), mp=180 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.18 (t, J=7.1 Hz, 3H, CH_3), 2.09 (m, J=4.0 Hz, 2H, CH_2), 2.21 (s, 3H, CH_3), 2.69–2.77 (m, 6H, 3×CH_2), 4.18 (t, J=5.2 Hz, 2H, CH_2), 4.29 (q, J=7.1 Hz, 2H, OCH_2), 7.17–7.23 (m, 3H, 3×CH of Ar), 7.54–7.57 (m, 1H, CH of Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=13.7, 15.1 (CH_3), 22.3, 23.4, 25.4, 29.4, 61.2, 65.9 (CH_2), 118.4, 120.7 (C), 126.2, 126.3, 127.2, 127.3 (CH), 129.5, 131.2, 133.9, 135.7, 138.6, 151.0,

169.7 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3414 (w), 2986 (m), 1717 (s), 1558 (m), 1415 (m), 1282 (s), 1188 (m), 1164 (m), 1070 (m), 1033 (m), 757 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=208 (4.49), 225 (4.38), 269 (4.12), 316 (3.87) nm. MS (EI, 70 eV): *m/z* (%)=323 ([M+1]$^+$, 22), 322 (M^+, 100), 277 (54), 32 (24), 28 (92). HRMS (ESI): calcd for $C_{21}H_{22}O_3$ ([M+1]$^+$): 323.16472; found: 323.16431. Anal. Calcd for $C_{21}H_{22}O_3$ (322.398): C, 78.23; H, 6.88. Found: C, 77.99; H, 7.29.

4.5.12. Ethyl 6-(2-chloroethyl)-5,7-dimethyl-3,4-dihydro-2*H*-chromene-8-carboxylate (4l). Starting with **3l** (0.308 g, 0.923 mmol), NaH (0.033 g, 1.36 mmol), and TBAI (0.603 g, 1.85 mmol) in THF (16 mL), **4l** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless solid (0.211 g, 77%), mp=103 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.37 (t, *J*=7.2 Hz, 3H, CH_3), 2.02 (m, *J*=7.5 Hz, 2H, CH_2), 2.18 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.63 (t, *J*=6.6 Hz, 2H, CH_2), 3.10 (m, 2H, CH_2), 3.47 (m, 2H, CH_2–Cl), 4.12 (t, *J*=5.2 Hz, 2H, CH_2), 4.37 (q, *J*=7.1 Hz, 2H, OCH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.2, 15.2, 16.5 (CH_3), 22.3, 23.2, 33.2, 42.3, 61.1, 65.9 (CH_2), 119.4, 122.4, 126.5, 131.4, 137.3, 150.4, 168.9 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2987 (m), 2939 (m), 1727 (s), 1579 (m), 1453 (s), 1308 (s), 1278 (s), 1244 (s), 1186 (s), 1115 (s), 1042 (s), 722 (w). UV–vis (CH_3CN, nm): λ_{max} (log ε)=208 (4.58), 288 (4.35) nm. MS (EI, 70 eV): *m/z* (%)=298 (M^+[^{37}Cl], 10), 296 (M^+[^{35}Cl], 34), 247 (100), 201 (17), 173 (3), 114 (4), 28 (7). HRMS (ESI): calcd for $C_{16}H_{21}ClO_3$ ([M+1]$^+$): 299.12280 [^{37}Cl], 297.12575 [^{35}Cl]; found: 299.12162 [^{37}Cl], 297.12476 [^{35}Cl]. Anal. Calcd for $C_{16}H_{21}ClO_3$ (296.789): C, 64.73; H, 7.13. Found: C, 64.73; H, 7.72.

4.5.13. Ethyl 6-(2-bromoethyl)-3,4-dihydro-5,7-dimethyl-2*H*-chromene-8-carboxylate (4m). Starting with **3m** (0.129 g, 0.34 mmol), NaH (0.012 g, 0.51 mmol), and TBAI (0.222 g, 0.68 mmol) in THF (6 mL), **4m** was isolated after chromatography (silica gel, *n*-hexane/EtOAc = 20:1) as a colorless solid (0.070 g, 60%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.36 (t, *J*=7.1 Hz, 3H, CH_3), 2.02 (quint, *J*=5.3 Hz, 2H, CH_2), 2.17 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.63 (t, *J*=6.6 Hz, 2H, CH_2), 3.06–3.19 (m, 2H, CH_2), 3.44–3.49 (m, 2H, CH_2), 4.12 (t, *J*=5.3 Hz, 2H, CH_2), 4.36 (q, *J*=7.2 Hz, 2H, OCH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=14.3, 15.2, 16.4 (CH_3), 22.3, 23.2, 33.2, 33.6, 61.1, 65.9 (CH_2), 119.5, 126.5, 131.3, 137.3, 150.4, 219.7 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3431 (m), 2981 (m), 2961 (m), 2937 (m), 1726 (s), 1581 (m), 1451 (s), 1305 (s), 1277 (s), 1186 (s), 1115 (s), 1041 (s), 962 (m), 793 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=210 (4.52), 289 (3.38) nm. MS (EI, 70 eV): *m/z* (%)=342 (M^+[^{81}Br], 6), 340 (M^+[^{79}Br], 5), 296 (23), 260 (33), 247 (100), 215 (30), 153 (9), 114 (10), 84 (88), 41 (29), 28 (78). HRMS (ESI): calcd for $C_{16}H_{21}BrO_3$ ([M+1]$^+$): 343.07317 [^{81}Br], 341.07522 [^{79}Br]; found: 343.07428 [^{81}Br], 341.07612 [^{79}Br].

4.5.14. Ethyl 3,4-dihydro-6-(2-hydroxybenzoyl)-2*H*-chromene-8-carboxylate (11a). A THF solution (5 mL) of **10a** (149 mg, 0.41 mmol) was added to a mixture of NaH (14.8 mg, 0.61 mmol) and TBAI (304 mg, 0.82 mmol). After stirring for 20 h at 20 °C, an aqueous solution of NH_3Cl (1 M, 4 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (5×10 mL). The layers were separated and the organic layer was washed with water, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc = 3:1→1:1) to give **11a** as a yellow solid (92 mg, 68%), mp=119 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.36 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 2.10 (m, 2H, $CH_2CH_2CH_2$), 2.90 (t, *J*=6.3 Hz, 2H, $ArCH_2$), 4.32–4.42 (m, 4H, CH_2Cl, OCH_2CH_3), 6.91 (m, 1H, Ar), 7.07 (dd, *J*=8.1 Hz, *J*=1.0 Hz, 1H, Ar), 7.51 (m, 1H, Ar), 7.61 (m, 2H, Ar), 7.99 (d, *J*=2.3 Hz, 1H, Ar), 11.89 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=14.25 (OCH_2CH_3), 21.33 ($CH_2CH_2CH_2$), 25.23 ($ArCH_2$), 61.10 (OCH_2CH_3), 67.64 (OCH_2), 118.41, 118.67 (CH), 119.16, 119.58, 123.76, 128.80 (C), 131.45, 133.08, 134.73, 136.04 (CH), 158.15, 162.96 (C), 165.30, 199.40 (C=O). IR (KBr): $\tilde{\nu}$ = 3070 (w), 3035 (w), 2941 (w), 1692 (s), 1626 (s), 1622 (s), 1480 (s), 1456 (m), 1335 (m), 1276 (s), 1250 (s), 1216 (s), 1184 (s), 1159 (s), 1135 (m), 1021 (m), 762 (w) cm^{-1}. UV–vis (CH_3CN): λ_{max} (log ε): 302 (3.99), 248 (4.07), 214 (4.29) nm. Fluorescence (CH_3CN): λ_{Ex} (Fλ_{max}): 340 (379) nm. MS (EI, 70 eV): *m/z* (%)=326 (M^+, 36), 270 (68), 234 (14), 210 (100), 182 (18), 161 (12), 128 (32), 77 (16). HRMS (FT-ICR): calcd for $C_{19}H_{19}O_5$ ([M+1]$^+$): 327.12270; found: 327.12296.

4.6. General procedure for the synthesis of (11b,e–h)

A THF solution of **10b**,**e**–**h** (1.0 equiv) was added to a mixture of NaH (1.5 equiv) and TBAI (2 equiv). After stirring for 20 h at 20 °C, an aqueous solution of hydrochloric acid (10%) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5×10 mL). The layers were separated and the organic layer was washed with water, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc = 20:1→10:1) to give **11b**,**e**–**h**.

4.6.1. 3,4-Dihydro-6-(2-hydroxy-5-methylbenzoyl)-2*H*-chromene-8-carboxylic acid (11b). Starting with **10b** (102 mg, 0.27 mmol) in 4 mL THF, NaH (10 mg, 0.405 mmol), and TBAI (176 mg, 0.54 mmol), **11b** was isolated as a yellow solid (80 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.18 (quint, *J*=5.2 Hz, 2H, CH_2), 2.26 (s, 3H, CH_3), 2.97 (t, *J*=6.1 Hz, 2H, CH_2), 4.55 (t, *J*=5.4 Hz, 2H, CH_2), 6.96 (d, *J*=7.8 Hz, 1H, Ar), 7.32–7.35 (m, 2H, Ar), 7.69 (d, *J*=2.2 Hz, 1H, Ar), 8.30 (d, *J*=2.2 Hz, 1H, Ar), 11.62 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=20.5 (CH_3), 21.2, 24.6, 68.9 (CH_2), 116.7 (C), 118.2 (CH), 118.6, 124.1, 128.1, 130.9 (C), 132.7, 133.2, 135.8, 137.5 (CH), 156.5, 160.9, 164.8, 199.2 (C). IR (KBr): $\tilde{\nu}$ = 3225 (m), 1731 (s), 1630 (m), 1594 (s), 1478 (s), 1427 (s), 1336 (s), 1249 (s), 1205 (s), 788 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%)=312 (M^+, 42), 264 (25), 57 (12), 44 (42), 28 (100). Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.64; H, 5.38.

4.6.2. 3,4-Dihydro-6-(5-chloro-2-hydroxy-4-methylbenzoyl)-2*H*-chromene-8-carboxylic acid (11e). Starting with **10e** (102 mg, 0.25 mmol) in 4 mL THF, NaH (9 mg, 375 mmol), and TBAI (163 mg, 0.5 mmol), **11e** was isolated

as yellow viscous oil (60 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.19 (quint, J=5.0 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.98 (t, J=6.2 Hz, 2H, CH_2), 4.56 (t, J=5.2 Hz, 2H, CH_2), 6.97 (s, 1H, Ar), 7.49 (s, 1H, Ar), 7.65 (t, J=1 Hz, 1H, Ar), 8.31 (d, J=2.3 Hz, 1H, Ar), 11.68 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=20.8 (CH_3), 21.2, 24.6, 68.9 (CH_2), 117.1, 117.9 (C), 120.5 (CH), 124.2, 130.5 (C), 132.3, 133.0, 135.6 (CH), 145.9, 156.7, 161.4, 164.5, 190.5, 197.9 (C). MS (EI, 70 eV): m/z (%)=348 (M^+[^{37}Cl], 21), 346 (M^+[^{35}Cl], 59), 205 (17), 178 (79), 168 (43), 161 (100), 77 (53).

4.6.3. 3,4-Dihydro-3-methyl-6-(2-hydroxybenzoyl)-2*H*-chromene-8-carboxylic acid (11f). Starting with **10f** (94 mg, 0.25 mmol) in 10 mL THF, NaH (9 mg, 0.37 mmol), and TBAI (163 mg, 0.50 mmol), **11f** was isolated as a yellow viscous oil (55 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.22 (d, J=6.5 Hz, 3H, CH_3(CH)), 2.34 (m, 1H, CH_3(CH)), 2.62 (q, J=9.8, 6.5 Hz, 1H, CH_2), 3.00 (dd, J=5.0, 9.5 Hz, 1H, CH_2), 4.04 (t, J=10.5 Hz, 1H, CH_2), 4.54–4.59 (qq, J=2.0, 9.0 Hz, 1H, CH_2), 6.99 (d, J=8.1 Hz, 1H, Ar), 7.32 (s, 1H, Ar), 7.35 (d, J=2.2 Hz, 1H, Ar), 7.68 (t, J=1.1 Hz, 1H, Ar), 8.32 (d, J=2.2 Hz, 1H, Ar), 11.63 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=16.5 (CH_3), 26.3 (CH), 32.7, 73.8 (CH_2), 116.6 (C), 118.5 (CH), 118.8 (C), 119.0 (CH), 123.8, 130.9 (C), 133.0, 133.3, 135.9, 136.4 (CH), 156.1, 163.0, 164.6, 199.1 (C). MS (EI, 70 eV): m/z (%)=312 (M^+, 64), 267 (20), 219 (26), 192 (100), 175 (39), 121 (60). IR (KBr): $\tilde{\nu}$ = 3296 (br, m), 2926 (m), 1733 (m), 1625 (s), 1598 (s), 1479 (s), 1329 (s), 1249 (s), 1158 (s), 762 (m) cm^{-1}. HRMS (ESI): calcd for $C_{18}H_{16}O_5$: 312.09977; found: 312.09901.

4.6.4. 3,4-Dihydro-3-methyl-6-(2-hydroxy-5-methylbenzoyl)-2*H*-chromene-8-carboxylic acid (11g). Starting with **10g** (194 mg, 0.50 mmol) in 10 mL THF, NaH (18 mg, 0.75 mmol), and TBAI (326 mg, 1.0 mmol), **11g** was isolated as a yellow solid (140 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.15 (d, J=6.8 Hz, 3H, CH_3(CH)), 2.26 (s, 3H, CH_3), 2.34 (m, 1H, CH_3(CH)), 2.62 (q, J=9.8, 6.5 Hz, 1H, CH_2), 3.00 (dd, J=5.0, 9.5 Hz, 1H, CH_2), 4.04 (t, J=10.5 Hz, 1H, CH_2), 4.54–4.59 (qq, J=2.0, 9.0 Hz, 1H, CH_2), 6.99 (d, J=8.1 Hz, 1H, Ar), 7.32 (s, 1H, Ar), 7.35 (d, J=2.2 Hz, 1H, Ar), 7.68 (t, J=1.1 Hz, 1H, Ar), 8.32 (d, J=2.2 Hz, 1H, Ar), 11.63 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=16.5, 20.5 (CH_3), 26.3 (CH), 32.8, 73.8 (CH_2), 116.5 (C), 118.2 (CH), 118.6, 123.8, 128.1, 131.2 (C), 132.7, 133.2, 135.8, 137.5 (CH), 156.0, 160.9, 164.7, 199.2 (C). IR (KBr): $\tilde{\nu}$ = 2956 (m), 2926 (m), 1670 (s), 1596 (s), 1479 (s), 1336 (s), 1246 (s), 1219 (s), 1173 (s), 792 (m) cm^{-1}. MS (EI, 70 eV): m/z (%)=326 (M^+, 90), 175 (100), 134 (91), 77 (15), 28 (29). HRMS (ESI): calcd for $C_{19}H_{18}O_5$: 326.11542; found: 326.11530. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.51; H, 5.56.

4.6.5. 3,4-Dihydro-3-methyl-6-(5-chloro-2-hydroxybenzoyl)-2*H*-chromene-8-carboxylic acid (11h). Starting with **10h** (261 mg, 0.64 mmol) in 10 mL THF, NaH (23 mg, 0.96 mmol), and TBAI (662 mg, 1.27 mmol), **11h** was isolated as a yellow solid (160 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.16 (d, J=6.8 Hz, 3H, CH_3(CH)), 2.34 (m, 1H, CH_3(CH)), 2.62 (q, J=9.8, 6.6 Hz, 1H, CH_2), 2.99–3.06 (dd, J=3.2, 13.3 Hz, 1H, CH_2), 4.04 (t, J=10.1 Hz, 1H, CH_2), 4.55–4.60 (qq, J=2.0, 8.6 Hz, 1H, CH_2), 7.04 (td, J=1.2, 6.9 Hz, 1H, Ar), 7.06–7.09 (dd, J=2.0, 7.6 Hz, 1H, Ar), 7.49–7.58 (m, 2H, Ar), 7.70 (quint, J=1.0 Hz, 1H, Ar), 8.34 (d, J=2.3 Hz, 1H, Ar), 11.82 (s, 1H, OH). ^{13}C NMR (DEPT, 75.5 MHz, $CDCl_3$): δ=16.5 (CH_3), 26.2 (CH), 32.8, 73.8 (CH_2), 116.9, 119.6 (C), 120.1 (CH), 123.6, 123.9, 130.3 (C), 131.8, 133.1, 135.7, 136.3 (CH), 156.5, 161.5, 164.6, 198.2 (C). IR (KBr): $\tilde{\nu}$ = 3069 (w), 2959 (m), 1735 (m), 1706 (m), 1674 (s), 1627 (s), 1596 (s), 1474 (s), 1466 (s), 1330 (s), 1249 (s), 1226 (s), 1185 (s), 1140 (m), 1001 (m), 790 (m) cm^{-1}. UV–vis (CH_3CN): λ_{max} (log ε)=209.1 (4.49), 291.6 (3.93), 344.8 (3.77) nm. MS (EI, 70 eV): m/z (%)=348 (M^+[^{37}Cl], 22), 346 (M^+[^{35}Cl], 62), 192 (100), 175 (66), 155 (24). Anal. Calcd for $C_{18}H_{15}O_5Cl$: C, 62.35; H, 4.36. Found: C, 62.11; H, 4.34.

4.6.6. 5-Bromo-2,3-dihydro-6-hydroxy-1*H*-naphtho-[2,3-*f*]chromene-7,12-dione (14). Starting with **13** (0.140 g, 0.44 mmol), NaH (0.016 g, 0.66 mmol), and TBAI (0.287 g, 0.88 mmol) in THF (7 mL), **14** was isolated after chromatography (silica gel, n-hexane/EtOAc = 20:1) as a yellowish solid (0.115 g, 73%), mp=235 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.10 (tt, J=5.5, 6.5 Hz, 2H, CH_2), 3.36 (t, J=6.7 Hz, 2H, CH_2), 4.44 (t, J=6.2 Hz, 2H, CH_2), 7.77–7.79 (m, 2H, 2×CH of Ar), 8.20–8.28 (m, 2H, 2×CH of Ar), 14.23 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C=21.9, 25.0, 67.9 (CH_2), 106.5, 111.4, 121.2 (C), 126.4, 127.2 (CH), 129.9, 132.2 (C), 133.8, 134.3, 134.4 (CH), 159.4, 160.2, 184.3, 187.4 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2921 (w), 1661 (m), 1631 (s), 1586 (s), 1556 (m), 1439 (m), 1396 (s), 1355 (s), 1282 (s), 1152 (s), 959 (m), 797 (m), 729 (m). UV–vis (CH_3CN, nm): λ_{max} (log ε)=206 (4.46), 250 (4.42), 277 (4.43), 332 (3.43), 414 (3.89) nm. MS (EI, 70 eV): m/z (%)=360 (M^+[^{81}Br], 16), 359 (96), 358 (M^+[^{79}Br], 21), 357 (100), 342.7 (28), 164.9 (11), 139.0 (12), 77.4 (8), 32.0 (20), 28 (89). Anal. Calcd for $C_{17}H_{11}BrO_4$ (359.171): C, 56.83; H, 3.09. Found: C, 56.43; H, 3.64.

Acknowledgements

We thank Dr. Dirk Michalik for NMR studies. Financial support by the state of Vietnam (MOET scholarship for V.T.H.N.), by the Deutsche Forschungsgemeinschaft, and by the state of Mecklenburg-Vorpommern (Landesforschungsschwerpunkt 'Neue Wirkstoffe und Screeningverfahren') is gratefully acknowledged.

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Tetrahedron 62 (2006) 7687–7698
Tetrahedron

Enantioselective synthesis of aurisides A and B, cytotoxic macrolide glycosides of marine origin

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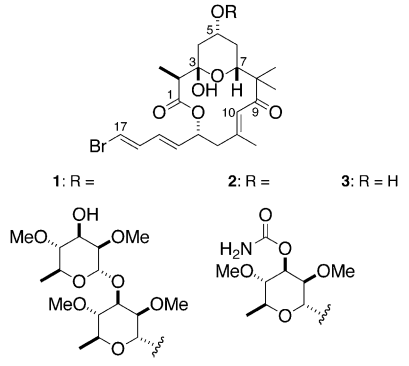
Received 24 March 2006; revised 22 May 2006; accepted 29 May 2006
Available online 21 June 2006

Abstract—The enantioselective synthesis of aurisides A and B, macrolide glycosides of marine origin, was achieved by a convergent approach. The C1–C9 segment **4** was prepared from (*R*)-pantolactone, and the C10–C17 segment **14** was synthesized from (*R*)-glycidyl trityl ether. The Nozaki–Hiyama–Kishi reaction between **4** and **14** and subsequent reactions gave seco acid **10**, which was converted into the aglycon (**3**) of aurisides by construction of the 14-membered lactone and bromine-substituted conjugated diene. The glycosylation reaction of the aglycon provided aurisides A and B.

1. Introduction

The sea hare *Dolabella auricularia* (Aplysiidae) is known to be a rich source of cytotoxic and/or antitumor peptides and other unique metabolites.[1,2] Aurisides A (**1**) and B (**2**) are macrolide glycosides isolated from Japanese sea hare *D. auricularia*, which exhibit cytotoxicity against HeLa S_3 cells with IC_{50} values of 0.17 and 1.2 μg mL^{-1}, respectively.[3] The main structural features of aurisides are a bromine-substituted conjugated diene, a 14-membered lactone, and a cyclic hemiacetal. The biological activity and structural novelty of aurisides prompted us to initiate the investigation toward the synthesis of **1** and **2**. We had achieved the synthesis of aglycon (**3**) of aurisides,[4] and synthetic studies of aurisides have been carried out by a few groups.[5] Recently, total synthesis of **1** and **2** were achieved by Paterson and co-workers.[6] Several natural products structurally related to **1** and **2** have been isolated,[7] and studies have been made on synthesis of these compounds.[8] We describe herein enantioselective synthesis of aurisides A (**1**) and B (**2**) according to a convergent synthetic methodology with some improvement of our previous synthesis of their aglycon (**3**).[4]



2. Results and discussions

The outline of our previous synthesis of the aglycon of aurisides is shown in Scheme 1. There are some serious problems in this route: (1) the macrolactonization of seco acid **5** required vigorous conditions because of steric hindrance of trityl group and led to elimination of methanol to give lactones **6a** and **6b**; (2) re-formation of the cyclic hemiacetal and construction of the bromine-substituted conjugated diene proceeded only in poor yields. Therefore, we began reinvestigating more efficient routes. The second-generation strategy is illustrated in Scheme 2. We planned to construct the cyclic structure of aurisides by the macrolactonization of seco acid **11** or **12**. We expected that macrolactonization of **11** or **12** provided lactone **9** or **10** without elimination of methanol under milder conditions than the previous synthesis, because the steric hindrance around 13-hydroxyl group

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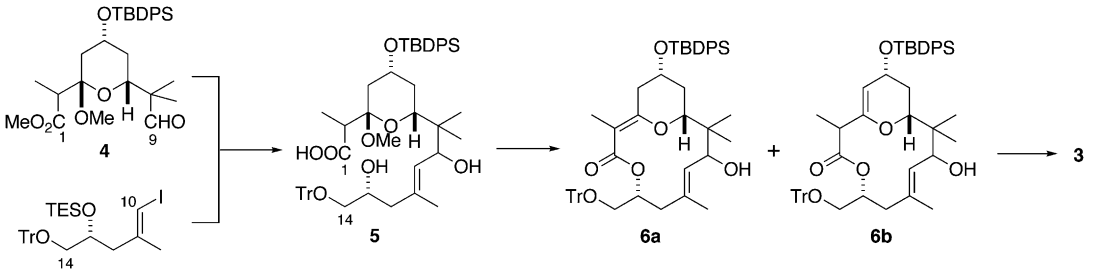
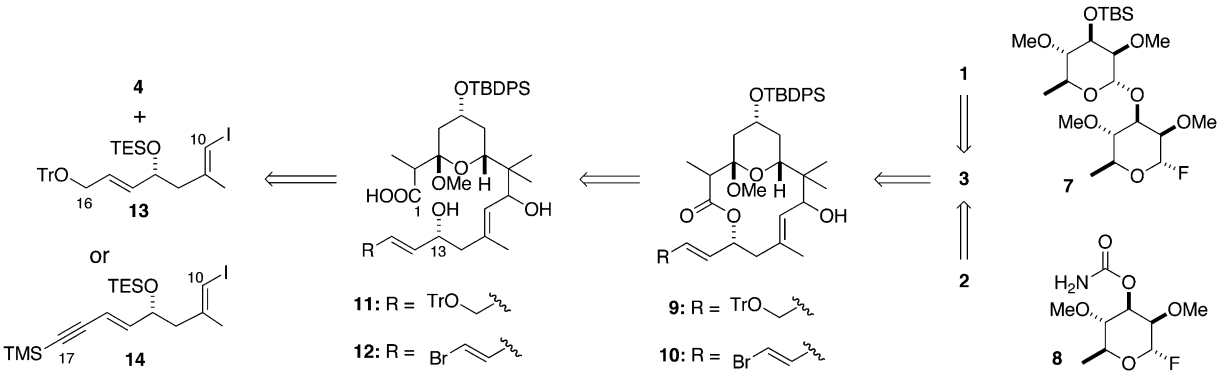
doi:10.1016/j.tet.2006.05.077



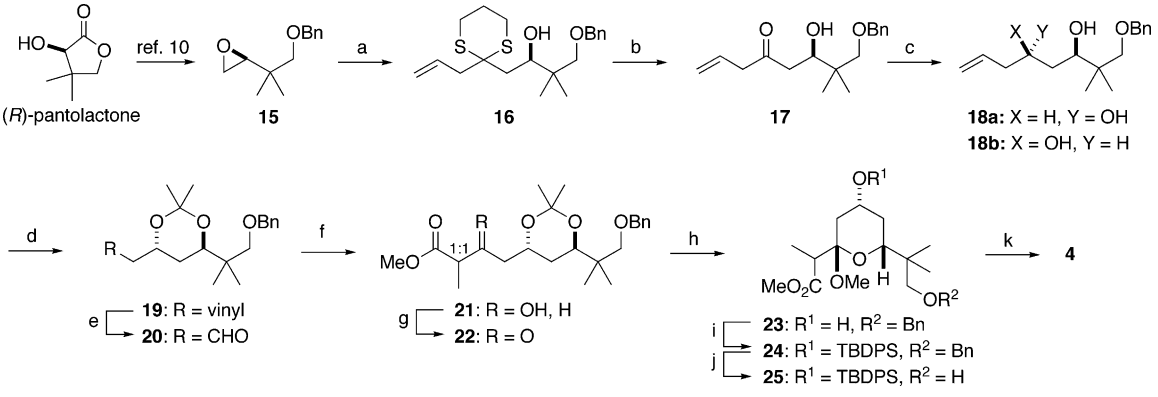
Scheme 1. Outline of the previous synthesis of aglycon (**3**) of aurisides.



Scheme 2. The second generation strategy for synthesis of aurisides A (**1**) and B (**2**).

in **11** and **12** are much smaller than that in **5**. The seco acid **11** could be synthesized from C1–C9 segment **4** and C10–C16 segment **13** by Nozaki–Hiyama–Kishi reaction as a key step. The seco acid **12** might be obtained from **4** and C10–C17 segment **14**, which possesses a conjugated enyne group, a precursor of the bromine-substituted conjugated diene. The glycosylation of **3** with fluorosugars **7** and **8** under the Mukaiyama protocol[9] could provide aurisides A (**1**) and B (**2**), respectively, in the same way as Paterson and co-workers.[6]

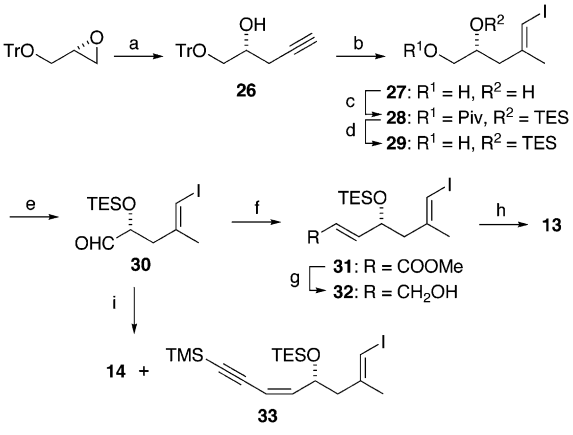
The synthesis of C1–C9 segment **4** started from commercially available (*R*)-pantolactone (Scheme 3). (*R*)-Pantolactone was converted into epoxide **15** by a four-step sequence of reactions.[10] Alkylation of the carbanion generated from 2-allyldithiane with **15** afforded alcohol **16** (92%). Careful deprotection[11] of the dithioacetal moiety in **16** gave ketone **17** (77%). Stereoselective reduction of **17** with tetramethylammonium triacetoxyborohydride[12] afforded *anti*-1,3-diol **18a** (86%) along with *syn*-1,3-diol **18b** (7%). *anti*-1,3-Diol **18a** was transformed into acetonide **19** (97%), the stereochemistry of which was confirmed to be *anti* by the ^{13}C chemical shifts of two acetonide methyls (δ_C 24.6 and 24.2).[13] Oxidative cleavage of the vinyl group in **19** gave aldehyde **20** (96%), rhodium-catalyzed Reformatsky-type reaction[14] of which with methyl 2-bromopropionate provided a diastereomeric mixture of β-hydroxy esters **21** (88%).[15] Swern oxidation of **21** afforded β-keto ester **22** as an inseparable 1:1 mixture of diastereomers concerning the secondary methyl group (88%). Acid treatment of **22** in methanol led to cyclic methyl acetal **23** (96%), the secondary hydroxyl



Scheme 3. (a) 2-Allyldithiane, BuLi, THF–hexane, −78 °C→−30 °C, 92%; (b) $(CF_3CO_2)_2IPh$, MeOH, 0 °C; H_2O, AcOH, THF, rt, 77%; (c) $Me_4NBH(OAc)_3$, AcOH, MeCN, −30 °C, 86%; (d) $(MeO)_2CMe_2$, CSA, acetone, rt, 97%; (e) OsO_4, NMO, acetone–^{t}BuOH, rt; $NaIO_4$, H_2O, rt, 96%; (f) methyl 2-bromopropionate, Et_2Zn, $RhCl(PPh_3)_3$, THF, 0 °C, 88%; (g) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; Et_3N, −78 °C→0 °C, 88%; (h) $CH(OMe)_3$, PPTS, MeOH, 50 °C, 96%; (i) TBDPSCl, imidazole, 0 °C, 100%; (j) H_2, 20% $Pd(OH)_2$–C, dioxane, rt, 96%; (k) DMSO, SO_3·pyridine, Et_3N, rt, 95%.

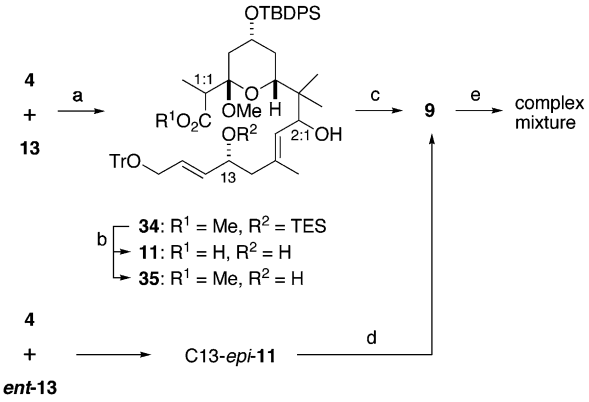
group of which was silylated to give silyl ether **24** (100%). Cleavage of the benzyl group in **24** afforded alcohol **25** (96%), which was oxidized to provide C1–C9 segment **4** (95%).

The synthesis of C10–C16 and C10–C17 segments, **13** and **14**, began with an alkylation reaction of lithium acetylide with (*R*)-glycidyl trityl ether to afford acetylene **26** in 97% yield (Scheme 4). Carbometallation of **26** followed by treatment with iodine gave vinyl iodide **27**,[16] accompanied by cleavage of the trityl group (50%). Protection of the primary hydroxyl group in **27** followed by silylation of the secondary hydroxyl group afforded silyl ether **28** (92%), which was converted into primary alcohol **29** (99%). Oxidation of **29** gave aldehyde **30** (95%), the Wittig reaction of which with $MeO_2CCH{=}PBu_3$[17] provided conjugated ester **31** as a sole product (92%). Reduction of **31** afforded alcohol **32** (86%), the hydroxyl group of which was tritylated to give C10–C16 segment **13** (89%). Wittig olefination reaction of aldehyde **30** with TMS–C≡CCH_2PPh_3Br and BuLi provided C10–C17 segment **14** (57%) along with *cis*-isomer **33** (9%).



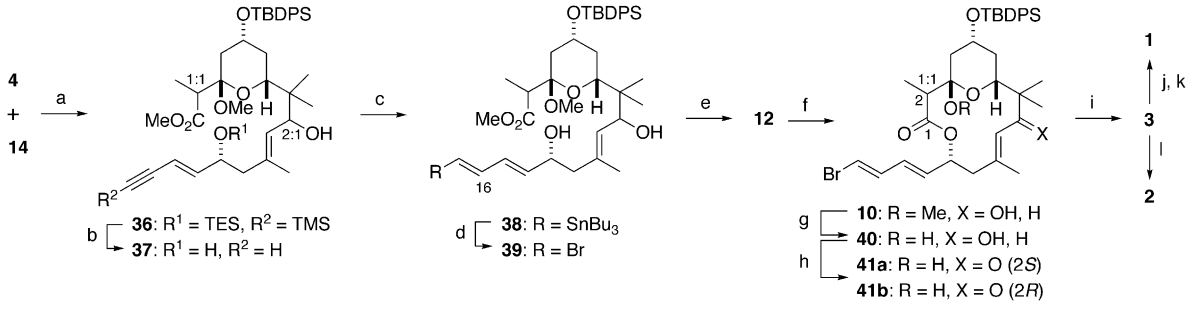
Scheme 4. (a) $LiC{\equiv}CH{\cdot}NH_2(CH_2)_2NH_2$, THF–DMSO, rt, 97%; (b) Cp_2ZrCl_2, Me_3Al, CH_2Cl_2, rt; I_2, THF, rt, 50%; (c) PivCl, pyridine, 0 °C→rt; TESCl, rt, 92%; (d) DIBAL, CH_2Cl_2, −78 °C, 99%; (e) Dess–Martin periodinane, CH_2Cl_2, pyridine, rt, 95%; (f) $MeO_2CCH{=}PBu_3$, benzoic acid, toluene, 90 °C, 92%; (g) DIBAL, THF–hexane, −78 °C, 86%; (h) TrCl, Et_3N, DMAP, CH_2Cl_2, rt, 89%; (i) TMS–C≡CCH_2PPh_3Br, BuLi, THF, (**14**) 57%, (**33**) 9%.

Coupling reaction between C1–C9 segment **4** and C10–C16 segment **13** was effected by means of Nozaki–Hiyama–Kishi reaction[18] to give alcohol **34** in 90% yield as a 2:1 mixture of diastereomers concerning the allylic hydroxyl group (Scheme 5). Hydrolysis of the methyl ester and silyl groups in **34** afforded seco acid **11** (69%) along with ester **35** (19%). The macrolactonization of **11** was accomplished by the Yamaguchi method[19] to give lactone **9** (29%) without elimination of methanol in contrast to that of **5**. To improve the yield of macrolactonization, we tried macrolactonization by an alternative method. Coupling reaction between C1–C9 segment **4** and *ent*-**13**, prepared from (*S*)-trityl glycidyl ether, gave seco acid C13-*epi*-**11**. Macrolactonization of C13-*epi*-**11** under Mitsunobu condition[20] provided lactone **9**, however, the yield was not improved (<30%). Treatment of **9** with formic acid in ether to remove the trityl group afforded not desired alcohol but a complex mixture. Therefore, another synthetic route was investigated.



Scheme 5. (a) 0.6% $NiCl_2$–$CrCl_2$, DMSO, rt, 90%; (b) LiOH, H_2O, MeOH, THF, (**11**) 69%, (**35**) 19%; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt; DMAP, toluene, 80 °C, 29%; (d) $^{i}PrO_2CN{=}NCO_2{}^{i}Pr$, PPh_3, toluene, 0 °C→rt, <30%; (e) HCO_2H, ether, rt.

Coupling reaction between C1–C9 segment **4** and C10–C17 segment **14** gave a diastereomeric mixture of alcohol **36** in 81% yield (Scheme 6). The trimethylsilyl and triethylsilyl groups in **36** were removed to give acetylene **37** (98%), hydrostannation of which afforded vinylstannane **38** (81%),[21] which was contaminated by (16*Z*)-isomer. The minor (16*Z*)-isomer could be separated by HPLC at a later stage in the synthesis. Treatment of **38** with NBS gave bromodiene **39** (98%), which was hydrolyzed under basic conditions to provide seco acid **12** (63%). The macrolactonization of **12** under Yamaguchi condition afforded lactone **10** (57%), which was treated with aqueous acid to give hemiacetal **40**



Scheme 6. (a) 0.5% $NiCl_2$–$CrCl_2$, DMSO, rt, 81%; (b) Bu_4NF, AcOH, THF, 0 °C, 98%; (c) Bu_3SnH, AIBN, THF, 70 °C, 81%; (d) NBS, THF, 0 °C, 98%; (e) NaOH, H_2O, MeOH, THF, 63%; (f) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt; DMAP, toluene, reflux, 57%; (g) H_2O, AcOH, acetone, rt, 86%; (h) Dess–Martin periodinane, CH_2Cl_2, pyridine, rt, (**41a**) 27%, (**41b**) 21%; (i) Bu_4NF, AcOH, THF, rt, 90% from **41a**, 96% from **41b**; (j) **7**, $SnCl_2$, $AgClO_4$, MS 4Å, Et_2O, 0 °C→rt; (k) HF·pyridine, THF, 0 °C→rt, 42% in two steps; (l) **8**, $SnCl_2$, $AgClO_4$, MS 4Å, Et_2O, 0 °C→rt, 68%.

(86%). The oxidation of allylic hydroxyl group in **40** gave a separable 1:1 mixture of conjugated enones, which was separated by HPLC to afford pure **41a** and **41b**. The minor (16*Z*)-isomer could be completely removed at this stage. The stereochemistry of **41a** and **41b** was determined by NOESY. Removal of the silyl group in **41a** gave the aglycon (**3**) of aurisides A and B (90%). Under the same condition, enone **41b** was converted into **3** with epimerization at C2 (96%). The glycosylation reaction of **3** with fluorosugar **7** followed by desilylation afforded auriside A (**1**) (42%).[6] Similarly, the reaction between **3** and **8** gave auriside B (**2**) (68%).[6] Synthetic aurisides A (**1**) and B (**2**) were found to be identical to natural **1** and **2** in all respects, respectively, including the spectroscopic (UV, IR, ^{1}H NMR, MS, and $[\alpha]_D$) and chromatographic properties.

3. Conclusion

In conclusion, enantioselective synthesis of aurisides A (**1**) and B (**2**) was achieved from (*R*)-pantolactone in 26 steps (1.4% overall yield) and 25 steps (2.3% overall yield), respectively. In comparison with the previous synthesis of the aglycon **3** of aurisides A (**1**) and B (**2**) reported as a communication[4] in 1998 (0.021% overall yield), the synthetic procedures of **3** have been much improved as regards overall yield (3.3%).

4. Experimental

4.1. General

Optical rotations were measured with a JASCO DIP-370 polarimeter or a JASCO DIP-1000 polarimeter. ^{1}H NMR spectra were recorded on a JEOL JNM-EX270 (270 MHz), a Bruker AVANCE-400M (400 MHz), or a Bruker AVANCE 500 (500 MHz) instrument. Chemical shifts are reported in parts per million from internal standards [tetramethylsilane (0.00 ppm) for $CDCl_3$ and C_6D_5H (7.16 ppm) for C_6D_6] and *J* values are in hertz. ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 (67.8 MHz) or a Bruker AVANCE 500 (125 MHz) instrument. Chemical shifts are reported in parts per million from the solvent peak (77.0 ppm for $CDCl_3$, 128.0 ppm for C_6D_6). IR spectra were recorded on a JASCO FT/IR-300 instrument. FAB mass spectra were recorded on a JEOL SX-102 instrument. ESI mass spectra were recorded on a QStar/Pulsar *i* spectrometer (Applied Biosystems). Both TLC analysis and preparative TLC were conducted on E. Merck precoated silica gel 60 F_{254} (0.25 mm layer thickness). Fuji Silysia silica gel BW-820 MH and FL-60D were used for column chromatography unless otherwise noted. Organic solvents for moisture-sensitive reactions were distilled from the following drying agents: THF and ether (Na–benzophenone ketyl), benzene and toluene (Na), acetonitrile and triethylamine (calcium hydride), DMSO (calcium hydride under reduced pressure), CH_2Cl_2 (P_2O_5), acetone (anhydrous K_2CO_3), and MeOH (Mg). All moisture-sensitive reactions were performed under an atmosphere of nitrogen, and the starting materials were azeotropically dried with benzene before use. All new compounds were determined to be >95% pure by ^{1}H NMR unless otherwise noted.

4.1.1. Alcohol 16. To a stirred solution of 2-allyldithiane (5.03 g, 31.4 mmol) in dry THF (50 mL) cooled at −78 °C was added a 1.6 M solution of *n*-BuLi in hexane (18.4 mL, 29.5 mmol) dropwise. The reaction mixture was stirred at −20 °C for 1.5 h. After cooling to −78 °C, a solution of epoxide **15** (4.05 g, 19.6 mmol) in THF (3 mL, 2×2 mL rinse) was added dropwise, and the mixture was kept at −30 °C for 2 h. The reaction was quenched with water (100 mL), and the mixture was extracted with Et_2O (2×100 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (200 g, hexane–ether 5:1) to give **16** (6.60 g, 92%) as a colorless oil: TLC, R_f 0.39 (hexane–ether 2:1); $[\alpha]_D^{25}$ +25.9 (*c* 1.02, $CHCl_3$); IR (neat) 3490, 2960, 2860, 1640, 1100 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 5.94 (m, 1H), 5.15 (d, *J*=17.0 Hz, 1H), 5.14 (d, *J*=10.3 Hz, 1H), 4.53 (d, *J*=12.2 Hz, 1H), 4.51 (d, *J*=12.2 Hz, 1H), 3.89 (dd, *J*=6.9, 3.6 Hz, 1H), 3.39 (d, *J*=8.9 Hz, 1H), 3.30 (d, *J*=8.9 Hz, 1H), 2.95–2.70 (m, 6H), 2.08 (m, 2H), 2.04–1.88 (m, 2H), 1.60 (br s, 1H), 0.96 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.0, 133.0, 128.2, 127.4, 127.3, 118.3, 78.4, 74.1, 73.4, 51.9, 43.6, 40.3, 39.0, 26.4, 26.1, 24.9, 22.6, 20.1; HRMS (ESI) calcd for $C_{20}H_{30}NaO_2S_2$ $(M+Na)^+$ 389.1585, found 389.1604.

4.1.2. Ketone 17. To a stirred solution of alcohol **16** (2.80 g, 7.64 mmol) in MeOH cooled at 0 °C was added [bis(trifluoroacetoxy)iodo]benzene (3.33 g, 7.74 mmol). The reaction mixture was stirred at 0 °C for 45 min and diluted with ether (100 mL), saturated aqueous $NaHCO_3$ (60 mL), and 5% aqueous $Na_2S_2O_3$ (60 mL). The organic layer was separated, and the aqueous layer was extracted with ether (100 mL, 50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (70 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was dissolved in THF (15 mL), H_2O (5 mL), and acetic acid (15 mL), and the solution was stirred at room temperature for 15 min. The reaction mixture was cooled at 0 °C, neutralized with saturated aqueous $NaHCO_3$ (225 mL), and extracted with ether (2×200 mL, 100 mL). The combined extracts were washed with H_2O (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (200 g, hexane–ether 10:1→5:1) to give **17** (1.63 g, 77%) as a colorless oil: TLC, R_f 0.36 (hexane–ether 1:1); $[\alpha]_D^{23}$ +45.5 (*c* 0.98, $CHCl_3$); IR (neat) 3480, 3030, 2960, 2870, 1710, 1640, 1100 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.92 (ddt, *J*=17.0, 10.3, 6.9 Hz, 1H), 5.17 (d, *J*=10.3 Hz, 1H), 5.13 (d, *J*=17.0 Hz, 1H), 4.52 (d, *J*=12.5 Hz, 1H), 4.48 (d, *J*=12.5 Hz, 1H), 4.02 (dd, *J*=8.6, 4.0 Hz, 1H), 3.35 (d, *J*=8.9 Hz, 1H), 3.30 (d, *J*=8.9 Hz, 1H), 3.23 (d, *J*=6.9 Hz, 2H), 2.57 (dd, *J*=16.0, 8.6 Hz, 1H), 2.50 (dd, *J*=16.0, 4.0 Hz, 1H), 1.64 (br s, 1H), 0.93 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 209.1, 137.8, 130.2, 128.2, 127.6, 127.5, 118.8, 78.5, 73.6, 73.4, 48.5, 44.3, 38.1, 22.2, 19.9; HRMS (ESI) calcd for $C_{17}H_{24}NaO_3$ $(M+Na)^+$ 299.1623, found 299.1650.

4.1.3. *anti*-1,3-Diol 18a and *syn*-1,3-diol 18b. To a stirred solution of tetramethylammonium triacetoxyborohydride (3.14 g, 11.9 mmol) in acetonitrile (10 mL) and acetic acid (10 mL) cooled at −40 °C was added a solution of ketone

17 (745 mg, 2.70 mmol) in acetonitrile (1.5 mL, 3×0.4 mL rinse). The reaction mixture was stirred at −40 °C, kept at −30 °C for 12 h, diluted with saturated aqueous Na/K tartrate (35 mL), stirred at room temperature for 50 min, and extracted with CH_2Cl_2 (3×60 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (70 mL), and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 100 g, hexane–EtOAc 4:1) to give **18a** (644 mg, 86%) and *syn*-1,3-diol **18b** (56 mg, 7%) as a colorless oil. Compound **18a**: TLC, R_f 0.39 (hexane–EtOAc 2:1); $[\alpha]_D^{23}$ +26.5 (*c* 1.32, $CHCl_3$); IR (neat) 3430, 3030, 2960, 2870, 1640, 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.83 (ddt, *J*=17.0, 10.3, 6.8 Hz, 1H), 5.12 (d, *J*=17.0 Hz, 1H), 5.10 (d, *J*=10.3 Hz, 1H), 4.54 (d, *J*=12.0 Hz, 1H), 4.48 (d, *J*=12.0 Hz, 1H), 3.98 (m, 1H), 3.83 (ddd, *J*=9.1, 3.8, 3.8 Hz, 1H), 3.60 (d, *J*=3.8 Hz, 1H), 3.40 (d, *J*=8.9 Hz, 1H), 3.33 (d, *J*=8.9 Hz, 1H), 2.60 (d, *J*=5.1 Hz, 1H), 2.30 (dd, *J*=6.8, 6.8 Hz, 2H), 1.62–1.48 (m, 2H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 137.5, 135.0, 128.1, 127.4, 127.2, 117.0, 79.5, 74.6, 73.4, 67.9, 41.8, 38.0, 36.9, 22.5, 19.6; HRMS (ESI) calcd for $C_{17}H_{26}NaO_3$ $(M+Na)^+$ 301.1780, found 301.1782. Compound **18b**: R_f 0.48 (hexane–EtOAc 2:1); ^1H NMR (270 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.85 (ddt, *J*=17.0, 10.3, 6.9 Hz, 1H), 5.10 (d, *J*=17.0 Hz, 1H), 5.08 (d, *J*=10.3 Hz, 1H), 4.53 (d, *J*=13.5 Hz, 1H), 4.48 (d, *J*=13.5 Hz, 1H), 4.12 (br s, 1H), 4.07–3.85 (m, 2H), 3.72 (br s, 1H), 3.39 (d, *J*=8.9 Hz, 1H), 3.29 (d, *J*=8.9 Hz, 1H), 2.25 (m, 2H), 1.60 (m, 1H), 1.41 (m, 1H), 0.91 (s, 3H), 0.90 (s, 3H).

4.1.4. Acetonide 19. To a stirred solution of *anti*-1,3-diol **18a** (482 mg, 1.73 mmol) in acetone (6 mL) were added 2,2-dimetoxypropane (2.9 mL, 24 mmol) and (±)-camphorsulfonic acid (23.4 mg, 0.101 mmol). The reaction mixture was stirred at room temperature for 19 h, diluted with saturated aqueous $NaHCO_3$ (10 mL), and extracted with ether (3×25 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (26 g, hexane–ether 25:1→10:1→2:1→1:2) to give **19** (540 mg, 97%) as a colorless oil: TLC, R_f 0.82 (hexane–EtOAc 5:1); $[\alpha]_D^{24}$ +29.8 (*c* 0.97, $CHCl_3$); IR (neat) 2980, 2880, 1220, 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5H), 5.80 (ddt, *J*=17.0, 10.3, 6.8 Hz, 1H), 5.09 (d, *J*=17.0 Hz, 1H), 5.03 (d, *J*=10.3 Hz, 1H), 4.51 (d, *J*=12.2 Hz, 1H), 4.45 (d, *J*=12.2 Hz, 1H), 3.79 (dd, *J*=10.3, 6.2 Hz, 1H), 3.75 (m, 1H), 3.29 (d, *J*=8.4 Hz, 1H), 3.17 (d, *J*=8.4 Hz, 1H), 2.30 (ddd, *J*=14.3, 6.8, 6.8 Hz, 1H), 2.18 (ddd, *J*=14.3, 6.8, 6.8 Hz, 1H), 1.77 (ddd, *J*=12.3, 10.3, 5.9 Hz, 1H), 1.40 (ddd, *J*=12.3, 9.7, 6.2 Hz, 1H), 1.30 (s, 6H), 0.90 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.9, 134.7, 128.2, 127.3, 127.2, 116.5, 100.2, 76.5, 73.2, 69.4, 66.7, 40.2, 37.6, 32.6, 24.6, 24.2, 20.5, 19.7; HRMS (ESI) calcd for $C_{20}H_{30}NaO_3$ $(M+Na)^+$ 341.2093, found 341.2081.

4.1.5. Aldehyde 20. To a stirred solution of acetonide **19** (1.58 g, 4.97 mmol) in acetone (48 mL) and H_2O (16 mL) were added *N*-methylmorpholine-*N*-oxide (1.02 g, 8.70 mmol) and a 0.078 M solution of osmium tetroxide in *tert*-butyl alcohol (2.8 mL, 0.22 mmol). After being stirred at room temperature for 2 h, a 0.4 M aqueous sodium periodate (34 mL, 13 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and extracted with EtOAc (3×50 mL). The combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane–EtOAc 5:1) to give **20** (1.53 g, 96%) as a colorless oil: TLC, R_f 0.71 (hexane–EtOAc 2:1); $[\alpha]_D^{22}$ +24.2 (*c* 1.03, $CHCl_3$); IR (neat) 2980, 2870, 1730, 1380, 1220, 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.75 (dd, *J*=2.6, 1.7 Hz, 1H), 7.35–7.26 (m, 5H), 4.51 (d, *J*=12.2 Hz, 1H), 4.44 (d, *J*=12.2 Hz, 1H), 4.25 (dddd, *J*=9.9, 8.3, 5.9, 4.6 Hz, 1H), 3.83 (dd, *J*=9.9, 6.6 Hz, 1H), 3.30 (d, *J*=8.6 Hz, 1H), 3.16 (d, *J*=8.6 Hz, 1H), 2.60 (ddd, *J*=16.5, 8.3, 2.6 Hz, 1H), 2.46 (ddd, *J*=16.5, 4.6, 1.7 Hz, 1H), 1.89 (ddd, *J*=12.5, 9.9, 5.9 Hz, 1H), 1.42 (ddd, *J*=12.5, 9.9, 6.6 Hz, 1H), 1.32 (s, 3H), 1.29 (s, 3H), 0.91 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 200.9, 138.7, 128.9, 128.1, 127.2, 100.6, 76.3, 73.2, 69.2, 62.6, 49.2, 37.7, 32.8, 24.7, 24.0, 20.6, 19.8; HRMS (FAB) calcd for $C_{19}H_{28}NaO_4$ $(M+Na)^+$ 343.1886, found 343.1857.

4.1.6. β-Hydroxy ester 21. To a stirred solution of $RhCl(PPh_3)_3$ (15.0 mg, 0.0160 mmol) in THF (4 mL) at 0 °C were added methyl 2-bromopropionate (0.045 mL, 0.40 mmol), a solution of aldehyde **20** (99.1 mg, 0.310 mmol) in THF (1.0 mL, 3×0.3 mL rinse), and a 1.0 M hexane solution of Et_2Zn (0.91 mL). The mixture was stirred at 0 °C for 20 min, and 2-bromopropionate (0.020 mL, 0.18 mmol) was added to the mixture. After being stirred at 0 °C for 15 min, saturated aqueous $NaHCO_3$ (10 mL) was added. The reaction mixture was filtered through Florisil, and the filtrate was extracted with EtOAc (20 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (7 g, hexane–EtOAc 3:1) to give **21** (107 mg, 88%) as a colorless oil: TLC, R_f 0.47 (hexane–EtOAc 3:1); IR (neat) 3500, 2990, 2860, 1740, 1220, 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 4.50 (d, *J*=12.3 Hz, 1H), 4.44 (d, *J*=12.3 Hz, 1H), 4.22–3.90 (m, 2H), 3.85–3.75 (m, 1H), 3.71 (s, 1.5H), 3.67 (s, 1.5H), 3.29 (d, *J*=8.6 Hz, 0.5H), 3.28 (d, *J*=8.6 Hz, 0.5H), 3.15 (d, *J*=8.6 Hz, 0.5H), 3.14 (d, *J*=8.6 Hz, 0.5H), 3.13 (d, *J*=6.2 Hz, 0.5H), 3.06 (d, *J*=4.3 Hz, 0.5H), 2.60–2.48 (m, 1H), 1.88–1.35 (m, 4H), 1.34 (s, 1.5H), 1.32 (s, 1.5H), 1.29 (s, 3H), 1.21 (d, *J*=7.1 Hz, 1.5H), 1.19 (d, *J*=7.1 Hz, 0.75H), 1.15 (d, *J*=7.1 Hz, 0.75H), 0.89 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 176.1, 176.0, 175.4, 175.3, 138.73, 138.67, 128.9, 128.09, 128.07, 128.05, 127.19, 127.17, 127.14, 125.1, 100.6, 100.41, 100.37, 76.4, 76.3, 73.2, 70.3, 69.4, 69.2, 68.7, 68.19, 68.12, 64.5, 64.3, 51.72, 51.67, 45.7, 45.5, 39.8, 39.5, 39.14, 39.09, 37.7, 37.6, 33.30, 33.23, 32.77, 32.72, 24.9, 24.7, 24.14, 24.09, 20.62, 20.59, 20.56, 19.7, 13.1, 12.1, 11.6; HRMS (ESI) calcd for $C_{23}H_{36}NaO_6$ $(M+Na)^+$ 431.2410, found 431.2396.

4.1.7. β-Keto ester 22. To a stirred solution of oxalyl chloride (0.047 mL, 0.54 mmol) in CH_2Cl_2 (1.5 mL) cooled at −78 °C was added a 3.6 M solution of DMSO in CH_2Cl_2 (0.35 mL, 1.3 mmol) dropwise. The resulting solution was

stirred at −78 °C for 5 min, and a solution of β-hydroxy ester **21** (198 mg, 0.485 mmol) in CH_2Cl_2 (1 mL, 0.5 mL rinse) was added dropwise. The mixture was stirred at −78 °C for 15 min, and triethylamine (0.20 mL, 1.43 mmol) was added. The resulting mixture was stirred at −78 °C for 5 min, warmed to 0 °C, and stirred for 10 min. The mixture was diluted with H_2O (3 mL) and extracted with ether (3×10 mL). The combined extracts were washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane–EtOAc 20:1→10:1→5:1) to give **22** (173 mg, 88%) as a colorless oil: TLC, R_f 0.57 (hexane–EtOAc 3:1); IR (neat) 2990, 2860, 1750, 1720, 1220, 1100 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 4.50 (d, J=12.3 Hz, 1H), 4.44 (d, J=12.3 Hz, 1H), 4.19 (m, 1H), 3.83–3.76 (m, 1H), 3.72 (s, 3H), 3.59 (q, J=7.1 Hz, 0.5H), 3.58 (q, J=7.1 Hz, 0.5H), 3.29 (d, J=8.6 Hz, 1H), 3.15 (d, J=8.6 Hz, 1H), 2.80 (dd, J=16.2, 7.9 Hz, 1H), 2.57 (dd, J=16.2, 5.1 Hz, 1H), 1.89 (m, 1H), 1.41–1.31 (m, 1H), 1.34 (d, J=7.1 Hz, 1.5H), 1.32 (d, J=7.1 Hz, 1.5H), 1.28 (s, 1.5H), 1.27 (s, 1.5H), 1.26 (s, 3H), 0.89 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 203.7, 170.8, 138.8, 128.14, 128.12, 127.25, 127.21, 127.20, 100.6, 100.4, 76.4, 73.2, 69.3, 69.2, 63.8, 63.6, 53.3, 53.1, 52.4, 47.7, 47.3, 37.7, 32.8, 24.6, 24.1, 20.6, 19.75, 19.72, 12.7, 12.5; HRMS (ESI) calcd for $C_{23}H_{34}NaO_6$ $(M+Na)^+$ 429.2253, found 429.2262.

4.1.8. Cyclic methyl acetal 23. To a stirred solution of β-keto ester **22** (1.20 g, 10.3 mmol) in methanol (30 mL) were added trimethyl orthoformate (4.7 mL, 43 mmol) and pyridinium *p*-toluenesulfonate (71.6 mg, 0.29 mmol). The mixture was stirred at room temperature for 1 h, diluted with saturated aqueous $NaHCO_3$ (35 mL), and extracted with ether (4×50 mL). The combined extracts were washed with H_2O and brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (40 g, hexane–EtOAc 3:1→2:1→1:1) to give **23** (785 mg, 96%) as a colorless oil: TLC, R_f 0.24 (hexane–EtOAc 2:1); IR (neat) 3450, 2950, 2870, 1740, 1100, 1030 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 4.51 (d, J=12.2 Hz, 0.5H), 4.50 (d, J=12.2 Hz, 0.5H), 4.43 (d, J=12.2 Hz, 0.5H), 4.42 (d, J=12.2 Hz, 0.5H), 4.08 (m, 1H), 3.67 (s, 1.5H), 3.63 (s, 1.5H), 3.58 (dd, J=11.9, 1.6 Hz, 0.5H), 3.57 (dd, J=11.9, 1.6 Hz, 0.5H), 3.49 (s, 1.5H), 3.40 (d, J=8.6 Hz, 0.5H), 3.38 (d, J=8.6 Hz, 0.5H), 3.17 (d, J=8.6 Hz, 0.5H), 3.14 (d, J=8.6 Hz, 0.5H), 3.10 (s, 1.5H), 3.07 (q, J=7.2 Hz, 0.5H), 3.02 (q, J=6.9 Hz, 0.5H), 2.10 (ddd, J=12.2, 4.6, 1.6 Hz, 0.5H), 2.00 (ddd, J=12.2, 4.8, 1.6 Hz, 0.5H), 1.94–1.81 (m, 1H), 1.74 (dd, J=12.2, 11.2 Hz, 0.5H), 1.40 (dd, J=12.2, 10.8 Hz, 0.5H), 1.27–1.06 (m, 1H), 1.21 (d, J=6.9 Hz, 1.5H), 1.11 (d, J=7.2 Hz, 1.5H), 0.95 (s, 1.5H), 0.93 (s, 1.5H), 0.89 (s, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.0, 173.2, 138.54, 138.47, 128.1, 127.2, 127.1, 101.3, 101.2, 73.1, 73.0, 72.5, 72.1, 65.4, 65.1, 51.7, 51.5, 47.3, 47.0, 44.8, 43.4, 38.3, 38.1, 38.0, 37.4, 34.0, 33.9, 21.4, 21.2, 20.4, 20.2, 13.2, 11.6; HRMS (ESI) calcd for $C_{21}H_{32}NaO_6$ $(M+Na)^+$ 403.2097, found 403.2118.

4.1.9. Silyl ether 24. To a stirred solution of cyclic methyl acetal **23** (445 mg, 1.17 mmol) and imidazole (263 mg, 3.86 mmol) in DMF (2.5 mL) was added *tert*-butyldiphenylsilyl chloride (0.46 mL, 1.8 mmol). The mixture was stirred at 0 °C for 2 h, diluted with 5% aqueous $NaHCO_3$ (30 mL), and extracted with EtOAc (3×20 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (46 g, hexane–EtOAc 8:1) to give **24** (739 mg, 100%) as a colorless oil: TLC, R_f 0.64 (hexane–EtOAc 3:1); IR (neat) 2960, 2860, 1740, 1110, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.74–7.60 (m, 4H), 7.43–7.21 (m, 11H), 4.40 (d, J=12.4 Hz, 1H), 4.35 (d, J=12.4 Hz, 1H), 4.22–4.05 (m, 1H), 3.63 (s, 1.5H), 3.62 (s, 1.5H), 3.49 (s, 1.5H), 3.33–3.25 (m, 2H), 3.06–3.00 (m, 1H), 2.97 (s, 1.5H), 2.93 (q, J=7.3 Hz, 1H), 2.13–1.09 (m, 4H), 1.16 (d, J=7.3 Hz, 1.5H), 1.05 (s, 9H), 1.01 (d, J=7.3 Hz, 1.5H), 0.79 (s, 1.5H), 0.77 (s, 1.5H), 0.74 (s, 1.5H), 0.73 (s, 1.5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.1, 173.2, 138.64, 138.56, 135.7, 134.7, 134.4, 134.3, 129.3, 128.1, 127.6, 127.37, 127.35, 127.2, 127.1, 101.3, 101.2, 77.2, 73.1, 72.3, 71.9, 67.2, 51.6, 51.4, 47.2, 46.9, 44.9, 43.4, 38.1, 38.0, 37.5, 34.5, 34.4, 27.09, 27.08, 26.6, 21.3, 21.1, 20.5, 20.2, 19.2, 14.3, 13.2, 11.6; HRMS (ESI) calcd for $C_{37}H_{50}NaO_6Si$ $(M+Na)^+$ 641.3274, found 641.3250.

4.1.10. Alcohol 25. A mixture of silyl ether **24** (66 mg, 0.13 mmol) and 20% $Pd(OH)_2$ on carbon (26 mg) in dioxane (3 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane–EtOAc 5:1→3:1) to give **25** (52 mg, 96%) as a colorless oil: TLC, R_f 0.57 (hexane–EtOAc 2:1); IR (neat) 3540, 2960, 2860, 1740, 1110, 1040, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.42–7.33 (m, 6H), 4.07 (m, 1H), 3.69 (s, 1.5H), 3.65 (s, 1.5H), 3.44–3.18 (m, 3H), 3.09 (s, 1.5H), 3.03 (s, 1.5H), 2.95 (q, J=7.3 Hz, 1H), 2.08–1.86 (m, 1H), 1.72–0.80 (m, 3H), 1.17 (d, J=7.3 Hz, 1.5H), 1.06 (s, 9H), 1.03 (d, J=7.3 Hz, 1.5H), 0.79 (s, 1.5H), 0.76 (s, 1.5H), 0.74 (s, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 174.0, 173.3, 136.1, 135.0, 134.9, 134.6, 129.9, 127.9, 102.3, 102.0, 78.3, 76.5, 72.1, 71.5, 67.2, 67.1, 52.3, 52.2, 48.2, 47.6, 45.6, 43.9, 39.0, 38.4, 38.1, 38.0, 35.4, 35.3, 27.51, 27.49, 23.1, 22.5, 20.0, 19.7, 19.6, 13.4, 11.8; HRMS (ESI) calcd for $C_{30}H_{44}NaO_6Si$ $(M+Na)^+$ 551.2805, found 551.2822.

4.1.11. C1–C9 segment 4. To a stirred solution of alcohol **25** (79 mg, 0.11 mmol) in DMSO (4.3 mL) were added triethylamine (0.42 mL, 3.0 mmol) and sulfur trioxide pyridine complex (153 mg, 0.961 mmol). The mixture was stirred at room temperature for 1 h, diluted with saturated aqueous $NaHCO_3$ (15 mL), and extracted with EtOAc (3×15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane–EtOAc 9:1) to give **4** (75 mg, 95%) as a colorless oil: TLC, R_f 0.63 (hexane–EtOAc 3:1); IR (neat) 2950, 2860, 1740, 1110, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.49 (s, 0.5H), 9.47 (s, 0.5H), 7.68–7.64 (m, 4H), 7.42–7.33 (m, 6H), 4.09 (m, 1H), 3.65 (s, 1.5H), 3.63 (s, 1.5H), 3.44 (dd, J=12.4, 2.1 Hz, 0.5H), 3.39 (dd, J=12.2, 2.1 Hz,

0.5H), 3.07 (s, 1.5H), 2.97 (s, 1.5H), 2.95 (q, J=7.6 Hz, 0.5H), 2.90 (q, J=7.6 Hz, 0.5H), 2.05–1.12 (m, 4H), 1.15 (d, J=7.6 Hz, 1.5H), 1.05 (s, 9H), 1.01 (d, J=7.6 Hz, 1.5H), 0.99 (s, 1.5H), 0.94 (s, 1.5H), 0.87 (s, 1.5H), 0.85 (s, 1.5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 205.3, 205.0, 173.8, 172.8, 135.62, 135.61, 134.39, 134.36, 134.1, 134.0, 129.51, 129.49, 129.48, 127.4, 101.7, 101.6, 73.1, 72.5, 66.49, 66.42, 51.7, 51.6, 48.9, 48.7, 47.5, 47.2, 44.6, 43.1, 38.1, 37.4, 34.35, 34.32, 27.0, 19.2, 19.0, 18.9, 16.65, 16.60, 13.1, 11.5; HRMS (ESI) calcd for $C_{37}H_{50}NaO_6Si$ $(M+Na)^+$ 549.2648, found 549.2648.

4.1.12. Acetylene 26. To a stirred solution of 90% lithium acetylide ethylenediamine complex (16.2 g, 158 mmol) in DMSO (90 mL) kept at 20 °C was added a solution of (*R*)-glycidyl trityl ether (25.0 g, 79.0 mmol) in THF (25 mL, 3 mL rinse) over 30 min. The mixture was stirred at room temperature for 30 min, cooled to 0 °C, diluted with saturated aqueous NH_4Cl (50 mL) and H_2O (20 mL), and extracted with ether (3×70 mL). The combined extracts were washed with brine (70 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane–EtOAc 8:1) to give **26** (26.2 g, 97%) as a colorless oil: TLC, R_f 0.49 (hexane–EtOAc 3:1); $[\alpha]_D^{24}$ −3.1 (*c* 1.11, $CHCl_3$); IR (neat) 3300, 3060, 2920, 1490, 1450, 1070, 760, 710 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.48–7.20 (m, 15H), 3.92 (m, 1H), 3.27 (dd, J=9.2, 4.6 Hz, 1H), 3.22 (dd, J=9.2, 5.9 Hz, 1H), 2.49 (ddd, J=11.9, 5.9, 2.6 Hz, 1H), 2.43 (ddd, J=11.9, 5.9, 2.3 Hz, 1H), 2.36 (d, J=5.3 Hz, 1H), 1.96 (dd, J=2.6, 2.3 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.5, 128.5, 127.7, 126.9, 86.7, 80.3, 70.5, 69.1, 66.0, 23.9; HRMS (ESI) calcd for $C_{24}H_{22}NaO_2$ $(M+Na)^+$ 365.1517, found 365.1494.

4.1.13. Vinyl iodide 27. A 2.0 M solution of trimethylaluminum in toluene (0.50 mL, 1.0 mmol) was added to a stirred suspension of zirconocene dichloride (57 mg, 0.19 mmol) in CH_2Cl_2 (1.0 mL). After being stirred at room temperature for 15 min, a solution of acetylene **26** (99 mg, 0.29 mmol) in CH_2Cl_2 (0.5 mL, 0.3 mL rinse) was added, and the resulting mixture was stirred at room temperature for 24 h. A solution of iodine (104 mg, 0.41 mmol) in THF (0.4 mL) was added, and the mixture was stirred at room temperature for 50 min. After the mixture was cooled to 0 °C, the reaction was quenched by addition of sodium fluoride (0.2 g) and THF–H_2O (5:1, 6 mL), and the mixture was stirred at room temperature for 15 min. After addition of magnesium sulfate (0.5 g), the mixture was further stirred for 15 min and filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate and the washings were combined and concentrated. The residual oil was dissolved in ether (10 mL), and the solution was washed with saturated aqueous $Na_2S_2O_3$ (3 mL). The aqueous layer was extracted with EtOAc (3×5 mL). The organic layers were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 8 g, benzene–acetonitrile 4:1 → 3:1) to give **27** (35 mg, 50%) as a colorless oil: TLC, R_f 0.55 (benzene–acetonitrile 1:1); $[\alpha]_D^{26}$ +8.7 (*c* 0.96, $CHCl_3$); IR (neat) 3370, 2930, 1270, 1090, 1040 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.06 (m, 1H), 3.87 (m, 1H), 3.67 (ddd, J=11.1, 6.4, 3.4 Hz, 1H), 3.47 (ddd, J=11.1, 6.4, 5.4 Hz, 1H), 2.42 (ddd, J=13.8, 7.9, 1.1 Hz, 1H), 2.35 (ddd, J=13.8, 5.9, 1.1 Hz, 1H), 2.02 (d, J=3.4 Hz, 1H), 1.90 (d, J=1.3 Hz, 3H), 1.86 (t, J=6.4 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.9, 77.7, 69.6, 66.0, 42.9, 24.2; HRMS (ESI) calcd for $C_6H_{11}INaO_2$ $(M+Na)^+$ 264.9701, found 264.9696.

4.1.14. Silyl ether 28. To a stirred solution of vinyl iodide **27** (5.05 g, 20.9 mmol) in pyridine (42 mL) cooled at 0 °C was added pivaloyl chloride (2.59 mL, 21.1 mmol). The mixture was stirred at 0 °C for 30 min, and triethylsilyl chloride (3.6 mL, 22 mmol) was added. The mixture was stirred at room temperature for 30 min, diluted with H_2O (50 mL), and extracted with hexane (3×50 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane–ether 50:1 → 10:1) to give **28** (8.44 g, 92%) as a colorless oil: TLC, R_f 0.65 (hexane–ether 9:1); $[\alpha]_D^{26}$ +9.1 (*c* 0.88, $CHCl_3$); IR (neat) 2960, 2870, 1730, 1460, 1280, 1150, 1000, 740 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.97 (s, 1H), 4.01–3.86 (m, 3H), 2.43 (dd, J=13.8, 5.1 Hz, 1H), 2.36 (dd, J=13.8, 5.9 Hz, 1H), 1.86 (s, 3H), 1.20 (s, 9H), 0.95 (t, J=7.6 Hz, 9H), 0.56 (q, J=7.6 Hz, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 178.1, 143.8, 77.9, 68.2, 67.4, 44.8, 38.8, 27.3, 24.5, 6.9, 5.0; HRMS (ESI) calcd for $C_{17}H_{33}INaO_3Si$ $(M+Na)^+$ 463.1141, found 463.1116.

4.1.15. Alcohol 29. To a stirred solution of silyl ether **28** (540 mg, 1.23 mmol) in CH_2Cl_2 (5 mL) cooled at −78 °C was added a 0.95 M solution of diisobutylaluminum hydride (2.9 mL, 2.7 mmol). The mixture was stirred at −78 °C for 1 h, and the reaction was quenched by addition of methanol (1 mL). The mixture was warmed to room temperature, diluted with saturated aqueous Na/K tartrate (40 mL), and stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×20 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (20 g, hexane–EtOAc 9:1) to give **29** (433 mg, 99%) as a colorless oil: TLC, R_f 0.45 (benzene–acetonitrile 9:1); $[\alpha]_D^{22}$ −0.47 (*c* 1.14, $CHCl_3$); IR (neat) 3450, 2950, 2870, 1240, 1110, 1000, 740 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.98 (m, 1H), 3.86 (m, 1H), 3.54 (dd, J=11.1, 3.8 Hz, 1H), 3.42 (dd, J=11.1, 3.8 Hz, 1H), 2.45 (ddd, J=12.7, 6.5, 1.1 Hz, 1H), 2.38 (ddd, J=12.7, 5.8, 1.1 Hz, 1H), 1.86 (d, J=1.1 Hz, 3H), 1.76 (br s, 1H), 0.96 (t, J=7.6 Hz, 9H), 0.61 (q, J=7.6 Hz, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 144.0, 77.9, 70.6, 65.9, 44.0, 24.5, 6.9, 5.1; HRMS (ESI) calcd for $C_{12}H_{25}INaO_2Si$ $(M+Na)^+$ 379.0566, found 379.0578.

4.1.16. Aldehyde 30. To a stirred solution of alcohol **29** (1.45 g, 4.07 mmol) in CH_2Cl_2 (41 mL) were added pyridine (4.5 mL, 57 mmol) and Dess–Martin periodinane (5.17 g, 12.2 mmol). The mixture was stirred at room temperature for 1.5 h, diluted with saturated aqueous $Na_2S_2O_3$ (50 mL) and saturated aqueous $NaHCO_3$ (50 mL), and stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×70 mL). The organic layers were combined, washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (30 g, hexane–EtOAc 9:1) to give **30** (1.37 g, 95%) as a colorless oil: TLC, R_f 0.48 (hexane–ether 3:1); $[\alpha]_D^{22}$ +45.6 (*c* 1.01,

$CHCl_3$); IR (neat) 2950, 2870, 1730, 1120, 1010, 740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.60 (d, J=1.8 Hz, 1H), 6.03 (m, 1H), 4.05 (ddd, J=7.6, 4.9, 1.8 Hz, 1H), 2.53 (ddd, J=13.8, 4.9, 0.8 Hz, 1H), 2.47 (ddd, J=13.8, 7.6, 0.8 Hz, 1H), 1.87 (d, J=1.1 Hz, 3H), 0.95 (t, J=7.6 Hz, 9H), 0.60 (q, J=7.6 Hz, 6H); HRMS (ESI) calcd for $C_{12}H_{23}INaO_2Si$ $(M+Na)^+$ 377.0410, found 377.0381.

4.1.17. C10–C17 segment 14. To a stirred solution of (3-trimethylsilyl-2-propynyl)triphenylphosphonium bromide (228 mg, 0.50 mmol) in THF (2.5 mL) cooled at −78 °C was added a 1.6 M solution of BuLi in hexane (0.28 mL, 0.45 mmol). After being stirred at −78 °C for 30 min, a solution of aldehyde **30** (148 mg, 0.42 mmol) in THF (3 mL, 2×1 mL rinse) was added. The mixture was stirred at −78 °C for 3 h, warmed to room temperature, diluted with H_2O, and extracted with hexane (3×5 mL). The combined extracts were washed with brine (7 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 8 g, hexane–benzene 15:1) to give **14** (105 mg, 57%) and its *cis*-isomer **33** (17 mg, 9%) as a colorless oil. Compound **14**: TLC, R_f 0.45 (hexane–benzene 5:1); $[\alpha]_D^{20}$ +13.2 (c 0.33, $CHCl_3$); IR (neat) 2960, 2880, 2150, 1250, 1080, 1010, 840, 740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.13 (dd, J=15.7, 5.4 Hz, 1H), 5.97 (s, 1H), 5.70 (dd, J=15.7, 1.6 Hz, 1H), 4.26 (m, 1H), 2.49 (dd, J=13.5, 6.8 Hz, 1H), 2.32 (dd, J=13.5, 5.4 Hz, 1H), 1.85 (s, 3H), 0.94 (t, J=7.6 Hz, 9H), 0.57 (q, J=7.6 Hz, 6H), 0.19 (s, 9H); HRMS (ESI) calcd for $C_{18}H_{33}INaOSi_2$ $(M+Na)^+$ 471.1013, found 471.1012. Compound **33**: TLC, R_f 0.40 (hexane–benzene 5:1); ^1H NMR (270 MHz, $CDCl_3$) δ 5.94 (s, 1H), 5.86 (dd, J=10.8, 8.6 Hz, 1H), 5.47 (dd, J=10.8, 0.8 Hz, 1H), 4.80 (m, 1H), 2.46 (dd, J=13.5, 7.3 Hz, 1H), 2.33 (dd, J=13.5, 4.3 Hz, 1H), 1.89 (s, 3H), 0.94 (t, J=7.6 Hz, 9H), 0.57 (q, J=7.6 Hz, 6H), 0.20 (s, 9H).

4.1.18. Conjugated ester 31. To a stirred solution of aldehyde **30** (129 mg, 0.364 mmol) in toluene (4.5 mL) heated at 90 °C were added benzoic acid (8.6 mg, 0.069 mmol) and 1 M solution of (methoxycarbonylmethylene)tributylphosphorane in toluene (0.70 mL, 0.70 mmol). The mixture was stirred at 90 °C for 15 min, diluted with saturated aqueous NH_4Cl (4 mL), and extracted with ether (3×4 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (4 mL) and brine (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–ether 50:1 → 15:1) to give **31** (138 mg, 92%) as a colorless oil: TLC, R_f 0.51 (hexane–ether 3:1); $[\alpha]_D^{22}$ +12.0 (c 1.05, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 6.89 (dd, J=15.7, 4.9 Hz, 1H), 6.00 (dd, J=15.7, 1.6 Hz, 1H), 5.98 (m, 1H), 4.40 (dddd, J=7.6, 4.9, 4.9, 1.6 Hz, 1H), 3.75 (s, 3H), 2.44 (ddd, J=13.8, 7.6, 1.1 Hz, 1H), 2.38 (ddd, J=13.8, 4.9, 0.8 Hz, 1H), 1.87 (d, J=1.4 Hz, 3H), 0.94 (t, J=7.6 Hz, 9H), 0.58 (q, J=7.6 Hz, 6H).

4.1.19. Alcohol 32. To a stirred solution of conjugated ester **31** (80 mg, 0.20 mmol) in THF (3 mL) cooled at −78 °C was added 0.93 M solution of diisobutylaluminum hydride in hexane (0.86 mL, 0.80 mmol). The mixture was stirred at −78 °C for 25 min, and the reaction was quenched by addition of methanol (0.1 mL). The mixture was warmed to room temperature, diluted with ether (3 mL) and saturated aqueous Na/K tartrate (5 mL), and stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with ether (3×5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane–EtOAc 20:1 → 10:1 → 7:1) to give **32** (66 mg, 86%) as a colorless oil: TLC, R_f 0.37 (hexane–EtOAc 3:1); $[\alpha]_D^{22}$ +6.5 (c 1.07, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 5.93 (q, J=0.8 Hz, 1H), 5.78 (ddt, J=15.6, 0.7, 5.1 Hz, 1H), 5.65 (ddt, J=15.6, 5.7, 0.8 Hz, 1H), 4.24 (m, 1H), 4.13 (dd, J=5.1, 0.8 Hz, 2H), 2.43 (dd, J=13.2, 7.3 Hz, 1H), 2.33 (dd, J=13.2, 5.4 Hz, 1H), 1.85 (d, J=0.8 Hz, 3H), 1.40 (br s, 1H), 0.94 (t, J=7.6 Hz, 9H), 0.57 (q, J=7.6 Hz, 6H).

4.1.20. C10–C16 segment 13. To a stirred solution of alcohol **32** (55 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL) were added triethylamine (0.06 mL, 0.4 mmol), 4-(dimethylamino)pyridine (3.3 mg, 0.027 mmol), and trityl chloride (69.7 mg, 0.250 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL) and extracted with ether (3×1 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane–EtOAc 50:1) to give **13** (80 mg, 89%) as a colorless oil: TLC, R_f 0.73 (hexane–EtOAc 3:1); $[\alpha]_D^{22}$ +9.7 (c 1.08, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.48–7.20 (m, 15H), 5.95 (s, 1H), 5.83 (dd, J=15.7, 5.9 Hz, 1H), 5.69 (dt, J=15.7, 4.6 Hz, 1H), 4.26 (m, 1H), 3.57 (d, J=4.6 Hz, 2H), 2.45 (dd, J=13.2, 7.3 Hz, 1H), 2.36 (dd, J=13.2, 5.1 Hz, 1H), 1.88 (s, 3H), 0.96 (t, J=7.6 Hz, 9H), 0.60 (q, J=7.6 Hz, 6H).

4.1.21. Alcohol 34. To a stirred solution of C1–C9 segment **4** (43 mg, 0.082 mmol) and C10–C16 segment **13** (225 mg, 0.36 mmol) in DMSO (1.5 mL) were added nickel chloride (0.6 mg, 0.0047 mmol) and chromium(II) chloride (203 mg, 1.65 mmol). The mixture was stirred at room temperature for 4 days, diluted with saturated aqueous NH_4Cl (4 mL), and extracted with ether (3×7 mL). The organic layers were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (8 g, hexane–EtOAc 50:1 → 10:1 → 6:1) to give a diastereomeric mixture of **34** (77 mg, 90%) as a colorless oil: TLC, R_f 0.50 (hexane–EtOAc 3:1); ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.42–7.16 (m, 21H), 5.80 (dd, J=15.4, 5.9 Hz, 1H), 5.65 (dt, J=15.4, 4.9 Hz, 1H), 5.21 (m, 1H), 4.36–4.20 (m, 1.5H), 4.15–4.00 (m, 1.5H), 3.64 (s, 3H), 3.60–3.50 (m, 2H), 3.30 (m, 1H), 3.11 (s, 0.5H), 3.09 (s, 1H), 3.06 (s, 0.5H), 3.03 (s, 1H), 2.94 (m, 1H), 2.40–1.10 (m, 6H), 1.68 (s, 2H), 1.62 (s, 1H), 1.17 (m, 1.5H), 1.06 (s, 9H), 1.05–0.93 (m, 10.5H), 0.76 (s, 3H), 0.67–0.56 (m, 9H). A signal due to one proton (OH) was not observed.

4.1.22. Seco acid 11. To a stirred solution of alcohol **34** (27 mg, 0.026 mmol) in THF (0.6 mL) and MeOH (0.3 mL) was added a 2 M aqueous NaOH (0.1 mL). The mixture was stirred at 40 °C for 29 h, acidified with 1 M aqueous HCl, and extracted with ether (4×5 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a oil, which was purified by column chromatography on silica gel (FL-60D, 3 g, hexane–EtOAc 3:1 → 2:1 → 1:1) to

give **11** (16 mg, 69%) and ester **35** (5 mg, 19%) as a colorless oil. Compound **11**: TLC, R_f 0.17–0.39 (hexane–EtOAc 1:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.46–7.19 (m, 21H), 5.88–5.73 (m, 2H), 5.32 (m, 1H), 4.41 (m, 1H), 4.25 (m, 1H), 4.12 (m, 1H), 3.67–3.56 (m, 2H), 3.35 (m, 1H), 3.04 (s, 3H), 2.91 (m, 1H), 2.30–1.10 (m, 6H), 1.72 (s, 2H), 1.67 (s, 1H), 1.17 (m, 1.5H), 1.06 (s, 9H), 0.96–0.81 (m, 4.5H), 0.67 (s, 0.5H), 0.60 (s, 1.5H), 0.55 (s, 1H). Signals due to three protons (COOH, OH) were not observed; MS (FAB) *m/z* 942 $(M+2Na-H)^+$. Compound **35**: TLC, R_f 0.55–0.71 (hexane–EtOAc 1:1); 7.70–7.64 (m, 4H), 7.46–7.19 (m, 21H), 5.88–5.73 (m, 2H), 5.21 (m, 1H), 4.40–4.20 (m, 2H), 4.09 (m, 1H), 3.66 (s, 3H), 3.67–3.56 (m, 2H), 3.33 (m, 1H), 3.08 (s, 1H), 3.04 (s, 2H), 2.95 (m, 1H), 2.35–1.12 (m, 6H), 1.71 (s, 3H), 1.20 (m, 1.5H), 1.06 (s, 9H), 1.04 (m, 1.5H), 0.96 (m, 3H), 0.63 (m, 3H). A signal due to one proton (OH) was not observed.

4.1.23. Lactone 9. A solution of triethylamine and 2,4,6-trichlorobenzoyl chloride in THF (0.25 mL, 0.054 mmol for Et_3N and 0.016 mmol for 2,4,6-$Cl_3C_6H_2COCl$), prepared from triethylamine (0.18 mL), 2,4,6-trichlorobenzoyl chloride (0.06 mL), and THF (6 mL), was added to seco acid **11** (11 mg, 0.012 mmol). The mixture was stirred at room temperature for 2.5 h and diluted with toluene (22 mL) to give a solution of mixed anhydride, which was added to a solution of 4-(dimethylamino)pyridine (14 mg, 0.12 mmol) in toluene (1.5 mL) warmed at 80 °C over 1 h. The mixture was stirred at 80 °C for 30 min, cooled to room temperature, and washed with brine (10 mL). The aqueous layer was extracted with ether (2×5 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (0.3 g, hexane–EtOAc 10:1→7:1→5:1) to give **9** (3.1 mg, 29%) as a colorless oil: TLC, R_f 0.50, 0.57, 0.64 (hexane–EtOAc 3:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.46–7.19 (m, 21H), 5.86–5.73 (m, 2H), 5.67–5.25 (m, 2H), 4.44–4.04 (m, 2H), 3.61 (m, 2H), 3.04 (s, 1.5H), 3.01 (m, 1H), 2.85 (s, 1.5H), 2.72 (m, 1H), 2.30–1.10 (m, 6H), 1.72 (m, 3H), 1.17 (m, 3H), 1.06 (s, 9H), 0.90–0.75 (m, 6H). A signal due to one proton (OH) was not observed; MS (FAB) *m/z* 901 $(M+Na)^+$.

4.1.24. *C*13-*epi*-Seco acid 11. TLC, R_f 0.17–0.39 (hexane–EtOAc 1:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.46–7.19 (m, 21H), 5.88–5.73 (m, 2H), 5.33 (m, 1H), 4.43 (m, 1H), 4.26 (m, 1H), 4.08 (m, 1H), 3.60 (m, 2H), 3.30 (m, 1H), 3.04 (m, 3H), 2.91 (m, 1H), 2.30–1.10 (m, 6H), 1.73 (s, 2H), 1.70 (s, 1H), 1.15 (m, 1.5H), 1.06 (s, 9H), 1.04 (m, 1.5H), 0.90 (m, 3H), 0.58 (m, 3H). Signals due to three protons (COOH, OH) were not observed; MS (FAB) *m/z* 942 $(M+2Na-H)^+$.

4.1.25. Alcohol 36. To a stirred solution of C1–C9 segment **4** (71.3 mg, 0.135 mmol) and C10–C17 segment **14** (519 mg, 1.16 mmol) in DMSO (2.7 mL) were added nickel chloride (1.7 mg, 0.013 mmol) and chromium(II) chloride (314 mg, 2.55 mmol). The mixture was stirred at room temperature for 5 days, diluted with saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (3×10 mL). The organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, hexane–EtOAc 18:1→7:1) to give a diastereomeric mixture of **36** (92.2 mg, 81%) as a colorless oil: TLC, R_f 0.60 (hexane–EtOAc 3:1); IR (neat) 3520, 2960, 2880, 2140, 1740, 1250, 1080, 840, 740, 700 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.69–7.62 (m, 4H), 7.45–7.32 (m, 6H), 6.14 (dd, *J*=15.9, 5.4 Hz, 1H), 5.63 (d, *J*=15.9 Hz, 1H), 5.20 (m, 1H), 4.36–4.02 (m, 3H), 3.69 (s, 1.5H), 3.65 (s, 1.5H), 3.45–3.31 (m, 1H), 3.10 (s, 1.5H), 3.05 (s, 1.5H), 2.95 (m, 1H), 2.35–1.12 (m, 6H), 1.67 (s, 3H), 1.17 (m, 1.5H), 1.06 (s, 9H), 1.02–0.80 (m, 13.5H), 0.63–0.53 (m, 9H), 0.18 (s, 9H). A signal due to one proton (OH) was not observed; HRMS (ESI) calcd for $C_{48}H_{76}NaO_7Si_3$ $(M+Na)^+$ 871.4797, found 874.4799.

4.1.26. Acetylene 37. To a stirred solution of alcohol **36** (70.0 mg, 0.824 mmol) in THF (2.7 mL) cooled at 0 °C was added a solution of tetrabutylammonium fluoride (Bu_4NF) and acetic acid (0.70 mL, 0.7 mmol for Bu_4NF and 0.6 mmol for acetic acid) prepared from a 1.0 M solution of Bu_4NF in THF (0.90 mL) and acetic acid (0.050 mL). The mixture was stirred at 0 °C for 4 h, diluted with brine (15 mL), and extracted with EtOAc (3×15 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane–EtOAc 2:1) to give **37** (53.4 mg, 98%) as a colorless oil: TLC, R_f 0.45 (hexane–benzene 5:1); IR (neat) 3300, 2960, 2860, 1740, 1210, 1110, 1040, 760, 700 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4H), 7.46–7.31 (m, 6H), 6.23 (dd, *J*=15.9, 5.1 Hz, 1H), 5.73 (d, *J*=15.9 Hz, 1H), 5.31 (d, *J*=9.2 Hz, 1H), 4.38–4.03 (m, 3H), 3.68 (s, 1.5H), 3.66 (s, 1.5H), 3.40–3.31 (m, 1H), 3.08 (s, 1.5H), 3.04 (s, 1.5H), 2.95 (m, 1H), 2.86 (s, 1H), 2.35–1.12 (m, 6H), 1.69 (s, 3H), 1.17 (m, 1.5H), 1.06 (s, 9H), 1.02–0.80 (m, 4.5H), 0.65 (s, 1.5H), 0.62 (s, 1.5H). Signals due to two protons (OH) were not observed; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.5, 145.9, 135.7, 134.7, 134.6, 134.1, 133.5, 129.49, 129.47, 127.43, 127.41, 102.2, 79.0, 77.2, 76.2, 75.6, 69.9, 66.5, 65.9, 61.1, 51.8, 47.3, 40.5, 30.4, 29.8, 29.1, 27.3, 27.0, 21.7, 19.19, 19.17, 17.2, 15.4, 13.8, 11.5, 11.3, 9.6; HRMS (ESI) calcd for $C_{39}H_{54}NaO_7Si$ $(M+Na)^+$ 685.3536, found 685.3547.

4.1.27. Vinylstannane 38. To a stirred solution of acetylene **37** (193 mg, 0.291 mmol) in THF (9.7 mL) were added tributyltin hydride (0.094 mL, 0.035 mmol) and 2,2′-azobisisobutyronitrile (10.6 mg, 0.0646 mmol). The mixture was stirred at 70 °C for 2 h, cooled to room temperature, and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–EtOAc 5:1→2:1) to give **38** (225 mg, 81%) as a colorless oil: TLC, R_f 0.50 (hexane–EtOAc 2:1); IR (neat) 3460, 2930, 2860, 1740, 1200, 1110, 1040, 700 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4H), 7.46–7.21 (m, 6H), 6.49 (dd, *J*=18.6, 10.0 Hz, 1H), 6.23 (d, *J*=18.6 Hz, 1H), 6.18 (dd, *J*=15.1, 10.0 Hz, 1H), 5.64 (dd, *J*=15.1, 6.2 Hz, 1H), 5.31 (d, *J*=9.2 Hz, 1H), 4.38–4.03 (m, 3H), 3.68 (s, 1.5H), 3.65 (s, 1.5H), 3.39–3.26 (m, 1H), 3.08 (s, 1.5H), 3.04 (s, 1.5H), 2.95 (m, 1H), 2.35–1.80 (m, 4H), 1.72–0.80 (m, 38H), 1.06 (s, 9H), 0.64 (s, 1.5H), 0.61 (s, 1.5H). Signals due to two protons (OH) were not observed; HRMS (ESI) calcd for $C_{51}H_{82}NaO_7Si^{120}Sn$ $(M+Na)^+$ 977.4761, found 977.4725.

4.1.28. Bromodiene 39. To a stirred solution of vinylstannane **38** (128 mg, 0.134 mmol) in THF (4.5 mL) cooled

at 0 °C was added *N*-bromosuccinimide (34.0 mg, 0.197 mmol). The mixture was stirred at 0 °C for 30 min, diluted with 10% aqueous $Na_2S_2O_3$ (10 mL), and extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (3 g, hexane–EtOAc 3:2) to give **39** (97.7 mg, 98%) as a colorless oil: TLC, R_f 0.50 (hexane–EtOAc 1:1); IR (neat) 3460, 2930, 2860, 1740, 1210, 1110, 1040, 760, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.45–7.31 (m, 6H), 6.69 (dd, *J*=13.5, 10.3 Hz, 1H), 6.31 (d, *J*=13.5 Hz, 1H), 6.18 (dd, *J*=15.1, 10.3 Hz, 1H), 5.73 (dd, *J*=15.1, 5.4 Hz, 1H), 5.31 (d, *J*=8.9 Hz, 1H), 4.38–4.03 (m, 3H), 3.69 (s, 1.5H), 3.65 (s, 1.5H), 3.39–3.30 (m, 1H), 3.08 (s, 1.5H), 3.04 (s, 1.5H), 2.95 (m, 1H), 2.31–1.12 (m, 6H), 1.70 (s, 3H), 1.17 (m, 1.5H), 1.06 (s, 9H), 1.02–0.80 (m, 4.5H), 0.64 (s, 1.5H), 0.61 (s, 1.5H). Signals due to two protons (OH) were not observed; HRMS (ESI) calcd for $C_{39}H_{55}{}^{79}BrNaO_7Si$ $(M+Na)^+$ 765.2798, found 765.2793.

4.1.29. Seco acid 12. To a stirred solution of bromodiene **39** (66.2 mg, 0.089 mmol) in THF (1.2 mL) and MeOH (0.6 mL) was added a 2 M aqueous NaOH (0.2 mL). The mixture was stirred at 40 °C for 23 h, acidified with 1 M aqueous HCl, and extracted with EtOAc (4×5 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a oil, which was purified by column chromatography on silica gel (FL-60D, 2 g, hexane–EtOAc 5:1→3:1→1:1) to give **12** (40.8 mg, 63%) as a colorless oil: TLC, R_f 0.08–0.39 (hexane–EtOAc 1:1); IR (neat) 3440, 2930, 2860, 1710, 1220, 1110, 1040, 980, 760, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.45–7.31 (m, 6H), 6.69 (dd, *J*=13.5, 10.3 Hz, 1H), 6.30 (d, *J*=13.5 Hz, 1H), 6.18 (dd, *J*=15.1, 10.3 Hz, 1H), 5.73 (dd, *J*=15.1, 5.7 Hz, 1H), 5.31 (d, *J*=8.6 Hz, 1H), 4.48–4.03 (m, 3H), 3.49–3.30 (m, 1H), 3.06 (s, 1.5H), 3.04 (s, 1.5H), 2.95 (m, 1H), 2.31–1.12 (m, 6H), 1.70 (s, 3H), 1.17 (m, 1.5H), 1.06 (s, 9H), 1.02–0.80 (m, 4.5H), 0.67 (s, 1.5H), 0.58 (s, 1.5H). Signals due to three protons (COOH, OH) were not observed; HRMS (ESI) calcd for $C_{38}H_{53}{}^{79}BrNaO_7Si$ $(M+Na)^+$ 751.2642, found 751.2612.

4.1.30. Lactone 10. A solution of triethylamine and 2,4,6-trichlorobenzoyl chloride in THF (0.47 mL, 0.082 mmol for Et_3N and 0.023 mmol for 2,4,6-$Cl_3C_6H_2COCl$), prepared from triethylamine (0.15 mL), 2,4,6-trichlorobenzoyl chloride (0.05 mL), and THF (6 mL), was added to seco acid **12** (15.3 mg, 0.0210 mmol). The mixture was stirred at room temperature for 2 h and diluted with toluene (35 mL) to give a solution of mixed anhydride, which was added to a solution of 4-(dimethylamino)pyridine (26.0 mg, 0.210 mmol) in refluxing toluene (7 mL) over 2 h. The mixture was heated at reflux for 30 min, cooled to room temperature, and washed with brine (10 mL). The aqueous layer was extracted with EtOAc (2×15 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 1 g, hexane–EtOAc 8:1) to give **10** (8.5 mg, 57%) as a colorless oil: TLC, R_f 0.34, 0.40, 0.50 (hexane–EtOAc 3:1); IR (neat) 3510, 2930, 2860, 1730, 1180, 1110, 1040, 760, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.45–7.31 (m, 6H), 6.70 (dd, *J*=13.5, 10.0 Hz, 1H), 6.34 (d, *J*=13.5 Hz, 0.5H), 6.33 (d, *J*=13.5 Hz, 0.5H), 6.09 (m, 1H), 5.80–5.58 (m, 2H), 5.43 (m, 1H), 4.05–3.85 (m, 2H), 3.09 (m, 1.5H), 3.01 (m, 1H), 2.86 (m, 1.5H), 2.74 (m, 1H), 2.17–1.00 (m, 6H), 1.65 (m, 3H), 1.26 (m, 3H), 1.05 (s, 9H), 0.93–0.80 (m, 6H). A signal due to one proton (OH) was not observed; HRMS (ESI) calcd for $C_{38}H_{51}{}^{79}BrNaO_6Si$ $(M+Na)^+$ 733.2536, found 733.2544.

4.1.31. Hemiacetal 40. A solution of lactone **10** (22.4 mg, 0.0315 mmol) in acetone (0.4 mL), H_2O (0.2 mL), and acetic acid (0.8 mL) was stirred at room temperature for 30 min. The mixture was concentrated and purified by column chromatography on silica gel (FL-60D, 1 g, hexane–EtOAc 7:1) to give **40** (19.0 mg, 86%) as a colorless oil: TLC, R_f 0.34, 0.44 (hexane–EtOAc 3:1); IR (neat) 3440, 2960, 2860, 1700, 1190, 1110, 1040, 980, 760, 700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.45–7.31 (m, 6H), 6.69 (dd, *J*=13.5, 10.8 Hz, 1H), 6.37 (d, *J*=13.5 Hz, 1H), 6.15 (dd, *J*=14.9, 10.8 Hz, 1H), 5.78–5.29 (m, 3H), 5.41 (d, *J*=2.2 Hz, 0.5H), 4.30–4.15 (m, 1.5H), 4.23 (d, *J*=2.2 Hz, 0.5H), 3.86 (m, 0.5H), 3.75 (d, *J*=8.9 Hz, 0.5H), 3.36 (d, *J*=8.9 Hz, 0.5H), 2.51 (m, 1H), 2.30–1.00 (m, 6H), 1.69 (s, 1.5H), 1.68 (s, 1.5H), 1.26 (m, 3H), 1.06 (s, 9H), 0.87 (m, 3H), 0.76 (m, 3H). A signal due to one proton (OH) was not observed; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 174.4, 173.7, 141.8, 136.9, 136.6, 136.3, 135.7, 134.5, 134.3, 134.0, 133.5, 133.3, 132.7, 132.6, 131.8, 130.0, 129.6, 128.9, 128.6, 128.5, 128.0, 127.5, 110.3, 110.2, 98.2, 97.71, 97.66, 94.7, 74.3, 73.9, 72.0, 71.9, 71.60, 71.55, 71.4, 71.1, 67.2, 67.1, 67.0, 50.1, 48.7, 48.1, 47.5, 47.4, 46.4, 41.3, 41.2, 41.0, 40.8, 40.4, 40.0, 38.9, 38.8, 35.3, 34.9, 34.8, 34.4, 29.7, 27.0, 25.2, 25.0, 24.4, 24.1, 22.7, 22.5, 19.3, 19.1, 15.7, 14.1, 13.6, 12.6, 11.5, 11.2, 11.1; HRMS (ESI) calcd for $C_{37}H_{49}{}^{79}BrNaO_6Si$ $(M+Na)^+$ 719.2379, found 719.2370.

4.1.32. Enones 41a and 41b. To a stirred solution of hemiacetal **40** (19.0 mg, 0.027 mmol) in CH_2Cl_2 (0.6 mL) were added pyridine (0.05 mL) and Dess–Martin periodinane (38.3 mg, 0.090 mmol). The mixture was stirred at room temperature for 1 h, diluted with saturated aqueous $Na_2S_2O_3$ (5 mL), stirred for 15 min, and extracted with ether (3×5 mL). The combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 1 g, hexane–EtOAc 9:1) to give a mixture of enones **41a** and **41b** (17.4 mg, 92%). The mixture of enones (43.9 mg) were purified by HPLC [Develosil ODS-HG-5 (ϕ 4.6× 250 mm), 95% MeOH, flow rate 5 mL min^{-1}, detection at 254 nm] to give crude enone **41a** (17.8 mg, t_R=47 min) and pure **41b** (13.0 mg, t_R=38 min, 27%) as a colorless oil. The crude enone **41a** was further purified by PLC (200×200×0.25 mm, two plates, hexane–ether 3:1) to give pure enone **41a** (10.2 mg, 21%) as a colorless oil. Compound **41a**: TLC, R_f 0.33 (hexane–ether 3:1); $[\alpha]_D^{20}$ +18.6 (*c* 0.196, $CHCl_3$); IR (neat) 3448, 1705, 1682, 1423, 1176, 1110, 980 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.68–7.63 (m, 4H), 7.45–7.33 (m, 6H), 6.70 (dd, *J*=13.5, 10.8 Hz, 1H), 6.40 (d, *J*=13.5 Hz, 1H), 6.23 (s, 1H), 6.18 (dd, *J*=15.0, 10.8 Hz, 1H), 5.72 (dd, *J*=15.0, 6.5 Hz, 1H), 5.66 (m, 1H), 4.32 (d, *J*=2.7 Hz, 1H), 4.17 (m, 1H), 3.45 (dd, *J*=11.9, 2.2 Hz, 1H), 2.56 (q, *J*=7.2 Hz, 1H), 2.30–2.23 (m, 2H), 2.06 (s, 3H), 2.03 (dd, *J*=11.9, 3.2 Hz, 1H), 1.30–1.15 (m, 3H), 1.19 (s, 3H), 1.07 (d, *J*=7.2 Hz, 3H), 1.07 (s, 9H),

0.80 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 204.6, 175.9, 147.7, 136.0, 135.6, 134.2, 134.1, 131.3, 129.6, 129.1, 127.5, 126.1, 110.6, 98.2, 74.1, 71.0, 66.7, 49.0, 47.9, 47.6, 41.3, 34.6, 27.1, 21.2, 19.3, 19.2, 18.7, 12.5; HRMS (FAB) calcd for $C_{37}H_{47}{}^{79}BrNaO_6Si$ $(M+Na)^+$ 717.2223, found 717.2234. Compound **41b**: TLC, R_f 0.28 (hexane–ether 3:1); $[\alpha]_D^{21}$ +11.4 (*c* 0.214, $CHCl_3$); IR (neat) 3437, 1697, 1427, 1261, 1169, 1107, 980 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.69–7.63 (m, 4H), 7.46–7.33 (m, 6H), 6.70 (dd, *J*=13.5, 10.8 Hz, 1H), 6.40 (d, *J*=13.5 Hz, 1H), 6.21 (s, 1H), 6.18 (dd, *J*=14.0, 10.8 Hz, 1H), 5.78–5.67 (m, 2H), 5.11 (d, *J*=2.7 Hz, 1H), 4.28 (m, 1H), 3.44 (dd, *J*=11.9, 2.2 Hz, 1H), 2.56 (q, *J*=7.0 Hz, 1H), 2.31–2.24 (m, 2H), 2.05 (s, 3H), 1.86 (dd, *J*=11.6, 3.0 Hz, 1H), 1.64–1.50 (m, 2H), 1.27 (m, 1H), 1.25 (d, *J*=7.0 Hz, 3H), 1.20 (s, 3H), 1.07 (s, 9H), 0.79 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 204.9, 173.3, 147.3, 136.0, 135.6, 135.6, 134.3, 134.1, 131.3, 129.6, 129.6, 129.1, 127.5, 126.3, 110.1, 98.4, 73.8, 71.2, 66.8, 49.3, 48.6, 47.3, 40.8, 34.3, 27.1, 21.1, 19.2, 18.4, 11.4; HRMS (FAB) calcd for $C_{37}H_{47}{}^{79}BrNaO_6Si$ $(M+Na)^+$ 717.2223, found 717.2200.

4.1.33. Aglycon 3. To a stirred solution of a diastereomeric mixture of enone **41a** (2.2 mg, 0.0032 mmol) in THF (0.5 mL) was added a solution of tetrabutylammonium fluoride (Bu_4NF) and acetic acid (0.19 mL, 0.18 mmol for Bu_4NF and 0.19 mmol for acetic acid) prepared from a 1.0 M solution of Bu_4NF in THF (0.85 mL) and acetic acid (0.050 mL). The mixture was stirred at room temperature for 20 h, diluted with brine (5 mL), and extracted with ether (3×4 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 0.3 g, toluene–acetone 9:1) to give **3** (1.3 mg, 90%) as a colorless oil. Using the same procedure as described above, **3** (1.7 mg, 96%) was obtained from **41b** (2.7 mg, 0.022 mmol). Compound **3**: TLC, R_f 0.35 (benzene–acetone 5:1), 0.37 (hexane–EtOAc 3:1); $[\alpha]_D^{31}$ +6.7 (*c* 0.045, MeOH); IR (neat) 3450, 2970, 2860, 1710, 1680, 1610, 1200, 1180, 980, 760 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 6.40 (dd, *J*=13.7, 10.8 Hz, 1H), 6.32 (d, *J*=1.0 Hz, 1H), 5.91 (d, *J*=13.7 Hz, 1H), 5.65 (dd, *J*=15.1, 10.8 Hz, 1H), 5.57 (m, 1H), 5.19 (dd, *J*=15.1, 6.3 Hz, 1H), 4.82 (d, *J*=3.0 Hz, 1H), 3.94 (m, 1H), 3.87 (dd, *J*=11.8, 2.0 Hz, 1H), 2.47 (q, *J*=7.3 Hz, 1H), 2.29 (d, *J*=1.0 Hz, 1H), 1.99 (m, 1H), 1.97 (dd, *J*=13.2, 11.7 Hz, 1H), 1.82 (dd, *J*=13.2, 2.5 Hz, 1H), 1.53 (m, 1H), 1.14 (s, 3H), 1.08 (s, 3H), 1.07 (m, 1H), 0.98 (d, *J*=7.3 Hz, 3H), 0.81 (dt, *J*=3.0, 11.2 Hz, 1H). A signal due to one proton (5-OH) was not observed; ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 176.1, 148.2, 136.1, 131.3, 129.3, 126.1, 110.8, 98.3, 74.3, 71.1, 64.9, 49.1, 47.8, 47.6, 41.1, 34.3, 21.3, 19.3, 18.6, 12.5; HRMS (ESI) calcd for $C_{21}H_{29}{}^{79}BrNaO_6$ $(M+Na)^+$ 479.1045, found 479.1041.

4.1.34. Auriside A (1). To a stirred suspension of stannous chloride (3.1 mg, 0.017 mmol), silver perchlorate (3.3 mg, 0.016 mmol), and MS 4Å (43 mg) in ether (0.2 mL) at 0 °C was added a solution of aglycon **3** (2.2 mg, 0.0048 mmol) and fluorosugar **7** (9.9 mg, 0.021 mmol) in ether (0.1 mL, 3×0.05 mL rinse). The mixture was stirred at room temperature for 24 h, diluted with saturated aqueous $NaHCO_3$ (3 mL), and extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 2 g, hexane–EtOAc 5:1) to give TBS ether of auriside A (1.9 mg) as a colorless oil.

To a stirred solution of TBS ether of auriside A (0.9 mg) in THF (0.06 mL) cooled at 0 °C was added HF·pyridine complex (0.013 mL). The mixture was stirred at room temperature for 18 h, diluted with saturated aqueous $NaHCO_3$ (2 mL), and extracted with EtOAc (3×10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 1 g, hexane–EtOAc 1:3) followed by HPLC [Develosil ODS-HG-5 (ϕ 4.6×250 mm), 75% MeOH, flow rate 5 mL min^{-1}, detection at 215 nm] to give auriside A (**1**) (0.8 mg, 42% in two steps) as a colorless oil: TLC, R_f 0.20 (hexane–EtOAc 1:4); $[\alpha]_D^{23}$ −31 (*c* 0.040, MeOH); ^{1}H NMR (500 MHz, C_6D_6) δ 6.40 (dd, *J*=13.5, 10.9 Hz, 1H), 6.35 (s, 1H), 5.91 (d, *J*=13.5 Hz, 1H), 5.63 (dd, *J*=15.4, 10.9 Hz, 1H), 5.56 (m, 1H), 5.34 (d, *J*=1.5 Hz, 1H), 5.18 (dd, *J*=15.4, 6.5 Hz, 1H), 5.04 (d, *J*=2.0 Hz, 1H), 4.93 (d, *J*=2.5 Hz, 1H), 4.30 (dd, *J*=9.5, 3.1 Hz, 1H), 4.26 (m, 1H), 4.24 (dd, *J*=9.5, 3.7 Hz, 1H), 4.09 (dq, *J*=9.5, 6.2 Hz, 1H), 3.94 (dd, *J*=11.8, 2.0 Hz, 1H), 3.90 (dq, *J*=9.5, 6.2 Hz, 1H), 3.68 (dd, *J*=3.1, 2.0 Hz, 1H), 3.56 (dd, *J*=3.7, 1.5 Hz, 1H), 3.49 (s, 3H), 3.46 (t, *J*=9.5 Hz, 1H), 3.31 (s, 3H), 3.26 (s, 3H), 3.16 (t, *J*=9.5 Hz, 1H), 3.07 (s, 3H), 2.48 (q, *J*=7.2 Hz, 1H), 2.33 (dd, *J*=11.8, 4.4 Hz, 1H), 2.30 (s, 3H), 2.18 (m, 1H), 1.97 (t, *J*=12.1 Hz, 1H), 1.82 (m, 1H), 1.81 (m, 1H), 1.43 (d, *J*=6.2 Hz, 1H), 1.35 (d, *J*=6.2 Hz, 1H), 1.24 (q, *J*=11.8 Hz, 1H), 1.14 (s, 3H), 1.05 (s, 3H), 1.03 (td, *J*=11.8, 2.5 Hz, 1H), 0.97 (d, *J*=7.2 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.3, 176.4, 147.5, 136.5, 131.7, 129.2, 126.4, 110.8, 98.6, 98.5, 96.3, 84.4, 83.3, 81.6, 81.5, 79.5, 74.6, 72.1, 71.3, 71.1, 69.1, 68.3, 60.8, 60.7, 58.8, 57.9, 49.3, 48.1, 47.5, 39.8, 31.5, 21.6, 19.5, 18.6, 18.4, 18.1, 12.4; MS (FAB) *m/z* 827 $(M+Na)^+$.

4.1.35. Auriside B (2). To a stirred suspension of stannous chloride (3.1 mg, 0.017 mmol), silver perchlorate (3.4 mg, 0.017 mmol), and MS 4Å (45 mg) in ether (0.2 mL) at 0 °C was added a solution of aglycon **3** (2.3 mg, 0.0050 mmol) and fluorosugar **8** (5.4 mg, 0.023 mmol) in ether (0.9 mL, 2×0.05 mL rinse). The mixture was stirred at room temperature for 2 h, diluted with saturated aqueous $NaHCO_3$ (5 mL), and extracted with EtOAc (3×15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (FL-60D, 1 g, hexane–EtOAc 1:2) followed by HPLC [Develosil ODS-HG-5 (ϕ 4.6×250 mm), 55% MeCN, flow rate 5 mL min^{-1}, detection at 215 nm] to give auriside B (**2**) (2.3 mg, 68%) as a colorless oil: R_f 0.30 (hexane–EtOAc 1:2); $[\alpha]_D^{19}$ −27 (*c* 0.080, MeOH); ^{1}H NMR (500 MHz, C_6D_6) δ 6.40 (dd, *J*=13.5, 10.8 Hz, 1H), 6.35 (s, 1H), 5.91 (d, *J*=13.5 Hz, 1H), 5.63 (dd, *J*=15.3, 10.8 Hz, 1H), 5.57 (m, 1H), 5.54 (dd, *J*=9.5, 3.2 Hz, 1H), 5.20 (dd, *J*=15.3, 6.6 Hz, 1H), 5.04 (d, *J*=2.0 Hz, 1H), 4.94 (d, *J*=1.9 Hz, 1H), 4.25 (m, 1H), 3.99 (dq, *J*=9.5, 6.2 Hz, 1H), 3.94 (dd, *J*=11.8, 1.9 Hz, 1H), 3.82 (dd, *J*=3.2, 2.0 Hz, 1H), 3.73 (br s, 2H), 3.52 (t, *J*=9.5 Hz, 1H), 3.36 (s, 3H), 3.22 (s, 3H), 2.49 (q, *J*=7.2 Hz, 1H), 2.30 (s, 3H), 2.27 (dd, *J*=11.8, 4.4 Hz,

1H), 1.97 (t, J=12.2 Hz, 1H), 1.80 (m, 1H), 1.80 (m, 1H), 1.37 (d, J=6.2 Hz, 1H), 1.23 (q, J=11.8 Hz, 1H), 1.16 (s, 3H), 1.06 (s, 3H), 0.97 (d, J=7.2 Hz, 1H),0.96 (dt, J=11.8, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.5, 176.5, 155.7, 147.4, 136.5, 131.7, 129.2, 126.4, 110.8, 98.5, 96.3, 81.4, 79.9, 75.0, 74.6, 71.3, 68.6, 60.4, 58.7, 49.3, 48.0, 47.4, 39.6, 31.4, 21.6, 19.4, 18.6, 18.1, 12.4; MS (FAB) m/z 696 $(M+Na)^+$.

Acknowledgements

This study was supported in part by the 21st Century COE program and Grants-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science and Technology, Suntory Institute for Bioorganic Research, Yamada Science Foundation, Astellas Foundation for Research on Medicinal Resources, the Naito Foundation, Shorai Foundation for Science and Technology, University of Tsukuba Research Projects, and Wako Pure Chemical Industries, Ltd. We are grateful to Daiso Co., Ltd for donation of chiral trityl glycidyl ether. The IR spectra and optical rotations were recorded at Chemical Analysis Center, University of Tsukuba.

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Design, synthesis and in vitro antimalarial activity of spiroperoxides

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Received 20 April 2006; revised 25 May 2006; accepted 26 May 2006
Available online 15 June 2006

Abstract—Several spiroperoxy antimalarial compounds were designed and synthesized using the hydrogen peroxide in UHP (urea–H_2O_2 complex) as the source of the peroxy bond. Incorporation of the H_2O_2 into the organic molecule framework through ketal exchange reaction in the present cases was greatly facilitated by the potential to form a five- or six-membered cyclic hemiketal due to the presence of a hydroxyl group γ or δ to the ketone carbonyl group. When the electron-withdrawing group in the Michael acceptor was a nitro group, the closure of the peroxy ring occurred readily under the hydroxidation conditions. Presence of a benzene ring fused to the peroxy ring effectively reduced the degrees of freedom in the transition state for the ring-closure step and made the otherwise very difficult seven-membered 1,2-dioxepane rather easy to form through the intramolecular Michael addition.

1. Introduction

Prompted by the excellent activity observed with qinghaosu[1] (artemisinin, **1**) and closely related peroxy compounds in the treatment of malaria including the multi drug-resistant variants, more and more organic chemists around the world are actively engaged in design and synthesis of novel organic peroxides since the late 1980's. Due to lack of generally feasible[2] synthetic methods for forming the O–O bond directly from two separate one oxygen-containing groups, up to now the peroxy bonds in organic peroxides are almost all derived from some species that already contain the O–O bond such as dioxygen[3] (O_2), ozone[4] (O_3), or hydrogen peroxide[5] (H_2O_2). Thus, what is special of synthesis of organic peroxides is that the way and the timing of introducing the fragile O–O bond must be taken into consideration in addition to all other factors encountered in synthesis in general. The limited source of the O–O bond-containing species decides that the span of the reactions that one can choose from is narrow. And the fragile nature of O–O bonds demands circumventing many transformations routinely employed in organic synthesis. Hence, development of new approaches to make facile use of the readily available O–O containing species is critical for synthesis of organic peroxides.

Formation of a carbon–oxygen bond to an inorganic O–O bond-containing reagent through ketalization is one of the most common ways of creating organic peroxy species. In 2001, Kobayashi[5e,f] and co-workers reported a new variant of this methodology, which utilized solid UHP (urea–H_2O_2 complex) instead of liquid H_2O_2 as the source of the peroxy bond. In MeOH with $Sc(OTf)_3$ as catalyst, they obtained MeO/OOH mixed ketals in high yields and successfully closed the peroxy ring by an intramolecular Michael addition catalyzed by $HNEt_2$ in F_3CCH_2OH. Impressed by the convenience of using UHP, we also tried to adopt Kobayashi's methodology in our own work. In the preliminary exploration[6] on the scope and limitation of the UHP protocol, we noticed that the original conditions appeared to be applicable only to synthesis of five- or six-membered peroxy rings in the monocyclic cases. And, the presence of, e.g., an ester group on the ketal carbonyl carbon also led to complete failure in the hydroperoxidation step. These observations, together with the relatively high cost of the essential catalyst $Sc(OTf)_3$, prompted us to turn to new structures with extra rings. Here in this article we wish to detail[7] some of our recent work along this line.

2. Results and discussions

As formation of the hydroperoxy hemiketal is a key step in incorporating H_2O_2 into an organic framework, we chose this as an entry point for this work. The first thing we looked into was whether the hydroperoxidation could be made easier by switching from the open-chain hemiketals to cyclic ones, i.e., to replace the methoxyl group in the monocyclic

Keywords: Peroxides; Spiroketals; Cyclizations; Hemiketals; Antimalarials.
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doi:10.1016/j.tet.2006.05.065

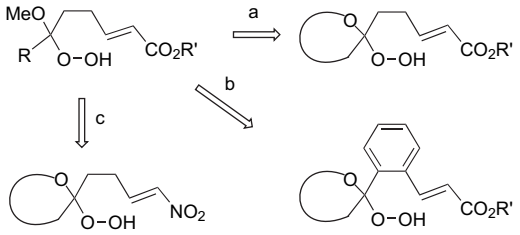


Figure 1. General illustration of the plans for this work: (a) the fundamental idea—switching from the open-chain hemiketal to cyclic hemiketals to facilitate hydroperoxyl group attachment. (b) Introducing UV chromophores to improve molecule-tracing property and facilitate synthesis. (c) Examining other electron-withdrawing groups in place of the ester group in the Michael acceptor.

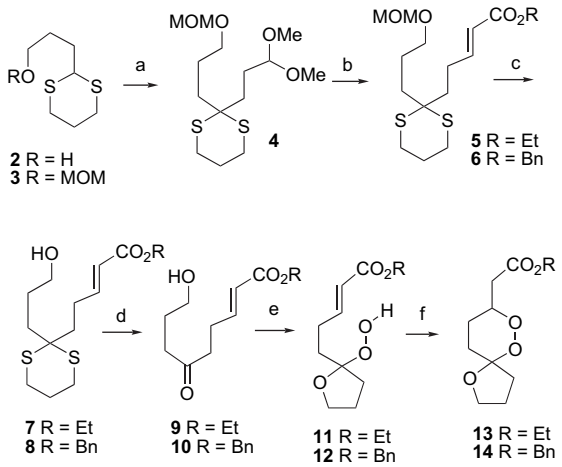
structures with an alkoxyl one that was connected to the ketal carbonyl carbon through a covalent chain (Fig. 1).

To facilitate future mechanistic investigations, it would be also desirable to incorporate some UV chromophore into the molecule. Such chromophore was better directly bonded to the carbon framework so that it would not be lost due to hydrolysis. From synthetic viewpoint, presence of such a chromophore as a benzene ring may also facilitate rapid construction of the molecule because the building blocks could be more readily accessible. Finally, whether the ester group in the Michael acceptor could be replaced by other electron-withdrawing groups was also among what we wished to explore.

Five- or six-membered cyclic hemiketals are generally expected to form easier than the non-cyclic ones. Although according to our experience that the population of the cyclic hemiketal can be rather small in solution (i.e., most of the substrate is present in the open chain form) in some cases, we believe that even very small amount of such cyclic hemiketals would also facilitate the critical exchange of the hemiketal hydroxyl group with the hydroperoxyl group. Once the hydroperoxyl group is introduced into the substrate, it is not so easy to leave as hydroxyl group. Therefore, the hydroperoxidation precursors of all target molecules in this work were designed to carry a hydroxyl group either γ or δ to the ketone carbonyl group.

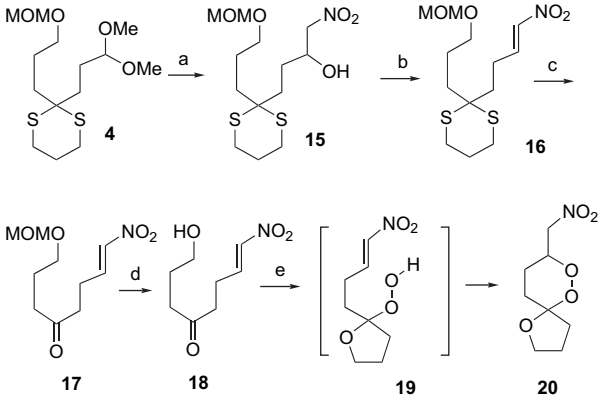
The simplest targets (**13** and **14**) were synthesized using the route shown in Scheme 1. The MOM protected dithiane **3**, which could be readily prepared from the corresponding alcohol (**2**[8]), was alkylated with $I(CH_2)_2CH(OMe)_2$[9] using the standard umpolung technique to give acetal **4**. Selective hydrolysis of the dimethyl acetal with PPTS in aqueous acetone afforded an intermediate aldehyde, which was immediately treated with either $Ph_3P{=}CHCO_2Et$ or $Ph_3P{=}CHCO_2Bn$ to yield **5** or **6**, respectively. The MOM protecting group was then removed and the resulting hydroxy ketone **9** or **10** was converted into the corresponding hydroperoxyl hemiketal **11** or **12**. The presence of an additional THF ring (cyclic hemiketal) did lead to facile incorporation of the hydroperoxyl group as expected. The expensive catalyst $Sc(OTf)_3$ that was essential in the non-cyclic cases were thus no longer necessary.

Next we examined to replace the ester functionality with a nitro group (Scheme 2). The hydrolysis of the acetal end



Scheme 1. (a) BuLi/HMPA/$I(CH_2)_2CH(OMe)_2$/0 °C/48 h, 88%; (b) i. PPTS/acetone/reflux/12 h; ii. $Ph_3P{=}CHCO_2Et$, 86% for **5** or $Ph_3P{=}CHCO_2Bn/CH_2Cl_2$/rt/12 h, 94% for **6** (yields from **4**); (c) *p*-TsOH/EtOH/reflux, 90% for **7** or 2 N HCl/THF/40–50 °C, 64% for **8**; (d) I_2/acetone/$NaHCO_3$/0 °C/30 min, 83% for **9** or 77% for **10**; (e) UHP/*p*-TsOH/MeOH/rt, 82% for **11** or 75% for **12** and (f) $HNEt_2/CF_3CH_2OH$/rt/24 h, 52% for either **13** or **14**.

of **4** was done as mentioned above. Then, the condensation was realized by using $MeNO_2$ instead of a Wittig reagent. The hydroxyl group was converted to the corresponding mesylate and eliminated immediately, yielding **16**. Up to this stage, the remaining tasks were removing the MOM and dithiane protecting groups. Attempts to hydrolyze the MOM group under similar conditions to those employed in the synthesis of **7/8** completely failed, presumably due to the too high reactivity of the Michael acceptor $–CH{=}CHNO_2$. Although this property turned out to be an advantage in a later stage of the synthesis when an intramolecular Michael addition was needed to construct the 1,2-dioxane ring, at this point we had to switch to an alternative approach—to free the carbonyl group first.

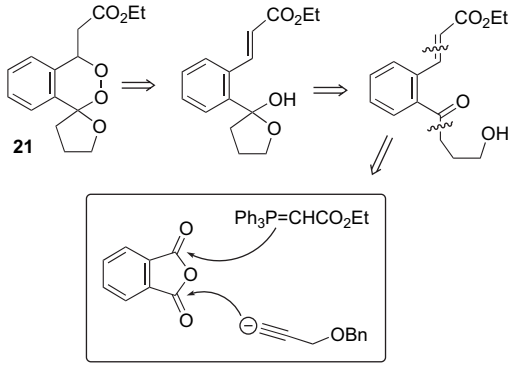


Scheme 2. (a) i. PPTS/acetone/reflux/12 h; ii. CH_3NO_2/DBU/rt/15 h, 94% from **4**; (b) MsCl/NEt_3/rt/24 h, 97%; (c) $I_2/NaHCO_3$/0 °C/30 min, 87%; (d) concd HCl/acetone–H_2O/rt/17 h, 21% and (e) UHP/*p*-TsOH/DME/rt/10.5 h, 35%.

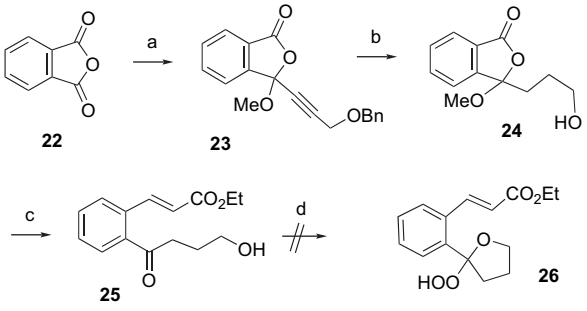
Under the conditions for the similar deprotections of **7** and **8**, the ketone **17** was readily obtained in 87% yield. The subsequent hydrolysis of the MOM group, however, was still very complicated. We managed to isolate the desired **18** in only 21%. Further treatment of **18** with the UHP/*p*-TsOH/DME

($MeO(CH_2)_2OMe$) led to direct formation of the end product **20**. Compound **19** could not be isolated at all. Here the non-alcohol solvent was essential for the hydroperoxidation. Using MeOH as in Kobayashi's original protocol, for instance, led to completely failure.

After completing the syntheses of **13** and **14**, we began to consider the possibility to introduce a benzene ring into the spiro[4,5]decane framework. The first designed structure was **21**, partially because the retrosynthetic analysis (Scheme 3) showed a possible rapid access from three readily available building blocks. Based on this design, we started the synthesis as shown in Scheme 4.



Scheme 3.

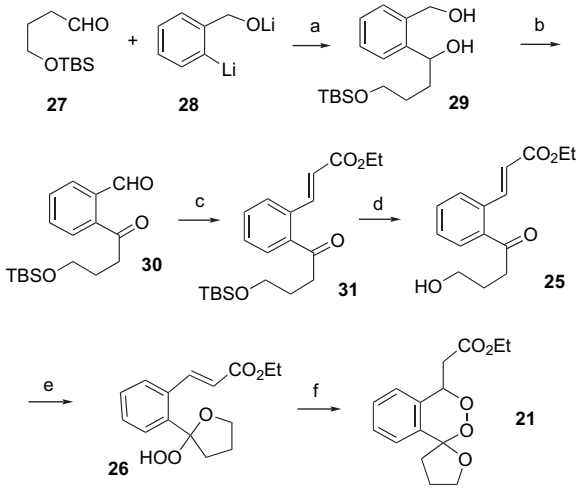


Scheme 4. (a) i. *n*-BuLi/$HC{\equiv}CCH_2OBn$/THF/−25 °C/1.5 h, then **22**/−70 °C/2 h; ii. CH_2N_2/0 °C, 43% from **22**; (b) H_2/Pd–C/MeOH/rt, 38%; (c) i. DIBAL-H/CH_2Cl_2/−75 °C/3 h; ii. MnO_2/$CHCl_3$/rt/4 d; iii. $Ph_3P{=}CHCO_2Et$/$CHCl_3$/rt/10 h, 47% from **24** and (d) UHP/*p*-TsOH or CSA/MeOH/rt.

Introduction of the three-carbon chain was performed as reported[10] in the literature. The resulting acid was converted to lactone-ketal **23** by treatment with diazomethane. The benzyl protecting group was then removed along with the hydrogenation of the triple bond, leading to **24** in low yield.

Conversion of the lactone **24** into the intermediate aldehyde was achieved by reduction with DIBAL-H to the corresponding triol, followed by a MnO_2 oxidation. A subsequent Wittig reaction with $Ph_3P{=}CHCO_2Et$ on the aldehyde carbonyl group gave the desired **25** in 47% yield (from **24**). The hydroperoxidation under the conditions for syntheses of **7** and **8**, however, did not lead to any discernible amounts of **26**.

Because the yields along the sequence shown in Scheme 4 were too low, before proceeding we decided to adopt another more practical approach (Scheme 5). Thus, the reaction of aldehyde **27**[11] with lithium species **28** (prepared in situ from the corresponding bromide) gave diol **29**. A Swern oxidation yielded the intermediate dicarbonyl species **30**, which was immediately treated with $Ph_3P{=}CHCO_2Et$ to afford **31**. The TBS protecting group was then removed and the resulting hydroxy ketone **25** was subjected to the hydroperoxidation.

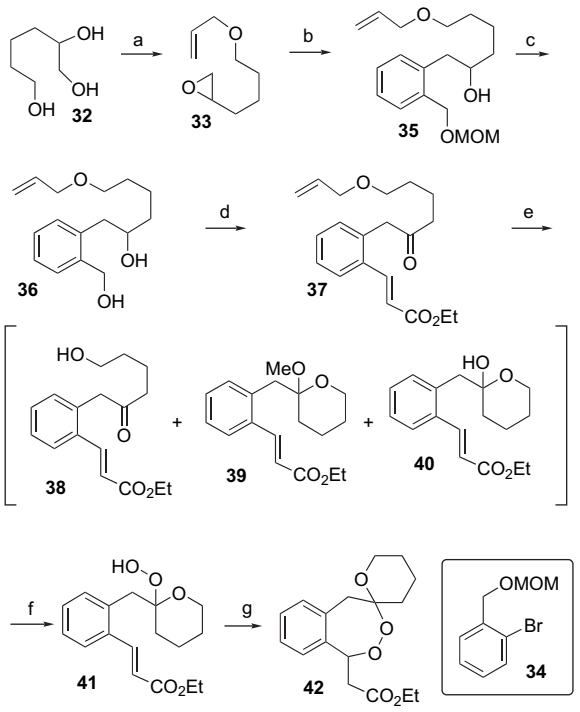


Scheme 5. (a) −78 °C/40min, 61%; (b) $(COCl)_2$/DMSO/CH_2Cl_2/NEt_3; (c) $Ph_3P{=}CHCO_2Et$/rt/3 h, 74% from **29**; (d) *p*-TsOH/rt/5 h, 96%; (e) UHP/CSA/DME/rt/18 h, 86% and (f) $HNEt_2$/F_3CCH_2OH/rt/2 h, 56% from **26**.

Because as mentioned above we already failed to obtain **26** in MeOH, this time tried to use DME as the solvent. Under such conditions, the desired **26** was formed in 86% yield. Further treatment with $HNEt_2$ in F_3CCH_2OH at the ambient temperature gave the end product **21** as a pair of separable diastereomers. It is interesting to note that this is the only case so far we found, where the diastereomers could be separated on silica gel. Interestingly, the two diastereomers showed different antimalarial activity in the in vitro testing.

Previously, we observed that using the intramolecular Michael addition of the hydroperoxyl group to close a seven-membered ring was impossible if all the bonds involved in the process were σ-bonds without any restrictions on their rotation. In this work, in combination with our intention to incorporate a UV chromophore into the carbon framework, we attempted to fuse a benzene ring to a 1,2-dioxepane ring. Such an additional ring would greatly reduce the degrees of freedom in the transition state for the formation of the seven-membered ring and therefore should increase the possibility to reach the 1,2-dioxepane.

As shown in Scheme 6, from the commercially available inexpensive triol **32** after a five-step sequence, an allyl group protected terminal epoxide **33** was conveniently obtained in 64% overall yield. Ring-opening of the epoxide with a lithium species prepared in situ from known bromide **34** led to alcohol **35**, which on hydrolytic removal of the MOM protecting group and a Swern oxidation followed by treatment with $Ph_3P{=}CHCO_2Et$ gave the **37**. Cleavage of the allyl protecting group was then achieved using $PdCl_2$/MeOH. The product was a mixture of several interchangeable species, which was therefore all utilized in the next step.

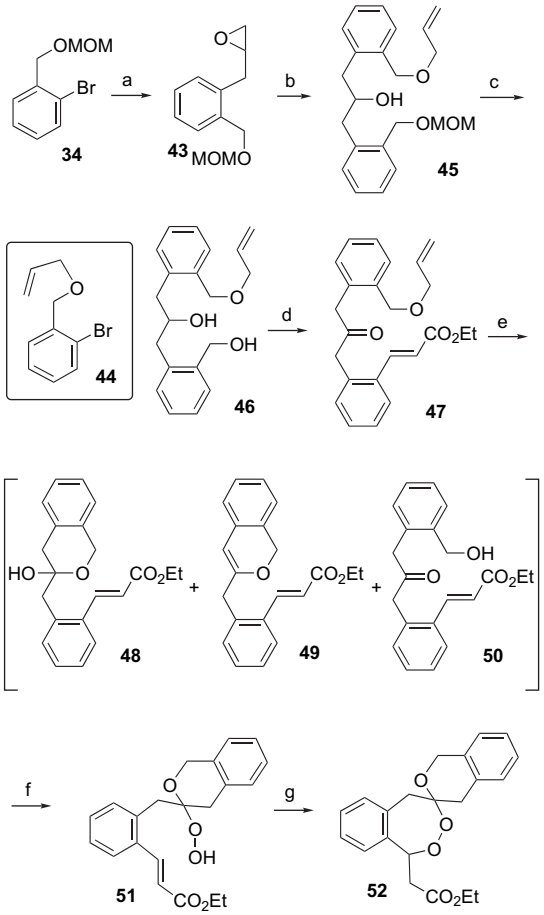


Scheme 6. (a) i. $Me_2C(OMe)_2$/acetone/*p*-TsOH/rt/22 h; ii. NaH/CH_2=$CHCH_2Br$/rt/10 h; iii. 2 N HCl/MeOH/rt/2 h; iv. *p*-TsCl/NEt_3/rt/12 h; v. KOH/Et_2O/rt/5.5 h, 64% from **32**; (b) *n*-BuLi/**34**/−78 °C/1 h, then **33**/$BF_3\cdot OEt_2$/−78 °C/1 h, 80%; (c) concd HCl/MeOH/rt/4 d, 93%; (d) i. $(COCl)_2$/DMSO/NEt_3; ii. Ph_3P=$CHCO_2Et$/rt/12 h, 85% from **36**; (e) $PdCl_2$/MeOH/rt/24 h, then 60 °C/4 h; (f) UHP/*p*-TsOH/DME/rt/22 h, 71% from **37** and (g) $HNEt_2$/CF_3CH_2OH/rt/19 h, 59%.

The hydroperoxidation turned out to be a smooth reaction as we had expected. The starting mixture of **38**, **39**, and **40** led to the hydroperoxy hemiketal **41** in 71% yield. Due to the presence of the additional benzene ring, the intramolecular Michael also proceeded very well, rendering the desired 1,2-dioxepane in 59% yield.

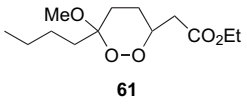
Using a similar strategy we also synthesized **52**, which contained two fused benzene rings. The synthetic sequence is depicted in Scheme 7. The initial steps were rather convenient due to the possibility to use **34**,[12] **44**,[13] and epichlorohydrin. Like in the case of deprotection of **37**, removal of the allyl protecting group in **47** also resulted in a mixture of several closely related species (**48**, **49**, and **50**). Treatment of this mixture with UHP/DME/CSA led to partial conversion of **48** into the anticipated hydroperoxy hemiketal **51**, along with recovered **49** and **50** (which reacted much more slowly than **48**). In order to speed up the reaction, higher doses of UHP (13 equiv) and CSA (5 equiv) were required. Increased amounts of UHP and CSA, however, created solubility problem. Fortunately we found that addition of a carefully controlled amount of EtOH could facilitate dissolution of the reagents without interfering the desired transformation. The presence of an additional benzene ring in **51** also created solubility problem in the final Michael addition step. Unlike **41**, the **51** was not so soluble in F_3CCH_2OH. Some CH_2Cl_2 must be added before the ring closure could proceed to a synthetically useful extent.

Apart from the spirosystems mentioned above, we also attempted to synthesize such bridged peroxides as **60**. As



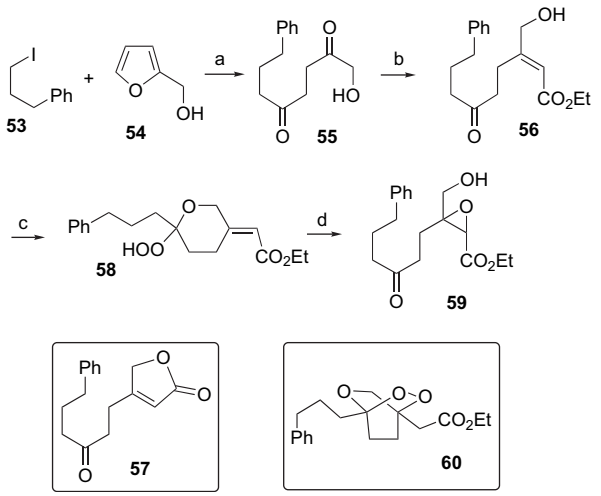
Scheme 7. (a) i. *n*-BuLi/$BF_3\cdot Et_2O$/epichlorohydrin/−78 °C/1 h; ii. NaH/rt/2.5 h, 67% from **34**; (b) *n*-BuLi/**44**/−78 °C/1 h, then **43**/$BF_3\cdot OEt_2$/−78 °C/1 h, 76%; (c) concd HCl/MeOH/rt/3 d, 99%; (d) i. $(COCl)_2$/DMSO/NEt_3; ii. Ph_3P=$CHCO_2Et$/rt/12 h, 77% from **46**; (e) $PdCl_2$/CuCl/DMF–H_2O/air/rt/12 h; (f) UHP/CSA/DME–EtOH/rt/7 d, 33% from **47** and (g) $HNEt_2$/CF_3CH_2OH/rt/21 h, 24%.

shown in Scheme 8, alkylation of furfuryl alcohol with **53** under the conditions similar to those reported[14] in the literature, followed by manipulation of the furan ring by MCPBA oxidation[15] and hydrogenation[16] led to compound **55**.



The hydroxyl group was then masked as an acetate by treatment with Ac_2O before selectively converting the carbonyl group closer to the acetate to an α,β-unsaturated ester. The isomer with ester group cis to the hydroxyl group formed the corresponding lactone **57** easily, which allowed for facile separation of the trans isomer **56** for further transformations. Again, the hydroperoxidation was apparently facilitated by the possibility to form a cyclic hemiketal. The hydroperoxy hemiketal **58** could be obtained in 44% yield. However, no peroxide **60** could be detected at all. Instead, an epoxide (**59**) was formed as the major product and isolated in 58% yield.

The results of the preliminary in vitro tests are shown in Table 1. The EC_{50} values for *Plasmodium falciparum* were



Scheme 8. (a) i. *n*-BuLi/−40 °C/4 h, then **53**/0 °C/43 h, 42%; ii. *m*-CPBA/rt/2 h, 95%; iii. H_2/Pd–C/rt/7 h, 40%; (b) i. Ac_2O/NEt_3/rt/5 h; ii. NaH/$(EtO)_2(O)P{=}CHCO_2Et$/rt/7 h; iii. 2 N HCl/EtOH/rt/2 d, 18% from **55**; (c) UHP/*p*-TsOH/DME/rt/24 h, 44% and (d) $HNEt_2/CF_3CH_2OH$/rt/10 h, 58% for **59**.

Table 1. The results of the preliminary in vitro tests[a]

Entry	Compd	EC_{50}(M)		Ratio[b]
		P. falciparum	FM3A	
1	**13**	8×10^{-6}	$>3.5\times10^{-5}$ (100% growth)	>5
2	**14**	7×10^{-6}	1×10^{-5}	2
3	**20**	$>4.8\times10^{-5}$ (70% growth)	$>4.8\times10^{-5}$ (100% growth)	
4	**21a**[c]	4×10^{-7}	$>2.7\times10^{-5}$ (100% growth)	>63
5	**21b**[d]	6×10^{-6}	1×10^{-5}	2
6	**42**	7×10^{-6}	8×10^{-6}	1
7	**52**	5×10^{-6}	7×10^{-6}	1
8	**61**[e]	6×10^{-7}	7×10^{-6}	12

[a] For detailed information about the biological testing, see the experimental part.
[b] The EC_{50} (*P. falciparum*)/EC_{50} (FM3A).
[c] The less polar diastereomer of **21**.
[d] The more polar diastereomer of **21**.
[e] Published in Ref. 6a (listed here for comparison).

within the range between 10^{-7} to 10^{-6} M, which were more or less the same as those reported[5d,6a] for the monocyclic simple analogues of peroxyplakoric acid. The nitro analogue **20**, however, was apparently less potent than other compounds tested, perhaps because the nitro group somehow interfered the radical reactions after the cleavage of the peroxy bond in the living cell. More work needs to be done before it is possible to give a more plausible explanation. It is also interesting to note that the two diastereomers of **21** showed significantly different activities.

3. Conclusions

Several spiroperoxy antimalarial compounds were designed and synthesized using the hydrogen peroxide in UHP (urea–H_2O_2 complex) as the source of the peroxy bond. Incorporation of the H_2O_2 into the organic molecule framework through ketal exchange reaction was greatly facilitated due to formation of a cyclic hemiketal. When the electron-withdrawing group in the Michael acceptor was a nitro group, the closure of the peroxy ring occurred readily under the hydroxidation conditions. Presence of a benzene ring fused to the peroxy ring effectively reduced the degrees of freedom in the transition state for the ring-closure step and made the otherwise very difficult seven-membered 1,2-dioxepane rather easy to form through the intramolecular Michael addition.

4. Experimental

4.1. General

The ^1H NMR and ^{13}C NMR spectra were recorded in deuterochloroform at ambient temperature using a Varian Mercury 300 or a Bruke Avance 300 instrument (operating at 300 MHz for proton). The FTIR spectra were scanned with a Nicolet Avatar 360 FTIR. EIMS and EIHRMS were recorded with an HP 5989A and a Finnigan MAT 8430 mass spectrometer, respectively. The ESIMS and ESIHRMS were recorded with a PE Mariner API-TOF and a APEX III (7.0 tesla) FTMS mass spectrometer, respectively. Elemental analyses were performed on an Elementar VarioEL III instrument. The melting point was uncorrected. Dry THF was distilled from Na/Ph_2CO under N_2. Dry CH_2Cl_2 was distilled over CaH_2 and kept over 4 Å molecular sieves. UHP was purchased from Acros. All other solvents and reagents were commercially available and used as received without any further purification.

4.2. MOM protection of 2 (3)

A solution of **2** (14.24 g, 80 mmol) and anhydrous LiBr (1.392 g, 16 mmol) in $CH(OMe)_2$ (160 mL) was stirred at the ambient temperature for 2 d. The mixture was partitioned between brine and Et_2O. The aqueous layer was back-extracted with Et_2O thrice. The combined ethereal phases were concentrated to dryness on a rotary evaporator. The residue was chromatographed on silica gel (20:1 *n*-hexane/EtOAc) to give **3** as a colorless oil (14.448 g, 81% yield). FTIR (film) 2932, 1422, 1276, 1147, 1111, 1041, 919, 771 cm^{-1}; ^1H NMR δ 4.61 (s, 2H), 4.05 (t, J=6.6 Hz, 1H), 3.55 (t, J=6.1 Hz, 2H), 3.36 (s, 3H), 2.89–2.84 (m, 4H), 1.89–1.80 (m, 6H); EIMS *m*/*z* (%) 222 (M^+, 1), 177 ($M^+-CH_2OCH_3$, 26), 103 (49), 45 (100). EIHRMS calcd for $C_9H_{18}O_2S_2$ 222.0748, found 222.0750.

4.3. Alkylation of 3 (4)

With cooling (−78 °C bath) and stirring *n*-BuLi (30.0 mL, 1.6 M) was added dropwise (via a syringe) to a solution of the dithiane **3** (9.033 g, 40.5 mmol) and Ph_3CH (15 mg, as an indicator) in dry THF (120 mL) under argon, followed by HMPA (7 mL, 40.7 mmol) (via a syringe). The bath was allowed to warm to −20 °C and the magenta solution was stirred at that temperature for 4 h, before the iodide (10.295 g, 44.8 mmol) was introduced via a syringe. After further stirring at 0 °C for 48 h, the mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated

on a rotary evaporator. The residue was chromatographed on silica gel (10:1 *n*-hexane/EtOAc) to give compound **4** (11.654 g, 88%). FTIR (film) 2933, 1451, 1383, 1151, 1128, 1041, 919 cm^{-1}; ^1H NMR δ 4.61 (s, 2H), 4.38 (t, J=5.4 Hz, 1H), 3.54 (t, J=6.0 Hz, 2H), 3.36 (s, 3H), 3.32 (s, 6H), 2.84–2.79 (m, 4H), 1.98–1.92 (m, 6H), 1.81–1.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2, 96.3, 67.4, 55.1, 52.7, 52.5, 35.1, 32.8, 27.2, 25.9, 25.3, 24.4; EIMS *m/z* (%) 324 (M^+, 73), 293 (M^+-OCH_3, 22), 75 (100); ESIHRMS calcd for $C_{14}H_{28}O_4S_2Na$ ($[M+Na]^+$) 347.1321, found 347.1326.

4.4. Synthesis of 5

A mixture of **4** (3.202 g, 9.9 mmol) and PPTS (588 mg, 2.4 mmol) in aqueous acetone (100 mL of acetone plus 10 mL water) was heated to reflux with stirring for 12 h, when TLC showed the hydrolysis to be complete. Acetone was removed on a rotary evaporator, and the residue was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator to give aldehyde as a yellowish oil (2.86 g), which was dissolved in CH_2Cl_2 (68 mL) and treated with $Ph_3P{=}CHCO_2Et$ (6.0 g, 18.9 mmol). The mixture was stirred at ambient temperature until TLC showed complete disappearance of the aldehyde. The solvent was removed on a rotary evaporator, and the residue was diluted with Et_2O. The solid–liquid mixture was filtered and the filtrate was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (6:1 *n*-hexane/EtOAc) to give compound **5** as a colorless oil (3.033 g, 86%). FTIR (film) 1717, 1269, 1042, 919 cm^{-1}; ^1H NMR δ 6.99 (dt, J=16, 6.8 Hz, 1H), 5.87(d, J=16 Hz, 1H), 4.63 (s, 2H), 4.20 (q, J=6.9 Hz, 2H), 3.56 (t, J=5.7 Hz, 2H), 3.37 (s, 3H), 2.84–2.81 (m, 4H), 2.43–2.35 (m, 2H), 2.07–1.95 (m, 6H), 1.80–1.73 (m, 2H), 1.30 (t, J=6.9 Hz, 3H); EIMS *m/z* (%) 348 (M^+, 17), 303 ($M^+-OCH_2CH_3$, 4), 45 (100); ESIHRMS calcd for $C_{16}H_{28}O_4S_2Na$ ($[M+Na]^+$) 371.1321, found 371.1312. Anal. calcd for $C_{16}H_{28}O_4S_2$: C, 55.14; H, 8.10. Found: C, 55.26; H, 8.23.

4.5. Removal of the MOM protecting group in 5 (7)

A mixture of **5** (1.946 g, 5.6 mmol) and *p*-TsOH (106 mg, 0.56 mmol) in EtOH (40 mL) was heated to reflux with stirring until TLC showed the hydrolysis to be complete. The mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give compound **7** as a colorless oil (1.52 g, 90%). FTIR (film) 3438, 1713, 1273, 1046, 908 cm^{-1}; ^1H NMR δ 6.99 (dt, J=15, 6.8 Hz, 1H), 5.88 (d, J=15 Hz, 1H), 4.20 (q, J=7.2 Hz, 2H), 3.71–3.68 (m, 2H), 2.85–2.81 (m, 4H), 2.43–2.35 (m, 2H), 2.07–1.94 (m, 6H), 1.78–1.69 (m, 2H), 1.30 (t, J=7.1 Hz, 3H); EIMS *m/z* (%) 304 (M^+, 9), 259 (M^+-OEt, 3), 245 (28), 197 (100); EIHRMS calcd for $C_{14}H_{24}O_3S_2Na$ ($[M+Na]^+$) 327.1059, found 327.1063. Anal. calcd for $C_{14}H_{24}O_3S_2$: C, 55.23; H, 7.95. Found: C, 55.39; H, 7.82.

4.6. Hydrolysis of the dithiane protecting group in 7 (9)

$NaHCO_3$ (6.183 g, 73.6 mmol) and I_2 (9.209 g, 36.3 mmol) were added to a solution of **7** (3.34 g, 11.0 mmol) in aqueous acetone (94 mL of acetone plus 17 mL water). The resulting mixture was stirred at 0 °C for 30 min until TLC showed complete disappearance of **7**. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and the mixture was diluted with Et_2O. The phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, water, and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel (2:1 *n*-hexane/EtOAc) to give **9** as a yellowish oil (3.892 g, 83%). FTIR (film) 1716, 1655, 1043, 979 cm^{-1}; ^1H NMR δ 6.93 (dt, J=16, 6.9 Hz, 1H), 5.83 (d, J=16 Hz, 1H), 4.18 (q, J=7.4 Hz, 2H), 3.66 (dt, J=10, 5.7 Hz, 2H), 2.65–2.56 (m, 4H), 2.53–2.45 (m, 2H), 1.91–1.82 (m, 2H), 1.28 (t, J=7.2 Hz, 3H); ESIMS *m/z* 232 ($[M+NH_4]^+$); EIHRMS calcd for $C_{11}H_{18}O_4Na$ ($[MNa]^+$) 237.1097, found 237.1089.

4.7. Synthesis of 13

p-TsOH (3.27 g, 17.2 mmol) and UHP (9.927 g, 105.5 mmol) were added to a solution of **9** (2.995 g, 14.0 mmol) in MeOH (280 mL). The resulting mixture was stirred at ambient temperature for 20 h. When TLC showed complete disappearance of **9**, the mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (4:1 *n*-hexane/EtOAc) to give compound **11** (2.633 g, 82%), which gave the following data: ^1H NMR δ 8.06 (s, 1H), 6.99 (dt, J=16, 6.7 Hz, 1H), 5.85 (dt, J=16, 1.3 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 4.02–3.97 (m, 2H), 2.27–2.05 (m, 4H), 2.05–1.79 (m, 4H), 1.29 (t, J=7.2 Hz, 3H). The **11** (2.633 g, 11.5 mmol) was then dissolved in CF_3CH_2OH (64 mL) containing $NHEt_2$ (100 μL). The mixture was stirred at the ambient temperature until TLC showed complete disappearance of **11**. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (5:1 *n*-hexane/EtOAc) to give compound **13** as a colorless oil (1.369 g, 52%). FTIR (film) 1737, 1445, 1370, 1289, 1184, 1032 cm^{-1}; ^1H NMR δ 4.56–4.54 (m, 1H), 4.15 (q, J=7.1 Hz, 2H), 4.08–4.02 (m, 2H), 2.56 (dd, J=7.4, 16 Hz, 1H), 2.39 (dd, J=6.0, 16 Hz, 1H), 2.05–1.74 (m, 8H), 1.25 (t, J=7.1 Hz, 3H); ESIMS *m/z* 248 ($[M+NH_4]^+$). Anal. calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.56; H, 7.87.

4.8. Synthesis of compound 6

Prepared from **4** in 94% yield using the same procedure for the synthesis of **5** described above except that $Ph_3P{=}CHCO_2Bn$ was utilized instead of $Ph_3P{=}CHCO_2Et$. Data for **6** (a colorless oil): FTIR (film) 1720, 1653, 1040, 919 cm^{-1}; ^1H NMR δ 7.39–7.32 (m, 5H), 7.04 (dt, J=16, 6.7 Hz, 1H), 5.92 (d, J=16 Hz, 1H), 5.18 (s, 2H), 3.54 (t, J=6.2 Hz, 2H), 3.34 (s, 3H), 2.81 (t, J=5.7 Hz, 4H), 2.43–2.35 (m, 2H), 2.05–1.93 (m, 6H), 1.78–1.89 (m, 2H); ESIMS

m/z 428 ([M+NH_4]$^+$). ESIHRMS calcd for $C_{21}H_{30}O_4S_2Na$ ([M+Na]+) 433.1478, found 433.1479. Anal. calcd for $C_{21}H_{30}O_4S_2$: C, 61.43; H, 7.36. Found: C, 61.45; H, 7.39.

4.9. Removal of the MOM group in 6 (8)

A solution of **6** (3.941 g, 9.6 mmol) in THF (30 mL) and 2 N HCl (15 mL) was stirred at 40–50 °C until TLC showed complete disappearance of **6**. The reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give **8** (2.246 g, 64%). FTIR (film) 3421, 1717, 1652, 1272, 1163, 1017, 978 cm^{-1}; ^{1}H NMR δ 7.39–7.27 (m, 5H), 7.04 (dt, J=16, 6.7 Hz, 1H), 5.92 (d, J=16 Hz, 1H), 5.18 (s, 2H), 3.67 (t, J=6.1 Hz, 2H), 2.83–2.79 (m, 4H), 2.43–2.35 (m, 2H), 2.06–1.92 (m, 6H), 1.76–1.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 148.8, 135.9, 128.4, 128.1, 121.2, 66.0, 62.4, 52.4, 36.2, 36.8, 27.2, 25.8, 25.1; ESIMS *m/z* 384 ([M+NH_4]$^+$); ESIHRMS calcd for $C_{19}H_{27}O_3S_2$ ([M+H]$^+$) 367.1396, found 367.1394.

4.10. Hydrolysis of the dithiane protecting group in 8 (10)

Compound **10** was obtained in 77% yield from **8** using the same procedure described above for the synthesis of **9**. Data for **10** (a colorless oil): FTIR (film) 3420, 1716, 1654, 1267, 1171, 1026, 699 cm^{-1}; ^{1}H NMR δ 7.38–7.27 (m, 5H), 6.98 (dt, J=15, 7.0 Hz, 1H), 5.88 (d, J=15 Hz, 1H), 5.17 (s, 2H), 3.64 (t, J=5.8 Hz, 2H), 2.64–2.45 (m, 6H), 1.89–1.80 (m, 2H); ESIMS *m/z* 294 ([M+NH_4]$^+$); ESIHRMS calcd for $C_{16}H_{20}O_4Na$ ([M+Na]$^+$) 299.1254, found 299.1240.

4.11. Synthesis of compound 14

Using the same procedure described above for converting **9** into **11**, the intermediate hydroperoxide **12** was obtained in 75% from **10**, which showed the following: ^{1}H NMR δ 8.14 (s, 1H), 7.39–7.32 (m, 5H), 7.05 (dt, J=15.3, 6.6 Hz, 1H), 5.91 (d, J=15.6 Hz, 1H), 5.18 (s, 2H), 4.01–3.96 (m, 2H), 2.41–2.15 (m, 3H), 2.08–1.77 (m, 5H). The **12** was then converted into **14** (1:4 mixture of two diastereomers) in 52% yield using the same procedure as described above for the conversion of **11** into **13**. Data for **14** (a colorless oil): FTIR (film) 1724, 1455, 1291,1033 cm^{-1}; ^{1}H NMR δ 7.37–7.31 (m, 5H), 5.14 (s, 2H), 4.63–4.56 (m, 1H), 4.11–4.00 (m, 2H), 2.88 and 2.64 (two doublets in 1:4 ratio, J=16, 7.4 Hz, 1H altogether, part of an AB system), 2.60 and 2.47 (two doublets in 1:4 ratio, J=16, 7.4 Hz, 1H altogether, part of an AB system), 2.06–1.75 (m, 8H); ESIMS *m/z* 310 ([M+NH_4]$^+$); ESIHRMS calcd for $C_{16}H_{20}O_5Na$ ([M+Na]$^+$) 315.1203, found 315.1210. Anal. calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.86; H, 6.97.

4.12. Conversion of 4 into 15

A mixture of **4** (6.3582 g, 19.6 mmol) and PPTS (523 mg, 2.0 mmol) in aqueous acetone (178 mL of acetone plus 18 mL of water) was heated to reflux with stirring until TLC showed completion of the hydrolysis (12 h). Acetone was removed on a rotary evaporator. The residue was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator to give the intermediate aldehyde as a yellowish oil (4.92 g), which was dissolved in MeCN (8 mL) and added to a mixture of DBU (0.39 mL, 2.64 mmol), $MeNO_2$ (3.22 g, 26.4 mmol, a commercially available 50% solution in MeOH), and MeCN (40 mL). The mixture was then stirred at the ambient temperature until TLC showed complete disappearance of the aldehyde (ca. 15 h). The reaction was quenched with saturated aqueous NH_4Cl. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel (3:1 *n*-hexane/EtOAc) to give **15** as a colorless oil (5.625 g, 94% overall). FTIR (film) 3425, 2932, 1553, 1383, 1109, 1036 cm^{-1}; ^{1}H NMR δ 4.63 (s, 2H), 4.46–4.42 (m, 2H), 3.56 (t, J=6.0 Hz, 2H), 3.37 (s, 3H), 2.83 (t, J=5.7 Hz, 4H), 2.73 (d, J=5.0 Hz, 1H), 2.25–2.15 (m, 1H), 1.99–1.94 (m, 6H), 1.74–1.70 (m, 4H); EIMS *m/z* (%) 339 (M^+, 4), 294 ($M^+-CH_2OCH_3$), 45 (100); ESIHRMS calcd for $C_{13}H_{25}NO_5S_2Na$ ([M+Na]$^+$) 362.1066, found 362.1075.

4.13. Elimination of the hydroxyl group in 15 (16)

With cooling (0 °C bath) and stirring, MsCl (2.3 mL, 30 mmol) and NEt_3 (5 mL, 36 mmol) were added to a solution of **15** (6.056 g, 17.86 mmol) in CH_2Cl_2 (90 mL). The stirring was continued at the ambient temperature for 24 h. The reaction was quenched with saturated aqueous NH_4Cl. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel (6:1 *n*-hexane/EtOAc) to give **16** as a yellowish colorless oil (5.588 g, 97%). FTIR (film) 2933, 1648, 1524, 1350, 1039 cm^{-1}; ^{1}H NMR δ 7.34–7.27 (m, 1H), 7.04 (d, J= 13 Hz, 1H), 4.63 (s, 2H), 3.55 (t, J=3.1 Hz, 2H), 3.37 (s, 3H), 2.83 (t, J=5.7 Hz, 4H), 2.53–2.45 (m, 2H), 2.10–2.04 (m, 2H), 2.01–1.96 (m, 4H), 1.79–1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 139.7, 96.3, 67.3, 55.1, 52.2, 36.1, 35.4, 25.9, 24.9, 24.5, 23.8; EIMS *m/z* (%) 321 (M), 275 (M^+-NO_2, 32), 218 ($M^+-C_2H_6OMOM$, 31), 45 (100); ESIHRMS calcd for $C_{13}H_{23}NO_4S_2Na$ ([M+Na]$^+$) 344.0961, found 344.0966.

4.14. Hydrolysis of the dithiane protecting group in 16 (17)

Compound **17** was obtained in 87% yield from **16** using the same procedure described above for the synthesis of **9**. Data for **17** (a colorless oil): FTIR (film): 1715, 1649, 1525, 1352, 1040 cm^{-1}; ^{1}H NMR δ 7.29–7.20 (m, 1H), 7.01 (d, J=14 Hz, 1H), 4.59 (s, 2H), 3.54 (t, J=6.3 Hz, 2H), 3.35 (s, 3H), 2.68 (t, J=6.7 Hz, 2H), 2.58–2.51 (m, 4H), 1.90 (quint, J=6.6 Hz, 2H); ESIMS *m/z* 254 ([M+Na]$^+$). Anal.

calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 52.13; H, 7.13; N, 6.06.

4.15. Synthesis of 20

Removal of the MOM group in **17**, utilizing the same procedure described above for transforming **5** into **7**, led to **18** in 21% yield (chromatography on silica gel eluting with 1:1 *n*-hexane/EtOAc). FTIR (film) 3411, 1712, 1650, 1525, 1352, 1058 cm^{-1}; ^1H NMR δ 7.30–7.20 (m, 1H), 7.01 (d, J=14 Hz, 1H), 3.85–3.91 (m, 1H), 3.67 (t, J=5.9 Hz, 2H), 2.72–2.67 (m, 2H), 2.61–2.54 (m, 4H), 1.93–1.85 (m, 2H). The **18** thus obtained (59 mg, 0.32 mmol) was immediately dissolved in DME (3.2 mL). *p*-TsOH (61 mg, 0.32 mmol) and UHP (208 mg, 2.2 mmol) were then added. The mixture was stirred at the ambient temperature until TLC showed complete disappearance of **18** (ca. 10.5 h). The mixture was diluted with Et_2O and washed with water. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (5:1 *n*-hexane/EtOAc) to give compound **20** (23 mg, 35%). FTIR (film) 2960, 1556, 1371, 1041 cm^{-1}; ^1H NMR δ 4.95–4.86 (m, 1H), 4.54 (dd, J=9.1, 14 Hz, 1H), 4.37 (dd, J=3.5, 13.8 Hz, 1H), 4.09–4.03 (m, 2H), 2.08–1.88 (m, 6H), 1.82–1.76 (m, 2H); ESIMS *m/z* 221 ($[M+NH_4]^+$); EIHRMS calcd for $C_8H_{13}NO_5$ (M^+) 203.0806, found 203.0818.

4.16. Synthesis of 23

With cooling (−70 °C bath), *n*-BuLi (13.7 mL, 1.6 M) was added dropwise (via a syringe) to a solution of $HC{\equiv}CCH_2OBn$ (3.193 g, 21.9 mmol) in dry THF (45 mL) stirred under argon. The bath was allowed to warm to −25 °C and kept at that temperature for 1.5 h before being added via a cannula to a solution of **22** (4.855 g, 32.8 mmol) in dry THF (55 mL) stirred at −70 °C under argon. The mixture was stirred at that temperature for 2 h. The reaction was quenched with water and acidified to pH 4 with 2 N HCl. The phases were separated. The aqueous layer was back-extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator to give the intermediate ketone-acid as a yellowish oil (3.906 g), which was dissolved in Et_2O (48 mL) and treated with an excess of CH_2N_2 (an ethereal solution prepared using standard procedure prior to use) at 0 °C. When TLC showed complete disappearance of the ketone-acid, the cooling bath was allowed to warm to the ambient temperature. The stirring was continued for another hour before removal of the solvent by rotary evaporation. The residue was chromatographed on silica gel (8:1 *n*-hexane/EtOAc) to give compound **23** as a yellowish oil (2.103 g, 43%). FTIR (film) 3031, 2951, 2221, 1732, 1650, 1260, 1074, 698 cm^{-1}; ^1H NMR δ 7.94–7.91 (m, 1H), 7.69–7.59 (m, 3H), 7.38–7.27 (m, 5H), 4.65 (s, 2H), 4.41 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 140.2, 139.4, 135.2, 135.1, 133.7, 132.8, 131.7, 131.3, 130.88, 130.86 (2C), 93.4, 87.4, 75.0, 59.8, 55.5; EIMS *m/z* (%) 293 (M^+−Me, 1), 263 (M^+−OEt, 54), 91 (M^+−Bn, 64), 170 (100); MALDIHRMS calcd for $C_{19}H_{16}O_4Na$ ($[M+Na]^+$) 331.0941, found 331.0942.

4.17. Synthesis of compound 24

A mixture of **23** (1.208 g, 3.9 mmol) and 10% palladium on charcoal (500 mg) in MeOH (20 mL) was stirred at the ambient temperature under H_2 (1 atm) until TLC showed complete disappearance of **23** (5.5 h). The catalyst was filtered off and the filtrate was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (4:1 *n*-hexane/EtOAc) to give compound **24** as a colorless oil (332 mg, 38%). FTIR (film) 3402, 2932, 1723, 1434, 1264, 1091 cm^{-1}; ^1H NMR δ 7.90 (d, J=7.1 Hz, 1H), 7.46–7.40 (m, 1H), 7.28–7.23 (m, 2H), 3.90 (s, 3H), 3.72 (t, J=5.6 Hz, 2H), 2.97 (t, J=7.7 Hz, 2H), 1.72–1.68 (m, 2H); ESIMS *m/z* 245 ($[M+Na]^+$); ESIHRMS calcd for $C_{12}H_{14}O_4Na$ ($[M+Na]^+$) 245.0784, found 245.0783.

4.18. Synthesis of compound 25 (from 24)

DIBAL-H (1.0 M solution in cyclohexane, 1.8 mL) was added (via a syringe) to a solution of **24** (132 mg, 0.59 mmol) in dry CH_2Cl_2 (3 mL) stirred at −75 °C under N_2. The stirring was continued at that temperature for 3 h. Then the bath was allowed to warm to the ambient temperature before the reaction was quenched with MeOH. The reaction mixture was shaken with aqueous saturated potassium sodium tartrate. The phases were separated. The aqueous layer was back-extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator to give the intermediate triol (160 mg), which was dissolved in $CHCl_3$ (3 mL) and treated with activated MnO_2 (262 mg, 3 mmol). The mixture was stirred at the ambient temperature for 4 d. The solids were filtered off (rinsed with $CHCl_3$) and the combined filtrate/washings were concentrated on a rotary evaporator and added to a solution of $Ph_3P{=}CHCO_2Et$ (150 mg, 0.43 mmol) in $CHCl_3$ (3 mL). The mixture was stirred at the ambient temperature for 10 h. The solvent was removed on a rotary evaporator. The solid residue was triturated with Et_2O. The solids were filtered off and the filtrate was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (4:1 *n*-hexane/EtOAc) to give compound **25** as a colorless oil (73 mg, 47%). FTIR (film) 3417, 2928, 1683, 1634, 1478, 1175, 1036 cm^{-1}; ^1H NMR δ 8.05 (d, J=16 Hz, 1H), 7.72 (d, J=7.7 Hz, 1H), 7.62–7.09 (m, 3H), 6.31 (d, J=16 Hz, 1H), 4.30 (q, J=7.2 Hz, 2H), 3.76 (t, J=5.8 Hz, 2H), 3.08 (t, J=6.8 Hz, 2H), 2.05–1.98 (m, 2H), 1.69 (br s, 1H), 1.34 (t, J=7.2 Hz, 3H); EIMS *m/z* (%) 245 (M^+−OH, 0.6), 189 (M^+−CO_2Et, 100), 217 (M^+−OEt, 2). Anal. calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.32; H, 6.79.

4.19. Synthesis of compound 29

n-BuLi (50 mL, 1.2 M) was added dropwise (via a syringe) to a solution of *o*-$BrC_6H_4CH_2OH$ (5.578 g, 29.8 mmol) in dry THF (150 mL) stirred at −78 °C under N_2. After the completion of the addition, the stirring was continued at that temperature for 1 h. Then, a solution of **27** (prepared by Swern oxidation from the corresponding alcohol (6.78 g, 33.2 mmol)) in dry THF (20 mL) was added dropwise via a syringe. The mixture was stirred at the same temperature for another 40 min before saturated aqueous NH_4Cl

was introduced to quench the reaction. The mixture was diluted with Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (4:1 *n*-hexane/EtOAc) to give compound **29** as a yellowish oil (5.577 g, 61% from **28**). FTIR (film) 3351, 2927, 1463, 1255, 1100 cm^{-1}; ^1H NMR δ 7.43–7.40 (m, 1H), 7.35–7.26 (m, 3H), 4.95 (dd, J=7.9, 5.0 Hz, 1H), 4.72 (s, 2H), 3.79–3.71 (m, 2H), 2.00–1.97 (m, 2H), 2.79–1.74 (m, 2H), 0.93 (s, 9H), 0.10 (s, 6H); EIMS *m/z* (%): 292 (M^+-H_2O, 0.9), 195 (M^+-TBS, 1.3), 143 (100); ESIHRMS calcd for $C_{17}H_{30}O_3SiNa$ ($[M+Na]^+$) 333.1856, found 333.1868. Anal. calcd for $C_{17}H_{30}O_3Si$: C, 65.76; H, 9.74. Found: C, 65.98; H, 9.64.

4.20. Synthesis of compound 31

With cooling (−70 °C bath) and stirring a solution of DMSO (7 mL, 97.4 mmol) was added dropwise (via a syringe) to a solution of $(COCl)_2$ (3.9 mL, 44.3 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at that temperature for 30 min before the alcohol **29** (3.269 g, 10.58 mmol) was introduced via a syringe. The bath was allowed to warm to −60 °C and the stirring was continued at that temperature for 30 min. Then, Et_3N (27 mL, 199.2 mmol) was added to the mixture and the reaction was continued at that temperature for another 30 min. After the reaction was quenched with 2 N HCl (40 mL), the cold bath was removed and the mixture was stirred at ambient temperature for 5 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator to give crude ketone–aldehyde **30** as a yellowish oil (3.578 g), which was then converted into α,β-unsaturated ester **31** as a red-orange oil (3.064 g, 74% from **29**) by a similar Wittig reaction as described above for the synthesis of **25**. Data for **31**: FTIR (film) 1716, 1256, 1177 cm^{-1}; ^1H NMR δ 8.02 (d, J=15.9 Hz, 1H), 7.70 (d, J=7.6 Hz, 1H), 7.55 (d, J=7.3 Hz, 1H), 7.49–7.41 (m, 2H), 6.25 (d, J=15.8 Hz, 1H), 4.24 (q, J=7.1 Hz, 2H), 3.66 (t, J=6.1 Hz, 2H), 2.98 (t, J=7.5 Hz, 2H), 1.95–1.85 (m, 2H), 1.29 (t, J=7.1 Hz, 3H), 0.85 (s, 9H), 0.00 (s, 6H); ESIMS *m/z*: 377 ($[M+H]^+$). Anal. calcd for $C_{21}H_{32}O_4Si$: C, 66.98; H, 8.57. Found: C, 67.10; H, 8.23.

4.21. Removal of the TBS group in 31 (25)

A mixture of **31** (2.916 g, 7.46 mmol) and *p*-TsOH (380 mg, 2 mmol) in aqueous THF (40 mL of THF plus 10 mL water) was stirred at ambient temperature for 5 h, when TLC showed the hydrolysis to be complete. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with Et_2O, and the phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (2:1 *n*-hexane/EtOAc) to give **25** (1.827 g, 96%). Data for **25** are given above under 'synthesis of **25** (from **24**)'.

4.22. Synthesis of compound 21

A solution of **25** (1.905 g, 7.3 mmol), CSA (5.0 g, 22.0 mmol), and UHP (4.7 g, 51 mmol) in DME (116 mL) was stirred at the ambient temperature until TLC showed complete disappearance of **25** (ca.18 h). The mixture was partitioned between Et_2O and water. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give compound **26** (1.744 g, 86%), which gave the following data: FTIR (film) 3375, 1712, 1633, 1316, 1183 cm^{-1}; ^1H NMR δ 8.32 (d, J=15.8 Hz, 1H), 8.17 (s, 1H), 7.79–7.76 (m, 1H), 7.59–7.56 (m, 1H), 7.39–7.35 (m, 1H), 6.28 (d, J=15.8 Hz, 1H), 4.31–4.19 (m, 4H altogether, including a quartet at δ 4.26, J=7.1 Hz), 2.52–2.45 (m, 1H), 2.18–2.00 (m, 3H), 1.34 (t, J=7.1 Hz, 3H). The **26** was then transformed into **21a** (the less polar diastereomer, 44.4% yield) and **21b** (the more polar diastereomer, 12.3% yield) using the same procedure described above for converting **9** into **11**. Data for **21a** (the less polar diastereomer): FTIR (film) 1736, 1453, 1374, 1281, 1053 cm^{-1}; ^1H NMR δ 7.37–7.30 (m, 3H), 7.13–7.10 (m, 1H), 5.70 (t, J=6.4 Hz, 1H), 4.26–4.19 (m, 4H), 2.91 (d, J=6.7 Hz, 2H), 2.43–2.36 (m, 4H), 1.29 (t, J=7.1 Hz, 3H); ESIMS *m/z* 296 ($[M+NH_4]^+$); ESIHRMS calcd for $C_{15}H_{18}O_5Na$ ($[M+Na]^+$) 301.1046, found 301.1042. Anal. calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.77; H, 6.52. Data for **21b** (the more polar diastereomer): FTIR (film) 1735, 1454, 1372, 1279, 1050 cm^{-1}; ^1H NMR δ 7.36–7.21 (m, 3H), 7.16–7.13 (m, 1H), 5.50 (dd, J=4.4, 9.0 Hz, 1H), 4.28–4.16 (m, 4H altogether, including a quartet at δ 4.20, J=7.2 Hz), 3.24 (dd, J=8.8, 16 Hz, 1H), 2.80 (dd, J=4.4, 16 Hz, 1H), 2.38–2.35 (m, 1H), 2.23–2.17 (m, 3H), 1.31 (t, J=7.2 Hz, 3H); ESIMS *m/z* 296 ($[M+NH_4]^+$); ESIHRMS calcd for $C_{15}H_{18}O_5Na$ ($[M+Na]^+$) 301.1046, found 301.1042.

4.23. Synthesis of compound 33

A mixture of 1,2,6-hexatriol (14.5 g, 108 mmol), *p*-TsOH (2.05 g, 10.8 mmol), and DMOP (20 mL, 162 mmol) in acetone (300 mL) was stirred at the ambient temperature for 22 h. Aqueous $NaHCO_3$ was added, followed by Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator to give a yellowish oil. This oil was added to a mixture of NaH (8.4 g, 210 mmol) in DMF (300 mL) stirred at 0 °C. $CH_2{=}CHCH_2Br$ (25.41 g, 210 mmol) was then introduced. The mixture was stirred at the ambient temperature for 10 h before being partitioned between water and Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and concentrated on a rotary evaporator. The residue was dissolved in MeOH (160 mL). HCl 2 N (80 mL) was then added. The mixture was stirred at the ambient temperature for 2 h before the solvent was removed on a rotary evaporator. The residue was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$, water, and brine, and dried over Na_2SO_4. Removal of the solvent on a rotary evaporator left a yellowish

oil, which was dissolved in a mixture of CH_2Cl_2 (422 mL) and NEt_3 (45 mL). The mixture was cooled in a 0 °C bath. *p*-TsCl (23.7 g, 123.5 mmol) was then added. The mixture was stirred at the ambient temperature for 12 h before diluting with CH_2Cl_2, washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was added to Et_2O (440 mL), followed by KOH (7.056 g, 126 mmol). The mixture was stirred at the ambient temperature for 5.5 h. Water was added and the phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (10:1 *n*-hexane/EtOAc) to give **33** as a colorless oil (10.761 g, 69% from 1,2,6-hexatriol). FTIR (film) 2932, 1458, 1360, 1179, 1105 cm^{-1}; ^1H NMR δ 5.92 (ddt, J=17, 10.6, 5.5 Hz, 1H), 5.72 (br d, J=17 Hz, 1H), 5.18 (br d, J=10 Hz, 1H), 3.97 (d, J=5.6 Hz, 2H), 3.45 (t, J=6.2 Hz, 2H), 2.92–2.89 (m, 1H), 2.75 (t, J=4.5 Hz, 1H), 2.48 (dd, J=2.8, 4.9 Hz, 1H), 1.70–1.47 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 116.7, 71.7, 70.0, 52.1, 47.0, 32.2, 29.4, 22.6; EIMS *m/z*: (%) 155 (M^+-H, 6), 99 ($M^+-Oallyl$, 1), 41 (100); EIHRMS calcd for $C_9H_{16}O_2$ (M^+) 156.1103, found 156.1154.

4.24. Synthesis of compound 35

n-BuLi (8.8 mL, 1.6 M) was added dropwise (via a syringe) to a solution of **34** (3.253 g, 14.1 mmol) in dry THF (50 mL) stirred at −70 °C under N_2. After the completion of the addition, the mixture was stirred at −70 °C for 1 h. A solution of epoxide **33** (2.197 g, 14.1 mmol) in dry THF (10 mL) was added, followed by $BF_3\cdot EtO_2$ (2.0 mL, 14.1 mmol). The stirring was continued at the same temperature for another hour. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (7:1 *n*-hexane/EtOAc) to give **35** (3.477 g, 80%). FTIR (film) 3470, 2936, 1453, 1100, 1040 cm^{-1}; ^1H NMR δ 7.36–7.23 (m, 4H), 5.92 (ddt, J=17, 10.2, 5.8 Hz, 1H), 5.27 (br d, J=18 Hz, 1H), 5.18 (br d, J=11 Hz, 1H), 4.71 (s, 4H), 4.67 (d, J=11 Hz, 2H, part of an AB system), 4.60 (d, J=11 Hz, 2H, part of an AB system), 3.97 (dt, J=4.3, 1.4 Hz, 2H), 3.83–3.80 (m, 1H), 3.45 (t, J=6.4 Hz, 2H), 3.42 (s, 3H), 2.91 (dd, J=15, 3.6 Hz, 1H), 2.75 (dd, J=14, 9.0 Hz, 1H), 2.42 (d, J=3.3 Hz, 1H), 1.68–1.58 (m, 6H); EIMS *m/z*: (%) 309 (M^++H, 0.03), 309 (M^+, 0.02), 104 (100); ESIHRMS calcd for $C_{18}H_{28}O_4Na$ ($[M+Na]^+$) 331.1880, found 331.1881. Anal. calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.72; H, 8.78.

4.25. Removal of the MOM group in 35 (36)

Compound **36** was prepared in 93% yield (chromatography on silica gel eluting with 2:1 *n*-hexane/EtOAc) from **35** using the same procedure described above for converting **6** into **8**. Data for **36** (a yellowish oil): FTIR (film) 3331, 2936, 1453, 1100, 1010 cm^{-1}; ^1H NMR δ 7.34–7.20 (m, 4H), 5.92 (ddt, J=17, 10, 5.8 Hz, 1H), 5.27 (br d, J=18 Hz, 1H), 5.18 (br d, J=10 Hz, 1H), 4.76 (d, J=12 Hz, 1H), 4.48 (d, J=12 Hz, 1H), 3.97 (dt, J=5.6, 1.4 Hz, 2H), 3.85–3.77 (m, 1H), 3.46 (t, J=6.4 Hz, 2H), 2.84 (s, 1H), 2.82 (d, J=3.8 Hz, 1H), 1.71–1.46 (m, 8H); EIMS *m/z* (%): 246 (M^+-H_2O, 0.86), 143 (20), 104 (100); ESIHRMS calcd for $C_{16}H_{24}O_3Na$ ($[M+Na]^+$) 287.1618, found 287.1624. Anal. calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.44; H, 9.36.

4.26. Synthesis of 37

Compound **37** was prepared in 85% yield (chromatography on silica gel eluting with 8:1 *n*-hexane/EtOAc) from compound **36** using the same procedure described above for converting **29** into **31**. Data for **37** (a yellowish oil): FTIR (film) 1713, 1634, 1314, 1178 cm^{-1}; ^1H NMR δ 7.81 (d, J=16 Hz, 1H), 7.61 (d, J=7.2 Hz, 1H), 7.37–7.26 (m, 2H), 7.23 (d, J=7.1 Hz, 1H), 6.36 (d, J=16 Hz, 1H), 5.89 (ddt, J=17, 11, 5.3 Hz, 1H), 5.25 (br d, J=17 Hz, 1H), 5.16 (br d, J=11 Hz, 1H), 4.26 (q, J=7.2 Hz, 2H), 3.93 (d, J=5.6 Hz, 2H), 3.86 (s, 2H), 3.40 (t, J=6.2 Hz, 2H), 2.51 (t, J=7.0 Hz, 2H), 1.71–1.51 (m, 4H), 1.33 (t, J=7.2 Hz, 3H); EIMS *m/z* (%): 330 (M^+, 0.97), 273 ($M^+-Oallyl$), 141 (100). Anal. calcd for $C_{20}H_{26}O_4$: C, 72.73; H, 7.88. Found: C, 72.71; H, 8.02.

4.27. Synthesis of compound 42

A mixture of **37** (3.551 g, 10.76 mmol) and $PdCl_2$ (383 mg, 2.15 mmol) in MeOH (54 mL) was stirred at 60 °C until TLC showed the complete disappearance of **37**. The reaction mixture was filtered. The filtrate was concentrated on a rotary evaporator to give an orange oil (a mixture containing **38**, **39**, and **40**, 2.458 g). This crude oil was added to the mixture of UHP (6.9 g, 73.4 mmol) and *p*-TsOH (1.85 g, 9.74 mmol) in DME (110 mL). The mixture was stirred at the ambient temperature until TLC showed disappearance of the starting material. The mixture was partitioned between Et_2O and water. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (5:1 *n*-hexane/EtOAc) to give compound **41** as a colorless oil (2.314 g, 71% from **37**), which gave the following data: FTIR (film) 3361, 2943, 1712, 1691, 1632, 1316, 1186 cm^{-1}; ^1H NMR δ 8.23 (s, 1H), 8.20 (d, J=16 Hz, 1H), 7.58 (d, J=7.7 Hz, 1H), 7.40–7.24 (m, 3H), 6.34 (d, J=16 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 3.88–3.77 (m, 2H), 3.41 (d, J=14 Hz, 1H, part of AB system), 3.13 (d, J=14 Hz, 1H, part of AB system), 1.51–1.03 (m, 6H), 0.88 (t, J=7.1 Hz, 3H). The **41** was then transformed into **42** (a 1:1 mixture of diastereomers) in 51% total yield (chromatography on silica gel eluting with 15:1 *n*-hexane/EtOAc) using the same procedure described above for converting **11** into **13**. Data for **42** (a colorless oil): FTIR (film) 1736, 1445, 1372, 1216, 1180, 1045 cm^{-1}; ^1H NMR δ 7.28–7.07 (m, 4H), 5.93 (dd, J=4.9, 8.4 Hz, 0.5H), 5.88 (dd, J=4.2, 9.1 Hz, 0.5H), 4.29–4.20 (m, 2H, including a quartet at δ 4.17, J=7.1 Hz), 4.15–3.94 (m, 1H), 3.84–3.66 (m, 2H altogether, including a doublet at δ 3.86, J=14 Hz), 3.22 (dd, J=9.1, 16 Hz, 0.5H), 3.01 (dd, J=3.9, 16 Hz, 0.5H), 2.84 (dd, J=8.0, 16 Hz, 0.5H), 2.71 (dd, J=4.9, 16 Hz, 0.5H), 2.59 (d, J=14 Hz, 1H), 1.80–1.40 (m, 6H), 1.31 and 1.25 (two

triplets in 1:1 ratio, J=7.3 Hz, 3H altogether); ESIMS m/z 324 ([M+NH_4]$^+$). Anal. calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.89; H, 7.37.

4.28. Synthesis of 43

Using the same procedure described above for the synthesis of **35** (except that epichlorohydrin (3.2 g, 41.1 mmol) was utilized as the epoxide instead of **33**) an intermediate alcohol (5.058 g) was obtained from **34** (6.329 g, 27.4 mmol). The crude alcohol–chloride was added to a mixture of NaH (914 mg, 22.8 mmol) in THF (104 mL) stirred at 0 °C. The bath was allowed to warm to ambient temperature and the reaction was continued until TLC showed complete disappearance of the chloride (2.5 h). The reaction was quenched with water and the reaction mixture was diluted with Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (15:1 *n*-hexane/EtOAc) to give **43** (3.827 g, 67% from **34**). FTIR (film) 2929, 1452, 1212, 1150, 1100 cm^{-1}; ^{1}H NMR δ 6.99–6.95 (m, 1H), 6.90–6.85 (m, 3H), 4.29 (s, 2H), 4.24 (s, 2H), 3.01 (s, 2H), 2.81–2.76 (m, 1H), 2.61 (dd, J=5.5, 15 Hz, 1H), 2.53 (dd, J=5.4, 15 Hz, 1H), 2.39 (t, J=7.4 Hz, 1H), 2.15–2.13 (m, 1H); EIMS m/z (%) 163 ($M^+-CH_2OCH_3$, 14), 133 ($M^+-CH_2OCH_2OCH_3$, 6.7), 91 (Bn, 31), 45 (100); MALDI-HRMS calcd for $C_{12}H_{16}O_3Na$ ([M+Na]$^+$) 231.0992, found 231.0999. Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.17; H, 7.59.

4.29. Synthesis of 45

Compound **45** was prepared from epoxide **43** and **44** in 76% yield (chromatography on silica gel eluting with 6:1 *n*-hexane/EtOAc) using the same procedure described above for converting **33** into **35** (but with **43** and **44** replacing **33** and **34**, respectively). Data for **45** (a colorless oil): FTIR (film) 3447, 2929, 1452, 1149, 1041 cm^{-1}; ^{1}H NMR δ 7.38–7.21 (m, 8H), 5.93 (ddt, J=17, 11, 5.5 Hz, 1H), 5.31 (br d, J=17 Hz, 1H), 5.22 (br d, J=9.5 Hz, 1H), 4.67 (s, 2H), 4.63 (d, J=2.7 Hz, 1H), 4.55 (d, J=11 Hz, 1H, part of an AB system), 4.60 (d, J=11 Hz, 1H, part of an AB system), 4.06–4.00 (m, 3H altogether, including a doublet at δ 4.01, J=5.4 Hz), 3.40 (s, 3H), 3.05 (d, J=3.8 Hz, 1H), 2.95–2.86 (m, 4H); EIMS m/z (%) 293 (M^+-OCH_2OMe, 1), 119 (−COBn, 7), 104 (100), 91 (Bn, 23). Anal. calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.15; H, 7.85.

4.30. Removal of the MOM group in 45 (46)

Compound **46** was prepared from **45** in 99% yield (chromatography on silica gel eluting with 4:1 *n*-hexane/EtOAc) using the same procedure described above for converting **6** into **8**. Data for **46** (a colorless oil): FTIR (film) 3325, 2923, 1452, 1053 cm^{-1}; ^{1}H NMR δ 7.34–7.19 (m, 8H), 5.85 (ddt, J=17, 10, 6.0 Hz, 1H), 5.27 (br d, J=17 Hz, 1H), 5.22 (br d, J=11 Hz, 1H), 4.72 (d, J=12 Hz, 1H, part of an AB system), 4.55–4.46 (m, 2H), 4.40 (d, J=11 Hz, 1H, part of an AB system), 4.05–3.97 (m, 5H), 3.04–2.85 (m, 4H); EIMS m/z (%) 313 (M^++H, 0.3), 191 (6), 105 (61), 104 (100). Anal. calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.77; H, 8.10.

4.31. Synthesis of 47

Compound **47** was prepared from **46** in 77% yield (chromatography on silica gel eluting with 10:1 *n*-hexane/EtOAc) using the same procedure described above for converting **29** into **31**). Data for **47** (a red-orange oil): FTIR (film) 1711, 1634, 1314, 1178 cm^{-1}; ^{1}H NMR δ 7.79 (d, J=16 Hz, 1H), 7.61–7.58 (m, 1H), 7.34–7.25 (m, 5H), 7.18–7.11 (m, 2H), 6.35 (d, J=16 Hz, 1H), 5.89 (ddt, J=17, 11, 6.0 Hz, 1H), 5.26 (br d, J=18 Hz, 1H), 5.18 (br d, J=12 Hz, 1H), 4.41 (s, 2H), 4.26 (q, J=7.2 Hz, 2H), 3.93–3.86 (m, 6H), 1.34 (t, J=7.1 Hz, 3H); ESIMS m/z 378 ([M+Na]$^+$); ESIHRMS calcd for $C_{24}H_{26}O_4Na$ ([M+Na]$^+$) 401.1723, found 401.1719. Anal. calcd for $C_{24}H_{26}O_4$: C, 76.17; H, 6.92. Found: C, 75.97; H, 7.04.

4.32. Synthesis of 52

A mixture of **47** (2.51 g, 6.64 mmol), $PdCl_2$ (1.175 g, 6.64 mmol), and CuCl (657 mg, 6.64 mmol) in DMF–H_2O (50 mL/5 mL) was stirred at the ambient temperature in an open flask (because air was needed in the reaction) until TLC showed completion of the deallylation (ca.12 h). The solids were filtered off. The filtrate was concentrated on a rotary evaporator to give an orange liquid–solid mixture (2.3 g), which was directly added to a mixture of UHP (7.94 g, 84.4 mmol) and CSA (7.83 g, 33.8 mmol) in DME–EtOH (96 mL/22 mL). The resulting mixture was stirred at the ambient temperature until the starting material disappeared on TLC. The mixture was partitioned between Et_2O and water. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (8:1 *n*-hexane/EtOAc) to give compound **51** (775 mg, 33% from **47**), which gave the following data: ^{1}H NMR δ 8.70 (s, 1H), 8.20 (d, J=16 Hz, 1H), 7.58 (d, J=7.6 Hz, 1H), 7.41–7.27 (m, 3H), 7.14–7.03 (m, 3H), 6.89 (d, J=6.6 Hz, 1H), 6.34 (d, J=16 Hz, 1H), 5.00 (d, J=14 Hz, 1H, part of an AB system), 4.77 (d, J=15 Hz, 1H, part of an AB system), 4.27 (q, J=7.1 Hz, 2H), 3.64 (d, J=14 Hz, 1H, part of AB system), 3.24 (d, J=15 Hz, 1H, part of AB system), 2.88 (d, J=17 Hz, 1H, part of an AB system), 2.41 (d, J=17 Hz, 1H, part of an AB system), 1.33 (t, J=7.1 Hz, 3H). A solution of **51** (105 mg, 0.28 mmol) and $NHEt_2$ (35 μL) in CF_3CH_2OH–CH_2Cl_2 (1.2 mL/0.6 mL) was stirred at ambient temperature for 21 h. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (16:1 *n*-hexane/EtOAc) to give compound **52** as a colorless oil (46 mg, 24% from **51**). FTIR (film) 1735, 1449, 1372, 1249, 1160, 1027 cm^{-1}; ^{1}H NMR δ 7.31–7.04 (m, 8H), 5.94 (dd, J=4.0, 8.5 Hz, 1H), 5.01 (dd, J=9.1, 15 Hz, 1H), 4.77 (dd, J=12.3, 15 Hz, 1H), 4.25–4.13 (m, 2H, including a quartet at δ 4.21, J=6.9 Hz), 4.03 (d, J=14 Hz, 0.5H), 3.94 (br d, J=14 Hz, 0.5H), 3.22 (dd, J=9.2, 16 Hz, 0.5H), 3.02 (dd, J=4.2, 16 Hz, 1H), 2.95 (d, J=17 Hz, 0.5H), 2.87 (dd, J=8.3, 16 Hz, 0.5H), 2.75 (dd, J=4.2, 16 Hz, 1H), 2.64 (d, J=14 Hz, 1H), 2.48 (d, J=17 Hz, 0.5H), 1.28 and 1.25 (two triplets in 1:1 ratio,

J=7.2 Hz, 3H altogether); ESIMS m/z 372 ($[M+NH_4]^+$); ESIHRMS calcd for $C_{21}H_{22}O_5Na$ ($[M+Na]^+$) 377.1359, found 377.1346. Anal. calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.52; H, 6.54.

4.33. Synthesis of 55

n-BuLi (1.6 M, in hexanes, 6.67 mL, 10 mmol) was added dropwise to a solution of **54** (0.43 mL, 5.0 mmol) in dry THF (22 mL) stirred at −40 °C under N_2. The mixture was stirred at the temperature for 4 h before a soluiton of **53** (2.139 g, 8.15 mmol) in dry THF (2 mL) was introduced. The stirring was continued at 0 °C for another 43 h. The reaction was quenched by addition of water. The mixture was extracted with Et_2O, washed with water, and brine, and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed on silica gel (4:1 *n*-hexane/EtOAc) to give the alkylation product as a yellow-greenish liquid (453 mg, 42% yield). A solution of this compound (300 mg, 1.38 mmol) and *m*-CPBA (261 mg, 1.53 mmol) in CH_2Cl_2 (7 mL) was stirred at the ambient temperature for 3 h. The mixture was partitioned between aqueous Na_2CO_3 and Et_2O. The ethereal layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography of the residue on silica gel (5:1 *n*-hexane/EtOAc) gave the furan ring opened product as a yellowish liquid (306 mg, 95% yield). A solution of this liquid (200 mg, 0.86 mmol) and 10% Pd–C (23 mg) in MeOH (5 mL) was stirred under H_2 (1 atm) for 7 h. The catalyst and the solvent were removed by filtration and rotary evaporation, respectively. The residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give **55** as a yellowish oil (81 mg. 40% yield). FTIR (film) 3426, 2924, 1711, 1406 cm^{-1}; ^1H NMR δ 7.32–7.16 (m, 5H), 4.34 (d, J=5.0 Hz, 2H), 3.00 (t, J=4.8 Hz, 1H), 2.80–2.76 (m, 2H), 2.64–2.59 (m, 4H), 2.47 (t, J=7.3 Hz, 2H), 1.97–1.87 (m, 2H); ESIMS m/z 235 ($[M+H]^+$); ESIHRMS calcd for $C_{14}H_{18}O_3Na$ ($[M+Na]^+$) 257.1148, found 257.1148.

4.34. Wittig reaction of 55 (56 and 57)

A solution of **55** (144 mg, 0.61 mmol) in Ac_2O (2 mL) and NEt_3 (0.3 mL) was stirred at the ambient temperature for 5 h. Aqueous saturated Na_2CO_3 was carefully added. The mixture was extracted with Et_2O thrice. The combined ethereal phases were washed with aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4. Removal of the solvent left a yellowish oil (170 mg, ca. 0.6 mmol), which was dissolved in dry THF (0.5 mL) and added to a mixture of $(EtO)_2(O)PCHCO_2Et$ (167 mg, 0.72 mmol) and NaH (33 mg, 0.72 mmol, washed with dry THF three times) in THF (0.5 mL) stirred at 0 °C. After completion of the addition, the mixture was stirred at the ambient temperature for 7 h. The reaction was quenched by addition of water and the mixture was extracted with Et_2O thrice. The combined ethereal phases were washed with aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4. Removal of the solvent left a yellowish oil (245 mg), which was dissolved in EtOH (4 mL) and 2 N HCl (0.5 mL). After stirring at the ambient temperature for 2 d, the mixture was extracted with Et_2O thrice. The combined ethereal phases were washed with aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give **56** (34 mg, 18% yield) and **57** (86 mg, 54% yield). Data for compound **56** (a colorless oil): FTIR (film) 3469, 2929, 1709, 1178 cm^{-1}; ^1H NMR δ 7.31–7.15 (m, 5H), 5.95 (s, 1H), 4.15 (q, J=7.1 Hz, 2H), 4.17 (d, J=14.0 Hz, 2H), 2.75–2.65 (m, 4H), 2.61 (t, J=7.5 Hz, 2H), 2.43 (t, J=7.2 Hz, 2H), 2.34 (t, J=6.1 Hz, 1H), 1.95–1.85 (m, 2H), 1.27 (t, J=7.0 Hz, 3H); ESIMS m/z 305 ($[M+H]^+$); ESIHRMS calcd for $C_{18}H_{24}O_4Na$ ($[M+Na]^+$) 327.1567, found 327.1568. Data for compound **57** (a white solid): mp 69–71 °C. FTIR 1789, 1748, 1638, 1496, 1176 cm^{-1}; ^1H NMR δ 7.33–7.16 (m, 5H), 5.78 (s, 1H), 4.75 (s, 2H), 2.75–2.62 (m, 6H), 2.47 (t, J=7.4 Hz, 2H), 2.00–1.90 (m, 2H); ESIMS m/z 259 ($[M+H]^+$); ESIHRMS calcd for $C_{16}H_{19}O_3Na$ ($[M+H]^+$) 259.1329, found 259.1327.

4.35. Hydroperoxidation of 56 and attempted cyclization (59)

A solution of **56** (26 mg, 0.085 mmol), *p*-TsOH (10 mg, 0.52 mmol), and UHP (30 mg, 0.32 mmol) in DME (1 mL) was stirred at the ambient temperature for 24 h. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give **58** as a colorless oil (12 mg, 44% yield), on which the following data were recorded: FTIR (film) 3480, 1747, 1714, 1200 cm^{-1}; ^1H NMR δ 7.65 (s, 1H), 7.30–7.18 (m, 5H), 5.70 (s, 1H), 4.46 (d, J=14 Hz, 1H, part of an AB system), 4.15 (q, J=7.2 Hz, 2H), 3.99 (d, J=14 Hz, 1H, part of an AB system), 3.12–3.05 (m, 1H), 2.84–2.76 (m, 1H), 2.64 (t, J=7.1 Hz, 2H), 2.05–1.63 (m, 6H), 1.25 (t, J=7.2 Hz, 3H). The **58** (12 mg, 0.037 mmol) was dissolved in CF_3CH_2OH (1 mL) and $HNEt_2$ (10 μL). The mixture was stirred at the ambient temperature for 10 h. The solvent was removed by rotary evaporation and the residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give **59** as a colorless oil (7 mg, 58% yield). FTIR (film) 3485, 1750, 1713, 1498, 1456, 1282, 1012, 896, 753, 699 cm^{-1}; ^1H NMR δ 7.32–7.15 (m, 5H), 4.28 (q, J=7.1 Hz, 2H), 3.74 (dd, J=13, 5.2 Hz, 1H), 3.63 (s, 1H), 3.61 (dd, J=13, 8.3 Hz, 1H), 2.65–2.55 (m, 4H), 2.44 (t, J=7.3 Hz, 2H), 2.21–2.16 (m, 1H), 2.04–1.86 (m, 4H), 1.30 (t, J=7.2 Hz, 3H); EIMS m/z (%) 292 ($M^+-CH_2{=}CH_2$, 5), 277 ($M^+-C_2H_4CH_3$, 11), 57 (100); MALDI-HRMS calcd for $C_{18}H_{24}O_5Na$ ($[M+Na]^+$) 343.1516, found 343.1523.

4.36. Antimalarial activities of peroxides in vitro

4.36.1. Malaria parasites. *P. falciparum* (ATCC 30932, FCR-3 strain) was used. *P. falciparum* was cultivated by a modification of the method of Trager and Jensen[17] using a 5% hematocrit of type A human red blood cells suspended in RPMI 1640 medium (Gibco, NY) supplemented with heat-inactivated 10% type A human serum. The plates were placed in a CO_2–O_2–N_2 incubator (5% CO_2, 5% O_2, and 90% N_2 atmosphere) at 37 °C, and the medium was changed daily until 5% parasitemia (which means that 5 parasite-infected erythrocytes in every 100 erythrocytes were existing).

4.36.2. Mammalian cells. Mouse mammary tumor FM3A cells (wild-type, subclone F28-7) 16 were supplied by the

Japanese Cancer Research Resources Bank (JCRB). FM3A cells were maintained in suspension culture at 37 °C in a 5% CO_2 atmosphere in plastic bottles containing ES medium (Nissui Pharmaceuticals, Tokyo, Japan) supplemented with 2% heat-inactivated fetal bovine serum (Gibco, NY).

4.36.3. In vitro antimalarial activity of peroxides. The following procedures were used for assay of antimalarial activity.[18,19] Asynchronously cultivated *P. falciparum* were used. Various concentrations of compounds in dimethylsulfoxide were prepared. Five microliters of each solution was added to individual wells of a multidish 24 wells. Erythrocytes with 0.3% parasitemia were added to each well containing 995 μL of culture medium to give a final hematocrit level of 3%. The plates were incubated at 37 °C for 72 h in a CO_2–O_2–N_2 incubator (5% CO_2, 5% O_2, and 90% N_2 atmosphere). To evaluate the antimalarial activity of test compound, we prepared thin blood films from each culture and stained them with Giemsa (E. Merck, Germany). Total 1×104 erythrocytes per one thin blood film were examined under microscopy. All of the test compounds were assayed in duplicate at each concentration. Drug-free control cultures were run simultaneously. All data points represent the mean of three experiments. Parasitemia in control was reaching between 4 and 5% at 72 h. The EC_{50} value refers to the concentration of the compound necessary to inhibit the increase in parasite density at 72 h by 50% of control.

4.36.4. Toxicity against mammalian cell line. FM3A cells grew with a doubling time of about 12 h. Prior to exposure to drugs, cell density was adjusted to 5×104 cells/mL. A cell suspension of 995 μL was dispensed to the test plate, and compound at various concentrations suspended in dimethylsulfoxide (5 μL), were added to individual wells of a multidish 24 wells. The plates were incubated at 37 °C in a 5% CO_2 atmosphere for 48 h. All of the test compounds were assayed in duplicate at each concentration. Cell numbers were measured using a microcell counter CC-130 (Toa Medical Electric Co., Japan). All data points represent the mean of three experiments. The EC_{50} value refers to the concentration of the compound necessary to inhibit the increase in cell density at 48 h by 50% of control. Selectivity refers to the mean of EC_{50} value for FM3A cells per the mean of EC_{50} value for *P. falciparum*.

Acknowledgements

This work was supported in China by the National Natural Science Foundation of China (20025207, 20272071, 20372075, 20321202), the Chinese Academy of Sciences ('Knowledge Innovation' project, KGCX2-SW-209), and the Major State Basic Research Development Program (G2000077502). In Japan, this work was supported in part by a Grant-in-Aid for Scientific Research (B) (16390031) from Japan Society for the Promotion of Sciences (JSPS) and by a Grant-in-Aid for Scientific Researches on Priority Areas from the Ministry of Education, Science, Culture, and Sports of Japan (14021072, 16017266).

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Synthesis of (*E*)-alkenes via hydroindation of C≡C in $InCl_3$–$NaBH_4$ system

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Received 9 April 2006; revised 25 May 2006; accepted 26 May 2006
Available online 16 June 2006

Abstract—In $InCl_3$–$NaBH_4$–MeCN system, terminal aryl alkynes could couple with aryl iodides and bromides to give disubstituted alkenes via hydroindation of C≡C. In the similar way, (*E*)-alkenylsilanes were synthesized via reduction of alkynylsilanes in tetrahydrofuran (THF) in high yields. The processes showed high regio- and stereoselectivity.

1. Introduction

During the past few decades, hydroboration and hydroalumination have proven reliable ways to reduce carbon–carbon multiple bonds to give alkenylmetals formed via hydrometalations of C≡C, which can then be utilized in various reactions.[1] But in these reactions expensive catalyst or high temperature is usually required. Although in the same group with boron and aluminum in the periodic table, the study of hydroindation is still limited compared to hydroboration and hydroalumination. However, since dichloroindium hydride (Cl_2InH) was generated firstly via combination of Indium(III) chloride and tributyltin hydride system,[2] Cl_2InH generated in situ has been applied to many organic reactions.[3–13] Especially, because of excellent properties, such as easy handling, mild conditions, and low toxicity, $InCl_3$–$NaBH_4$ system has attracted much interest.[3–7]

In the presence of a catalytic amount of triethylborane as a radical initiator, hydroindation of terminal alkynes with Cl_2InH generated in situ by a combination of $InCl_3$ and DIBAL-H gives (*Z*)-alkenylindiums, which couple with aryl iodides to form (*Z*)-alkenes smoothly.[12] However, up to now, coupling reaction of alkenylindium with halides to give (*E*)-alkenes in $InCl_3$–$NaBH_4$ system has not been reported.

In addition, it has been reported that alkynylsilanes were reduced via hydroboration and hydroalumination to form alkenylsilanes, which are important intermediates in organic synthesis.[13–15] But little attention was paid to hydroindation of alkynylsilanes. Recently, we have reported some facile hydroindations of alkyne in $InCl_3$–$NaBH_4$–MeCN system.[6,7] The good results stimulated us to further explore the reactivity of this system. We herein present a convenient and efficient method to synthesize (*E*)-alkenes under mild conditions via reduction of alkynylsilanes or coupling reactions of terminal alkynes with aryl iodides or bromides in an $InCl_3$–$NaBH_4$ system.

2. Results and discussion

2.1. Synthesis of (*E*)-alkenes via coupling reaction of terminal alkynes with aryl halides in $InCl_3$–$NaBH_4$–MeCN system

Initially, anhydrous $InCl_3$, $NaBH_4$, MeCN, phenyl acetylene, and iodobenzene were added in sequence in one-pot at −15 °C under nitrogen atmosphere. After the reaction was stirred overnight at room temperature, it was found that the only coupling product (*E*)-stilbene (**2a**) was obtained smoothly in 78% yield without **3a** and **4a** as byproducts (**2a**:**3a**:**4a**=100:0:0), showing high regio- and stereoselectivity. The product was determined by ^{1}H NMR (500 MHz) and MS. The *E* or *Z* stereochemistry in the double bond C=C of products was assigned on the basis of the value of ^{1}H NMR coupling constants between the olefinic protons and comparison of their ^{1}H NMR spectra with those previously reported.

Under the above reaction conditions, a variety of cross-coupling reactions of the different terminal alkynes and halides were examined. It was found that all the terminal aryl alkynes could couple with aryl iodides or bromides

Keywords: Hydroindation; Alkynes; (*E*)-Alkenes; (*E*)-Alkenylsilanes; $InCl_3$–$NaBH_4$ system.
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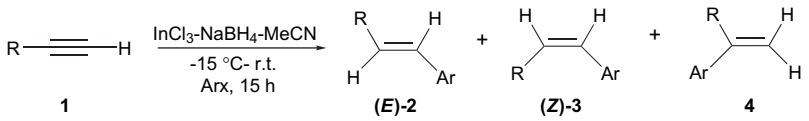
doi:10.1016/j.tet.2006.05.066

Table 1. The coupling reactions of terminal alkynes and halides in $InCl_3$–$NaBH_4$–MeCN system



Entry	R	Halides	**2**:**3**:**4**[a]	Yield (**2**+**3**%)[b]	Ref.
a	Ph	PhI	100:0:0	78	16
b	*p*-CH_3Ph	PhI	91:9:0	80	16
c	*p*-BrPh	PhI	95:5:0	72	16
d	*p*-CH_3OPh	PhI	94:6:0	73	16
e	*n*-Bu	PhI	—	—	—
f	$C_6H_{13}OCH_2$	PhI	—	—	—
g	Ph	*p*-ClC_6H_4I	95:5:0	77	17
h	*p*-CH_3Ph	*p*-ClC_6H_4I	91:9:0	74	18
i	*p*-BrPh	*p*-ClC_6H_4I	88:12:0	56	18
j	*p*-CH_3OPh	*p*-ClC_6H_4I	90:10:0	61	17
k	*n*-Bu	*p*-ClC_6H_4I	—	—	
l	$C_6H_{13}OCH_2$	*p*-ClC_6H_4I	—	—	
m	Ph	PhBr	92:8:0	72	16
n	*p*-CH_3Ph	PhBr	92:8:0	67	16
o	*p*-BrPh	PhBr	93:7:0	58	16
p	*p*-CH_3OPh	PhBr	88:12:0	62	16
q	*n*-Bu	PhBr	—	—	—
r	$C_6H_{13}OCH_2$	PhBr	—	—	—
s	Ph	PhCl	—	—	—
t	1-Cyclohexen-1-yl	PhI	92:8:0	68	6

[a] Determined by ^{1}H NMR.
[b] Isolated by terminal alkynes.

well. The regio-, stereoselectivity, and the yield were satisfactory. In all the reactions, no compound **4** was detected. On the other hand, aryl chloride failed to couple with aryl alkenylindium in $InCl_3$–$NaBH_4$–MeCN system (Table 1, entry **s**). We also attempted to apply this reaction to aliphatic alkynes and aliphatic bromides. But the results showed that no coupling product was obtained (Table 1, entries **e**–**f**, **k**–**l**, and **q**–**r**). It was interesting that the desired coupling product was obtained when (1-cyclohexen-1-yl) ethyne was used as the aliphatic terminal alkyne. It was considered that the conjugated structure in the compound (1-cyclohexen-1-yl)-ethyne stabilized the intermediate. All the results were summarized in Table 1.

2.2. Synthesis of (*E*)-alkenylsilanes via hydroindation of alkynylsilanes in $InCl_3$–$NaBH_4$–THF system

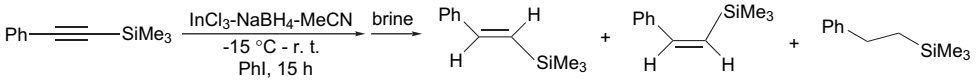
Considerable efforts have been devoted to develop the novel methods of forming vinylsilanes due to their versatile role as intermediates in organic synthesis.[19] Presently, there are no reports of vinylsilane synthesis via hydroindation of alkynylsilanes. So under the same conditions, the coupling of 2-phenylalkynylsilane and iodobenzene was also tested in the $InCl_3$–$NaBH_4$–MeCN system. Unexpectedly, the reaction worked poorly in this system, which was proved to be more excellent than others in many reactions. Only 2-phenylvinylsilanes (**6a**+**7a**) were obtained in only 2.5% conversion by GC–MS analysis even after stirring for 20 h. In order to improve the conversion, the reaction conditions were optimized involving solvent and the amount of $NaBH_4$. At first, various solvents instead of MeCN were tested under the conditions of entry 1 (Table 2). Attempts using solvents such as ethyl ether, CH_2Cl_2, toluene, and acetone all failed in which only a trace amount of the expected products were obtained (Table 2, entries 2–5). Interestingly, THF was found to be the best solvent in which the starting material could be consumed completely after carrying out this reaction for 3 h. But a large amount of over-reduced product (**8a**) was obtained (Table 2, entry 6). Thus, the ratio of $NaBH_4$ and phenylalkynylsilane was decreased to 1:1, and that led to high selectivity (**6a**/**7a**/**8a**=90:5:5) with 92% total yield (Table 2, entry 7). The products were determined by ^{1}H NMR and GC–MS. All the results were summarized in Table 2.

A variety of alkynylsilanes were examined (1 mmol) under the optimized reaction conditions [$InCl_3$ (1 mmol), $NaBH_4$ (1 mmol), THF (5 mL), −15 °C to rt, 2–4 h] (Table 2, entry 7; Scheme 2). It was found that all the arylalkynylsilanes could react well. Both stereoselectivities and yields were satisfactory. When the hydrogen atom, at the *para* position of benzene ring, was substituted by a methyl group (Table 3, entry **b**), the stereoselectivity decreased slightly, and more starting material was over-reduced than phenylalkynylsilane (Table 3, entry **a**). In contrast, the stereoselectivity and the yield were rather high when this hydrogen atom was substituted by an electron-withdrawing group such as F, Cl, and Br (Table 3, entries **c**–**e**). When R was C_4H_9 or C_5H_{11}, a mixture was obtained. About half of the starting material was over-reduced to **8f** or **8g** by GC–MS (Table 3, entries **f**–**g**). Diastereoisomeric excess (*E*/*Z*) determined by ^{1}H NMR was 3:1. Reduction of aliphatic alkynylsilanes to vinylsilanes is mostly difficult to control. All the results are summarized in Table 3.

2.3. Synthesis of (*E*)-2-phenylvinylphosphonate via hydroindation of phenylalkynylphosphonate in $InCl_3$–$NaBH_4$–MeCN system

Vinylphosphonates have been widely used as synthetic intermediates in organic chemistry[20] and investigated as biologically active compounds.[21] Recently, our group has afforded

Table 2. Study of the system in reduction of phenylalkynylsilane[a]

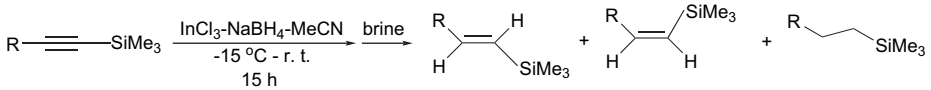


5a **(*E*)-6a** **(*Z*)-7a** **8a**

Entry	Solvent	**6a**:**7a**:**8a**[b,c]	Yield (**6a**+**7a**%)[b]
1	MeCN	—	2.5
2	Ethyl ether	—	—
3	CH_2Cl_2	—	Trace
4	Toluene	—	Trace
5	Acetone	—	Trace
6[d]	THF	56:7:37	61
7[e]	THF	90:5:5	92

[a] $InCl_3/NaBH_4$/phenylalkynylsilane = 1:2:1 and 20 h except that pointed out especially.
[b] Determined by GC–MS.
[c] Determined by ^1H NMR.
[d] 3 h.
[e] $InCl_3/NaBH_4$/phenylalkynylsilane = 1:1:1, 4 h.

Table 3. Synthesis of vinylsilanes in $InCl_3$–$NaBH_4$–THF system[a]



5 **(*E*)-6** **(*Z*)-7** **8**

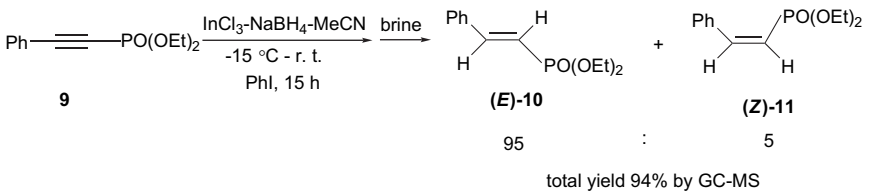
Entry	R	**6**:**7**:**8**[b,c]	Total Yield (**6**+**7**%)[b]
a	Ph	90:5:5	92
b	*p*-CH_3Ph	70:5:25	70
c	*p*-FPh	88:5:7	88
d	*p*-BrPh	95:2:3	94
e	*p*-ClPh	90:4:6	93
f	*n*-C_4H_9	3:1:4	Mixture
g	*n*-C_5H_{11}	3:1:3	Mixture

[a] Reaction conditions: $InCl_3$ (1 mmol), $NaBH_4$ (1 mmol), THF (5 mL), −15 °C to rt, 2∼4 h.
[b] Determined by GC–MS.
[c] Determined by ^1H NMR.

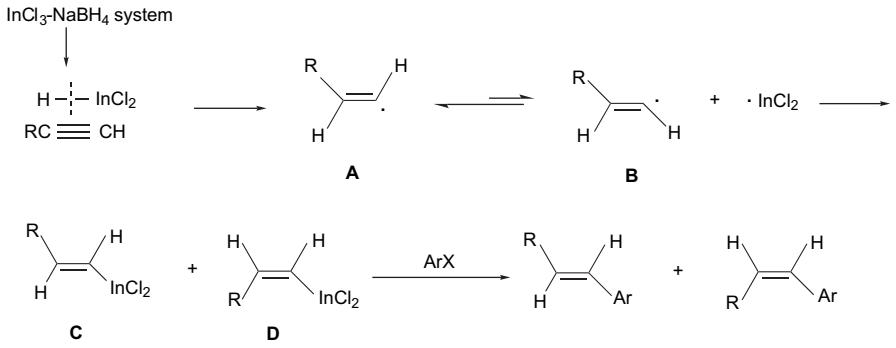
a convenient and efficient method to synthesize vinylphosphonates via hydroindation of 2-arylalkynylphosphonates in $InCl_3$–$NaBH_4$–MeCN system.[7] In the same way, the coupling reaction of phenylalkynylphosphonate and iodobenzene was tested. Only 2-phenylvinylphosphonates (**10**:**11**=95:5) were obtained in 94% yield without any desired coupling products (Scheme 1).

2.4. Proposed mechanism

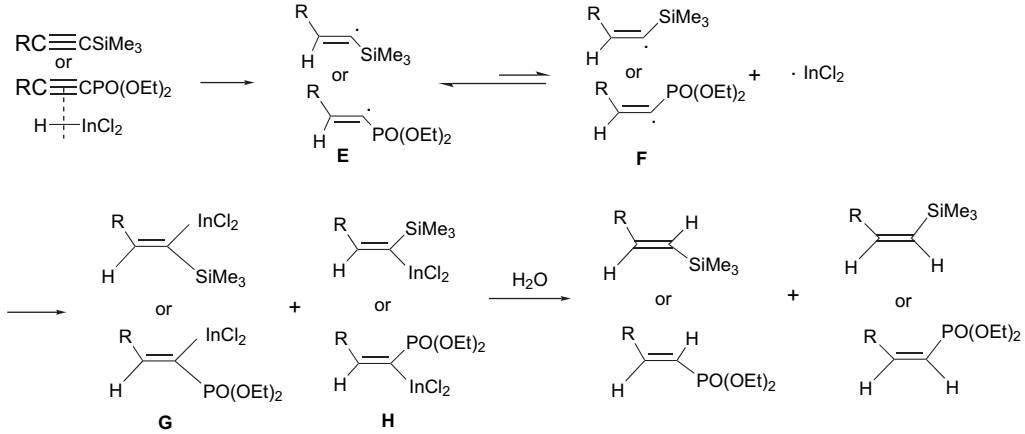
In accordance with previous reports, a similar mechanism is presently proposed (Schemes 2 and 3).[17,18] During the reaction *E*-configuration of the alkenyl radical (**A** or **E**) is more stable than *Z*-configuration (**B** or **F**). So hydroindation of alkynes gave (*E*)-alkenylindiums as major intermediate and (*Z*)-alkenylindiums as minor intermediate. At last, alkenylindiums (**C** and **D**) coupled with aryl iodides or bromides afforded alkenes. It was supposed that chlorobenzene was not active enough to couple with alkenylindiums. For alkynylphosphonates and alkynylsilanes, the intermediate **G** or **H** could not couple with iodobenzene to give the corresponding products because of steric hindrance. In our experiments, alkynylsilanes could be over-reduced. But in similar reaction system only alkenylphosphonates were obtained without any over-reduced products detected by GC–MS. The reasons have not been clarified. It may be explained that aliphatic alkenyl intermediates are not stable enough to couple with aryl halides in our experiments.



Scheme 1. Synthesis of (*E*)-2-phenylvinylphosphonate via hydroindation of phenylalkynylphosphonate in $InCl_3$–$NaBH_4$–MeCN system.



Scheme 2. Proposed mechanism of the coupling reaction of terminal alkynes with aryl halides in $InCl_3$–$NaBH_4$ system.



Scheme 3. Proposed mechanism of reduction of alkynylsilanes in $InCl_3$–$NaBH_4$ system.

3. Conclusion

$InCl_3$–$NaBH_4$ system was applied to the coupling reactions of the terminal aryl alkynes with aryl iodides or bromides in one-pot successfully. But in this system alkynylphosphonates and alkynylsilanes were only reduced to alkenylindiums, which could not couple with iodobenzene to synthesize trisubstituted alkenes. Moreover, it was found that $InCl_3$–$NaBH_4$–THF system is more active than $InCl_3$–$NaBH_4$–MeCN system in reduction of alkynylsilanes. Finally, many alkenylphosphonates and alkenylsilanes were obtained by hydrolyzation of alkenylindiums. An effective and simple approach to (*E*)-alkenes from alkynes was developed in the absence of expensive catalyst under the mild conditions.

4. Experimental

4.1. General

All the terminal alkynes and halides were purchased from J&K chemical Co., or other commercial suppliers and were used after appropriate purification (distillation). Alkynylsilane[22] and alkynylphosphonates[23] were prepared according to the literature. Acetonitrile was freshly distilled from phosphorus pentoxide before use. The ^1H NMR spectra were obtained with a Bruker AVANCE DRX-500 NMR spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. GC–MS data were recorded by TRACE 2000 GC/MS (USA TRACE Company). Precoated thin-layer plates of silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co. Ltd, Qingdao, China) were used for analytical purposed. The reactions were carried out in pre-dried (150 °C, 4 h) glassware under the atmosphere of dry nitrogen. All solvents and reagent were dried, deoxygenated, and redistilled before use.

4.2. General procedure for the cross-coupling reactions of terminal alkynes and halides in $InCl_3$–$NaBH_4$–MeCN system

After a mixture of $InCl_3$ (2.0 mmol) in dry MeCN (10 mL) and $NaBH_4$ (10 mmol) was stirred for 30 min at −15 °C under nitrogen, terminal alkyne (2 mmol) and aryl iodide or bromide (2 mmol) were added in sequence by syringe. The cooling bath was removed. The reaction mixture was warmed to room temperature, and stirred overnight. Saturated NH_4Cl solution (5 mL) was added to the reaction mixture to destroy excessive $NaBH_4$. The reaction mixture was stirred for another 10 min and then filtered. The filtrate was extracted with ether (20 mL×3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuum. Purification by silica gel column (petroleum ether bp 60–90 °C as eluent) could afford the corresponding products, which were identified by ^1H NMR and MS.

4.2.1. 1-[(*E*)-2-Phenylethenyl]benzene (2a). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.12 (2H, s), 7.25–7.28 (2H, m), 7.36 (4H, t, J=7.5 Hz), 7.52 (4H, d, J=7.5 Hz); MS, m/z 180 (M^+).

4.2.2. 1-Methyl-4-[(*E*)-2-phenylethenyl]benzene (2b). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.29 (3H, s), 7.00–7.45 (11H, m); MS, *m*/*z* 194 (M^+).

4.2.3. 1-Bromo-4-[(*E*)-2-phenylethenyl]benzene (2c). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.07–7.52 (11H, m); MS, *m*/*z* 258 (M^+).

4.2.4. 1-Methoxyl-4-[(*E*)-2-phenylethenyl]benzene (2d). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.90–7.48 (11H, m), 3.86 (3H, s); MS, *m*/*z* 210 (M^+).

4.2.5. 1-Chloro-4-[(*E*)-2-phenylethenyl]benzene (2g). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.06–7.51 (11H, m); MS, *m*/*z* 214 (M^+).

4.2.6. 1-[(*E*)-2-(4-Chlorophenyl)ethenyl]-4-methylbenzene (2h). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.96–7.48 (10H, m), 2.36 (3H, s); MS, *m*/*z* 228 (M^+).

4.2.7. 1-[(*E*)-2-(4-Chlorophenyl)ethenyl]-4-bromobenzene (2i). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.00–7.51 (10H, m); MS, *m*/*z* 292 (M^+).

4.2.8. 1-[(*E*)-2-(4-Chlorophenyl)ethenyl]-4-methoxylbenzene (2j). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.90–7.48 (10H, m), 3.84 (3H, s); MS, *m*/*z* 244 (M^+).

4.2.9. 1-[(*E*)-2-Phenylethenyl]cyclohexene (2t). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.65–2.26 (8H, m), 5.69 (1H, t, *J*=4.5 Hz), 6.43 (1H, d, *J*=16.5 Hz), 6.74 (1H, d, *J*=16.5 Hz), 7.13–7.31 (5H, m); MS, *m*/*z* 184 (M^+).

4.3. General procedure for the synthesis of (*E*)-vinylsilanes in $InCl_3$–$NaBH_4$ system

$InCl_3$ (1 mmol), dry solvent (5 mL), and $NaBH_4$ (1 mmol) were mixed at −15 °C under nitrogen. After the mixture was stirred for 30 min, alkynylsilanes (1 mmol) were added by syringe. The cooling bath was removed. The reaction mixture was warmed to room temperature, stirred for 2–4 h. Completion of the reaction was monitored by TLC. In order to destroy the excessive $NaBH_4$ saturated NH_4Cl solution (5 mL) was added to the reaction mixture. The reaction mixture was stirred for another 10 min and filtered. The filtrate was extracted with ethyl ether (10 mL×3). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuum. Purification by silica gel column chromatography (200–300 mesh), using petroleum ether (60–90 °C) as eluent could afford the corresponding products, which were identified by ^{1}H NMR and MS.

4.3.1. (*E*)-2-(Phenylethenyl)trimethylsilane (6a). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.18–7.43 (5H, m), 6.87 (1H, d, *J*=19.5 Hz), 6.48 (1H, d, *J*=19.5 Hz), 0.15 (9H, s); MS, *m*/*z* 176 (M^+).

4.3.2. (*E*)-2-(4-Methylphenylethenyl)trimethylsilane (6b). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.07–7.34 (4H, m), 6.81 (1H, d, *J*=19.2 Hz), 6.34 (1H, d, *J*=19.2 Hz), 2.59 (3H, s), 0.15 (9H, s); MS, *m*/*z* 190 (M^+).

4.3.3. (*E*)-2-(4-Fluorophenylethenyl)trimethylsilane (6c). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.00–7.39 (4H, m), 6.80 (1H, d, *J*=19.5 Hz), 6.35 (1H, d, *J*=19.5 Hz), 0.14 (9H, s); MS, *m*/*z* 194 (M^+).

4.3.4. (*E*)-2-(4-Chlorophenylethenyl)trimethylsilane (6d). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.10–7.34 (4H, m), 6.78 (1H, d, *J*=19.7 Hz), 6.42 (1H, d, *J*=19.7 Hz), 0.14 (9H, s); MS, *m*/*z* 210 (M^+).

4.3.5. (*E*)-2-(4-Bromophenylethenyl)trimethylsilane (6e). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.05–7.46 (4H, m), 6.78 (1H, d, *J*=19.3 Hz), 6.42 (1H, d, *J*=19.3 Hz), 0.14 (9H, s); MS, *m*/*z* 254 (M^+).

Acknowledgements

The generous financial support of Natural Science Foundation of China (20375036) is gratefully acknowledged.

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Tetrahedron 62 (2006) 7718–7725
Tetrahedron

A novel series of oligomers from 4-aminomethyl-tetrahydrofuran-2-carboxylates with 2,4-*cis* and 2,4-*trans* stereochemistry

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Received 22 March 2006; revised 9 May 2006; accepted 25 May 2006
Available online 16 June 2006

Abstract—Two tetrahydrofuran-based γ-amino acids [2,4-*cis* and 2,4-*trans*] were subjected to iterative peptide-coupling procedures to afford dimeric, tetrameric and hexameric carbopeptoids in good yield. These homooligomers were prepared for secondary structural study—to ascertain the conformational preference inherent in the monomer units. The L-*xylo* oligomers were protected with triethylsilyl ethers to increase the range of solvents suitable for structural investigation. Initial secondary structure data indicate the presence of hydrogen-bonded conformations in the L-*ribo* series.

1. Introduction

Peptides and proteins are coded by sequences of α-amino acids but efforts to decipher this complexity has only been partially successful.[1] Peptides are key to the development of new drugs however the low oral bioavailability of peptides has been a long-standing issue.[2,3] Initial synthetic efforts to circumvent this issue focused on the chemical modification of peptide libraries; more recent synthetic endeavours have led to an ever-expanding catalogue of peptidomimetics. Numerous β-amino acids, homologues of α-amino acids have been prepared and their oligomers extensively studied. These have been found to be stable to proteolytic enzymes and adopt an array of secondary structures akin to those observed in α-peptides (see Fig. 1a).[4–10] This concept has been expanded to include γ- and δ-amino acids; δ-amino acids may be regarded as dipeptide isosteres.[11,12] γ-Amino acids are found in nature, e.g., γ-aminobutyric acid (GABA) is an inhibitory neurotransmitter and tubulysins are potent antimitotic agents.[13,14]

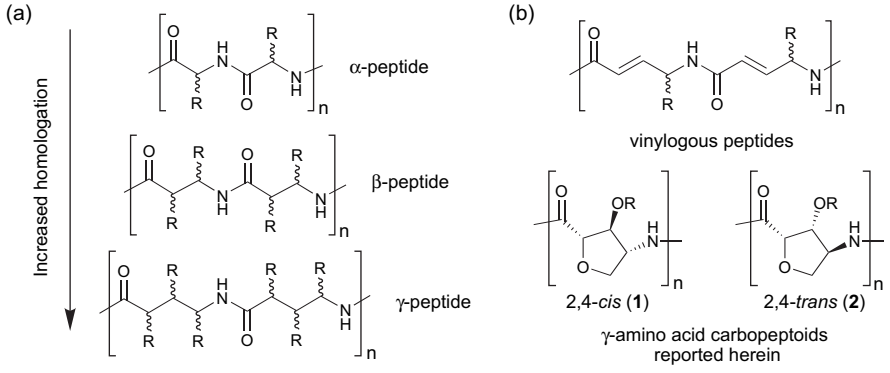

Figure 1. (a) From α-peptides to γ-peptides and (b) examples of γ-peptides.

Keywords: Sugar amino acids; Peptidomimetics; Gamma amino acids; Foldamers.
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0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.05.067

Acyclic γ-amino acids of vinylogous systems and their corresponding saturated analogues, have been prepared employing various side chains and substitution patterns to achieve structural diversity.[15–18,10,11] In addition to the adoption of an array of peptide-like secondary structures and resistance to proteolytic degradation,[19–21,9,10] a γ-dipeptide was found to exhibit affinity for human somatostatin receptors.[22] Oligomers of ureas, carbamates, phosphodiesters and vinylogous sulfonamidopeptides have also been prepared as γ-peptide analogues.[23] The first cyclically constrained γ-amino acids were prepared as GABA analogues and based upon a cyclopentane scaffold; the enantiomer was employed by Woll et al. to prepare a parallel sheet secondary structure.[24,25] Furanose-based and sugar-fused GABA analogues have since been prepared.[24,26] More recent synthetic efforts have included cyclic scaffolds, which are (poly)hydroxylated cyclohexanes,[27,28] contain a lactam[29] or are based on proline, cyclopropane or bicylic scaffolds.[30–32]

Sugar scaffolds with amine and carboxylic acid moieties, aka sugar amino acids (SAAs), have been used to create cyclically constrained α-, β-, γ-, δ- and ε-amino acids.[33–36] SAAs have been employed as peptidomimetics[37–39] and library scaffolds and their oligomers (carbopeptoids) examined as foldamers, which can adopt an array of secondary structures such as helices and β-turns.[40–43] Kessler et al. have reported a pyranose-based γ-SAA, which predetermines a β-turn conformation in synthetic peptides[36] and a heterooligomer composed of a furanose γ-SAA and GABA, with no stable conformation in solution.[44] Furanose- and pyranose-based γ-SAAs have been utilised to prepare 99-member and 384-member libraries, respectively.[45,46]

Recently, our group has reported the synthesis of two new furanose γ-SAA scaffolds,[47–49] herein we report the preparation of the oligomers of β-hydroxy γ-azido esters (see Fig. 1b). The dimer arising from the 2,4-*cis*-SAA (**3**) was shown to adopt a γ-turn type conformation in solid phase. γ-Turns in α-peptides require three residues and are stabilised by a hydrogen bond from CO^{i} to NH^{i+2};[50,51] they exist as two possible enantiomers with respect to the main chain structure, the inverse turn being more common than the classic turn. Studies of existing protein data[52] and prediction attempts[53,54] have been conducted in an attempt to understand the features that govern such turns. Mimics of γ-turns have been prepared[55–60] and analogues of bradykinin,[61] the peptide hormone vasopressin[62] and angiotensin receptor ligands[63] based on γ-turn mimics. Several different strategies have been reported in the attempt to prepare γ-turns.[64,65]

2. Results and discussion

2.1. Strategy

γ-Azido esters **1** and **2** have been prepared as part of the ongoing search for peptidomimetics with secondary structural preferences.[49,47] To investigate the conformational preferences of the γ-azido esters, they require to be coupled to form homooligomers. These homooligomers can be studied using solution- and solid-phase techniques to ascertain whether the oligomers adopt compact secondary structures in relatively short sequences, i.e., are foldamers.[40]

The L-*ribo* γ-azido ester **1** and L-*xylo* γ-azido ester **2** are available in seven steps starting from the acetonide of L-arabinose **5** and D-ribose **6**, respectively (Fig. 2).[47,49] The homooligomers of THF γ-azido esters **1** and **2** were prepared using established solution-phase coupling procedures with *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) as the coupling agent.[66] The formation of the tetrameric and hexameric homooligomers was achieved via an iterative approach.

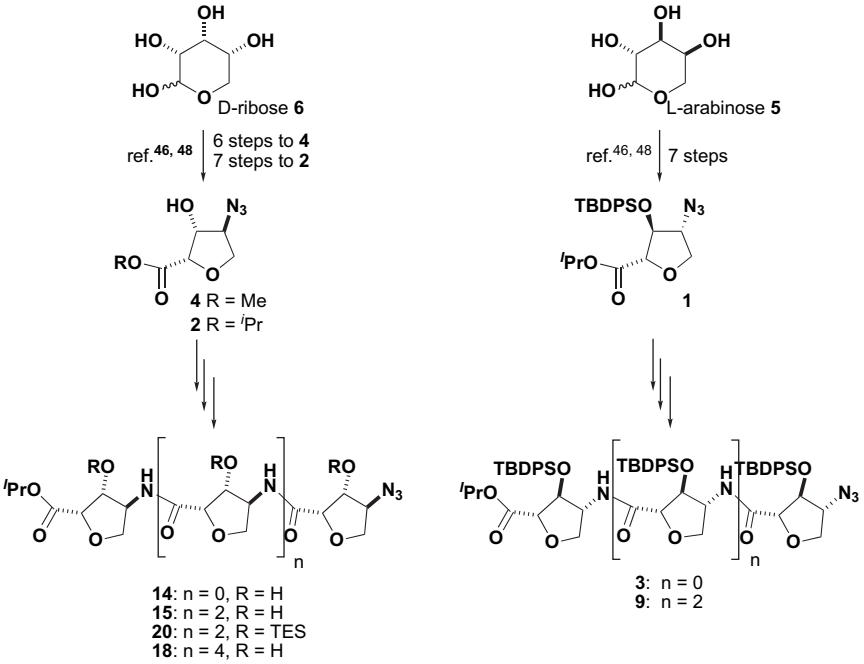


Figure 2. Homooligomers from the 2,4-*cis* and 2,4-*trans* γ-azido esters (**1** and **2**, respectively).

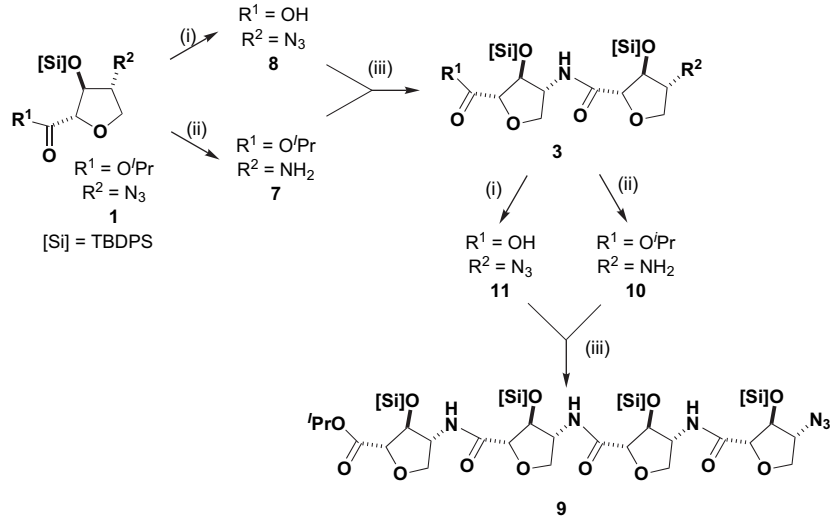
2.2. Synthesis of homooligomers from the L-*ribo* γ-azido ester 1

Hydrogenation of the azido group in isopropyl L-*ribo* γ-azide **1** with 10% palladium on carbon in propan-2-ol proceeded smoothly to afford amine **7**, which was used without further purification (Scheme 1). Hydrolysis of the ester functionality in **1** with aqueous methanolic potassium hydroxide followed by short exposure to Amberlite H^+ resin generated the desired acid **8**. Acid **8** was coupled to amine **7** using standard peptide-coupling conditions with TBTU and *N*,*N*-diisopropylethylamine (DIPEA) in *N*,*N*-dimethylformamide (DMF) to yield dimer **3** in 80% yield from azide **1**. The structure of dimer **3** was confirmed by X-ray crystallography.[67]

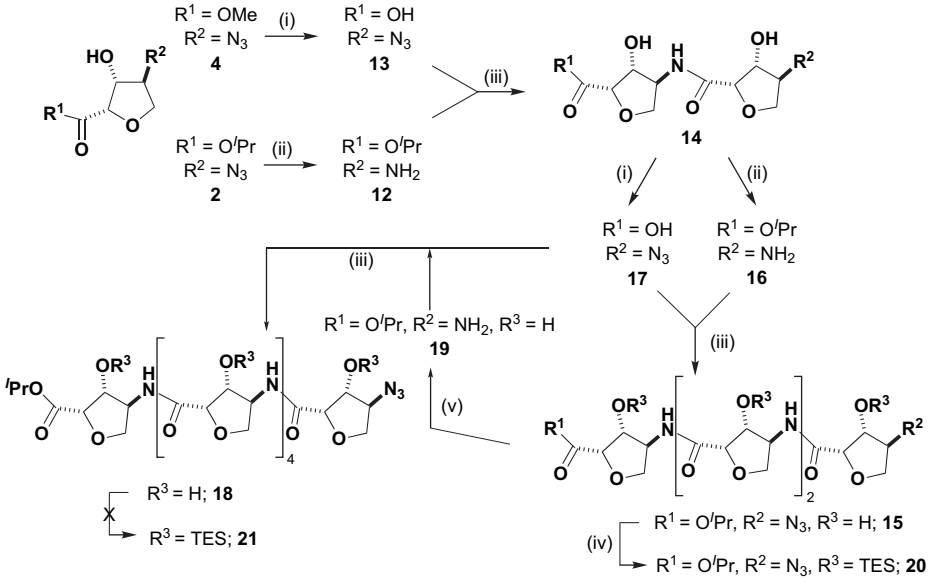
An iterative approach was adopted to synthesise the tetrameric carbopeptoid **9**; thus the azide function of dimer **3** was reduced by hydrogenation in propan-2-ol in the presence of 10% palladium on carbon to afford the N-terminal amine **10**. Treatment of dimer **3** with aqueous methanolic potassium hydroxide followed by short exposure to Amberlite H^+ resin gave access to acid **11**, which was coupled to amine **10** with TBTU/DIPEA in DMF. Purification of the crude product by flash chromatography afforded tetramer **9**, albeit in poor yield (26%).

2.3. Synthesis of homooligomers from the L-*xylo* γ-azido ester 2

Amine **12** was afforded by hydrogenation of the azido group in the isopropyl L-*xylo* γ-azide **2** with 10% palladium on carbon in propan-2-ol and was used without further purification (Scheme 2). Hydrolysis of the ester functionality in the methyl L-*xylo* γ-azide **4** was achieved with aqueous sodium hydroxide in dioxane with subsequent treatment with Amberlite H^+ resin to give the desired acid **13**. Acid **13** was coupled to amine **12** with TBTU and triethylamine



Scheme 1. *Reagents and conditions*: (i) KOH, MeOH, H_2O, rt then Amberlite IR-120 (H^+) resin; (ii) 10% Pd/C, propan-2-ol, H_2, rt; (iii) DIPEA, TBTU, DMF, rt.



Scheme 2. *Reagents and conditions*: (i) NaOH, dioxane, H_2O, rt then Amberlite IR-120 (H^+) resin; (ii) 10% Pd/C, propan-2-ol, H_2, rt; (iii) TEA, TBTU, DMF, rt; (iv) TES-OTf, pyridine, −20 °C to rt, 14 h; (v) 10% Pd/C, DMF, H_2, rt.

(TEA) in DMF to yield the desired dimer **14** in 61% yield from the azide (**2** or **4**).

Tetramer **15** was prepared from the amine and acid derived from dimer **14**. The azide function of dimer **14** was reduced by hydrogenation in propan-2-ol in the presence of 10% palladium on carbon to afford the N-terminal amine **16**. Treatment of dimer **14** with aqueous sodium hydroxide in dioxane followed by short exposure to Amberlite H^+ resin gave access to acid **17**, which was coupled to amine **16** using TBTU/TEA in DMF. Purification of the crude product by flash chromatography and size exclusion chromatography afforded tetramer **15** in good yield (60%).

Hexamer **18** was prepared from the amine derived from tetramer **15** and acid **17** derived from dimer **14**. The azide function of tetramer **15** was reduced by hydrogenation in DMF (**15** was not soluble in propan-2-ol) in the presence of 10% palladium on carbon to afford the N-terminal amine **19**. Acid **17** was coupled to amine **19** with TBTU/TEA in DMF. Purification of the crude product by flash chromatography and size exclusion chromatography afforded hexamer **18,** albeit in poor yield (25%).

2.4. Protection of the free hydroxyls of the homooligomers (from 2)

Protection of the free hydroxyls of tetramer **15** and hexamer **18** would enable further investigation of the secondary structural preference of the systems. The hydroxyl derivatisation would enable solubilisation of the homooligomers in solvents such as chloroform and would enable solution-state IR spectra to be recorded. Triethylsilyl ethers were chosen for hydroxyl protection as they are related to the protection used in the L-*ribo* homooligomers. More importantly, they do not contain the phenyl residues, which complicate observation of amide protons by ^{1}H NMR spectroscopy and study of the amide chromophores by circular dichroism.

The silyl protection of tetramer **15** was achieved by treatment of **15** with a large excess of triethylsilyl trifluoromethanesulfonate in pyridine (Scheme 2). Purification via flash chromatography on basic alumina afforded the silylated tetramer **20** in 13% yield. Attempts to protect hexamer **18** in a similar manner were unsuccessful—no silylated products were observed by electrospray mass spectrometry. The poor yields achieved for the silylation of the homooligomers may be related to steric hindrance due to the bulkiness of the triethylsilyl group. Sufficient material was isolated from the silylated tetramer **20** to allow secondary structure investigation.

2.5. Secondary structure

Initial examination of ^{1}H NMR spectroscopic and crystallographic data provided important secondary structural evidence. The X-ray crystal structure of dimer **3** revealed a hydrogen-bonded turn conformation akin to that of a γ-turn (see Fig. 3).[67] The high δ_{NH} of **3** by ^{1}H NMR spectroscopy ($CDCl_3$, 500 MHz) indicated that this conformation may also be present in solution. Further to this, the corresponding tetramer **9** has similar high δ_{NH} (benzene-d_6, 500 MHz) for NH^B and NH^C suggesting that it may adopt a related

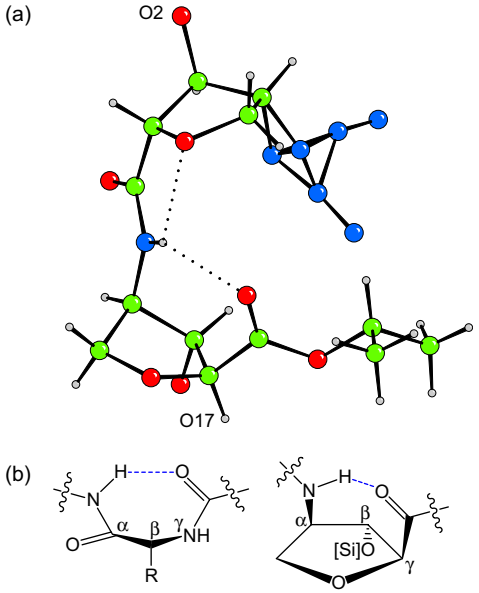


Figure 3. (a) The solid-state conformation of dimer **3**, as revealed by single crystal X-ray diffraction, clearly showing a seven-membered ring hydrogen-bonded γ-turn like structure. The hydrogen bonds are shown as dotted lines. TBDPS groups attached to O2 and O17 have been omitted for clarity. Note that the azide group (N_3) is not fully refined; (b) γ-Turns in an α-peptide and SAA dimer **3**.

hydrogen-bonded conformation. In contrast to the L-*ribo* series, the L-*xylo* oligomers have relatively low δ_{NH} suggesting the absence of a hydrogen-bonded conformation. A full secondary structural study of these oligomers will be reported in due course.

3. Conclusion

Tetrahydrofuran-based γ-amino acids (2,4-*cis* **1** and 2,4-*trans* **2**) were subjected to iterative peptide-coupling procedures to afford dimeric, tetrameric and hexameric carbopeptoids in good yield. These homooligomers were prepared to enable secondary structural study—to ascertain the conformational preference inherent in the monomer units **1** and **2**. Such information is of great significance for the design of compounds with predisposed conformation, e.g., peptidomimetics and nanomaterials.

4. Experimental

4.1. General

The general methods used have been described previously[49] although there are several further comments. Reactions were performed under an atmosphere of nitrogen or argon, unless stated otherwise. Sheets were visualised using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid or 0.5% ninhydrin in methanol (particularly for amines). Flash chromatography was performed on Sorbsil C60 40/60 silica and, where stated, on basic alumina [Actal UGI (aluminium oxide—activated) from Rockwood Additives Ltd.]. Size exclusion chromatography was performed using Sephadex LH-20. For NMR assignment of the furanose residues, the residues were labelled sequentially from the N to C terminus, e.g., in a tetramer, residue A

contains the azide and residue D contains the ester. Residual signals from the solvents were used as an internal reference. ^{1}H and ^{13}C spectral assignments were achieved using a combination of COSY, TOCSY, HSQC, Tr-ROESY and HMBC. ^{13}C data have been quoted to two decimal places for several oligomers to clarify the assignment given.

4.1.1. Isopropyl 4-amino-2,5-anhydro-3-*O*-*tert*-butyldiphenylsilyl-4-*N*-(2,5-anhydro-4-azido-3-*O*-*tert*-butyldiphenylsilyl-4-deoxy-L-ribonyl)-4-deoxy-L-ribonate 3. A solution of isopropyl 2,5-anhydro-4-azido-3-*O*-*tert*-butyldiphenylsilyl-4-deoxy-L-ribonate **1** (0.39 g, 0.86 mmol) in propan-2-ol (10 mL) containing palladium (10 wt % on carbon, 50 mg) was vigorously stirred under an atmosphere of hydrogen. After 13 h, TLC (dichloromethane) showed the absence of the starting material (R_f 0.42) and the presence of a major product (R_f 0.12). The reaction mixture was degassed, purged with nitrogen and filtered through Celite (eluent: propan-2-ol). The filtrate was concentrated in vacuo to afford amine **7** as a colourless oil, which was used without further purification.

Potassium hydroxide (0.063 g, 1.1 mmol) was added to a stirred solution of isopropyl azido ester **1** (0.39 g, 0.86 mmol) in methanol (5 mL) containing water (1 mL). After 16 h, TLC (dichloromethane) showed the absence of the starting material (R_f 0.42). The reaction mixture was stirred with excess Amberlite IR-120 (H^+) resin for 2 min and filtered. The filtrate was concentrated in vacuo to afford acid **8** as a colourless oil, which was used without further purification.

DIPEA (0.31 mL, 1.8 mmol) and TBTU (0.57 g, 1.71 mmol) were added to a stirred solution of acid **8** and amine **7** in DMF (2 mL). After 23 h, TLC (dichloromethane) revealed the formation of a major product (R_f 0.42). The mixture was concentrated in vacuo and purified by flash chromatography (ethyl acetate–pet. ether, 1:9) to yield dimer **3** as a white solid (0.58 g, 80%): mp 127–128 °C (MeOH); $[\alpha]_D^{23}$ +91.0 (*c* 0.51 in $CHCl_3$); (HRMS (ESI+ve): Found 843.3572. $C_{45}H_{56}N_4O_7Si_2Na$ ($M+Na^+$) requires *m/z*, 843.3580); Isotope distribution *m/z* (ES+ve) found: 843.36 (100), 844.29 (60), 845.31 (20%). $C_{45}H_{56}N_4O_7Si_2Na$ ($M+Na^+$) requires: 843 (100), 844 (61), 845 (26%); ν_{max} (thin film): 3360 (NH, amide), 2106 (N_3), 1738 (C=O, ester), 1681 (C=O, amide) cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 0.97 (3H, d, *J* 6.3, $CH(CH_3)_2$), 1.10 (9H, s, $SiC(CH_3)_3$), 1.15 (9H, s, $SiC(CH_3)_3$), 1.16 (3H, d, *J* 6.3, $CH(CH_3)_2$), 3.51 (1H, d, *J* 3.9, H-4^A), 3.89 (1H, d, $J_{5A,5'A}$ 9.7, H-5^A), 4.04 (1H, d, *J* 9.0, H-5^B), 4.15 (1H, dd, $J_{5'A,4A}$ 3.9, $J_{5A,5'A}$ 9.7, H-$5'^A$), 4.18 (1H, br s, H-3^B), 4.32 (1H, br s, H-2^B), 4.36 (1H, dd, *J* 4.4, *J* 9.1, H-$5'^B$), 4.45 (1H, br s, H-2^A), 4.56 (1H, br s, H-3^A), 4.60 (1H, a-dd, *J* 4.2, *J* 10.0, H-4^B), 4.87 (1H, sept, *J* 6.3, $CH(CH_3)_2$), 7.26–7.41 (6H, m, 6×Ar*H*), 7.42–7.48 (7H, m, NH^B and 6×Ar*H*), 7.60–7.80 (8H, m, 8×Ar*H*); δ_C ($CDCl_3$, 125.7 MHz) 19.0 ($SiC(CH_3)_3$), 19.1 ($SiC(CH_3)_3$), 21.3 ($CH(CH_3)$), 21.7 ($CH(CH_3)$), 26.7 ($SiC(CH_3)_3$), 26.8 ($SiC(CH_3)_3$), 56.7 (C-4^B), 66.7 (C-4^A), 69.1 ($CH(CH_3)_2$), 71.7 (C-5^A), 73.8 (C-5^B), 80.4 (C-3^A), 81.3 (C-3^B), 84.8 (C-2^B), 85.2 (C-2^A), 127.6, 127.7, 127.8, 128.0 (8×Ar*C*H), 129.8, 129.9, 130.2, 130.2 (4×Ar*C*H), 132.1, 132.2, 132.9, 133.1 (4×Ar*C*), 135.6, 135.7, 135.9 (8×Ar*C*H), 168.4 (C=O^A), 171.1 (C=O^B); *m/z* (ESI+ve): 879 (100%, $M+MeCN+NH_4^+$).

4.1.2. Isopropyl 4-amino-2,5-anhydro-3-*O*-*tert*-butyldiphenylsilyl-4-*N*-(4-amino-2,5-anhydro-3-*O*-*tert*-butyldiphenylsilyl-4-*N*-(4-amino-2,5-anhydro-3-*O*-*tert*-butyldiphenylsilyl-4-*N*-(2,5-anhydro-4-azido-3-*O*-*tert*-butyldiphenylsilyl-4-deoxy-L-ribonyl)-4-deoxy-L-ribonyl)-4-deoxy-L-ribonyl)-4-deoxy-L-ribonate 9. A solution of dimer **3** (0.16 g, 0.19 mmol) in propan-2-ol (10 mL) containing palladium (10 wt % on carbon, 50 mg) was vigorously stirred under an atmosphere of hydrogen. After 15 h, TLC (dichloromethane) showed the absence of the starting material (R_f 0.40) and the presence of a major product (R_f 0.10). The reaction mixture was degassed, purged with nitrogen and filtered through Celite (eluent: propan-2-ol). The filtrate was concentrated in vacuo to afford dimer-amine **10** as colourless oil, which was used without further purification.

Potassium hydroxide (0.014 g, 0.25 mmol) was added to a stirred solution of dimer **3** (0.16 g, 0.19 mmol) in methanol (5 mL) containing water (1 mL). After 20 h, TLC (dichloromethane) showed the absence of the starting material (R_f 0.40). The reaction mixture was stirred with excess Amberlite IR-120 (H^+) resin for 2 min and filtered. The filtrate was concentrated in vacuo to afford dimer-acid **11** as colourless oil, which was used without further purification.

DIPEA (0.043 mL, 0.25 mmol) and TBTU (0.08 g, 0.25 mmol) were added to dimer-amine **10** and dimer-acid **11** in dry DMF (1 mL). After 28 h, TLC (ethyl acetate–pet. ether, 3:1) revealed the formation of a major product (R_f 0.56). The mixture was concentrated in vacuo and purified by flash chromatography (ethyl acetate–pet. ether, 1:9) to yield tetramer **9** as a white solid (0.056 g, 26%); mp 74–75 °C (MeOH); $[\alpha]_D^{23}$ +70.8 (*c* 0.5 in $CHCl_3$); Isotope distribution *m/z* (ES+ve) found: 1555.74 (70), 1556.63 (90) 1557.68 (70), 1558.58 (35), 1559.19 (20%). $C_{87}H_{106}N_6O_{13}Si_4Na$ ($M+Na^+$) requires: 1555 (76), 1556 (90) 1557 (65), 1558 (32), 1559 (15%); ν_{max} (thin film): 3386 (NH, amide), 2106 (N_3), 1727 (C=O, ester), 1668, 1679, 1692 (C=O, amide) cm^{-1}; δ_H (C_6D_6, 500 MHz) 0.73 (3H, d, *J* 6.2, $CH(CH_3)_2$), 0.82 (3H, d, *J* 6.2, $CH(CH_3)_2$), 1.13 (9H, s, $SiC(CH_3)_3$), 1.15 (9H, s, $SiC(CH_3)_3$), 1.18 (9H, s, $SiC(CH_3)_3$), 1.19 (9H, s, $SiC(CH_3)_3$), 3.14 (1H, d, *J* 3.8, H-4^A), 3.56 (1H, d, *J* 9.8, H-5^A), 3.64 (1H, d, *J* 9.2, H-5^D), 3.68 (1H, dd, *J* 3.7, 6.1, H-$5'^A$), 3.70 (1H, br s, H-5^C), 3.81 (1H, d, *J* 8.9, H-5^B), 4.10–4.14 (2H, m, H-$5'^B$ and H-$5'^C$), 4.17 (1H, dd, *J* 4.2, 9.2, H-$5'^D$), 4.25 (1H, d, *J* 1.15, H-2^C), 4.35 (1H, q, *J* 4.1, H-4^D), 4.40 (1H, br s, H-2^B), 4.42 (1H, br s, H-2^D), 4.51 (1H, br s, H-3^C), 4.55 (1H, br s, H-3^D), 4.59–4.64 (2H, m, H-4^B and H-3^C), 4.65 (1H, br s, H-2^A), 4.72 (1H, sept, *J* 6.2, $CH(CH_3)_2$), 4.78 (1H, m, H-4^B), 4.80 (1H, br s, H-3^A), 6.50 (1H, d, *J* 8.3, NH^D), 7.20–7.36 (24H, m, 24×Ar*H*), 7.49 (1H, d, *J* 9.1, NH^C), 7.69 (2H, m, 2×Ar*H*), 7.73 (2H, m, 2×Ar*H*), 7.78–7.85 (13H, m, NH^B and 12×Ar*H*); δ_C (C_6D_6, 125.7 MHz) 19.62, 19.62, 19.69, 19.73 (4×$SiC(CH_3)_3$), 21.70 ($CH(CH_3)_2$), 27.34, 27.39, 27.48, 27.52 (4×$SiC(CH_3)_3$), 57.93, 58.13, 58.2 (C-4^B, C-4^C and C-4^D), 67.22 (C-4^A), 69.49 ($CH(CH_3)_2$), 71.99 (C-5^A), 73.39 (C-5^D), 73.99 (C-5^C), 74.26 (C-5^B), 81.57 (C-3^A and C-3^D), 81.87 (C-3^C), 82.50 (C-3^B), 85.31 (C-2^D), 86.70 (C-2^A), 87.10, 87.32 (C-2^B and C-2^C), 128.52, 128.56, 128.61, 128.68, 128.70, 128.76, 128.80 (16×Ar*C*H), 130.49, 130.53, 130.69, 130.75, 130.85,

130.89 (8×Ar*C*H), 133.06, 133.29, 133.41, 133.44 133.84, 133.88, 134.06, 134.18 (8×Ar*C*), 136.43, 136.50, 136.53, 136.60, 136.65, 136.68, 136.71 (16×Ar*C*H), 169.01 (C=O^{B}), 170.05 (C=O^{C}), 170.12 (C=O^{D}), 171.91 (C=O^{A}).

4.1.3. Isopropyl 2,5-anhydro-4-*N*-(2,5-anhydro-4-azido-4-deoxy-L-xylonamido)-4-deoxy-L-xylonate 14. A solution of isopropyl 2,5-anhydro-4-azido-4-deoxy-L-xylonate **2** (221 mg, 1.03 mmol) in propan-2-ol (11 mL) containing palladium (10 wt % on carbon, 23 mg) was vigorously stirred under an atmosphere of hydrogen. After 5 h, TLC (ethyl acetate–pet. ether, 2:1) showed the absence of the starting material (R_f 0.5) and the presence of a major product (R_f 0.0). The reaction mixture was degassed, purged with nitrogen and filtered through Celite (eluent: propan-2-ol). The filtrate was concentrated in vacuo to afford amine **12** as a colourless oil, which was used without further purification.

Sodium hydroxide (1 M aq, 1.2 mL) was added to a stirred solution of methyl 2,5-anhydro-4-azido-4-deoxy-L-xylonate **4** (192 mg, 1.03 mmol) in dioxane (1.2 mL) and water (2.4 mL). After 3 h, TLC (ethyl acetate–pet. ether, 2:1) showed the absence of the starting material (R_f 0.3) and the formation of a major product (R_f 0.0). The reaction mixture was concentrated in vacuo and the resulting residue was redissolved in water. The reaction mixture was stirred with excess Amberlite IR-120 (H^+) resin for 30 min and filtered. The filtrate was concentrated in vacuo to afford acid **13** as a colourless oil, which was used without further purification.

Triethylamine (204 μL, 1.45 mmol) and TBTU (406 mg, 1.26 mmol) were added to a stirred solution of amine **12** and acid **13** in DMF (11 mL). After 12 h, TLC (ethyl acetate) revealed the formation of a major product (R_f 0.2) and a minor product (R_f 0.3). The reaction mixture was concentrated in vacuo and redissolved in water (30 mL). Chloroform was added to the solution and the organic layer was extracted with water. The combined aqueous extracts were concentrated in vacuo and purified by flash chromatography (ethyl acetate–pet. ether, 1:1) to yield dimer **14** (216 mg, 61%) as a white solid: mp 48–49 °C; $[\alpha]_D^{24}$ −25.9 (*c* 1.03 in $CHCl_3$); (HRMS (CI+ve): Found 345.1410. $C_{13}H_{21}N_4O_7$ (M+H$^+$) requires *m/z*, 345.1410); ν_{max} (thin film): 3392 (OH), 2108 (N_3), 1739 (C=O) 1652, 1538 (C=O, amide) cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 1.26 (3H, d, *J* 6.2, CH(CH_3)$_2$), 1.27 (3H, d, *J* 6.2, CH(CH_3)$_2$), 3.84 (1H, dd, $J_{4B,5B}$ 1.7, $J_{5B,5'B}$ 9.8, H-5^B), 3.94 (1H, d, $J_{5A,5'A}$ 9.8, H-5^A), 4.13 (1H, d, $J_{4A,5'A}$ 4.5, H-4^A), 4.24–4.27 (2H, m, H-5′^{A} and H-4^B) 4.37 (1H, dd, $J_{4B,5'B}$ 4.8, $J_{5B,5'B}$ 9.8, H-5′^{B}), 4.48 (2H, m, H-2 and O*H*), 4.53–4.57 (3H, m, H-2, H-3^A and H-3^B), 4.64 (1H, d, *J* 2.5, O*H*), 5.11 (1H, sept, *J* 6.2, C*H*(CH$_3$)$_2$), 7.03 (1H, d, *J* 6.4, NH^B); δ_C ($CDCl_3$, 125.7 MHz) 22.0, 22.1 (CH(*C*H$_3$)$_2$), 58.3 (C-4^B), 66.9 (C-4^A), 69.4 (*C*H(CH$_3$)$_2$), 71.4 (C-5^B), 71.8 (C-5^A), 75.9, 77.0 (C-3^A and C-3^B), 80.6, 82.3 (C-2^A and C-2^B), 169.4 (C=O^B), 170.9 (C=O^A); *m/z* (APCI+ve) 303 (100), 345 (M+H$^+$, 64%).

4.1.4. Isopropyl 2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-azido-4-deoxy-L-xylonamido)-4-deoxy-L-xylonamido)-4-deoxy-L-xylonamido)-4-deoxy-L-xylonate 15. A solution of dimer **14** (100 mg, 0.29 mmol) in propan-2-ol (3 mL) containing palladium (10 wt % on carbon, 21 mg) was vigorously stirred under an atmosphere of hydrogen. After 23 h, TLC (ethyl acetate) showed the absence of the starting material (R_f 0.2) and the presence of a major product (R_f 0.0). The reaction mixture was degassed, purged with nitrogen and filtered through Celite (eluent: propan-2-ol). The filtrate was concentrated in vacuo to afford dimer-amine **16** as a colourless oil, which was used without further purification.

Sodium hydroxide (1 M aq, 344 μL) was added to dimer **14** (100 mg, 0.29 mmol) in dioxane (0.4 mL) and water (0.7 mL). After 3 h, TLC (ethyl acetate) showed the absence of the starting material (R_f 0.2) and the formation of a major product (R_f 0.0). The reaction mixture was concentrated in vacuo and the resulting residue was redissolved in water. The reaction mixture was stirred with excess Amberlite IR-120 (H^+) resin for 30 min and filtered. The filtrate was concentrated in vacuo to afford dimer-acid **17** as a colourless oil, which was used without further purification.

Triethylamine (56 μL, 0.40 mmol) and TBTU (112 mg, 0.35 mmol) were added to a stirred solution of dimer-amine **16** and dimer-acid **17** in DMF (3 mL). After 19 h, TLC (ethyl acetate–methanol, 7:3) revealed the formation of a major product (R_f 0.5). The reaction mixture was concentrated in vacuo and purified by flash chromatography (ethyl acetate–methanol–water, 4:6:3). The resulting residue was further purified by size exclusion chromatography (methanol), to yield tetramer **15** (105 mg, 60%) as a white solid: mp 170–171 °C (decomp.); $[\alpha]_D^{24}$ −13.4 (*c* 1.06 in MeOH); (HRMS (CI+ve): Found 603.2262. $C_{23}H_{35}N_6O_{13}$ (M+H$^+$) requires *m/z*, 603.2262); Isotope distribution *m/z* (ES+ve) found: 625.28 (100), 626.23 (28), 627.25 (7%). $C_{23}H_{34}N_6O_{13}Na$ (M+Na$^+$) requires: 625.20 (100), 626.21 (25), 627.21 (2%); ν_{max} (KBr): 3400 (OH), 2111 (N_3), 1736 (C=O), 1655, 1541 (C=O, amide) cm^{-1}; δ_H (C_5D_5N, 500 MHz) 1.17 (3H, d, *J* 6.3, CH(CH_3)$_2$), 1.20 (3H, d, *J* 6.3, CH(CH_3)$_2$), 3.93 (1H, d, $J_{5A,5'A}$ 9.2, H-5^A), 4.03–4.05 (2H, m, H-5^B and H-5^D), 4.12 (1H, dd, $J_{4C,5C}$ 2.2, $J_{5C,5'C}$ 9.0, H-5^C), 4.31–4.36 (2H, m, H-4^A and H-5′^{A}), 4.39–4.42 (2H, m, H-5′^{B} and H-5′^{D}), 4.60 (1H, dd, $J_{4C,5'C}$ 5.3, $J_{5C,5'C}$ 9.0, H-5′^{C}), 4.85–4.91 (5H, m, H-2^A H-3^A, H-4^B, H-4^C and H-4^D), 4.97–5.00 (3H, m, H-2^B, H-2^D and H-3^C), 5.11 (1H, m, H-2^C), 5.13–5.15 (2H, m, H-3^B and H-3^D), 5.20 (1H, sept, *J* 6.3, C*H*(CH$_3$)$_2$), 8.45 (1H, d, *J* 7.2, NH^C), 8.47 (1H, d, *J* 7.1, NH^B), 8.53 (1H, d, *J* 6.7, NH^D); δ_C (C_5D_5N, 125.7 MHz) 22.2, 22.3 (CH(*C*H$_3$)$_2$), 59.2, 59.2, 59.3 (C-4^B, C-4^C and C-4^D), 68.3 (C-4^A), 68.5 (*C*H(CH$_3$)$_2$), 71.9 (C-5^A), 72.3 (C-5^C), 72.4, 72.5 (C-5^B and C-5^D), 76.4 (C-3), 77.2 (C-3^A), 77.3 (C-3), 77.8 (C-2^C), 82.0 (C-3^C), 83.5, 83.5, 83.5 (C-2^B, C-2^A and C-2^D), 170.4 (C=O^C), 170.5 (C=O^D), 170.9 (C=O^A), 171.0 (C=O^B).

4.1.5. Isopropyl 2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-azido-4-deoxy-L-xylonamido)-4-deoxy-L-xylonamido)-4-deoxy-L-xylonamido)-4-deoxy-L-xylonamido)-4-deoxy-L-xylonate 18. A solution of tetramer **15** (43 mg, 0.07 mmol) in DMF (5 mL) containing palladium (10 wt % on carbon, 8 mg) was vigorously stirred under an atmosphere of hydrogen. After 3 h, TLC (ethyl acetate–methanol, 7:3) showed the

absence of the starting material (R_f 0.5) and the presence of a major product (R_f 0.0). The reaction mixture was degassed, purged with nitrogen and filtered through Celite (eluent: DMF). The filtrate was concentrated in vacuo to afford tetramer-amine **19** as a colourless oil, which was used without further purification.

Sodium hydroxide (1 M aq, 85 μL) was added to a stirred solution of dimer **14** (100 mg, 0.29 mmol) in dioxane (85 μL) and water (171 μL). After 3 h, TLC (ethyl acetate) showed the absence of the starting material (R_f 0.2) and the formation of a major product (R_f 0.0). The reaction mixture was concentrated in vacuo and the resulting residue was redissolved in water. The reaction mixture was stirred with excess Amberlite IR-120 (H^+) resin for 30 min and filtered. The filtrate was concentrated in vacuo to afford dimer-acid **17** as colourless oil, which was used without further purification.

Triethylamine (14 μL, 0.10 mmol) and TBTU (28 mg, 0.09 mmol) were added to a stirred solution of tetramer-amine **19** and dimer-acid **17** in DMF (0.5 mL). After 13 h, TLC (acetonitrile–water, 9:1) revealed the formation of a major product (R_f 0.2). The reaction mixture was concentrated in vacuo and purified by flash chromatography (acetonitrile–water, 9:1). The resulting residue was further purified by size exclusion chromatography (methanol) to yield hexamer **18** (15 mg, 25%) as a white solid: mp 159–160 °C; $[\alpha]_D^{24}$ −33.8 (*c* 0.24 in MeOH); (HRMS (CI+ve): Found 883.2933. $C_{33}H_{48}N_8O_{19}Na$ ($M+Na^+$) requires *m/z*, 883.2933); Isotope distribution *m/z* (ES+ve) found: 883.36 (100), 884.28 (39), 885.28 (8%). $C_{23}H_{34}N_6O_{13}Na$ ($M+Na^+$) requires: 883 (100), 884 (40), 885 (12%); ν_{max} (KBr): 3394 (OH), 2111 (N_3), 1737 (C═O), 1661, 1534 (C═O, amide) cm^{-1}; δ_H (C_5D_5N, 500 MHz) 1.18 (3H, d, *J* 6.5, $CH(CH_3)_2$), 1.21 (3H, d, *J* 6.5, $CH(CH_3)_2$), 3.94 (1H, d, $J_{5,5'}$ 9.2, H-5), 4.02–4.06 (3H, m, 4×H-5), 4.13 (1H, dd, $J_{4,5'}$ 2.1, *J* 8.8, H-5), 4.32–4.43 (6H, m, H-4^A and 5×H-5′), 4.62 (1H, dd, $J_{4,5'}$ 5.1, $J_{5,5'}$ 8.8, H-5′), 4.87–5.10 (17H, m, 6×H-2, 6×H-3 and 5×H-4), 5.22 (1H, sept, *J* 6.5, $CH(CH_3)_2$), 8.35–8.38 (4H, m, 4×NH), 8.51 (1H, d, *J* 6.4, NH); δ_C (C_5D_5N, 125.7 MHz) 22.26, 22.31 ($CH(CH_3)_2$), 59.19, 59.26, 59.32 (6×C-4), 68.35, 68.39, 71.92, 72.33, 72.54, 72.58, 72.62 (6×C-5 and $CH(CH_3)_2$), 76.43, 77.30, 77.34, 77.88 (6×C-3), 82.01, 82.12, 83.12, 83.58, 83.66 (6×C-2), 170.33, 170.49, 170.79, 170.82, 171.99 (6×C═O).

4.1.6. Isopropyl 2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-*N*-(2,5-anhydro-4-azido-4-deoxy-3-*O*-triethylsilyl-L-xylonamido)-4-deoxy-3-*O*-triethylsilyl-L-xylonamido)-4-deoxy-3-*O*-triethylsilyl-L-xylonamido)-4-deoxy-3-*O*-triethylsilyl-L-xylonate 20. Triethylsilyl trifluoromethanesulfonate (0.17 mL, 0.75 mmol) was added to a stirred solution of tetramer **15** (19 mg, 0.03 mmol) in pyridine (0.5 mL) at −20 °C. The reaction mixture was allowed to warm to room temperature over 6 h. After 14 h, TLC (ethyl acetate–pet. ether, 3:1) showed some starting materials (R_f 0.0) and the presence of a major product (R_f 0.2). The reaction mixture was concentrated in vacuo and purified by flash chromatography on basic alumina (ethyl acetate–pet. ether, 3:1) to yield the silylated tetramer **20** (4 mg, 13%) as a colourless oil: $[\alpha]_D^{24}$ −23.4 (*c* 0.47 in $CHCl_3$); Isotope distribution *m/z* (ES+ve) found: 1059.53 (100), 1060.48 (80), 1061.55 (43), 1062.44 (18), 1063.38 (9%). $C_{47}H_{91}N_6O_{13}Si_4$ ($M+H^+$) requires: 1059 (100), 1060 (75), 1061 (44), 1062 (18), 1063 (6%); ν_{max} (thin film): 3410 (NH), 2105 (N_3), 1740 (C═O), 1637, 1540 (C═O, amide) cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 0.61–0.71 (24H, m, 4×Si(CH_2CH_3)$_3$), 0.92–0.98 (36H, m, 4×Si(CH_2CH_3)$_3$), 1.26–1.30 (6H, m, $CH(CH_3)_2$), 3.78–3.80 (3H, m, H-5^B, H-5^C and H-5^D), 3.92–3.96 (2H, m, H-4^A and H-5^A), 4.16–4.21 (3H, m, H-4^B, H-4^C and H-4^D), 4.27 (1H, dd, $J_{5'A,4A}$ 4.1, $J_{5A,5'A}$ 9.5, H-$5'^A$), 4.30–4.40 (5H, m, H-2^C, H-2^D, H-$5'^B$, H-$5'^C$ and H-$5'^D$), 4.43–4.46 (2H, m, H-2^B and H-3^A), 4.48–4.49 (2H, m, H-3^C and H-3^D), 4.52–4.55 (2H, m, H-2^A and H-3^B), 5.07 (1H, sept, *J* 6.2, $CH(CH_3)_2$), 6.52 (1H, d, *J* 6.7, NH^D), 6.55 (1H, d, *J* 6.7, NH^C), 6.60 (1H, d, *J* 6.4, NH^B); δ_C ($CDCl_3$, 125.7 MHz) 4.66, 4.68, 4.76 (4×Si(CH_2CH_3)$_3$), 6.83, 6.90 (4×Si(CH_2CH_3)$_3$), 22.10, 22.17 ($CH(CH_3)_2$), 57.71, 57.74 (3×C-4), 67.53 (C-4^A), 68.99 ($CH(CH_3)_2$), 71.59, 71.86, 72.33, 72.45 (4×C-5), 76.78, 77.43, 77.88 (4×C-3), 81.47, 82.54, 82.56, 82.64 (4×C-2), 168.60 (C═O^A), 168.77 (C═O^B), 169.00, 169.02 (C═O^D and C═O^C); *m/z* (APCI+ve) 156 (100), 1059 ($M+H^+$, 95%).

Acknowledgements

Support from the EPSRC (A.A.E.) and DST, New Delhi, for a BOYCAST Fellowship (G.J.S.) is gratefully acknowledged.

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Tetrahedron 62 (2006) 7726–7732
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Novel tandem reactions of ethyl acetoacetate with aromatic aldehydes: product- and stereo-selective formation of highly functionalised cyclohexanones

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Received 21 March 2006; revised 11 May 2006; accepted 25 May 2006
Available online 16 June 2006

Abstract—The five-component tandem reaction of ethyl acetoacetate with aromatic aldehydes in the presence of pyrrolidine affords *t*(3),*t*(5)-diaryl-*t*(4)-[(*E*)-3-aryl-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanones stereoselectively in good yields presumably via a tandem Knoevenagel condensation–Michael addition–condensation via enamine-deethoxycarbonylation–Michael addition sequence. The same reactants in the presence of DBU led to the formation of *t*(3)-aryl-*r*(2),*c*(4)-bisethoxycarbonyl-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones in excellent yields via a tandem Knoevenagel condensation–Michael addition–aldol reaction sequence.

1. Introduction

Cyclohexanone constitutes the backbone of many systems, which display biological activities such as herbicidal,[1] antibacterial,[2] antifungal,[2] convulsant,[3] anticonvulsant,[3,4] *anti*-implantation[5] and antiasthmone,[6] besides being useful in organic synthesis and in industry.

Tandem or cascade processes are one-pot multistep reactions providing rapid access to complex structures, and hence powerful for synthetic transformations.[7–10] Tandem reactions fall under the fold of green chemistry as the intermediates are not isolated and purified thus minimising the waste associated with solvent, adsorbent and loss of product during purification using crystallisation/column chromatography, besides minimising energy, labour and time.[11] In this paper, we report a one-pot tandem sequence for the diastereoselective synthesis of *t*(3),*t*(5)-diaryl-*t*(4)-[(*E*)-3-aryl-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanones and *t*(3)-aryl-*r*(2),*c*(4)-bisethoxycarbonyl-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones (Fig. 1) by the reaction of ethyl acetoacetate with aromatic aldehydes in the presence of pyrrolidine or DBU, respectively, at ambient temperature. These cyclohexanones could serve as useful synthons in further synthetic endeavours, as the former has α,β-unsaturated carbonyl and β-keto ester functionalities and the latter has β-keto ester and β-hydroxy ester functionalities.

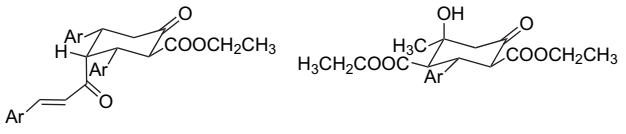
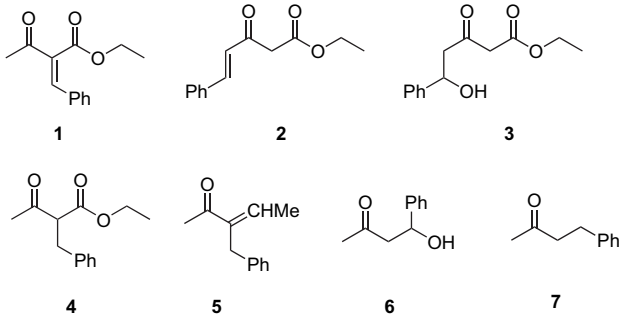


Figure 1.

The reaction of aromatic aldehydes with ethyl acetoacetate in the presence of different catalysts has been investigated.[12–23] The reaction of ethyl acetoacetate and benzaldehyde in the presence of piperidine,[12] sodium carbonate,[13,14] triethyl amine,[15] potassium carbonate–polyethylene glycol,[16] bismuth trichloride[17] and piperidine–acetic acid[18,19] afford ethyl 2-benzylidene-3-oxobutanoate **1**. The same reaction in the presence of titanium tetrachloride–triethyl amine,[15] sodium hydride–butyl lithium[20] and chlorotrimethylsilane–sodium iodide–acetonitrile[21] affords ethyl 3-oxo-5-phenylpent-4-enoate **2**, ethyl 5-hydroxy-3-oxo-5-phenylpentanoate **3** and ethyl 2-benzyl-3-oxobutanoate **4**, respectively. Alternatively in the presence of sodium



Keywords: Pyrrolidine; DBU; Ethyl acetoacetate; Tandem; Knoevenagal; Michael; Cyclohexanone; Enamine; Aldol; Aldehyde.
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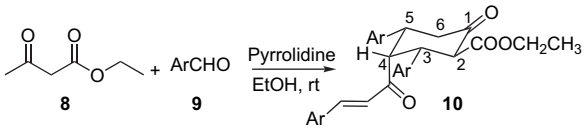
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.05.068

hydroxide–pyridine,[22] the reaction leads to a mixture of 3-phenylpent-3-en-2-one **5** and 4-hydroxy-4-phenylbutan-2-one **6**. The same reactants in the presence of potassium tetracarbonylhydridoferrate furnishes 4-phenylbutan-2-one **7**.[23]

2. Results and discussion

2.1. Synthesis of *t*(3),*t*(5)-diaryl-*t*(4)-[(*E*)-3-aryl-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanones

In the present investigation, the reaction of ethyl acetoacetate **8** with aromatic aldehydes **9** in a 2:3 molar ratio in the presence of pyrrolidine at ambient temperature affords after 2–5 days *t*(3),*t*(5)-diaryl-*t*(4)-[(*E*)-3-aryl-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanones **10** (Scheme 1). The products **10** were isolated in a pure state by flash chromatography in 58–68% yield.



9 and 10	Ar
a	C_6H_5
b	4-ClC_6H_4
c	4-$CH_3C_6H_4$
d	4-$CH_3OC_6H_4$
e	2-ClC_6H_4
f	2-$CH_3OC_6H_4$
g	2-$CH_3C_6H_4$

Scheme 1.

This reaction was investigated in different solvents with varying amounts of pyrrolidine with a view to (i) investigating the influence of the solvent on the course of the reaction and (ii) optimising the yield of **10**. The data furnished (Table 1) reveal that the yield of **10** remains constant when the amount of pyrrolidine employed in this reaction is between 25 and 100 mol % and the reaction was found to be slow in the presence of 10 mol % or less. The reaction of ethyl acetoacetate with aromatic aldehydes in a 2:3 molar ratio using 25 mol % of pyrrolidine in DMSO took 4 days for completion, affording **10a** in 58% (entry 1). In ethanol, the reaction was complete within 2 days furnishing a slightly enhanced yield of **10a** (62%; entry 4). In both the solvents, the amount of pyrrolidine was varied, viz. 25, 50, 100 mol %, whereupon the yield does not alter. The use of CH_3OH, DMF or CH_3CN as solvent has little effect on the yield of **10a** (entries 7–9) revealing that this tandem reaction is unaffected by the solvent.

Table 1. Pyrrolidine-catalysed reactions of ethyl acetoacetate with aromatic aldehydes affording **10**

Entry	Compound	Pyrrolidine (mol %)	Solvent	Yield	Reaction time (days)
1	**10a**	25	DMSO	58	4
2	**10a**	50	DMSO	59	4
3	**10a**	100	DMSO	60	3
4	**10a**	25	EtOH	62	2
5	**10a**	50	EtOH	63	2
6	**10a**	100	EtOH	63	2
7	**10a**	25	MeOH	61	4
8	**10a**	25	DMF	60	5
9	**10a**	25	CH_3CN	58	4
10	**10b**	25	EtOH	66	2
11	**10c**	25	EtOH	62	2
12	**10d**	25	EtOH	60	2
13	**10e**	25	EtOH	68	2
14	**10f**	25	EtOH	68	2
15	**10g**	25	EtOH	59	3
16	**10h**	25	EtOH	58	3

The structure of ketone **10** is in accord with the NMR spectroscopic data as illustrated for the representative example **10a**. The one proton doublet at 4.93 ppm (J=12.9 Hz) is assigned to H-2, as this is the only ring proton that has one coupling partner, viz. H-3. The proton, H-3, gives a doublet of doublets at 3.94 ppm (J=12.9 and 4.4 Hz), ascribed respectively, to vicinal couplings with adjacent H-2 and H-4. The triplet at 3.85 ppm (J=4.4 Hz) for one proton is assigned to H-4, which couples equally with the adjacent axial protons, H-3 and H-5. These assignments are also supported by H–H-COSY and HMBC correlations shown by thick bonds and curved arrows, respectively, in Figure 2. The HMBC correlation is also useful in assigning the ^{13}C signal at 202.7 ppm to the carbonyl of the 3-aryl-2-propenonyl moiety attached to C-4.

That the multiplet at 3.67 ppm is due to H-5 is evident from a H–H-COSY correlation with H-4 and the diastereotopic methylene protons (6-CH_2). The H-6eq appears as a doublet of doublets at 2.66 ppm (J=12.9 and 1.8 Hz) arising from geminal and vicinal axial–equatorial couplings, while the H-6ax appears as a triplet at 3.69 ppm (J=12.9 Hz), the diaxial and geminal couplings being fortuitously equal. The HMBC correlation (Fig. 2) between the H-6eq/H-6ax protons and the carbon at 206.1 ppm points to the assignment of the latter to C-1. The multiplet at 4.06 ppm for two protons is assigned to the diastereotopic CH_2 protons of the ester group, which also shows a HMBC correlation with the ester carbonyl at 169.7 ppm. The above ^1H NMR spectroscopic features reveal that the ester function at C-2 and the aryl rings at C-3 and C-5 are all equatorially oriented, while the (*E*)-3-aryl-2-propenonyl group at C-4 is oriented axially.

The doublets at 5.78 and 6.83 ppm (J=16.2 Hz) of **10a** are assigned to H-α and H-β of the (*E*)-3-aryl-2-propenonyl group. These assignments are evident from the HMBC correlations of H-α and H-β with the neighbouring carbons, especially from the correlation of H-β with the signal at 127.8 ppm due to the *ortho*-carbon in the phenyl ring of the cinnamoyl group (Fig. 2). Both these protons appear unusually upfield than would normally be expected for an α,β-unsaturated carbonyl system, presumably due to shielding by the neighbouring two aryl rings at the C-3 and C-5 positions. This conclusion is also in accord with the MM2 minimised structure of **10a** given in Figure 3.

The ^{13}C NMR spectra of compounds **10a–h** are also in agreement, their spectra having one signal in the range of 206.0–207.5 ppm and another in the range of 201.4–202.9 ppm ascribable to C-1 and the 3-aryl-2-propenonyl

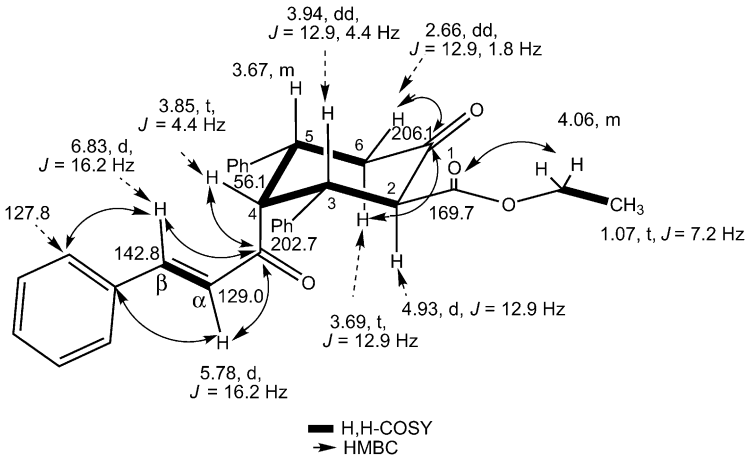


Figure 2. Selected ^{1}H and ^{13}C NMR parameters and 2D NMR correlations for **10a**.

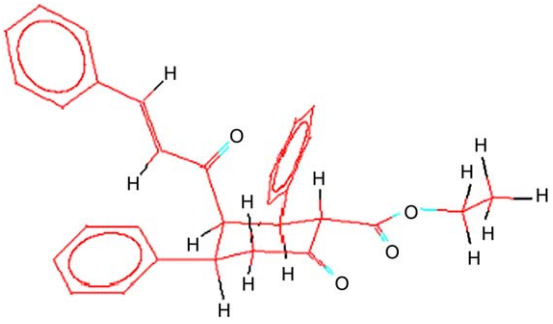


Figure 3. Geometry for **10a** optimised by molecular mechanics calculations.

carbonyls, respectively. The spectra of **10a–h** have a signal in the range of 169.6–170.6 ppm due to the ester carbonyl at C-2. The resonances of **10a–h** in the range 114.7–142.8 ppm are due to the aromatic carbons, among which the less intense ones in the region, 130.2–142.8 ppm, are attributed to the *ipso* carbons. The cyclohexanone ring carbon signals, C-2 to C-6, occur in the range, 42.1–61.8 ppm, and individual assignments are readily achieved from the proton chemical shifts and C–H-COSY correlations (Table 2).

This reaction can be envisaged to occur via an initial Knoevenagel condensation of the aromatic aldehyde with ethyl acetoacetate, affording **1**, followed by Michael addition of ethyl acetoacetate to **1** furnishing symmetrical intermediate **11**. Dione **11** could then condense with two molecules of the aromatic aldehyde via dienamine **12** to afford **13**, which subsequently could suffer deethoxycarbonylation with concomitant intramolecular Michael addition either simultaneously or in a stepwise manner affording **10** (Scheme 2). It is also possible that the latter two reactions occur in the reverse order, first Michael and then deethoxycarbonylation, although this sequence appears to be less likely in view of the steric hindrance due to the two aryl rings at the 2- and 6-positions of the cyclohexanone that would be formed during the Michael addition. Our efforts to isolate and characterise one or more of the intermediates such as **1**, **11** or **13** in Scheme 2 by intercepting and analysing the reaction mixture at different stages during the course of the reaction before completion were unsuccessful as the reaction mixture comprised a mixture of products/intermediates with similar R_f.

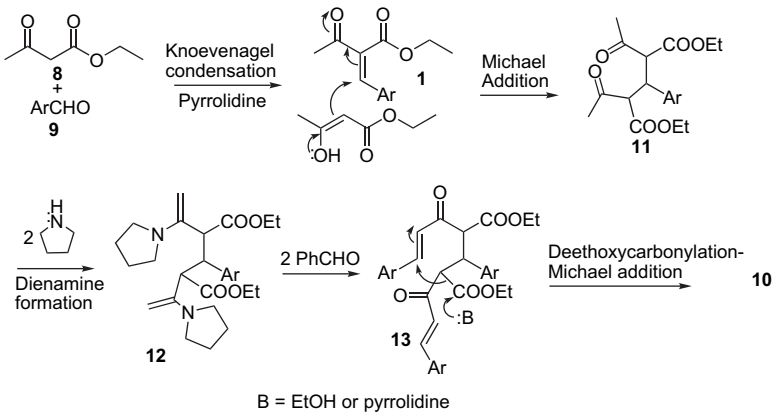
Table 2. ^{1}H and ^{13}C NMR spectroscopic data of **10a**

H-atom	δ_H	δ_C
2	4.93 (1H, d, *J*=12.9 Hz)	58.1
3	3.94 (1H, dd, *J*=12.9, 4.4 Hz)	49.3
4	3.85 (1H, t, *J*=4.4 Hz)	56.1
5	3.67 (1H, m)	46.4
6ax	3.69 (1H, t, *J*=12.9 Hz)	42.3
6eq	2.66 (1H, dd, *J*=12.9, 1.8 Hz)	
α-H	5.78 (1H, d, *J*=16.2 Hz)	129.0
β-H	6.83 (1H, d, *J*=16.2 Hz)	142.8
Aromatic	7.03–7.26 (m, 15H)	127.5, 127.8, 127.9, 128.6, 128.7, 129.0, 129.2, 130.8, 134.5, 139.3, 140.2
Ethyl	4.06 (m), 1.07 (t, *J*=7.2 Hz)	14.4, 61.3
Carbonyl	—	202.7 (3-aryl-2-propenonyl), 206.1 (C-1), 169.7 (ester)

2.2. Diastereoselective synthesis of *t*(3)-aryl-*r*(2),*c*(4)-bisethoxycarbonyl-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones (15)

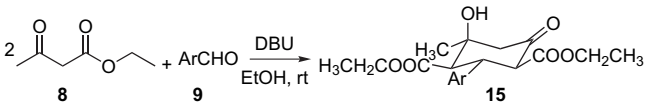
The formation of the cyclohexanones **10** provided impetus to investigate the reaction between ethyl acetoacetate and aromatic aldehyde in the presence of DBU, a stronger base which cannot form enamine intermediates, in order to understand (i) the roles of different bases in these tandem reactions and (ii) whether the formation of **10** in the pyrrolidine-catalysed reaction requires the intervention of the enamine intermediates depicted in Scheme 2.

It was found that even when aromatic aldehydes and ethyl acetoacetate were taken in a 3:2 molar ratio in the presence of DBU, only **15** was obtained. Under these conditions, the cyclohexanones **10** could not be detected even in trace amounts. This can probably be taken as indirect evidence for the formation of **10**, in the presence of pyrrolidine, via enamine intermediates (Scheme 2). In the present work, eight compounds **15a–h** were synthesised by the reaction of ethyl acetoacetate with aromatic aldehydes in a molar ratio of 2:1 in the presence of DBU (Scheme 3). During the preparation of the manuscript we happen to find the work of Pandiarajan et al.[24] on the synthesis of the keto esters **15** by condensing ethyl acetoacetate with aromatic aldehyde



Scheme 2. Mechanism for the pyrrolidine-catalysed formation of **10**.

in the presence of methylamine as base. A significantly increased yield of **15a–h** 85–95% (Table 3) is obtained in the present work relative to 65–75% reported by Pandiarajan et al.[24]



9 and **15**	Ar
a	C_6H_5
b	4-ClC_6H_4
c	4-$CH_3C_6H_4$
d	4-$CH_3OC_6H_4$
e	4-$O_2NC_6H_4$
f	4-FC_6H_4
g	3-$O_2NC_6H_4$
h	2-ClC_6H_4

Scheme 3.

The structure of the cyclohexanones **15a–h** has been elucidated using elemental analysis and NMR spectroscopic data as illustrated below for ketone **15a**. The three-proton singlet at 1.34 ppm is assigned to the methyl group. The H–H-COSY spectrum shows that the triplets at 0.79 and 1.04 ppm and the multiplets at 3.84 and 4.01 ppm are ascribable to the ethyl ester. The 1H doublet at 3.68 ppm with J=12.6 Hz is assigned to H-2, which has a H–H-COSY correlation with the multiplet centred at 4.00 ppm assignable to H-3. The other doublet at 3.03 ppm is assigned to H-4 since it shows H–H-COSY correlation with H-3. That the diastereotopic protons at C-6 give one doublet at 2.72 ppm (J=14.2 Hz) and a doublet of doublets at 2.51 ppm (J=14.2 and 2.5 Hz), is evident from their HMBC correlations (Fig. 4) with the signal of the C-1 at 201.7 ppm. The doublet at 3.73 ppm (J=2.5 Hz) is due to the OH proton, which has a long-range coupling with H-6ax due to W arrangement (Fig. 4), which is probably stabilised by some electrostatic attraction between the ester carbonyl and the OH proton. That the W arrangement is possible only between the OH proton and H-6ax (but not with H-6eq) is helpful in distinguishing the signals of H-6ax and H-6eq. The appearance of the signal of the OH proton upfield at 3.73 ppm suggests that the intramolecular hydrogen bonding between the ester carbonyl and the OH is not strong. Probably, the distance between the OH proton and the ester carbonyl is more than that required for optimal hydrogen bonding in this system. The fairly large ^4J value of 2.5 Hz suggests that the rotamer depicted in Figure 4 probably is the most populated one enabling facile W arrangement between the hydroxyl and H-6ax protons.

Table 3. Yields and mp of *t*(3)-aryl-*r*(2),*c*(4)-bisethoxycarbonyl-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones **15**

Compd	mp °C (lit. mp °C)	Lit. yield (%)	Yield (%)
15a	155 (156)[24]	75	90
15b	160 (162)[24]	73	95
15c	146[a]	—	86
15d	142 (144)[24]	75	88
15e	189 (188)[24]	68	86
15f	162[a]	—	91
15g	151 (152)[24]	65	85
15h	154[a]	—	87

[a] New compounds.

The ^{13}C NMR spectra of each of the compounds of **15a–h** have two signals in the range 166.8–174.5 ppm ascribable to the ester carbonyl carbons at C-2 and C-4. They also have a signal in the range of 200.8–203.7 ppm ascribable to C-1. The signals of **15a–h** in the range 114.1–158.8 ppm are due to the aromatic carbons, among which the less intense ones in the region, 130.2–158.8 ppm, arise from the *ipso* carbons. The saturated carbon signals of the ring system, C-2 to C-6, occur in the range 43.5–73.8 ppm, assigned using proton chemical shifts and C–H-COSY correlations. The NMR spectroscopic data and assignments of the signals for **15** in the present work are in good agreement with those reported for five compounds in the literature.[24]

The probable mechanism for the formation of **15**, in the presence of DBU via intermediate **11** is depicted in Scheme 4. This intermediate **11** is common to the formation of **10** as well (Scheme 2). In the presence of DBU, **11** presumably forms enol **14**, which undergoes an intramolecular aldol reaction resulting in the formation of the six-membered ring **15** (Scheme 4). This occurs preferentially to the intermolecular reaction with an aromatic aldehyde, which could subsequently lead to the formation of **10** explicable by entropy considerations. The formation of **15** from the dienamine in

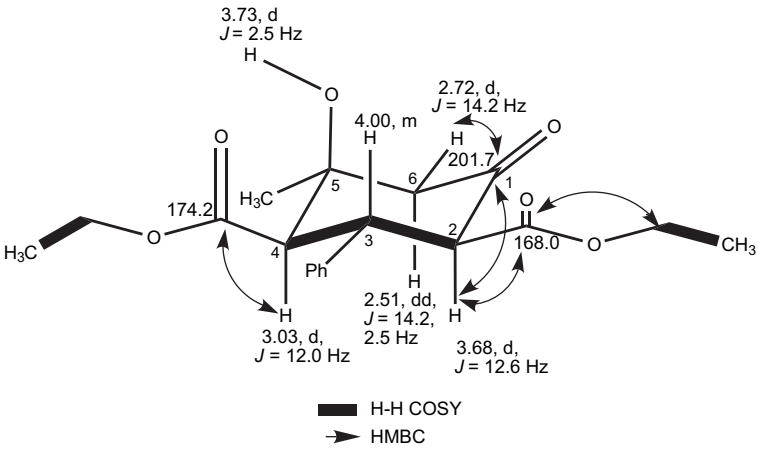
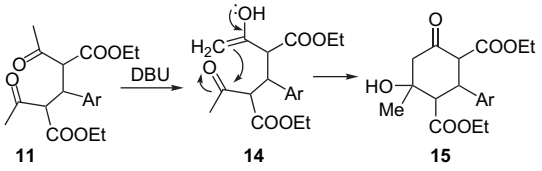
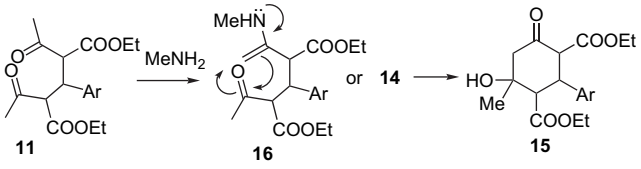


Figure 4. Selected 1D NMR data and 2D NMR correlations for **15a**.

the pyrrolidine-catalysed reaction appears unlikely as this would require the reaction between two nucleophilic enamine functionalities. From the selective formation of **10** in the presence of pyrrolidine, it is further clear that the monoenamine that would be formed initially from **11** en route to **12**, also presumably finds it facile either to undergo an intermolecular reaction with an aldehyde or to form the dienamine, relative to the intramolecular reaction with the keto functionality which would yield **15**. In the case of methylamine,[24] enamine intermediates (mono- and di-enamines) can be formed. However, in view of the diminished steric hindrance associated with the monoenamine **16** (relative to the pyrrolidine enamine), **16** can undergo an intramolecular reaction with the acetyl group affording **15** (Scheme 5). It is also possible for the methylamine catalysed reaction to proceed via the mechanism depicted in Scheme 4 alternatively through enol **14**. Thus the product selectivity of the reaction of ethyl acetoacetate with aromatic aldehyde is delicately tuned by the nature of the catalysts employed.



Scheme 4. Mechanism for the DBU catalysed formation of **15**.



Scheme 5. Mechanism for the methylamine catalysed formation of **15**.

3. Conclusion

A rapid one-pot five-component tandem protocol has been developed for the stereoselective synthesis of novel cyclohexanones **10** from ethyl acetoacetate and aromatic aldehydes in the presence of pyrrolidine. Further advantages of this method are the ready availability of the reagents, their low cost and mild conditions rendering it a useful and attractive strategy for the rapid synthesis of cyclohexanones **10**. The reaction of ethyl acetoacetate with aromatic aldehydes in the presence of DBU provided a better yield of **15** than the literature method. The present work demonstrates that the product selectivity of the reaction of ethyl acetoacetate with aromatic aldehyde can be fine-tuned by employing appropriate catalysts, which incidentally provides a deeper insight into the mechanistic aspects underlying these reactions.

4. Experimental

4.1. General methods

The mp of the cyclohexanones are uncorrected. Unless stated otherwise, solvents and chemicals were obtained from commercial sources and were used without further purification. Flash chromatography was performed on silica gel (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker (Avance) NMR spectrometer at 300 and 75 MHz, respectively, and the chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. Two-dimensional NMR spectra were also measured in the same instrument employing standard Bruker software throughout. Elemental analyses were performed on a Perkin–Elmer 2400 Series II Elemental CHNS Analyser. Optimisation of molecular geometry using MM2 calculations was performed by Hyperchem version 7.0 software. Petroleum ether employed in column chromatographic purification refers to the fraction, which boils at 40–60 °C.

4.2. General procedure for the synthesis of *t*(3),*t*(5)-diaryl-*t*(4)-[(*E*)-3-aryl-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanones 10a–g

To a mixture of pyrrolidine (0.08 ml, 0.98 mmol) and ethyl acetoacetate **8** (0.5 ml, 3.9 mmol), aromatic aldehyde **9** (Ar=C_6H_5) (0.6 ml, 5.9 mmol) and ethanol (3 ml) were added and the reaction mixture stirred at room temperature for 2–6 days to ensure completion of the reaction, which was monitored using TLC. Then the reaction mixture was extracted with chloroform (15 ml), washed with water, dried over (Na_2SO_4) and concentrated under reduced pressure.

The crude product was purified by flash column chromatography on silica gel [pet. ether/ethyl acetate (4:1 v/v) as eluent].

4.2.1. *t*(3),*t*(5)-Diphenyl-*t*(4)-[(*E*)-3-phenyl-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10a. Isolated as a pale yellow solid (63%), mp=208 °C; IR (KBr) ν 1740, 1733, 1704, 1648 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.08 (t, J=7.2 Hz, 3H), 2.66 (dd, J=12.9 and 1.8 Hz, 1H), 3.67 (m, 1H), 3.69 (t, J=12.9 Hz, 1H), 3.85 (t, J=4.4 Hz, 1H), 3.94 (dd, J=12.9 and 4.4 Hz, 1H), 4.06 (m, 2H), 4.93 (d, J=12.9 Hz, 1H), 5.78 (d, J=16.2 Hz, 1H), 6.83 (d, J=16.2 Hz, 1H), 7.03–7.26 (m, 15H). ^{13}C NMR: δ 14.4, 42.3, 46.4, 49.3, 56.1, 58.1, 61.3, 127.5, 127.8, 127.9, 128.6, 128.7, 129.0, 129.0, 129.2, 130.8, 134.5, 139.3, 140.2, 142.8, 169.7, 202.7, 206.1.

Anal. Calcd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.24; Obsd C, 79.55; H, 6.15.

4.2.2. *t*(3),*t*(5)-Bis(4-chlorophenyl)-*t*(4)-[(*E*)-3-(4-chlorophenyl)-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10b. Isolated as a pale yellow solid (66%), mp=215 °C; IR (KBr) ν 1749, 1718, 1697, 1643 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.09 (t, J=7.2 Hz, 3H), 2.63 (dd, J=12.9 and 2.2 Hz, 1H), 3.64 (m, 1H), 3.71 (t, J=12.9 Hz, 1H), 3.83 (t, J=4.4 Hz, 1H), 3.97 (dd, J=12.9 and 4.4 Hz, 1H), 4.12 (m, 2H), 4.98 (d, J=12.9 Hz, 1H), 5.82 (d, J=15.9 Hz, 1H), 6.91 (d, J=15.9 Hz, 1H), 7.12–7.29 (m, 12H). ^{13}C NMR: δ 14.1, 42.6, 46.5, 49.1, 56.5, 58.4, 61.2, 127.1, 127.6, 127.7, 128.4, 128.6, 129.2, 129.3, 129.5, 130.4, 134.8, 139.8, 140.7, 142.4, 169.9, 202.3, 206.0.

Anal. Calcd for $C_{30}H_{25}Cl_3O_4$: C, 64.82; H, 4.53; Obsd C, 64.76; H, 4.49.

4.2.3. *t*(3),*t*(5)-Bis(4-methylphenyl)-*t*(4)-[(*E*)-3-(4-methylphenyl)-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10c. Isolated as a pale yellow solid (62%), mp=193 °C; IR (KBr) ν 1742, 1727, 1701, 1652 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.08 (t, J=7.2 Hz, 3H), 2.21 (s, 6H), 2.23 (s, 3H), 2.65 (dd, J=12.9 and 1.8 Hz, 1H), 3.60 (m, 1H), 3.69 (t, J=12.9 Hz, 1H), 3.84 (t, J=4.4 Hz, 1H), 3.96 (dd, J=12.9 and 4.4 Hz, 1H), 4.15 (m, 2H), 4.95 (d, J=12.9 Hz, 1H), 5.78 (d, J=16.2 Hz, 1H), 6.95 (d, J=16.2 Hz, 1H), 7.10–7.41 (m, 12H). ^{13}C NMR: δ 13.9, 21.0, 21.1, 21.2, 42.2, 46.3, 49.1, 56.7, 58.5, 61.6, 127.3, 127.9, 128.1, 128.6, 128.8, 129.5, 129.6, 129.8, 130.7, 135.1, 139.9, 140.8, 142.7, 170.2, 201.4, 207.1.

Anal. Calcd for $C_{33}H_{34}O_4$: C, 80.13; H, 6.93; Obsd C, 80.20; H, 6.96.

4.2.4. *t*(3),*t*(5)-Bis(4-methoxyphenyl)-*t*(4)-[(*E*)-3-(4-methoxyphenyl)-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10d. Isolated as a pale yellow solid (60%), mp=185 °C; IR (KBr) ν 1738, 1719, 1706, 1660 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.04 (t, J=7.2 Hz, 3H), 2.61 (dd, J=13.2 and 2.2 Hz, 1H), 3.62 (m, 1H), 3.71 (t, J=13.2 Hz, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 3.84 (t, J=4.4 Hz, 1H), 3.95 (dd, J=13.2 and 4.4 Hz, 1H), 4.11 (m, 2H), 4.95 (d, J=13.2 Hz, 1H), 5.84 (d, J=16.2 Hz, 1H), 6.90 (d, J=16.2 Hz, 1H), 6.89–7.27 (m, 12H). ^{13}C NMR: δ 13.8, 42.1, 45.9, 48.6, 54.9, 55.0, 55.1, 55.9, 58.1, 61.4, 114.7, 115.0, 115.3, 127.1, 128.1, 128.4, 129.0, 129.3, 130.2, 134.7, 139.6, 140.5, 142.3, 169.9, 202.9, 206.1.

Anal. Calcd for $C_{33}H_{34}O_7$: C, 73.04; H, 6.32; Obsd C, 72.93; H, 6.25.

4.2.5. *t*(3),*t*(5)-Bis(2-chlorophenyl)-*t*(4)-[(*E*)-3-(2-chlorophenyl)-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10e. Isolated as a pale yellow solid (68%), mp=210 °C; IR (KBr) ν 1745, 1730, 1697, 1647 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.06 (t, J=7.2 Hz, 3H), 2.65 (dd, J=12.9 and 1.8 Hz, 1H), 3.65 (m, 1H), 3.70 (t, J=12.9 Hz, 1H), 3.85 (t, J=4.4 Hz, 1H), 3.97 (dd, J=12.9 and 4.4 Hz, 1H), 4.11 (m, 2H), 4.99 (d, J=12.9 Hz, 1H), 5.83 (d, J=16.2 Hz, 1H), 6.90 (d, J=16.2 Hz, 1H), 7.12–7.35 (m, 12H). ^{13}C NMR: δ 14.0, 42.7, 46.6, 49.2, 56.6, 58.5, 61.1, 127.0, 127.3, 127.6, 127.7, 128.1, 128.3, 128.4, 128.6, 129.1, 129.2, 129.3, 129.5, 129.7, 130.3, 134.7, 139.9, 140.6, 142.3, 142.6, 169.7, 201.8, 206.9.

Anal. Calcd for $C_{30}H_{25}Cl_3O_4$: C, 64.82; H, 4.53; Obsd C, 64.70; H, 4.44.

4.2.6. *t*(3),*t*(5)-Bis(2-methoxyphenyl)-*t*(4)-[(*E*)-3-(2-methoxyphenyl)-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10f. Isolated as a pale yellow solid (59%), mp=172 °C; IR (KBr) ν 1741, 1722, 1690, 1651 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.06 (t, J=7.2 Hz, 3H), 2.60 (dd, J=13.2 and 1.8 Hz, 1H), 3.63 (m, 1H), 3.70 (t, J=13.2 Hz, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 3.85 (t, J=4.4 Hz, 1H), 3.96 (dd, J=13.2 and 4.4 Hz, 1H), 4.13 (m, 2H), 4.97 (d, J=13.2 Hz, 1H), 5.86 (d, J=15.8 Hz, 1H), 6.96 (d, J=15.8 Hz, 1H), 6.85–7.37 (m, 12H). ^{13}C NMR: δ 13.5, 42.5, 46.2, 48.8, 54.9, 55.0, 55.1, 56.2, 58.3, 61.5, 114.9, 115.1, 115.5, 127.1, 127.2, 128.3, 128.5, 128.6, 129.2, 129.7, 129.8, 129.9, 130.2, 130.6, 130.9, 134.7, 139.6, 140.5, 142.5, 169.6, 201.7, 206.6.

Anal. Calcd for $C_{33}H_{34}O_7$: C, 73.04; H, 6.32; Obsd C, 73.13; H, 6.25.

4.2.7. *t*(3),*t*(5)-Bis(2-methylphenyl)-*t*(4)-[(*E*)-3-(2-methylphenyl)-2-propenonyl]-*r*(2)-ethoxycarbonylcyclohexanone 10g. Isolated as a pale yellow solid (58%), mp=178 °C; IR (KBr) ν 1750, 1720, 1695, 1640 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 1.12 (t, J=7.2 Hz, 3H), 2.23 (s, 3H), 2.24 (s, 3H), 2.26 (s, 3H), 2.68 (dd, J=12.9 and 1.8 Hz, 1H), 3.65 (m, 1H), 3.70 (t, J=12.9 Hz, 1H), 3.89 (t, J=4.4 Hz, 1H), 4.01 (dd, J=12.9 and 4.4 Hz, 1H), 4.16 (m, 2H), 4.96 (d, J=12.9 Hz, 1H), 5.83 (d, J=16.2 Hz, 1H), 6.98 (d, J=16.2 Hz, 1H), 7.07–7.58 (m, 12H). ^{13}C NMR: δ 13.4, 21.0, 21.1, 21.2, 42.6, 46.7, 49.5, 56.8, 58.9, 61.8, 126.8, 127.1, 127.4, 127.7, 127.9, 128.2, 128.4, 128.6, 128.8, 129.5, 129.6, 129.7, 129.8, 130.5, 130.7, 135.3, 139.4, 140.5, 142.3, 170.6, 202.5, 207.5.

Anal. Calcd for $C_{33}H_{34}O_4$: C, 80.13; H, 6.93; Obsd C, 80.26; H, 6.90.

4.3. General procedure for the synthesis of *t*(3)-aryl-*r*(2),*c*(4)-bisethoxycarbonyl-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones[25]

A mixture of ethyl acetoacetate (0.5 ml, 3.9 mmol), aromatic aldehyde (2 mmol) and DBU (0.15 ml, 1 mmol) in ethanol (3 ml) was stirred at room temperature for about 5–10 h. The precipitate formed was filtered and purified by recrystallisation from ethanol.

4.3.1. *t*(3)-(4-Methylphenyl)-*r*(2),*c*(4)-bisethoxycarbonyl-*c*(5)-hydroxy-*t*(5)-methylcyclohexanone 15c. Isolated as colourless needles (86%), mp=146 °C; IR (KBr) ν 3432, 1741, 1724 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 0.83 (t, J=7.2 Hz, 3H), 1.03 (t, J=7.2 Hz, 3H), 1.34 (s, 3H), 2.53 (dd, J=14.2 and 2.4 Hz, 1H), 2.73 (d, J=14.2 Hz, 1H), 3.04 (d, J=12.0 Hz, 1H), 3.67 (d, J=12.6 Hz, 1H), 3.74 (d, J=2.4 Hz, O*H*), 3.86 (m, 2H), 3.99 (m, 1H), 4.03 (m, 2H), 7.15–7.26 (m, 4H). ^{13}C NMR: δ 14.1, 14.3, 29.1, 45.5, 53.2, 57.5, 61.7, 63.1, 73.7, 128.6, 129.5, 129.9, 138.5, 168.1, 174.4, 201.4.

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23; Obsd C, 66.17; H, 7.21.

4.3.2. *t*(3)-(4-Fluorophenyl)-*r*(2),*c*(4)-bisethoxycarbonyl-*t*(5)-hydroxy-*c*(5)-methylcyclohexanone 15f. Isolated as colourless needles (91%), mp=162 °C; IR (KBr) ν 3513, 1735, 1714 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 0.84 (t, J=7.2 Hz, 3H), 1.11 (t, J=7.2 Hz, 3H), 1.39 (s, 3H), 2.56 (dd, J=14.2 and 2.2 Hz, 1H), 2.70 (d, J=14.2 Hz, 1H), 3.06 (d, J=12.2 Hz, 1H), 3.69 (m, 2H), 3.95 (m, 3H), 4.08 (m, 2H), 7.15–7.28 (m, 4H). ^{13}C NMR: δ 14.3, 14.5, 29.3, 45.2, 53.1, 57.5, 61.9, 63.0, 73.8, 124.5, 124.8, 127.6, 127.8, 132.4, 135.4, 166.8, 174.2, 202.6.

Anal. Calcd for $C_{19}H_{23}FO_6$: C, 62.29; H, 6.33; Obsd C, 62.25; H, 6.38.

4.3.3. *t*(3)-(2-Chlorophenyl)-*r*(2),*c*(4)-bisethoxycarbonyl-*t*(5)-hydroxy-*c*(5)-methylcyclohexanone 15h. Isolated as colourless needles (87%), mp=154 °C; IR (KBr) ν 3470, 1748, 1710 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ 0.81 (t, J=7.2 Hz, 3H), 1.04 (t, J=7.2 Hz, 3H), 1.31 (s, 3H), 2.48 (dd, J=14.2 and 2.2 Hz, 1H), 2.68 (d, J=14.2 Hz, 1H), 2.94 (d, J=12.0 Hz, 1H), 3.56 (m, 2H), 3.78 (m, 3H), 4.05 (m, 2H), 7.11–7.35 (m, 4H). ^{13}C NMR: δ 14.5, 14.7, 28.7, 44.5, 52.6, 56.8, 61.4, 62.4, 73.1, 118.7, 119.3, 129.7, 129.9, 133.5, 136.7, 168.1, 174.2, 203.7.

Anal. Calcd for $C_{19}H_{23}ClO_6$: C, 59.61; H, 6.06; Obsd C, 59.69; H, 6.16.

Acknowledgements

S.P. thanks the CSIR and DST, New Delhi, for funds under major research projects. S.P. also thanks DST for funds under the IRHPA programme for the purchase of a high-resolution NMR spectrometer and UGC for funds under the DRS and ASIST programmes. M.S. thanks CSIR for the award of a Senior Research Fellowship.

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Tetrahedron 62 (2006) 7733–7737

Convenient oxidation of alkylated phenols and methoxytoluenes to antifungal 1,4-benzoquinones with hydrogen peroxide (H_2O_2)/methyltrioxorhenium (CH_3ReO_3) catalytic system in neutral ionic liquid

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Received 9 March 2006; revised 11 May 2006; accepted 25 May 2006
Available online 15 June 2006

Abstract—Alkylated phenol and methoxytoluene derivatives were catalytically and selectively oxidized to the corresponding 1,4-benzoquinones in good conversions and yields. Reactions were performed with hydrogen peroxide (H_2O_2)/methyltrioxorhenium (CH_3ReO_3) in 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4, a neutral ionic liquid. Compounds were tested in vitro for their antifungal activity against the growth of several widespread soil fungi. Some of them were proved to be potent inhibitors of *Fusarium* sp. than ketoconazole, a commercially available and expensive antifungal agent.

1. Introduction

Benzoquinone derivatives are an important class of organic compounds playing a vital role in biosynthetic routes and being interesting starting materials for fine chemicals. Their redox properties are essential for the functioning of living cells. In fact, ubiquinones (coenzymes Q) act as biochemical oxidizing agents to mediate the electron-transfer processes involved in energy production; in plant tissues, plastoquinones perform a similar function in photosynthetic processes.[1] The 1,4-benzoquinone structure is often associated with several biological activities.[2] Among them, the efficiency against the growth of some fungal species was tested.[3] In addition, these compounds are useful intermediates for pharmaceutical and fine chemical synthesis. For example, 2,3,5-trimethyl-1,4-benzoquinone is a key compound in the synthesis of vitamin E; 2,3-dimethoxy-5-methyl-1,4-benzoquinone is useful for production of coenzyme Q; 2-methyl-1,4-naphthoquinone is the simplest synthesized vitamin K (vitamin K_3) and used for producing vitamin K_1;[4] substituted quinones are used as dienophiles for the synthesis of polycyclic compounds in the Diels–Alder reaction.[5]

Considering their various industrial applications, a selective and efficient method of obtaining 1,4-benzoquinones is an important goal. The simplest procedure is based on the oxidation of phenol derivatives, commercially available and inexpensive starting materials. In the last few years, the development of clean catalytic methods to perform this organic transformation selectively has received increasing attention as an alternative to the stoichiometric methods using ceric ammonium nitrate (CAN),[6] thallium(III) nitrate,[7] hypervalent iodine,[8] silver oxide or silver carbonate,[9] dipotassium nitrosodisulfonate (Fremy's salt),[10] Jones' reagent[11] or other toxic and hazardous reagents. The environmentally friendly procedures are typically based on the use of hydrogen peroxide (H_2O_2) as oxygen atom donor. Among the reported catalysts are diphenyl diselenide,[12] cobalt(II) and manganese(II) acetate,[13] titanium silicate,[14] titanium superoxide,[15] titanium aluminophosphates,[16] ruthenium(II)

Keywords: Hydrogen peroxide/methyltrioxorhenium; Catalytic oxidations; 1-Butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4; 1,4-Benzoquinones; Antifungal activity.
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0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.05.069

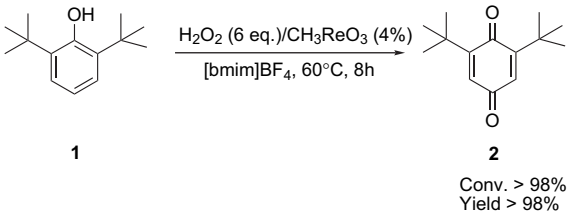
complex,[17] copper(II)–resin system,[18] titanium and silicon mixed oxides[19] and methyltrioxorhenium (CH_3ReO_3, MTO).[20,21] We focused our attention on the last catalyst utilized for oxidations in homogeneous as well as heterogeneous conditions in conventional organic solvents. Nevertheless, in homogeneous phase, strong acid conditions are required in the reaction medium and concentrated explosive hydrogen peroxide (83% water solution) was used.[20] In heterogeneous phase, less drastic experimental conditions have been utilized by some of us to oxidize simple methylphenols, anisoles and cardanol derivatives (ethanol, hydrogen peroxide 35% water solution).[21]

Continuing our studies on the environmentally friendly oxidative conversion of natural organic compounds in ionic liquids,[22] we report here the catalytic oxidation of alkylated phenol and methoxybenzene derivatives with the homogeneous hydrogen peroxide (H_2O_2)/methyltrioxorhenium (CH_3ReO_3) catalytic system in 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4, a neutral ionic liquid, to perform cleaner oxidative processes and to obtain biologically active compounds.

Ionic liquids are new generation solvents, which have received a great deal of attention in the last few years due to their broad range of potential use as reaction media in organic synthesis.[23] Their low vapour pressure, good thermal stability and high polarity make them even more attractive, environmentally friendly solvents for catalytic reactions with transition metal complexes.[24] To the best of our knowledge, only an interesting aerobic oxidation with copper(II) chloride of 2,3,6-trimethylphenol to the corresponding quinone was reported in ionic liquid but *n*-butanol was needed as co-solvent to increase the selectivity and activity of the catalyst.[25]

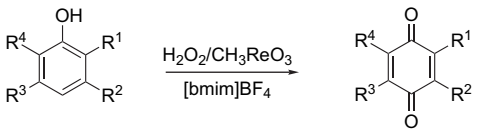
2. Results and discussion

As a model substrate for our initial experiments, we chose 2,6-di-*tert*-butylphenol **1** (Scheme 1). The substrate (1 mmol) was solubilized in 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 (1 ml) at 60 °C. Then, methyltrioxorhenium and hydrogen peroxide (50% water solution) were added. A quantitative and selective conversion of the phenol to the corresponding 1,4-benzoquinone was obtained after 8 h, adding an excess of hydrogen peroxide (6 equiv) and 4% of methyltrioxorhenium. It is known that this hindered benzoquinone is an interesting anticarcinogen but nontoxic agent (LD_{50}=3085 mg/kg).[26] We found that the hydrogen peroxide/methyltrioxorhenium catalytic system must be added in several batches (2 equiv of H_2O_2 and 1% of MTO) during the course of the experiment. In fact, if the catalytic system was added once, a lower conversion of substrate and yield of the quinone were obtained (30%). Probably, the catalyst decomposes during oxidation as reported by other authors.[20b] Therefore, in these experimental conditions, any attempts to make this process catalytic failed. In fact, at the end of first reaction, benzoquinone was extracted from the ionic solution by several small portions of diethyl ether, while a new substrate and more hydrogen peroxide were added into the ionic liquid solution to attempt to recycle the solvent. A dramatic decrease of the activity of the catalyst was observed (conversion and yield: 30%).



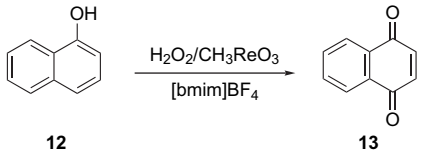
Scheme 1. Oxidation of 2,6-di-*tert*-butylphenol **1** with H_2O_2/CH_3ReO_3 catalytic system in [bmim]BF_4.

The good yield of the oxidative conversion of 2,6-di-*tert*-butylphenol **1** to the bioactive 1,4-benzoquinone **2** compared with the results obtained in acetic acid,[20a] and the environmentally friendly character of this methodology carried out in neutral reaction medium, encouraged us to extend it to other alkylated phenols and simple methoxytoluene derivatives to prepare useful active quinones. In fact, in similar experimental conditions, 2,6-diisopropylphenol **3**, 2,3,5-trimethylphenol **5**, 2,3,6-trimethylphenol **7**, 2-*tert*-butyl-5-methylphenol **8**, 2-*tert*-butyl-6-methylphenol **10** and 1-naphthol **12** were selectively converted to the corresponding 1,4-benzoquinones **4**, **6**, **9**, **11** and **13** in good conversions and yields (Schemes 2 and 3, Table 1). Benzoquinones **4** and **11** are very interesting compounds being potent inhibitors of DNA–benzo[*a*]pyrene adduct formation.[27] Good yields of 1,4-benzoquinones **15**, **17** and **19** (ubiquinone 0) were also obtained starting from 3,4-dimethoxytoluene **14**, 3,5-dimethoxytoluene **16** and 3,4,5-trimethoxytoluene **18** (Scheme 4, Table 2). In all cases, the oxidations in [bmim]BF_4 proceeded in good conversions and yields with an improvement with respect to those reported in acetic acid solutions.[20] Furthermore, reaction times were shorter and a lower amount of catalyst in ionic liquid solution was needed with respect to the oxidations in heterogeneous conditions.[21]



3, 4: R_1=R_4=$CH(CH_3)_2$, R_2=R_3=H
5, 6: R_1=R_2=R_3=CH_3, R_4=H
7: R_1=R_2=R_4=CH_3, R_3=H
8, 9: R_1= $C(CH_3)_3$, R_2= R_4=H, R_3=CH_3
10, 11: R_1= $C(CH_3)_3$, R_2= R_3=H, R_4=CH_3

Scheme 2. Oxidation of alkylated phenols **3**, **5**, **7**, **8** and **10** with the H_2O_2/CH_3ReO_3 catalytic system in [bmim]BF_4.

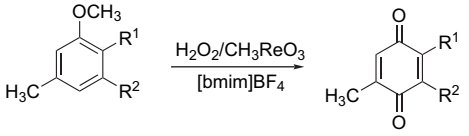


Scheme 3. Oxidation of 1-napthol **12**.

Table 1. Oxidation of phenols depicted in Schemes 2 and 3

Entry	Substrate	Conditions	Conversion (%)	Yield (%)[a]
1	**3**	H_2O_2 (6 equiv), MTO (4%), 60 °C, 6 h	>98	**4**: 82
2	**5**	H_2O_2 (6 equiv), MTO (4%), 40 °C, 6 h	>98	**6**: >98
3	**7**	H_2O_2 (6 equiv), MTO (4%), 40 °C, 6 h	>98	**6**: >98
4	**8**	H_2O_2 (6 equiv), MTO (4%), 60 °C, 10 h	>98	**9**: >98
5	**10**	H_2O_2 (6 equiv), MTO (4%), 60 °C, 12 h	>98	**11**: >98
6	**12**	H_2O_2 (8 equiv), MTO (4%), 60 °C, 24 h	>98	**13**: >98

[a] Conversions and yields were calculated by gas chromatographic analysis.



14, 16, 18 **15, 17, 19**

14, 15: R_1=OCH_3, R_2=H
16, 17: R_1=H, R_2=OCH_3
18, 19: R_1=R_2=OCH_3

Scheme 4. Oxidation of methoxybenzene derivatives **14**, **16** and **18** with the H_2O_2/CH_3ReO_3 catalytic system in [bmim]BF_4.

Table 2. Experimental data of oxidation of methoxybenzenes **14**, **16** and **18** in [bmim]BF_4[a]

Entry	Substrate	Conditions	Conversion (%)	Yield (%)
1	**14**	H_2O_2 (15 equiv), MTO (5%), 25 °C, 8 h	>98	**15**: >98
2	**16**	H_2O_2 (12 equiv), MTO (5%), 60 °C, 7 h	>98	**17**: 70
3	**18**	H_2O_2 (12 equiv), MTO (4%), 25 °C, 7 h	>98	**19**: >98

[a] Conversions and yields were calculated by gas chromatographic analysis.

3. Biological assay

The antifungal activity of some 1,4-benzoquinones obtained was investigated. Specifically, 2,6-di-*tert*-butyl-1,4-benzoquinone **2**, 2,3,5-trimethyl-1,4-benzoquinone **6**, 2-*tert*-butyl-5-methyl-1,4-benzoquinone **9**, 2-*tert*-butyl-6-methyl-1,4-benzoquinone **11**, 2,3-dimethoxy-6-methyl-1,4-benzoquinone **15** and 2,3-dimethoxy-5-methyl-1,4-benzoquinone **19** were tested in vitro for their growth inhibitory activity against some widespread soil fungi *Trichoderma koningii*, *Paecilomyces lilacinum*, *Aspergillus flavus*, *Penicillium roseopurpureum*, *Geomyces pannorum var. pannorum*, *Fusarium* sp. and a secondary plant pathogen *Pestalotia* sp. by the standard method.[28] The MIC values of these benzoquinones were determined and compared with the ketoconazole, a well known commercially available and expensive compound possessing strong antifungal activity, used as positive control in all tests. As indicated in Table 3, only quinones **6** and **9** were active against *A. flavus* and *Pestalotia* sp. These same compounds exhibited antifungal activities also against *T. koningii*, *P. roseopurpureum*, *G. pannorum* var. *pannorum* but weaker than ketoconazole; on the contrary, they are more potent inhibitors against *Fusarium* sp. than ketoconazole as well as quinones **15** and **19**.

4. Conclusions

An efficient and environmentally friendly procedure for the selective conversion of alkylated phenols and methoxytoluenes to the corresponding 1,4-benzoquinones is described. Reactions were performed with a hydrogen peroxide (H_2O_2)/methyltrioxorhenium (CH_3ReO_3) catalytic system in 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4, a neutral ionic liquid, as solvent. The antifungal activity of some of these 1,4-benzoquinones was investigated in vitro against some widespread soil fungi *T. koningii*, *P. lilacinum*, *A. flavus*, *P. roseopurpureum*, *G. pannorum var. pannorum*, *Fusarium* sp. and a secondary plant pathogen *Pestalotia* sp. Compounds **6**, **9**, **15** and **19** were proved more potent inhibitor against *Fusarium* sp. than ketoconazole, a commercially available antifungal agent.

5. Experimental

Phenols and methoxybenzenes are commercially available (Aldrich) and were used as purchased. 1-Butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 was prepared according to Ref. 29. Thin layer chromatography was carried out using Merck platen Kieselgel 60 F254. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). NMR spectra were recorded on a Bruker (200 MHz) spectrometer and are reported in δ values.

Table 3. Antifungal activity of *p*-benzoquinones **2**, **6**, **9**, **11**, **15** and **19** in vitro against soil fungi *Trichoderma koningii*, *Paecilomyces lilacinum*, *Aspergillus flavus*, *Penicillium roseopurpureum*, *Geomyces pannorum var. pannorum*, *Fusarium* sp. and a secondary plant pathogen, *Pestalotia* sp. compared with ketoconazole (standard agent)

	MIC[a] (μg/ml)						
Tested compound	*Trichoderma koningii*	*Paecilomyces lilacinum*	*Aspergillus flavus*	*Penicillium roseopurpureum*	*Geomyces pannorum var. pannorum*	*Fusarium* sp.	*Pestalotia* sp.
2	100	—	—	100	100	—	—
6	50	50	100	50	25	100	100
9	100	25	100	25	12.5	100	50
11	100	100	—	50	50	—	—
15	50	50	—	12.5	25	100	—
19	50	100	—	25	12.5	100	—
Ketoconazole	3.12	1.56	0.37	1.56	0.20	>100	6.25

[a] The MIC value (minimum inhibitory concentration) was defined as the lowest concentration of the antifungal agent at which there was no visible colonial growth.

Mass spectra were recorded on a VG 70/250S spectrometer with an electron beam of 70 eV. Melting points were determined on a Buchi SMP apparatus.

5.1. Oxidation of phenols: general procedure

The substrate (1.0 mmol) was solubilized in [bmim]BF_4 (1 ml) at 25–60 °C. Then, hydrogen peroxide (50% aqueous solution, 6–12 equiv) and methyltrioxorhenium (4–5%) were added in several batches (2 equiv of H_2O_2 and 1% of MTO) during the course of the experiment (6–24 h). Reactions were monitored by thin layer chromatography and by gas chromatography, using dodecane as an internal standard. The GC analysis was performed using a CP-SIL 8 CB-MS column (25 m×0.25 mm and 0.25 mm film thickness) and an isothermal temperature profile of 60 °C for 2 min, followed by a 10 °C/min temperature gradient to 250 °C for 10 min. The injector temperature was 250 °C. The oxidation products were extracted with diethyl ether and the organic layer was evaporated under vacuum. Benzoquinones were purified by flash column chromatography on silica gel and were identified by spectroscopic analysis, mass spectrometry and comparison with authentic commercial samples.

5.1.1. 2,6-Di-*tert*-butyl-1,4-benzoquinone (2). Orange solid; mp 66–68 °C (lit.[30] 65–68 °C).

5.1.2. 2,6-Diisopropyl-1,4-benzoquinone (4). Yellow oil.[31] [Found: C, 75.2; H, 8.0; O, 16.8. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4; O, 16.6%]; ν_{max} (KBr): 1605, 1650, 3050 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 1.14 (12H, d, $2CH(CH_3)_2$), 3.08 (2H, hept, J=6.8 Hz, $CH(CH_3)_2$), 6.47 (2H, s, CH=$CCH(CH_3)_2$); δ_C (200 MHz, $CDCl_3$) 21.1, 27.0, 129.8, 155.3, 186.8, 188.6; m/z 192 (M^+).

5.1.3. 2,3,5-Trimethyl-1,4-benzoquinone (6). Yellow solid; mp 27–29 °C (lit.[32] 29 °C).

5.1.4. 2-*tert*-Butyl-5-methyl-1,4-benzoquinone (9). Yellow oil. [Found: C, 74.5; H, 7.7; O, 17.8. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9; O, 18.0%]; ν_{max} (KBr): 1605, 1650, 2960, 3060 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 1.19 (9H, s, $C(CH_3)_3$), 1.96 (3H, d, J=1.5 Hz, CH_3), 6.46 (1H, q, J=1.5 Hz, CH=CCH_3), 6.52 (1H, s, CH=$CC(CH_3)_3$); δ_C (200 MHz, $CDCl_3$) 14.9, 29.1, 131.5, 135.9, 144.1, 156.0, 187.8, 188.9; m/z 178 (M^+).

5.1.5. 2-*tert*-Butyl-6-methyl-1,4-benzoquinone (11). Yellow oil. [Found: C, 74.5; H, 7.6; O, 17.9. $C_{11}H_{14}O_2$ requires C, 74.8; H, 7.4; O, 17.8%]; ν_{max} (KBr): 1600, 1650, 2960, 3060 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 1.10 (9H, s, $C(CH_3)_3$), 1.91 (3H, d, J=1.3 Hz, CH_3), 6.41 (2H, m, CH=CCH_3 and CH=$CC(CH_3)_3$); δ_C (200 MHz, $CDCl_3$) 16.1, 28.7, 131.3, 131.9, 147.6, 156.2, 187.6, 188.6; m/z 178 (M^+).

5.1.6. 1,4-Naphthoquinone (13). Yellow solid; mp 118–121 °C (lit.[33] 119–120 °C).

5.1.7. 2-Methoxy-5-methyl-1,4-benzoquinone (15). Yellow solid; mp 172–173 °C (lit.[34] 170–171 °C).

5.1.8. 2-Methoxy-6-methyl-1,4-benzoquinone (17). Yellow oil.[21] [Found: C, 63.8; H, 5.0; O, 31.2. $C_8H_8O_3$ requires C, 63.2; H, 5.3; O, 31.5%]; ν_{max} (KBr): 1665, 2850, 2920 cm^{-1}. δ_H (200 MHz, $CDCl_3$) 2.00 (3H, d, J=1.6 Hz, CH_3), 3.77 (3H, s, OCH_3), 5.83 (1H, s, CH=$COCH_3$), 6.48 (1H, q, J=1.6 Hz, CH=CCH_3); δ_C (200 MHz, $CDCl_3$) 15.0, 56.3, 107.2, 133.8, 142.1, 158.0, 181.0, 186.2; m/z 152 (M^+).

5.1.9. 2,3-Dimethoxy-5-methyl-1,4-benzoquinone (19). Red solid; mp 57–59 °C (lit.[35] 59 °C).

5.2. Assay of fungistatic activity of benzoquinone derivatives

Ketoconazole is commercially available (Merck) and was used as purchased. Antifungal activities were tested in modified Sabouraud dextrose agar (Difco Lab.)[36] against the following fungal strains: *A. flavus*, *G. pannorum var. pannorum*, *Fusarium* sp., *P. lilacinum*, *P. roseopurpureum*, *T. koningii* and *Pestalotia* sp. Stock solutions of quinones **2**, **6**, **9**, **11**, **15** and **19** were obtained in DMSO (5 mg/ml). These compounds were tested in the 0.1–100 μg/ml range, that was added to the modified Sabouraud dextrose agar. The fungi were applied to the surface of the agar (inoculum sizes approximately 1×10^7 conidia/ml). They were incubated at 28 °C up to a clearly visible growth on drug-free control. MIC values were read after 24 h for *P. roseopurpureum* and *T. koningii* and after 48 h for the *A. flavus*, *G. pannorum var. pannorum*, *Fusarium* sp., *P. lilacinum* and *Pestalotia* sp.

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Tetrahedron 62 (2006) 7738–7743
Tetrahedron

Oxazinins from toxic mussels: isolation of a novel oxazinin and reassignment of the C-2 configuration of oxazinin-1 and -2 on the basis of synthetic models

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Received 9 March 2006; revised 9 May 2006; accepted 25 May 2006
Available online 21 June 2006

Abstract—The analysis of a batch of toxic mussels (*Mytilus galloprovincialis*) from the Northern Adriatic Sea led to the isolation of a novel oxazinin, oxazinin-4. Its structure including the relative stereochemistry has been elucidated through extensive NMR analysis. A synthetic route to oxazinins has been crucial in establishing the absolute stereochemistry of oxazinin-4 and for reassigning the absolute C-2 configuration of oxazinin-1 and -2 previously isolated from toxic shellfish and stereostructurally characterized.

1. Introduction

During our continuous analysis on toxic shellfish from the Northern Adriatic Sea,[1] we have isolated and fully characterized several cytotoxic compounds[2–4] in addition to typical marine biotoxins. These cytotoxic compounds appear to be of great interest not only for their quite unique structural features, but also because they cause human seafood intoxication. In 2001, we reported the structure and the relative stereochemistry of three novel compounds oxazinin-1, -2, and -3 of which oxazinin-1 has emerged as a cytotoxic molecule.[5]

Subsequently, we have assigned the absolute stereochemistry of both oxazinin-1 and -2[6] by applying the Riguera's method (Fig. 1).[7] Recently, Couladouros et al. reported an effective synthesis of oxazinin-1, -2, and -3, which has allowed the absolute stereochemistry of these compounds to be determined (Fig. 2).[8]

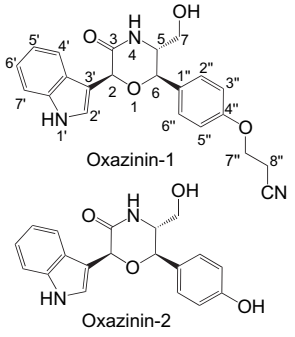

Figure 1. Previously reported stereostructures of oxazinin-1 and -2.[5]

In the present paper we report the structure of a novel diastereoisomer of oxazinin-1 (oxazinin-4) isolated from toxic mussels. The successive elucidation of the relative stereostructure of oxazinin-4 in combination with the isolation of a further amount of oxazinin-1 gave us the chance to

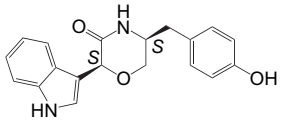

Figure 2. Stereostructure of oxazinin-3.

Keywords: Oxazinins; Adriatic shellfish; Natural products; Synthetic models; *Mytilus galloprovincialis*; NMR spectroscopy.
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doi:10.1016/j.tet.2006.05.070

reassess and correct the relative configuration of both oxazinin-1 and -2. A synthetic study allowed us to definitively confirm the C-2 configuration of oxazinin-1 and -2 and unambiguously assign the absolute stereochemistry of oxazinin-4.

2. Results and discussion

A toxic batch of mussels (*Mytilus galloprovincialis*) was collected along the Emilia Romagna coasts, Italy in March 2002 during a period of high toxicity. Oxazinin-4 was successfully isolated according to the previous reported procedure.[5] The chromatographic behavior, the preliminary NMR data, and the mass spectrum of this novel compound (Table 2 and Section 3) indicated a similar structure as oxazinin-1. Such a consideration eased us to individuate the presence of both an indole ring substituted at C-3 and a *para*-disubstituted phenyl ring linked to a $-OCH_2CH_2CN$ moiety. Running COSY, HOHAHA, and ROESY spectra were crucial to determine the spin system including C-5, C-6, C-7, and H-N-4. A strong IR absorption band at 1661 cm^{-1} along with a carbonyl carbon resonating at δ 169.4 ppm pointed out an amide functionality. Finally, correlations emerging from a HMBC experiment (Fig. 3) allowed to establish the planar structure of oxazinin-4.

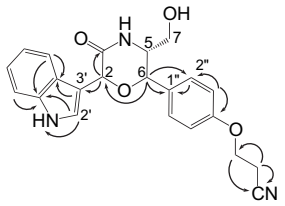


Figure 3. HMBC correlations for oxazinin-4.

Since the structure of oxazinin-4 was coincident with that reported for oxazinin-1 only a diastereoisomeric relationship between the two compounds could explain the significant differences in their chromatographic and NMR properties (Tables 1 and 2). A ROESY spectrum was indispensable for assigning the relative configuration of oxazinin-4. Assuming that this compound presented a preferential chair-like conformation in analogy with oxazinin-1,[5–6] an intense

Table 2. ^{13}C and ^{1}H NMR spectroscopic data[a] of oxazinin-4 and **9b** (CD_3CN)

Position	Oxazinin-4			Compound **9b**		
	δ_C (ppm)	δ_H (ppm)	J (Hz)	δ_C (ppm)	δ_H (ppm)	J (Hz)
2	75.3	5.48		75.6	5.43	
3	169.4			170.7		
4		6.61			6.66	
5	60.8	3.93		60.7	3.88	
6	77.6	4.79	9.7	78.1	4.69	9.9
7a	62.0	3.36		62.0	3.31	
7b		3.49			3.44	
1′		9.28			9.26	
2′	126.8	7.37		126.2	7.33	
3′	112.8			112.0		
3′a	126.8			126.9		
4′	120.0	7.42	8.2	120.3	7.41	8.2
5′	118.4	7.12	7.5, 8.2	120.5	7.08	7.7, 8.2
6′	120.1	7.20	7.5, 8.2	122.8	7.16	7.7, 8.2
7′	112.4	7.72	8.2	112.4	7.71	8.2
7′a	137.9			137.6		
1″	132.0			129.7		
2″–6″	130.4	7.41	8.4	129.8	7.25	8.2
3″–5″	116.0	6.98	8.4	116.1	6.79	8.2
4″	160.4			158.0		
7″	64.2	4.21	6.0			
8″	19.6	2.87	6.0			
CN	118.9					
7-OH		3.05			3.05	

[a] Assignments are based on HMQC and HMBC experiments.

Table 1. ^{13}C and ^{1}H NMR spectroscopic data of oxazinin-1, -2,[5] and **9a**[a] (CD_3CN)

Position	Oxazinin-1			Oxazinin-2			Compound **9a**		
	δ_C (ppm)	δ_H (ppm)	J (Hz)	δ_C (ppm)	δ_H (ppm)	J (Hz)	δ_C (ppm)	δ_H (ppm)	J (Hz)
2	72.9	5.59		72.8	5.57		72.8	5.57	
3	170.1			170.1			170.1		
4		6.70			6.64			6.64	
5	59.9	3.71		59.9	3.70		59.9	3.70	
6	71.1	4.61	9.2	71.2	4.56	9.2	71.2	4.56	9.2
7a	62.0	3.26		62.1	3.26		62.1	3.26	
7b		3.43			3.42			3.42	
1′		9.40			9.37			9.37	
2′	126.1	7.29		126.1	7.28		126.1	7.28	
3′	112.3			112.4			112.4		
3′a	127.5			127.5			127.5		
4′	120.1	7.58	8.2	120.1	7.58	8.2	120.1	7.58	8.2
5′	120.3	6.99	7.5, 8.2	120.3	7.00	7.7, 8.2	120.3	7.00	7.7, 8.2
6′	122.8	7.13	7.5, 8.0	122.8	7.14	7.7, 7.9	122.8	7.14	7.7, 7.9
7′	112.4	7.43	8.0	112.4	7.42	7.9	112.4	7.42	7.9
7′a	137.4			137.4			137.4		
1″	131.8			130.0			130.0		
2″–6″	130.0	7.20	8.4	129.9	7.08	8.4	129.9	7.08	8.4
3″–5″	115.5	6.88	8.4	116.0	6.73	8.4	116.0	6.73	8.4
4″	159.0			157.9			157.9		
7″	63.9	4.14	6.0						
8″	19.0	2.82	6.0						
CN	118.9								
7-OH		3.12			3.10			3.10	

[a] Assignments are based on HMQC and HMBC experiments.

ROE correlation between H-2 and H-6 was a clear clue of their cis-relationship, while the high coupling constant between H-5 and H-6 suggested their trans-orientation (Fig. 4).

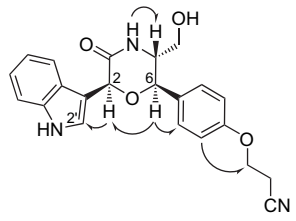
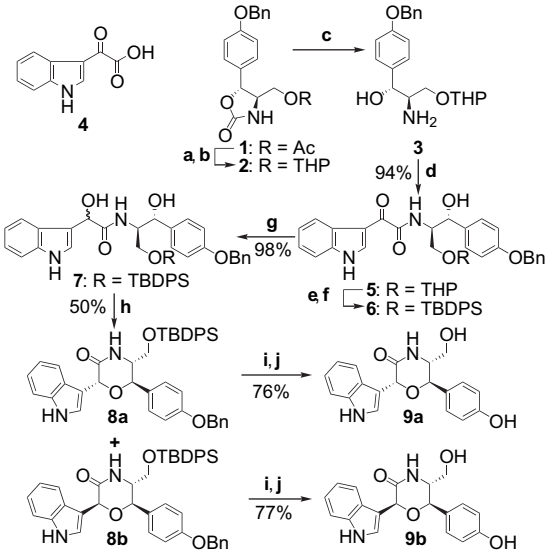


Figure 4. ROE correlations for oxazinin-4.

These data surprisingly pointed to the same relative stereochemistry reported for oxazinin-1. In order to clarify such an ambiguity, we decided to re-examine the ROE correlations of oxazinin-1. This time we did not detect any correlation between H-2 and H-6 in oxazinin-1 indicating an actual trans-orientation of the two protons. Since this time we could employ a more powerful NMR instrument, such as a 700 MHz instead of the 500 MHz, and rely on a larger availability of pure oxazinin-1 isolated along with oxazinin-4, we can confidently conclude that the H-2/H-6 ROE correlation described for oxazinin-1 in our precedent paper was actually an artifact possibly due to the low signal–noise ratio of the former experiment.

In order to unambiguously prove the stereochemistry of oxazinin-1 and -4, we undertook the synthesis set up by Couladouros et al. (Scheme 1). Thus, the prerequisite amine **3** was obtained by protective group manipulation of the known[9] tyrosine derivative **1**. Subsequent coupling with 3-indoleglyoxylic acid **4**[10] afforded amide **5**. A further protecting group switched to the more stable *tert*-butyldiphenylsilyl ether **6**. Subsequent reduction of the keto functionality with $NaBH_4$ provided diol **7**, as a 1:1 mixture of diastereomers, thus setting the stage for the crucial morpholinone ring-forming step. Treatment of a solution of diol **7** in refluxing acetonitrile with PPTS afforded C-2 epimers **8a** and **8b**. Finally, debenzylation and silyl deprotection gave phenols **9a** and **9b**.



Scheme 1. Preparation of morpholinones **9a** and **9b**. Reagents and conditions: (a) 3 N $LiOH_{(aq)}$/THF/MeOH (1:10:10 v/v), 0 °C, 10 min; (b) DHP, PPTS, CH_2Cl_2, reflux, 1 h, 93% for two steps; (c) 3% $KOH_{(aq)}$/toluene (1:1 v/v), reflux; (d) **4**, EDC, HOBt, *N*,*N*-diisopropylethylamine, CH_2Cl_2/DMF (14:1 v/v), 0 °C→2 h, rt→22 h, 94% for two steps; (e) TsOH, MeOH, rt, 20 min, 98%; (f) TBDPSCl, 2,6-lutidine, 55 °C, 24 h, 95%; (g) $NaBH_4$, MeOH/THF (1:1 v/v), 0 °C→rt, 30 min, 98%; (h) PPTS, CH_3CN, reflux, 2 h, 50% combined yield; (i) H_2, $Pd(OH)_2$/C, EtOAc/EtOH (4:1 v/v), rt, 8 h; (j) 1.0 M TBAF, THF, rt, 30 min; **9a** 76% for two steps, **9b** 77% for two steps.

Once isolated, compounds **9a** and **9b** were fully investigated by NMR. Basically, a difference in their ROESY spectra was observed: a strong correlation peak between H-2 and H-6 was present in the spectrum of **9b**, while it was missing in the spectrum of **9a** (Fig. 5).

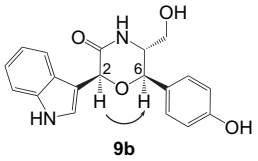


Figure 5. ROE correlation in compound **9b** indicating the cis-relationship of H-2 and H-6.

A comparison of NMR data and optical rotation collected on both the synthetic compounds with those recorded for the natural molecules (Tables 1 and 2) led us to unambiguously correlate **9a** to oxazinin-2. This was crucial for confirming the absolute stereochemistry previously assigned at C-5 and C-6, and for re-examining and properly reassigning the stereochemistry at C-2 as *R* (Fig. 6). Once established the overlapping of oxazinin-2 with **9a**, we could extend our analysis to oxazinin-1. In fact, the difference between oxazinin-1 and **9a**/oxazinin-2 is restricted to the presence of the $-OCH_2CH_2CN$ segment, which does not affect significantly the optical rotation. As a consequence, the absolute stereochemistry at C-5 and C-6 of oxazinin-1 was confirmed and the stereochemistry at C-2 was reassigned again as *R* (Fig. 6). Similarly, the absolute stereochemistry of oxazinin-4 was achieved on the basis of the parallelism of the

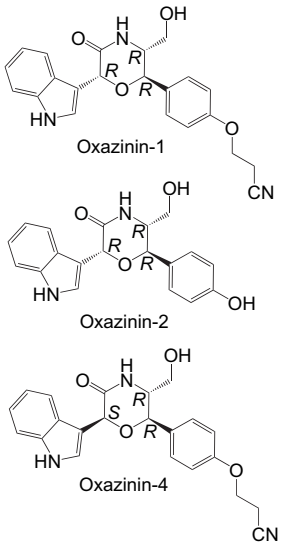


Figure 6. Absolute stereochemistry of oxazinin-1, -2, and -4.

optical rotation and NMR properties of oxazinin-4 with those of compound **9b** (Table 2; Fig. 6).

In conclusion, a novel oxazinin has been isolated and stereostructurally characterized; and a synthetic route to oxazinin-2 has given the opportunity to correct the absolute stereochemistry of oxazinin-1 and -2.

3. Experimental

3.1. General

NMR spectra were measured on a Varian Unity Inova700 spectrometer and the solvent was used as an internal standard (CD_3CN: δ_H 1.94; δ_C 1.3 and 118.2). ESI positive ion mode spectra were obtained on a API-2000 triple quadrupole mass spectrometer equipped with a turbo ion spray source (Applied biosystem, Thornhill, ON, Canada). Optical rotations were measured on a Perkin–Elmer 192 polarimeter in methanol solution, using a sodium lamp at 589 nm. NMR and MS experiments were performed at 'Centro di Servizi Interdipartimentale di Analisi Strumentale', Università degli Studi di Napoli Federico II.

Medium-pressure liquid chromatography (MPLC) was performed on a Buchi 861 apparatus equipped with Develosil ODS and Toyopearl HW-40 SF columns. HPLC separations were performed on a Varian apparatus equipped with Waters 490 MS UV and RI-3 index detectors and Luna 5u C18 and Luna 5u Silica columns. UV detector was set at 230 nm; TLC was performed on silica gel 60 plates (Merck, precoated), with EtOAc/MeOH (95:5) as a mobile phase; the oxazinins were detected by heating the plates after spraying with 50% sulfuric acid. All reactions were carried out under a dry argon atmosphere with anhydrous, freshly distilled solvents under anhydrous conditions unless otherwise noted. All reactions were magnetically stirred with Teflon stir bars, and temperatures were measured externally. Reactions requiring anhydrous conditions were carried out in oven dried (120 °C, 24 h) or flame dried (vacuum<0.5 Torr) glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR) obtained homogeneous materials. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

3.2. Collection and extraction

Toxic mussels *M. galloprovincialis* were collected along the coasts of Cesenatico (Adriatic Sea) in March 2002 at 3 m depth, which corresponds to the upper levels of mussel farm in this area. Reference specimens were deposited at the Dipartimento di Chimica delle Sostanze Naturali, Napoli, Italy. After collection, the mussels were stored at −20 °C until extraction. The digestive glands (5000 g of dry weight after extraction) were removed, homogenized with a Waring blender and extracted with CH_3CN/H_2O 8:2—0.1% HCOOH twice at room temperature. The combined extracts, after filtration, were concentrated in vacuo to give a residue, which was dissolved in CH_3CN/H_2O 2:1 and partitioned with CH_2Cl_2. The dichloromethane layer was concentrated and then chromatographed by MPLC on a Develosil ODS column using a solvent gradient system from 60% to 100% of methanol. The fraction eluted with 90% of methanol was successively separated on a Toyopearl HW-40 SF column with 100% methanol as an eluent. The fraction containing oxazinins was first purified on reverse phase HPLC eluted with $CH_3CN/H_2O/CH_3OH$ 15:50:35 and then on a silica gel HPLC column using EtOAc/CH_3OH 95:5 as an eluent to afford 1.2 mg of pure oxazinin-4.

3.2.1. Oxazinin-4. $[\alpha]_D^{25}$ +60.0 (*c* 0.2, MeOH). ν_{max} (KBr) 3478, 3342, 3186, 2930, 2262, 1661, 1623 cm^{-1}. ESI positive ion mode MS: *m/z* 391.9 $[M+H]^+$ and *m/z* 413.7 $[M+Na]^+$. HRMS (ESI positive ion mode): $[M+H]^+$, found 392.1627. $C_{22}H_{22}N_3O_4$ requires 392.1610. ^{1}H and ^{13}C NMR spectroscopic data (CD_3CN) are reported in Table 1. ^{1}H–^{1}H COSY correlations: H-5/H-6; H-5/H_2-7; H-5/7-OH; H-1′/H-2′; H-4′/H-5′; H-5′/H-6′; H-6′/H-7′; H-2″(6″)/H-3″(5″); $H_2$7″/$H_2$8″. HMBC correlations: H-2/C-3,C-2′, C-3′,C-3′a,C-6; H-6/C-2,C-1″,C-2″(6″); H-2′/C-3′,C-3′a, C-7′a; H-4′/C-3′,C-6′,C-7′a; H-5′/C-3′a,C-7′; H-6′/C-5′,C-7′a; H-7′/C-5′,C-3′a; H-2″(6″)/C-6,C-4″,C-6″(2″); H-3″(5″)/C-1″,C-4″,C-5″(3″); H-7″/CN; H-8″/C-7″,CN.

3.3. Synthetic studies

3.3.1. THP ether 2. Acetate **1** (1.5 g, 4.39 mmol) was dissolved in a mixture of THF/MeOH (40:40 mL), the solution was cooled to 0 °C, and aqueous LiOH (3 N, 4 mL) was added slowly. After 10 min the solution was neutralized with a 1 N aqueous HCl and extracted with EtOAc (3×50 mL). The combined organic extracts were washed with brine (2×30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. To a stirred solution of the above crude product (1.3 g) in dichloromethane (80 mL), 3,4-dihydro-2*H*-pyran (8 mL) was added at ambient temperature, followed by a catalytic amount of pyridinium *p*-toluenesulfonate (20 mg) and the mixture was refluxed at 80 °C. After 1 h the reaction mixture was poured into water (50 mL) and extracted with dichloromethane (2×50 mL). The combined organic extracts were washed with brine (2×50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc in hexane) affording 1.56 g (4.07 mmol) of the tetrahydropyranyl ether **2** (93% combined yield for two steps) as colorless amorphous solid. R_f=0.38 (60% EtOAc in hexane); $[\alpha]_D^{25}$ +62 (*c* 0.30, Acetone); ν_{max} (KBr) 3284, 1758, 1614, 1514 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.24 (m, 14H, Ar*H*), 7.00 (d, *J*=8.7 Hz, 4H, Ar*H*), 6.37 (d, *J*=3.7 Hz, 1H, N*H*CO), 6.30 (d, *J*=5.7 Hz, 1H, N*H*CO), 5.21 (m, 2H, ArC*H*OCO), 5.08 (s, 4H, OCH_2Ph), 4.65 (br s, 2H, OC*H*O), 3.97–3.80 (m, 6H, CH_2OTHP+ CH_2C*H*HO), 3.63–3.50 (m, 4H, C*H*NH+CH_2CH*H*O), 1.85–1.54 (m, 12H, CH_2CH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 159.1, 158.9, 136.6, 130.6, 130.5, 128.5, 128.5, 128.4, 128.2, 128.0, 127.4, 127.3, 127.2, 115.1, 99.4, 99.1, 80.1, 80.0, 70.0, 69.0, 68.8, 62.4, 62.3, 60.2, 59.9, 30.3, 30.2, 25.2, 25.1, 19.2, 19.1. HRMS (ESI positive ion mode): $[M+H]^+$, found 384.1828. $C_{22}H_{26}NO_5$ requires 384.1811.

3.3.2. Amide 5. An aqueous solution of 3% KOH (40 mL) was added to a stirred solution of cyclic carbamate **2** (1.5 g, 3.91 mmol) in toluene (40 mL) and the mixture was

warmed to reflux for 24 h. After cooling to ambient temperature the reaction mixture was poured into a saturated aqueous ammonium chloride (30 mL) neutralized with a 1 N aqueous HCl (pH=8) and extracted with EtOAc (3× 100 mL). The combined organic extracts were washed with brine (2×50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. To a stirred solution of the crude amine **3** (1.4 g, 3.91 mmol) and 3-indoleglyoxylic acid **4** (874 mg, 4.62 mmol) in a mixture of dichloromethane (500 mL) and DMF (36 mL) were added at 0 °C *N*,*N*-diisopropylethylamine (867 μL, 4.98 mmol), 1-hydroxy-benzotriazole (720 mg, 5.33 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (954 mg, 4.98 mmol). The temperature was maintained at 0 °C for 2 h, and then the mixture was warmed gradually to ambient temperature. After 22 h the reaction mixture was poured into water (200 mL) and extracted with dichloromethane (2× 200 mL). The combined organic extracts were washed with brine (2×200 mL), dried over Na_2SO_4, and concentrated under reduced pressure; the residue was purified by flash column chromatography (50% EtOAc in hexane) affording 1.95 g (3.68 mmol) of the amide **5** (94% yield) as colorless oil. R_f=0.30 (50% EtOAc in hexanes); $[\alpha]_D^{25}$ −80 (*c* 0.80, $CHCl_3$); ν_{max} (NaCl) 3393, 3284, 1743, 1683, 1633, 1500, 1455 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.08 (br s, 2H, ArN*H*), 8.92 (s, 2H, Ar*H*), 8.43 (d, *J*=7.6 Hz, 2H, Ar*H*), 8.29 (d, *J*=8.8 Hz, 1H, Ar*H*), 8.14 (d, *J*=8.8 Hz, 1H, Ar*H*), 7.44–7.24 (m, 20H, Ar*H*+N*H*CO), 6.94 (d, *J*=7.2 Hz, 4H, Ar*H*), 5.10 (m, 2H, C*H*OH), 5.02 (s, 4H, OCH_2Ph), 4.64 (br s, 1H, OC*H*O), 4.57 (br s, 1H, OC*H*O), 4.31 (m, 2H, C*H*NH), 3.98–3.79+3.69–3.53 (m, 4H+m, 6H, CH_2OTHP+ CH_2CH_2O+OH), 1.78–1.50 (m, 12H, CH_2CH_2CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.7, 180.3, 163.0, 162.8, 158.4, 138.2, 138.2, 135.7, 133.3, 128.5, 128.3, 127.9, 127.5, 126.6, 124.1, 124.1, 123.4, 123.3, 122.4, 114.8, 111.6, 99.8, 99.5, 74.3, 73.7, 70.0, 68.4, 68.0, 63.2, 62.5, 55.2, 54.7, 30.7, 30.3, 29.7, 25.2, 25.2, 19.9, 19.4; HRMS (ESI positive ion mode): $[M+H]^+$, found 529.2329. $C_{31}H_{33}N_2O_6$ requires 529.2338.

3.3.3. Amide 6-deprotection. To a stirred solution of amide **5** (1.95 g, 3.68 mmol) in MeOH (100 mL) was added a catalytic amount of *p*-toluenesulfonic acid monohydrate (30 mg) at ambient temperature. After 20 min the acid was quenched with a saturated aqueous $NaHCO_3$ (2 mL), the reaction mixture was poured into water (100 mL) and extracted with EtOAc (4×100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure; the residue was purified by flash column chromatography (50–80% EtOAc in hexane) affording 1.60 g (3.60 mmol) of the corresponding diol (98% yield) as amorphous white solid. R_f=0.33 (80% EtOAc in hexane); $[\alpha]_D^{25}$ −112 (*c* 0.98, Acetone); ν_{max} (KBr) 3395, 3286, 1736, 1684, 1618, 1509, 1431 cm^{-1}. ^1H NMR (500 MHz, Acetone-d_6): δ 11.3 (br s, 1H, ArN*H*), 8.99 (d, *J*=3.1 Hz, 1H, Ar*H*), 8.38 (m, 1H, Ar*H*), 8.03 (m, 1H, Ar*H*), 7.56 (m, 1H, Ar*H*), 7.46–7.26 (m, 8H, Ar*H*), 6.96 (d, *J*=8.7 Hz, 2H, Ar*H*), 5.17 (m, 1H, C*H*OH), 5.05 (s, 2H, OCH_2Ph), 4.87 (m, 1H, N*H*CO), 4.27 (m, 1H, OH), 4.17 (m, 1H, C*H*NH), 3.84 (m, 1H, CH*H*OH), 3.74 (m, 1H, C*H*HOH), 2.99 (s, 1H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.6, 163.3, 159.0, 139.7, 138.4, 137.2, 136.1, 129.2, 128.5, 128.4, 128.1, 127.7, 124.4, 124.4, 123.5, 122.7, 115.2, 113.1, 72.0, 70.3, 62.8, 57.9; HRMS (ESI positive ion mode): $[M+H]^+$, found 445.1777. $C_{26}H_{25}N_2O_5$ requires 445.1763.

3.3.4. Amide 6-protection. The above diol (1.1 g, 2.47 mmol) was dissolved in 2,6-lutidine (4 mL) and TPSCl (1.3 mL, 4.95 mmol) was added at ambient temperature. The mixture was warmed to 55 °C and stirred for 24 h. The reaction mixture was poured into saturated aqueous ammonium chloride (50 mL) and extracted with EtOAc (3×50 mL). The combined organic extracts were washed with saturated aqueous copper sulfate (2×30 mL) brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% EtOAc in hexane) affording 1.60 g (2.35 mmol) of the amide **6** (95% yield) as colorless oil. R_f=0.60 (50% EtOAc in hexane); $[\alpha]_D^{25}$ −29.0 (*c* 0.48, Acetone); ν_{max} (NaCl) 3398, 1739, 1681, 1641, 1635, 1510, 1430 cm^{-1}. ^1H NMR (500 MHz, CD_3CN): δ 10.2 (br s, 1H, ArN*H*), 8.83 (d, *J*=3.2 Hz, 1H, Ar*H*), 8.33 (m, 1H, Ar*H*), 7.86 (d, *J*=9.3 Hz, 1H, Ar*H*), 7.75–7.62 (m, 5H, Ar*H*), 7.55 (m, 1H, Ar*H*), 7.46–7.26 (m, 14H, Ar*H*+CON*H*), 6.92 (d, *J*=8.6 Hz, 2H, Ar*H*), 5.05 (br s, 3H, OCH_2Ph+C*H*OH), 4.23 (br s, 1H, OH), 4.18 (m, 1H, C*H*NH), 3.80 (m, 1H, CH*H*OTBDPS), 3.67 (m, 1H, C*H*HOTBDPS), 1.01 (s, 9H, (CH_3)$_3$C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.8, 136.4, 136.4, 135.6, 130.9, 130.4, 129.4, 129.3, 128.8, 128.6, 128.5, 124.8, 123.9, 122.7, 115.4, 113.3, 72.2, 70.5, 64.4, 57.7, 27.2, 27.0; HRMS (ESI positive ion mode): $[M+H]^+$, found 683.2920. $C_{42}H_{43}N_2O_5Si$ requires 683.2941.

3.3.5. Diol 7. Sodium borohydride (56 mg, 1.5 mmol) was added in small portions to a stirred solution of amide **6** (500 mg, 0.73 mmol) in a mixture of MeOH (5 mL) and THF (5 mL) at 0 °C. The reaction was warmed to ambient temperature and after 30 min saturated aqueous ammonium chloride (10 mL) was carefully added. The mixture was extracted with EtOAc (3×30 mL); the combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (80% EtOAc in hexane) affording 490 mg (0.72 mmol) of the diol **7** (98% yield) as amorphous white solid. R_f=0.15, 0.22 (50% EtOAc in hexane); ν_{max} (KBr) 3394, 1729, 1664, 1516, 1462 cm^{-1}. ^1H NMR (500 MHz, CD_3CN): δ 9.25 (br s, 1H, ArN*H*), 9.21 (br s, 1H, ArN*H*), 7.67–7.58 (m, 6H, Ar*H*), 7.54–7.29 (m, 30H, Ar*H*), 7.27–7.18 (m, 3H, Ar*H*), 7.15–6.86 (m, 8H, Ar*H*), 6.75 (d, *J*=8.5 Hz, 2H, Ar*H*), 6.63 (br s, 1H, N*H*CO), 5.22 (br s, 1H, COC*H*OH), 5.20 (s, 1H, COC*H*OH), 5.09 (br s, 1H, CHC*H*OH), 5.05 (s, 2H, OCH_2Ph), 5.03 (s, 2H, OCH_2Ph), 4.97 (br s, 1H, CHC*H*OH), 4.09 (br m, 4H, C*H*NH+O*H*), 3.90–3.80 (m, 2H, O*H*), 3.78–3.57 (m, 4H, CH_2OTBDPS), 1.05 (s, 18H, (CH_3)$_3$C); HRMS (ESI positive ion mode): $[M+H]^+$, found 685.3117. $C_{42}H_{45}N_2O_5Si$ requires 685.3097.

3.3.6. Morpholinones 8a and 8b. A catalytic amount of pyridinium *p*-toluenesulfonate (10 mg) was added to a stirred solution of diol **7** (490 mg, 0.72 mmol) in acetonitrile (100 mL) at ambient temperature and the mixture was warmed to 80 °C. After completion of the reaction (2 h) half of the volume of the solvent was removed under reduced pressure and the rest was poured into water (30 mL) and

extracted with EtOAc (3×30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc in hexane) affording, in order of elution, morpholinones **8a** (122 mg, 0.183 mmol) and **8b** (120 mg, 0.180 mmol) (50% combined yield) as colorless oils.

3.3.6.1. Compound 8a. R_f=0.46 (50% EtOAc in hexane); $[\alpha]_D^{25}$ +36.9 (*c* 0.80, MeOH); ν_{max} (NaCl) 3398, 3289, 1666, 1612, 1513, 1454 cm^{-1}. ^1H NMR (500 MHz, CD_3CN): δ 9.35 (br s, 1H, ArN*H*), 7.58 (m, 3H, Ar*H*), 7.52 (d, *J*=6.8 Hz, 2H, Ar*H*), 7.48–7.22 (m, 13H, Ar*H*), 7.17 (t, *J*=7.4 Hz, 1H, Ar*H*), 7.06 (d, *J*=8.6 Hz, 2H, Ar*H*), 6.97 (t, *J*=7.4 Hz, 1H, Ar*H*), 6.82 (d, *J*=8.6 Hz, 2H, Ar*H*), 6.64 (br s, 1H, N*H*CO), 5.59 (s, 1H, COC*H*O), 5.03 (s, 2H, OCH_2Ph), 4.73 (d, *J*=9.2 Hz, 1H, CHC*H*O), 3.83 (m, 1H, C*H*NHCO), 3.56 (dd, *J*=11.0, 2.9 Hz, 1H, CH*H*OTPS), 3.38 (dd, *J*=11.0, 4.7 Hz, 1H, C*H*HOTPS), 1.03 (s, 9H, (CH_3)$_3$C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 159.8, 136.5, 136.4, 130.9, 130.9, 130.1, 129.5, 129.3, 128.9, 128.8, 128.8, 128.6, 127.5, 126.1, 122.9, 120.4, 120.3, 115.6, 112.5, 112.2, 73.4, 70.9, 70.6, 64.1, 59.6, 27.3, 19.8; HRMS (ESI positive ion mode): $[M+H]^+$, found 667.3018. $C_{42}H_{43}N_2O_4Si$ requires 667.2992.

3.3.6.2. Compound 8b. R_f=0.20 (50% EtOAc in hexane); $[\alpha]_D^{25}$ +71.7 (*c* 1.69, MeOH); ν_{max} (NaCl) 3396, 3283, 1676, 1613, 1514, 1460 cm^{-1}. ^1H NMR (500 MHz, CD_3CN): δ 9.28 (br s, 1H, ArN*H*), 7.68 (d, *J*=7.8 Hz, 1H, Ar*H*), 7.61 (m, 3H, Ar*H*), 7.56 (t, *J*=6.4 Hz, 1H, Ar*H*), 7.47–7.28 (m, 13H, Ar*H*), 7.21 (d, *J*=8.5 Hz, 2H, Ar*H*), 7.16 (t, *J*=7.4 Hz, 1H, Ar*H*), 7.09 (t, *J*=7.4 Hz, 1H, Ar*H*), 6.87 (d, *J*=8.5 Hz, 2H, Ar*H*), 6.72 (br s, 1H, N*H*CO), 5.46 (s, 1H, COC*H*O), 5.04 (s, 2H, OCH_2Ph), 4.78 (d, *J*=9.7 Hz, 1H, CHC*H*O), 3.96 (m, 1H, C*H*NHCO), 3.53 (d, *J*=4.3 Hz, 2H, CH_2OTPS), 1.06 (s, 9H, (CH_3)$_3$C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 160.5, 137.1, 137.0, 131.6, 131.6, 130.7, 130.4, 130.1, 129.5, 129.2, 127.7, 126.9, 123.4, 121.2, 121.0, 116.4, 113.1, 78.5, 76.3, 71.3, 64.8, 61.0, 27.9, 20.4; HRMS (ESI positive ion mode): $[M+H]^+$, found 667.2971. $C_{42}H_{43}N_2O_4Si$ requires 667.2992.

3.3.7. General procedure for the preparation of 9a and 9b. To a solution of **8a** or **8b** (30 mg, 0.045 mmol) in a mixture of EtOAc/EtOH (25 mL, 4:1 v/v) at ambient temperature was added a catalytic amount of $Pd(OH)_2$/C (10 mg) and the mixture was stirred under a hydrogen atmosphere for 8 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give the corresponding free phenol as a white amorphous solid. A solution of the above phenol in THF (1 mL) was treated for 30 min at ambient temperature with 1.0 M solution of TBAF in THF (50 μL). The reaction mixture was poured into saturated aqueous ammonium chloride (5 mL) and extracted with EtOAc (3×5 mL). The combined organic phases were washed with water (3 mL), brine (3 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% acetone in dichloromethane) affording 11.6 mg of morpholinone **9a** (0.034 mmol, 76% yield for two steps) or 11.7 mg of morpholinone **9b** (0.035 mmol, 77% yield for two steps) as colorless oils.

3.3.7.1. Compound 9a. R_f=0.27 (50% acetone in dichloromethane); $[\alpha]_D^{25}$ +132.5 (*c* 0.2, MeOH); ν_{max} (NaCl) 3274, 1663, 1618, 1520, 1460 cm^{-1}. ^1H and ^{13}C NMR spectroscopic data (CD_3CN) are reported in Table 1. HRMS (ESI positive ion mode): $[M+H]^+$, found 339.1361. $C_{19}H_{19}N_2O_4$ requires 339.1345.

3.3.7.2. Compound 9b. R_f=0.43 (50% acetone in dichloromethane); $[\alpha]_D^{25}$ +73.2 (*c* 0.6, MeOH); ν_{max} (NaCl) 3314, 1656, 1616, 1518, 1453 cm^{-1}. ^1H and ^{13}C NMR spectroscopic data (CD_3CN) are reported in Table 2. HRMS (ESI positive ion mode): $[M+H]^+$, found 339.1350. $C_{19}H_{19}N_2O_4$ requires 339.1345.

Acknowledgements

This work is a result of research supported by BIOTOX marin 2005 and PRIN 2004 'Algal toxins contaminating shellfish in Italian coastal waters: monitoring, isolation and structural characterization'.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.05.070.

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Tetrahedron 62 (2006) 7744–7746
Tetrahedron

Synthesis and X-ray crystal structure of pyrrolo[1,2-*a*]benzimidazoles

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Received 31 January 2006; revised 8 May 2006; accepted 25 May 2006
Available online 19 June 2006

Abstract—Reaction of nitrilimines **1** with 2-cyanomethylbenzimidazole **2** gave the 3-arylazo-2-methylpyrrolo[1,2-*a*]benzimidazole **4a** rather than the reported 2-arylazo-3-methylpyrrolo[1,2-*a*]benzimidazole **3a**. The correct structure of the product was determined using X-ray crystal structure analysis. The similar reaction of nitrilimines with 2-aminobenzimidazole **5** gave the acyclic nucleophilic addition product **6**.

1. Introduction

Nitrilimines are widely used for the synthesis of heterocycles. They are well known to undergo three types of reactions: 1,3-dipolar cycloaddition leading to five-membered ring heterocycles, cyclocondensation reactions leading to five, six, or larger heterocycles, and nucleophilic addition leading to acyclic adducts. Examples of these modes of reactions were recently reviewed by us for the reactions of hydrazones and oximes with nitrilimines and nitrile oxides.[1]

Benzimidazoles represent an important heterocyclic system due to their pharmacological activity. The benzo-fused-imidazoles derivative (Rifaximin) is used as antineoplastic and anticancer agents.[2]

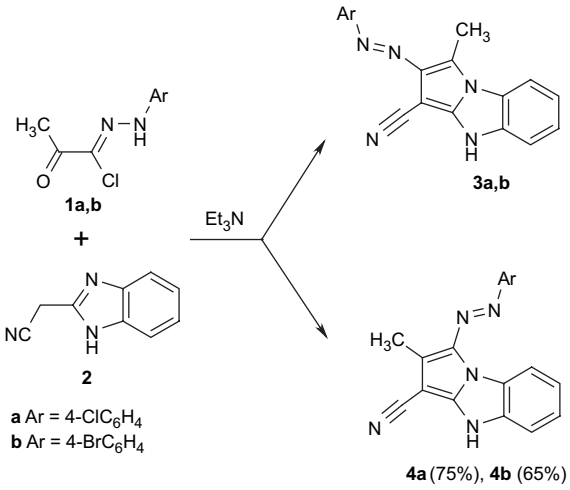
Many efforts have been made to develop methods for preparation of pyrrolo[1,2-*a*]benzimidazoles. They are prepared via 1,3-dipolar cycloaddition of fluoroalkenes to *N*-ylides.[3] The reaction between dilithiated 2-methylbenzimidazole and diimidoyl dichlorides gave 1-arylimino-1*H*-pyrrolo[1,2-*a*]benzimidazole-2-amines.[4]

C-Acetyl-*N*-arylnitrilimines were recently reported to react with 2-aminonicotinic acid leading to imidazo[1,2-*a*]pyridines,[5] and with 2-aminopyrazines leading to imidazo[1,2-*a*]-pyrazines.[6] These reactions start by nucleophilic addition of the lone pair of electrons of nitrilimines to the electrophilic carbon, followed by cyclization of the amino group with C=O.

In this work, we reinvestigated the reaction of 2-cyanomethylbenzimidazole **2** with hydrazonoyl halides **1**. This reaction was recently reported by Elwan to give pyrrolo[1,2-*a*]benzimidazoles **3**.[7] The reaction of 2-aminobenzimidazoles **5** with hydrazonoyl halides **1** was investigated.

2. Results and discussion

The reaction of hydrazonoyl halides **1** with 2-cyanomethylbenzimidazole **2** was reinvestigated in tetrahydrofuran at room temperature (Scheme 1). The product obtained from **1a** is believed to be the same compound **3a** that was obtained by Elwan when the reaction was done in refluxing chloroform.[7] This is based on the similarity of their physical



Scheme 1. Synthesis of pyrrolo[1,2-*a*]benzimidazoles **4a**,**b**.

Keywords: Nitrilimines; 2-Cyanomethylbenzimidazole; 2-Aminobenzimidazole; Pyrrolo[1,2-*a*]benzimidazole.
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doi:10.1016/j.tet.2006.05.071

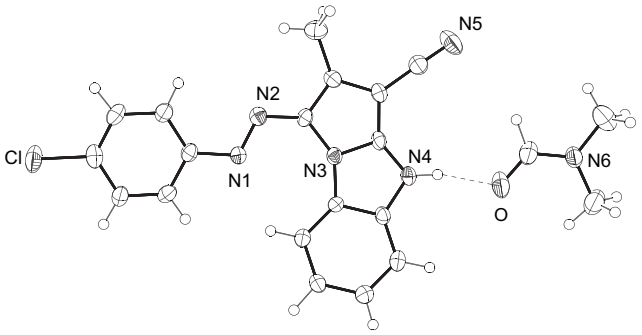


Figure 1. The molecular unit of **4a**·DMF in the crystal, Ortep representation, 50% probability ellipsoids (hydrogen atoms) are represented by cycles of arbitrary size.

properties including mp, MS, IR, ^{1}H NMR, and ^{13}C NMR. However, we suggested that this compound was the regioisomer **4a**. Since the two isomers are very similar, and the spectroscopic analysis (IR, MS, and NMR) cannot differentiate easily between them, we obtained an X-ray structure. The structure revealed that the compound is indeed **4a** rather than **3a** (Fig. 1). Thus the reaction should start by nucleophilic attack of the lone pair of electrons of the benzimidazole nitrogen at the electrophilic carbon of the nitrilimine, followed by cyclization of the carbanion generated at the methylene group at the carbonyl carbon of the nitrilimine. Crystal data and selected bond angles and bond lengths of **4a** are given in Tables 1 and 2, respectively.

Table 1. Crystal data for **4a**·DMF

Formula	$C_{21}H_{19}ClN_6O$
Molecular weight	406.12
Crystal size	0.3×0.3×0.1 mm
Crystal color	Orange red
a	762.0(3) pm
b	2144.5(8) pm
c	1231.7(5) pm
β	96.45(1)°
V	$2000.0\cdot10^6$ pm^3
Space group	$P2_1/c$
Z	4
T	−100 °C
μ	0.22 mm^{-1}
Measured reflections	18899
Unique reflections	4832
R(int)	0.104
$2\theta_{max}$	56.26°
Parameters	331
Goodness-of-fit	1.049
R_1	0.095
wR_2	0.2238

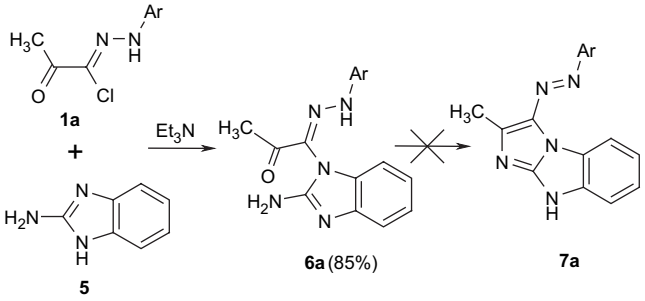
Table 2. Some bond lengths [pm] and angles [°] of **4a**·DMF

C1−Cl	174.3(5)	N1–N2–C4	113.6(4)
N1–N2	128.8(5)	N2–N1–C6	115.3(4)
C–C (ring)	136.5(7)–140.7(6)	C14–C17≡N	178.4(6)
C14–C17(≡N)5	140.9(6)		
C17≡N5	116.1(6)		
C–N(ring)	134.6(6)–141.7(6)		
O(DMF)···H211−N4	185.5(45)		

2.1. Description of the crystal structure

The structure of **4a**·DMF is shown in Figure 1. The substitution pattern is obvious, and the identification of nitrogen atoms versus carbon atoms is straightforward. All ring hydrogen atoms including the aldehydic hydrogen atom have been located in differential Fourier maps, only the methyl group hydrogen atoms have been located by a riding model. Compound **4a** and DMF are connected by a C═O…H–N bridge of 185 pm in length. This hydrogen bridge also enlarges the C═O bond length somewhat 123.1(6) pm in length. Another special feature of the molecular unit **4a**·DMF is its overall planarity, only the methyl hydrogen atoms are not in plane. The maximal deviation of any non-hydrogen atom from the best plane of the entire unit is only 32 pm (C23 of DMF). Compound **4a** alone is even closer to planarity, the largest deviation from this best plane is 26 pm (C3).

A similar reaction of hydrazonoyl halides **1a** with 2-aminobenzimidazole **5** was also investigated. This reaction gave the acyclic adduct **6a** rather than the imidazobenzimidazole **7a** (Scheme 2).



a Ar = 4-ClC$_6$H$_4$

Scheme 2. Reaction of nitrilimines with 2-aminobenzimidazole.

3. Experimental

3.1. General

Melting points were determined on an Electrothermal Mel. Temp apparatus and are uncorrected. IR spectra were obtained by using Perkin–Elmer 237 infrared spectrometer (KBr discs). ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 300 MHz instrument for solutions in DMSO-d_6 at 21 °C, using TMS as an internal reference. Electron impact mass spectra were run on Finnigan Mat 8200 spectrometer at 70 eV. Elemental analyses were done at Institut für Chemie der Freien Universität, Berlin. Hydrazonoyl halides **1a** and **2a**,[8] were prepared as previously described. 2-Cyanomethylbenzimidazole **2** and 2-aminobenzimidazole **5** were purchased from Acros.

3.2. Reaction of nitrilimines 1 with 2-cyanomethylbenzimidazole 2

Triethylamine (0.01 mol, 1.4 mL) was dropwise added to a mixture of hydrazonoyl halides **1** (0.01 mol) and 2-cyanomethylbenzimidazole **2** (0.01 mol, 1.57 g) in tetrahydrofuran

(50 mL) at room temperature. The reaction mixture was stirred for two days. The precipitated salt was filtered off, and the solvent was then evaporated. The residual solid was washed twice with water, and then triturated with ethanol. The orange solid was collected using suction filtration and crystallized from hot dimethylformamide. Crystals from **4a** were formed upon slow evaporation of a dimethylformamide solution of the compound. An authentic sample of **4a** was also prepared utilizing a procedure similar to that reported by Elwan.[7] Thus, triethylamine (0.005 mol, 0.7 mL) was dropwise added to a mixture of hydrazonoyl halides **1** (0.01 mol) and 2-cyanomethylbenzimidazole **2** (0.005 mol, 0.79 g) in chloroform (50 mL) at room temperature. The reaction mixture was refluxed for 8 h. The precipitated orange product was filtered, and found to be identical with the product **4a** obtained from the above reaction applying THF as a solvent. The identity was based on TLC, mixed melting points, and IR spectra.

3.3. 3-(4-Chlorophenylazo)-1-cyano-2-methyl-9*H*-pyrrolo[1,2-*a*]benzimidazole 4a

Yield: 2.5 g, 75%, orange solid, mp 278–280 °C (literature mp 280 °C).[6] The IR, MS, and NMR data for this compound are identical to that reported by Elwan. However, X-ray crystal structure analysis showed it to have structure **4a** rather than the reported structure **3a**.

3.4. 3-(4-Bromophenylazo)-1-cyano-2-methyl-9*H*-pyrrolo[1,2-*a*]benzimidazole 4b

Yield 2.5 g, 65%, orange solid, mp 264–265 °C; [found: C, 56.98; H, 3.29; N, 18.43. $C_{18}H_{12}BrN_5$ requires C, 57.16; H, 3.20; N, 18.52%]; IR (KBr) ν 3151 (NH), 2214 (CN) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.5 (s, 3H, CH_3), 7.2 (1H, t, J 7.0 Hz, ArC–H), 7.3 (1H, t, J 7.0 Hz, ArC–H), 7.4 (1H, d, J 7.0 Hz, ArC–H), 7.6 (4H, 2d, J 8.0 Hz, 4-BrC_6H_4), 8.5 (1H, d, J 8.0 Hz, ArC–H), 13.3 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 12.0, 112.4, 115.3, 117.60, 117.65, 121.0, 121.5, 123.2, 125.0, 127.3, 132.3, 135.76, 135.83, 144.32, 144.37, 152.7; MS m/z (377/379 $M^{+\bullet}$, bromine isotopes).

3.5. 1-(4-Chlorophenylhydrazono)-1-(2-aminobenzimidazol-1-yl)-2-propanone 6a

Yield 2.8 g, 85%, yellow solid, mp 255–257 °C; [found: C, 58.88; H, 4.41; N, 21.51. $C_{16}H_{14}ClN_5O$ requires C, 58.63; H, 4.31; N, 21.37%]; IR (KBr) ν 3416, 3310, 3297 (3NH), 1683 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.5 (s, 3H, CH_3), 6.4 (s, 2H, NH_2), 6.6 (1H, d, J 7.0 Hz, ArC–H), 6.8 (1H, t, J 7.0 Hz, ArC–H), 7.0 (1H, t, J 7.0 Hz, ArC–H), 7.2 (1H, d, J 7.0 Hz, ArC–H), 7.4 (4H, 2d, J 9.0 Hz, 4-ClC_6H_4), 11.0 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 191.2 (C=O), 155.1, 144.7 (2C=N), 142.6, 134.1, 128.8, 126.7 (4ArC), 129.6, 121.7, 118.9, 117.0, 115.4, 108.1 (6ArC–H), 25.6 (CH_3); MS m/z (327/329 $M^{+\bullet}$, chlorine isotopes).

3.6. Experimental (of the crystal structure of 4a)

A suitable crystal is mounted on a Bruker Smart CCD-1000 TM diffractometer and measured at −100 °C, with Mo Kα radiation source of λ=71.069 pm and graphite monochromator: scan width of 0.3° in ω, measuring 20 sec/frame, and 1800 frames for a full shell up to θ=28°, no absorption correction. The SHELX programs are used for structure solution and refinement.[9] All atoms except hydrogen are refined with anisotropic displacement parameters. Aromatic hydrogen atoms and the aldehydic hydrogen atom in DMF are refined isotropically with individual displacement parameters, the methyl hydrogen atoms are refined with one combined displacement parameter. Experimental data and results are summarized in Tables 1 and 2, and Figure 1. Further details of the crystal structure determination can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ. Tel.: +44 1223 336 408; fax: +44 1223 336 033. E-mail: deposit@ccde.com.ac.uk by quoting the depository number CCDC 295742.

Acknowledgements

One of the authors, A.A., is thankful to the ministry of education and higher education of Palestine for financial support, and to Dr. Jalal Ahmed (Jordan University) for measuring the NMR of the new compounds.

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Tetrahedron 62 (2006) 7747–7755
Tetrahedron

11,16 Oxetane lactones. Spectroscopic evidences and conformational analysis

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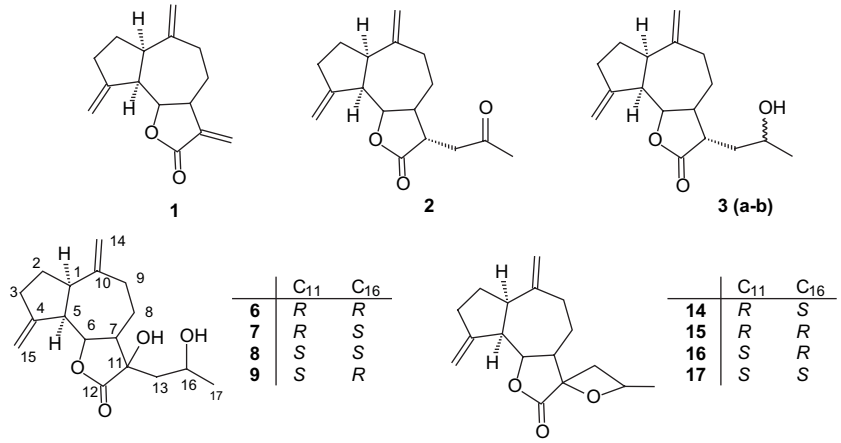
Received 2 May 2006; revised 20 May 2006; accepted 24 May 2006
Available online 16 June 2006

Abstract—Sesquiterpene lactones constitute a wide group of compounds with several biological activities, including allelopathic. The naturally occurring sesquiterpene lactones dehydrocostuslactone and cynaropicrin have been modified in three different ways: preparation of 11,13-oxetane lactones, addition of a second Michael acceptor and reduction of the α-methylene-γ-lactone in order to future structure–activity relationship (SAR) studies. We have obtained all oxetane lactones stereoisomers at C-11 and C-16 positions. This fact has allowed us to establish some correlations between experimental data, derived by NMR and X-ray analysis, and the configuration at C-11 and C-16, which could be a useful tool to establish the stereochemistry as well as to confirm the presence of an oxetane ring on similar compounds. Comparative conformational analyses as a key aspect in the biological behaviour of those compounds in future structure–activity relationship (SAR) studies are presented.

1. Introduction

Five natural oxetane lactones, clementein, clementein B, clementein C, subexpinnatin B and subexpinnatin C, were isolated from *Centaurea clementei* Boiss,[1] and *Centaurea canariensis* Brous. Var. *subexpinnata* Burchd (Fig. 1),[2] and some of them have been obtained later by hemi-synthetic methods.[3] Oxetane ring containing compounds have been reported to display a wide range of biological activities and this structural feature is regarded to be essential for their bioactivity.[4–6] However, despite the efforts, in many cases the biochemical behaviour of the oxetane ring remains unclear and more research on both conformational and electronic effects needs to be done. In this way, we have achieved



	C_{11}	C_{16}
6	*R*	*R*
7	*R*	*S*
8	*S*	*S*
9	*S*	*R*

	C_{11}	C_{16}
14	*R*	*S*
15	*R*	*R*
16	*S*	*R*
17	*S*	*S*

Figure 1. Natural oxetane lactones and synthetic intermediates.

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0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.05.058

the preparation of four new oxetane lactones (compounds **14**–**17**) from (**1**) as starting material. The accomplished semi-synthesis also yielded six other derivatives (compounds **2**, **3**(**a**–**b**) and **6**–**9**), which present different stereochemistries and have been afforded for first time in this study (Fig. 1). The fact that we have obtained all oxetane lactones stereoisomers at C-11 and C-16 positions has allowed us to establish some correlations between experimental data, derived by NMR and X-ray analysis, and the configuration at C-11 and C-16, that could be a useful tool in proposing the stereochemistry as well as in confirming the presence of an oxetane ring on similar compounds. Moreover, we carried out a comparative conformational analysis as a key aspect in the biological behaviour of those compounds in future structure–activity relationship (SAR) studies.

Herein, we present the methodology, which has been accomplished to obtain the new oxetane lactones as well as the prior results derived from their spectroscopic and conformational analysis.

2. Results and discussion

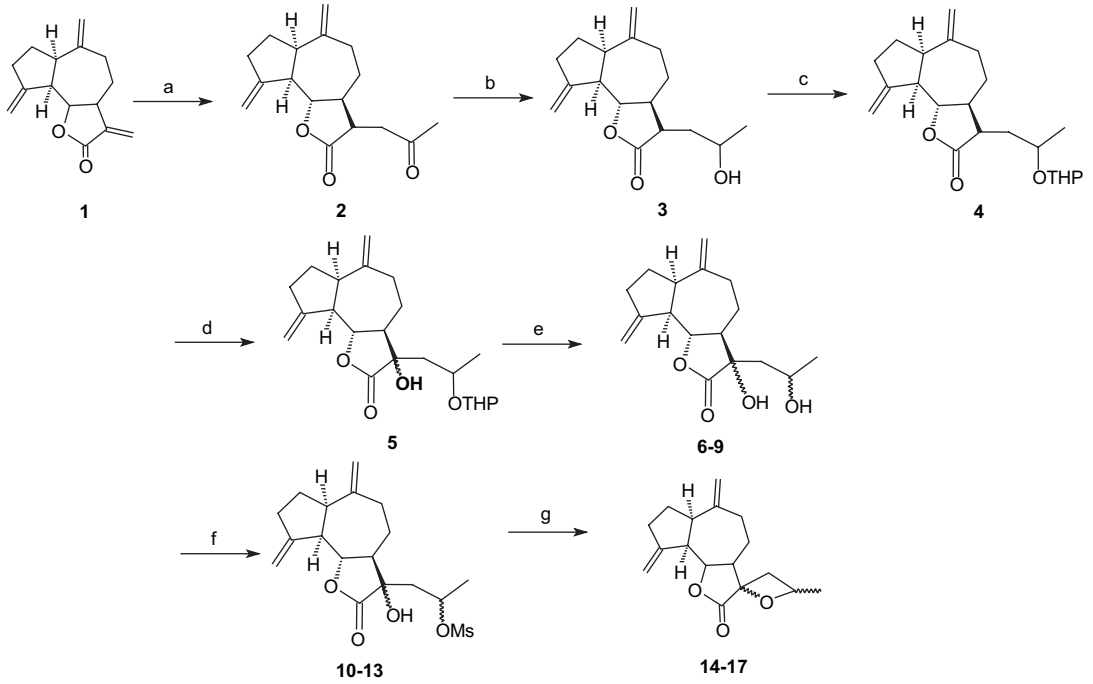
In order to perform the hemi-synthesis, we employed the previously reported methodology[7] for the formation of an oxetane ring at C-11 and C-13 positions from the corresponding α-methylene-γ-lactone using dehydrocostuslactone (**1**) as starting material. This natural product in one of the major constituents obtained from the root of the Chinese plant *Saussurea lappa* and, therefore, it is readily available in the amounts needed to accomplish the synthesis in seven steps as shown in Scheme 1.

The first step was the photoaddition of acetaldehyde to dehydrocostuslactone (**1**) providing the methylketone (**2**) (66% yield) (step a). Reduction of compound (**2**) with sodium borohydride at 0 °C afforded the 1:1 mixture of epimers at C-16, **3** (**a**–**b**) in 98% yield (step b). The new hydroxyl group formed is protected with DHP and *p*-toluenesulfonic acid as catalyst, yielding an epimeric mixture of diastereoisomers **4** (step c).

The α-hydroxylation of **4** to obtain the mixture of diastereoisomers **5** was carried out under the specific conditions as shown below. First, the enolate at C-11 of **4** is generated at −73 °C in THF by deprotonation with potassium hexamethyldisilazide (KHMDS) under a restricted dry argon atmosphere. Then, dry oxygen is bubbled through the solution for an hour in order to achieve the corresponding hydroperoxide ion. The latter treatment with triethylphosphite as 'in situ' reducing agent afforded the mixture **5** (step d). Both the 11*R* and the 11*S* configurations were obtained as it was deduced after step **5**.

Mild acid treatment of **5** (*p*-TsOH, ethyl acetate) provided the diols **6**, **7**, **8** and **9** and not the oxetane lactones as we expected (step e). Thus, it was necessary to include two more steps into the sequence. The above four diols were isolated in 20% yield each as crystalline compounds, allowing us to establish the structures of compounds **6** and **7** by X-ray analysis. The absolute configuration of compound **7** was also determined using Cu Kα radiation, establishing the absolute configuration of the entire series.

The introduction of the mesyl moiety as leaving group at C-16 to afford compounds **10**, **11**, **12** and **13** (90%) was accomplished by the reactions of diols with mesyl chloride in pyridine at 0 °C (step f). Basic treatment of mesylated compounds **10**, **11**, **12** and **13** with butyllithium in THF led to the ring closure with inversion in the configuration at C-16 yielding the oxetane lactones **14**, **15**, **16** and **17** (step g)



Scheme 1. (a) CH_3CHO, hν; (b) $NaBH_4$, MeOH, 0 °C; (c) DHP, *p*-Toluenesulfonic acid, THF; (d) KHMDS, THF, −73 °C; (e) *p*-Toluenesulfonic acid, AcOEt; (f) MesCl, py, 0 °C and (g) BuLi, THF.

Table 1

Compounds	δ H-5	δ H-6	δ H-7	δ H-13	δ H-13′	δ H-16	δ H-17	C-11	C-16
14	2.69	4.05	2.01	2.71	2.61	5.10	1.35	*R*	*S*
15	2.68	4.05	1.93	2.96	2.22	4.75	1.50	*R*	*R*
16	2.80	3.78	2.35	2.84	2.24	4.84	1.60	*S*	*R*
17	2.83	3.78	2.26	2.56	2.44	5.24	1.39	*S*	*S*
1	2.78	3.92	—	—	—	—	—	—	—

with an overall yield of 21%. Since compounds **15** and **16** were crystalline, we confirmed the proposed mechanism of the step g based on their X-ray analyses and, consequently, we established the stereochemistry of compounds **14** and **17**.

Once we obtained the four oxetane lactones their configurations at C-11 and C-16 were assigned, a depth analysis of their ^{1}H NMR and ^{13}C NMR spectra revealed some interesting relationships, especially for the NMR data corresponding to the nucleus found in the area close to the oxetane ring.

In Table 1, we present the ^{1}H NMR chemical shifts for H-5, H-6, H-7, H-13, H-13′, H-16 and H-17, as well as the assigned configuration at C-11 and C-16 for the compounds **14**, **15**, **16** and **17**.

A slight shift downfield is observed for H-6 signals when the configuration at C-11 is *R* (compounds **14** and **15**), which may be due to the paramagnetic effect that the oxygen nucleus of the oxetane rings induce over those signals. On the other hand, a similar effect occurs for the H-5 and H-7 signals in case of the (*S*)-configuration at C-11 (compounds **16** and **17**). With respect to the configuration at C-16, for oxetane lactones **15** and **16** (16*S*) a shift downfield is also observed for the H-17 signals and, it is worth noting that, in the latter compounds, the difference between the chemical shifts for H-13 and H-13′ is 0.68±0.08 ppm, being 0.11±0.01 ppm for the oxetane lactones **14** and **17** (16*R*). Furthermore, these results show how it may be possible to make the C-11 and C-16 configuration assignments in other oxetane lactones using their experimental data derived from ^{1}H NMR. In Table 1, the chemical shifts for H-5 and H-6 of dehydrocostuslactone (**1**) is also included, because comparing those with the respective signals of the lactones can be an interesting clue for C-11 configuration assignment, to determine whether we obtained one of the possible diastereoisomers.

Determining the presence of the oxetane ring moiety can be difficult, so a comparative NMR spectroscopic study between the oxetane lactones and the corresponding diols was undertaken to provide evidence, which may be useful to overcome the problem. The most significant results derived from this comparative analysis are shown in Table 2.

It is interesting to note the large downfield for the H-13 and H-13′ signals when the ring closure occurs. Following with the analysis of these signals, it is relevant the $J_{H13–H16}$ and $J_{H13'–H16}$ coupling constants, which are similar on the oxetane lactones whereas the differences among them are far longer on the corresponding diols. These results are consistent with the relative angle formed between protons H-13 and H-13′ with proton H-16 at the oxetane moiety. With respect to the ^{13}C NMR spectra, we emphasize the shift downfield for C-11 and C-16 signals as well as the contrary effect for C-13 as a result of the ring closure in compounds **14**, **15**, **16** and **17**.

Regardless, it is well established that conformational aspects are a keystone for the biological activity; little has been done about the conformational changes that the oxetane ring induces on the guaianolide backbone. Following this way, we have carried out a comparative structural study of the oxetane lactones **15** and **16** with the corresponding α-methylene-γ-lactone, dehydrocostuslactone (**1**). To perform that, we used the experimental data obtained from the X-ray analysis of the crystalline compounds **1**,[8] **15** and **16**, which are shown in Figure 2.

Comparing the resultant geometries reveals that the essential difference appears to be the conformation of the cycloheptane ring. Whereas in compound **1** the cycloheptane presents the theoretical lowest energy conformer (twist-chair), in both oxetane lactones (**15** and **16**) the heptane ring is in a chair conformation.[9] Those preferential conformations are in good agreement with the coupling constants $J_{H9β–H8β}$, $J_{H9β–H8α}$, $J_{H9α–H8β}$ and $J_{H9α–H8α}$ derived from ^{1}H NMR analysis of **15** and **16** (see Table 3).[10]

In Figure 2, the modification of the relative positions of C-2, C-9, C-10 and C-14 with respect to the guaianolide backbone, as a result of the different seven-membered ring conformations is shown. With regard to this matter, we have prepared other guaianolide-type sesquiterpene lactones, both natural and semi-synthetic (**18**, **19**,[11] **20**, **21** and **22**[12]) and revised other published results (**23**[13] and **24**[14]). Different behaviours have been observed in guaianolides with a methylene at C-10 (Fig. 3). Thus, **1**, **20** and **24** possess an α-methylene-γ-lactone moiety twist-chair conformation, whereas **6**,

Table 2

	6	**14**	**7**	**15**	**8**	**16**	**9**	**17**
δ H-13	1.89	2.71	1.73	2.84	1.94	2.96	1.76	2.56
δ H-13′	1.65	2.61	1.55	2.24	1.79	2.22	1.68	2.44
$J_{13–16}$	10.8	6.4	11.2	7.7	10.3	7.0	8.5	7.6
$J_{13'–16}$	2.7	7.8	2.2	6.5	3.0	7.3	2.7	7.5
δ C-11	75.7	81.7	76.4	82.9	76.4	82.3	76.4	82.8
δ C-13	41.4	32.5	37.8	32.4	43.1	32.4	43.3	32.3
δ C-16	64.9	75.3	65.7	75.3	64.7	75.3	64.7	75.2

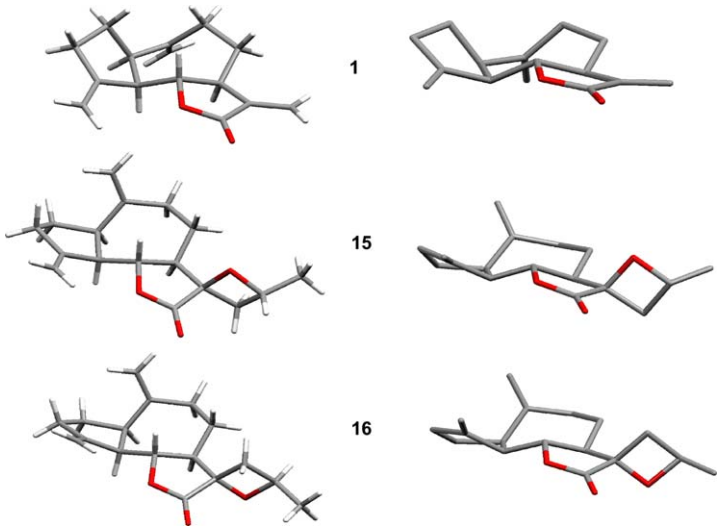


Figure 2. Conformations of **1**, **15** and **16** obtained by X-ray analysis.

Table 3

Compound	$J_{H9\beta-H8\beta}$	$J_{H9\beta-H8\alpha}$	$J_{H9\alpha-H8\beta}$	$J_{H9\alpha-H8\alpha}$	Conformations
1	4.9	5.8	5.9	4.4	Twist-chair
15	7.0	6.8	10.1	4.0	Chair
16	7.3	7.5	11.3	4.0	Chair

7, **15**, **16**, **18**, **19** and **23** lacking that functionalization showed chair conformation in the seven-membered ring. Nevertheless, the influence of the functionalization of the other five-membered ring is also important (Fig. 4). Thus, **21** and **22** that have the α-methylene-γ-lactone and a carbonyl group at C-3 showed a chair conformation. So, the functionalization and hybridization of both five-membered rings of guaianolides do influence the conformation of the seven-membered group ring and, probably, their biological activities. So, any structure–activity relationship study of this type of compounds should consider this parameter.

3. Experimental

3.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded at 399.952 and 100.577 MHz, respectively, on a Varian UNITY-400 spectrometer using $CDCl_3$ as solvent. The resonances of residual chloroform at δ_H 7.25 ppm in the ^{1}H spectra and of δ_C at 77.00 ppm in the ^{13}C spectra were used as internal references. Mass spectra were obtained by using a VG 1250 or a Kratos MS-80-RFA instrument at 70 eV. The infrared (IR) spectra were recorded on a PERKIN Elmer Spectrum BX. Column chromatography (CC) was performed on silica gel (35–75 mesh). For HPLC, LiChrosorb silica 60 was used in the normal-phase mode using differential LaChrom RI L-7490 refractometer and UV–vis LaChrom L-7420 detectors, with an HPLC MERCK HITACHI instrument. All solvents were of spectral grade or distilled from glass prior to use. The diffraction data were collected at low temperature

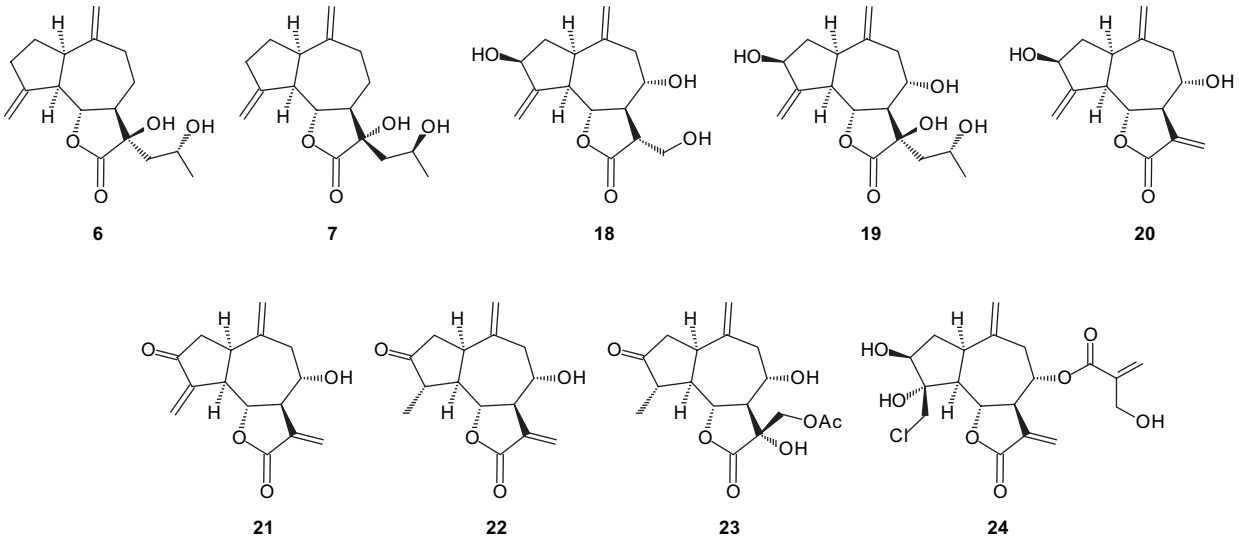


Figure 3. Natural and semi-synthetic guaianolides to be studied.

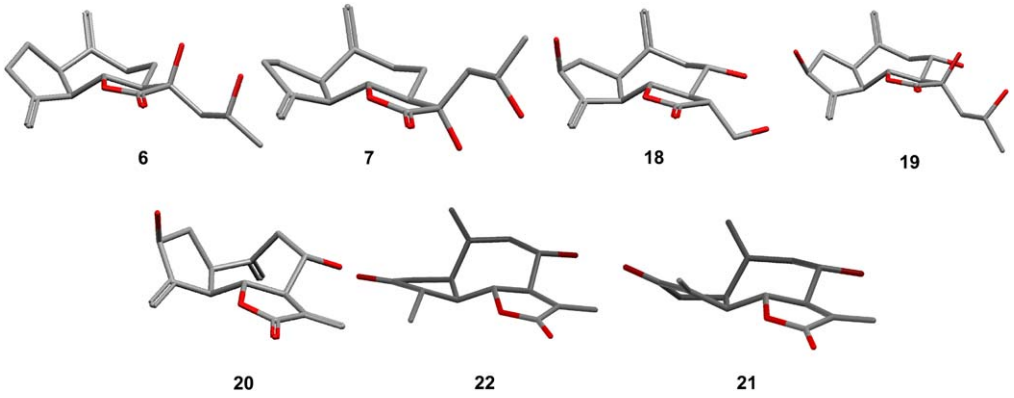


Figure 4. Conformations obtained for **6**, **7**, **18**, **19**, **20**, **22** and **21** by X-ray analysis.

on a KappaCCD diffractometer equipped with Mo Kα radiation and an Oxford Cryosteam sample chiller. Room-T Cu Kα was also collected for **7** in order to determine its absolute configuration.

3.2. Starting material

Dehydrocostuslactone (**1**) was obtained from crude costus-resin oil (*S. lappa*) by previous column chromatography (CC) separation and then purified by crystallization from hexane/ethyl acetate mixtures.

3.3. 13-Acetylmokkolactone (2)

Photochemical reactions were carried out in a modified Hanovia reactor equipped with a Pyrex jacket as filter and a 125 W Hg/medium pressure lamp. The filter solution contained $NiSO_4 \cdot 6H_2O$ (46 g) and $CoSO_4 \cdot 7H_2O$ (14 g) per 100 mL of water. Compound **1** (250 mg, 1.08 mmol) in freshly distilled acetaldehyde (100 mL) was irradiated for 1 h with stirring. The reaction was kept fresh by a water recirculation device. The reaction mixture was concentrated under reduced pressure with the addition of small amounts of cyclohexane. This procedure was repeated ten times. The reaction mixtures were purified by means of CC (Hexane–EtOAc 9:1) to afford 13-acetylmokkolactone **2** (7.17 mmol, 66%). Colourless oil. IR (neat, KBr) ν_{max}, 1719 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 274 $[M]^+$ (25), 232 $[M-C_2H_6O]^+$ (15). ^1H NMR, see Table 4. ^{13}C NMR, see Table 5; HREIMS (M^+) found 274.1571, $C_{17}H_{22}O_3$ requires 274.1568.

3.4. 13-(1′-Hydroxyethyl)-mokkolactone (3)

A 2 mL methanolic solution with 7.1 mmol of compound **2** was kept in a Dewar glass at 0 °C. While the solution was stirring, $NaBH_4$ (1.4 equiv) was added during the first 5 min of reaction. After 1 h, the reaction was stopped by addition of 2 mL of distilled water. Extraction with AcOEt yielded the mixture 1:1 of epimers at C-16, **3** (**a**–**b**) in 98% yield (6.96 mmol). Compound **3**: colourless oil. IR (neat, KBr) ν_{max} 3670 (hydroxyl group), 1750 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 276 $[M]^+$ (10), 258 $[M-H_2O]^+$ (10); HREIMS (M^+) found 276.1746, $C_{17}H_{24}O_3$ requires 274.1725. ^1H NMR (400 MHz, $CDCl_3$) δ 5.17 (1H, dd, *J*=2.2 and 2.2, H-15), 5.03 (1H, dd, *J*=2.3 and 2.3, H-15′), 4.86 (1H, s, H-14), 4.76 (1H, s, H-14′), 4.20a and 4.00b (1H, m, H-16), 4.00a and 3.95 (1H, dd, *J*=9.7 and 9.3, H-6), 2.84 (1H, m, H-1), 2.82 (1H, m, H-5), 2.51 (1H, m, H-3α), 2.47 (1H, ddd, *J*=12.6, 8.9 and 3.8, H-11β), 2.38 (1H, ddd, *J*=11.6, 8.5 and 4.4, H-9α), 2.11 (1H, m, H-8α), 2.10 (1H, m, H-7), 1.99 (1H, m, H-9β), 1.95 (1H, m, H-2α), 1.93 (1H, m, H-3β), 1.86 (1H, m, H-2β), 1.84 (1H, ddd, *J*=14.5, 9.0 and 3.7, H-13), 1.66 (1H, ddd, *J*=14.5, 8.9 and 3.1, H-13′), 1.34 (1H, m, H-8β), 1.22a and 1.20 (3H, d, *J*=6.2, H-17). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1 and 179.4 (C-12), 151.6 and 151.5 (C-10), 149.8 and 149.6 (C-4), 112.1 and 111.9 (C-14), 109.3 and 109.1 (C-15), 86.4 and 85.9 (C-6), 67.1 and 64.8 (C-16), 51.9 and 51.8 (C-5), 48.4 and 47.4 (C-7), 47.1 and 46.4 (C-1), 43.4 and 43.3 (C-11), 38.3 and 38.2 (C-13), 38.2 and 37.5 (C-9), 32.6 and 32.5 (C-3), 32.3 and 32.2 (C-2), 30.1 and 29.7 (C-8) 24.2 and 23.8 (C-17).

3.5. 13-[1′-(2″-Tetrahydropyranyloxy)-ethyl]-mokkolactone (4)

To a solution of **3** (**a**–**b**) (6.96 mmol) in dry THF (50 mL), fresh distilled DHP (500 mL) and a few crystals of *p*-toluenesulfonic acid were added. After 3 h, anhydrous potassium carbonate was added and the mixture is kept during an hour. The salts were separated by filtration and the mixture was purified by means of CC (Hexane–Et_2O 9:1) to give the mixture of diastereoisomers **4**. Compound **4**: IR (neat, KBr) ν_{max}, 1746 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 360 $[M]^+$ (2), 85 $[C_5H_9O]^+$ (100); HREIMS (M^+) found 360.2354, $C_{22}H_{32}O_4$ requires 360.2301. ^1H NMR (400 MHz, $CDCl_3$) δ 5.18 (1H, s, H-15), 5.03 (1H, s, H-15′), 4.85 (1H, s, H-14), 4.75 (1H, s, H-14′), 4.49 (1H, m, H-2-THP), 4.20a and 4.13 (1H, ddq, *J*=9.8, 6.1 and 3.3, H-16), 3.91a and 3.90b (1H, dd, *J*=9.2 and 9.1, H-6), 3.43 (2H, m, H-6-THP), 2.84 (1H, m, H-1), 2.79 (1H, m, H-5), 2.47 (1H, m, H-3), 2.43 (1H, ddd, *J*=11.6, 8.5 and 4.4, H-9), 2.32 (1H, ddd, *J*=12.0, 8.6 and 3.5, H-11β), 2.11 (1H, m, H-7), 1.99 (1H, m, H-9′), 1.98 (1H, m, H-8), 1.95 (1H, m, H-2), 1.93 (1H, m, H-3′), 1.86 (1H, m, H-2′), 1.75 (1H, ddd, *J*=14.5, 9.8 and 3.5, H-13), 1.66 (1H, ddd, *J*=14.5, 8.6 and 3.3, H-13′), 1.63–1.45 (6H, m, H-3-THP, H-4-THP, H-5-THP), 1.28 (1H, m, H-8′), 1.26a and 1.13b (3H, d, *J*=6.2, H-17). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6 and 179.0 (C-12), 150.8 and 149.9 (C-10), 147.6 and 146.6 (C-4), 111.5 and 111.3 (C-14), 108.8 and 108.1

Table 4. ^{1}H NMR data for compounds **2**, **6–9** and **14–17** (400 MHz in $CDCl_3$, signal of residual $CHCl_3$ centred at δ 7.25 ppm)

	2	**6**	**7**	**8**	**9**	**14**	**15**	**16**	**17**
1	2.81 m	2.84 ddd	2.86 m	2.86 ddd	2.84 m	2.85 ddd	2.85 ddd	2.88 m	2.86 m
2α	2.15 m	2.00 m	1.92 m	2.00 m	1.81 m	2.03 m	1.88 m	1.95 m	2.23 m
2β	1.84 m	1.86 m	1.81 m	1.86 m	1.75 m	1.88 m	1.82 m	1.82 m	2.00 m
3α	2.43 m	2.54 ddd	2.48 m	2.55 m	2.48 m	2.54 m	2.48 m	2.47 m	2.49 m
3β	1.93 m	1.79 m	1.95 m	1.73 m	1.95 m	2.20 m	2.13 m	2.42 m	2.22 m
5	2.82 m	2.69 ddd	2.85 m	2.69 ddd	2.87 m	2.69 m	2.68 m	2.80 m	2.83 m
6	3.92 dd	4.21 dd	3.86 dd	4.24 dd	3.96 dd	4.05 dd	4.05 dd	3.78 dd	3.78 dd
7	2.13 m	1.87 ddd	2.36 ddd	2.07 ddd	2.37 ddd	2.01 ddd	1.93 ddd	2.35 ddd	2.26 ddd
8α	1.95 m	2.45 m	2.08 m	1.87 m	1.97 m	2.45 m	2.45 m	2.45 m	1.95 m
8β	1.29 m	1.79 m	1.31 m	1.77 m	1.31 m	1.79 m	1.78 m	1.57 m	1.82 m
9α	2.41 m	2.47 ddd	2.52 m	2.47 m	2.51 m	2.48 ddd	2.54 ddd	2.58 ddd	2.46 ddd
9β	1.97 m	2.01 m	1.96 m	2.01 m	2.08 m	2.24 ddd	2.09 ddd	2.08 ddd	2.24 ddd
11	2.64 ddd								
13	2.88 dd	1.89 dd	1.73 dd	1.94 dd	1.76 dd	2.71 dd	2.96 dd	2.89 dd	2.56 dd
13′	2.65 dd	1.65 dd	1.55 dd	1.79 dd	1.68 dd	2.61 dd	2.22 dd	2.24 dd	2.44 dd
14	4.81 s	4.97 s	4.86 s	4.87 s	4.88 s	4.87 s	4.88 s	4.89 s	4.89 s
14′	4.72 s	4.86 s	4.75 s	4.79 s	4.79 s	4.79 s	4.79 s	4.77 s	4.77 s
15	5.15 d	5.18 d	5.18 d	5.18 d	5.16 d	5.17 d	5.17 d	5.14 d	5.16 d
15′	5.00 dd	5.03 dd	5.03 d	5.03 dd	5.06 dd	5.03 d	5.03 d	5.03 d	5.04 d
16	—	4.97 ddq	4.27 ddq	4.16 ddq	4.27 ddq	4.75 ddq	5.10 ddq	4.84 ddq	5.24 ddq
17	2.17 s	1.23 d	1.21 d	1.27 d	1.21 d	1.50 d	1.35 d	1.59 d	1.39 d

J (Hz): (**2**) 6,7=9.5; 6,5=9.3; 11,7=11.8; 11,13=6.3; 11,13′=5.7; 13,13′=16.8; 15,3=1.0; 15′,3=1.9; 15′,5=0.8. (**6**) 1,2β=14.7; 1,5=8.0; 1,2α=7.5; 3α,3β=11.3; 3α,2α=8.9; 3α,2β=1.86; 5,6=9.7; 5,15=2.2; 6,7=9.5; 7,8β=12.7; 7,8α=3.9; 9α,9β=12.9; 9α,8α=4.6; 9α,8β=9.6; 13,13′=14.5; 13,16=10.8; 13′,16=2.7; 16,17=6.2; 15,3=1.3; 15′,3=0.9. (**7**) 6,7=10.2; 6,5=8.7; 7,8β=12.4; 7,8α=3.0; 13,13′=14.7; 13,16=11.2; 13′,16=2.2; 16,17=6.1; 15,3=2.0; 15′,5=2.0. (**8**) 1,2β=15.0; 1,5=8.0; 1,2α=6.7; 5,6=9.6; 5,15=2.2; 6,7=9.8; 7,8β=13.0; 7,8α=3.7; 13,13′=15.0; 13,16=10.3; 13′,16=3.0; 16,17=6.2; 15,3=2.0; 15′,3=0.7. (**9**) 6,7=10.2; 6,5=8.9; 7,8β=12.6; 7,8α=3.3; 13,13′=14.7; 13,16=8.5; 13′,16=2.7; 16,17=6.2; 15,3=3.0; 15′,5=2.1; 15′,5=0.6. (**14**) 1,2β=14.6; 1,5=7.4; 1,2α=7.2; 6,7=9.5; 6,5=9.6; 7,8β=11.5; 7,8α=3.4; 9α,9β=13.2; 9α,8α=4.6; 9α,8β=10.6; 9β,8α=7.3; 9β,8β=7.6; 13,13′=11.7; 13,16=6.4; 13′,16=7.8; 16,17=6.1; 15,3=2.0; 15′,5=2.1. (**15**) 1,2β=15.0; 1,5=7.7; 1,2α=6.6; 5,6=9.6; 5,15′=1.5; 6,7=9.6; 7,8β=12.6; 7,8α=3.6; 9α,9β=13.0; 9α,8α=4.0; 9α,8β=10.1; 9β,8α=6.8; 9β,8β=7.0; 13,13′=11.5; 13,16=7.0; 13′,16=7.3; 16,17=6.0; 15,3=1.9. (**16**) 6,7=9.8; 6,5=9.0; 7,8β=12.6; 7,8α=3.6; 9α,9β=12.9; 9α,8α=4.0; 9α,8β=11.3; 9β,8α=7.5; 9β,8β=7.3; 13,13′=11.5; 13,16=7.7; 13′,16=6.5; 16,17=6.2; 15,3=2.3; 15′,5=1.7. (**17**) 6,7=8.9; 6,5=9.9; 7,8β=12.8; 7,8α=3.2; 9α,9β=12.8; 9α,8α=4.2; 9α,8β=11.1; 9β,8α=7.2; 9β,8β=6.9; 13,13′=11.4; 13,16=7.6; 13′,16=7.5; 16,17=6.1; 15,3=2.2; 15′,5=2.0.

(C-15), 84.8 (C-6), 72.5 (C-2-THP), 68.2 (C-16), 63.4 (C-6-THP), 51.7 (C-5), 47.2 (C-7), 46.8 (C-1), 42.9 and 42.7 (C-11), 37.4 and 37.3 (C-13), 36.4 and 36.1 (C-9), 32.1 (C-8), 32.0 (C-3), 31.1 and 29.8 (C-2), 25.1 (C-17), 22.2 (C-3-THP), 20.1 (C-5-THP), 19.5 (C-4-THP).

3.6. 11-Hydroxy-13-[1′-(2″-tetrahydropyranyloxy)-ethyl]-mokkolactone (5)

To a solution of **4** (100 mg) in dry THF (25 mL) at −73 °C a 0.4 M solution of KHMDS (8 mL) in dry THF was added under Ar. After 30 min of stirring at −73 °C a current of dry oxygen was bubbled for 1 h. At this point, treatment with triethylphosphite (50 μL) as a reducing agent took place. Then, the mixture was warmed to −20 °C and a buffer solution (pH=7) was added (20 mL). Extractive workup with Et_2O and CC separation (Hexane–EtOAc 9:1) gave the diastereoisomers **5**. This procedure was repeated with different amounts of the mixture **4**. Compound **5**: IR (neat, KBr) ν_{max}, 3540 (hydroxyl group), 1763 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 376 $[M]^+$ (2), 85 $[C_5H_9O]^+$ (100); HREIMS (M^+) found 376.2215, $C_{22}H_{32}O_5$ requires 376.2250. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (1H, d, *J*=2.4, H-15), 5.05 (1H, dd, *J*=2.8 and 0.8, H-15′), 4.86 (1H, s, H-14),

Table 5. ^{13}C NMR data for compounds **2**, **6–9** and **14–17** (400 MHz in $CDCl_3$, signal of residual $CHCl_3$ centred at δ 77.0 ppm)

	2	**6**	**7**	**8**	**9**	**14**	**15**	**16**	**17**
1	47.0	47.6	46.8	47.5	47.6	47.8	47.6	46.9	46.6
2	30.0	30.0	30.0	30.1	30.0	30.1	30.1	30.1	30.1
3	32.3	32.1	32.4	32.2	32.2	32.1	32.2	31.2	31.2
4	149.6	149.8	150.3	149.5	149.2	148.4	149.4	149.9	150.0
5	51.8	52.3	52.3	52.1	52.3	52.1	52.2	52.4	52.2
6	85.5	83.4	82.7	84.7	83.4	83.8	83.5	82.2	82.4
7	47.3	52.2	52.2	51.4	52.1	50.2	50.3	50.2	50.3
8	32.4	25.1	27.1	25.7	25.1	25.7	25.7	29.2	29.2
9	37.3	35.8	37.6	35.8	36.3	35.6	35.8	37.5	37.5
10	151.5	151.3	151.5	151.2	151.6	151.1	151.0	151.2	151.0
11	42.4	75.7	76.4	76.4	76.5	81.7	82.3	82.9	82.8
12	177.4	177.5	178.3	178.1	178.1	174.7	175.7	177.4	177.3
13	41.6	41.4	37.8	43.1	41.3	32.5	32.4	32.4	32.3
14	111.9	112.1	111.7	112.3	112.0	111.8	112.4	111.9	111.7
15	109.1	109.7	109.4	109.8	109.6	109.6	109.8	109.4	109.3
16	205.3	64.9	65.7	64.7	65.3	75.3	75.3	75.3	75.2
17	30.1	25.0	24.6	24.8	24.5	23.6	23.5	23.8	23.7

4.77 (1H, s, H-14′), 4.57 (1H, m, H-2-THP), 4.25 (1H, ddq, J=7.4, 6.2 and 4.1, H-16), 3.89 (1H, dd, J=10.2 and 8.2, H-6), 3.48 (2H, m, H-6-THP), 2.87 (1H, br dd, J=11.0 and 8.2, H-5), 2.84 (1H, ddd, J=11.0, 10.3 and 8.7, H-1), 2.50 (1H, m, H-3), 2.48 (1H, m, H-9), 2.37 (1H, ddd, J=12.3, 10.2 and 3.2, H-7), 1.98 (1H, m, H-9′), 1.96 (1H, m, H-8), 1.95 (1H, m, H-3′), 1.93 (1H, m, H-2), 1.93 (1H, dd, J=14.9 and 4.1, H-13), 1.82 (1H, dd, J=14.8 and 7.4, H-13′), 1.83 (1H, m, H-2′), 1.65–1.40 (6H, m, H-3-THP, H-4-THP, H-5-THP), 1.36 (1H, dddd, J=16.7, 12.4, 12.0 and 4.10, H-8), 1.21 (3H, d, J=6.2, H-17). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0 (C-12), 150.3 (C-10), 148.0 (C-4), 111.5 (C-14), 109.3 (C-15), 83.9 (C-6), 76.2 (C-11), 72.4 (C-2-THP), 67.9 (C-16), 63.3 (C-6-THP), 52.0 (C-5), 47.6 (C-7), 47.2 (C-1), 38.3 (C-13), 37.9 (C-9), 33.0 (C-8), 32.8 (C-3), 31.1 (C-2), 26.0 (C-17), 22.8 (C-3-THP), 21.1 (C-5-THP), 19.7 (C-4-THP).

3.7. Diols 6, 7, 8 and 9

The mixture **4** was dissolved in EtOAc (25 mL) with a few crystal of *p*-toluenesulfonic acid. After 24 h potassium carbonate was added and the mixture stirred for several minutes. The salts were removed by filtration and the purification was accomplished by CC (Hexane–EtOAc 8:2) to yield diols (11*R*,16*R*) 11-hydroxy-13-(1′-hydroxyethyl)-mokkolactone (**6**) (1.39 mmol, 20%), (11*R*,16*S*) 11-hydroxy-13-(1′-hydroxyethyl)-mokkolactone (**7**) (1.53 mmol, 22%), (11*S*,16*S*) 11-hydroxy-13-(1′-hydroxyethyl)-mokkolactone (**8**) (1.32 mmol, 19%) and (11*S*,16*R*) 11-hydroxy-13-(1′-hydroxyethyl)-mokkolactone (**9**) (1.39 mmol, 20%). Compound **5**: colourless crystal. IR (neat, KBr) ν_{max}, 3490 (hydroxyl group), 1765 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 292 [M]$^+$ (9), 274 [M−H_2O]$^+$ (38); HREIMS (M$^+$) found 292.1620, $C_{17}H_{24}O_4$ requires 292.1675.^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. Compound **6**: colourless crystal. IR (neat, KBr) ν_{max}, 3450 (hydroxyl group), 1770 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 292 [M]$^+$ (7), 274 [M−H_2O]$^+$ (14); HREIMS (M$^+$) found 292.1677, $C_{17}H_{24}O_4$ requires 292.1675.^{1}H NMR, see Table 4. ^{13}C NMR, see Table 5. Compound **7**: colourless crystal. IR (neat, KBr) ν_{max}, 3460 (hydroxyl group), 1772 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 292 [M]$^+$ (3), 274 [M−H_2O]$^+$ (4); HREIMS (M$^+$) found 292.1703, $C_{17}H_{24}O_4$ requires 292.1675. ^{1}H NMR, see Table 4. ^{13}C NMR, see Table 5. Compound **8**: colourless crystal. IR (neat, KBr) ν_{max}, 3460 (hydroxyl group), 1772 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 292 [M]$^+$ (3), 274 [M−H_2O]$^+$ (4); HREIMS (M$^+$) found 292.1703, $C_{17}H_{24}O_4$ requires 292.1675. ^{1}H NMR, see Table 4. ^{13}C NMR, see Table 5.

3.8. Reaction of mesylation

Diols **6**–**9**, separately, were dissolved in pyridine (15 mL) and 1.5 equiv of mesyl chloride was added at 0 °C with stirring. After 24 h the reaction was stopped by addition of 2 mL of distilled water. The reaction mixture was extracted with AcOEt (5×), and the combined organic phases were washed with aq saturated $CuSO_4$ (3×). The organic phase was dried over anhydrous sodium sulfate, the solvent evaporated under vacuum, and the crude product of the reaction purified by CC (Hexane–EtOAc 8:2), yielding the corresponding mesylated compounds (11*R*,16*R*) 11-hydroxy-13-(1′-(methylsulfonyloxy)-ethyl)-mokkolactone (**10**) (1.36 mmol, 98%), (11*R*,16*S*) 11-hydroxy-13-(1′-(methylsulfonyloxy)-ethyl)-mokkolactone (**11**) (1.49 mmol, 98%), 11-hydroxy-13-(1′-(methylsulfonyloxy)-ethyl)-mokkolactone (**12**) (1.29 mmol, 98%) and (11*S*,16*R*) 11-hydroxy-13-(1′-(methylsulfonyloxy)-ethyl)-mokkolactone (**13**) (1.36 mmol, 98%). Compound **10**: colourless oil. IR (neat, KBr) ν_{max}, 3440 (hydroxyl group), 1770 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 370 [M]$^+$ (10), 275 [M−OMs]$^+$ (12); HREIMS (M$^+$) found 370.4410, $C_{18}H_{26}O_6S$ requires 370.1450. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (1H, ddq, J=9.8, 6.2 and 3.2, H-16), 5.17 (1H, d, J=1.2, H-15), 5.05 (1H, d, J=2.0, H-15′), 4.88 (1H, s, H-14), 4.79 (1H, s, H-14′), 4.21 (1H, dd, J=10.0 and 9.7, H-6), 3.02 (3H, s, H-Ms), 2.88 (1H, ddd, J=14.3, 8.1 and 7.3, H-1), 2.80 (1H, dd, J=9.7 and 8.1, H-5), 2.50 (1H, ddd, J=11.3, 8.9 and 4.5, H-3), 2.46 (1H, ddd, J=12.7, 9.3 and 4.2, H-9), 2.45 (1H, m, H-8), 2.33 (1H, dd, J=14.5 and 9.8, H-13), 2.01 (1H, ddd, J=12.7, 10.1 and 4.8, H-9′), 2.01 (1H, m, H-2), 1.85 (1H, ddd, J=12.7, 10.0 and 3.9, H-7), 1.86 (1H, m, H-2′), 1.79 (1H, m, H-8′), 1.86 (1H, dd, J=14.5 and 3.2, H-13′), 1.78 (1H, ddd, J=11.3, 5.1 and 2.0, H-3′), 1.52 (3H, d, J=6.2, H-17). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C-12), 151.3 (C-10), 149.8 (C-4), 112.1 (C-14), 109.7 (C-15), 83.4 (C-6), 75.7 (C-11), 63.0 (C-16), 52.3 (C-5), 52.2 (C-7), 47.6 (C-1), 41.6 (C-13), 38.2 (C-Ms), 35.8 (C-9), 32.1 (C-3), 30.0 (C-2), 25.1 (C-8), 23.2 (C-17). Compound **11**: colourless oil. IR (neat, KBr) ν_{max}, 3434 (hydroxyl group), 1774 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 370 [M]$^+$ (7), 275 [M−OMs]$^+$ (15); HREIMS (M$^+$) found 370.4411, $C_{18}H_{26}O_6S$ requires 370.1450. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (1H, d, J=1.2, H-15), 5.10 (1H, ddq, J=9.7, 6.1 and 3.3, H-16), 5.03 (1H, d, J=2.0, H-15′), 4.86 (1H, s, H-14), 4.76 (1H, s, H-14′), 3.87 (1H, dd, J=10.1 and 8.9, H-6), 3.02 (3H, s, H-Ms), 2.84 (1H, m, H-1), 2.83 (1H, m, H-5), 2.52 (1H, ddd, J=15.3, 8.5 and 4.5, H-3), 2.48 (1H, m, H-9), 2.28 (1H, ddd, J=12.7, 10.1 and 3.9, H-7), 2.15 (1H, dd, J=14.7 and 9.7, H-13), 2.00 (1H, m, H-8), 1.99 (1H, m, H-9′), 1.93 (1H, m, H-2), 1.92 (1H, m, H-3′), 1.86 (1H, dd, J=14.7 and 3.3, H-13′), 1.83 (1H, m, H-2′), 1.46 (3H, d, J=6.1, H-17), 1.35 (1H, m, H-8′). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (C-12), 151.4 (C-10), 150.3 (C-4), 111.8 (C-14), 109.4 (C-15), 83.4 (C-6), 76.4 (C-11), 63.1 (C-16), 52.3 (C-5), 52.2 (C-7), 46.8 (C-1), 42.1 (C-13), 38.1 (C-Ms), 37.8 (C-9), 32.1 (C-3), 30.1 (C-2), 27.2 (C-8), 22.8 (C-17). Compound **12**: colourless oil. IR (neat, KBr) ν_{max}, 3456 (hydroxyl group), 1768 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 370 [M]$^+$ (10), 275 [M−OMs]$^+$ (18); HREIMS (M$^+$) found 370.4409, $C_{18}H_{26}O_6S$ requires 370.1450. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (1H, d, J=1.2, H-15), 5.12 (1H, ddq, J=9.9, 6.2 and 3.5, H-16), 5.03 (1H, d, J=2.0, H-15′), 4.88 (1H, s, H-14), 4.80 (1H, s, H-14′), 4.26 (1H, dd, J=10.1 and 9.6, H-6), 3.02 (3H, s, H-Ms), 2.84 (1H, ddd, J=14.3, 8.1 and 7.3, H-1), 2.68 (1H, dd, J=9.7 and 8.1, H-5), 2.51 (1H, m, H-3), 2.48 (1H, m, H-9), 2.23 (1H, dd, J=14.8 and 9.9, H-13), 2.03 (1H, ddd, J=12.7, 10.1 and 3.9, H-7), 2.01 (1H, m, H-9′), 1.99 (1H, m, H-2), 1.85 (1H, m, H-8), 1.84 (1H, m, H-2′), 1.83 (1H, dd, J=14.8 and 3.5, H-13′), 1.73 (1H, m, H-8′), 1.72 (1H, m, H-3′), 1.45 (3H, d, J=6.2, H-17). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C-12), 151.2 (C-10), 149.5 (C-4), 112.8 (C-14),

109.7 (C-15), 84.4 (C-6), 76.4 (C-11), 62.9 (C-16), 52.1 (C-5), 51.0 (C-7), 47.8 (C-1), 42.6 (C-13), 38.2 (C-Ms), 35.7 (C-9), 32.1 (C-3), 30.1 (C-2), 25.2 (C-8), 23.6 (C-17). Compound **13**: colourless oil. IR (neat, KBr) ν_{max}, 3448 (hydroxyl group), 1763 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 370 $[M]^+$ (8), 275 $[M-OMs]^+$ (9); HREIMS (M^+) found 370.4406, $C_{18}H_{26}O_6S$ requires 370.1450. ^1H NMR (400 MHz, $CDCl_3$) δ 5.26 (1H, ddq, *J*=8.4, 6.2 and 3.2, H-16), 5.16 (1H, d, *J*=2.0), 5.04 (H-15′, d, *J*=2.1, H-15), 4.88 (1H, s, H-14), 4.80 (1H, s, H-14′), 3.95 (1H, dd, *J*=10.3 and 8.9, H-6), 3.02 (3H, s, H-Ms), 2.84 (1H, m, H-1), 2.83 (1H, m, H-5), 2.51 (1H, m, H-9), 2.49 (1H, m, H-3), 2.33 (1H, ddd, *J*=12.7, 10.1 and 3.9, H-7), 2.30 (1H, dd, *J*=14.7 and 8.4, H-13), 2.04 (1H, m, H-9′), 2.02 (1H, m, H-8), 1.95 (1H, m, H-3′), 1.82 (1H, m, H-2), 1.77 (1H, m, H-2′), 1.74 (1H, dd, *J*=14.7 and 3.2, H-13′), 1.48 (3H, d, *J*=6.2, H-17), 1.35 (1H, m, H-8′). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C-12), 151.4 (C-10), 149.8 (C-4), 112.6 (C-14), 109.4 (C-15), 84.4 (C-6), 76.6 (C-11), 63.0 (C-16), 52.3 (C-5), 51.2 (C-7), 47.8 (C-1), 40.1 (C-13), 38.2 (C-Ms), 36.3 (C-9), 32.1 (C-3), 30.2 (C-2), 25.8 (C-8), 23.2 (C-17).

3.9. Oxetane lactones 14, 15, 16 and 17

The mesylated compounds **10**, **11**, **12** and **13**, separately, were dissolved in dry THF (20 mL). While the solution was stirring, BuLi (1.5 equiv) was added dropwise at 0 °C. After 12 min the mixture was warmed up to 55 °C and maintained for 2 h. The reaction was quenched by addition of 2 mL of distilled water and was extracted with AcOEt (5×). The organic phase was dried over anhydrous sodium sulfate, the solvent evaporated under vacuum, and the crude product of the reaction purified by CC (Hexane–EtOAc 9:1), yielding the oxetane lactones (11*R*,16*S*) 11,16-epoxy-13-ethylmokkolactone (**14**) (0.27 mmol, 20%), (11*R*,16*R*) 11,16-epoxy-13-ethylmokkolactone (**15**) (0.31 mmol, 21%), (11*S*,16*R*) 11,16-epoxy-13-ethylmokkolactone (**16**) (0.24 mmol, 19%) and (11*S*,16*S*) 11,16-epoxy-13-ethylmokkolactone (**17**) (0.29 mmol, 22%). Compound **14**: colourless crystal. IR (neat, KBr) ν_{max}, 1782 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 274 $[M]^+$ (15), 248 $[M-44]^+$ (36); HREIMS (M^+) found 274.1619, $C_{17}H_{22}O_3$ requires 274.1569. ^1H NMR, see Table 4. ^{13}C NMR, see Table 5. Compound **15**: colourless crystal. IR (neat, KBr) ν_{max}, 1766 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 274 $[M]^+$ (12), 248 $[M-44]^+$ (39); HREIMS (M^+) found 274.1656, $C_{17}H_{22}O_3$ requires 274.1569. ^1H NMR, see Table 4. ^{13}C NMR, see Table 5. Compound **16**: colourless crystal. IR (neat, KBr) ν_{max}, 1766 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 274 $[M]^+$ (11), 248 $[M-44]^+$ (38); HREIMS (M^+) found 274.1586, $C_{17}H_{22}O_3$ requires 274.1569. ^1H NMR, see Table 4. ^{13}C NMR, see Table 5. Compound **17**: colourless crystal. IR (neat, KBr) ν_{max}, 1766 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 274 $[M]^+$ (9), 248 $[M-44]^+$ (42); ^1H NMR, see Table 4. ^{13}C NMR see Table 5.

3.10. 11,13-Dihydro-13-hydroxy-deacylcynaropicrin (18) and deacylcynaropicrin (20)

Cynaropicrin was isolated from *Cynara scolimus*.[15] Cynaropicrin (400 mg, 1.15 mmol) was mixed with aq 10% K_2CO_3 (200 mL) and stirred for 24 h at 50 °C. After acidification with diluted HCl, the mixture was extracted with ethyl acetate. The organic solution was washed with water, dried and the solvent evaporated. The reaction mixture was chromatographed on silica gel using hexane/AcOEt (3:2) as eluent yielding 94 mg of **18** (60%, 0.69 mmol) and 182 mg of **20** (29%, 0.34 mmol). Compound **18**: colourless crystal. IR (neat, KBr) ν_{max}, 3548 (hydroxyl group), 1772 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 280.1310 $[M]^+$ (18), 272.1519 $[M-18]^+$ (21); ^1H NMR (400 MHz, $CDCl_3$) δ 5.19 (1H, br s, H-15), 5.17 (1H, br s, H-15′), 4.92 (1H, s, H-14), 4.85 (1H, s, H-14′), 4.34 (1H, br dd, *J*=8.1 and 7.4, H-3), 3.96 (1H, dd, *J*=9.8 and 9.7, H-6), 3.95 (1H, dd, *J*=11.0 and 3.7, H-13), 3.54 (1H, dd, *J*=11.0 and 8.2, H-13′), 3.53 (1H, ddd, *J*=9.0, 7.6 and 5.0, H-8), 2.73 (1H, ddd, *J*=9.1, 9.0 and 8.4, H-1), 2.64 (1H, dd, *J*=9.8 and 9.1, H-5), 2.60 (1H, ddd, *J*=11.0, 9.7 and 7.6, H-7), 2.57 (1H, dd, *J*=12.2 and 5.0, H-9), 2.12 (1H, ddd, *J*=11.0, 8.2 and 3.7, H-11), 2.11 (1H, ddd, *J*=13.1, 8.4 and 7.4, H-2), 2.08 (1H, dd, *J*=12.2 and 7.6, H-9′), 1.58 (1H, ddd, *J*=13.1, 9.0 and 8.1, H-2′). ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.8 (C-8), 73.2 (C-3), 62.1 (C-13), 54.7 (C-11), 50.3 (C-5), 50.1 (C-7), 44.1 (C-1), 43.7 (C-9), 39.0 (C-2), 175.6 (C-12), 153.2 (C-10), 143.6 (C-4), 116.1 (C-14), 111.6 (C-15), 79.6 (C-6). Compound **20**: colourless crystal. IR (neat, KBr) ν_{max}, 3427 (hydroxyl group), 1754 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 262.1198 $[M]^+$ (30), 244.1096 $[M-18]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 6.25 (1H, dd, *J*=3.3 and 0.7, H-13), 6.13 (1H, dd, *J*=3.1 and 0.8, H-13′), 5.47(1H, dd, *J*=1.9 and 1.6, H-15), 5.31 (1H, dd, *J*=1.7 and 1.4, H-15′), 4.97 (1H, dd, *J*=0.6 and 0.4, H-14), 4.94 (1H, dd, *J*=0.6 and 0.4, H-14′), 4.54 (1H, br dd, *J*=7.4 and 2.1, H-3), 4.14 (1H, dd, *J*=10.6 and 9.1, H-6), 3.96 (1H, br ddd, *J*=9.1, 5.0 and 4.0, H-8), 3.10 (1H, br ddd, *J*=10.0, 9.1, 3.3 and 3.1, H-7), 2.96 (1H, br ddd, *J*=11.0, 9.4 and 8.0, H-1), 2.79 (1H, br dd, *J*=10.5 and 9.7, H-5), 2.69 (1H, dd, *J*=14.1 and 5.1, H-9β), 2.28 (1H, dd, *J*=14.1 and 3.9, H-9α), 2.22 (1H, ddd, *J*=13.2, 7.6 and 7.4, H-2β), 1.72 (1H, ddd, *J*=13.2, 11.0 and 7.6, H-2α). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5 (C-12), 152.4 (C-10), 142.7 (C-4), 138.1 (C-11), 123.2 (C-13), 117.4 (C-14), 113.1 (C-15), 78.8 (C-6), 73.7 (C-3), 70.9 (C-8), 51.2 (C-7), 50.9 (C-5), 45.1 (C-1), 41.3 (C-9), 39.2 (C-2).

3.11. 8α-Hydroxy-dehydrozaluzanin C (21)

Compound **20** (100 mg, 0.38 mmol) was dissolved in dried CH_2Cl_2 (20 mL). SeO_2 (45 mg, 0.40 mmol) was added over the stirred solution, and allowed to react for 24 h. Filtering the reaction mixture through silica gel stopped the reaction, the solvent was then evaporated under vacuum. The crude product was purified by CC using hexane/ethyl acetate mixtures as eluent, yielding 78 mg of **21** (79%, 30 mmol). Compound **21**: colourless crystal. IR (neat, KBr) ν_{max}, 3430 (hydroxyl group), 1762 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 260.1098 $[M]^+$ (21), 242.1069 $[M-18]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 6.36 (1H, dd, *J*=3.4 and 0.9, H-13), 6.30 (1H, dd, *J*=3.0 and 0.9, H-13′), 6.26 (1H, d, *J*=2.5, H-15), 5.87 (1H, d, *J*=2.2, H-15′), 5.03 (1H, s, H-14), 4.83, (1H, s, H-14′), 3.98 (1H, dd, *J*=9.5 and 9.2, H-6), 3.96 (1H, br ddd, *J*=9.1, 5.0 and 4.0, H-8), 3.25 (1H, ddd, *J*=9.5, 8.6 and 2.5, H-5α), 3.11 (1H, br ddd, *J*=8.2, 8.6 and 5.2, H-1α), 3.06 (1H, dddd, *J*=9.3,

9.2, 3.4 and 3.0, H-7), 2.79 (1H, dd, J=13.1 and 5.6, H-9β), 2.60 (1H, dd, J=13.2 and 8.2, H-2β), 2.49 (1H, dd, J=18.5 and 5.2, H-2α), 2.30 (1H, dd, J=3.1 and 7.0, H-9α). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2 (C-3), 169.5 (C-12), 143.1 (C-11), 136.5 (C-10), 130.1 (C-4), 125.9 (C-13), 123.5 (C-15), 117.1 (C-14), 80.0 (C-6), 73.2 (C-8), 49.6 (C-7), 49.3 (C-5), 46.5 (C-9), 43.7 (C-2), 40.6 (C-1).

CCDC 602144-602148 and CCDC 605928-605933 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223 336033; email: deposit@ccdc.cam.ac.uk].

4. Conclusions

The achievement of the four oxetane lactones using dehydrocostuslactone as starting material has provided some correlations, which can be useful tools in future researches with this type of molecules. Thus, a deep analysis of the NMR and X-ray derived data of the obtained oxetane lactones has allowed us to find some relationships that can be helpful in order to detect the presence of the oxetane ring as well as to establish its stereochemistry on similar compounds.

Furthermore, the results of the conformational analysis may also be important findings due to the key aspect that the molecular conformations play on the biological activity. We have found that guaianolides having the α-methylene-γ-lactone moiety and non-bulky substituents prefer a twist-chair conformation at the cycloheptane ring, whereas a chair conformation occurs when the lack of the α-methylene-γ-lactone group takes place.

Acknowledgements

This research was supported by the Ministerio de Educación y Ciencia, Spain (MEC; Project No. AGL2004-08357-C04-04/AGR and AGL2005-05190/AGR).

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Tetrahedron 62 (2006) 7756–7761
Tetrahedron

A straightforward synthesis of *glyco*-2,7- and 2,8-dienes

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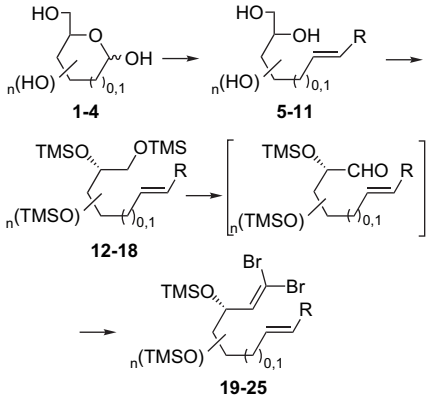
Received 21 April 2006; revised 23 May 2006; accepted 24 May 2006
Available online 15 June 2006

Abstract—In this paper, we report the efficient preparation of carbohydrate-derived 2,7- and 2,8-dienes. By our synthetic approach, we have quickly converted D-glucose **1** to (*E*)-ethyl-2,3-dideoxy-D-*gluco*-oct-2-enoate **5**, which led to the desired (*E*)-ethyl-9,9-dibromo-2,3,8,9-tetradeoxy-4,5,6,7-tetra-*O*-trimethylsilyl-D-*gluco*-nona-2,8-dienoate **19** with satisfying yield.

1. Introduction

Synthesis of well-defined polyhydroxylated chiral building blocks remains of interest in synthetic chemistry.[1] Toward this goal, the chiral pool is an attractive and economic source of enantiomerically pure starting materials. The main task remains to convert efficiently and rapidly these chiral materials into useful synthetic scaffolds for the construction of useful ring systems.[2] Part of our studies is to start from carbohydrates to achieve the synthesis of chain-elongated sugars. A few years ago, we tuned a Wittig type reaction that allowed us to work on free carbohydrates.[3] When aldoses were reacted with methyl bromoacetate, tri-*n*-butylphosphine, and zinc, they gave the corresponding *E*-unsaturated Wittig products in good yields and high stereoselectivity. Moreover this procedure suppressed classical side reactions. As a result of these studies, we conclude that it would be of great value to transpose such smooth conditions to the reaction with dibromotriphenylphosphonium bromide. This goal was achieved by overcoming some difficulties, and we have reported the synthesis of 1,1-dibromo-1-alkenes from partially protected and unprotected aldoses.[4] These compounds were interesting scaffolds that can be used in many transformations.[5] Here we report the efficient synthesis of (*E*)-alkyl-9,9-dibromo-D-*glyco*-nona-2,8-dienoates, (*E*)-9,9-dibromo-D-*gluco*-nona-2,8-dienonitrile, and (*E*)-ethyl-8,8-dibromo-D-*ribo*-octa-2,7-dienoate in a few steps from commercially available monosaccharides. As shown in Scheme 1, these 2,7- and 2,8-dienes were readily obtained from aldoses. Our strategy is based on the prior transformation of the hemiacetal position from which we generated a carbon–carbon double bond (**5**–**11**) by a Wittig type reaction and in a second time on the creation of the second unsaturated bond (**19**–**25**) from the primary hydroxyl group via a Corey–Fuchs reaction. In this strategy, we used TMS group as protecting groups for hydroxyls because a transformation can be carried out by a one-pot procedure to selectively deprotect and then oxidize the primary alcohol.[6]



Scheme 1.

2. Results and discussion

2.1. Synthesis of olefins 5–11

The reaction of D-glucose **1** with ethyl bromoacetate, *tert*-butyl bromoacetate, methyl bromoacetate or bromoacetonitrile, and tri-*n*-butylphosphine in the presence of zinc in refluxing 1,4-dioxane afforded mainly *E*-unsaturated Wittig products **5**–**8** with yields ranging from 52% to 70%. NMR and mass spectrometry experiments were used to establish the structure of olefins **5**–**8**. Indeed, as example, the NMR spectra of **5** exhibited two characteristic peaks 148.2 and 121.6 ppm attributed, respectively, to C-3 and C-2 and 7.06 (dd) and 6.15 (dd) attributed, respectively, to H-3 and H-2 and with J=15.7 Hz. So, the mildness of our conditions

Keywords: Carbohydrate-derived 2,7- and 2,8-dienes; Oxidation; Wittig type reaction; Corey–Fuchs reaction.
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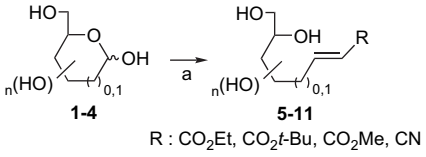
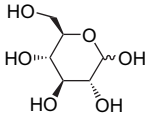
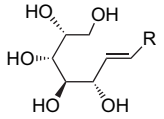
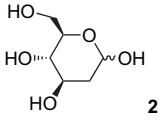
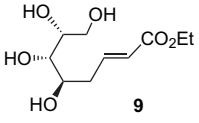
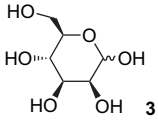
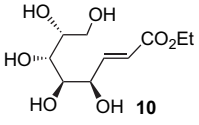
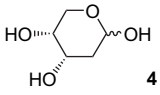
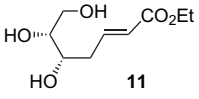
doi:10.1016/j.tet.2006.05.057

allowed us to form *E*-olefin on naked aldoses, preventing formation of C-glycosides. 2-Deoxy-D-glucose **2** treated with ethyl bromoacetate, tri-*n*-butylphosphine in the presence of zinc in refluxing 1,4-dioxane led to the desired compound **9** in 80% yield. It appears that from 2-deoxy-D-glucose **2** the yield was better than the one for D-glucose **1** in this Wittig type reaction. When these conditions were applied to D-mannose **3** and 2-deoxy-D-ribose **4**, the expected olefins **10** and **11** were obtained in 70% and 73% yields, respectively (Scheme 2, Table 1).



Scheme 2. Synthesis of olefins **5**–**11**. Reagents and conditions: (a) $BrCH_2R$ (2 equiv), *n*-Bu_3P (2 equiv), Zn (2 equiv), 1,4-dioxane, reflux.

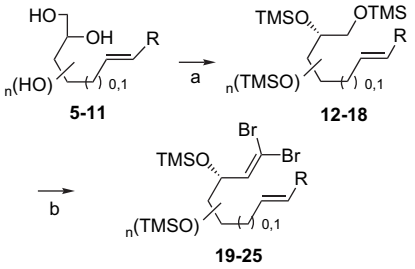
Table 1. Synthesis of olefins **5**–**11**

Aldoses **1**–**4**	Olefins **5**–**11**	Yields[a] (%)
 **1**	 **5** : R = CO_2Et **6** : R = CO_2t-Bu **7** : R = CO_2Me **8** : R = CN	69 52 70 70
 **2**	 **9**	80
 **3**	 **10**	70
 **4**	 **11**	73

[a] Yield represents isolated yield.

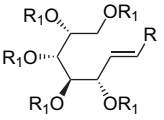
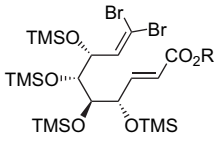
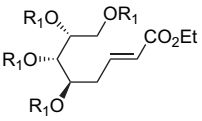
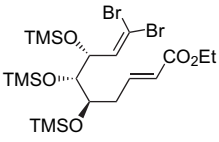
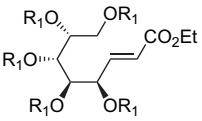
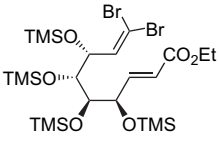
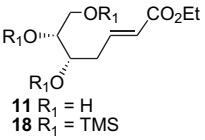
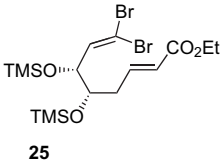
2.2. Synthesis of 2,7- and 2,8-dienes 19–25

The activated DMSO reagents, well-known for oxidizing alcohol to the corresponding carbonyl compounds under mild conditions, can also oxidize trimethyl and triethylsilyl ethers.[5] Furthermore, primary trimethyl and triethylsilyl ethers are more reactive than their secondary analogues, allowing the selective oxidation of the former in the presence of the latter by the Swern reagent, oxalyl chloride, a good activator for DMSO.[7] So, in a three-step procedure on olefin **5**, we carried out a standard silylation (trimethylsilyl chloride, triethylamine in dichloromethane at room temperature) followed by a Swern oxidation and an addition of dibromotriphenylphosphonium bromide, *t*-BuOK in THF. Unfortunately we could not recover more than 30% of the desired diene **19**. TLC monitoring of the reaction showed that the silylation step was neither clean nor complete. Reaction with HMDS as the silylating reagent leaded to the same kind of results. The prior isolation of the persilylated compound **12** was not a positive solution either, due to the relative instability of the TMS groups on silica gel and use of fluorisil as a separative agent was not practicable enough on a reasonable scale. We then searched for a powerful silylating reagent, which would in the same time create only easily removable by-products. We turned our focus to *N*,*O*-bis-(trimethylsilyl)carbamate, and indeed BSC was the reactant of choice since the only by-products of silylation are the gases NH_3 and CO_2 and the products can be used in subsequent reactions without any treatment but a simple removal of the solvent.[8] (Scheme 3, Table 2)



Scheme 3. Synthesis of dienes **19**–**25**. Reagents and conditions: (a) BSC (1.2 equiv per OH), TBAF (0.01 equiv), NMP, rt. (b) (i) $(COCl)_2$ (3 equiv), DMSO (6 equiv), CH_2Cl_2, −70 °C then Et_3N, (ii) Ph_3PCHBr_3 (2.2 equiv), *t*-BuOK (2.1 equiv), THF, rt.

Table 2. Synthesis of dienes **19**–**25**

Olefins **5**–**11**	Dienes **19**–**25**	Yields[a] (%)
 **5** R_1 = H, R = CO_2Et **6** R_1 = H, R = CO_2t-Bu **7** R_1 = H, R = CO_2Me **8** R_1 = H, R = CN **12** R_1 = TMS, R = CO_2Et **13** R_1 = TMS, R = CO_2t-Bu **14** R_1 = TMS, R = CO_2Me **15** R_1 = TMS, R = CN	 **19** R = CO_2Et **20** R = CO_2t-Bu **21** R = CO_2Me **22** R = CN	59 69 56 49
 **9** R_1 = H **16** R_1 = TMS	 **23**	59
 **10** R_1 = H **17** R_1 = TMS	 **24**	50
 **11** R_1 = H **18** R_1 = TMS	 **25**	57

[a] Yield represents isolated yield from persylilated olefins **12**–**18**.

We have tested these silylation conditions (BSC, TBAF in catalytic quantity in 1-methyl-2-pyrrolidinone (NMP) at room temperature). So the starting material **5** was successfully converted into **19** (59% yield) by this sequence involving silylation with BSC followed by Swern oxidation and an addition of dibromotriphenylphosphonium bromide, *t*-BuOK in THF. The structure of **19** was confirmed by NMR spectroscopy experiments, with the characteristic resonances observed at δ=149.2, 139.7, 120.0, 89.8 ppm attributed to C-3, C-8, C-2, C-9, respectively, and those at δ=7.23, 6.60, 5.97 ppm attributed to H-3, H-8, H-2, respectively. We then extended this three-step procedure to the other olefins (**6**–**11**) described above, converting them into their corresponding 2,7- and 2,8-dienes. These conditions on olefins derived from D-glucose **6**–**9** afford the desired compounds **20**–**23** with satisfying yields. When the reaction is performed on olefins **10** and **11** derived from D-mannose and D-ribose, respectively, the corresponding dienes are isolated with 50% and 57% yields, respectively.

In summary, several polyhydroxylated 2,7- and 2,8-dienes were prepared in a versatile manner in four steps from commercially available monosaccharides with satisfying yields. The quickness and efficiency of this methodology to prepare functionalized chiral polyols is noticeable. Such compounds are interesting scaffolds, in particular for the obtaining of polyhydroxylated carbocycles and for the construction of bridged and fused bicyclic systems. Indeed, a study toward their cyclization is currently in progress in our laboratory and any interesting result will be reported in due course. As well, we are pursuing our study on conversion of carbohydrates in interesting polyhydroxylated chiral scaffold derivatives.

3. Experimental

3.1. General

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF was distilled from lithium aluminum hydride immediately before use. CH_2Cl_2 was distilled from calcium chloride under argon. Moisture sensitive reactions were conducted in oven-dried glassware under an argon atmosphere. Flash chromatography was carried out on Kieselgel 60 (230–400 mesh, Merck) and analytical thin-layer chromatography (TLC) was performed on E. Merck glass-backed silica gel sheets (Silica Gel 60 F254). Melting points are uncorrected. Optical rotations were measured using a sodium lamp (λ=589 nm) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Spectra were recorded in $CDCl_3$, C_5D_5N, D_2O, or CD_3OD and chemicals shifts (δ) were expressed in parts per million relative to residual $CHCl_3$ or an internal standard. All signals in ^{13}C NMR spectra were assigned through C,H-correlated spectra. IR spectra were recorded as neat films (NaCl cell) and KBr pellets (for solids). Infusion electrospray mass spectra in the positive-ion mode were obtained with an updated (3.6 GHz TDC) Q-TOF hybrid quadrupole-time-of-flight instrument, equipped with a pneumatically assisted electrospray ion source (Z-spray).

3.1.1. Preparation of olefins 5–11. General procedure 1: To an anhydrous 1,4-dioxane solution (3.6 mL, 1 mmol) of zinc (2 equiv) were successively added tri-*n*-butylphosphine (2 equiv), ethyl bromoacetate or *tert*-butyl bromoacetate or bromonitrile (2 equiv), and starting material (**1**–**4**). The reaction was stirred under an argon atmosphere and allowed to reflux. The reaction was monitored by TLC, and after completion the mixture was cooled to room temperature and filtered on sintered glass. After concentration, the crude residue was purified by flash chromatography.

3.1.1.1. (*E*)-Ethyl-2,3-dideoxy-D-*gluco*-oct-2-enoate (5). The compound **5** was prepared by general procedure 1 from D-glucose **1** (1.37 g, 7.65 mmol). The reaction was completed after 1 h. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 95:5, 90:10, and then 85:15), and **5** was obtained as a colorless oil (1.32 g, 69%). R_f=0.44 (CH_2Cl_2/MeOH 80:20); $[\alpha]_D^{27}$ −90 (*c* 1.0, MeOH); IR: ν_{max} 3300, 1780, 1640, 1250, 1150, and 960 cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.06 (dd, 1H, *J*=5.3, 15.7 Hz, 3-H), 6.15 (dd, 1H, *J*=1.6, 15.7 Hz, 2-H), 4.50 (dt, 1H, *J*=1.6, 5.3, 5.3 Hz, 4-H), 4.20 (q, 2H, OCH_2CH_3), 3.80 (m, 2H, 5-H, 8a-H), 3.61 (m, 3H, 6-H, 7-H, 8b-H), 1.20 (t, 3H, OCH_2CH_3); ^{13}C NMR (CD_3OD): δ 167.2, 148.2, 121.6, 72.9, 72.9, 72.7, 71.6, 63.7, 60.7, 13.6; Anal. Calcd for $C_{10}H_{18}O_7$: C, 48.00; H, 7.25. Found: C, 48.29; H, 7.37; MS: *m*/*z* 273.2 [M+Na]$^+$.

3.1.1.2. (*E*)-*tert*-Butyl-2,3-dideoxy-D-*gluco*-oct-2-enoate (6). The compound **6** was prepared by general procedure 1 from D-glucose **1** (1 g, 5.55 mmol). The reaction was completed after 1 h. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 90:10), and **6** was obtained as a colorless oil (0.8 g, 52%). R_f=0.4 (CH_2Cl_2/MeOH 80:20); $[\alpha]_D^{24}$ −39 (*c* 1.0, MeOH); IR: ν_{max} 3300, 1760, 1630, 1250, 1150, and 960 cm^{-1}; ^{1}H NMR (CD_3OD): δ 7.01 (dd, 1H, *J*=5.5, 15.6 Hz, 3-H), 6.03 (dd, 1H, *J*=1.6, 15.6 Hz, 2-H), 4.39 (ddd, 1H, *J*=1.6, 5.5, 6.2 Hz, 4-H), 3.78 (dd, 1H, *J*=1.7, 4.2 Hz, 8a-H), 3.68 (m, 1H, 5-H), 3.63 (m, 3H, 6-H, 7-H, 8b-H), 1.52 (s, 9H, $OC(CH_3)_3$); ^{13}C NMR (CD_3OD): δ 167.0, 147.0, 123.3, 81.7, 73.9, 73.8, 72.9, 72.7, 64.8, 28.4; Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97. Found: C, 51.89; H, 8.11; MS: *m*/*z* 301.3 [M+Na]$^+$.

3.1.1.3. (*E*)-Methyl-2,3-dideoxy-D-*gluco*-oct-2-enoate (7). The compound **7** was prepared by general procedure 1 from D-glucose **1** (1 g, 5.55 mmol). The reaction was completed after 1 h. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 85:15), and **7** was obtained as a colorless oil (0.91 g, 70%). R_f=0.38 (CH_2Cl_2/MeOH 80:20); $[\alpha]_D^{27}$ −60 (*c* 1.0, MeOH); IR: ν_{max} 3300, 1780, 1640, 1250, 1150, and 960 cm^{-1}; ^{1}H NMR (D_2O): δ 7.01 (dd, 1H, *J*=5.7, 15.5 Hz, 3-H), 6.17 (dd, 1H, *J*=1.6, 15.5 Hz, 2-H), 4.48 (ddd, 1H, *J*=1.5, 1.6, 5.7 Hz, 4-H), 3.85 (dd, 1H, *J*=1.5, 1.8 Hz, 5-H), 3.82 (dd, 1H, *J*=2.0, 11.7 Hz, 8b-H), 3.73 (ddd, 1H, *J*=2.2, 6.1, 6.5 Hz, 7-H), 3.63 (dd, 1H, *J*=6.1, 11.7 Hz, 8a-H), 2.69 (dd, 1H, *J*=1.8, 6.5 Hz, 6-H), 3.80 (s, 3H, OCH_3); ^{13}C NMR (D_2O): δ 172.0, 150.4, 124.8, 73.9, 73.7, 72.8, 72.3, 64.6, 53.9; Anal. Calcd for $C_9H_{16}O_7$: C, 45.76; H, 6.83. Found: C, 45.89; H, 6.98; MS: *m*/*z* 259.2 [M+Na]$^+$.

3.1.1.4. (*E*)-2,3-Dideoxy-D-*gluco*-oct-2-enonitrile (8). The compound **8** was prepared by general procedure 1

from D-glucose **1** (1 g, 5.55 mmol). The reaction was completed after 1 h. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 95:5), and **8** was obtained as a colorless oil (0.796 g, 70%). R_f=0.33 (CH_2Cl_2/MeOH 80:20); $[\alpha]_D^{25}$ −11 (*c* 0.9, MeOH); IR: ν_{max} 3300, 2250, 1600, 1250, 1150, and 960 cm^{-1}; ^1H NMR (C_5D_5N): δ 7.03 (dd, 1H, *J*=4.3, 16.3 Hz, 3-H), 5.82 (dd, 1H, *J*=2.0, 16.3 Hz, 2-H), 4.50 (dt, 1H, *J*=2.0, 4.3, 5.3 Hz, 4-H), 3.81 (m, 2H, 5-H, 8a-H), 3.62 (m, 3H, 6-H, 7-H, 8b-H); ^{13}C NMR (C_5D_5N): δ 158.5, 120.0, 100.2, 74.9, 73.8, 72.8, 63.8; Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.42; H, 6.59; N, 6.91; MS: *m/z* 226.2 $[M+Na]^+$.

3.1.1.5. (*E*)-Ethyl-2,3,4-trideoxy-D-*gluco*-oct-2-enoate (9). The compound **9** was prepared by general procedure 1 from 2-deoxy-D-glucose **2** (1 g, 6.1 mmol). The reaction was completed after 1 h. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 95:5), and **9** was obtained as a solid (1.14 g, 80%). R_f=0.43 (CH_2Cl_2/MeOH 85:15); $[\alpha]_D^{23}$ +17 (*c* 1.4, MeOH); mp=114–117 °C; IR: ν_{max} 3300, 1770, 1640, 1250, 1150, and 960 cm^{-1}; ^1H NMR (CD_3OD): δ 7.06 (dt, 1H, *J*=3.2, 3.2, 15.7 Hz, 3-H), 6.00 (dt, 1H, *J*=1.5, 1.5, 15.7 Hz, 2-H), 4.20 (q, 2H, OCH_2CH_3), 3.98 (ddd, 1H, *J*=1.7, 5.5, 7.4 Hz, 5-H), 3.80 (dd, 1H, *J*=3.0, 10.6 Hz, 8a-H), 3.69 (ddd, 1H, *J*=3.0, 5.6, 8.1 Hz, 7-H), 3.63 (dd, 1H, *J*=5.6, 10.6 Hz, 8b-H), 3.37 (dd, 1H, *J*=1.7, 8.1 Hz, 6-H), 2.49 (m, 2H, 4a-H, 4b-H), 1.30 (t, 3H, OCH_2CH_3); ^{13}C NMR (CD_3OD): δ 167.0, 147.0, 123.0, 73.1, 71.9, 69.5, 64.0, 60.4, 36.8, 13.5; Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.43; H, 7.99; MS: *m/z* 257.3 $[M+Na]^+$.

3.1.1.6. (*E*)-Ethyl-2,3-dideoxy-D-*manno*-oct-2-enoate (10). The compound **10** was prepared by general procedure 1 from D-mannose **3** (1.5 g, 8.3 mmol). The reaction was completed after 40 min. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 95:5, 90:10, and then 85:15), and **10** was obtained as a colorless oil (1.45 g, 70%). R_f=0.42 (CH_2Cl_2/MeOH 85:15); $[\alpha]_D^{28}$ +20 (*c* 1.0, MeOH); IR: ν_{max} 3300, 1780, 1640, 1250, 1150, and 960 cm^{-1}; ^1H NMR (CD_3OD): δ 8.02 (dd, 1H, *J*=4.0, 15.7 Hz, 3-H), 6.70 (dd, 1H, *J*=1.8, 15.7 Hz, 2-H), 5.18 (ddd, 1H, *J*=1.8, 4.0, 8.3 Hz, 4-H), 4.85 (dd, 1H, *J*=2.0, 8.2 Hz, 6-H), 4.60 (m, 1H, 7-H), 4.68 (dd, 1H, *J*=2.0, 8.3 Hz, 5-H), 4.50 (dd, 1H, *J*=3.8, 10.9 Hz, 8a-H), 4.35 (dd, 1H, *J*=2.9, 10.9 Hz, 8b-H), 4.20 (q, 2H, OCH_2CH_3), 1.20 (t, 3H, OCH_2CH_3); ^{13}C NMR (CD_3OD): δ 167.1, 153.0, 120.9, 74.0, 73.7, 72.0, 72.0, 61.8, 60.4, 14.5; Anal. Calcd for $C_{10}H_{18}O_7$: C, 48.00; H, 7.25. Found: C, 48.23; H, 7.39; MS: *m/z* 273.3 $[M+Na]^+$.

3.1.1.7. (*E*)-Ethyl-2,3,4-trideoxy-D-*ribo*-hept-2-enoate (11). The compound **11** was prepared by general procedure 1 from 2-deoxy-D-ribose **4** (1 g, 7.45 mmol). The reaction was completed after 1 h. The crude residue was purified by two consecutive flash chromatographies (CH_2Cl_2/MeOH 98:2, 97:3, 95:5, and then EtOAc), and **11** was obtained as a colorless oil (1.13 g, 73%). R_f=0.63 (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{26}$ −7 (*c* 1.8, $CHCl_3$); IR: ν_{max} 3300, 1780, 1650, 1250, 1150, and 960 cm^{-1}; ^1H NMR (CD_3OD): δ 7.08 (dt, 1H, *J*=7.4, 7.4, 15.7 Hz, 3-H), 5.94 (dt, 1H, *J*=1.5, 1.5, 15.7 Hz, 2-H), 4.18 (q, 2H, OCH_2CH_3), 3.75 (dd, 1H, 3.9, 11.3 Hz, 7a-H), 3.60 (ddd, 1H, *J*=3.3, 7.1, 8.8 Hz, 5-H), 3.59 (dd, 1H, 6.2, 11.3 Hz, 7b-H), 3.47 (ddd, 1H, *J*=3.9, 6.2, 7.1 Hz, 6-H), 2.63 (dddd, 1H, *J*=1.5, 3.3, 7.4, 14.7 Hz, 4a-H), 2.37 (dddd, 1H, *J*=1.5, 7.4, 8.8, 14.7 Hz, 4b-H), 1.30 (t, 3H, OCH_2CH_3); ^{13}C NMR (CD_3OD): δ 167.2, 147.0, 123.2, 74.8, 71.2, 63.7, 60.3, 36.2, 13.6; Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.99; H, 8.09; MS: *m/z* 227.3 $[M+Na]^+$.

3.1.2. Preparation of persilylated compounds 12–18. General procedure 2: To the starting material (**5**–**11**) dissolved in 1-methyl-2-pyrrolidinone (NMP) (1 g/10 mL) were successively added *N*,*O*-bis-(trimethylsilyl)carbamate (1.2 equiv per OH) and dropwise tetra-*n*-butylammonium fluoride (TBAF 1 M solution in THF) (0.01 equiv). The reaction was stirred under an argon atmosphere for 24 h at room temperature as monitored by TLC. Methanol was added (3 mL) and the mixture was concentrated, and the residue was diluted in hexane (3 mL hexane/1 mL NMP) and washed with water. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue (**12**–**18**) was used in subsequent reactions without further treatment.

3.1.2.1. (*E*)-Ethyl-2,3-dideoxy-4,5,6,7,8-penta-*O*-trimethylsilyl-D-*gluco*-oct-2-enoate (12). The compound **12** was prepared by general procedure 2 from **5** (1.32 g, 5.27 mmol). The reaction was treated after 24 h. Compound **12** was obtained as a colorless oil. R_f=0.8 (Hexane/EtOAc 95:5); ^1H NMR ($CDCl_3$): δ 7.30 (dd, 1H, *J*=3.2, 15.7 Hz, 3-H), 6.00 (dd, 1H, *J*=2.0, 15.7 Hz, 2-H), 4.45 (ddd, 1H, *J*=2.0, 3.2, 5.6 Hz, 4-H), 4.20 (q, 2H, OCH_2CH_3), 3.92 (ddd, 1H, *J*=3.1, 5.2, 7.7 Hz, 7-H), 3.69 (dd, 1H, *J*=3.1, 10.4 Hz, 8a-H), 3.60 (dd, 2H, 5-H, 6-H), 3.53 (dd, 1H, *J*=7.7, 10.4 Hz, 8b-H), 1.20 (t, 3H, OCH_2CH_3), 0.08–0.15 (s, 45H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 167.0, 149.0, 121.0, 77.0, 77.0, 75.9, 74.0, 64.3, 60.5, 14.7, −0.1–1.4.

3.1.2.2. (*E*)-*tert*-butyl-2,3-dideoxy-4,5,6,7,8-penta-*O*-trimethylsilyl-D-*gluco*-oct-2-enoate (13). The compound **13** was prepared by general procedure 2 from **6** (0.8 g, 2.88 mmol). The reaction was treated after 24 h. Compound **13** was obtained as a colorless oil. R_f=0.8 (Hexane/EtOAc 95:5); ^1H NMR ($CDCl_3$): δ 7.01 (dd, 1H, *J*=5.5, 15.6 Hz, 3-H), 6.03 (dd, 1H, *J*=1.6, 15.6 Hz, 2-H), 4.39 (ddd, 1H, *J*=1.6, 5.5, 6.2 Hz, 4-H), 3.78 (dd, 1H, *J*=1.7, 4.2 Hz, 8a-H), 3.68 (m, 1H, 5-H), 3.63 (m, 3H, 6-H, 7-H, 8b-H), 1.52 (s, 9H, $OC(CH_3)_3$), 0.30–1.12 (s, 45H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 166.7, 147.2, 122.7, 80.4, 77.8, 77.3, 75.3, 74.0, 64.1, 28.5, 0.1–0.2.

3.1.2.3. (*E*)-Methyl-2,3-dideoxy-4,5,6,7,8-penta-*O*-trimethylsilyl-D-*gluco*-oct-2-enoate (14). The compound **14** was prepared by general procedure 2 from **7** (0.91 g, 3.88 mmol). The reaction was treated after 24 h. Compound **14** was obtained as a colorless oil. R_f=0.85 (Hexane/EtOAc 95:5); ^1H NMR ($CDCl_3$): δ 7.26 (dd, 1H, *J*=3.5, 15.7 Hz, 3-H), 5.95 (dd, 1H, *J*=2.6, 15.7 Hz, 2-H), 4.40 (ddd, 1H, *J*=1.4, 2.6, 3.5 Hz, 4-H), 3.86 (m, 2H, 7-H, 8b-H), 3.60 (s, 3H, OCH_3), 3.58 (dd, 1H, *J*=1.7, 6.4 Hz, 6-H), 3.50 (dd, 1H, *J*=1.4, 1.7 Hz, 5-H), 3.48 (dd, 1H, *J*=6.0, 11.6 Hz, 8a-H), −0.9–0.1 (s, 45H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 167.0, 149.1, 120.1, 76.8, 76.8, 75.7, 73.9, 64.1, 51.4, −0.3–1.6.

3.1.2.4. (*E*)-2,3-Dideoxy-4,5,6,7,8-penta-*O*-trimethylsilyl-D-*gluco*-oct-2-enonitrile (15). The compound **15** was prepared by general procedure 2 from **8** (0.79 g, 3.9 mmol). The reaction was treated after 24 h. Compound **15** was obtained as a colorless oil. R_f=0.8 (Hexane/EtOAc 95:5); ^{1}H NMR ($CDCl_3$): δ 7.30 (dd, 1H, J=4.3, 15.9 Hz, 3-H), 5.80 (dd, 1H, J=2.0, 15.9 Hz, 2-H), 4.45 (ddd, 1H, J=2.0, 4.3, 5.6 Hz, 4-H), 3.92 (ddd, 1H, J=3.3, 5.0, 7.7 Hz, 7-H), 3.81 (dd, 1H, J=3.3, 10.7 Hz, 8a-H), 3.72 (m, 2H, 5-H, 6-H), 3.62 (dd, 1H, J=7.7, 10.7 Hz, 8b-H), 0.08–0.15 (s, 45H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 157.0, 120.2, 100.4, 77.0, 77.0, 76.0, 74.3, 63.9, 0.1–1.4.

3.1.2.5. (*E*)-Ethyl-2,3,4-trideoxy-5,6,7,8-tetra-*O*-trimethylsilyl-D-*gluco*-oct-2-enoate (16). The compound **16** was prepared by general procedure 2 from **9** (1.06 g, 4.53 mmol). The reaction was treated after 24 h. Compound **16** was obtained as a colorless oil. R_f=0.9 (Hexane/EtOAc 95:5); ^{1}H NMR ($CDCl_3$): δ 6.95 (m, 1H, J=1.0, 15.7 Hz, 3-H), 5.85 (dt, 1H, J=1.0, 1.0, 15.7 Hz, 2-H), 4.21 (q, 2H, J=8.0 Hz, OCH_2CH_3), 3.75 (m, 2H, 5-H, 7-H), 3.71 (dd, 1H, J=4.0, 10.4 Hz, 8b-H), 3.58 (dd, 1H, J=3.1, 5.4 Hz, 6-H), 3.40 (dd, 1H, J=6.8, 10.4 Hz, 8a-H), 2.45 (m, 2H, 4a-H, 4b-H), 1.30 (t, 3H, OCH_2CH_3), 0.1–1.1 (s, 36H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 167.7, 146.9, 123.6, 78.6, 73.6, 74.7, 64.2, 60.5, 37.1, 14.7, 0.1–1.4.

3.1.2.6. (*E*)-Ethyl-2,3-dideoxy-4,5,6,7,8-penta-*O*-trimethylsilyl-D-*manno*-oct-2-enoate (17). The compound **17** was prepared by general procedure 2 from **10** (1.45 g, 5.79 mmol). The reaction was treated after 24 h. Compound **17** was obtained as a colorless oil. R_f=0.6 (Hexane/EtOAc 95:5); ^{1}H NMR ($CDCl_3$): δ 7.11 (dd, 1H, J=4.6, 15.6 Hz, 3-H), 6.01 (dd, 1H, J=1.8, 15.6 Hz, 2-H), 4.50 (m, 1H, 4-H), 4.22 (q, 2H, J=8.1 Hz, OCH_2CH_3), 3.90 (m, 1H, 5-H), 3.80 (m, 1H, 7-H), 3.78 (m, 1H, 6-H), 3.72 (dd, 1H, J=4.7, 10.1 Hz, 8a-H), 3.48 (dd, 1H, J=6.4, 10.1 Hz, 8b-H), 1.18 (t, 3H, OCH_2CH_3), 0.1–0.3 (s, 45H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 167.1, 149.3, 120.9, 77.4, 76.7, 74.5, 74.2, 63.4, 60.5, 14.7, 0.1–1.4.

3.1.2.7. (*E*)-Ethyl-2,3,4-trideoxy-5,6,7-tri-*O*-trimethylsilyl-D-*ribo*-hept-2-enoate (18). The compound **18** was prepared by general procedure 2 from **11** (1.03 g, 5.04 mmol). The reaction was treated after 24 h. Compound **18** was obtained as a colorless oil. R_f=0.7 (Hexane/EtOAc 95:5); ^{1}H NMR ($CDCl_3$): δ 6.94 (dt, 1H, J=7.7, 7.7, 15.6 Hz, 3-H), 5.82 (dt, 1H, J=0.5, 0.5, 15.6 Hz, 2-H), 4.20 (q, 2H, J=8.1 Hz, OCH_2CH_3), 3.77 (dt, 1H, J=4.7, 4.7, 7.2 Hz, 5-H), 3.58 (dt, 1H, J=4.7, 4.7, 12.0 Hz, 6-H), 3.48 (m, 2H, 7a-H, 7b-H), 2.35 (m, 2H, 4a-H, 4b-H), 1.20 (t, 3H, OCH_2CH_3), 0.1–0.2 (s, 27H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 167.0, 147.0, 123.7, 77.0, 72.7, 64.3, 60.5, 36.4, 14.7, 0.1–1.4.

3.1.3. Preparation of 2,7- and 2,8-dienes 19–25. General procedure 3: To a CH_2Cl_2 (10 mL) solution of oxalyl chloride (3 equiv) was added dropwise dry methyl sulfoxide (6 equiv) at −70 °C under an argon atmosphere. After 5 min under stirring, a solution of substrate (**12**–**18**) in CH_2Cl_2 (5 mL) was added. The reaction was monitored by TLC. After 30 min, triethylamine (9 equiv) was then carefully added. After being stirred at low temperature for 20 min, the reaction mixture was warmed to room temperature, and a saturated solution of NH_4Cl was added. The mixture was extracted and the combined organic layers were washed with water, dried (Na_2SO_4), and concentrated. The residue was diluted in dry THF. The flask was then immersed in a water bath. Dibromomethylenetriphenylphosphorane, prepared from dibromomethyltriphenylphosphonium bromide[4] (2.2 equiv) and *t*-BuOK (2.1 equiv) in THF (10 mL) at room temperature under an argon atmosphere for 15 min, was then added dropwise. After filtration with Buchner, the mixture was concentrated and the residue (**19**–**25**) was purified by flash chromatography.

3.1.3.1. (*E*)-Ethyl-9,9-dibromo-2,3,8,9-tetradeoxy-4,5,6,7-tetra-*O*-trimethylsilyl-D-*gluco*-nona-2,8-dienoate (19). The compound **19** was prepared by general procedure 3 from **12** (1.32 g, 5.27 mmol). The crude residue was purified by two consecutive flash chromatographies (Hexane/CH_2Cl_2 75:25 and Hexane/$CHCl_3$ 75:25), and **19** was obtained as a colorless oil (2.14 g, 59%). R_f=0.8 (Hexane/EtOAc 90:10); $[\alpha]_D^{23}$ +119 (*c* 1.0, CH_2Cl_2); IR ($CHCl_3$): ν_{max} 1730, 840, and 750 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.23 (dd, 1H, J=4.1, 15.7 Hz, 3-H), 6.60 (d, 1H, J=8.7 Hz, 8-H), 5.97 (dd, 1H, J=1.8, 15.7 Hz, 2-H), 4.46 (m, 1H, 4-H), 4.41 (dd, 1H, J=2.6, 8.7 Hz, 7-H), 4.20 (q, 2H, J=7.1 Hz, OCH_2CH_3), 3.72 (dd, 1H, J=2.6, 6.3 Hz, 6-H), 3.44 (t, 1H, J=6.3, 6.3 Hz, 5-H), 1.28 (t, 3H, OCH_2CH_3), 0.09–0.14 (s, 36H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 167.0, 149.2, 139.7, 120.0, 89.8, 76.5, 76.0, 75.5, 73.9, 60.5, 14.7, 0.6–0.7; Anal. Calcd for $C_{23}H_{48}Br_2O_6Si_4$: C, 39.88; H, 6.98. Found: C, 40.11; H, 6.75; MS: *m*/*z* 713.7 $[M+Na]^+$.

3.1.3.2. (*E*)-*tert*-Butyl-9,9-dibromo-2,3,8,9-tetradeoxy-4,5,6,7-tetra-*O*-trimethylsilyl-D-*gluco*-nona-2,8-dienoate (20). The compound **20** was prepared by general procedure 3 from **13** (0.80 g, 2.88 mmol). The crude residue was purified by flash chromatography (Hexane/CH_2Cl_2 60:40), and **20** was obtained as a colorless oil (1.42 g, 69%). R_f=0.8 (Hexane/EtOAc 90:10); $[\alpha]_D^{27}$ +29 (*c* 1.0, CH_2Cl_2); IR ($CHCl_3$): ν_{max} 1730, 840, and 750 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.05 (dd, 1H, J=4.3, 15.7 Hz, 3-H), 6.63 (d, 1H, J=8.8 Hz, 8-H), 5.88 (dd, 1H, J=1.8, 15.7 Hz, 2-H), 4.40 (m, 1H, 7-H), 4.39 (m, 1H, 4-H), 3.72 (dd, 1H, J=2.7, 6.2 Hz, 6-H), 3.43 (t, 1H, J=6.2 Hz, 5-H), 1.52 (s, 9H, $OC(CH_3)_3$), 1.2–0.3 (s, 36H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 166.3, 147.6, 139.5, 122.7, 80.4, 80.3, 77.8, 77.4, 75.3, 74.0, 28.5, 0.0–0.2; Anal. Calcd for $C_{25}H_{52}Br_2O_6Si_4$: C, 41.66; H, 7.27. Found: C, 41.79; H, 7.57; MS: *m*/*z* 743.8 $[M+Na]^+$.

3.1.3.3. (*E*)-Methyl-9,9-dibromo-2,3,8,9-tetradeoxy-4,5,6,7-tetra-*O*-trimethylsilyl-D-*gluco*-nona-2,8-dienoate (21). The compound **21** was prepared by general procedure 3 from **14** (0.91 g, 3.88 mmol). The crude residue was purified by flash chromatography (Hexane/CH_2Cl_2 60:40), and **21** was obtained as a colorless oil (1.47 g, 56%). R_f=0.8 (Hexane/EtOAc 95:5); $[\alpha]_D^{25}$ +89 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} 1730, 840, and 750 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.25 (dd, 1H, J=4.2, 15.7 Hz, 3-H), 6.63 (d, 1H, J=8.7 Hz, 8-H), 5.97 (dd, 1H, J=1.7, 15.7 Hz, 2-H), 4.44 (m, 2H, 4-H, 7-H), 3.70 (m, 4H, 6-H, OCH_3), 3.44 (t, 1H, J=6.0, 6.0 Hz, 5-H), −0.9–0.1 (s, 36H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 167.4, 149.7, 144.0, 120.0, 89.8, 76.5, 76.1, 75.5, 73.9, 51.7, 0.0; Anal. Calcd for $C_{22}H_{46}Br_2O_6Si_4$: C,

38.93; H, 6.83. Found: C, 39.00; H, 6.78; MS: *m/z* 701.7 $[M+Na]^+$.

3.1.3.4. (*E*)-9,9-dibromo-2,3,8,9-tetradeoxy-4,5,6,7-tetra-*O*-trimethylsilyl-D-*gluco*-nona-2,8-dienonitrile (22). The compound **22** was prepared by general procedure 3 from **15** (0.79 g, 3.90 mmol). The crude residue was purified by flash chromatography (Hexane/CH_2Cl_2 75:25), and **22** was obtained as a colorless oil (1.23 g, 49%). R_f=0.75 (Hexane/EtOAc 90:10); $[\alpha]_D^{23}$ +49 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} 2230, 1730, 840, and 750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.03 (dd, 1H, *J*=4.2, 15.7 Hz, 3-H), 6.48 (d, 1H, *J*=8.8 Hz, 8-H), 6.00 (dd, 1H, *J*=1.9, 15.7 Hz, 2-H), 4.61 (dd, 1H, *J*=2.5, 8.8 Hz, 7-H), 4.45 (m, 1H, 4-H), 3.73 (dd, 1H, *J*=2.5, 6.1 Hz, 6-H), 3.47 (t, 1H, *J*=6.1, 6.1 Hz, 5-H), 0.09–0.14 (s, 36H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 158.2, 140.1, 120.0, 100.0, 90.0, 75.0, 74.9, 73.5, 72.9, 0.6–0.7; Anal. Calcd for $C_{21}H_{43}Br_2NO_4Si_4$: C, 39.06; H, 6.71; N, 2.17. Found: C, 39.33; H, 6.57; N, 2.23; MS: *m/z* 668.7 $[M+Na]^+$.

3.1.3.5. (*E*)-Ethyl-9,9-dibromo-2,3,4,8,9-pentadeoxy-5,6,7-tri-*O*-trimethylsilyl-D-*gluco*-nona-2,8-dienoate (23). The compound **23** was prepared by general procedure 3 from **16** (1.06 g, 4.53 mmol). The crude residue was purified by flash chromatography (Cyclohexane/EtOAc 99:1), and **23** was obtained as a colorless oil (1.6 g, 59%). R_f=0.5 (Cyclohexane/EtOAc 95:5); $[\alpha]_D^{23}$ +9 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): ν_{max} 1730, 840, and 750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.90 (ddd, 1H, *J*=7.7, 7.9, 15.7 Hz, 3-H), 6.53 (d, 1H, *J*=9.0 Hz, 8-H), 5.82 (d, 1H, *J*=15.7 Hz, 2-H), 4.41 (dd, 1H, *J*=3.4, 9.0 Hz 7-H), 4.16 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 3.68 (m, 1H, 5-H), 3.57 (dd, 1H, *J*=3.4, 5.1 Hz, 6-H), 2.48 (m, 1H, 4a-H), 2.31 (m, 1H, 4b-H), 1.19 (t, 3H, OCH_2CH_3), 0.08–0.11 (s, 27H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 166.3, 146.8, 139.3, 123.5, 90.6, 78.6, 73.8, 73.2, 60.0, 36.4, 14.2, 0.5–0.6; Anal. Calcd for $C_{20}H_{40}Br_2O_5Si_3$: C, 39.73; H, 6.67. Found: C, 39.98; H, 6.83; MS: *m/z* 627.6 $[M+Na]^+$.

3.1.3.6. (*E*)-Ethyl-9,9-dibromo-2,3,8,9-tetradeoxy-4,5,6,7-tetra-*O*-trimethylsilyl-D-*manno*-nona-2,8-dienoate (24). The compound **24** was prepared by general procedure 3 from **17** (1.45 g, 5.79 mmol). The crude residue was purified by flash chromatography (Hexane/CH_2Cl_2 7:3), and **24** was obtained as a colorless oil (2 g, 50%). R_f=0.7 (Hexane/EtOAc 95:5); $[\alpha]_D^{23}$ +9 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} 1730, 840, and 750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.05 (dd, 1H, *J*=4.1, 15.7 Hz, 3-H), 6.57 (d, 1H, *J*=8.7 Hz, 8-H), 6.00 (dd, 1H, *J*=1.8, 15.7 Hz, 2-H), 4.31 (ddd, 1H, *J*=1.8, 4.1, 6.3 Hz, 4-H), 4.28 (dd, 1H, *J*=2.6, 8.7 Hz, 7-H), 4.20 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 3.67 (dd, 1H, *J*=2.6, 6.3 Hz, 6-H), 3.56 (t, 1H, *J*=6.3 Hz, 5-H), 1.28 (t, 3H, OCH_2CH_3), 0.09–0.14 (s, 36H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 167.0, 148.6, 138.9, 122.1, 91.7, 76.6, 74.6, 73.8, 60.3, 14.5, 0.9–1.1; Anal. Calcd for $C_{23}H_{48}Br_2O_6Si_4$: C, 39.88; H, 6.98. Found: C, 40.11; H, 6.75; MS: *m/z* 713.7 $[M+Na]^+$.

3.1.3.7. (*E*)-Ethyl-8,8-dibromo-2,3,4,7,8-pentadeoxy-5,6-di-*O*-trimethylsilyl-D-*ribo*-octa-2,7-dienoate (25). The compound **25** was prepared by general procedure 3 from **18** (1.03 g, 5.04 mmol). The crude residue was purified by flash chromatography (Pentane/Et_2O 98:2), and **25** was obtained as a colorless oil (1.44 g, 57%). R_f=0.8 (Hexane/EtOAc 95:5); $[\alpha]_D^{23}$ −13 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): ν_{max} 1728, 840, and 750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.95 (ddd, 1H, *J*=7.2, 7.8, 15.7 Hz, 3-H), 6.35 (d, 1H, *J*=8.0 Hz, 7-H), 5.85 (d, 1H, *J*=15.7 Hz, 2-H), 4.20 (m, 3H, 6-H, OCH_2CH_3), 3.70 (m, 1H, 5-H), 2.35 (m, 2H, 4a-H, 4b-H), 1.20 (t, 3H, OCH_2CH_3), 0.49–0.76 (s, 18H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 166.4, 145.8, 139.0, 124.0, 90.6, 76.8, 75.1, 60.3, 36.9, 14.6, 0.4–0.7; Anal. Calcd for $C_{16}H_{30}Br_2O_4Si_2$: C, 38.25; H, 6.02. Found: C, 38.33; H, 6.31; MS: *m/z* 525.4 $[M+Na]^+$.

Acknowledgements

We thank the *Conseil Régional de Picardie* for financial support. F.D. is grateful to the French Ministry of Education, Research, and Technology (MENRT) for a doctoral fellowship.

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Tetrahedron 62 (2006) 7762–7771
Tetrahedron

Ring-opening of tertiary cyclopropanols derived from β-diketones

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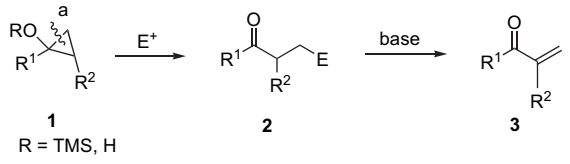
Received 10 April 2006; revised 24 May 2006; accepted 25 May 2006
Available online 19 June 2006

Dedicated to Professor Yaozhong Jiang on the occasion of his 70th birthday

Abstract—The ring-opening reaction of 1,2-disubstituted cyclopropanols, prepared from β-diketones, mediated by $Cu(NO_3)_2$, *p*-TsOH, and NaOH is reported. The Cu(II)-mediated ring-opening of cyclopropanols gave α-methylene-γ-diketones in good yields. The reaction took place at the less substituted carbon of the cyclopropanols, involving mild conditions and a simple procedure. The reaction induced by *p*-TsOH in CH_2Cl_2 afforded α-methyl-γ-diketones as the major product with minor amounts of δ-diketones. The 2,3,5-trisubstituted furans were obtained in high yields when the ring-opening reaction was mediated by *p*-TsOH in methanol under reflux conditions. In the presence of sodium hydroxide the reaction proceeded smoothly in preference to the formation of δ-diketones, particularly for substrates with an aromatic group on the cyclopropane.

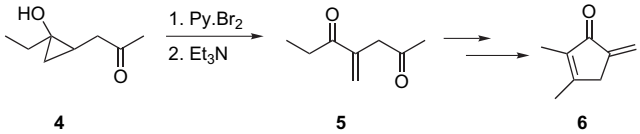
1. Introduction

The unique reactivity of cyclopropanes due to their high level of strain offers considerable utility in organic synthesis. Many applications of cyclopropanes as useful building blocks have been described but not for regio- and stereo-controlled ring-opening reactions of substituted cyclopropanes.[1] However, heteroatom-substituted cyclopropanes exhibit enhanced reactivity and also undergo regio- and stereo-controlled ring cleavage.[2] Among those heteroatom-substituted cyclopropanes, the ring-opening of cyclopropanols and its derivatives, which are important intermediates in organic synthesis, have been reported in the literature.[3] Typically, tertiary cyclopropyl silyl ethers **1** (R=TMS) are easily prepared from the cyclopropanation of enol silyl ethers and can be converted into the corresponding carbonyl compounds via ring-opening reactions.[4] Several methods have been developed to achieve α-methylene ketones **3** by the specific cleavage at bond 'a' of compound **1** (Scheme 1).[5] Reactions of cyclopropyl silyl ethers **1** with $SnCl_4$,[5a] $TeCl_4$,[5b] and Br_2 gave β-trichlorostannyl, β-trichlorotelluro, and β-bromo ketones **2**, respectively, followed by treatment with DMSO or Et_3N to furnish α-methylene ketones **3** in good yields. Recently, the use of cyclopropanols as synthetic intermediates has increased since the advent of the Kulinkovich reaction.[6] Also, the cyclopropanols can be converted into α-methylene ketones **3** in the presence of $Py\cdot Br_2$ or NBS, followed by addition of Et_3N.



Scheme 1.

Among those α-methylene ketones, α-methylene-γ-diketones are important precursors for the synthesis of substituted cyclopentenones, five-membered heterocyclic compounds, and natural products. In 2000, Chevtchouk reported an operationally simple approach to synthesize the cyclopentenoid antibiotic methylenomycin B **6**. The key intermediate **5** of this reaction was prepared in a reasonable yield via ring-opening of 1,2-disubstituted cyclopropanol **4** in the presence of $Py\cdot Br_2$, followed by addition of Et_3N (Scheme 2).[7] Though these elegant ring-opening reactions to synthesize α-methylene ketones are simple to perform, the main disadvantage of the above procedures is the requirement of long reaction times and the utility of toxic reagents.



Scheme 2.

Keywords: 1,2-Disubstituted cyclopropanol; $Cu(NO_3)_2$; α-Methyl-γ-diketone; 2,3,5-Trisubstituted furans.
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doi:10.1016/j.tet.2006.05.064

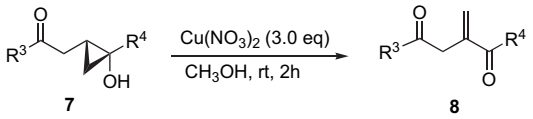
The bond 'a' in the tertiary cyclopropyl silyl ethers **1** can be specially cleaved with silver(I) tetrafluoroborate and copper(II) tetrafluoroborate.[8] Surprisingly, Cu(II)-mediated ring-opening of unprotected hydroxyl-cyclopropanes has not been reported. Herein, we develop a mild and efficient procedure to synthesize α-methylene-γ-diketones from cyclopropanols, prepared from β-diketones, in a one-pot reaction mediated by $Cu(NO_3)_2$. To the best of our knowledge, this is the first report on the use of $Cu(NO_3)_2$ for the synthesis of α-methylene-γ-diketones from 1,2-disubstituted cyclopropanols. At the same time, the procedure for cyclopropanol conversion to γ- and δ-diketones under basic or acidic conditions is described.

2. Results and discussion

2.1. Copper(II)-mediated ring-opening reaction

Very recently, we have developed a new procedure for the synthesis of 1,2-disubstituted cyclopropanols from β-diketones.[9] Treatment of 1-phenyl-butane-1,3-diketone with 4.0 equiv of Et_2Zn, 2.0 equiv of CF_3CO_2H, and 4.0 equiv of CH_2I_2 resulted in the formation of the *trans*-1,2-disubstituted cyclopropanol **7a**, an analog of compound **4**, in 93% yield. It was found that Cu(II)-induced ring-opening reaction of various cyclopropanols **7** in methanol worked efficiently and gave rise to α-methylene-γ-diketones **8** in good yields. To begin our study, we chose cyclopropanol **7a** as the standard substrate to search for suitable reaction conditions. The results are shown in Table 1. The amount of $Cu(NO_3)_2$ and solvent were crucial for efficient ring-opening reaction. Treatment of **7a** with 1.0 equiv of $Cu(NO_3)_2$ in CH_3OH gave 3-methylene-1-phenyl-pentane-1,4-dione **8a** in 37% yield at room temperature over 5 h (entry 1, Table 1). When the amount of $Cu(NO_3)_2$ was increased to 3.0 equiv, clean reaction took place to give the desired compound **8a** in 90% isolated yield at room temperature over 2 h (entry 3, Table 1). The reaction performed in toluene and CH_2Cl_2 afforded trace amount of the product **8a** under the same reaction conditions. These poor results may be due to the insolvable $Cu(NO_3)_2$ in a non-polar solvent. The desired product **8a** was obtained in 62% yield when the reaction was carried out in THF. $Cu(OAc)_2$ and $Cu(SO_4)_2$ were also acceptable as a mediated resource, which afforded **8a** in 74 and 70% yields, respectively (entries 7 and 8, Table 1). However, treatment of **7a** with $CuCl_2$ in CH_3OH gave a complex reaction mixture.

Table 2. $Cu(NO_3)_2$-mediated ring-opening of tertiary cyclopropanols



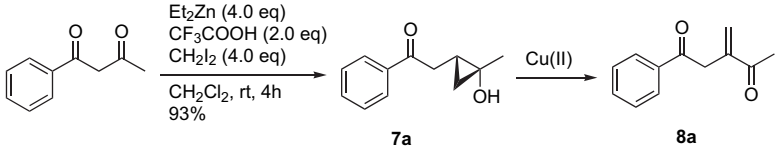
7 8

Entry	R^3	R^4	Product	Yield[a] (%)
1	C_6H_5	Me	**8a**	90
2	*p*-MeC_6H_4	Me	**8b**	80
3	*p*-$MeOC_6H_4$	Me	**8c**	93
4	*p*-ClC_6H_4	Me	**8d**	85
5	*p*-FC_6H_4	Me	**8e**	80
6	*m,p*-$(MeO)_2C_6H_3$	Me	**8f**	75
7	*p*-$MeOC_6H_4$	*n*-Pr	**8g**	77
8	*p*-$MeOC_6H_4$	C_6H_5	**8h**	67
9	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	**8i**	76
10	C_6H_5	C_6H_5	**8j**	73
11	C_6H_5	*p*-ClC_6H_4	**8k**	89
12	*p*-ClC_6H_4	C_6H_5	**8l**	75
13	2-Thienyl	Me	**8m**	75
14	Me	*o*-$MeOC_6H_4$	**8n**	76
15	CH_3CH_2	CH_3CH_2	**8o**	64
16	But	Me	**8p**	70

[a] Isolated yields.

With the optimized reaction conditions established, various substrates were subjected to the ring-opening reactions. These cyclopropanols reacted smoothly using 3.0 equiv of $Cu(NO_3)_2$ at room temperature in CH_3OH. Representative results are given in Table 2. R^3 group with an electron-donating or electron-withdrawing substituent on the benzene ring has little effect on the reaction yield. However, the reaction is sensitive to R^4 group substitution of the substrates. When the R^4 was varied from a methyl to a propyl group, the yield of the corresponding product decreased (entries 3 and 7, Table 2). A lower yield was obtained when R^4 was a phenyl group (entry 8, Table 2). Similarly, a bulky group resulted in the loss of yield apparently due to steric effect. It is notable that when R^4 was 4-chlorophenyl group, the substrate could afford the product **8k** in 89% yield. On the basis of these

Table 1. Copper(II)-mediated ring-opening of compound **7a**



7a 8a

Entry	Solvent	Copper salts	Time (h)	Yield[a] (%)
1	CH_3OH	$Cu(NO_3)_2$, 1 equiv	5	37
2	CH_3OH	$Cu(NO_3)_2$, 2 equiv	2	72
3	CH_3OH	$Cu(NO_3)_2$, 3 equiv	2	90
4	Toluene	$Cu(NO_3)_2$, 3 equiv	2	Trace
5	CH_2Cl_2	$Cu(NO_3)_2$, 3 equiv	2	Trace
6	THF	$Cu(NO_3)_2$, 3 equiv	2	62
7	CH_3OH	$Cu(OAc)_2$, 3 equiv	2	74
8	CH_3OH	$Cu(SO_4)_2$, 3 equiv	2	70
9	CH_3OH	$CuCl_2$, 3 equiv	1	Complex mixture

[a] Isolated yields.

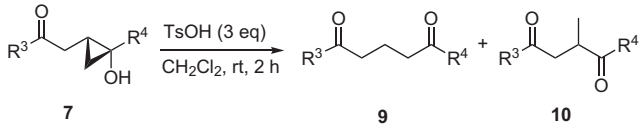
results, a new procedure for the synthesis of α-methylene-γ-diketones, the analog of compound **5**, was developed. The ring-opening reaction mediated by $Cu(NO_3)_2$ was remarkably clean and efficient, involving mild reaction conditions and a simple procedure.

2.2. Acid-catalyzed ring-opening reaction

We have reported a new procedure for the synthesis of γ-diketones from β-diketones.[9] Practical application of this methodology appeared limited to the use of α-substituted β-diketones, since substitution at the α-position resulted in no reaction. Now, we report a variation on the ring-opening reaction that provides a partial solution to this problem. The cyclopropanols **7** will be converted into α-methyl-γ-diketones via ring-opening reaction under acidic conditions. For example, treatment of **7a** with 3.0 equiv of *p*-TsOH in CH_2Cl_2 for 2 h at room temperature afforded α-methyl γ-diketone **10a** in 72% yield, along with a 16% yield of the isomer δ-diketone **9a** (entry 1, Table 3). Various 1,2-disubstituted cyclopropanols could be efficiently converted into the corresponding diketones in good yields. The reaction is also sensitive to the R^4 group of the substrates. When the R^4 varied from a methyl to a propyl group, the yield of isomer **9e** increased to 24%, but that of compound **10e** decreased to 66% (entry 5, Table 3). When both R^3 and R^4 were phenyl groups, the ring-opening reaction did not occur after stirring at room temperature for 6 h, even at reflux. The reason may be the steric hindrance of the aromatic ring under the reaction conditions.

In the process of optimizing reaction conditions, it was found that the ring-opening reaction in methanol solvent worked inefficiently. For example, treatment of **7a** with 3.0 equiv of *p*-TsOH in methanol for 5 h at room temperature afforded trace amount of the diketone, even after prolonging the reaction time. When the reaction was carried out at reflux, a new compound was obtained in a 91% isolated yield. This compound was determined to be 2,3,5-trisubstituted furan **11a** by NMR and HRMS spectra. It was notable that the isomer **9a** was not observed under the reaction conditions. However, the reaction performed in CH_2Cl_2 under reflux for 6 h could afford trisubstituted furan **11a** in 65% yield along with a 13% yield of the isomer **9a** and trace amount of **10a**. The furan moieties are common structures in numerous natural products, such as kallolides and

Table 3. Acid-catalyzed ring-opening of tertiary cyclopropanols

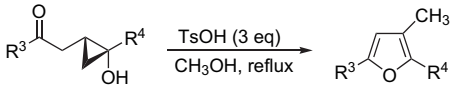


7 9 10

Entry	R^3	R^4	**9**, yield[a] (%)	**10**, yield[a] (%)
1	C_6H_5	Me	**9a**, 16	**10a**, 72
2	*p*-MeC_6H_4	Me	**9b**, 23	**10b**, 75
3	*p*-$MeOC_6H_4$	Me	**9c**, 18	**10c**, 72
4	2-Thienyl	Me	**9d**, 20	**10d**, 78
5	*p*-$MeOC_6H_4$	*n*-Pr	**9e**, 24	**10e**, 66
6	C_6H_5	C_6H_5	NR[b]	

[a] Isolated yields.
[b] NR=no reaction.

Table 4. Synthesis of 2,3,5-trisubstituted furans from 1,2-disubstituted cyclopropanols



7 11

Entry	R^3	R^4	Time (h)	Product	Yield[a] (%)
1	C_6H_5	Me	5	**11a**	91
2	*p*-MeC_6H_4	Me	6	**11b**	90
3	*p*-$MeOC_6H_4$	Me	3	**11c**	92
4	*p*-ClC_6H_4	Me	8	**11d**	87
5	*p*-FC_6H_4	Me	6	**11e**	89
6	*p*-$MeOC_6H_4$	*n*-Pr	3	**11f**	69
7	*p*-$MeOC_6H_4$	$C_6H_5CH_2CH_2$	10	**11g**	66
8	*m*,*p*-$(MeO)_2C_6H_3$	CH_3CH_2	6	**11h**	80
9	2-Thienyl	Me	8	**11i**	75
10	Me	*o*-$MeOC_6H_4$	6	**11j**	41
11[b]	C_6H_5	C_6H_5	24	**11k**	50

[a] Isolated yields.
[b] Performed in THF at reflux.

cembranolides.[10] Highly substituted furans play an important role in organic chemistry, not only as key structural units in many natural products, but also as useful building blocks in synthetic chemistry.[11] Many strategies have been developed for the preparation of furans.[12] Typically, the most widely used approach to furan synthesis is the Paal–Knorr reaction in which 1,4-dicarbonyl compounds are converted to furan derivatives induced by acid, such as HCl, H_2SO_4, P_2O_5, *p*-TsOH.[13] Recently, radical cyclization of divinyl ethers, gold(III) porphyrin-catalyzed cycloisomerization of allenones, palladium-catalyzed reaction of 2-propynyl-1, 3-dicarbonyls, and microwave-mediated Paal–Knorr cyclization reaction to give the corresponding 2,3,5-trisubstituted furans were reported.[14] Herein, we report a new procedure to synthesize 2,3,5-trisubstituted furans by the *p*-TsOH induced ring-opening of 1,2-disubstituted cyclopropanols. The reactions were completed in methanol at reflux for 3–8 h, and the products were easily purified by silica gel chromatography. Various 1,2-disubstituted cyclopropanols underwent smooth cyclization to give the corresponding trisubstituted furans in high yields under the reaction conditions. These results are summarized in Table 4. The R^4 group on the three-membered ring has an obvious influence on the reaction yield. When the R^4 varied from a methyl to a propyl group, the yield of **11f** decreased to 69%. A bulky phenethyl group resulted in a dramatic loss of yield under the same conditions, thus prolonging reaction time was required (entry 7, Table 2). When R^4 was *o*-methoxy-phenyl group, the yield of the desired product **11j** was dramatically decreased to 41% (entry 10, Table 4). However, when both R^3 and R^4 were phenyl groups, no reaction was noticed in methanol under reflux for 6 h. The reaction performed in THF, in place of methanol, under reflux for 24 h could give the desired compound **11k** in 50% isolated yield.

2.3. Base-catalyzed ring-opening reaction

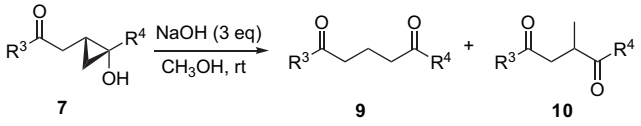
It has been reported that cyclopropanols are converted into 2-methyl ketones in the presence of sodium hydroxide.[15] Acidic treatment of the compound **7a** afforded a 4.5:1 mixture of the two regioisomers **10a** and **9a** in combined 88% yield (entry 1, Table 3). However, treatment of **7a** with

Table 5. Base-catalyzed ring-opening of tertiary cyclopropanols

Entry	R^3	R^4	Time (h)	**9**, yield[a] (%)	**10**, yield[a] (%)
1	*p*-$MeOC_6H_4$	*n*-Pr	24	**9e**, 14	**10e**, 24
2[b]	*p*-$MeOC_6H_4$	*n*-Pr	2	**9e**, 35	**10e**, 62
3	C_6H_5	C_6H_5	1	**9f**, 81	**10f**, 13
4	*p*-$MeOC_6H_4$	C_6H_5	2	**9g**, 80	**10g**, 14
5	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	3	**9h**, 80	**10h**, 15
6	*m,p*-$(MeO)_2C_6H_3$	C_6H_5	2	**9i**, 66	**10i**, 14

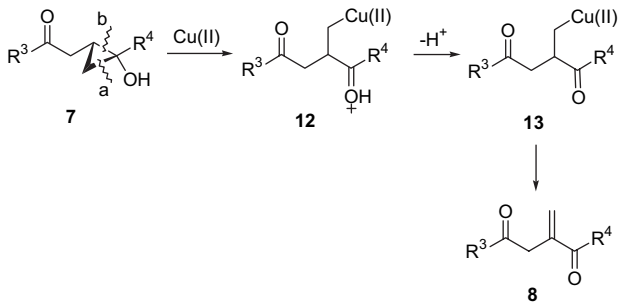
[a] Isolated yields.
[b] Performed at reflux.

sodium hydroxide resulted in a complex mixture, probably due to the formation of the diketone, which easily carried out condensation reaction under strong basic conditions. So we turned our attention to the ring-opening of cyclopropanols with a bulky R^4 substitution. When R^4 was propyl group, the ring-opening reaction performed at room temperature for 24 h afforded **9e** and **10e** in 14 and 24% yields, respectively. It was found that the reaction worked efficiently under reflux conditions. The cyclopropanol was consumed completely within 2 h affording the major product **10e** in 62% yield along with a 35% yield of **9e**. Interestingly, when both R^3 and R^4 were aromatic group, the ring-opening reaction of cyclopropanols with 3.0 equiv of sodium hydroxide in methanol at room temperature worked smoothly and afforded the δ-diketones **9f–i** in good yields. For example, 81% yield of **9f** was obtained under the standard conditions, along with a 13% yield of **10f** (Table 5). Whereas no reaction was observed when the ring-opening reaction of this type of cyclopropanols was induced by *p*-TsOH (Table 5).



2.4. Plausible mechanism of the ring-opening reaction

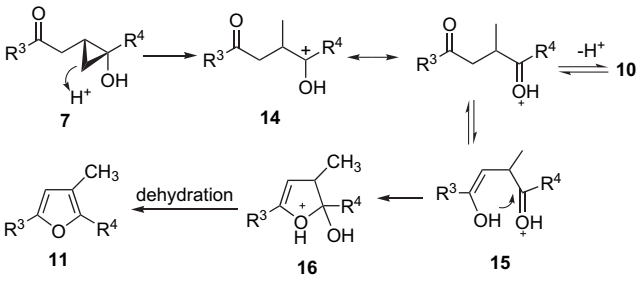
The Cu(II)-mediated ring-opening of cyclopropanols **7** to α-methylene-γ-diketones **8** occurred with site-selective cleavage of the cyclopropane ring at the bond 'a', and no product arising from bond 'b' scission was obtained. This high regioselectivity may be explained by attack of Cu(II) at the least hindered site.[16] A possible ring-opening reaction pathway is shown in Scheme 3. The electrophilic attack of Cu(II) at the least sterically crowded site of **7** followed by



Scheme 3.

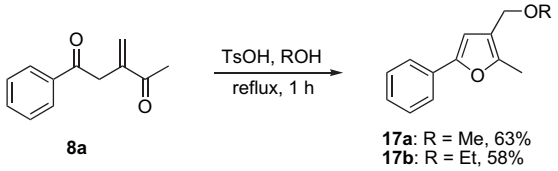
elimination of H^+ via **12** would give the β-copper(II) diketone **13**. Subsequently, the intermediate **13** would undergo elimination to form the desired α-methylene-γ-diketone **8**.[8]

The acid-catalyzed ring-opening reaction of cyclopropanols to form carbonyl compounds was assigned an S_E2 mechanism.[4] Therefore, a proposed mechanism for the acid-promoted ring-opening and cyclization reaction of 1,2-disubstituted cyclopropanols **7** to synthesize trisubstituted furans **11** is given in Scheme 4. The first step is the acid-catalyzed ring-opening reaction of **7** to furnish species **14**. The species **14** undergoes enolization to generate intermediate **15**. The trisubstituted furans **11** are formed via intramolecular nucleophilic attack of the enol oxygen upon the electrophilic carbon of the protonated carbonyl group, followed by dehydration of **16**. The species **14** gave compound **10** via deprotonation when the reaction conditions were mild at room temperature. When the reaction was carried out in methanol at reflux, the species **14** were easily converted into trisubstituted furans **11**. These results demonstrated that the conversion of **15** to **16** was the rate-controlling step in the reaction.[17,14a]



Scheme 4.

To corroborate the proposed mechanism, in which the species **14** is the key intermediate, exposure of 3-methyl-1-phenyl-pentane-1,4-dione **10a** to 1.0 equiv of *p*-TsOH in methanol at reflux for 1 h provided the furan **11a** in 91% yield. Furthermore, α-methylene-γ-diketones **8** afforded 2,3,5-trisubstituted furans under the similar reaction conditions. For example, treatment of the compound **8a** with 1.0 equiv of *p*-TsOH in methanol and ethanol at reflux for 1 h afforded compounds **17a** and **17b** in 63 and 58% yields, respectively (Scheme 5). The reaction may occur through Michael addition of alcohol to unsaturated diketone and subsequent cyclization under acidic conditions.



Scheme 5.

We have also investigated the direct conversion of cyclopropanol **7a** to **17a** in one-pot reaction. Treatment of **7a** with 3.0 equiv of $Cu(NO_3)_2$ in methanol at room temperature for 2 h, then followed by addition of 1.0 equiv of *p*-TsOH,

afforded the corresponding compound **17a** in 49% isolated yield under reflux for additional 1 h.

3. Conclusion

In conclusion, we have reported the first examples of the use of $Cu(NO_3)_2$ induced ring-opening reaction of 1,2-disubstituted cyclopropanols to synthesize α-methylene-γ-diketones in good yields. The reaction is easy and simple to perform under mild conditions. In addition, the cyclopropanols can be converted into diketones under acidic or basic solutions. When R^4 is a bulky alkyl group, both *p*-TsOH and NaOH can induce the ring-opening reaction in preference to formation of α-methyl-γ-diketones. When R^4 is aromatic group, the ring-opening of cyclopropanols takes place in preference to formation of δ-diketones under basic conditions. Furthermore, treatment of cyclopropanols with *p*-TsOH in methanol at reflux affords the corresponding 2,3,5-trisubstituted furans in high yields.

4. Experimental

4.1. General

All melting points were uncorrected. Chromatographic purification was performed on silica gel (100–200 mesh) and analytical thin layer chromatography (TLC) on silica gel 60-F_{254} (Qindao) was detected by fluorescence and then charring with 10% ethanolic solution of sulfuric acid. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured with a Bruker AC 300 spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. High-resolution mass spectra (HRMS) were obtained with a Micromass GCT-TOF mass spectrometer. IR spectra were recorded as thin films or as solids in KBr pellets on a Perkin–Elmer FT210 spectrophotometer.

4.2. General procedure for $Cu(NO_3)_2$-mediated ring-opening of 1,2-disubstituted cyclopropanols

To a round-bottomed flask containing a stirring bar were added $Cu(NO_3)_2 \cdot 3H_2O$ (217 mg, 0.9 mmol), 1,2-substituted cyclopropanol **7a** (57 mg, 0.3 mmol), and 2 mL of methanol sequentially. After stirring at room temperature for 2 h, the reaction mixture was concentrated under reduced pressure on a rotary evaporator, and water (4 mL) was added. The mixture was extracted with diethyl ether (3×10 mL). The combined organic layers were washed twice with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography with petroleum ether/EtOAc (25:1–10:1) to afford 51 mg (90%) of **8a**.

4.2.1. 3-Methylene-1-phenyl-pentane-1,4-dione (8a). Light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.90 (d, *J*=7.2 Hz, 2H), 7.49 (t, *J*=7.2 Hz, 1H), 7.40 (t, *J*=7.2 Hz, 2H), 6.16 (s, 1H), 5.86 (s, 1H), 3.89 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 198.8, 197.2, 143.4, 136.6, 133.3, 128.7, 128.4, 128.3, 40.8, 25.4. IR (neat; cm^{-1}): ν 1674, 1636. HRMS (EI): calcd for $C_{12}H_{12}O_2$ (M^+), 188.0837; found, 188.0844.

4.2.2. 3-Methylene-1-*p*-tolyl-pentane-1,4-dione (8b). White solid (48 mg, 80% yield). Mp: 64–65 °C. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.82 (d, *J*=7.6 Hz, 2H), 7.21 (d, *J*=7.6 Hz, 2H), 6.17 (s, 1H), 5.87 (s, 1H), 3.89 (s, 2H), 2.36 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 198.8, 196.9, 144.1, 143.6, 134.2, 129.4, 128.5, 128.1, 40.6, 25.5, 21.7. IR (KBr; cm^{-1}): ν 1673, 1606. HRMS (EI): calcd for $C_{13}H_{14}O_2$ (M^+), 202.0994; found, 202.0993.

4.2.3. 1-(4-Methoxy-phenyl)-3-methylene-pentane-1,4-dione (8c). Light yellow solid (61 mg, 93% yield). Mp: 51–53 °C. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.89 (dd, *J*=6.9, 2.0 Hz, 2H), 6.86 (dd, *J*=6.9, 2.0 Hz, 2H), 6.14 (s, 1H), 5.85 (s, 1H), 3.85 (s, 2H), 3.79 (s, 3H), 2.34 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 198.9, 195.8, 163.7, 143.6, 130.7, 130.6, 129.7, 128.1, 113.9, 55.6, 40.4, 25.5. IR (KBr; cm^{-1}): ν 1679, 1603.1. HRMS (EI): calcd for $C_{13}H_{14}O_3$ (M^+), 218.0943; found, 218.0942.

4.2.4. 1-(4-Chloro-phenyl)-3-methylene-pentane-1,4-dione (8d). Oil (57 mg, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.88 (d, *J*=8.6 Hz, 2H), 7.40 (d, *J*=8.6 Hz, 2H), 6.21 (s, 1H), 5.91 (s, 1H), 3.87 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 198.7, 196.1, 143.2, 139.8, 135.0, 129.8, 129.0, 128.6, 40.7, 25.4. IR (neat; cm^{-1}): ν 1675, 1587. HRMS (EI): calcd for $C_{12}H_{11}O_2Cl$ (M^+), 222.0448; found, 222.0439.

4.2.5. 1-(4-Fluoro-phenyl)-3-methylene-pentane-1,4-dione (8e). Oil (49 mg, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.95–7.90 (m, 2H), 7.08–7.03 (m, 2H), 6.17 (s, 1H), 5.88 (s, 1H), 3.85 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 198.7, 195.6, 165.9 (d), 143.2, 133.1 (d), 31.1 (d), 128.4, 115.7 (d), 40.6, 25.4. IR (neat; cm^{-1}): ν 1675, 1597. HRMS (EI): calcd for $C_{12}H_{11}O_2F$ (M^+), 206.0743; found, 206.0745.

4.2.6. 1-(3,4-Dimethoxy-phenyl)-3-methylene-pentane-1,4-dione (8f). Light yellow solid (56 mg, 75% yield). Mp: 66–68 °C. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.56 (dd, *J*=8.4, 2.0 Hz, 1H), 7.45 (d, *J*=2.0 Hz, 1H), 6.80 (d, *J*=8.4 Hz, 1H), 6.15 (s, 1H), 5.86 (s, 1H), 3.88 (s, 3H), 3.86 (s, 2H), 3.85 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 198.9, 195.9, 153.5, 149.1, 143.6, 129.9, 128.1, 123.2, 110.6, 110.2, 56.2, 56.1, 40.3, 25.5. IR (KBr; cm^{-1}): ν 1672, 1587. HRMS (EI): calcd for $C_{14}H_{16}O_4$ (M^+), 248.1049; found, 248.1046.

4.2.7. 1-(4-Methoxy-phenyl)-3-methylene-heptane-1,4-dione (8g). Solid (57 mg, 77% yield). Mp: 41–43 °C. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.89 (dd, *J*=8.7, 1.5 Hz, 2H), 6.87 (dd, *J*=8.7, 1.5 Hz, 2H), 6.13 (s, 1H), 5.80 (s, 1H), 3.84 (s, 2H), 3.79 (s, 3H), 2.67 (t, *J*=7.2 Hz, 2H), 1.61 (sextet, *J*=7.2 Hz, 2H), 0.88 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 201.2, 196.0, 163.6, 143.4, 130.7, 129.7, 126.9, 113.8, 55.5, 40.7, 39.3, 17.9, 13.9. IR (KBr; cm^{-1}): ν 2932, 1674, 1595, 1263, 1028, 822. HRMS (EI): calcd for $C_{15}H_{18}O_3$ (M^+), 246.1256; found, 246.1264.

4.2.8. 4-(4-Methoxy-phenyl)-2-methylene-1-phenyl-butane-1,4-dione (8h). Light yellow solid (56 mg, 67% yield). Mp: 55–57 °C. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.92 (d, *J*=7.2 Hz, 2H), 7.81 (d, *J*=7.2 Hz, 2H), 7.48

(t, J=7.2 Hz, 1H), 7.38 (t, J=7.2 Hz, 2H), 6.88 (d, J=7.2 Hz, 2H), 5.88 (s, 1H), 5.72 (s, 1H), 4.11 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 197.5, 195.8, 163.8, 142.7, 137.4, 132.3, 130.7, 130.0, 129.5, 128.4, 128.2, 113.9, 55.5, 42.4. IR (KBr; cm^{-1}): ν 1654, 1597. HRMS (EI): calcd for $C_{18}H_{16}O_3$ (M^+), 280.1099; found, 280.1106.

4.2.9. 1,4-Bis(4-methoxy-phenyl)-2-methylene-butane-1,4-dione (8i). Colorless crystals (71 mg, 76% yield). Mp: 75–77 °C. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.93–7.84 (m, 4H), 6.89–6.84 (m, 4H), 5.79 (s, 1H), 5.66 (s, 1H), 4.10 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 196.2, 195.9, 163.7, 163.2, 142.8, 132.4, 130.7, 130.4, 130.0, 129.6, 126.7, 113.9, 113.5, 55.5, 42.8. IR (KBr; cm^{-1}): ν 2938, 1674, 1646, 1603, 1255, 1170. HRMS (EI): calcd for $C_{19}H_{18}O_4$ (M^+), 310.1205; found, 310.1204.

4.2.10. 2-Methylene-1,4-diphenyl-butane-1,4-dione (8j). Colorless solid (55 mg, 73% yield). Mp: 40–42 °C. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.92 (d, J=8.1 Hz, 2H), 7.81 (d, J=8.1 Hz, 2H), 7.48 (m, 2H), 7.42–7.38 (m, 4H), 5.90 (s, 1H), 5.75 (s, 1H), 4.16 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$; δ, ppm): 197.4, 197.3, 142.5, 137.4, 136.5, 133.4, 132.4, 130.0, 128.7, 128.4, 128.3, 42.7. IR (KBr; cm^{-1}): ν 1683, 1658. HRMS (EI): calcd for $C_{17}H_{14}O_2$ (M^+), 250.0994; found, 250.0989.

4.2.11. 1-(4-Chloro-phenyl)-2-methylene-4-phenyl-butane-1,4-dione (8k). Colorless solid (76 mg, 89% yield). Mp: 65–67 °C. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.90 (d, J=8.4 Hz, 2H), 7.80 (d, J=8.4 Hz, 2H), 7.49 (t, J=8.4 Hz, 1H), 7.40–7.18 (m, 4H), 5.88 (s, 1H), 5.70 (s, 1H), 4.17 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$; δ, ppm): 197.2, 196.2, 142.4, 138.9, 136.4, 133.5, 131.4, 130.3, 128.8, 128.6, 128.4, 128.3, 42.6. IR (KBr; cm^{-1}): ν 2967, 2918, 1682, 1660, 1589, 1269, 1091, 1014, 800. HRMS (EI): calcd for $C_{17}H_{13}O_2Cl$ (M^+), 284.0604; found, 284.0608.

4.2.12. 4-(4-Chloro-phenyl)-2-methylene-1-phenyl-butane-1,4-dione (8l). Colorless solid (64 mg, 75% yield). Mp: 67–69 °C. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.88 (dd, J=6.9, 2.4 Hz, 2H), 7.79 (d, J=7.2 Hz, 2H), 7.48 (t, J=7.2 Hz, 1H), 7.38 (m, 4H), 5.91 (s, 1H), 5.77 (s, 1H), 4.11 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 197.2, 196.1, 142.1, 139.9, 137.3, 134.8, 132.4, 131.4, 129.9, 129.8, 129.1, 128.3, 42.6. IR (KBr; cm^{-1}): ν 2924, 1696, 1600, 1085. HRMS (EI): calcd for $C_{17}H_{13}O_2Cl$ (M^+), 284.0604; found, 284.0599.

4.2.13. 3-Methylene-1-thiophen-2-yl-pentane-1,4-dione (8m). Light yellow oil (44 mg, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.71 (dd, J=3.8, 1.0 Hz, 1H), 7.57 (dd, J=5.0, 1.0 Hz, 1H), 7.06 (dd, J=5.0, 3.8 Hz, 1H), 6.18 (s, 1H), 5.93 (s, 1H), 3.83 (s, 2H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 198.6, 189.9, 143.8, 142.8, 132.6, 128.6, 128.2, 41.1, 25.4. IR (neat; cm^{-1}): ν 1659, 1605. HRMS (EI): calcd for $C_{10}H_{10}O_2S$ (M^+), 194.0402; found, 194.0397.

4.2.14. 1-(2-Methoxy-phenyl)-2-methylene-pentane-1,4-dione (8n). Oil (50 mg, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.33 (td, J=7.5, 1.5 Hz, 1H), 7.25 (dd, J=7.5, 1.5 Hz, 1H), 6.91 (q, J=7.5 Hz, 2H), 5.92 (s, 1H), 5.75 (s, 1H), 3.72 (s, 3H), 3.46 (s, 2H), 2.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 205.6, 197.1, 157.2, 143.2, 131.7, 131.6, 129.4, 128.3, 120.3, 111.5, 55.8, 45.5, 29.9. IR (neat; cm^{-1}): ν 1716, 1659. HRMS (EI): calcd for $C_{13}H_{14}O_3$ (M^+), 218.0943; found, 218.0934.

4.2.15. 4-Methylene-octane-3,6-dione (8o). Oil (30 mg, 64% yield). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 6.09 (s, 1H), 5.76 (s, 1H), 3.29 (s, 2H), 2.69 (q, J=7.2 Hz, 2H), 2.47 (q, J=7.2 Hz, 2H), 1.03 (t, J=7.2 Hz, 3H), 0.98 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 208.8, 202.1, 143.3, 127.4, 45.3, 36.5, 30.9, 8.7, 8.3. IR (neat; cm^{-1}): ν 1718, 1682. HRMS (EI): calcd for $C_9H_{14}O_2$ (M^+), 154.0994; found, 154.0993

4.2.16. 6,6-Dimethyl-3-methylene-heptane-2,5-dione (8p). Oil (32 mg, 63% yield). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 6.08 (s, 1H), 5.74 (s, 1H), 3.41 (s, 2H), 2.29 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 212.8, 198.9, 143.8, 127.9, 44.4, 39.4, 26.6, 25.4. IR (neat; cm^{-1}): ν 1709, 1680. HRMS (EI): calcd for $C_{10}H_{16}O_2$ (M^+), 168.1150; found, 168.1152.

4.3. General procedure for acid-catalyzed ring-opening of 1,2-disubstituted cyclopropanols

A 25 mL round-bottomed flask was equipped with a stirring bar and charged with methylene chloride (3 mL). p-TsOH·H_2O (171 mg, 0.9 mmol) and 1,2-substituted cyclopropanol **7a** (57 mg, 0.3 mmol) were added. The reaction mixture was stirred at room temperature for 2 h. Water (3 mL) was added and the mixture was extracted with diethyl ether (3×10 mL). The combined organic layers were washed twice with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography with petroleum ether/EtOAc (20:1–10:1) to afford **9a** (9 mg) and **10a** (41 mg) in 16 and 72% yields, respectively.

4.3.1. 1-Phenyl-hexane-1,5-dione (9a). White solid. Mp: 65–67 °C (lit.[18] mp: 66–67 °C). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.88 (dd, J=7.8 Hz, 2H), 7.47 (t, J=7.8 Hz, 1H), 7.38 (t, J=7.8 Hz, 2H), 2.94 (t, J=7.0 Hz, 2H), 2.50 (t, J=7.0 Hz, 2H), 2.08 (s, 3H), 1.97 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 208.6, 199.9, 136.9, 133.2, 128.7, 128.1, 42.7, 37.5, 30.1, 18.3. IR (KBr; cm^{-1}): ν 1712, 1670. HRMS (EI): calcd for $C_{12}H_{14}O_2$ (M^+), 190.0994; found, 190.1001.

4.3.2. 3-Methyl-1-phenyl-pentane-1,4-dione (10a). Light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.96 (d, J=8.1 Hz, 2H), 7.53 (t, J=8.1 Hz, 1H), 7.44 (t, J=8.1 Hz, 2H), 3.54 (dd, J=18.0, 9.0 Hz, 1H), 3.27–3.20 (m, 1H), 2.95 (dd, J=18.0, 4.5 Hz, 1H), 2.29 (s, 3H), 1.20 (d, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 211.5, 198.6, 136.7, 133.2, 128.6, 128.1, 41.9, 41.8, 28.7, 16.8. IR (neat; cm^{-1}): ν 1712, 1682. HRMS (EI): calcd for $C_{12}H_{14}O_2$ (M^+), 190.0994; found, 190.0987.

4.3.3. 1-*p*-Tolyl-hexane-1,5-dione (9b). White solid (14 mg, 23% yield). Mp: 74–76 °C. ^{1}H NMR (300 MHz,

$CDCl_3$; δ, ppm): 7.79 (d, *J*=8.1 Hz, 2H), 7.16 (d, *J*=8.1 Hz, 2H), 2.91 (t, *J*=7.0 Hz, 2H), 2.49 (d, *J*=7.0 Hz, 2H), 2.33 (s, 3H), 2.07 (s, 3H), 1.93 (quintet, *J*=7.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 208.6, 199.5, 143.9, 134.5, 129.4, 128.3, 42.8, 37.4, 30.0, 21.7, 18.4. IR (neat; cm^{-1}): ν 1710, 1674. HRMS (EI): calcd for $C_{13}H_{16}O_2$ (M^+), 204.1150; found, 204.1159.

4.3.4. 3-Methyl-1-*p*-tolyl-pentane-1,4-dione (10b). Light yellow oil (46 mg, 75% yield). ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.79 (d, *J*=8.1 Hz, 2H), 7.16 (d, *J*=8.1 Hz, 2H), 3.44 (dd, *J*=18.0, 8.7 Hz, 1H), 3.19–3.12 (m, 1H), 2.87 (dd, *J*=18.0, 4.8 Hz, 1H), 2.33 (s, 3H), 2.23 (s, 3H), 1.13 (d, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 211.6, 198.2, 144.0, 134.2, 129.3, 128.2, 41.85, 41.81, 28.7, 21.6, 16.8. IR (neat; cm^{-1}): ν 1718, 1682. HRMS (EI): calcd for $C_{13}H_{16}O_2$ (M^+), 204.1150; found, 204.1145.

4.3.5. 1-(4-Methoxy-phenyl)-hexane-1,5-dione (9c). White solid (12 mg, 18% yield). Mp: 80–81 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.88 (d, *J*=9.0 Hz, 2H), 6.87 (d, *J*=9.0 Hz, 2H), 3.79 (s, 3H), 2.88 (t, *J*=7.2 Hz, 2H), 2.49 (t, *J*=7.2 Hz, 2H), 2.07 (s, 3H), 1.93 (quintet, *J*=7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 208.6, 198.4, 163.6, 130.4, 130.1, 113.8, 55.6, 42.8, 37.2, 30.0, 18.6. IR (KBr; cm^{-1}): ν 1710, 1668. HRMS (EI): calcd for $C_{13}H_{16}O_3$ (M^+), 220.1099; found, 220.1097.

4.3.6. 1-(4-Methoxy-phenyl)-3-methyl-pentane-1,4-dione (10c). Light yellow crystals (48 mg, 72% yield). Mp: 51–53 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.87 (dd, *J*=6.9, 2.0 Hz, 2H), 6.85 (dd, *J*=6.8, 2.0 Hz, 2H), 3.79 (s, 3H), 3.41 (dd, *J*=18.0, 8.6 Hz, 1H), 3.21–3.17 (m, 1H), 2.28 (dd, *J*=18.0, 4.8 Hz, 1H), 2.22 (s, 3H), 1.13 (d, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 211.8, 197.2, 163.7, 130.4, 129.9, 113.8, 55.5, 41.9, 41.6, 28.8, 16.8. IR (KBr; cm^{-1}): ν 2924, 1711, 1672, 1599, 1260. HRMS (EI): calcd for $C_{13}H_{16}O_3$ (M^+), 220.1099; found, 220.1097.

4.3.7. 1-Thiophen-2-yl-hexane-1,5-dione (9d). White solid (12 mg, 20% yield). Mp: 30–32 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.66 (dd, *J*=3.9, 0.9 Hz, 1H), 7.56 (dd, *J*=4.8, 0.9 Hz, 1H), 7.05 (dd, *J*=4.8, 3.9 Hz, 1H), 2.88 (t, *J*=7.2 Hz, 2H), 2.50 (t, *J*=7.2 Hz, 2H), 2.07 (s, 3H), 1.94 (quintet, *J*=7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 208.4, 192.8, 144.3, 133.6, 132.0, 128.2, 42.6, 38.2, 30.0, 18.7. IR (KBr; cm^{-1}): ν 1715, 1600. HRMS (EI): calcd for $C_{10}H_{12}O_2S$ (M^+), 196.0588; found, 196.0564.

4.3.8. 3-Methyl-1-thiophen-2-yl-pentane-1,4-dione (10d). Light yellow oil (46 mg, 78% yield). ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.67 (d, *J*=3.9 Hz, 1H), 7.56 (d, *J*=5.1 Hz, 1H), 7.05 (dd, *J*=4.8, 3.9 Hz, 1H), 3.40 (dd, *J*=17.4, 8.4 Hz, 1H), 3.18–3.13 (m, 1H), 2.83 (dd, *J*=17.4, 4.8 Hz, 1H), 2.21 (s, 3H), 1.14 (d, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 211.3, 191.5, 143.9, 133.7, 132.1, 128.2, 42.2, 41.9, 31.6, 28.7, 16.8. IR (neat; cm^{-1}): ν 1710, 1659. HRMS (EI): calcd for $C_{10}H_{12}O_2S$ (M^+), 196.0558; found, 196.0554.

4.3.9. 1-(4-Methoxy-phenyl)-octane-1,5-dione (9e). White solid (18 mg, 24% yield). Mp: 66–67 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.88 (d, *J*=9.0 Hz, 2H), 6.87 (d, *J*=9.0 Hz, 2H), 3.79 (s, 3H), 2.88 (t, *J*=7.0 Hz, 2H), 2.45 (t, *J*=7.0 Hz, 2H), 2.31 (t, *J*=7.0 Hz, 2H), 1.93 (quintet, *J*=7.2 Hz, 2H), 1.54 (td, *J*=7.0 Hz, 2H), 0.84 (t, *J*=7.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 208.8, 198.5, 163.6, 130.4, 130.1, 113.8, 55.5, 44.8, 41.8, 37.3, 18.6, 17.4, 13.8. IR (KBr; cm^{-1}): ν 1710, 1666. HRMS (EI): calcd for $C_{15}H_{20}O_3$ (M^+), 248.1412; found, 248.1417.

4.3.10. 1-(4-Methoxy-phenyl)-3-methyl-heptane-1,4-dione (10e). Light yellow oil (49 mg, 66% yield). ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.87 (dd, *J*=6.9, 2.1 Hz, 2H), 6.85 (dd, *J*=6.9, 2.1 Hz, 2H), 3.79 (s, 3H), 3.43 (dd, *J*=17.6, 9.0 Hz, 1H), 3.19–3.11 (m, 1H), 2.83 (dd, *J*=17.6, 4.5 Hz, 1H), 2.51–2.50 (m, 2H), 1.60–1.53 (m, 2H), 1.10 (d, *J*=7.2 Hz, 3H), 0.86 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3; δ, ppm): 213.9, 197.3, 163.6, 130.4, 129.9, 113.8, 55.5, 43.5, 41.6, 41.2, 17.1, 17.0, 13.9. IR (neat; cm^{-1}): ν 2933, 1711, 1675, 1601, 1260. HRMS (EI): calcd for $C_{15}H_{20}O_3$ (M^+), 248.1412; found, 248.1413.

4.4. General procedure for preparation of 2,3,5-trisubstituted furans

A 25 mL round-bottomed flask was equipped with a stirring bar and charged with methanol (3 mL). *p*-$TsOH\cdot H_2O$ (171 mg, 0.9 mmol) and 1,2-disubstituted cyclopropanol **7a** (57 mg, 0.3 mmol) were added under nitrogen. The reaction mixture was stirred for 5 h under nitrogen at reflux. Then the reaction mixture was concentrated under reduced pressure on the rotary evaporator. To the residue was added water (5 mL) and the solution extracted with diethyl ether (3×10 mL). The combined organic layers were washed twice with brine and then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography with petroleum ether/EtOAc (50:1–25:1), affording **11a** in (47 mg) 91% yield.

4.4.1. 2,3-Dimethyl-5-phenyl-furan (11a). Light yellow oil. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.52 (dd, *J*=8.4, 1.2 Hz, 2H), 7.25 (t, *J*=8.4 Hz, 1H), 7.11 (td, *J*=8.4, 1.2 Hz, 2H), 6.35 (s, 1H), 2.19 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 151.0, 147.4, 131.4, 128.6, 126.6, 123.4, 116.2, 108.5, 11.6, 10.0. IR (neat; cm^{-1}): ν 1601, 1555, 1260. HRMS (EI): calcd for $C_{12}H_{12}O$ (M^+), 172.0888; found, 172.0891.

4.4.2. 2,3-Dimethyl-5-*p*-tolyl-furan (11b). White solid (50 mg, 90% yield). Mp: 52–54 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.40 (d, *J*=8.1 Hz, 2H), 7.06 (d, *J*=8.1 Hz, 2H), 6.28 (s, 1H), 2.24 (s, 3H), 2.17 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 151.2, 147.0, 136.4, 129.3, 128.7, 123.3, 116.1, 107.7, 21.3, 11.5, 10.0. IR (KBr; cm^{-1}): ν 2924, 1554, 1504, 1055, 808. HRMS (EI): calcd for $C_{13}H_{14}O$ (M^+), 186.1045; found, 186.1053.

4.4.3. 5-(4-Methoxy-phenyl)-2,3-dimethyl-furan (11c). White solid (56 mg, 92% yield). Mp: 54–56 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.45 (dd, *J*=6.9, 2.1 Hz, 2H), 6.80 (dd, *J*=6.9, 2.1 Hz, 2H), 6.22 (s, 1H), 3.74 (s, 3H), 2.18 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 158.6, 151.1, 146.6, 124.7, 124.6, 116.0, 114.1,

106.9, 55.4, 29.8, 11.5, 10.0. IR (KBr; cm^{-1}): ν 2920, 2849, 1612, 1584, 1500, 1248. HRMS (EI): calcd for $C_{13}H_{14}O_2$ (M^+), 202.0994; found, 202.0997.

4.4.4. 5-(4-Chloro-phenyl)-2,3-dimethyl-furan (11d). White solid (54 mg, 87% yield). Mp: 87–89 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.45 (d, J=8.4 Hz, 2H), 7.20 (d, J=8.4 Hz, 2H), 6.35 (s, 1H), 2.19 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 150.0, 147.8, 132.0, 129.9, 128.8, 124.5, 116.4, 109.0, 11.6, 10.0. IR (KBr; cm^{-1}): ν 2963, 2923, 1547, 1418, 1261, 1088, 808. HRMS (EI): calcd for $C_{12}H_{11}OCl$ (M^+), 206.0498; found, 206.0491.

4.4.5. 5-(4-Fluoro-phenyl)-2,3-dimethyl-furan (11e). Oil (51 mg, 89% yield). Mp: 67–69 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.49–7.44 (m, 2H), 6.97–6.92 (m, 2H), 6.28 (s, 1H), 2.18 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 161.8 (d), 150.2, 147.4, 127.8 (d), 125.0, 124.8 (d), 116.2, 115.6 (d), 108.1 (d), 11.5, 10.0. IR (neat; cm^{-1}): ν 2924, 1729, 1598, 1496, 1232, 1096. HRMS (EI): calcd for $C_{12}H_{11}OF$ (M^+), 190.0794; found, 190.0785.

4.4.6. 5-(4-Methoxy-phenyl)-3-methyl-2-propyl-furan (11f). Oil (48 mg, 69% yield). ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.45 (d, J=9.0 Hz, 2H), 6.81 (d, J=9.0 Hz, 2H), 6.22 (s, 1H), 3.73 (s, 3H), 2.49 (t, J=7.2 Hz, 2H), 1.89 (s, 3H), 1.59 (sextet, J=7.2 Hz, 2H), 0.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 158.6, 151.0, 150.7, 124.7, 116.0, 114.1, 106.8, 55.4, 28.1, 22.1, 13.8, 10.0. IR (neat; cm^{-1}): ν 2960, 2925, 2558, 1500, 1248, 1034. HRMS (EI): calcd for $C_{15}H_{18}O_2$ (M^+), 230.1307; found, 230.1315.

4.4.7. 5-(4-Methoxy-phenyl)-3-methyl-2-phenethyl-furan (11g). White solid (58 mg, 66% yield). Mp: 94–96 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.45 (d, J=8.7 Hz, 2H), 7.22–7.08 (m, 2H), 6.84 (d, J=8.7 Hz, 2H), 6.20 (s, 1H), 3.75 (s, 3H), 2.91–2.80 (m, 4H), 1.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 158.7, 151.2, 149.5, 141.6, 128.6, 128.4, 126.0, 124.8, 124.6, 116.6, 114.2, 106.9, 55.4, 35.1, 28.3, 9.8. IR (KBr; cm^{-1}): ν 2932, 1504, 1247, 1208, 808. HRMS (EI): calcd for $C_{20}H_{20}O_2$ (M^+), 292.1463; found, 292.155.

4.4.8. 5-(3,4-Dimethoxy-phenyl)-2-ethyl-3-methyl-furan (11h). Colorless oil (59 mg, 80% yield). ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.10 (dd, J=8.4, 1.8 Hz, 1H), 7.05 (d, J=1.8 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 6.25 (s, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 2.57 (q, J=7.5 Hz, 2H), 1.91 (s, 3H), 1.17 (t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 152.0, 150.9, 149.2, 148.2, 124.9, 116.1, 115.2, 111.6, 107.3, 107.0, 56.1, 56.0, 19.6, 13.2, 9.9. IR (neat; cm^{-1}): ν 2932, 1588, 1556, 1506, 1460, 1265, 1027. HRMS (EI): calcd for $C_{15}H_{18}O_3$ (M^+), 246.1256; found, 246.1258.

4.4.9. 2,3-Dimethyl-5-thiophen-2-yl-furan (11i). Light yellow oil (40 mg, 75% yield). ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.06 (m, 2H), 7.91 (dd, J=5.0, 3.8 Hz, 1H), 6.21 (s, 1H), 2.17 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 147.1, 146.6, 134.5, 127.6, 123.2, 121.5, 116.2, 108.6, 11.5, 9.9. IR (neat; cm^{-1}): ν 2922, 1636, 1429, 1261, 1083, 1026. HRMS (EI): calcd for $C_{10}H_{10}OS$ (M^+), 178.0452; found, 178.0459.

4.4.10. 2-(2-Methoxy-phenyl)-3,5-dimethyl-furan (11j). Oil (25 mg, 41% yield). ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.31 (dd, J=7.5, 1.7 Hz, 1H), 7.22 (td, J=7.5, 1.7 Hz, 1H), 6.91 (q, J=7.5 Hz, 2H), 5.86 (s, 1H), 3.76 (s, 3H), 2.23 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 156.7, 151.1, 144.9, 130.6, 129.0, 121.1, 120.5, 118.8, 111.4, 110.3, 55.6, 13.7, 11.3. IR (neat; cm^{-1}): ν 2926, 1730, 1463, 1261, 910. HRMS (EI): calcd for $C_{13}H_{14}O_2$ (M^+), 202.0994; found, 202.0991.

4.4.11. 2-Methyl-2,5-diphenyl-furan (11k). White solid (35 mg, 50% yield). Mp: 30–32 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.65 (d, J=8.4 Hz, 4H), 7.35–7.26 (m, 4H), 7.22–7.15 (m, 2H), 6.51 (s, 1H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 151.8, 148.3, 131.9, 130.9, 128.8, 128.7, 126.8, 125.3, 123.8, 118.7, 110.9, 12.2. IR (neat; cm^{-1}): ν 2921, 1595, 1493, 1261, 763. HRMS (EI): calcd for $C_{17}H_{14}O$ (M^+), 234.1045; found, 234.1037.

4.5. General procedure for base-catalyzed ring-opening of 1,2-disubstituted cyclopropanols

To a magnetically stirred solution of sodium hydroxide (22 mg, 0.9 mmol) in methanol (2 mL) was added the cyclopropanol (**7**, R^3=R^4=Ph) (76 mg, 0.3 mmol). The reaction mixture was stirred at room temperature for 1 h. The methanol solvent was removed on the rotary evaporator. To the residue was added water (3 mL) and the solution extracted with diethyl ether (3×10 mL). The combined organic layers were washed with brine and then dried over anhydrous magnesium sulfate, filtered, and concentrated on the rotary evaporator. The residue was purified by silica gel chromatography with petroleum ether/EtOAc (20:1–10:1), affording **9f** (61 mg) and **10f** (10 mg) in 81 and 13% yields, respectively.

4.5.1. 1,5-Diphenyl-pentane-1,5-dione (9f). White crystals (61 mg, 81% yield). Mp: 64–65 °C (lit.[18] mp: 65–66 °C). ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.89 (d, J=7.2 Hz, 4H), 7.48 (t, J=7.2 Hz, 2H), 7.38 (t, J=7.2 Hz, 4H), 3.05 (t, J=6.9 Hz, 4H), 2.13 (quintet, J=6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 199.9, 137.0, 133.2, 128.7, 128.2, 37.7, 18.9. IR (KBr; cm^{-1}): ν 1682.

4.5.2. 2-Methyl-1,4-diphenyl-butane-1,4-dione (10f). White solid (10 mg, 13% yield). Mp: 81–83 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.97 (d, J=7.2 Hz, 2H), 7.88 (d, J=7.2 Hz, 2H), 7.48–7.34 (m, 6H), 4.13–4.06 (m, 1H), 3.65 (dd, J=18.0, 8.4 Hz, 1H), 3.05 (dd, J=18.0, 4.8 Hz, 1H), 1.21 (d, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 203.5, 198.6, 136.8, 136.3, 133.3, 133.1, 128.8, 128.7, 128.6, 128.2, 42.5, 36.4, 18.1. IR (KBr; cm^{-1}): ν 1672, 1596. HRMS (EI): calcd for $C_{17}H_{16}O_2$ (M^+), 252.1150; found, 252.1155.

4.5.3. 1-(4-Methoxy-phenyl)-5-phenyl-pentane-1,5-dione (9g). Colorless crystals (68 mg, 80% yield). Mp: 78–79 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.92–7.88 (m, 4H), 7.41 (t, J=7.2 Hz, 1H), 7.38 (t, J=7.2 Hz, 2H), 6.87 (d, J=9.0 Hz, 2H), 3.79 (s, 3H), 3.01 (m, 4H), 2.12 (quintet, J=6.9 Hz, 2H). ^{13}C NMR (75 MHz, CDCl3; δ, ppm): 200.2, 198.5, 163.5, 137.0, 133.1, 130.4, 130.1,

128.6, 128.1, 113.8, 55.5, 37.7, 37.3, 19.0. IR (KBr; cm^{-1}): ν 1683, 1658. HRMS (EI): calcd for $C_{18}H_{18}O_3$ (M^+), 282.1256; found, 282.1261.

4.5.4. 4-(4-Methoxy-phenyl)-2-methyl-1-phenyl-butane-1,4-dione (10g). Colorless crystals (12 mg, 14% yield). Mp: 87–88 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.98 (d, J=7.2 Hz, 2H), 7.90 (d, J=9.0 Hz, 2H), 7.47 (t, J=9.0 Hz, 1H), 7.41 (t, J=9.0 Hz, 2H), 6.86 (d, J=7.2 Hz, 2H), 4.13–4.06 (m, 1H), 3.79 (s, 3H), 3.60 (dd, J=17.7, 8.1 Hz, 1H), 3.02 (dd, J=17.7, 5.1 Hz, 1H), 1.21 (d, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 203.7, 197.1, 163.7, 133.0, 130.5, 128.8, 128.6, 113.8, 55.6, 42.1, 36.5, 18.0. IR (KBr; cm^{-1}): ν 2962, 1729, 1674, 1598, 1260, 1094, 1022, 799. HRMS (EI): calcd for $C_{18}H_{18}O_3$ (M^+), 282.1256; found, 282.1249.

4.5.5. 1,5-Bis(4-methoxy-phenyl)-pentane-1,5-dione (9h). Colorless crystals (75 mg, 80% yield); Mp: 95–96 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.91 (d, J=9.0 Hz, 2H), 6.88 (d, J=9.0 Hz, 2H), 3.80 (s, 3H), 2.99 (t, J=6.9 Hz, 2H), 2.11 (quintet, J=6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 198.6, 163.6, 130.5, 130.2, 113.8, 55.6, 37.5, 19.4; IR (neat; cm^{-1}): ν 1682. HRMS (EI): calcd for $C_{19}H_{20}O_4$ (M^+), 312.1362; found, 312.1363.

4.5.6. 1,4-Bis(4-methoxy-phenyl)-2-methyl-butane-1,4-dione (10h). White solid (14 mg, 15% yield). Mp: 143–145 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.98 (d, J=9.0 Hz, 2H), 7.90 (d, J=9.0 Hz, 2H), 6.90 (d, J=9.0 Hz, 2H), 6.84 (d, J=9.0 Hz, 2H), 4.08 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.57 (dd, J=17.7, 8.1 Hz, 1H), 2.95 (dd, J=17.7, 5.1 Hz, 1H), 1.20 (d, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 202.2, 197.2, 163.7, 163.6, 130.9, 130.5, 130.1, 129.2, 113.9, 113.8, 55.6, 42.1, 36.1, 29.8, 18.3. IR (KBr; cm^{-1}): ν 1674, 1595. HRMS (EI): calcd for $C_{19}H_{20}O_4$ (M^+), 312.1362; found, 312.1368.

4.5.7. 1-(3,4-Dimethoxy-phenyl)-5-phenyl-pentane-1,5-dione (9i). Colorless crystals (61 mg, 65% yield). Mp: 69–70 °C. ^1H NMR (300 MHz, $CDCl_3$; δ, ppm): 7.92 (d, J=8.4 Hz, 2H), 7.59 (dd, J=8.4, 2.0 Hz, 2H), 7.50 (t, J=8.4 Hz, 1H), 7.41 (t, J=8.4 Hz, 2H), 6.85 (d, J=8.4 Hz, 2H), 3.89 (s, 6H), 3.09–3.00 (m, 4H), 2.15 (quintet, J=7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 200.0, 198.6, 153.3, 149.1, 136.9, 133.1, 130.2, 128.6, 128.1, 122.8, 110.2, 110.1, 56.1, 56.0, 37.7, 37.2, 19.2. IR (KBr; cm^{-1}): ν 2960, 1730, 1676, 1261, 1022. HRMS (EI): calcd for $C_{19}H_{20}O_4$ (M^+), 312.1362; found, 312.1366.

4.5.8. 4-(3,4-Dimethoxy-phenyl)-2-methyl-1-phenyl-butane-1,4-dione (10i). White solid (14 mg, 15% yield). Mp: 65–66 °C. ^1H NMR (75 MHz, $CDCl_3$; δ, ppm): 8.00 (m, 2H), 7.57 (dd, J=8.4, 2.0 Hz, 1H), 7.48–7.42 (m, 4H), 6.83 (d, J=8.4 Hz, 1H), 4.14–4.07 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.63 (dd, J=16.8, 8.4 Hz, 1H), 3.05 (dd, J=16.8, 4.8 Hz, 1H), 1.20 (d, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$; δ, ppm): 203.7, 197.2, 153.5, 149.1, 136.3, 133.0, 130.1, 128.8, 128.7, 123.0, 110.3, 110.2, 56.2, 56.1, 42.1, 36.5, 29.8, 18.0. IR (KBr; cm^{-1}): ν 1730, 1670. HRMS (EI): calcd for $C_{19}H_{20}O_4$ (M^+), 312.1362; found, 312.1371.

Acknowledgements

We express our appreciation to the National Natural Science Foundation of China (20572104 and 20202009) for financial support.

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Tetrahedron 62 (2006) 7772–7775
Tetrahedron

A new and efficient synthesis of 2-azatryptophans

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Received 21 April 2006; revised 22 May 2006; accepted 24 May 2006
Available online 16 June 2006

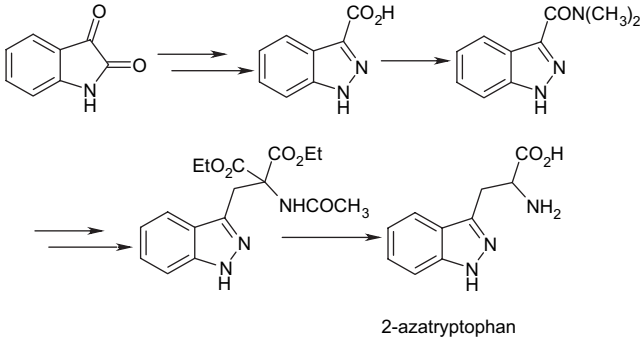
Abstract—This paper describes a new and simple synthesis of 2-azatryptophans in five steps from 2-ethylaniline. This methodology allows to obtain either the amino acid or the amino ester, according to the treatment and the reaction time, and its scaling up for multigram synthesis.

1. Introduction

Among heterocyclic scaffolds that are usable to prepare new valuable medicinal chemistry building blocks, the indazole nucleus[1] is always much less studied than some of its bioisosteres like indole, quinolines or benzimidazole. However, some indazole derivatives have been developed to give leads in medicinal chemistry such as 7-NI (nitric oxide synthase inhibitor),[2] YC-1 (guanylyl cyclase activator),[3] granisetron (5HT-3 receptor antagonist),[4] lonidamine (cytotoxic modulator),[5] SE063 (HIV protease inhibitor),[6] and recently with new protein kinase Cβ inhibitors[7] and oestrogen receptor ligands.[8]

It is for this reason why our group has been interested for a long time in the design and synthesis of new indazole libraries, in particular synthesis of 2-aza bioisosteres of tryptamine, serotonine or melatonine.[9]

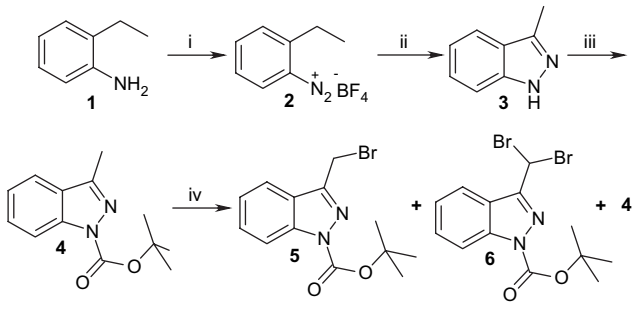
Herein, we would like to report a new efficient method for the synthesis of both 2-azatryptophan and its corresponding ethyl ester. One chemical pathway was found in a survey of literature described in the pioneering work of Snyder,[10] starting from isatine via 3-indazolecarboxylic acid (11 steps, 7% overall yield) as summarized in Scheme 1.



Scheme 1. Snyder's synthesis.[10]

2. Results and discussion

Since scalability of this reported sequence is not feasible, we reconsidered the strategy, taking into account our know-how in the laboratory about the cyclization of indazole[11] and the results of bromination reported by Henke et al.[12] The first part of the synthesis was the preparation of *N*-Boc-3-bromomethylindazole **5**, which was obtained in four steps starting from 2-ethylaniline **1** (Scheme 2).



Scheme 2. Reagents and conditions: (i) aq HBF_4 50%, aq $NaNO_2$, 0 °C, 84%; (ii) AcOK, 18-crown-6, $CHCl_3$, rt, 37%; (iii) $(Boc)_2O$, Et_3N, DMAP, CH_3CN, rt, 97%; (iv) NBS, *m*CPBA, CCl_4, 85 °C, 61% of **5**, 7% of **6**, and 32% of **4**.

Diazotization of 2-ethylaniline **1** with aqueous sodium nitrite (1 equiv) in fluoroboric acid (50% solution in water) at 0 °C gave the corresponding diazonium tetrafluoroborate salt **2** in 84% yield. This hygroscopic diazonium tetrafluoroborate salt was directly cyclized by reaction with potassium acetate (2 equiv) and 18-crown-6 (0.05 equiv) in dry chloroform at room temperature to obtain compound **3** with 37% yield. Protection of the N1 nitrogen by $(Boc)_2O$ followed

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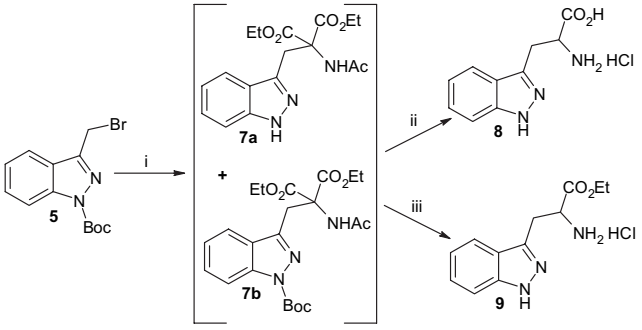
doi:10.1016/j.tet.2006.05.061

by radical bromination with NBS (1.1 equiv) and *m*CPBA (0.1 equiv) as free radical initiator in tetrachloromethane at 85 °C provided the protected indazole bromide **5** in 61% yield. This reaction, followed by TLC, not only gave the desired brominated product **5**, but also dibromo compound **6** and starting material **4** in, respectively, 61, 7, and 32% yields (Scheme 2).

The second part was the introduction of glycine moiety.[13] This was accomplished by the nucleophilic substitution of compound **5** by the carbanion of diethyl acetamidomalonate, formed by reaction with sodium metal in ethanol, to give a mixture of two products **7a** and **7b**, which were not separated (Scheme 3).



Scheme 3. Reagents and conditions: (i) $AcHNCH(CO_2Et)_2$, Na, EtOH, 70 °C; (ii) (1) NaOH, EtOH, H_2O, reflux, 4 h; (2) HCl (37%), reflux, 70%; (iii) (1) NaOH, H_2O, reflux, 1.5 h; (2) HCl (37%), reflux, 76%.

Indeed ^{1}H NMR of the resulting reaction product indicated that the Boc protecting group was not totally cleaved. Since deprotection of the *N*-Boc group would readily occur in the course of the following reactions, mixture of unprotected **7a** and protected **7b** was used without further purification for the final step. Saponification was realized with sodium pellets either in a water/ethanol mixture for 4 h or in water for 1.5 h, and then decarboxylation and hydrolysis were attempted in hydrochloric acid (37%) under reflux conditions.

In this way, hydrochloride of either amino acid **8** or amino ester **9** was obtained, respectively, in 70 and 76% yield from **5** according to the treatment and the reaction time (Scheme 3). Finally these two compounds were obtained as racemic mixtures from readily available starting materials under mild reaction conditions in five steps with a 14% overall yield.

In summary, we have developed a straightforward and efficient method to give in five steps 2-azatryptophan and its ethyl ester in good to very good yields. The unusual 2-azatryptophan residues can now be easily prepared from 3-(bromomethyl)-1-(*tert*-butoxycarbonyl)indazole **5** as described in this paper. This method was already easily scaled up for the synthesis of multigram amounts of amino acid or amino ester.

3. Experimental

3.1. General

All commercial reagents were used as received without further purification. Reaction mixture were stirred magnetically and monitored by TLC using 0.2 mm Macherey-Nagel Polygram SIL G/UV_{254} precoated plates. Column chromatography was performed using CarloErba-SDS 60A 70-200 μm silica gel. Melting points (uncorrected) were determined on a Köfler melting point apparatus. IR spectra were taken with a Perkin–Elmer spectrum X FTIR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts (δ) are expressed in parts per million downfield from tetramethylsilane as an internal standard and the coupling constants are given in hertz. Mass spectra were recorded on a JEOL JMS GCMate with ionizing potential of 70 eV and with PFK as internal standard for high-resolution. Elemental analyses were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen, France).

3.2. Synthesis of 3-methyl-1*H*-indazole (3)

A cooled solution of sodium nitrite (5.79 g in 6 mL H_2O, 83.92 mmol) was added at 0 °C dropwise to an ice solution of 2-ethylaniline **1** (10.17 g, 83.92 mmol) dissolved in fluoroboric acid (50% solution in water, 13 mL). After the end of the addition, the mixture was stirred for 2 h, and the resulting precipitate was filtered and then washed with Et_2O (3×100 mL) to obtain 2-ethylphenyldiazonium tetrafluoroborate salt **2** (15.38 g, 84%) as a very hygroscopic white solid; IR (KBr): ν=3436, 2259, 1564, 1051 cm^{-1}. The diazonium tetrafluoroborate salt **2** (15.38 g, 69.92 mmol) was added under nitrogen in one portion to a stirred mixture of potassium acetate (13.72 g, 139.84 mmol) and 18-crown-6 (1.30 g, 3.49 mmol) in dry chloroform (600 mL). After 2 h, the resulting precipitate was filtered and washed with chloroform. The organic layer was concentrated in vacuo and the residual gum was purified by column chromatography on silica gel (EtOAc/cyclohexane, 1:3) to give compound **3** (3.40 g, 37%) as a beige solid. Mp 113 °C. TLC R_f=0.3 (EtOAc/cyclohexane, 2:3). IR (KBr): ν=3307, 1338, 1007, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.61 (s, 3H, C*H*$_3$), 7.15 (t, 1H, *J*=7.8 Hz), 7.37 (t, 1H, *J*=7.6 Hz), 7.43 (d, 1H, *J*=8.6 Hz), 7.69 (d, 1H, *J*=8.0 Hz), 11.37 (br s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.0 (*C*H$_3$), 109.6, 120.1, 120.2, 122.8, 126.7, 141.1, 143.6. MS (EI): *m*/*z* (%)=132 (M^+, 100), 131 (84), 104 (14), 77 (13). Anal. Calcd for $C_8H_8N_2$ (132.17): C, 72.70; H, 6.10; N, 21.20; found: C, 72.27; H, 6.12; N, 20.87. Lit.[14]

3.3. Synthesis of 1-(*tert*-butoxycarbonyl)-3-methylindazole (4)

To a cooled solution of indazole **3** (3.56 g, 26.96 mmol) in CH_3CN (110 mL) were added successively DMAP (6.59 g, 53.92 mmol), Et_3N (7.5 mL, 53.92 mmol), and $(Boc)_2O$ (11.77 g, 53.92 mmol). The resultant reaction mixture was stirred for 1 h at 0 °C and then for 2 h at room temperature. The solvent was removed in vacuo, and then the crude material was taken up in EtOAc (100 mL) and washed with H_2O (2×100 mL). The aqueous layer was extracted with EtOAc (2×100 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 1:3) to give compound **4** (6.04 g, 97%) as a pale orange oil. TLC R_f=0.5 (EtOAc/cyclohexane, 1:4). IR (KBr): ν=3056, 2981, 1732, 1372,

1247, 1154, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=1.72 (s, 9H, C(CH_3)$_3$), 2.60 (s, 3H, CH_3), 7.30 (t, 1H, J=7.9 Hz), 7.51 (t, 1H, J=7.4 Hz), 7.65 (d, 1H, J=7.9 Hz), 8.11 (d, 1H, J=8.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.2 (CH_3), 28.2 (C(CH_3)$_3$), 84.4 (C(CH_3)$_3$), 114.6, 120.2, 123.1, 125.9, 128.7, 140.1, 148.4, 149.2. MS (EI): m/z (%)=232 (M^+, 14), 159 (14) 132 (100), 131 (38), 77 (9). HRMS/ESI Calcd for $C_{13}H_{16}N_2O_2Na$ $[M+Na]^+$ 255.1109; found 255.1110. Lit.[12]

3.4. Synthesis of 3-(bromomethyl)-1-(*tert*-butoxycarbonyl)indazole (5) and 3-(dibromomethyl)-1-(*tert*-butoxycarbonyl)indazole (6)

To a solution of protected indazole **4** (1.65 g, 7.10 mmol) heated in CCl_4 (90 mL) in an oil bath at 65 °C were added half of a mixture of NBS (1.39 g, 7.81 mmol) and *m*CPBA (123 mg, 0.71 mmol). Then other half was added at 85 °C. The resulting solution was heated in reflux conditions for 6.5 h and then cooled in an ice-bath. Then the reaction mixture was filtered through a pad of Celite and the solvent was evaporated in vacuo. The residual material was purified by column chromatography on silica gel (EtOAc/cyclohexane, 1:6) to give, after trituration with petroleum ether, compound **5** (1.34 g, 61%) as a pale yellow solid, compound **6** (200 mg, 7%) as a white solid, and compound **4** (528 mg, 32%).

Compound **5**: mp 84 °C. TLC R_f=0.5 (EtOAc/cyclohexane, 1:6). IR (KBr): ν=3030, 2980, 1737, 1433, 1370, 1252, 1153, 1010, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=1.70 (s, 9H, C(CH_3)$_3$), 4.77 (s, 2H, CH_2), 7.33 (t, 1H, J=7.6 Hz), 7.52 (t, 1H, J=7.3 Hz), 7.82 (d, 1H, J=8.0 Hz), 8.10 (d, 1H, J=8.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.9 (CH_2), 28.1 (C(CH_3)$_3$), 85.3 (C(CH_3)$_3$), 114.9, 120.7, 123.7, 124.0, 129.3, 140.7, 147.2, 148.9. MS (EI): m/z (%)=312 (M+1, 17), 310 (M−1, 17), 239 (8), 237 (8), 212 (32), 211 (14), 210 (33), 209 (11), 187 (14), 131 (100), 102 (43), 77 (18). Anal. Calcd for $C_{13}H_{15}BrN_2O_2$ (311.18): C, 50.18; H, 4.86; N, 9.00; found: C, 50.14; H, 4.44; N, 8.86. Lit.[12]

Compound **6**: mp 91–93 °C. TLC R_f=0.8 (EtOAc/cyclohexane, 1:6). IR (KBr): ν=3031, 2978, 1733, 1613, 1505, 1360, 1342, 1292, 1248, 1151, 1075, 851, 764, 739, 613 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=1.73 (s, 9H, C(CH_3)$_3$), 6.97 (s, 1H, C*H*), 7.44 (t, 1H, J=7.6 Hz), 7.59 (t, 1H, J=7.3 Hz), 8.16 (d, 1H, J=8.3 Hz), 8.23 (d, 1H, J=7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.1 (C(CH_3)$_3$), 30.3 (*C*H), 85.7 (C(CH_3)$_3$), 115.0, 121.8, 122.4, 123.7, 129.5, 141.2, 148.7, 148.9. MS (EI): m/z (%)=392 (M+2, 2), 390 (M^+, 4), 388 (M−2, 2), 311 (5), 309 (5), 212 (10), 211 (97), 210 (11), 209 (100), 101 (19). Anal. Calcd for $C_{13}H_{14}Br_2N_2O_2$ (390.08): C, 40.03; H, 3.62; N, 7.18; found: C, 40.22; H, 3.80; N, 7.16.

3.5. Synthesis of 2-amino-3-(1*H*-indazol-3-yl)propanoic acid hydrochloride (8)

In a three-necked flask under nitrogen were placed successively absolute ethanol (12 mL) and sodium (52 mg, 2.25 mmol). To this solution was added diethyl acetamidomalonate (489 mg, 2.25 mmol) in absolute ethanol (16 mL), and after few minutes of stirring and apparition of a yellow color, protected brominated indazole **5** (700 mg, 2.25 mmol) in warm absolute ethanol (15 mL) was obtained. This mixture was heated with stirring in an oil bath at 70 °C overnight. After being cooled to room temperature, the solution was concentrated in vacuo, then taken up in dichloromethane, and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo, and yellow solid obtained was placed in water (10 mL), ethanol (4 mL), and sodium hydroxide pellets (1.60 g) and heated under reflux for 4 h. Then 37% hydrochloric acid (20 mL) was added and the reaction mixture was heated under reflux conditions for 68 h. Solvent was completely evaporated, and the residue was extracted with boiling ethanol (4×15 mL). The combined extracts were concentrated in vacuo and cooled to give compound **8** (380 mg, 70%) as a white solid. Mp>260 °C. IR (KBr): ν=3435, 1626, 1438 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO + ε D_2O): δ=3.03 (dd, 1H, J=15.1 and 9.6 Hz, CH_2), 3.39 (dd, 1H, J=15.0 and 3.7 Hz, CH_2), 3.54 (dd, 1H, J=9.4 and 3.6 Hz, C*H*), 7.06 (t, 1H, J=7.3 Hz), 7.32 (t, 1H, J=7.2 Hz), 7.45 (d, 1H, J=8.4 Hz,), 7.78 (d, 1H, J=8.2 Hz). ^{13}C NMR (100 MHz, d_6-DMSO + ε D_2O): δ=27.3 (CH_2), 51.9 (*C*H), 110.9, 120.2, 121.0, 122.1, 127.3, 139.9, 141.3, 170.4 (CO_2H). Anal. Calcd for $C_{10}H_{12}N_3O_2\cdot HCl\cdot 0.5H_20$ (250.69): C, 47.91; H, 5.23; N, 16.76; found: C, 48.03; H, 5.33; N, 16.90.

3.6. Synthesis of 2-amino-3-(1*H*-indazol-3-yl)propanoic acid ethyl ester hydrochloride (9)

In a three-necked flask under nitrogen was placed successively absolute ethanol (25 mL) and sodium (323 mg, 11.05 mmol). To this solution was added diethyl acetamidomalonate (1.61 g, 7.39 mmol) in absolute ethanol (20 mL), and after few minutes of stirring and apparition of a yellow color, protected brominated indazole **5** (2.30 g, 7.39 mmol) in warm absolute ethanol (15 mL) was obtained. This mixture was stirred in an oil bath at 70 °C overnight. After being cooled to room temperature, the solution was concentrated in vacuo, then taken up in dichloromethane, and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo, and yellow solid obtained was placed in water (30 mL) and sodium hydroxide pellets (1.60 g) and heated under reflux for 1.5 h. Then 37% hydrochloric acid (20 mL) was added and the reaction mixture was heated under reflux for 20 h. Solvents were completely evaporated, and the residue was extracted with boiling ethanol (4× 15 mL). The combined extracts were concentrated in vacuo and cooled to give compound **9** (1.51 g, 76%) as a white solid. Mp 212 °C (dec). IR (KBr): ν=3423, 2896, 1743, 1637, 1515, 1436 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO): δ=1.01 (t, 3H, J=7.1 Hz, CH_3), 3.38 (q, 2H, J=7.1 Hz, OCH_2), 3.43–3.60 (m, 2H, CH_2), 4.25–4.31 (m, 1H, C*H*), 7.07 (t, 1H, J=7.3 Hz), 7.32 (t, 1H, J=7.3 Hz), 7.49 (d, 1H, J=8.3 Hz), 7.78 (d, 1H, J=8.1 Hz), 8.63 (br s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO): δ=18.7 (CH_3), 27.3 (CH_2), 51.6 (*C*H), 56.1 (OCH_2), 110.4, 120.0, 120.1, 121.8, 126.4, 139.3, 140.9, 170.2 (CO_2). Anal. Calcd for $C_{12}H_{15}N_3O_2\cdot HCl\cdot 0.5H_2O$ (278.74): C, 51.71; H, 6.15; N, 15.07; found: C, 51.76; H, 6.21; N, 15.16.

Acknowledgements

We thank Dr. Christophe Philippo for helpful discussions.

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Tetrahedron 62 (2006) 7776–7782
Tetrahedron

Phosphonylated thiocarbonyl ylides from the reaction of aromatic thioketones with diethyl diazomethylphosphonates

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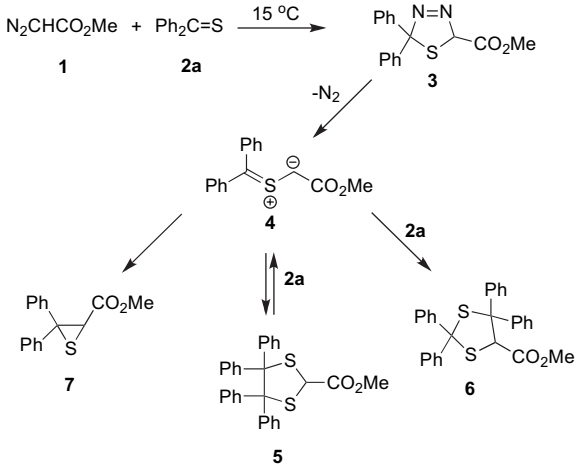
Received 20 April 2006; revised 16 May 2006; accepted 24 May 2006
Available online 16 June 2006

Abstract—The reaction of diazomethylphosphonates with aromatic thioketones at −65 °C to room temperature yields 2,5-dihydro-1,3,4-thiadiazole-2-phosphonates, which eliminates N_2 to give phosphonylated thiocarbonyl ylides as reactive intermediates. These sulfur-centered 1,3-dipoles undergo typical reactions of thiocarbonyl ylides, i.e., 1,3-dipolar cycloadditions, cyclodimerization, and electrocyclic ring closure, depending on the involved thioketone and, therefore, on the reaction conditions. In the case of the most reactive thiofluorenone, the phsophonylated thiocarbonyl methanide can be intercepted with thiobenzophenone, a phosphonodithioformate, and tetracyanoethylene. In the absence of such reactive dipolarophiles, cyclodimerization occurs to give the corresponding 1,4-dithiane.

1. Introduction

In contrast to the widely explored diazoacetates,[1] diazomethylphosphonates are rarely used in 1,3-dipolar cycloadditions. Only recently, reactions with imines to give 4,5-dihydro-1,2,3-thiazole-4-phosphonates or aziridine-2-phosphonates have been reported.[2] It is well established that reactions of diazo compounds with thiocarbonyl dipolarophiles lead to 2,5-dihydro-1,3,4-thiadiazoles, which offer a convenient access to reactive thiocarbonyl ylides.[3,4]

Diazoacetates were also applied in this reaction, even at a time when the reaction mechanism for the formation of thiiranes and 1,3-dithiolanes was not known.[5,6] The reaction of methyl diazoacetate (**1**) with thiobenzophenone (**2a**) was a key experiment in the elucidation of the reaction mechanism for the formation of 1,3-dithiolanes (so-called Schönberg products).[7] Interestingly, the regioisomeric 1,3-dithiolanes **5** and **6** were formed in a ratio of 1:1. The analogous reaction with 9*H*-fluorene-9-thione (**2b**) was reported to give the corresponding product of type **5** exclusively. Heating of the 'labile' isomer **5** to 100 °C resulted in the formation of a mixture of **6** and methyl 3,3-diphenylacrylate, which is the product of desulfurization of thiirane **7** (Scheme 1). The later reported reaction of diazoacetate with 9*H*-xanthene-9-thione (**2c**), which is less reactive than **2a**, in THF at 60 °C yielded only the corresponding acrylate.[8] In the same paper, the reaction of ethyl diazoacetate with sterically hindered cycloaliphatic thiones, derived from 2,2,4,4-tetramethylcyclobutane-1,3-dione, was reported to give only thiiranes. In a reaction of adamantanethione with ethyl



Scheme 1.

Keywords: Diazo compounds; Thioketones; Thiocarbonyl ylides; [2+3] Cycloadditions; Cyclodimerization; X-ray crystallography.
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† In part from the Ph.D. thesis of P.W., University of Łódź, 2004.

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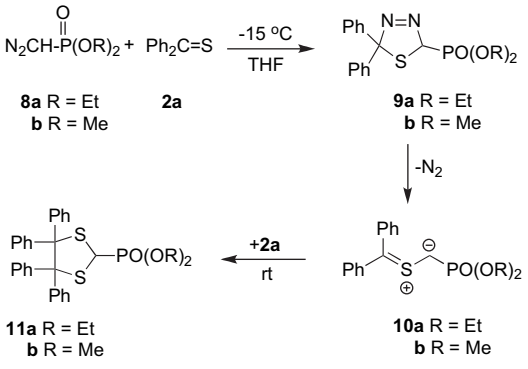
doi:10.1016/j.tet.2006.05.062

diazoacetate, which was catalyzed by $LiClO_4$, the sterically less hindered 1,3-dithiolane of type **6** was the sole product.[8] More complex reaction mixtures were obtained when ethyl diazoacetate was reacted with 4,4-disubstituted 1,3-thiazole-5(4*H*)-thiones.[9]

Phosphonylated thiocarbonyl ylides are attractive building blocks for the synthesis of phosphonylated sulfur heterocycles, which are difficult to access by other methods. Recently, these versatile dipolar species were generated from diazomethane and dialkyl phosphonodithioformates.[10,11] In the present paper, a different approach based on [2+3] cycloaddition of diazomethylphosphonates (**8**) with aromatic thioketones is described.

2. Results and discussion

Unlike the reaction with methyl diazoacetate (**1**, Scheme 1), the blue solution of thiobenzophenone (**2a**) in THF decolorized within ca. 30 min of the addition of an equimolar amount of **8a** at −15 °C, which indicates that **8a** is significantly more reactive than **1**. During the reaction, a slow evolution of nitrogen was observed. At room temperature, addition of **8a** to a solution of **2a** or vice versa was accompanied by a vigorous gas evolution. In the crude reaction mixture, a new product **11a** and unconsumed **8a** were found in a ratio of ca. 1:1 (^{1}H NMR). By trituration with hexane, **11a** was isolated as a colorless solid. Its structure was established as symmetrical 1,3-dithiolane on the basis of its ^{1}H and ^{13}C NMR spectra (Scheme 2). The most indicative signal is that for C(4) and C(5) appearing at 79.6 ppm ($^3J_{CP}$=7 Hz). The signal of C(2), which bears the phosphonate group, is located at 40.8 ppm as a doublet with $^1J_{CP}$=150.9 Hz. An analogous result was obtained in the case of dimethyl diazomethylphosphonate (**8b**).



Scheme 2.

Finally, the structure of **11a** was established by X-ray crystallography (Fig. 1). The five-membered heterocycle has a half-chair conformation twisted on S(1)–C(5). One ethyl group is disordered over two conformations.

In comparison with the result obtained with **1** (Scheme 1), the most important difference is that only the sterically more congested 1,3-dithiolane was formed, i.e., the [2+3] cycloaddition of **10** with **2a** occurs with high regioselectivity.

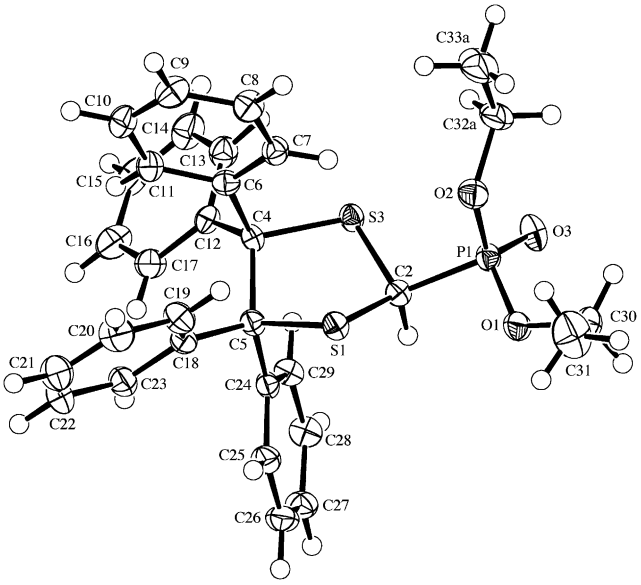


Figure 1. ORTEP-plot[13] of the molecular structure (conformation A) of **11a** (arbitrary numbering of atoms, 50% probability ellipsoids).

According to the reactivity scale elaborated for the [2+3] cycloaddition of diphenyldiazomethane and C=S dipolarophiles, 9*H*-fluoren-9-thione (**2b**) is approximately 100× more reactive than **2a**.[12] The enhanced reactivity of **2b** was confirmed in the reaction with **8a**. The decolorization of the 1:1 mixture occurred smoothly at −65 °C without evolution of nitrogen. The evolution of N_2 started between −50 and −45 °C, and after warming to room temperature, the crude mixture showed the presence of a single product (^{1}H NMR), with a characteristic signal at 4.84 ppm ($^2J_{HP}$=24.9 Hz, $^3J_{HP}$=12.6 Hz). The integration of this signal, which originates from **8a**, and the aromatic protons reveals a ratio of 1:8, which indicates that the starting materials reacted in a 1:1 ratio. The elemental analysis was in accordance with the values for the thiocarbonyl ylide **10c**, while the CIMS showed the $[M+1]^+$ peak at *m/z* 693. Therefore, the isolated product is a dimer of **10c**. Finally, the structure of the compound was established by X-ray crystallography (Fig. 2) as *trans*-1,4-dithiane-2,3-diphosphonate **12** (Scheme 3). The six-membered heterocycle

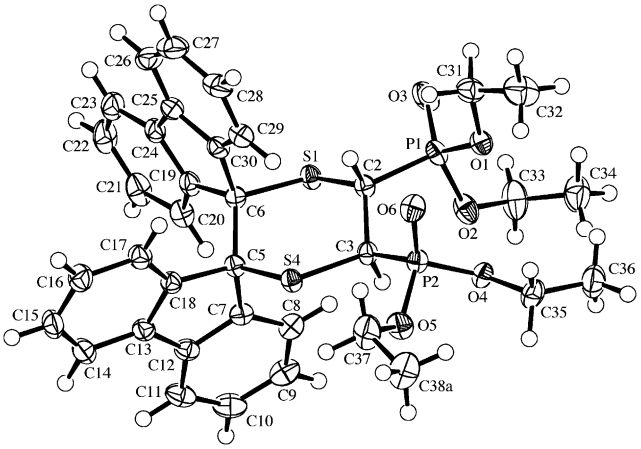
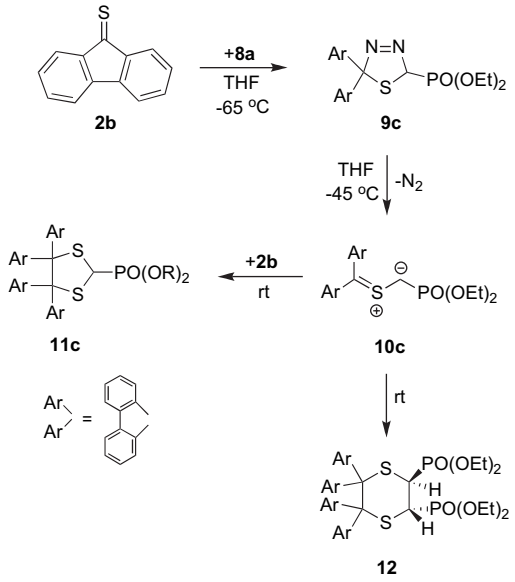


Figure 2. ORTEP-plot[13] of the molecular structure (conformation A) of **12** (arbitrary numbering of atoms, 50% probability ellipsoids).

has a chair conformation with the phosphonate substituents in equatorial positions. The fluorene groups are quite planar. The terminal methyl group of one ethoxy group is disordered over two conformations.

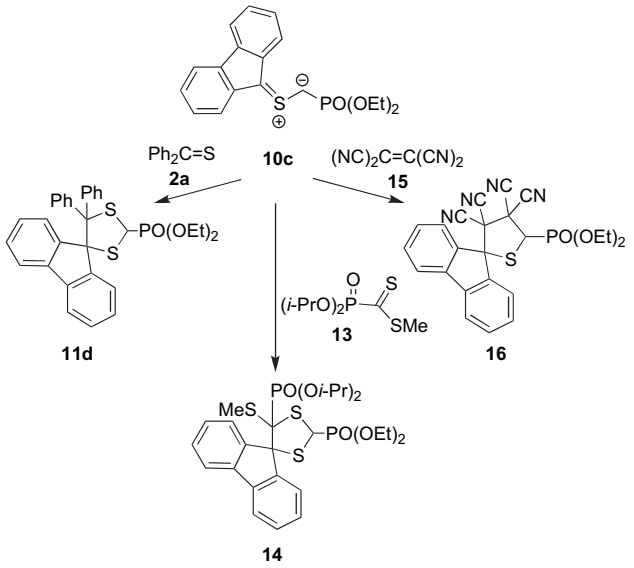


Scheme 3.

The experiment shows that the highly reactive **2b** already undergoes the [2+3] cycloaddition with **8a** at −65 °C to give regioselectively the 2,5-dihydro-1,3,4-thiadiazole **9c**, which is stable at this temperature. The decomposition starts only at ca. −45 °C, and thiocarbonyl ylide **10c** is formed as a transient species. In the absence of any intercepting agent, **10c** dimerizes regio- and stereoselectively to give **12** exclusively. Under these conditions, 1,3-dipolar electrocyclization to the corresponding thiirane is completely suppressed by the dimerization process. The mechanism of the head-to-head dimerization can be formulated in line with earlier results to occur via a 1,6-diradical.[14]

When **2b** was added to a freshly prepared solution of **9c** at −65 °C and the mixture was subsequently warmed to room temperature, typical workup by crystallization gave the 1,3-dithiolane-2-phosphonate **11c** in almost quantitative yield (Scheme 3). Similar to **11a**, in the ^{1}H NMR spectrum, H–C(2) appears at 5.52 ppm as a doublet ($^2J_{HP}$=6.6 Hz), and C(2) appears as a doublet at 43.6 ppm ($^1J_{CP}$=152.4 Hz). As no dimer **12** could be detected in the crude mixture (^{1}H NMR), thiocarbonyl ylide **10c** must have been trapped completely by the 'superdipolarophile' **2b**. A similar result was obtained with **2a** instead of **2b**. Also in this case, no dimerization was observed, and the structure of the mixed 1,3-dithiolane **11d** was attributed to the product isolated by crystallization (Scheme 4).

In addition to the thioketones **2a** and **2b**, *S*-methyl diisopropyl phosphonodithioformate (**13**) was tested as a C=S dipolarophile. Recently, it has been shown that **13** is an efficient interceptor of aromatic and cycloaliphatic thiocarbonyl *S*-methanides.[15] The reaction with **10c**, generated at −45 °C, led to the expected 1,3-dithiolane-2,4-diphosphonate **14**[16] (Scheme 4). Again, neither the corresponding thiirane nor

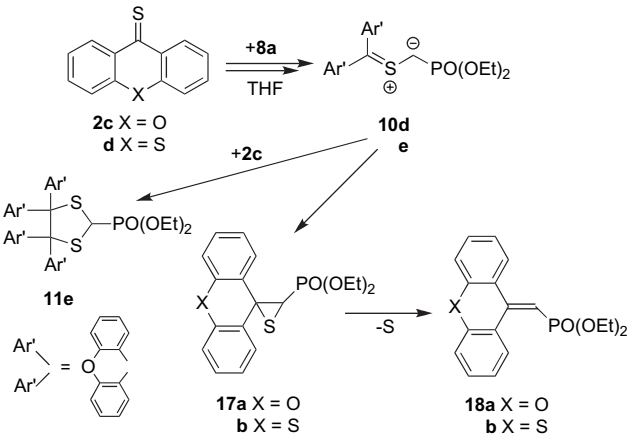


Scheme 4.

the dimer could be detected. Therefore it can be concluded that **13** is a superior dipolarophile, comparable with the frequently used **2a** and **2b**.

From the selected *C*,*C*-dipolarophiles, i.e., maleic anhydride, *N*-cyclohexylmaleimide, and tetracyanoethane, only the latter was able to trap **10c** to yield tetrahydrothiophene **16** (Scheme 4). No formation of any side-product was observed in this reaction.

It is well known that 9*H*-xanthene-9-thione (**2c**) and 9*H*-thioxanthene-9-thione (**2d**) belong to the moderately reactive aromatic thioketones.[12] With **8a** in THF, **2c** reacted slowly at room temperature with evolution of nitrogen. The mixture decolorized within 24 h and gave two products **11e** and **18a** in a ratio of 5:1 (Scheme 5). In the ^{1}H NMR spectrum, **11e** showed a doublet at 5.53 ppm ($^1J_{HP}$=6.1 Hz), whereas the corresponding signal of **18a** appeared at 5.92 ppm ($^1J_{HP}$=8.9 Hz). The same products were obtained when the reaction was carried out in boiling THF, but in this case, the ratio was determined as 2:3. Finally, after addition of **2c** to a boiling solution of **8a** in toluene, only the

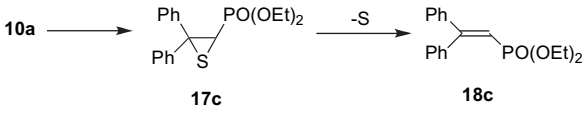


Scheme 5.

vinylphosphonate **18a** was formed. In this system, the intermediate **10d** undergoes an electrocyclic ring closure to give **17a** or enter a competitive [2+3] cycloaddition with the parent thioketone **2c**. Spontaneous desulfurization of **17a** leads to the isolated product **18a**. Consequently, higher dilution and increased temperature favor the formation of **18a**.

The less reactive **2d** reacted with **8a** only at enhanced temperature to give two products characterized as thiirane **17b** and vinylphosphonate **18b**, but no formation of a 1,3-dithiolane of type **11** was observed. Whereas the doublet for =CH– of **18b** was observed in the ^{1}H NMR spectrum in the typical region at ca. 6 ppm, the signal of the corresponding H–C(2) of **17b** was found at 2.74 ppm ($^1J_{HP}$=11.0 Hz). In boiling THF, the ratio of the two products was ca. 9:1 in favor of **17b**, whereas in boiling toluene, the proportion of **18b** increased (ratio 3:1). The separation of the products was achieved by chromatography.

Prompted by the results obtained with **2c** and **2d**, the reactions of **8a** with **2a** and **2b** (Scheme 2) were repeated in boiling toluene. In the case of **2a**, the corresponding vinylphosphonate **18c** was obtained as the sole product (Scheme 6). However, the reaction with **2b**, despite higher dilution, led to 1,3-dithiolane **11c** (Scheme 3) exclusively, which confirmed the outstanding dipolarophilicity of this thioketone.



Scheme 6.

3. Conclusion

In conclusion, the described results show that diazomethylphosphonates are attractive reagents for 1,3-dipolar cycloadditions, which in the case of C=S dipolarophiles exceed the reactivity of the frequently used diazoacetates. The presence of the phosphono group strongly influences the reactivity of the resulting thiocarbonyl ylides. The synthetic applications of these intermediates are limited by the availability of their precursors, and only 'thiofluorenone' **2b** is sufficiently reactive toward **8a** to give the appropriate 2,5-dihydro-1,3,4-thiadiazole derivative **9c**. The dominant tendency for cyclodimerization of **10c** can be suppressed only by addition of very reactive dipolarophiles to the reaction mixture.

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded at ca. 21 °C with a Varian Gemini 200 BB VT (^{1}H at 200.1 MHz, ^{13}C at 50.3 MHz) or a Bruker-AC-300 (^{1}H at 300.1 MHz, ^{13}C at 75.5 MHz) spectrometer using $CDCl_3$ as a solvent. Chemical shifts (δ) are reported in parts per million downfield from internal TMS. The majority of signals were assigned with the aid of ATP or DEPT spectra. IR spectra were recorded in KBr pellets or as films on a Thermo-Nicolet Nexus FTIR spectrometer. Low- and high-resolution EI mass spectra (MS and HRMS) were taken on a Finnigan MAT 95 spectrometer at 70 eV. Melting points (uncorrected) were determined in capillary or on a Boëtius apparatus.

Column chromatography was carried out using silica gel (Merck 60, 0.063–0.200 μm). Thin layer chromatography (TLC) was performed on Merck 5554 aluminum-backed SiO_2 plates; products were visualized by UV light.

Toluene and THF were distilled from the blue solution of sodium benzophenone ketyl.

Thiobenzophenone (**2a**),[17] 9*H*-fluorene-9-thione (**2b**),[18] 9*H*-xanthene-9-thione (**2c**),[17] and 9*H*-thioxanthene-9-thione (**2d**)[17] were prepared following the literature procedure.

Methyl and ethyl diazomethylphosphonates (**8**) were prepared by the Seyferth method.[19]

4.2. Reaction of thiobenzophenone (2a) with diethyl and dimethyl diazomethylphosphonate (8a) and (8b)

To a solution of 1 mmol of thiobenzophenone (**2a**) in dry THF (1 mL) at −65 °C, 1 mmol of diazomethylphosphonate **8a** or **8b**, respectively, was added drop-wise. The mixture was stirred and allowed to warm to room temperature (decolorization of the mixture was observed at −15 °C). The solvent was evaporated and the solid residue was purified by recrystallization.

An analogous experiment was carried out at room temperature leading to the same result.

4.2.1. Diethyl (4,4,5,5-tetraphenyl-[1,3]dithiolan-2-yl)-phosphonate (11a). Yield: 200 mg (74%). Colorless solid. Mp 114–118 °C (decomp.; hexane/AcOEt). ^{1}H NMR: δ 1.41 (t, J=7.0 Hz, $2CH_3$), 4.16 (d, $^2J_{HP}$=6.6 Hz, CH), 4.20–4.34 (m, $2CH_2O$), 6.94–7.79 (m, 20arom. H). ^{13}C NMR: δ 16.4 (d, $^3J_{CP}$=5.9 Hz, $2CH_3$), 40.8 (d, $^1J_{CP}$=150.9 Hz, CHP), 63.6 (d, $^2J_{CP}$=6.7 Hz, $2CH_2O$), 79.6 (d, $^3J_{CP}$=7.0 Hz, $2C_q$), 126.1, 126.5, 126.6, 127.7, 127.9, 129.0, 131.1, 131.9 (20arom. CH), 142.4, 142.6 (4arom. C_q). IR (KBr, cm^{-1}): 3059m, 2981m, 1490s, 1443s, 1258s (P=O), 1043s and 1020s (P–O–C), 738m, 696s, 532m. ESI-MS m/z (%): 569 (100, $[M+Na]^+$). Anal. Calcd for $C_{31}H_{31}O_3PS_2$ (546.69): C 68.11, H 5.72; found: C 68.24, H 5.46.

4.2.2. Dimethyl (4,4,5,5-tetraphenyl-[1,3]dithiolan-2-yl)-phosphonate (11b). Yield: 250 mg (96%). Colorless solid. Mp 84–86 °C (decomp.; hexane/Et_2O). ^{1}H NMR: δ 3.90 (d, $^3J_{HP}$=11 Hz, $2CH_3O$), 4.20 (d, $^2J_{HP}$=6.9 Hz, CH), 6.80–7.70 (m, 20arom. H). ^{13}C NMR: δ 40.6 (d, $^1J_{CP}$=151.4 Hz, CHP), 54.3 (d, $^2J_{CP}$=6.7 Hz, $2CH_3O$), 79.9 (d, $^3J_{CP}$=7.3 Hz, $2C_q$), 126.7, 127.1, 127.3, 131.6, 132.3 (20arom. CH), 142.9 (4arom. C_q). IR (KBr, cm^{-1}): 3056m, 2953m, 1490s, 1443s, 1262s (P=O), 1054s and 1032s (P–O–C), 739m, 700s, 532m. EIMS m/z (%): 518 (<1, M^+), 288 (9), 211 (22), 210 (100), 198 (30), 197 (9), 178 (27), 165 (46), 121 (26).

4.3. Reaction of diethyl diazomethylphosphonate (8a) with 9*H*-fluorene-9-thione (2b)

To a solution of 1 mmol of 9*H*-fluorene-9-thione (**2b**) in dry THF (1 mL), 1 mmol of diethyl diazomethylphosphonate (**8a**) was added drop-wise at −65 °C. After 10 min stirring at −65 °C, decolorization of the mixture was observed. For the synthesis of **12**, the mixture was stirred and allowed to warm to room temperature. For the synthesis of **11c**, **11d**, **14**, and **16**, a respective dipolarophile **2a**, **2b**, **13** or **15** (1 mmol) was added. The mixture was stirred and allowed to warm to room temperature. The solvent was removed in vacuum and the solid residue purified by recrystallization.

4.3.1. Tetraethyl dispiro[9*H*-fluorene-9,2′-[1,4]dithiane-3′,9″-[9*H*]fluorene]-5′,6′-diphosphonate (12). Yield: 160 mg (46%). Colorless solid. Mp 230–235 °C (decomp.; hexane/dichloromethane). ^{1}H NMR: δ 1.36 (t, J=7.0 Hz, 2CH$_3$), 1.37 (t, J=7.0 Hz, 2CH$_3$), 4.16–4.36 (m, 4CH$_2$O), 4.84 (dd, $^2J_{HP}$=24.9 Hz, $^3J_{HP}$=12.6 Hz, 2CH), 6.16–6.19 (m, 2arom. H), 6.63–6.69 (m, 2arom. H), 7.01–7.64 (m, 10arom. H), 9.05–9.10 (m, 2arom. H). ^{13}C NMR: δ 16.1 (s, 4CH$_3$), 38.0 (d, $^1J_{CP}$=133.1 Hz, 2*C*HP), 57.0 (2C$_q$), 63.1 (d, $^2J_{CP}$=58.6 Hz, 4CH$_2$O), 119.1, 120.1, 125.1, 126.4, 126.7, 127.7, 128.4, 128.6 (16arom. CH), 139.8, 140.5, 142.2, 148.3 (8arom. C$_q$). IR (KBr, cm^{-1}): 2983m, 1630w, 1446m, 1249s (P═O), 1023vs (P–O–C), 976s, 742s, 553m. CIMS (NH$_3$) *m*/*z* (%): 693 (100, [M+1]$^+$), 329 (21), 318 (45), 197 (17). Anal. Calcd for $C_{36}H_{38}O_6P_2S_2$ (692.77): C 62.42, H 5.53, S 9.26; found: C 62.10, H 5.50, S 9.22.

4.3.2. Diethyl dispiro[9*H*-fluorene-9,4′-[1,3]dithiolan-5′,9″-[9*H*]fluorene]-2′-phosphonate (11c). Yield: 400 mg (74%). Colorless solid. Mp 242–252 °C (decomp.; hexane/dichloromethane). ^{1}H NMR: δ 1.41 (t, J=7.0 Hz, 2CH$_3$), 4.28–4.38 (m, 2CH$_2$O), 5.52 (d, $^2J_{HP}$=6.6 Hz, CH), 7.09–7.64 (m, 20arom. H). ^{13}C NMR: δ 16.4 (d, $^3J_{CP}$=5.8 Hz, 2CH$_3$), 43.6 (d, $^1J_{CP}$=152.4 Hz, CHP), 63.9 (d, $^2J_{CP}$=6.8 Hz, 2CH$_2$O), 75.0 (d, $^3J_{CP}$=7.0 Hz, 2C$_q$), 119.0, 119.5, 126.1, 126.7, 128.6, 128.7 (20arom. CH), 127.7, 140.1 (4arom. C$_q$). IR (KBr, cm^{-1}): 3055m, 2981m, 2905m, 1476m, 1446s, 1259vs (P═O), 1047vs and 1020vs (P–O–C), 964s, 741vs, 650m, 533m. CIMS (NH$_3$) *m*/*z* (%): 562 (15), 561 (37), 560 (100, [M+NH$_4$]$^+$), 543 (15), 349 (13), 348 (17), 329 (21), 202 (28), 200 (15), 197 (27). Anal. Calcd for $C_{31}H_{27}O_3PS_2$ (542.66): C 68.61, H 5.02, S 11.82; found: C 68.50, H 4.95, S 12.33.

4.3.3. Diethyl 5′,5′-diphenylspiro[9*H*-fluorene-9,4′-[1,3]dithiolane]-2-phosphonate (11d). Yield: 200 mg (37%). Colorless solid. Mp 172–178 °C (decomp.; hexane/Et$_2$O). ^{1}H NMR: δ 1.42 (t, J=7.0 Hz, 2CH$_3$), 4.29–4.38 (m, 2CH$_2$O), 5.01 (d, $^2J_{HP}$=6.7 Hz, CH), 5.65–5.67 (m, 1arom. H), 6.73–7.36 (m, 13arom. H), 7.73–7.80 (m, 4arom. H). ^{13}C NMR: δ 16.5 (d, $^3J_{CP}$=6.0 Hz, 2CH$_3$), 42.1 (d, $^1J_{CP}$=149.7 Hz, CHP), 63.8 (d, $^2J_{CP}$=6.9 Hz, CH$_2$O), 63.9 (d, $^2J_{CP}$=6.7 Hz, CH$_2$O), 75.9, 78.0 (2C$_q$), 120.1, 120.5, 124.7, 126.5, 126.7, 127.1, 127.5, 127.7, 128.1, 128.2, 129.0 (18arom. CH), 132.0, 138.3, 140.4, 142.8, 145.1, 148.0 (6arom. C$_q$). IR (KBr, cm^{-1}): 3055m, 2981m, 2905m, 1475m, 1444s, 1257s (P═O), 1046vs and 1020vs (P–O–C), 975s, 745vs, 699s, 536m. CIMS (NH$_3$) *m*/*z* (%): 563 (37, [M+NH$_4$]$^+$), 562 (100), 546 (8, [M+1]$^+$), 545 (21, M$^+$), 366 (38), 349 (20), 317 (45), 210 (18), 200 (16), 199 (78), 197 (33). Anal. Calcd for $C_{31}H_{29}O_3PS_2$ (544.68): C 68.36, H 5.37, S 11.77; found: C 67.88, H 5.30, S 12.22.

4.3.4. Diisopropyl [2-(diethoxyphosphoryl)-5-methylsulfanylspiro[9*H*-fluorene-9,4′-[1,3]dithiolane]-5-phosphonate (14). Yield: 260 mg (43%). Colorless solid. Mp 160–170 °C (decomp.; hexane/dichloromethane). ^{1}H NMR: δ 0.74 (d, J=6.2 Hz, CH$_3$), 0.93 (d, J=6.2 Hz, CH$_3$), 1.16 (d, J=6.1 Hz, CH$_3$), 1.30 (d, J=6.1 Hz, CH$_3$), 1.59 (t, J=6.9 Hz, CH$_3$), 1.60 (t, J=6.9 Hz, CH$_3$), 2.73 (s, CH$_3$S), 4.43–4.68 (m, 2CH$_2$O, 2CHO), 5.40 (dd, $^2J_{HP}$=4.6, $^4J_{HP}$=1.1 Hz, CH), 7.36–7.79 (m, 6arom. H), 8.34–8.37 (m, 1arom. H), 8.68–871 (m, 1arom. H). ^{13}C NMR: δ 16.3 (d, $^3J_{CP}$=7.2 Hz, *C*H$_3$CH$_2$O), 16.5 (d, $^3J_{CP}$=14.0 Hz, *C*H$_3$CH$_2$O), 22.0 (d, $^3J_{CP}$=6.4 Hz, CH$_3$S), 23.0, 23.5, 23.6, 23.9 (2(*C*H$_3$)$_2$CH), 42.7 (dd, $^1J_{CP}$=150.0, $^3J_{CP}$=11.0 Hz, CHP), 63.6 (d, $^2J_{CP}$=6.9 Hz, CH$_2$O), 64.4 (d, $^2J_{CP}$=6.6 Hz, CH$_2$O), 71.0 (d, $^2J_{CP}$=8.3 Hz, (CH$_3$)$_2$*C*H), 73.3 (d, $^2J_{CP}$=7.9 Hz, (CH$_3$)$_2$*C*H), (2C$_q$ not found), 118.4, 119.3, 125.9, 126.6, 128.5, 129.1, 129.2, 130.7 (8arom. CH), 139.2, 140.3, 142.6, 149.4 (4arom. C$_q$). IR (KBr, cm^{-1}): 3058w, 2979m, 2925w, 1448m, 1386m, 1256s, 1244s (P═O), 1046s, 1010vs and 985vs (P–O–C), 743vs, 534m. CIMS (NH$_3$) *m*/*z* (%): 604 (32, [M+1]$^+$), 603 (100, M$^+$), 389 (28), 375 (11), 202 (12), 200 (16).

4.3.5. Diethyl 3,3,4,4-tetracyano-spiro[9*H*-fluorene-9,2′-thiolane]-5-phosphonate (16). Yield: 240 mg (51%). Pale-yellow solid. Mp 159–162 °C (decomp.; Et$_2$O). ^{1}H NMR: δ 1.40–1.47 (m, 2CH$_3$), 4.31–4.44 (m, 2CH$_2$O), 4.70 (d, $^2J_{HP}$=16.3 Hz, CH), 7.18–7.77 (m, 7arom. H), 8.15–8.17 (m, 1arom. H). ^{13}C NMR: δ 16.2 (d, $^3J_{CP}$=5.1 Hz, CH$_3$), 16.2 (d, $^3J_{CP}$=4.6 Hz, CH$_3$), 49.5 (d, $^1J_{CP}$=147.3 Hz, CHP), 52.1, 60.0 (2C$_q$), 65.4 (d, $^2J_{CP}$=6.9 Hz, CH$_2$O), 65.8 (d, $^2J_{CP}$=6.9 Hz, CH$_2$O), 107.5, 109.2, 109.4, 109.5 (4CN), 120.7, 120.8, 126.6, 128.2, 128.3, 128.7, 131.5, 131.8 (8arom. C), 139.8, 141.2, 142.7 (4arom. C$_q$). IR (KBr, cm^{-1}): 3064w, 2987m, 2920m, 2255w, 1451m, 1264s (P═O), 1043vs and 1017vs (P–O–C), 752s, 744s, 548m. CIMS (NH$_3$) *m*/*z* (%): 492 (100, [M+NH$_4$]$^+$), 292 (40), 264 (27). Anal. Calcd for $C_{31}H_{19}N_4O_3PS_2$ (474.48): C 60.75, H 4.04, N 11.85, S 6.76; found: C 60.55, H 4.04, N 11.64, S 6.61.

4.4. Reaction of diethyl diazomethylphosphonate (8a) with 9*H*-xanthene-9-thione (2c) and 9*H*-thioxanthene-9-thione (2d)

To a solution of 1 mmol of 9*H*-xanthene-9-thione (**2c**) in dry THF (1 mL), 1 mmol of diethyl diazomethylphosphonate (**8a**) was added drop-wise at room temperature. After 24 h stirring, decolorization of the mixture was observed. The solvent was removed under vacuum and compound **11e** was separated and purified by recrystallization. The same reaction in boiling THF gave products **11e** and **18a** in a 2:3 ratio, whereas in boiling toluene the formation of only **18a** was observed. The reaction with **2d** was carried out in boiling toluene. Two products were separated chromatographically on silica gel (hexane/AcOEt).

4.4.1. Diethyl dispiro[9*H*-xanthene-9,4′-[1,3]dithiolane-5′,9″-[9*H*]xanthene]-2′-phosphonate (11e). Yield: 180 mg (63%). Colorless solid. Mp 156–158 °C (decomp.; hexane/dichloromethane). ^{1}H NMR: δ 1.48 (t, J=7.0 Hz, 2CH$_3$), 4.37–4.47 (m, 2CH$_2$O), 5.53 (d, $^2J_{HP}$=6.1 Hz, CH), 6.67–7.52 (m, 14arom. H), 8.04–8.07 (m, 2arom. H). ^{13}C NMR: δ 16.5 (d, $^3J_{CP}$=5.8 Hz, 2CH$_3$), 43.9 (d, $^1J_{CP}$=153.3 Hz, CHP), 63.9 (d, $^2J_{CP}$=6.9 Hz, 2CH$_2$O), 74.5 (d, $^3J_{CP}$=7.1 Hz, 2C$_q$), 115.5, 116.0, 121.9, 128.7, 128.9, 130.3 (16arom. CH), 151.3, 151.8 (4arom. C$_q$). IR (KBr, cm^{-1}): 2983w, 2915w, 1597m, 1474s, 1443s, 1308m, 1281m, 1246s (P═O), 1044s and 1017vs (P–O–C), 749s, 536m. ESI-MS m/z (%): 597 ([M+Na]$^+$). Anal. Calcd for $C_{31}H_{27}O_5PS_2$ (574.65): C 64.53, H 4.68, S 10.95; found: C 64.79, H 4.74, S 11.16.

4.4.2. Diethyl (9*H*-xanthen-9-ylidene)methylphosphonate (18a). Yield: 200 mg (61%). Colorless solid. Mp 72–73 °C (hexane). ^{1}H NMR: δ 1.22 (t, J=7.0 Hz, 2CH$_3$), 3.98–4.12 (m, 2CH$_2$O), 5.92 (d, $^2J_{HP}$=8.9 Hz, CH), 7.16–7.28 (m, 4arom. H), 7.38–7.47 (m, 2arom. H), 7.71–7.74 (m, 1arom. H), 8.52–8.55 (m, 1arom. H). ^{13}C NMR: δ 16.2 (d, $^3J_{CP}$=6.6 Hz, 2CH$_3$), 61.8 (d, $^2J_{CP}$=6.0 Hz, 2CH$_2$O), 105.3 (d, $^1J_{CP}$=198.2 Hz, CHP), 116.6, 117.2 (2arom. C), 119.8 (d, $^2J_{CP}$=7.1 Hz, C$_q$), 123.2, 124.1, 124.2, 129.6, 130.8, 131.5 (8arom. CH), 143.8, 143.9, 151.3, 152.0 (4arom. C$_q$). IR (KBr, cm^{-1}): 3058w, 3033w, 2985m, 2900w, 1604s, 1564m, 1477m, 1456s, 1391w, 1361w, 1320m, 1284m, 1245s 1236s (P═O), 1047s and 1035s (P–O–C), 966s, 788s, 770s, 547m. CIMS (NH$_3$) m/z (%): 348 (7, [M+NH$_4$]$^+$), 333 (8), 332 (20), 331 (100, [M+1]$^+$). Anal. Calcd for $C_{18}H_{19}O_4P$ (330.32): C 65.45, H 5.80; found: C 65.30, H 5.92.

4.4.3. Spiro[thiirane-2,9′-[9*H*]thioxanthene]-3-phosphonate (17b). Yield: 190 mg (50%). Eluted with hexane/AcOEt 1:1 and recrystallized from hexane. Pale-yellow solid. Mp 69–72 °C (hexane). ^{1}H NMR: δ 1.16 (t, J=7.1 Hz, CH$_3$), 1.18 (t, J=7.1 Hz, CH$_3$), 2.74 (d, $^2J_{HP}$=11.0 Hz, CH), 3.76–3.92 (m, 2CH$_2$O), 7.19–7.28 (m, 4arom. H), 7.45–7.49 (m, 2arom. H), 7.60–7.63 (m, 1arom. H), 7.68–7.71 (m, 1arom. H). ^{13}C NMR: δ 16.3 (d, $^3J_{CP}$=4.2 Hz, 2CH$_3$), 40.7 (d, $^1J_{CP}$=184.1 Hz, CHP), 55.1 (C$_q$), 62.4 (d, $^2J_{CP}$=6.5 Hz, CH$_2$O), 63.0 (d, $^2J_{CP}$=6.7 Hz, CH$_2$O), 126.1, 126.2, 126.6, 126.8, 127.5, 127.7, 130.3 (8arom. CH), 133.0, 136.1, 136.4, 137.0 (4arom. C$_q$). IR (KBr, cm^{-1}): 3057w, 2982m, 2929w, 2904w, 1457m, 1441m, 1263s, 1243m (P═O), 1045s and 1027s (P–O–C), 971s, 787m, 742s, 545m. CIMS (NH$_3$) m/z (%): 380 (5), 379 (10), 378 (44, M$^+$), 365 (10), 363 (46), 347 (21), 346 (100, [M−S]$^+$), 332 (20), 331 (13). Anal. Calcd for $C_{18}H_{19}O_3PS_2$ (378.45): C 57.13, H 5.06, S 16.94; found: C 57.16, H 4.99, S 16.83.

4.4.4. Diethyl (9*H*-thioxanthen-9-ylidene)methylphosphonate (18b). Yield: 100 mg (29%). Eluted with AcOEt and recrystallized from hexane. Colorless solid. Mp 74–75 °C (hexane). ^{1}H NMR: δ 1.11 (t, J=7.1 Hz, CH$_3$), 1.12 (t, J=7.1 Hz, CH$_3$), 3.86–3.97 (m, 2CH$_2$O), 5.92 (d, $^2J_{HP}$=12.5 Hz, CH), 7.26–7.36 (m, 4arom. H), 7.43–7.49 (m, 2arom. H), 7.63–7.66 (m, 1arom. H), 8.19–8.22 (m, 1arom. H). ^{13}C NMR: δ 16.0 (d, $^3J_{CP}$=6.8 Hz, 2CH$_3$), 61.8 (d, $^2J_{CP}$=6.1 Hz, 2CH$_2$O), 115.4 (d, $^1J_{CP}$=191.6 Hz, CHP), 125.8, 125.9, 126.1, 126.3, 127.1, 128.4, 128.9, 130.2 (8arom. CH), 131.9 (d, $^2J_{CP}$=5.6 Hz, C$_q$), 136.0, 136.3, 151.9, 152.0 (4arom. C$_q$). IR (KBr, cm^{-1}): 3053w, 2980w, 2934w, 2903w, 1586m, 1559w, 1464w, 1438m, 1241s (P═O), 1160w, 1049s and 1035s (P–O–C), 960s, 934w, 843m, 778m, 764m, 548m. CIMS (NH$_3$) m/z (%): 364 (10, [M+NH$_4$]$^+$), 363 (46), 348 (13), 347 (21), 346 (100, M$^+$). Anal. Calcd for $C_{18}H_{19}O_3PS$ (346.39): C 62.42, H 5.53, S 9.26; found: C 62.35, H 5.38, S 9.32.

4.5. X-ray crystal-structure determination of 11a and 12

All measurements were performed on a Nonius KappaCCD area-diffractometer[20] using graphite-monochromated Mo Kα radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given below[21] and views of the molecules are shown in Figures 1 and 2. Data reduction was performed with HKL Denzo and Scalepack.[22] The intensities were corrected for Lorentz and polarization effects, and absorption corrections based on the multi-scan method[23] were applied. Equivalent reflections were merged. The structures were solved by direct methods using SIR92[24] in the case of **11a** and SHELXS97[25] in the case of **12**, which revealed the positions of all non-H-atoms. In the case of **11a**, one ethyl group is disordered over two conformations. Two sets of overlapping positions were defined for the atoms of the disordered ethyl group and the site occupation factor of the major conformation of the group refined to 0.818(6). In the case of **12**, the terminal methyl group of one ethoxy moiety is disordered over two conformations. Two positions were defined for the atoms of the disordered methyl group and the site occupation factor of the major conformation refined to 0.51(3). For both structures, similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered C-atoms, while neighboring atoms within and between each conformation of the disordered ethyl groups were restrained to have similar atomic displacement parameters. The non-H-atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom (1.5U_{eq} for the methyl groups). The refinement of the structures was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\sum w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied in the case of **12**. In **11a** and **12**, three and one reflections, respectively, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral atom scattering factors for non-H-atoms were taken from Ref. 26, and the scattering factors for H-atoms were taken from Ref. 27. Anomalous dispersion effects were included in F_c;[28] the values for f' and f'' were those of Ref. 29. The values of the mass attenuation coefficients are those of Ref. 30. All calculations were performed using the SHELXL97[31] program.

Crystal data for **11a**: $C_{31}H_{31}O_3PS_2$, M=546.68, colorless, prism, crystal dimensions 0.15×0.25×0.32 mm, triclinic, space group $P\bar{1}$, Z=2, reflections for cell determination 32 546, 2θ range for cell determination 4–50°, a=8.4060(3) Å, b=9.8163(4) Å, c=17.4649(7) Å, α=87.447(3)°, β=76.876(2)°, γ=77.811(2)°, V=1371.84(9) Å^3,

T=160 K, D_X=1.323 g cm^{-3}, μ(Mo Kα)=0.284 mm^{-1}, scan type ω, $2\theta_{(max)}$=50°, transmission factors (min; max) 0.757; 0.966, total reflections measured 17 711, symmetry independent reflections 4832, reflections with $I>2\sigma(I)$ 3935, reflections used in refinement 4829, parameters refined 356; restraints 38, $R(F)$ [$I>2\sigma(I)$ reflections]=0.0407, $wR(F^2)$ [all data]=0.1055 ($w=[\sigma^2(F_o^2)+(0.0471P)^2+0.7354P]^{-1}$, where $P=(F_o^2+2F_c^2)/3$), goodness of fit 1.064, final Δ_{max}/σ=0.002, $\Delta\rho$ (max; min)=0.34; −0.50 e Å^{-3}.

Crystal data for **12**: $C_{36}H_{38}O_6P_2S_2$, M=692.76, colorless, prism, crystal dimensions 0.10×0.22×0.22 mm, monoclinic, space group $P2_1/n$, Z=4, reflections for cell determination 63 677, 2θ range for cell determination 4–60°, a=12.1758(1) Å, b=13.0645(1) Å, c=21.1455(2) Å, β=93.5396(7)°, V=3357.21(5) Å^3, T=160 K, D_X=1.370 g cm^{-3}, μ(Mo Kα)=0.300 mm^{-1}, scan type ϕ and ω, $2\theta_{(max)}$=60°, transmission factors (min; max) 0.868; 0.973, total reflections measured 89 162, symmetry independent reflections 9809, reflections with $I>2\sigma(I)$ 7639, reflections used in refinement 9808, parameters refined 431; restraints 7, $R(F)$ [$I>2\sigma(I)$ reflections]=0.0443, $wR(F^2)$ [all data]=0.1198 ($w=[\sigma^2(F_o^2)+(0.0536P)^2+1.7904P]^{-1}$, where $P=(F_o^2+2F_c^2)/3$), goodness of fit 1.062, secondary extinction coefficient 0.0021(6), final Δ_{max}/σ=0.001, $\Delta\rho$ (max; min)=0.36; −0.53 e Å^{-3}.

Acknowledgements

This project was supported by the grant No. 505/681/2004 from the University of Łódź. We acknowledge the financial support by the Polish State Committee for Scientific Research (Grant No. 4 T09A 046 25) and F. Hoffmann-La Roche AG, Basel.

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Tetrahedron 62 (2006) 7783–7792
Tetrahedron

Diastereoselective synthesis of enantioenriched homopropargyl amino alcohols from α-dibenzylamino aldehydes and their use as chiral synthons

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Received 6 April 2006; revised 22 May 2006; accepted 24 May 2006
Available online 12 June 2006

Abstract—Homochiral α-dibenzylamino aldehydes, prepared from the corresponding α-amino acids, react with propargyl bromide and zinc in DMF/THF (1:1) or DMF/Et_2O (1:1) at 20 °C to afford, in good yields and *dr*, homopropargylic 1,2-amino alcohols. *anti* Diastereomers were always formed as major products in this reaction. These compounds are versatile intermediates for a variety of synthetic targets: γ-amino-β-hydroxy-ketones, 4-amino-1,3-diols, 1,7-diamino-2,6-diols, and ω-amino-δ-hydroxy esters.

1. Introduction

Homopropargyl alcohols are interesting intermediates in organic synthesis that are prepared by reaction of carbonyl compounds with propargyl or allenyl organometallics.[1] In some cases, mixtures of allenyl and homopropargyl alcohols are obtained depending on the nature of the carbonyl compound, propargyl halide, and the metal and solvent used in the reaction.[2]

The diastereoselective propargylation of carbonyl compounds was first described for α-alkoxy aldehydes with zinc and propargyl bromide in DMF/THF leading to the *anti* adducts as major diastereoisomers in good yield and diastereomeric excess (de).[3,4] Propargylation of some protected α-amino aldehydes has also been studied. For instance, *N*-Boc-leucinal reacts with propargyl bromide and zinc in DMF/Et_2O leading to the corresponding *anti* homopropargyl amino alcohol with very good de,[5] and diastereoselective propargylation of α-acetamido aldehyde constitutes a key step in the synthesis of Neu5Ac.[6] There are no antecedents on propargylation of α-dibenzylamino aldehydes although allenylation of 2-dibenzylamino-3-phenylpropionaldehyde leads to the *anti* homopropargyl amino alcohol in moderate de,[7] and some enantioselective propargylation of aldehydes leading to homochiral propargyl alcohols are also known.[8]

As a part of a project on the reactivity of α-dibenzylamino aldehydes with different nucleophiles,[9] we present now the results obtained on the diastereoselective propargylation of those compounds and the transformation of the resulting homopropargyl amino alcohols into useful synthetic intermediates.

2. Results and discussion

The reaction of α-dibenzylamino aldehydes with propargyl bromide and zinc dust was initially tested by taking L-alaninal derivative **1a** as a model. The reaction did not take place when diethyl ether was used as a solvent (entry 1 in Table 1), but led to a mixture of diastereomeric dibenzylamino homopropargyl alcohols *anti*-**2a** and *syn*-**2a** in good yield and de when the reaction was carried out in mixtures of Et_2O or THF and DMF as solvents (entries 2–6 in Table 1). The ratio of diastereoisomers did not appreciably change with the

Table 1. Stereoselective propargylation of α-dibenzylamino aldehydes **1a–f**

Entry	**1**[a]	Solvent	T[a] (°C)	Yield (%)[b]	*anti*/*syn*[c]
1	**1a**	Et_2O	20	—	—
2	**1a**	DMF/Et_2O (1:1)	20	**2a** (63)	80:20
3	**1a**	DMF/Et_2O (1:1)	0→20	**2a** (71)	81:19
4	**1a**	DMF/THF (1:1)	0→20	**2a** (81)	82:18
5	**1a**	DMF/Et_2O (1:5)	0	**2a** (60)	82:18
6	**1a**	DMF/Et_2O (5:1)	0	**2a** (54)	85:15
7	**1b**	DMF/Et_2O (1:1)	20	**2b** (80)	90:10
8	**1c**	DMF/Et_2O (1:1)	0→20	**2c** (70)	85:15
9	**1d**	DMF/THF (1:1)	0→20	**2d** (57)	89:11
10	**1e**	DMF/THF (1:1)	0→20	**2e** (61)	70:30
11	**1f**	DMF/Et_2O (1:1)	0→20	**2f** (61)	18:82

[a] Reactions were run with 2 equiv of propargyl bromide and 3 equiv of zinc.
[b] Numbers correspond to combined yield of pure and isolated diastereoisomers.
[c] The diastereomeric ratio was determined by integration of the signals of ^{1}H NMR spectra of the reaction mixture.

Keywords: Propargylation; Amino acids; Amino aldehydes; Asymmetric synthesis; Zinc.
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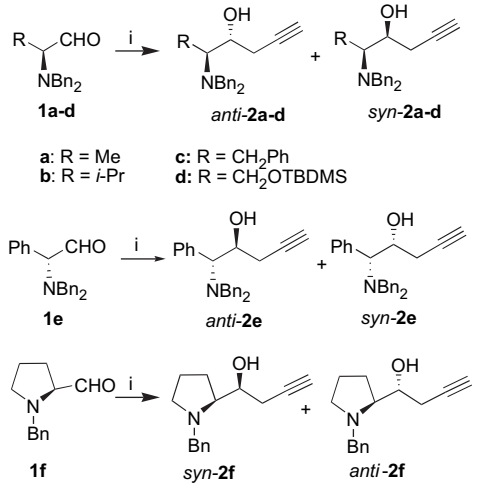
doi:10.1016/j.tet.2006.05.060

temperature of the reaction or by the ethereal solvent or by the ratio of Et_2O and DMF, but the best yield was obtained for the reaction in THF/DMF at 0–20 °C (entry 4 in Table 1). The best diastereoselection for the reaction was observed when a mixture of DMF/Et_2O 5:1 was used as solvent (entry 6 in Table 1). The reaction was extended to dibenzylamino aldehydes **1b–f** and the results are summarized in Scheme 1 and Table 1.



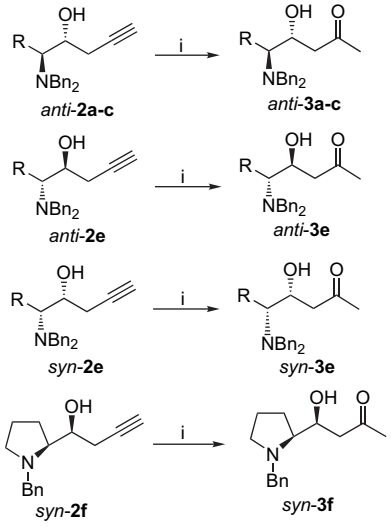
Scheme 1. Reagents and conditions: (i) 1. Zn dust, HC≡CCH_2Br, DMF/THF (1:1) or DMF/Et_2O (1:1), rt. 2. NH_4Cl.

The stereoselection was improved when increasing the size of the chain in the starting amino aldehyde, raising to ca. 9:1 for L-dibenzylamino valinal **1b** and L-dibenzylamino serinal derivative **1d**. On the contrary, the presence of a phenyl group in **1e** decreased the ratio of diastereoisomers to 7:3 (entry 10 in Table 1). This fact has been previously observed for nucleophilic additions to phenylglycinal derivatives.[9b–d]

Interestingly, the reaction of L-*N*-benzyl prolinal **1f** with propargyl bromide and zinc dust in DMF/Et_2O at room temperature leads to a mixture of *anti*- and *syn*-**2f** in moderate yield and good de, but in this case the *syn* adduct was formed as major diastereoisomer. This behavior, which can be explained through a Cram-chelated model, had been previously observed for additions to prolinal derivatives.[9c,10]

All the diastereoisomers, except *anti*- and *syn*-**2d**, were purified by flash chromatography and their stereochemistry was determined on the basis of ^1H NMR spectral data[9c,10,11] and confirmed for *anti*-**2b** by transformation into (3*S*,4*R*)-3-dibenzylamino-2-methyl-4-heptanol by reduction on Pearlman's catalyst and dibenzylation with benzyl bromide and K_2CO_3 in acetonitrile. This amino alcohol was also obtained by reaction of **1b** with propylmagnesium bromide as previously described.[12]

γ-Amino-β-hydroxy carbonyl compounds are important parts of biologically interesting molecules,[13] and their synthesis has attracted much attention.[14] In this way, we consider the transformation of dibenzylamino homopropargyl alcohols **2** into γ-amino-β-hydroxy ketones **3** as an alternative to the aldol type reaction of α-amino aldehydes with acetone.[15] The versatility of our method allowed the synthesis of either *anti*- or *syn* diastereoisomers depending on the stereochemistry of the starting compound, avoiding the stereochemical problem associated with the aldol reaction. To this end, *anti*-**2a–e** and *syn*-**2e**,**f** were subjected to hydration by reaction with 10% solution of H_2SO_4 and a catalytic amount of $HgSO_4$ at room temperature.[16] Ketones *anti*-**3a–e** and *syn*-**3e**,**f** were isolated in moderate to good yield as single diastereoisomers (Scheme 2 and Table 2), as shown by the identity of their physical and spectral data with those previously described for *anti*-**3a** and **3b**.[15]



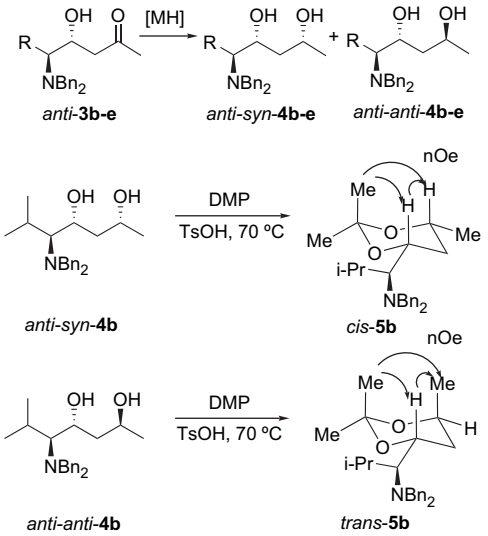
Scheme 2. Reagents and conditions: (i) H_2SO_4, $HgSO_4$, MeOH, rt.

Table 2. Hydration of the triple bond of compounds *syn*- and *anti*-**2**

Entry	**2**	R	*t* (h)	Aldol	Yield (%)[a]
1	*anti*-**2a**	Me	7	*anti*-**3a**	75
2	*anti*-**2b**	^{i}Pr	5	*anti*-**3b**	65
3	*anti*-**2c**	$PhCH_2$	6	*anti*-**3c**	75
4	*syn*-**2e**	Ph	3	*syn*-**3e**	51
5	*anti*-**2e**	Ph	5	*anti*-**3e**	56
6	*syn*-**2f**	—	5	*syn*-**3f**	51

[a] Numbers correspond to yield of pure and isolated products.

Compounds **3b–e** were transformed into 4-amino-1,3-diols **4b–e** in moderate to good yields and excellent de by reduction with different complex metal hydrides (Scheme 3 and



Scheme 3.

Table 3. Stereoselective reduction of β-hydroxy ketones *anti*-**3**

Entry	**3**	Hydride	Solvent	T[a] (°C)	Yield[a] (%)	*syn*/*anti*[b]
1	*anti*-**3b**	$NaBH_4$	MeOH	−20	62	80:20
2	*anti*-**3b**	$Et_3B/NaBH_4$	THF/MeOH (4:1)	−78	52	>95:5
3	*anti*-**3b**	$NaBH(OAc)_3$	CH_3CN/HOAc	−40	66	23:77
4	*anti*-**3c**	$Et_3B/NaBH_4$	THF/MeOH (4:1)	−78	50	>95:5
5	*anti*-**3c**	$NaBH(OAc)_3$	CH_3CN/HOAc	−40	40	34:66
6	*anti*-**3e**	$Et_3B/NaBH_4$	THF/MeOH (4:1)	−78	68	>95:5
7	*anti*-**3e**	$NaBH(OAc)_3$	CH_3CN/HOAc	−40	88	37:63

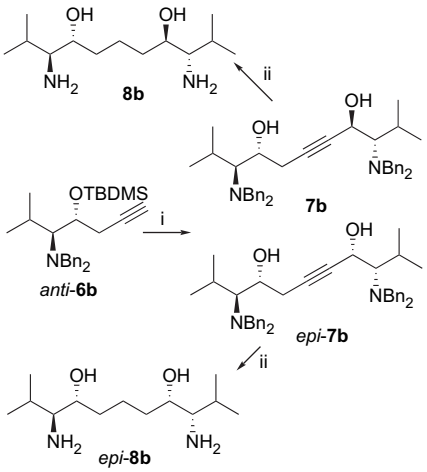
[a] Numbers correspond to combined yield of pure and isolated diastereoisomers.
[b] The diastereomeric ratio was determined by integration of the signals of ^1H NMR spectra of the reaction mixture.

Table 3). The selection of the reducing agent allowed the preparation of either diastereoisomers of **4b–e**.

The reduction of *anti*-**3b** with $NaBH_4$ in methanol yielded a mixture of *anti-syn*-**4b** and *anti-anti*-**4b** in a ratio 4:1 but the reduction in the presence of Et_2BOMe, generated in situ from Et_3B and MeOH,[17] leads to *anti-syn*-**4b** as a single diastereoisomer. Alternatively, the reaction of *anti*-**3b** with Evans's reagent ($NaBH(OAc)_3$)[18] in a mixture of acetonitrile/acetic acid as solvent at −40 °C gave *anti-anti*-**4b** as major diastereoisomer although in moderate de (entry 3 in Table 3). The reduction of *anti*-**3c–e** follows the same pattern as described for *anti*-**3b**. The reduction with $NaBH_4$/Et_2BOMe yielded *anti-syn*-**4c–e** as a single diastereoisomer, whereas the reaction with $NaBH(OAc)_3$ leads to *anti-anti*-**4c–e** as major isomers in moderate de.

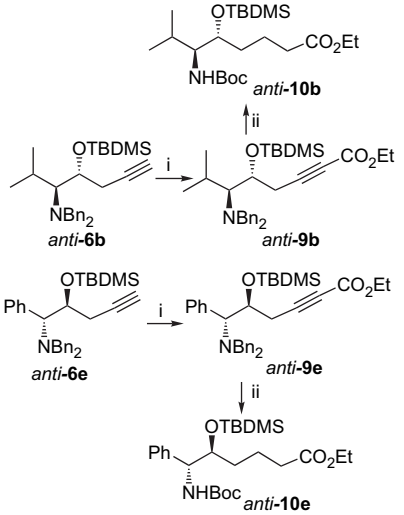
The stereochemistry of the amino diols *anti-syn*-**4b** and *anti-anti*-**4b** was established by transformation into 1,3-dioxane derivatives *cis*-**5b** and *trans*-**5b**, respectively, by reaction with 2,2-dimethoxypropane and *p*-toluenesulfonic acid as catalyst (Scheme 3). The NOESY experiment of *cis*-**5b** shows cross peak for the signal of the axial methyl group at C-2 and the hydrogen atoms at C-4 and C-6, demonstrating the *cis*-relationship of the substituents at C-4 and C-6. For *trans*-**5b** the cross peaks appeared for the signals of the methyl groups at C-2 and C-4 and the hydrogen atom at C-6 in the dioxane ring, pointing a *trans*-disposition of the methyl at C-4 and the substituent at C-6. The stereochemistry was generalized for amino diols **4c–e**.

The interest in homopropargyl amino alcohols **2** as synthetic intermediates was extended to the preparation of ω-amino-δ-hydroxy acids and C_2-symmetrical 1,7-diamino-2,6-diols previously used as chiral ligands[19] and in the synthesis of pharmacological active compounds.[20] Homopropargyl amino alcohol *anti*-**2b** was transformed into *anti*-**6b** by treatment with TBDMSCl and imidazole in DMF. Lithium acetylide, prepared by deprotonation of *anti*-**6b** with *n*-BuLi in THF at −78 °C, was reacted with L-dibenzylamino valinal **1b** and after desilylation with TBAF yielded a mixture (4:1) of diastereomeric bis-amino alcohols **7b** and *epi*-**7b** in 66% yield (Scheme 4). After separation, the major diastereoisomer **7b** was transformed into the homochiral C_2-symmetrical 1,7-diamino-2,6-diol derivative **8b** by hydrogenation/hydrogenolysis on Pearlman's catalyst. The same treatment on *epi*-**7b** leads to *epi*-**8b** also in excellent yield.



Scheme 4. Reagents and conditions: (i) 1. *n*-BuLi (1.1 equiv), THF, −78 °C, 1 h. 2. **1b** (1.1 equiv), THF, −78 °C, 1 h. 3. TBAF (1.2 equiv), THF, 0 °C, 5 h. 4. NH_4Cl. (ii) H_2, $Pd(OH)_2/C$, MeOH.

Finally, both *anti*-**6b** and *anti*-**6e** were transformed into the ω-amino-δ-hydroxy ethyl esters *anti*-**10b** and *anti*-**10e**, respectively, in two steps as summarized in Scheme 5. Deprotonation with *n*-BuLi in THF at −78 °C of *anti*-**6b** and **6e**, followed by reaction with ethyl chloroformate in THF at −40 °C lead to esters *anti*-**9b** and *anti*-**9e** in good yields. These esters cannot be purified because extensive decomposition was observed when subjected to flash chromatography, but they were transformed in moderate yields into the saturated amino hydroxyl ester derivatives *anti*-**10b** and *anti*-**10e** by hydrogenation on Pearlman's catalyst in the presence of Boc_2O using EtOAc as solvent.



Scheme 5. Reagents and conditions: (i) 1. *n*-BuLi (1.5 equiv), THF, −78 °C, 1 h. 2. $ClCO_2Et$ (2 equiv), THF, −78 °C to −40 °C, 0.5 h. 3. NH_4Cl. (ii) H_2, $Pd(OH)_2/C$, Boc_2O, EtOAc.

In summary, reaction of chiral α-dibenzylamino aldehydes with propargyl bromide and zinc yielded *anti* amino alcohols as major diastereoisomer. As an alternative to the aldol reaction, these compounds were transformed in good yields to γ-amino-β-hydroxy ketones, by hydration of the triple bond. In a different way, lithium derivatives of these homopropargyl amino alcohols reacted with ethyl chloroformate to

yield enantioenriched ω-amino-δ-hydroxy esters or with chiral α-dibenzylamino aldehydes leading to propargyl diamino diols, which were further elaborated to the corresponding saturated homochiral C_2 diamino diols.

3. Experimental

3.1. General

The reactions were carried out in oven-dried glassware under argon atmosphere and using anhydrous solvents. Starting *N*,*N*-dibenzyl α-amino aldehydes **1a–e** were prepared as previously described.[9a] Propargyl bromide, as 80 wt % solution in toluene, is commercially available. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were registered using TMS as an internal standard. IR spectra were recorded as film or KBr dispersion. Optical rotations were measured in a 1 dm cell. Microanalyses were performed by the Departamento de Química Inorgánica.

3.2. General procedure for propargylation of α-amino aldehydes

The amino aldehyde (2 mmol) and propargyl bromide (80 wt % in toluene, 0.44 mL, 4 mmol) were dissolved in a mixed solvent (DMF/ether or DMF/THF, 1:1, 8 mL). To this well-stirred solution was added activated zinc dust (washed with 2% HCl, water, methanol, and dried in vacuum; 392 mg, 6 mmol) slowly at 0 °C. After 5 min, the exothermic reaction brought itself to reflux. The whole reaction mixture was stirred at room temperature until the reaction was finished (TLC) and then quenched with aqueous saturated solution of ammonium chloride (20 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were eliminated under vacuum and the residue was purified by flash chromatography (silica gel, hexane/ethyl acetate 15:1 to 50:1).

3.2.1. (2*S*,3*R*)-2-Dibenzylaminohex-5-yn-3-ol (*anti*-2a). This compound was obtained as the major diastereomer in the propargylation of amino aldehyde **1a** (760 mg, 3 mmol) and purified by flash chromatography (silica gel, hexane/EtOAc 15:1): 586 mg (2.0 mmol, 67%). Colorless oil. $[\alpha]_D^{23}$ +37.8 (*c* 1.0, $CHCl_3$). IR (film): 3435, 3300, 2117, 1028, 748, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.20 (d, 3H, *J*=6.6 Hz, C*H*$_3$); 1.96 (t, 1H, *J*=2.6 Hz, ≡C–*H*); 2.12 (br s, 1H, O*H*); 2.27 (ddd, *J*=16.7, 8.0, 2.6 Hz, C*H*HCHOH); 2.72 (dq, 1H, *J*=8.2, 6.6 Hz, C*H*N); 2.82 (ddd, *J*=16.7, 3.6, 2.7 Hz, CH*H*CHOH); 3.44 (d, 2H, *J*=13.7 Hz, C*H*HPh); 3.76 (d, 2H, *J*=13.7 Hz, CH*H*Ph); 7.20–7.45 (m, 10H, *H*ar). ^{13}C NMR ($CDCl_3$): 8.3 (*C*H$_3$); 25.1 (*C*H$_2$C≡C); 54.3 (*C*H$_2$Ph); 56.7 (*C*HN); 70.7 (C≡*C*H); 71.8 (*C*HOH); 81.5 (CH≡*C*); 126.9, 128.2, 128.7 (*C*Har); 139.6 (*C*ar). $C_{20}H_{23}NO$ (293.4): calcd C 81.87, H 7.90, N 4.77; found C 81.64, H 7.75, N 4.65.

3.2.2. (4*R*,5*S*)-5-Dibenzylamino-6-methylhept-1-yn-4-ol (*anti*-2b). This compound was obtained as the major diastereoisomer in the propargylation of amino aldehyde **1b** (844 mg, 3 mmol) and purified by flash chromatography (silica gel, hexane/EtOAc 30:1): 694 mg (2.16 mmol, 72%). Colorless oil. $[\alpha]_D^{23}$ −5.5 (*c* 1.0, $CHCl_3$). IR (film): 3568, 3457, 3303, 2116, 1064, 748, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.03 (d, 1H, *J*=6.7 Hz, C*H*$_3$); 1.13 (d, 1H, *J*=6.9 Hz, C*H*$_3$); 1.98 (m, 1H, ≡C*H*); 2.24 (m, 1H, C*H*(CH$_3$)$_2$); 2.30 (m, 1H, C*H*HCHOH); 2.43 (m, 2H, C*H*N and O*H*); 2.62 (ddd, 1H, *J*=16.6, 3.5, 2.5 Hz, CH*H*CHOH); 3.64 (d, 2H, *J*=13.5 Hz, C*H*HPh); 3.96 (d, 2H, *J*=13.5 Hz, CH*H*Ph); 7.15–7.40 (m, 10H, *H*ar). ^{13}C NMR ($CDCl_3$): 20.0 (*C*H$_3$); 23.4 (*C*H$_3$); 25.5 (*C*H$_2$–C≡C); 26.3 (*C*H(CH$_3$)$_2$); 55.2 (*C*H$_2$Ph); 65.4 (*C*HN); 68.7 (*C*HOH); 70.4 (≡*C*H); 81.9 (*C*≡CH); 127.0, 128.3, 129.0 (*C*Har); 139.5 (*C*ar). $C_{22}H_{27}NO$ (321.5): calcd C 82.20, H 8.47, N 4.36; found C 82.34, H 8.30, N 4.49.

3.2.3. (2*S*,3*R*)-2-Dibenzylamino-1-phenylhex-5-yn-3-ol (*anti*-2c). This compound was obtained as the major diastereomer in the propargylation of amino aldehyde **1c** (659 mg, 2 mmol) and purified by flash chromatography (silica gel, hexane/EtOAc 15:1): 440 mg (1.19 mmol, 60%). Colorless oil. $[\alpha]_D^{23}$ +14.3 (*c* 1.1, $CHCl_3$). IR (film): 3450, 3297, 3300, 2117, 1072, 744, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.95 (t, 1H, *J*=2.6 Hz, ≡C*H*); 2.05 (br s, 1H, O*H*); 2.24 (ddd, 1H, *J*=16.7, 8.4, 2.6 Hz, C*H*HC≡CH); 2.60 (ddd, 1H, *J*=16.7, 4.2, 2.7 Hz, CH*H*C≡CH); 3.61 (d, 2H, *J*=13.8 Hz, NC*H*HPh); 3.02 (m, 3H, C*H*$_2$C*H*N); 3.73 (d, 2H, *J*=13.8 Hz, NCH*H*Ph); 3.99 (m, 1H, C*H*OH); 7.15–7.35 (m, 15H, *H*ar). ^{13}C NMR ($CDCl_3$): 25.7 (*C*H$_2$C≡C); 32.0 (*C*H$_2$Ph); 54.6 (N*C*H$_2$Ph); 62.7 (*C*HN); 70.5 (*C*HOH); 70.8 (C≡*C*H); 81.2 (*C*≡CH); 125.8, 126.9, 128.2, 128.3, 128.7, 129.4 (*C*Har); 139.5, 140.8 (*C*ar). $C_{26}H_{27}NO$ (369.5): calcd C 84.51, H 7.37, N 3.79; found C 84.28, H 7.07, N 3.94.

3.2.4. (2*S*,3*S*)-2-Dibenzylamino-1-phenylhex-5-yn-3-ol (*syn*-2c). This compound was obtained as the minor diastereomer in the propargylation of amino aldehyde **1c** (659 mg, 2 mmol) and purified by flash chromatography (silica gel, hexane/EtOAc 15:1): 74 mg (0.2 mmol, 10%). Colorless oil. $[\alpha]_D^{23}$ +23.0 (*c* 0.54, $CHCl_3$). IR (film): 3300, 2118, 1072, 744, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.81 (t, 1H, *J*=2.6 Hz, ≡C*H*); 2.15 (ddd, 1H, *J*=17.0, 6.3, 2.6 Hz, C*H*HC≡CH); 2.25 (ddd, 1H, *J*=17.0, 3.6, 2.6 Hz, CH*H*C≡CH); 2.76 (dd, 1H, *J*=13.0, 6.0 Hz, PhC*H*H); 3.09 (m, 2H, C*H*N and CH*H*Ph); 3.39 (d, 2H, *J*=13.2 Hz, NC*H*HPh); 3.94 (d, 2H, *J*=13.2 Hz, NCH*H*Ph); 3.69 (m, 1H, C*H*OH); 4.31 (br s, 1H, O*H*); 7.10–7.40 (m, 15H, *H*ar). ^{13}C NMR ($CDCl_3$): 24.6 (*C*H$_2$C≡C); 32.0 (*C*H$_2$Ph); 54.1 (N*C*H$_2$Ph); 62.5 (*C*HN); 68.9 (*C*HOH); 70.1 (C≡*C*H); 80.9 (*C*≡CH); 126.4, 127.2, 128.4, 128.6, 129.1, 129.2 (*C*Har); 138.7, 139.8 (*C*ar). $C_{26}H_{27}NO$ (369.5): calcd C 84.51, H 7.37, N 3.79; found C 84.36, H 7.22, N 3.59.

3.2.5. (2*S*,3*R*)-2-Dibenzylamino-1-(*tert*-butyldimethylsilyloxy)hex-5-yn-3-ol (*anti*-2d). This compound was obtained as the major product together with the diastereomer *syn*-**2b** in the propargylation of amino aldehyde **1d** (1.53 g, 4 mmol) and purified by flash chromatography (silica gel, hexane/EtOAc 50:1): 970 mg (2.3 mmol, 57% combined yield, de=78%). Colorless oil. $[\alpha]_D^{23}$ +39.5 (*c* 1.1, $CHCl_3$). IR (film): 3307, 1602, 1493, 1089, 777, 746, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.94 (t, 1H, *J*=2.6 Hz,

*H*C≡); 2.29 (ddd, 1H, *J*=16.7, 7.7, 2.6 Hz, C*H*HCHOH); 2.77 (m, 2H, C*H*N, CH*H*CHOH); 3.63 (d, 1H, *J*=13.7 Hz, CH*H*Ph); 3.90 (d, 1H, *J*=13.7 Hz, C*H*HPh); 4.07 (m, 3H, C*H*OH, CH_2OTBDMS); 7.20–7.40 (m, 10H, *H*ar). ^{13}C NMR ($CDCl_3$): 18.0 ($C(CH_3)_3$); 25.2 ($CH_2C{\equiv}C$); 25.8 ($C(CH_3)_3$); 55.1 (CH_2Ph); 60.5 (CH_2O); 60.8 (*C*HN); 70.1 (*C*HOH); 126.9 (*C*≡C); 128.2, 128.4, 128.8 (*C*Har); 139.6 (*C*ar).

3.2.6. (1*R*,2*S*)-1-Dibenzylamino-1-phenylpent-4-yn-2-ol (*anti*-2e). This compound was obtained as the major diastereomer in the propargylation of amino aldehyde **1e** (1.58 g, 5 mmol) and purified by flash chromatography (silica gel, hexane/EtOAc 15:1): 759 mg (2.14 mmol, 43%). Colorless oil. $[\alpha]_D^{23}$ −110.0 (*c* 0.9, $CHCl_3$). IR (film): 3550, 3447, 3300, 2118, 1028, 748, 703 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.99 (t, 1H, *J*=2.6 Hz, ≡C*H*); 2.43 (ddd, 1H, *J*=16.9, 7.9, 2.6 Hz, C*H*HCHOH); 3.02 (m, 1H, CH*H*CHOH); 3.07 (d, 2H, *J*=13.7 Hz, C*H*HPh); 3.67 (d, 1H, *J*=9.2 Hz, C*H*N); 3.83 (d, 2H, *J*=13.7 Hz, CH*H*Ph); 4.45 (m, 1H, C*H*OH); 7.20–7.55 (m, 15H, *H*ar). ^{13}C NMR ($CDCl_3$): 24.8 (CH_2); 54.6 (CH_2Ph); 66.7 (*C*HN); 69.1 (*C*HOH); 70.8 (C≡*C*H); 81.4 (*C*≡CH); 127.1, 127.8, 128.3, 128.4, 128.8, 129.9 (*C*Har); 134.4, 139.1 (*C*ar). $C_{25}H_{25}NO$ (355.5): calcd C 84.47, H 7.09, N 3.94; found C 84.23, H 6.95, N 4.10.

3.2.7. (1*R*,2*R*)-1-Dibenzylamino-1-phenylpent-4-yn-2-ol (*syn*-2e). This compound was obtained as the minor diastereomer in the propargylation of amino aldehyde **1e** (1.58 g, 5 mmol) and purified by flash chromatography (silica gel, hexane/EtOAc 15:1): 325 mg (0.91 mmol, 18%). Colorless oil. $[\alpha]_D^{23}$ −74.9 (*c* 1.1, $CHCl_3$). IR (film): 3405, 3305, 1074, 753, 702 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.81 (t, 1H, *J*=2.6 Hz, ≡C*H*); 1.92 (ddd, 1H, *J*=17.0, 6.5, 2.6 Hz, C*H*HCHOH); 2.28 (ddd, 1H, *J*=17.0, 3.2, 2.6 Hz, CH*H*CHOH); 3.05 (d, 2H, *J*=13.2 Hz, CH*H*Ph); 3.72 (d, 1H, *J*=10.3 Hz, C*H*N); 3.95 (d, 2H, *J*=13.2 Hz, C*H*HPh); 4.36 (ddd, 1H, *J*=10.3, 6.5, 3.2 Hz, C*H*OH); 4.62 (br s, 1H, O*H*); 7.20–7.50 (m, 15H, *H*ar). ^{13}C NMR ($CDCl_3$): 23.8 (CH_2); 53.6 (CH_2Ph); 66.1 (*C*HN); 66.5 (*C*HOH); 69.9 (≡*C*H); 80.4 (C≡*C*H); 127.3, 128.2, 128.5, 128.6, 129.0, 129.8 (*C*Har); 133.1, 138.3 (*C*ar). $C_{25}H_{25}NO$ (355.5): calcd C 84.47, H 7.09, N 3.94; found C 84.27, H 6.92, N 3.99.

3.2.8. (*R*)-1-[(*S*)-1-Benzyl-2-pyrrolidinyl]but-3-yn-1-ol (*anti*-2f). This compound was obtained as the minor diastereomer in the propargylation of amino aldehyde **1f** (568 mg, 3 mmol) and purified by flash chromatography (silica gel, hexane/EtOAc 2:1): 62 mg (0.27 mmol, 9%). Colorless oil. $[\alpha]_D^{23}$ +20.5 (*c* 0.3, MeOH). IR (film): 3198, 1617, 1388, 1053, 733, 706 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.73 (m, 4H, CH_2); 2.03 (t, 1H, *J*=5.4 Hz, C≡C*H*); 2.15 (s, 1H, C*H*HCN); 2.28 (m, 1H, C*H*HC≡C); 2.57 (ddd, 1H, *J*=9.6, 7.0, 2.7 Hz, CH*H*C≡C); 2.80 (td, 1H, *J*=7.7, 2.7 Hz, C*H*N); 2.97 (m, 1H, CH*H*CN); 3.32 (d, 1H, *J*=13.0 Hz, C*H*HPh); 3.98 (dt, 1H, *J*=7.2, 2.7 Hz, C*H*OH); 4.06 (d, 1H, *J*=13.0 Hz, CH*H*Ph); 7.20–7.45 (m, 5H, *H*ar). ^{13}C NMR ($CDCl_3$): 22.9, 23.0 (CH_2); 23.1 ($CH_2C{\equiv}CH$); 54.4 (CH_2Ph); 58.1 (CH_2N); 66.2 (*C*HN); 67.2 (*C*HOH); 69.8 (C≡*C*H); 80.8 (*C*≡CH); 127.0, 128.3, 128.7 (*C*Har); 139.0 (*C*ar). $C_{15}H_{19}NO$ (229.3): calcd C 78.56, H 8.35, N 6.11; found C 78.71, H 8.42, N 6.04.

3.2.9. (*S*)-1-[(*S*)-1-Benzyl-2-pyrrolidinyl]but-3-yn-1-ol (*syn*-2f). This compound was obtained as the major diastereomer in the propargylation of amino aldehyde **1f** (568 mg, 3 mmol) and purified by flash chromatography (silica gel, hexane/EtOAc 2:1): 282 mg (1.23 mmol, 41%). Colorless oil. $[\alpha]_D^{23}$ −24.7 (*c* 1.0, MeOH). IR (film): 3410, 3293, 2117, 1072, 744, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.70 (m, 3H, CH_2 and C*H*HCN); 1.97 (m, 1H, CH*H*CHN); 2.03 (t, 1H, *J*=2.6 Hz, C≡C*H*); 2.38 (m, 1H, C*H*HN); 2.43 (m, 2H, C*H*HC≡CH); 2.91 (m, 1H, CH*H*N); 3.05 (ddd, 1H, *J*=8.9, 5.2, 3.3 Hz, C*H*N); 3.48 (q, 1H, *J*=6.3, 5.2 Hz, C*H*OH); 3.58 (d, 1H, *J*=13.3 Hz, C*H*HPh); 4.02 (d, 1H, *J*=13.3 Hz, CH*H*Ph); 7.20–7.30 (m, 5H, *H*ar). ^{13}C NMR ($CDCl_3$): 24.5, 24.7 (CH_2); 29.1 ($CH_2C{\equiv}C$); 54.3 (CH_2Ph); 61.6 (CH_2N); 66.3 (*C*HN); 70.1 (C≡*C*H); 72.0 (*C*HOH); 81.2 (*C*≡CH); 127.0, 128.1, 128.3, 128.4 (*C*Har); 139.4 (*C*ar). $C_{15}H_{19}NO$ (229.3): calcd C 78.56, H 8.35, N 6.11; found C 78.75, H 8.29, N 6.04.

3.2.10. (4*R*,5*S*)-5-Dibenzylamino-4-hydroxyhexan-2-one (*anti*-3a). To a solution of amino alcohol *anti*-**2a** (293 mg, 1.0 mmol) and $HgSO_4$ (75 mg, 0.25 mmol) in MeOH (4 mL) at 0 °C was added 10% H_2SO_4 (1.0 mL), and the resultant reaction mixture was stirred at room temperature for 2–5 h (TLC). The pH of the reaction was adjusted to 7 with saturated $NaHCO_3$ and the mixture extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, concentrated, and chromatographed (silica gel, hexane/EtOAc 6:1): 232 mg of *anti*-**3a** (0.75 mmol, 75%). Colorless oil. $[\alpha]_D^{23}$ +43.5 (*c* 1, $CHCl_3$). Lit.[15] $[\alpha]_D^{23}$ +45.2 (*c* 1.1, $CHCl_3$). IR (film): 3452, 1704, 1061, 748, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.16 (d, 3H, *J*=6.6 Hz, CH_3CH); 2.08 (s, 3H, CH_3CO); 2.37 (dd, 1H, *J*=18.1, 8.9 Hz, C*H*HCO); 2.64 (dq, 1H, *J*=8.6, 6.6 Hz, C*H*N); 3.03 (dd, 1H, *J*=18.1, 2.3 Hz, CH*H*CO); 3.06 (br s, 1H, O*H*); 3.39 (d, 2H, *J*=13.6 Hz, CH*H*Ph); 3.72 (d, 2H, *J*=13.6 Hz, C*H*HPh); 3.98 (m, 1H, C*H*OH); 7.20–7.40 (m, 10H, *H*ar). ^{13}C NMR ($CDCl_3$): 8.2 (CH_3CH); 30.6 (CH_3CO); 47.5 (CH_2CO); 54.2 (CH_2Ph); 56.4 (*C*HN); 69.6 (*C*HOH); 126.8, 128.2, 128.7 (*C*Har); 139.7 (*C*ar); 210.7 (*C*O).

3.2.11. (4*R*,5*S*)-5-Dibenzylamino-4-hydroxy-6-methylheptan-2-one (*anti*-3b). This compound was obtained from *anti*-**2b** (450 mg, 1.4 mmol), by the method described for *anti*-**3a** and purified by flash chromatography (silica gel, hexane/EtOAc 8:1): 309 mg (0.91 mmol, 65%). Colorless oil. $[\alpha]_D^{23}$ +10.6 (*c* 1.1, $CHCl_3$). Lit.[15] $[\alpha]_D^{23}$ +10.3 (*c* 1.0, $CHCl_3$). IR (film): 3470, 1705, 1069, 749, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.08 (d, 3H, *J*=6.7 Hz, CH_3); 1.18 (d, 3H, *J*=6.8 Hz, CH_3); 2.17 (s, 3H, CH_3CO); 2.22 (m, 1H, $CH(CH_3)_2$); 2.45 (t, 1H, *J*=6.3 Hz, C*H*N); 2.56 (dd, 1H, *J*=17.0, 10.0 Hz, C*H*HCO); 2.76 (dd, 1H, *J*=17.0, 2.0 Hz, CH*H*CO); 3.20 (br s, 1H, O*H*); 3.70 (d, 2H, *J*=13.6 Hz, CH*H*Ph); 3.76 (d, 2H, *J*=13.6 Hz, C*H*HPh); 4.34 (m, 1H, C*H*OH); 7.20–7.40 (m, 10H, *H*ar). ^{13}C NMR ($CDCl_3$): 20.0 (CH_3); 23.3 (CH_3); 26.4 ($CH(CH_3)_2$); 30.8 (CH_3CO); 48.2 (CH_2CO); 55.1 (CH_2Ph); 65.3 (*C*HN); 66.3 (*C*HOH); 127.0, 128.3, 129.3 (*C*Har); 139.6 (*C*ar); 209.9 (*C*O).

3.2.12. (4*R*,5*S*)-5-Dibenzylamino-4-hydroxy-6-phenylhexan-2-one (*anti*-3c). This compound was obtained from *anti*-**2c** (259 mg, 0.7 mmol) by the method described for

anti-**3a** and purified by flash chromatography (silica gel, hexane/EtOAc 8:1): 203 mg (0.52 mmol, 75%). Colorless oil. $[\alpha]_D^{23}$ +17.2 (*c* 1.1, $CHCl_3$). IR (film): 3482, 1706, 1365, 1073, 736, 702 cm^{-1}. ^1H NMR ($CDCl_3$): 2.06 (s, 3H, C*H*$_3$); 2.41 (dd, 1H, *J*=17.8, 9.5 Hz, C*H*HCO); 2.77 (dd, 1H, *J*=17.8, 2.3 Hz, CH*H*CO); 2.92 (m, 1H, C*H*N); 3.00 (m, 1H, C*H*HPh); 3.08 (dd, 1H, *J*=14.0, 7.6 Hz, CH*H*Ph); 3.61 (d, 2H, *J*=13.8 Hz, CH*H*Ph); 3.72 (d, 2H, *J*=13.8 Hz, C*H*HPh); 4.27 (m, 1H, C*H*OH); 7.15–7.35 (m, 15H, *H*ar). ^{13}C NMR ($CDCl_3$): 30.6 (*C*H$_3$); 32.1 (*C*H$_2$Ph); 48.0 (*C*H$_2$CO); 54.5 (N*C*H$_2$Ph); 62.7 (*C*HN); 68.1 (*C*HOH); 125.8, 126.8, 128.1, 128.2, 128.7, 129.4 (*C*Har); 139.6, 141.1 (*C*ar); 210.2 (*C*O). $C_{26}H_{29}NO_2$ (387.5): calcd C 80.59, H 7.54, N 3.61; found C 80.74, H 7.74, N 3.42.

3.2.13. (4*S*,5*R*)-5-Dibenzylamino-4-hydroxy-5-phenylpentan-2-one (*anti*-3e). This compound was obtained from *anti*-**2e** (427 mg, 1.2 mmol) by the method described for *anti*-**3a** and purified by flash chromatography (silica gel, hexane/EtOAc 8:1): 250 mg (0.67 mmol, 56%). Colorless solid, mp 112–113 °C. $[\alpha]_D^{23}$ −119.8 (*c* 1, $CHCl_3$). IR (KBr): 3581, 1716, 748, 701 cm^{-1}. ^1H NMR ($CDCl_3$): 2.20 (s, 3H, C*H*$_3$); 2.45 (br s, 1H, O*H*); 2.54 (dd, 1H, *J*=17.7, 9.2 Hz, C*H*HCO); 3.07 (d, 2H, *J*=13.7 Hz, CH*H*Ph); 3.29 (dd, 1H, *J*=17.7, 2.3 Hz, CH*H*CO); 3.62 (d, 1H, *J*=9.5 Hz, C*H*N); 3.83 (d, 2H, *J*=13.7 Hz, C*H*HPh); 4.78 (m, 1H, C*H*OH); 7.20–7.50 (m, 15H, *H*ar). ^{13}C NMR ($CDCl_3$): 30.9 (*C*H$_3$); 47.8 (*C*H$_2$CO); 54.4 (*C*H$_2$Ph); 66.3 (*C*HN); 66.9 (*C*HOH); 127.0, 127.6, 128.2, 128.3, 128.8, 129.9 (*C*Har); 134.5, 139.3 (*C*ar); 209.7 (*C*O). $C_{25}H_{27}NO_2$ (373.5): calcd C 80.40, H 7.29, N 3.75; found C 80.50, H 7.45, N 3.60.

3.2.14. (4*R*,5*R*)-5-Dibenzylamino-4-hydroxy-5-phenylpentan-2-one (*syn*-3e). This compound was obtained from *syn*-**2e** (355 mg, 1.0 mmol) by the method described for *anti*-**3a** and purified by flash chromatography (silica gel, hexane/EtOAc 6:1): 190 mg (0.51 mmol, 51%). Colorless solid, mp 100–101 °C (from hexane). $[\alpha]_D^{23}$ −132.4 (*c* 1, $CHCl_3$). IR (KBr): 3388, 1710, 1076, 757, 701 cm^{-1}. ^1H NMR ($CDCl_3$): 2.04 (s, 3H, C*H*$_3$); 2.10 (dd, 1H, *J*=16.0, 2.2 Hz, C*H*HCO); 2.30 (dd, 1H, *J*=16.0, 9.1 Hz, CH*H*CO); 3.02 (d, 2H, *J*=13.3 Hz, CH*H*Ph); 3.50 (d, 1H, *J*=10.4 Hz, C*H*N); 3.98 (d, 2H, *J*=13.3 Hz, C*H*HPh); 4.40 (br s, 1H, O*H*); 4.74 (m, 1H, C*H*OH); 7.15–7.50 (m, 15H, *H*ar). ^{13}C NMR ($CDCl_3$): 30.8 (*C*H$_3$); 47.9 (*C*H$_2$CO); 53.4 (*C*H$_2$Ph); 64.5 (*C*HN); 66.9 (*C*HOH); 127.2, 128.1, 128.5, 128.9, 129.7 (*C*Har); 133.1, 138.3 (*C*ar); 207.2 (*C*O). $C_{25}H_{27}NO_2$ (373.5): calcd C 80.40, H 7.29, N 3.75; found C 80.03, H 7.13, N 3.75.

3.2.15. (*S*)-4-[(*S*)-1-Benzyl-2-pyrrolidinyl]-4-hydroxybutan-2-one (*syn*-3f). This compound was obtained from *syn*-**2f** (92 mg, 0.4 mmol) by the method described for *anti*-**3a** and purified by flash chromatography (silica gel, hexane/EtOAc 3:2): 52 mg (0.21 mmol, 52%). Colorless oil. $[\alpha]_D^{23}$ −53.1 (*c* 0.52, $CHCl_3$). IR (film): 3438, 1711, 1357, 1073, 746, 701 cm^{-1}. ^1H NMR ($CDCl_3$): 1.69 (m, 3H, C*H*$_2$ and C*H*HCHN); 1.93 (m, 1H, CH*H*CHN); 2.21 (s, 3H, C*H*$_3$CO); 2.39 (m, 1H, C*H*HN); 2.53 (dd, 1H, *J*=16.2, 9.1 Hz, CH*H*CO); 2.64 (dd, 1H, *J*=16.2, 3.4 Hz, C*H*HCO); 2.82 (m, 1H, C*H*N); 2.93 (m, 1H, CH*H*N); 3.54 (d, 1H, *J*=13.2 Hz, C*H*HPh); 3.88 (m, 1H, C*H*OH); 3.96 (d, 1H, *J*=13.2 Hz, CH*H*Ph); 7.30–7.40 (m, 5H, *H*ar). ^{13}C NMR ($CDCl_3$): 24.2 (*C*H$_2$); 27.5 (*C*H$_2$); 30.9 (*C*H$_3$); 47.3 (*C*H$_2$CO); 54.2 (*C*H$_2$Ph); 61.1 (*C*H$_2$N); 67.4 (*C*HN); 69.7 (*C*HOH); 126.9, 128.3, 128.5 (*C*Har); 139.5 (*C*ar); 209.0 (*C*O). $C_{15}H_{21}NO_2$ (247.3): calcd C 72.84, H 8.56, N 5.66; found C 72.72, H 8.40, N 5.80.

3.2.16. (2*R*,4*R*,5*S*)-5-Dibenzylamino-6-methylheptane-2,4-diol (*anti-syn*-4b). A solution of triethylborane (1.0 M in hexane, 0.23 mL, 0.23 mmol, 1.1 equiv) was added to a mixture of anhydrous THF (2 mL) and MeOH (0.5 mL) at 0 °C under nitrogen. After stirring for 1 h at room temperature, the mixture was cooled to −78 °C followed by the addition of β-hydroxy ketone *anti*-**3b** (71 mg, 0.21 mmol, 1 equiv) in THF (0.5 mL) and stirring was continued for 30 min. Then sodium borohydride (10 mg, 0.25 mmol, 1.2 equiv) was added, and the mixture was stirred for 3–4 h, depending on the substrate used. The reaction mixture was quenched with aqueous NH_4Cl (3 mL) and extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and the volatiles were evaporated. The crude product was dissolved in THF (1 mL) and aqueous 10% NaOH solution (1 mL) and the mixture was stirred vigorously for 1 h. Then THF was removed and the aqueous phase was extracted with $CHCl_3$ (3×5 mL). The combined organic extracts were washed with H_2O and dried with anhydrous $MgSO_4$. The solvents were eliminated under vacuum and the residue was purified by flash chromatography (silica gel, hexane/EtOAc 6:1): 37 mg (0.11 mmol, 52%). Colorless oil. $[\alpha]_D^{23}$ −12.1 (*c* 0.5, $CHCl_3$). IR (film): 3380, 1452, 1070, 749, 699 cm^{-1}. ^1H NMR ($CDCl_3$): 0.91 (d, 3H, *J*=6.6 Hz, (C*H*$_3$)$_2$CH); 1.16 (d, 3H, *J*=6.2 Hz, (C*H*$_3$CH)); 1.28 (d, 3H, *J*=6.5 Hz, (C*H*$_3$)$_2$CH); 1.50 (m, 1H, C*H*HCHOH); 1.61 (m, 1H, CH*H*CHOH); 2.16 (m, 1H, C*H*(CH$_3$)$_2$); 2.54 (dd, 1H, *J*=10.3, 4.9 Hz, C*H*N); 3.69 (m, 1H, C*H*OH); 3.74 (d, 2H, *J*=13.3 Hz, CH*H*Ph); 3.93 (d, 2H, *J*=13.3 Hz, C*H*HPh); 3.95 (m, 1H, CH$_3$C*H*OH); 4.17 (br s, 1H, O*H*); 7.20–7.40 (m, 10H, *H*ar). ^{13}C NMR ($CDCl_3$): 20.8 (*C*H$_3$); 23.2 (*C*H$_3$); 23.7 (*C*H$_3$); 28.4 (*C*H(CH$_3$)$_2$); 39.8 (*C*H$_2$); 56.4 (*C*H$_2$Ph); 66.8 (*C*HOH); 69.5 (*C*HOH); 71.7 (*C*HN); 127.5, 128.6, 129.2 (*C*Har); 139.4 (*C*ar). $C_{22}H_{31}NO_2$ (341.5): calcd C 77.38, H 9.15, N 4.10; found C 77.21, H 9.29, N 3.98.

3.2.17. (2*S*,4*R*,5*S*)-5-Dibenzylamino-6-methylheptane-2,4-diol (*anti-anti*-4b). To a solution of $NaBH(OAc)_3$ (407 mg, 1.92 mmol, 8 equiv) in anhydrous acetonitrile (1 mL) was added anhydrous acetic acid (1 mL) and the mixture was stirred at ambient temperature for 30 min. The mixture was cooled to −40 °C and a solution of hydroxy ketone *anti*-**3b** (81 mg, 0.24 mmol, 1 equiv) in anhydrous acetonitrile (0.5 mL) was added via syringe. After stirring at −40 °C for 2 h (TLC), the reaction mixture was quenched by addition of 0.5 M aqueous sodium potassium tartrate (3 mL). The mixture was allowed to warm to 23 °C and stirred for 30 min. The mixture was then diluted with CH_2Cl_2 (5 mL) and washed with aqueous saturated $NaHCO_3$ (5 mL). The aqueous layer was back extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were washed with aqueous saturated $NaHCO_3$, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was dissolved in THF (1 mL) and aqueous 10% NaOH solution (1 mL) and then the mixture was stirred vigorously for 1 h. Then THF was removed and the aqueous phase was

extracted with $CHCl_3$ (3×5 mL). The combined organic extracts were washed with H_2O and dried with anhydrous $MgSO_4$. The solvents were eliminated under vacuum and the residue was purified by flash chromatography (silica gel, hexane/EtOAc 6:1) to give 42 mg of *anti-anti*-**4b** (0.12 mmol, 51%) and 12 mg of *anti-syn*-**4b** (0.036 mmol, 15%). Colorless oil. $[\alpha]_D^{23}$ +20.3 (*c* 0.66, $CHCl_3$). IR (film): 3398, 1452, 1070, 759, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 0.95 (d, 3H, *J*=6.6 Hz, $(CH_3)_2CH$); 1.19 (d, 3H, *J*=6.3 Hz, (CH_3CH)); 1.25 (d, 3H, *J*=6.6 Hz, $(CH_3)_2CH$); 1.54 (ddd, 1H, *J*=13.9, 7.4, 2.0 Hz, C*H*HCHOH); 1.67 (ddd, 1H, *J*=13.9, 10.7, 3.1 Hz, CH*H*CHOH); 2.16 (m, 1H, $CH(CH_3)_2$); 2.58 (dd, 1H, *J*=9.5, 5.3 Hz, C*H*N); 3.25 (br s, 1H, O*H*); 3.73 (d, 2H, *J*=13.4 Hz, CH*H*Ph); 3.89 (d, 2H, *J*=13.4 Hz, C*H*HPh); 3.93 (m, 1H, C*H*OH); 4.03 (m, 1H, CH_3CHOH); 7.15–7.40 (m, 10H, *H*ar). ^{13}C NMR ($CDCl_3$): 20.6 (CH_3); 23.4 (CH_3); 28.1 ($CH(CH_3)_2$); 39.8 (CH_2); 56.3 (CH_2Ph); 65.8 (*C*HOH); 66.7 (*C*HOH); 66.9 (*C*HN); 127.4, 128.5, 129.2 (*C*Har); 139.7 (*C*ar). $C_{22}H_{31}NO_2$ (341.5): calcd C 77.38, H 9.15, N 4.10; found C 77.24, H 9.28, N 4.24.

3.2.18. (2*R*,4*R*,5*S*)-5-Dibenzylamino-6-phenylhexane-2,4-diol (*anti-syn*-4c). This compound was obtained from *anti*-**3c** (77 mg, 0.2 mmol), by the method described for *anti-syn*-**4b** and purified by flash chromatography (silica gel, hexane/EtOAc 4:1): 39 mg (0.1 mmol, 50%). Colorless oil. $[\alpha]_D^{23}$ +16.7 (*c* 0.7, $CHCl_3$). IR (film): 3378, 1602, 1452, 1121, 1072, 744, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 1.20 (d, 3H, *J*=6.2 Hz, C*H*$_3$); 1.48 (m, 1H, C*H*HCHOH); 1.76 (m, 1H, CH*H*CHOH); 2.78 (dd, 1H, *J*=12.9, 6.5 Hz, PhC*H*HCHN); 3.04 (m, 1H, C*H*N); 3.11 (m, 1H, PhCH*H*CHN); 3.45 (s broad, 2H, O*H*); 3.57 (d, 1H, *J*=13.6 Hz, NC*H*HPh); 3.81 (d, 1H, *J*=13.6 Hz, NCH*H*Ph); 3.83 (m, 1H, C*H*OH); 3.91 (m, 1H, CH_3CHOH); 7.15–7.35 (m, 15H, *H*ar). ^{13}C NMR ($CDCl_3$): 24.0 (CH_3); 31.9 (CH_2CHN); 41.4 (CH_2CHOH); 55.2 (NCH_2Ph); 63.3 (CH_3CHOH); 69.3 (*C*HN); 72.6 (*C*HOH); 126.1, 127.2, 128.4, 128.5, 128.8, 129.2 (*C*Har); 139.4, 140.0 (*C*ar). $C_{26}H_{31}NO_2$ (389.5): calcd C 80.17, H 8.02, N 3.60; found C 80.01, H 7.90, N 3.55.

3.2.19. (2*S*,4*R*,5*S*)-5-Dibenzylamino-6-phenylhexane-2,4-diol (*anti-anti*-4c). This compound was obtained as the major diastereomer in the reaction of *anti*-**3c** (85 mg, 0.22 mmol) with $NaBH(OAc)_3$ by the method described for *anti-anti*-**4b** and purified by flash chromatography (silica gel, hexane/EtOAc 4:1): 23 mg (0.06 mmol, 27%). Colorless oil. $[\alpha]_D^{23}$ +27.8 (*c* 0.36, $CHCl_3$). IR (film): 3368, 1453, 1122, 1074, 740, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 1.16 (d, 3H, *J*=6.3 Hz, C*H*$_3$); 1.63 (m, 2H, C*H*$_2$CHOH); 2.86 (dd, 1H, *J*=12.7, 5.8 Hz, C*H*HCHN); 3.07 (m, 1H, C*H*N); 3.12 (m, 1H, CH*H*CHN); 3.59 (d, 1H, *J*=13.7 Hz, NCH*H*Ph); 3.79 (d, 1H, *J*=13.7 Hz, NC*H*HPh); 3.93 (m, 1H, CH_3CHOH); 4.05 (m, 1H, C*H*OH); 7.15–7.35 (m, 15H, *H*ar). ^{13}C NMR ($CDCl_3$): 23.3 (CH_3); 32.1 (CH_2CHN); 40.9 (CH_2CHOH); 55.0 (CH_2Ph); 63.2 (CH_3CHOH); 65.7 (*C*HN); 68.9 (*C*HOH); 126.0, 127.1, 128.3, 128.4, 128.8, 129.3 (*C*Har); 139.5, 140.6 (*C*ar). $C_{26}H_{31}NO_2$ (389.5): calcd C 80.17, H 8.02, N 3.60; found C 80.34, H 7.91, N 3.71.

3.2.20. (1*R*,2*S*,4*S*)-1-Dibenzylamino-1-phenylpentane-2,4-diol (*anti-syn*-4e). This compound was obtained from *anti*-**3e** (45 mg, 0.12 mmol), by the method described for *anti-syn*-**4b** and purified by flash chromatography (silica gel, hexane/EtOAc 4:1): 30 mg (0.08 mmol, 68%). Colorless oil. $[\alpha]_D^{23}$ −48.1 (*c* 0.5, $CHCl_3$). IR (film): 3385, 1452, 1070, 744, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 1.26 (d, 3H, *J*=6.1 Hz, CH_3); 1.38 (ddd, 1H, *J*=14.7, 10.1, 5.4 Hz, CH*H*CHOH); 2.37 (ddd, 1H, *J*=14.7, 2.3, 1.9 Hz, C*H*HCHOH); 3.10 (d, 1H, *J*=13.8 Hz, C*H*HPh); 3.58 (d, *J*=8.8 Hz, C*H*N); 3.84 (d, 1H, *J*=13.8 Hz, CH*H*Ph); 4.10 (m, 1H, CH_3CHOH); 4.50 (m, 1H, C*H*OH); 7.20–7.50 (m, 15H, *H*ar). ^{13}C NMR ($CDCl_3$): 24.1 (CH_3); 42.0 (CH_2); 54.7 (CH_2Ph); 68.3 (CH_3CHOH); 68.9 (*C*HN); 72.0 (*C*HOH); 127.1, 127.9, 128.4, 128.7, 128.9, 130.0 (*C*Har); 134.5, 139.4 (*C*ar). $C_{25}H_{29}NO_2$ (375.5): calcd C 79.96, H 7.78, N 3.73; found C 80.17, H 7.95, N 3.82.

3.2.21. (1*R*,2*S*,4*R*)-1-Dibenzylamino-1-phenylpentane-2,4-diol (*anti-anti*-4e). This compound was obtained as the major diastereomer in the reaction of *anti*-**3e** (49 mg, 0.13 mmol) with $NaBH(OAc)_3$ by the method described for *anti-anti*-**4b** and purified by flash chromatography (silica gel, hexane/Et_2O 1:1): 27 mg (0.07 mmol, 55%). Colorless oil. $[\alpha]_D^{23}$ −102.3 (*c* 0.44, $CHCl_3$). IR (film): 3402, 1452, 1071, 741, 701 cm^{-1}. ^1H NMR ($CDCl_3$): 1.26 (d, 3H, *J*=6.2 Hz, C*H*$_3$); 1.81 (ddd, 1H, *J*=14.6, 7.7, 2.5 Hz, C*H*HCHOH); 2.16 (ddd, 1H, *J*=14.6, 8.5, 3.1 Hz, CH*H*CHOH); 3.10 (d, 1H, *J*=13.7 Hz, C*H*HPh); 3.70 (d, 1H, *J*=9.3 Hz, C*H*N); 3.9 (d, 1H, *J*=13.7 Hz, CH*H*Ph); 3.80 (m, 1H, CH_3CHOH), 4.70 (dt, 1H, *J*=9.1, 3.0 Hz, C*H*OH); 7.20–7.50 (m, 15H, *H*ar). ^{13}C NMR ($CDCl_3$): 23.6 (CH_3); 40.7 (CH_2); 54.5 (CH_2Ph); 65.1 (CH_3CHOH); 67.1 (*C*HN); 68.1 (*C*HOH); 127.8, 128.3, 128.8, 130.0 (*C*Har); 134.7, 139.4 (*C*ar). $C_{25}H_{29}NO_2$ (375.5): calcd C 79.96, H 7.78, N 3.73; found C 79.85, H 7.90, N 3.80.

3.2.22. (2*R*,4*R*,5*S*)-5-Dibenzylamino-2,4-isopropylidendioxy-6-methylheptano (*cis*-5b). To a solution of amino diol *anti-syn*-**4b** (34 mg, 0.1 mmol) in 2,2-dimethoxypropane (2 mL), at room temperature, was added *p*-$TsOH\cdot H_2O$ (8 mg). The mixture was stirred at 70 °C for 2 h, and then quenched with aqueous saturated solution of $NaHCO_3$ (3 mL). The aqueous phase was extracted with EtOAc (3×10 mL) and dried over anhydrous $MgSO_4$. The solvents were eliminated under vacuum and the residue was purified by flash chromatography (silica gel, hexane/EtOAc 30:1) to yield 33 mg of *cis*-**5b** (0.087 mmol, 87%) as a colorless oil. $[\alpha]_D^{23}$ −21.1 (*c* 0.5, $CHCl_3$). IR (film): 1454, 1378, 1258, 1179, 746, 698 cm^{-1}. ^1H NMR ($CDCl_3$): 0.99 (d, 3H, *J*=6.6 Hz, $(CH_3)_2CH$); 1.02 (d, 3H, *J*=6.1 Hz, $(CH_3)_2CH$); 1.17 (d, 3H, *J*=6.1 Hz, CH_3CH); 1.35 (s, 3H, C*H*$_3$); 1.48 (s, 3H, C*H*$_3$); 1.67 (m, 1H, C*HH*CHO); 2.20 (m, 1H, $CH(CH_3)_2$); 2.30 (dd, 1H, *J*=6.5, 4.4 Hz, C*H*N); 3.61 (d, 2H, *J*=13.7 Hz, CH*H*Ph); 3.67 (d, 2H, *J*=13.7 Hz, C*H*HPh); 3.99 (m, 1H, CH_3CHO); 4.25 (ddd, 1H, *J*=11.7, 6.2, 2.4 Hz, C*H*O); 7.20–7.40 (m, 10H, *H*ar). ^{13}C NMR ($CDCl_3$): 19.4, 20.0 ($(CH_3)_2CH$); 22.4 (CH_3CHO); 23.1 (CH_3); 25.5 ($CH(CH_3)_2$); 30.2 (CH_3); 38.1 (CH_2); 54.8 (CH_2Ph); 65.2 (*C*HO); 65.6 (CH_3CHO); 67.3 (*C*HN); 98.2 ($O_2C(CH_3)_2$), 126.8, 128.1, 128.9 (*C*Har); 140.1 (*C*ar). $C_{25}H_{35}NO_2$ (381.5): calcd C 78.70, H 9.25, N 3.67; found C 78.49, H 9.30, N 3.51.

3.2.23. (2*S*,4*R*,5*S*)-5-Dibenzylamino-2,4-isopropylidendioxy-6-methylheptane (*trans*-5b). This compound was

obtained from *anti-anti*-**4b** (34 mg, 0.1 mmol), by the method described for *cis*-**5b** and purified by flash chromatography (silica gel, hexane/EtOAc 15:1): 18 mg (0.048 mmol, 48%). Colorless oil. $[\alpha]_D^{23}$ −11.7 (*c* 0.5, $CHCl_3$). IR (film): 1454, 1378, 1224, 1120, 748, 701 cm^{-1}. ^1H NMR ($CDCl_3$): 1.03 (d, 3H, *J*=6.6 Hz, $(CH_3)_2CH$); 1.04 (d, 3H, *J*=6.5 Hz, $(CH_3)_2CH$); 1.21 (d, 3H, *J*=6.2 Hz, CH_3CH); 1.33 (s, 3H, CH_3); 1.45 (s, 3H, CH_3); 1.60 (ddd, 1H, *J*=12.7, 9.8, 7.0 Hz, CHHCHO); 1.74 (ddd, 1H, *J*=12.7, 9.3, 5.6 Hz, CHHCHO); 2.25 (m, 1H, $CH(CH_3)_2$); 2.28 (m, 1H, CHN); 3.57 (d, 2H, *J*=13.7 Hz, CHHPh); 3.73 (d, 2H, *J*=13.7 Hz, CHHPh); 3.88 (m, 1H, CH_3CHO); 4.27 (ddd, 1H, *J*=12.2, 9.2, 7.0 Hz, CHO); 7.20–7.40 (m, 10H, Har). ^{13}C NMR ($CDCl_3$): 20.2, 21.6 ($(CH_3)_2CH$); 22.8 (CH_3CHO); 24.5 (CH_3); 25.0 (CH_3); 25.9 ($CH(CH_3)_2$); 40.1 (CH_2); 54.7 (CH_2Ph); 62.8 (CHO); 64.3 (CH_3CHO); 65.3 (CHN); 100.3 ($O_2C(CH_3)_2$); 126.7, 128.1, 129.0 (CHar); 140.2 (Car). $C_{25}H_{35}NO_2$ (381.5): calcd C 78.70, H 9.25, N 3.67; found C 78.55, H 9.20, N 3.60.

3.2.24. (4*R*,5*S*)-5-Dibenzylamino-4-(*tert*-butyldimethylsilyloxy)-6-methyl-1-heptyne (*anti*-6b). To a solution of *anti*-**2b** (482 mg, 1.55 mmol) and imidazole (270 mg, 4.5 mmol, 3 equiv) in DMF (3 mL) was added TBDMSCl (340 mg, 2.25 mmol, 1.5 equiv) at 0 °C and the mixture was stirred at room temperature overnight. The reaction mixture was quenched with aqueous saturated NH_4Cl solution (10 mL) and decanted. The aqueous phase was extracted with ether (3×10 mL), and the combined organic phases were washed with brine, dried ($MgSO_4$), and the solvent was evaporated. The product was purified by flash chromatography (silica gel, hexane/EtOAc 50:1) yielding *anti*-**6b** as a colorless solid: 425 mg (0.98 mmol, 65%). Mp 57–58 °C. $[\alpha]_D^{23}$ −19.8 (*c* 1.2, $CHCl_3$). IR (film): 3310, 1952, 1090, 745, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 0.20, 0.21 (s, 3H, CH_3Si); 0.92 (s, 9H, $(CH_3)_3C$); 0.97 (d, 3H, *J*=6.6 Hz, CH_3); 1.09 (d, 3H, *J*=6.8 Hz, CH_3); 1.94 (t, 1H, *J*=2.8 Hz, ≡CH); 2.22 (m, 1H, $CH(CH_3)_2$); 2.52 (m, 2H, $CH_2C{\equiv}CH$); 3.50 (d, 2H, *J*=14.1 Hz, CHHPh); 3.91 (d, 2H, *J*=14.1 Hz, CHHPh); 4.37 (m, 1H, CHO); 7.15–7.45 (m, 10H, Har). ^{13}C NMR ($CDCl_3$): −4.4, −3.3 (CH_3Si); 18.1 ($(CH_3)_3CSi$); 21.2, 21.8 (CH_3); 25.9 ($(CH_3)_3C$); 27.0 ($(CH_3)_2CH$); 28.1 ($CH_2C{\equiv}CH$); 54.7 (CH_2Ph); 66.1 (CHN); 69.5 (CHOTBDMS); 71.0 (C≡CH); 81.8 (C≡CH); 126.6, 127.9, 129.0 (CHar); 140.4 (Car). $C_{28}H_{41}NOSi$ (435.7): calcd C 77.18, H 9.48, N 3.21; found C 76.76, H 9.08, N 2.99.

3.2.25. (4*S*,5*R*)-5-Dibenzylamino-4-(*tert*-butyldimethylsilyloxy)-5-phenyl-1-pentyne (*anti*-6e). This compound was obtained from *anti*-**2e** (249 mg, 0.7 mmol) by the method described for *anti*-**6b** and purified by flash chromatography (silica gel, hexane/EtOAc 50:1): 221 mg (0.47 mmol, 67%). Colorless oil. $[\alpha]_D^{23}$ −45.0 (*c* 0.77, $CHCl_3$). IR (film): 3309, 2122, 1454, 1252, 1109, 745, 699 cm^{-1}. ^1H NMR ($CDCl_3$): −0.31 (s, 3H, CH_3Si); 0.08 (s, 3H, CH_3Si); 0.62 (s, 9H, $(CH_3)_3C$); 1.91 (t, 1H, *J*=2.6 Hz, ≡CH); 2.69 (ddd, 1H, *J*=16.9, 4.9, 2.6 Hz, CHHCHO); 3.01 (m, 1H, CHHCHO); 3.16 (d, 2H, *J*=13.7 Hz, CHHPh); 3.79 (d, 1H, *J*=9.1 Hz, CHN); 3.90 (d, 2H, *J*=13.7 Hz, CHHPh); 4.53 (m, 1H, CHOTBDMS); 7.20–7.50 (m, 15H, Har). ^{13}C NMR ($CDCl_3$): −5.4, −4.0 (CH_3Si); 17.8 ($(CH_3)_3CSi$); 25.1 (CH_2); 25.5 ($(CH_3)_3CSi$); 54.5 (CH_2Ph); 66.4 (CHN); 70.5 (C≡CH); 71.7 (CHO); 82.1 (C≡CH); 126.9, 127.1, 127.7, 128.3, 128.9, 130.3 (CHar); 135.7, 139.4 (Car). $C_{31}H_{39}NOSi$ (469.7): calcd C 79.26, H 8.37, N 2.98; found C 79.02, H 8.18, N 2.86.

3.2.26. (3*S*,4*R*,8*R*,9*S*)-3,9-Bis-dibenzylamino-2,10-dimethyl-5-undecyne-4,8-diol (7b). To a solution of *anti*-**6b** (323 mg, 0.74 mmol) in anhydrous THF (4 mL) at −78 °C was added 1.6 M *n*-BuLi in hexane (0.51 mL, 0.81 mmol, 1.1 equiv) under argon. After the mixture was stirred for 1 h at −78 °C, a solution of amino aldehyde **1b** (229 mg, 0.81 mmol, 1.1 equiv) in THF was added. The mixture was kept at −78 °C for 2 h and then allowed to warm to room temperature overnight. Then, TBAF (281 mg, 0.89 mmol, 1.2 equiv) was added at 0 °C and the mixture was stirred at room temperature for 6 h. Saturated aqueous NH_4Cl (5 mL) was added to quench the reaction, then THF was removed, and the aqueous phase was extracted with $CHCl_3$ (3×10 mL). The organic extracts were combined, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/ethyl acetate 15:1 to 8:1): 235 mg (0.39 mmol, 53%). Colorless oil. $[\alpha]_D^{23}$ −68.0 (*c* 0.6, $CHCl_3$). IR (film): 3415, 2227, 1736, 1604, 750, 695 cm^{-1}. ^1H NMR ($CDCl_3$): 0.96 (d, 3H, *J*=6.4 Hz, CH_3); 0.98 (d, 3H, *J*=6.5 Hz, CH_3); 1.08 (d, 3H, *J*=6.8 Hz, CH_3); 1.30 (d, 3H, *J*=7.1 Hz, CH_3); 2.20 (m, 2H, $CH(CH_3)_2$ and CHHC≡C); 2.32 (m, 1H, CHHC≡C); 2.41 (m, 1H, $CH(CH_3)_2$); 2.53 (dd, 1H, *J*=10.6, 4.6 Hz, CHN); 2.64 (dd, 1H, *J*=16.7, 3.0 Hz, CHN) 3.60 (s, 4H, CH_2Ph); 3.73 (d, 2H, *J*=13.1 Hz, CHHPh); 3.93 (m, 1H, CH_2CHOH); 4.25 (m, 1H, CHOH); 4.31 (d, 2H, *J*=13.1 Hz, CHHPh); 7.15–7.35 (m, 20H, Har). ^{13}C NMR ($CDCl_3$): 20.0 (CH_3); 20.6 (CH_3); 22.5 (CH_3); 23.3 (CH_3); 26.1 ($CH(CH_3)_2$); 26.4 (CH_2CHOH); 29.2 ($CH(CH_3)_2$); 55.0, 55.9 (CH_2Ph); 60.3 (CHOH); 65.6 (CHN); 66.5 (CHN); 68.9 (CH_2CHOH); 82.1 (C≡C); 83.2 (C≡C); 126.9, 127.2, 128.2, 128.4, 128.9, 129.3 (CHar); 139.6 (Car). $C_{41}H_{50}N_2O_2$ (602.8): calcd C 81.69, H 8.36, N 4.65; found C 81.25, H 7.96, N 4.34.

3.2.27. (3*S*,4*S*,8*R*,9*S*)-3,9-Bis-dibenzylamino-2,10-dimethyl-5-undecyne-4,8-diol (*epi*-7b). This compound was obtained as the minor product in the reaction of the lithiated compound derived from *anti*-**6b** (323 mg, 0.74 mmol) with the amino aldehyde **1b** and purified by flash chromatography (silica gel, hexane/EtOAc 15:1 to 8:1): 60 mg (0.1 mmol, 13%). Colorless oil. $[\alpha]_D^{23}$ −52.0 (*c* 1.1, MeOH). $[\alpha]_D^{23}$ −2.0 (*c* 1.1, $CHCl_3$). IR (film): 3405, 2232, 1450, 745, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 1.05 (d, 3H, *J*=6.7 Hz, CH_3); 1.10 (d, 3H, *J*=7.0 Hz, CH_3); 1.13 (d, 3H, *J*=6.8 Hz, CH_3); 1.15 (d, 3H, *J*=6.9 Hz, CH_3); 2.28 (m, 2H, $CH(CH_3)_2$); 2.40 (m, 2H, $CH_2C{\equiv}C$); 2.61 (dd, 1H, *J*=8.5, 3.8 Hz, CHN); 2.71 (d, 1H, *J*=16.6 Hz, CHN); 3.58 (d, 2H, *J*=13.2 Hz, CHHPh); 3.66 (d, 2H, *J*=13.6 Hz, CHHPh); 3.73 (d, 2H, *J*=13.6 Hz, CHHPh); 3.84 (d, 2H, *J*=13.2 Hz, CHHPh); 4.04 (m, 1H, CH_2CHOH); 4.46 (d, 1H, *J*=8.5 Hz, CHOH); 7.20–7.45 (m, 20H, Har). ^{13}C NMR ($CDCl_3$): 19.5 (CH_3); 20.1 (CH_3); 23.4 (CH_3); 25.8 ($CH(CH_3)_2$); 26.2 ($CH(CH_3)_2$); 26.4 (CH_2CHOH); 53.8, 55.1 (CH_2Ph); 59.2 (CHOH); 65.4 (CHN); 66.8 (CHN); 68.7 (CH_2CHOH); 82.1 (C≡C); 83.9 (C≡C); 127.0,

127.3, 128.3, 128.4, 129.0, 129.2 (*C*Har); 138.8, 139.7 (*C*ar). $C_{41}H_{50}N_2O_2$ (602.8): calcd C 81.69, H 8.36, N 4.65; found C 81.32, H 8.05, N 4.40.

3.2.28. (3*S*,4*R*,8*R*,9*S*)-3,9-Diamino-2,10-dimethylundecane-4,8-diol (8b). To a solution of diol **7b** (316 mg, 0.52 mmol) in MeOH (5 mL) was added $Pd(OH)_2$/C (95 mg) in one portion. The mixture was stirred under hydrogen for 1 h and the catalyst was removed by filtration and washed with methanol. The solvent was evaporated under reduced pressure to give **8b** as a colorless solid: 128 mg (0.52 mmol, 100%). Mp 152–153 °C. $[\alpha]_D^{23}$ +38.8 (*c* 1.0, MeOH). IR (KBr): 3348, 1598, 1473, 1062, 980 cm^{-1}. ^1H NMR (CD_3OD): 0.96 (d, 6H, *J*=6.8 Hz, CH_3); 0.97 (d, 6H, *J*=6.7 Hz, CH_3); 1.35–1.65 (m, 6H, CH_2CH_2CH_2); 1.86 (m, 2H, CH(CH_3)$_2$); 2.56 (dd, 2H, *J*=6.6, 5.4 Hz, CHN); 3.65 (m, 2H, CHOH). ^{13}C NMR (CD_3OD): 18.7 (*C*H_3); 20.6 (*C*H_3); 23.7 (*C*H_2); 30.1 (*C*H(CH_3)$_2$); 32.0 (*C*H_2CHOH); 63.1 (*C*HN); 72.4 (*C*HOH). $C_{13}H_{30}N_2O_2$ (246.4): calcd C 63.37, H 12.27, N 11.37; found C 63.30, H 12.11, N 11.49.

3.2.29. (3*S*,4*S*,8*R*,9*S*)-3,9-Diamino-2,10-dimethylundecane-4,8-diol (*epi*-8b). This compound was obtained by debenzylation of *epi*-**7b** (54 mg, 0.09 mmol) as described for **8b**: 15 mg (0.063 mmol, 70%). Colorless solid. $[\alpha]_D^{23}$ +15.9 (*c* 0.3, MeOH). ^1H NMR (CD_3OD): 1.00 (d, 6H, *J*=6.9 Hz, CH_3); 1.03 (d, 3H, *J*=6.9 Hz, CH_3); 1.06 (d, 3H, *J*=7.0 Hz, CH_3); 1.30–1.85 (m, 6H, CH_2CH_2CH_2); 1.94 (m, 1H, CH(CH_3)$_2$); 1.99 (m, 1H, CH(CH_3)$_2$); 2.76 (m, 2H, CHN); 3.73 (dd, 1H, *J*=8.4, 4.4 Hz, CHOH); 3.80 (dd, 1H, *J*=10.0, 4.6 Hz, CHOH). ^{13}C NMR (CD_3OD): 17.9 (*C*H_3); 19.2 (*C*H_3); 20.2 (*C*H_3); 20.3 (*C*H_3); 23.2 (*C*H_2); 29.3 (*C*H(CH_3)$_2$); 29.8 (*C*H(CH_3)$_2$); 31.4 (*C*H_2CHOH); 35.3 (*C*H_2CHOH); 62.4 (*C*HN); 63.6 (*C*HN); 70.1 (*C*HOH); 70.6 (*C*HOH). $C_{13}H_{30}N_2O_2$ (246.4): calcd C 63.37, H 12.27, N 11.37; found C 63.56, H 12.37, N 11.22.

3.2.30. (5*R*,6*S*)-Ethyl 6-dibenzylamino-5-*tert*-butyldimethylsilyloxy-7-methyloct-2-ynoate (*anti*-9b). To a solution of *anti*-**6b** (958 mg, 2.2 mmol) in anhydrous THF (20 mL) at −78 °C was added 1.6 M *n*-BuLi in hexane (2.1 mL, 3.3 mmol, 1.5 equiv) under argon. After the mixture was stirred for 1 h at −78 °C, ethyl chloroformate (0.42 mL, 4.4 mmol, 2 equiv) was added. The mixture was kept at −40 °C for 1 h and then allowed to warm to 0 °C and quenched with saturated aqueous NH_4Cl solution (20 mL). Then THF was removed and the aqueous phase was extracted with Et_2O (3×20 mL). The organic extracts were combined, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield an oil that was used without further purification in the next step: 970 mg (1.91 mmol, 87%). Colorless oil. IR (film): 2234, 1712, 1252, 1072, 748, 699 cm^{-1}. ^1H NMR ($CDCl_3$): 0.19 (s, 6H, CH_3Si); 0.90 (s, 9H, (CH_3)$_3$C); 0.96 (d, 3H, *J*=6.5 Hz, CH_3CH); 1.05 (d, 3H, *J*=6.8 Hz, CH_3CH); 1.31 (t, 3H, *J*=7.1 Hz, CH_3CH$_2$); 2.19 (m, 1H, CH(CH_3)$_2$); 2.42 (dd, 1H, *J*=7.6, 2.9 Hz, CHN); 2.65 (d, 2H, *J*=6.6 Hz, CH_2CHO); 3.50 (d, 2H, *J*=13.9 Hz, CHHPh); 3.86 (d, 2H, *J*=13.9 Hz, CHHPh); 4.23 (q, 2H, *J*=7.1 Hz, CH_2CH$_3$); 4.37 (m, 1H, CHO); 7.15–7.45 (m, 10H, *H*ar). ^{13}C NMR ($CDCl_3$): −4.4, −3.5 (*C*H_3Si); 14.0 (*C*H_3CH$_2$); 18.1 (*C*(CH_3)$_3$); 21.1, 21.8 (*C*H_3CH); 25.9 ((*C*H_3)$_3$C); 26.9 ((CH$_3$)$_2$*C*H); 28.1 (CH_2CHO); 54.8 (*C*H_2Ph); 61.7 (*C*H_2CH$_3$); 66.5 (*C*HN); 69.1 (*C*HO); 75.1 (C≡*C*CO$_2$Et); 86.5 (*C*≡CCO$_2$Et); 126.7, 128.0, 128.9 (*C*Har); 140.0 (*C*ar); 153.5 (*C*O$_2$Et).

3.2.31. (5*S*,6*R*)-Ethyl 6-dibenzylamino-5-(*tert*-butyldimethylsilyloxy)-6-phenyl hex-2-ynoate (*anti*-9e). This compound was obtained as a product in the reaction of the lithiated compound derived from *anti*-**6e** (188 mg, 0.4 mmol) with ethyl chloroformate by the procedure described for *anti*-**9b**. Yield: 145 mg (0.27 mmol, 67%). Colorless oil. IR (film): 2238, 1710, 1254, 1100, 750, 700 cm^{-1}. ^1H NMR ($CDCl_3$): −0.42 (s, 3H, CH_3Si); 0.02 (s, 3H, CH_3Si); 0.55 (s, 9H, (CH_3)$_3$C); 1.28 (t, 3H, *J*=7.1 Hz, CH_3CH$_2$); 2.75 (dd, 1H, *J*=17.4, 5.5 Hz, CHHC≡C); 3.08 (d, 2H, *J*=13.7 Hz, CHHPh); 3.19 (dd, 1H, *J*=17.4, 3.7 Hz, CHHC≡C); 3.63 (d, 1H, *J*=9.4 Hz, CHN); 3.81 (d, 2H, *J*=13.7 Hz, CHHPh); 4.18 (q, 2H, *J*=7.1 Hz, CH_2CH$_3$); 4.51 (m, 1H, CHO); 7.15–7.45 (m, 15H, *H*ar). ^{13}C NMR ($CDCl_3$): −5.5, −4.2 (*C*H_3Si); 14.0 (*C*H_3CH$_2$); 17.8 ((CH$_3$)$_3$*C*Si); 25.4 ((*C*H_3)$_3$C); 25.6 (*C*H_2C≡C); 54.5 (*C*H_2Ph); 61.6 (*C*H_2CH$_3$); 66.8 (*C*HN); 70.9 (*C*HOTBDMS); 75.0 (C≡*C*CO$_2$Et); 87.5 (*C*≡CCO$_2$Et); 127.0, 127.3, 127.9, 128.4, 128.7, 130.3 (*C*Har); 135.2, 139.1 (*C*ar); 153.6 (*C*O$_2$Et).

3.2.32. (5*R*,6*S*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-6-*tert*-butoxycarbonylamino-7-methyl octanoate (*anti*-10b). To a solution of *anti*-**9b** (1.02 g, 2 mmol) in EtOAc (20 mL) were added di-*tert*-butyl dicarbonate (655 mg, 3 mmol, 1.5 equiv) and $Pd(OH)_2$/C (250 mg) in one portion. The mixture was stirred under 1 hydrogen atmosphere and the reaction was monitored by TLC. When the reaction was completed, the catalyst was removed by filtration and washed with EtOAc. The solvent was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel, hexane/EtOAc 30:1): 276 mg (0.64 mmol, 32%). Colorless oil. $[\alpha]_D^{23}$ −10.0 (*c* 1.0, $CHCl_3$). IR (film): 3462, 3369, 1734, 1720, 1705, 1171, 837 cm^{-1}. ^1H NMR ($CDCl_3$): 0.05 (s, 3H, CH_3Si); 0.07 (s, 3H, CH_3Si); 0.87 (d, 3H, *J*=6.8 Hz, CH_3CH); 0.89 (s, 9H, (CH_3)$_3$CSi); 0.92 (d, 3H, *J*=6.8 Hz, CH_3CH); 1.25 (t, 3H, *J*=7.1 Hz, CH_3CH$_2$); 1.43 (s, 9H, (CH_3)$_3$CO); 1.63 (m, 4H, CH_2CH_2CH$_2$CO$_2$Et); 1.92 (m, 1H, CH(CH_3)$_2$); 2.29 (m, 2H, CH_2CO$_2$Et); 3.49 (m, 1H, CHN); 3.72 (m, 1H, CHO); 4.12 (q, 2H, *J*=7.1 Hz, CH_2CH$_3$); 4.53 (d, 1H, *J*=10.3 Hz, NH). ^{13}C NMR ($CDCl_3$): −4.8, −4.5 (*C*H_3Si); 14.1 (*C*H_3CH$_2$); 17.4 (*C*H_3CH); 17.9 ((CH$_3$)$_3$*C*Si); 20.8 (*C*H_3CH and *C*H_2); 25.8 ((*C*H_3)$_3$CSi); 27.5 ((CH$_3$)$_2$*C*H); 28.3 ((*C*H_3)$_3$CO); 32.9 (*C*H_2); 34.4 (CH$_2$); 57.5 (*C*HN); 60.1 (*C*H_2CH$_3$); 73.1 (*C*HO); 78.7 ((CH$_3$)$_3$*C*O); 155.8 (*C*O$_2^t$Bu); 173.2 (*C*O$_2$Et). $C_{22}H_{45}NO_5Si$ (431.7): calcd C 61.21, H 10.51, N 3.24; found C 61.39, H 10.59, N 3.30.

3.2.33. (5*S*,6*R*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-6-*tert*-butoxycarbonylamino-6-phenyl hexanoate (*anti*-10e). This compound was obtained from *anti*-**9e** (135 mg, 0.25 mmol) by the method described for *anti*-**10b** and purified by flash chromatography (silica gel, hexane/EtOAc 15:1): 55 mg (0.12 mmol, 47%). Colorless oil. $[\alpha]_D^{23}$ −14.9 (*c* 1.0, $CHCl_3$). IR (film): 3366, 1713, 1170, 776, 701 cm^{-1}. ^1H NMR ($CDCl_3$): 0.08 (s, 3H, CH_3Si); 0.09 (s,

3H, CH_3Si); 0.92 (s, 9H, (CH_3)$_3$CSi); 1.20 (t, 3H, J=7.2 Hz, CH_3CH$_2$); 1.40 (s, 9H, (CH_3)$_3$CO$_2$); 1.65 (m, 4H, CH_2CH_2CHO); 2.19 (m, 2H, CH_2CO$_2$Et); 3.98 (m, 1H, C*H*O); 4.06 (q, 2H, J=7.2 Hz, CH_2CH$_3$); 4.65 (m, 1H, CHN); 5.28 (m, 1H, N*H*); 7.15–7.35 (m, 5H, *H*ar). ^{13}C NMR ($CDCl_3$): −4.7, −4.5 (*C*H$_3$Si); 14.1 (*C*H$_3$); 18.1 ((CH$_3$)$_3$*C*Si); 21.1 (*C*H$_2$); 25.9 ((*C*H$_3$)$_3$CSi); 28.3 ((*C*H$_3$)$_3$CO$_2$C); 32.8 (*C*H$_2$CHO); 34.2 (*C*H$_2$CO$_2$); 60.2 (*C*H$_2$CH$_3$); 74.4 (*C*HOTBDMS); 79.3 ((CH$_3$)$_3$*C*O$_2$); 127.3, 128.0, 128.1 (*C*Har); 155.2 (NH*C*O$_2$^{t}Bu); 173.2 (*C*O$_2$Et). $C_{25}H_{43}NO_5Si$ (465.7): calcd C 64.48, H 9.31, N 3.01; found C 64.57, H 9.14, N 3.05.

Acknowledgements

Authors thank the Spanish Ministerio de Educación y Ciencia (DGI, Project CTQ2005-01191/BQU) for financial support.

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A new Vilsmeier-type reaction for one-pot synthesis of pH sensitive fluorescent cyanine dyes

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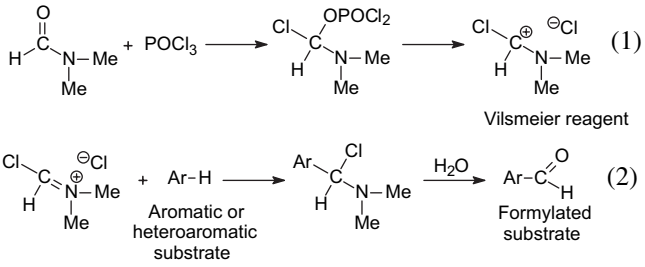
Received 30 March 2006; revised 16 May 2006; accepted 24 May 2006
Available online 12 June 2006

Abstract—A new Vilsmeier-type reaction is suggested for the synthesis of novel indocarbocyanine pH sensors, which are fluorescent when protonated but nonfluorescent upon proton abstraction. These sensors show significant ratiometric UV–visible as well as fluorescence spectral changes upon subtle variation of pHs with pK_a values near neutral.

1. Introduction

Cyanines exhibit large extinction coefficients ($\varepsilon>10^5$ $M^{-1}\,cm^{-1}$) and moderate fluorescence quantum yields, leading to widespread applications such as photosensitizers, stains, and fluorescent labels and sensors.[1] Chemical sensors are now recognized as a valid alternative to conventional instrumentation. This is especially true for analytical problems requiring on-site and real-time acquisition of data such as process control, environmental, and biomedical monitoring.[2] In particular, acid/base sensors capable of indicating the presence or absence of protons are of great importance akin to life sciences, detectors responding to environmental changes, and memories or logic gates in nanotechnology.[3–8] A fluorescence-based technique for pH measurement offers significant advantages over other techniques due to its generally nondestructive character, high sensitivity, and specificity. Numerous fluorescent systems displaying bimodal response on and off at near neutral pH 4.5–8 have been reported and have led to practical applications for intracellular pH measurements.[9] Cyanine dyes have been used as sensor molecules for the fluorescent detection of analytes in diagnostics.[10–12] Despite their success, only few examples of fluorescent cyanine biosensors sensitive to proton concentration have been reported.[11–13]

Since the first publication appeared in 1927, the Vilsmeier or Vilsmeier–Haack reaction has been applied to an immense variety of substrates, from substituted benzenes to complex heterocycles.[14] Vilsmeier reagent, an iminium salt with weak electrophilic character, results from the reaction between an acid chloride (e.g., $POCl_3$, $SOCl_2$, $(COCl)_2$, and $COCl_2$) and an amide, usually DMF. Further reaction of Vilsmeier reagent with a reactive aromatic substrate[15] followed by basic workup affords acylation products via electrophilic aromatic substitution.[14] If DMF is used in the reaction, the product of Vilsmeier reaction is an aldehyde, thus Vilsmeier reaction is often called as Vilsmeier formylation (Scheme 1).



Scheme 1. Vilsmeier–Haack reaction.[14]

Vilsmeier reaction has been utilized in the synthesis of asymmetric cyanines via formylation of Fischer's base followed by Knoevenagel condensation with the CH-acidic compound as electron acceptor.[16,17] During our investigations into the syntheses of pH sensitive cyanines, we envisioned the possibility of using a new type of Vilsmeier reaction in one-pot process to obtain the desired products. This route, if realized, would allow among other possibilities, an easy access to new pH sensitive cyanines containing sulfonic acid group that aids solubility in aqueous media and

Keywords: Fluorescent pH sensors; Vilsmeier reaction; Vilsmeier–Haack reaction; Cyanine dyes.
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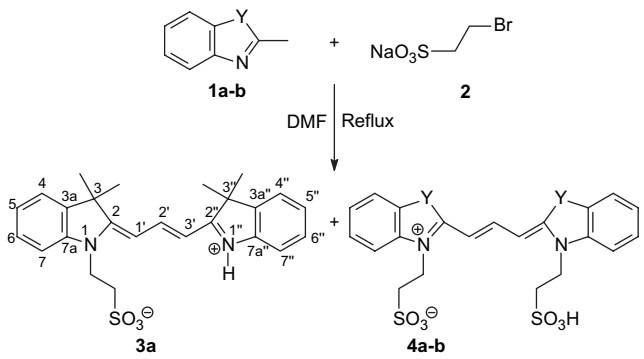
doi:10.1016/j.tet.2006.05.063

also reduces sensor aggregation in solution.[18] Herein, we wish to report the synthesis, reaction mechanism, and spectroscopic characterization of the new trimethine cyanine pH sensor dyes.

2. Results and discussion

2.1. Synthesis

Generally, the standard methods for preparation of cyanine dyes are based on the condensation of suitable heterocyclic salt with polymethine forming agent in the presence of base.[19] Similarly, pH sensor cyanine dyes are prepared from the condensation of heterocyclic salt with heterocyclic base and polymethine forming agent in the presence of acid and its anhydride together with pyridine.[11,13] The synthesis reported here involves a single step where the heterocyclic base **1a** was refluxed with excess of bromoethanesulfonate **2** in DMF to give the pH sensor dye **3a** in a mixture with the corresponding symmetric indocarbocyanine **4a** (Scheme 2). Purification of the crude product by silica gel chromatography using gradients of $MeOH/CH_2Cl_2$ afforded the first fraction **3a** as a red crystal in 32% yield followed by the second one **4a** as a red powder in 52% yield. On the other hand, the heterocyclic base **1b**, where Y=S did afford only the corresponding symmetric thiacarbocyanine **4b** as a violet crystal in 8% yield after being purified in a similar manner to **4a**.

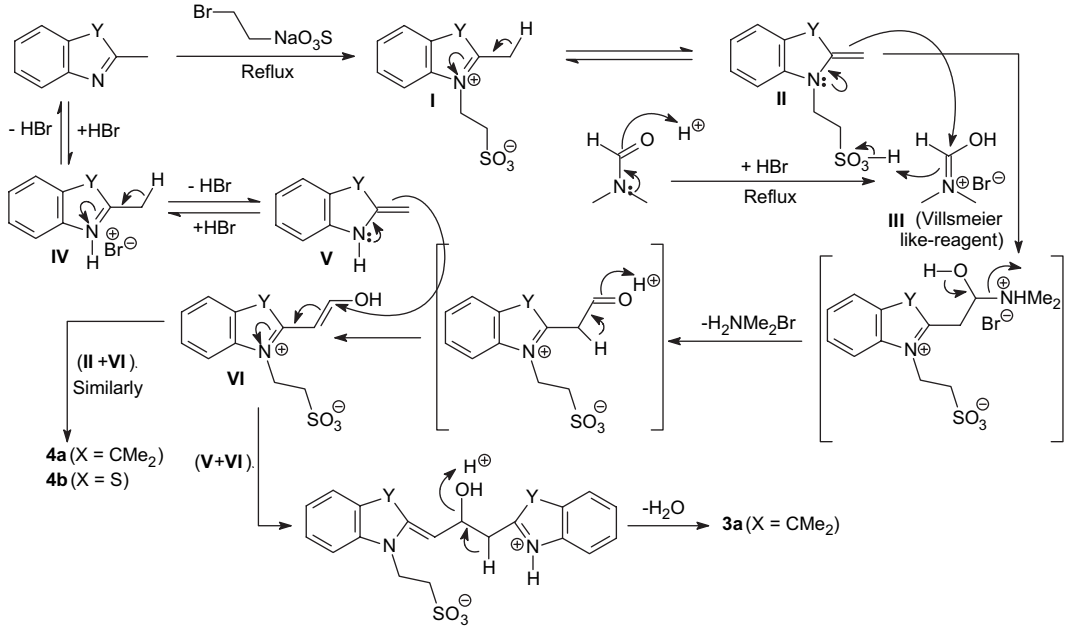


Scheme 2. One-pot synthesis of pH sensor dye **3a**.

The structures of the new dyes **3a**, **4a**,[20] and **4b** were evidenced by their HRMS, ^1H NMR, ^{13}C NMR, and IR data.

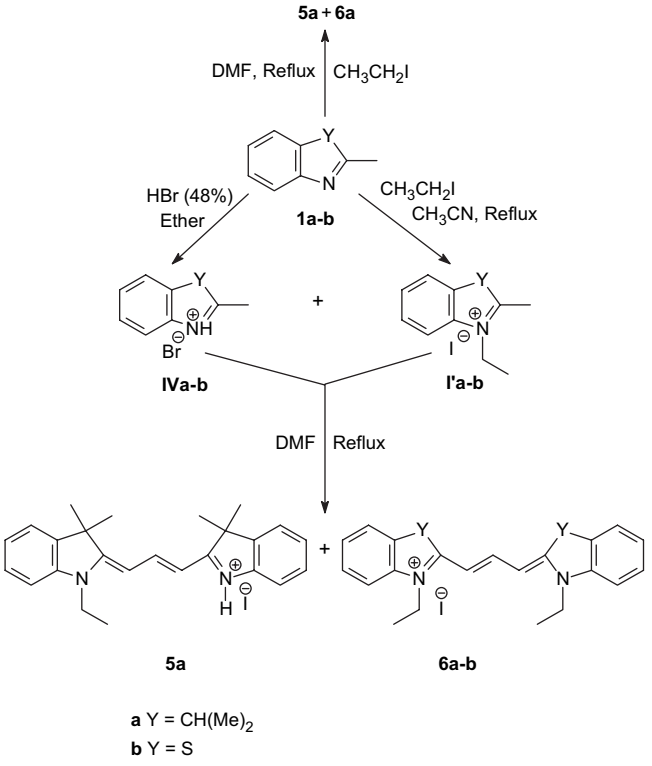
2.2. Proposed new Vilsmeier-type reaction

The formation of pH sensor dye **3a** as well as its corresponding symmetric indocarbocyanine one **4a** in one-pot synthesis could be explained by the mechanism proposed in Scheme 3. The reaction starts from the expected formation of the betaine salt **I** together with the protonated form **IV** and Vilsmeier-like reagent **III**, both formed by reflux in the presence of traces of hydrobromic acid generated in situ. Formylation of base **II** (obtained in situ from **I**) with Vilsmeier-like reagent **III** affords the enolated betaine form **VI** after elimination of dimethylammonium bromide. Condensation of **VI** with either **V** or **II** would lead to the formation of pH sensor dye **3a** or carbocyanine dyes **4a** and **4b**, respectively. It is known that indolenine quaternary ammonium salts **I** and **IV** (Y=CMe_2) undergo elimination of acid halide even in neutral conditions to afford the isolable and stable Fischer's base **II** and **V** (Y=CMe_2), respectively,[16,17,21,22] whereas in the case of benzothiazole quaternary ammonium salt (Y=S) the acid halide elimination would be improbable because the methylenic base obtained necessarily requires basic conditions for the de-aromatization of the thiazole moiety. Therefore, it is expected that the yield and the reaction pathway of indolenine compared with benzothiazole one will be different. Indeed, indolenine led to the formation of pH sensor dye **3a** and indocarbocyanine dye **4a** in an overall 84% yield whereas benzothiazole led to the formation of only thiacarbocyanine dye **4b** in 8% yield.



Scheme 3. Proposed reaction mechanism for the synthesis of pH sensor dye **3a**.

Looking for further evidences for this proposed mechanism, we synthesized the heterocyclic salt and protonated forms similar to the intermediates postulated here, in order to verify whether their mixture in DMF would produce similar products to those indicated above. As shown in Scheme 4, the treatment of an ethereal solution of the heterocyclic base **1a**,**b** with HBr (48%) at room temperature affords the corresponding protonated form **IVa**,**b** quantitatively.[23]



Scheme 4. Synthesis of the pH sensor dye **5a**.

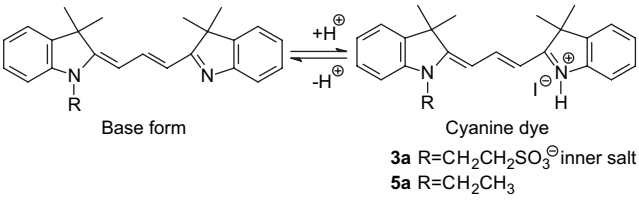
1-Ethyl-2,3,3-trimethylindolium (**I′a**) iodide and 1-ethyl-2-methylbenzothiazolium iodide (**I′b**) were prepared by refluxing a mixture of **1a** and **1b**, respectively, in the presence of an excess of ethyl iodide in acetonitrile.[24] DMF reflux of a mixture of **IVa** and **I′a** afforded the pH sensor dye **5a** together with its corresponding indocarbocyanine dye **6a**. Purification of the crude product by silica gel chromatography using gradients of MeOH/CH_2Cl_2 afforded the first fraction **5a** as a red crystal in 48% yield followed by the second one **6a** as a red crystal in 10% yield. Whereas in the case of **1b** the only obtained product was the thiacarbocyanine dye **6b** as a violet crystal in 8% yield after being purified in a similar manner to **6a**. These results would give not only an additional confirmation to the proposed mechanism but also did well reveal the differences between indolenine and benzothiazole behavior related to the reaction pathways.

Furthermore, DMF reflux for 20 h of one-pot reaction of ethyl iodide with indolenine in 1.14:2 molar ratio affords the same products **5a** and **6a** in 33 and 5% yield, respectively.

The structure of the new pH sensor dye **5a** was evidenced by its HRMS, ^{1}H NMR, ^{13}C NMR, and IR data. The ^{1}H and ^{13}C NMR spectral data for all dyes reported here were fully assigned with the aid of HMQC (Heteronuclear Multiple Quantum Coherence), HMBC (Heteronuclear Multiple Bond Correlation), and COSY (Correlated Spectroscopy) experiments.

2.3. pH-Dependent fluorescence and absorption spectra

As presented in Scheme 5, these pH sensors exist either as fluorescent cyanine dye or as complementary nonfluorescent base. The intense cyanine dye absorption and emission properties are mainly consequence of the resonance effect that exists due to the electronic push/pull effect between the two nitrogen atoms of the indole rings via the conjugated trimethine bridge. Therefore, abstraction of a proton from this system destroys this resonance, and subsequently leads to the nonfluorescent base form.



Scheme 5. Cyanine dye-base form of the pH sensors **3a** and **5a**.

The fluorescent properties of dyes **3a** and **5a** as a function of pH are shown in Figures 1 and 2. It can be observed that the fluorescent characteristics of the sensors are greatly reduced

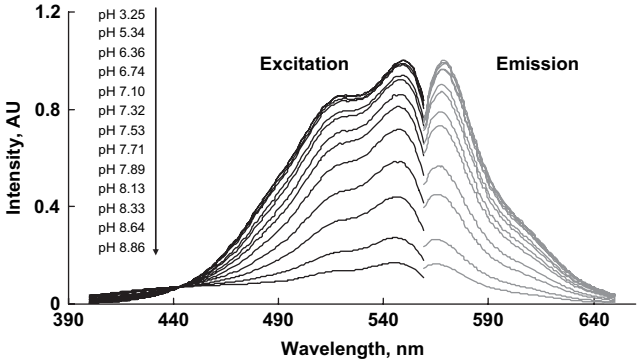


Figure 1. Excitation and emission spectra of dye **3a** (5×10^{-6} M, λ_{ex}= 550 nm and λ_{em}=569 nm) in aqueous buffer solutions at 25 °C as a function of pH.

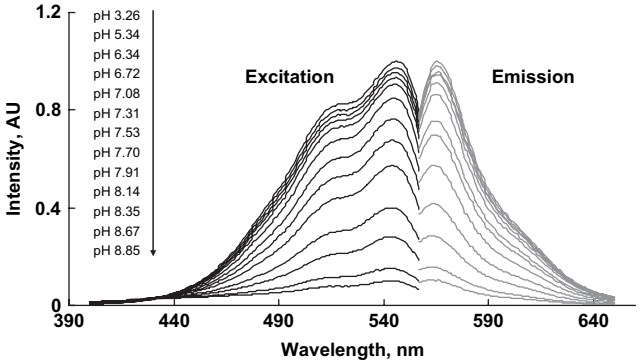


Figure 2. Excitation and emission spectra of dye **5a** (5×10^{-6} M, λ_{ex}= 546 nm and λ_{em}=565 nm) in aqueous buffer solutions at 25 °C as a function of pH.

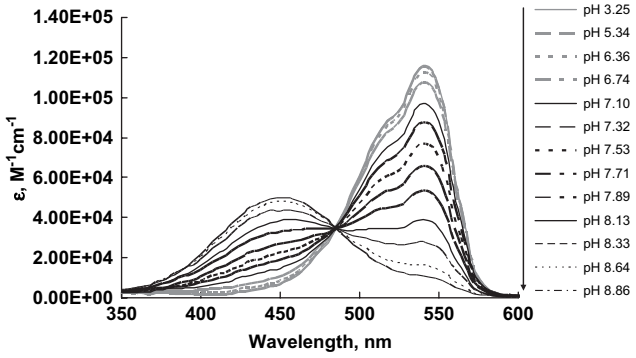


Figure 3. UV–visible absorption spectra of dye **3a** in aqueous buffer solutions (5×10^{-6} M) at 25 °C as a function of pH.

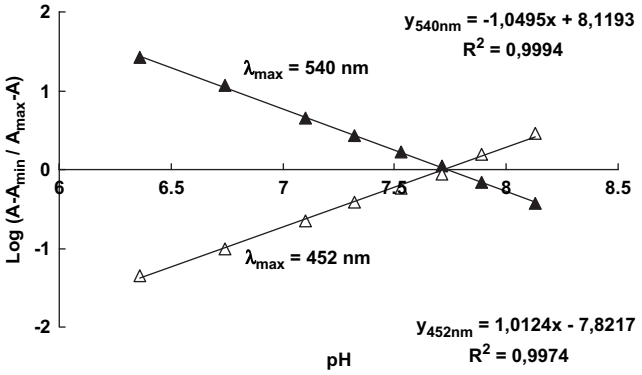


Figure 5. Determination of the pK_a value for dye **3a** (5×10^{-6} M) in aqueous buffer solutions.

as the buffer becomes less acidic, due to an increased deprotonation of the cyanine dye leading to a larger population of the nonfluorescent base species.

UV–visible spectra of both sensors as a function of pH prove the existence of acid/base equilibrium between the base and cyanine forms. It can be seen (Figs. 3 and 4) that as the buffer solutions become less acidic, the characteristic absorption maximum for the trimethine cyanine dye at 540 nm is greatly reduced as a new peak evolves at 452 nm. This absorption peak is due to the increased presence of the base form of the sensor by proton abstraction from the trimethine cyanine dye. Furthermore, the existence of an isosbestic point at 484 nm for both dyes reveals not only the presence of acid/base equilibrium between the two forms, but also gives a good indication that the solutions are all of similar ionic strength[25] and therefore minimizes the effect that others ions may cause on the spectral receptor in relation to protons. Figures 1 and 3 for sensor **3a** and Figures 2 and 4 for sensor **5a** show a coincidence between absorption and excitation indicating the purity of the sensors. Moreover, the existence of mirror image between excitation and emission spectra reveals a constant geometry of the molecule upon excitation.

The pH dependence of fluorescence intensity (F) shown in Figures 1 and 2 for dyes **3a** and **5a** can be analyzed using Eq. 1[26,27] in order to calculate their pK_a values. The pK_a may be defined as the pH, whereby 50% of the dye population in solution is protonated. The pK_a values can also be obtained from the pH dependence absorption intensity (A) shown in Figures 3 and 4 using Eq. 2,[28,29] where F_{max} or A_{max} is the maximum fluorescence or absorbance of the protonated form at a given wavelength and F_{min} or A_{min} is the minimum fluorescence or absorbance. pK_a of 7.73 and 7.53 were calculated for dyes **3a** and **5a**, respectively from the plot of log $(A-A_{min}/A_{max}-A)$ versus pH as shown in Figures. 5 and 6.

$$\mathrm{pH} = \mathrm{p}K_a \pm \log[(F_{max}-F)/(F-F_{min})] \quad (1)$$

$$\mathrm{pH} = \mathrm{p}K_a \pm \log[(A_{max}-A)/(A-A_{min})] \quad (2)$$

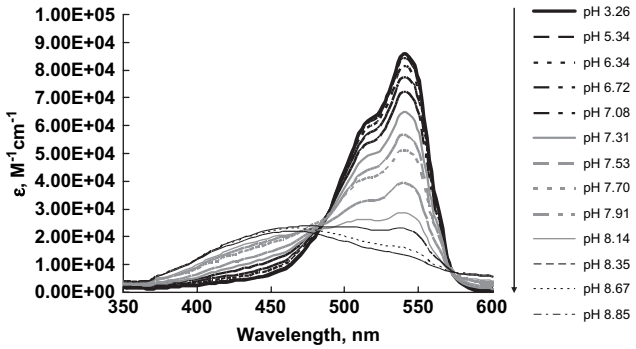


Figure 4. UV–visible absorption spectra of dye **5a** in aqueous buffer solutions (5×10^{-6} M) at 25 °C as a function of pH.

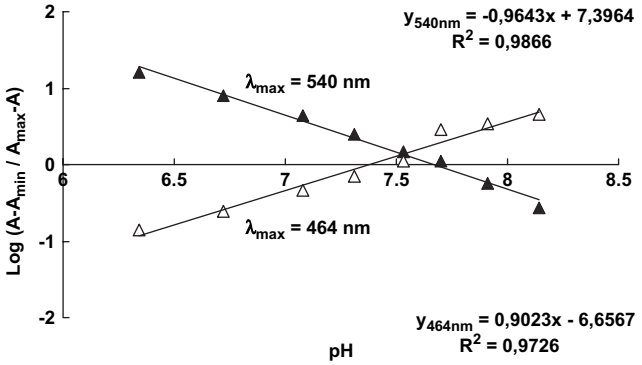


Figure 6. Determination of the pK_a value for dye **5a** (5×10^{-6} M) in aqueous buffer solutions.

3. Conclusions

A new Vilsmeier-type reaction is proposed for the synthesis of indocarbocyanine pH sensors. The in situ formation of Fischer's base reveals to be crucial for the preparation of the pH sensor dyes **3a** and **5a**, with a pK_a of 7.73 and 7.53, respectively. The observable changes of fluorescent emission within the critical intracellular pH range (6–8) make these probes very suitable for biological applications. The scope and limitation of the applicability of the presented reaction in the synthesis of different cyanine pH sensors will be the subject of a future work.

4. Experimental

4.1. General

All reagents were of the highest purity available, purchased from Sigma–Aldrich Company, and were used as received. Solvents were of analytical grade. Dry *N*,*N*-dimethylformamide and acetonitrile were used. All new dyes were determined to be >95% pure by ^{1}H NMR. All reactions were monitored by thin-layer chromatography (TLC) on aluminum plates precoated with Merck silica gel 60 F_{254} (0.25 mm) using dichloromethane or chloroform/methanol (5–30%) and the spots having been examined under 254, 312, and 365 nm UV light. Column chromatography was performed on silica gel 60 (70–230 mesh) from Macherey-Nagel, Germany. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solution on a Brücker ACP 250 (250.13 and 62.90 MHz) or Brücker ARX 400 (400.13 and 100.62 MHz) spectrometers. Chemical shifts are reported in parts per million and coupling constants (*J*) are given in hertz. HMQC, HMBC, and COSY spectra were acquired on Brücker ARX 400 spectrometer. Infrared spectra were performed on a Mattson 5000-FTS FTIR spectrometer. All samples were prepared by mixing FTIR-grade KBr with 1% (w/w) compound and grinding to a fine powder. Spectra were recorded over the 400–4000 cm^{-1} range without baseline corrections. More intensive bands are given in inverse centimeter. High Resolution Fast Atom Bombardment Mass Spectra (HR FABMS) were recorded in a Micromass AutoSpec M, operating at 70 eV, using a matrix of 3-nitrobenzyl alcohol (3-NBA). Melting points were determined in open capillary tubes in a Büchi 530 melting point apparatus and are uncorrected. All pH values were determined by a 744 pH meter (Metrohm Instrument).

4.2. pH-Spectral changes

Stock solutions of the analyzed dyes (5×10^{-5} M) were prepared in ethanol from which 5 ml was mixed with 17.5 ml of McIlvaine buffer solution (pH 3.25–8.68)[30] containing 5 ml of 0.5 M sodium chloride to adjust the ionic strength. Then the mixture was made up to 50 ml by adding distilled water to obtain dye solutions in ethanol/water (1:9) mixture with concentration of 5×10^{-6} M. Absorption titration curves were made on an Unicam HeλIOSα spectrophotometer and the uncorrected fluorescence ones were made on a SPEX FluoroMax 3109 spectrofluorophotometer with the excitation and emission wavelengths indicated.

4.3. Synthesis

4.3.1. Typical procedure for the one-pot Vilsmeier-type reaction. A mixture of 2,3,3-trimethylindolenine **1a** (0.159 g, 1.0 mmol) and 2-bromoethanosulfonic acid sodium salt (0.317 g, 1.5 mmol) in DMF (2.0 ml) was refluxed for 48 h. After cooling to room temperature the reaction mixture was treated several times with ether to eliminate DMF and other impurities. The colored residue so formed was chromatographed on a silica gel column with gradients of MeOH/$CHCl_3$ (5–30%) to afford the first fraction containing the pH sensor dye **3a** as a dark red crystal in 32% and a second fraction as the corresponding symmetric indocarbocyanine dye **4a** as a dark red powder in 52% yield. Using the same procedure and starting from 2-methylbenzothiazole **1b** (0.149 g, 1.0 mmol), the unique dye obtained was the symmetric thiacarbocyanine dye **4b** as a violet powder in 8% yield.

4.3.1.1. 2-[3-(3,3-Dimethyl-1,3-dihydroindol-2-ylidene)-propenyl]-3,3-dimethyl-1-(2-sulfoethyl)-3*H*-indolium, inner salt (3a). Mp 229–232 °C, from $CHCl_3$/ether. IR (KBr) ν (cm^{-1}): 3445, 2924, 1564, 1474, 1466, 1395, 1175, 1148, 1109, 1034, 926, 748. ^{1}H NMR (400.13 MHz, DMSO-d_6) δ (ppm): 1.47 (6H, s, 3″-(CH_3)$_2$), 1.67 (6H, s, 3-(CH_3)$_2$), 2.94 (2H, t, *J*=6.8 Hz, CH_2SO$_3$), 4.35 (2H, t, *J*=7.2 Hz, 1-NCH_2), 6.16 (1H, d, *J*=13.2 Hz, 3′-C*H*), 6.40 (1H, d, *J*=13.5 Hz, 1′-C*H*), 7.18 (1H, t, *J*=7.5 Hz, 5″-C*H*), 7.26 (1H, d, *J*=7.5 Hz, 7″-C*H*), 7.27 (1H, t, *J*=7.3 Hz, 5-C*H*), 7.36 (1H, t, *J*=7.4 Hz, 6″-C*H*), 7.38 (1H, d, *J*=7.1 Hz, 7-C*H*), 7.42 (1H, t, *J*=7.8 Hz, 6-C*H*), 7.53 (1H, d, *J*=7.3 Hz, 4″-C*H*), 7.61 (1H, d, *J*=7.4 Hz, 4-C*H*), 8.50 (1H, t, *J*=13.1 Hz, 2′-C*H*), 12.75 (1H, br s, 1″-N*H*). ^{13}C NMR (100.62 MHz, DMSO-d_6) δ (ppm): 25.5 (3″-(*C*H$_3$)$_2$), 27.0 (3-(*C*H$_3$)$_2$), 41.1 (1-N*C*H$_2$), 47.4 (*C*H$_2$SO$_3$), 49.2 (3″-C), 49.3 (3-C), 100.8 (3′-*C*H), 102.0 (1′-*C*H), 111.3 (7-*C*H), 111.7 (7″-*C*H), 122.3 (4-*C*H), 122.8 (4″-*C*H), 124.0 (5″-*C*H), 124.9 (5-*C*H), 128.3 (6-*C*H, 6″-*C*H), 139.4 (3a″-*C*), 140.9 (3a-*C*), 141.3 (7a″-*C*), 141.8 (7a-*C*), 149.5 (2′-*C*H), 174.1 (2″-*C*), 177.0 (2-*C*). UV–visible (ethanol): λ_{max}=556 nm and ε_{max}=102,491 M^{-1} cm^{-1}. HRMS (FAB, 3-NBA): M+H, found 437.1900; $C_{25}H_{29}N_2O_3S$ requires 437.1899.

4.3.1.2. 3-(2-Sulfoethyl)-2-{3-[3-(2-sulfoethyl)-3*H*-benzothiazol-2-ylidene]-propenyl}-benzothiazol-3-ium (4b). Mp>300 °C; from water/acetone. IR (KBr) ν (cm^{-1}): 3399, 1557, 1447, 1425, 1343, 1209, 1036, 752. ^{1}H NMR (250.13 MHz, DMSO-d_6) δ (ppm): 2.99 (4H, t, *J*=7.0 Hz, CH_2SO$_3$), 4.51 (4H, br s, 1-NCH_2), 6.58 (2H, d, *J*=12.5 Hz, 1′-C*H*, 3′-C*H*), 7.35 (2H, t, *J*=7.6 Hz, 6-C*H*, 6″-C*H*), 7.52 (2H, t, *J*=7.4 Hz, 5-C*H*, 5″-C*H*), 7.63–7.73 (3H, m, 4-C*H*, 2′-C*H*, 4″-C*H*), 7.92 (2H, d, *J*=8.0 Hz, 7-C*H*, 7″-C*H*). ^{13}C NMR (62.90 MHz, DMSO-d_6) δ (ppm): 43.5 (*C*H$_2$SO$_3$), 47.9 (1-N*C*H$_2$), 99.3 (1′-*C*H, 3′-*C*H), 113.8 (4-*C*H, 4″-*C*H), 122.9 (7-*C*H, 7″-*C*H), 125.0 (7a-*C*, 7a″-*C*), 125.1 (6-*C*H, 6″-*C*H), 128.0 (5-*C*H, 5″-*C*H), 141.3 (3a-*C*, 3a″-*C*), 146.5 (2′-*C*H), 164.7 (2-*C*, 2″-*C*). UV–visible (water): λ_{max}=560 nm and ε_{max}=132,062 M^{-1} cm^{-1}. HRMS (FAB, 3-NBA): M$^+$, found 525.0264; $C_{21}H_{21}N_2O_6S_4$ requires 525.0282.

4.3.2. Typical procedure for the confirmation of the proposed mechanism. A mixture of the protonated indole form **IVa** (0.293 g, 1.22 mmol) and the salt **I′a** (0.281 g, 0.89 mmol) in DMF (4 ml) was refluxed for 20 h. After cooling to room temperature the reaction mixture was treated several times with 0.1 N HCl followed by distilled water to eliminate DMF and other impurities. The colored residue so formed was chromatographed on a silica gel column with gradients of MeOH/CH_2Cl_2 (5–20%) to afford the first fraction as the crude yellow dye **5a**, which was re-dissolved in dichloromethane and treated with 1 N HI solution (20 ml) and 14% KI (20 ml). The aqueous layer was further extracted with dichloromethane and the combined extracts were dried with anhydrous sodium sulfate and evaporated. Crystallization from chloroform/petroleum ether affords

dye **5a** as a dark red crystal in 48% yield. The second fraction so obtained was the corresponding symmetric indocarbocyanine dye **6a** as a dark red crystal in 10% yield, mp 273–276 °C (260–263 °C).[19a] Using the same procedure and starting from protonated benzothiazole **IVb** (0.234 g, 1.02 mmol) and salt **I′b** (0.315 g, 1.02 mmol), the unique dye so obtained was the symmetric thiacarbocyanine **6b** as a violet crystal in 8% yield, mp 267–268 °C (269 °C).[19a]

4.3.2.1. 2-[3-(3,3-Dimethyl-1,3-dihydroindol-2-ylidene)-propenyl]-1-ethyl-3,3-dimethyl-3*H*-indolium iodide (5a). Mp 140–142 °C; from $CHCl_3$/petroleum ether. IR (KBr) ν (cm^{-1}): 2967, 1562, 1491, 1464, 1379, 1194, 1115, 1079, 928, 752. ^1H NMR (250.13 MHz, DMSO-d_6) δ (ppm): 1.29 (3H, t, J=6.7 Hz, CH_2CH_3), 1.47 (6H, s, 3″-$(CH_3)_2$), 1.71 (6H, s, 3-$(CH_3)_2$), 4.17 (2H, q, J=7.4 Hz, 1-NCH_2), 6.19 (1H, d, J=13.0 Hz, 3′-C*H*), 6.44 (1H, d, J=13.9 Hz, 1′-C*H*), 7.20 (1H, t, J=7.4 Hz, 5″-C*H*), 7.28–7.46 (5H, m, 5-C*H*, 6-C*H*, 7-C*H*, 6″-C*H*, 7″-C*H*), 7.55 (1H, d, J=7.2 Hz, 4″-C*H*), 7.68 (1H, d, J=7.5 Hz, 4-C*H*), 8.50 (1H, t, J=13.2 Hz, 2′-C*H*), 12.76 (1H, br s, 1″-N*H*). ^{13}C NMR (62.90 MHz, DMSO-d_6) δ (ppm): 12.3 (CH_2CH_3), 25.8 (3″-$(CH_3)_2$), 27.3 (3-$(CH_3)_2$), 38.5 (1-NCH_2), 49.2 (3″-C), 49.4 (3-C), 100.5 (3′-*C*H), 101.9 (1′-*C*H), 111.3 (7-*C*H), 111.8 (7″-*C*H), 122.6 (4-*C*H), 123.1 (4″-*C*H), 124.1 (5″-*C*H), 125.2 (5-*C*H), 128.5 (6-*C*H, 6″-*C*H), 139.3 (3a″-*C*), 141.4 (3a-*C*, 7a-*C*, 7a″-*C*), 149.7 (2′-*C*H), 173.9 (2″-*C*), 176.9 (2-*C*). UV–visible (ethanol): λ_{max}=552 nm and ε_{max}=82,511 $M^{-1}\,cm^{-1}$. HRMS (FAB, 3-NBA): M^+, found 357.2325; $C_{25}H_{29}N_2$ requires 357.2330.

Acknowledgements

Thanks are due to Fundação para a Ciência e Tecnologia, Portugal, POCTI and FEDER, for the funding of the Project 'Development of New Supports for Dye-Affinity Chromatography' (POCTI/2002/QUI/44776) and for granting Reda M. El-Shishtawy a Post-doctoral fellowship (SFRH/BPD/14618/2003).

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Tetrahedron
Tetrahedron 62 (2006) 7799–7808

Conjugates of methyl 6-aminopenicillanate with biscatechol-hydroxamate chelators: synthesis and siderophoric activity

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Received 27 March 2006; revised 10 May 2006; accepted 24 May 2006
Available online 15 June 2006

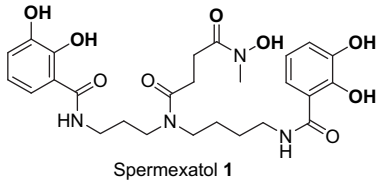
Abstract—A synthesis of biscatechol-hydroxamate and triscatechol chelators and of conjugates of the former with methyl 6-aminopenicillanate is described. It is based on the multiple use of the ylide Ph_3PCCO as a C_2 building block in one-pot coupling reactions between aldehydes and alcohols or amines. These conjugates were actively internalized into siderophore-deficient *Escherichia coli* mutant H5596.

1. Introduction

Resistance of microbial pathogens against β-lactam antibiotics is a haunting problem for the clinician, which partakes of a vicious circle as the main reason for it is an overprescription of antibiotics by physicians and GPs in particular. Mechanistically, β-lactam resistance can arise from various factors. Gram-negative bacteria are especially hard to tackle due to their outer membrane permeability barrier,[1,2] which can be overcome, though, by transporter-mediated active internalization[2,3] of specific compounds such as siderophores. These microbial secondary metabolites are iron chelators excreted to sequester extracellular ferric ions under iron starvation conditions.[2–6] Specific outer membrane receptors recognize the siderophore–iron complex and initiate its transport into the cell. Many natural siderophores are trisbidentate ligands employing catechol, salicylate or hydroxamate groups in iron complexation. On the other hand, this active import of ferrisiderophores also opens a flank in the microbial defence strategy. There are many examples of natural conjugates of siderophores with antibiotic effectors mainly produced by *Streptomyces* (sideromycins),[7] which are actively taken up into bacterial target cells via iron transport systems.

Following this 'trojan horse' strategy new antibiotics against Gram-negative pathogenic bacteria were devised, including covalent β-lactam–siderophore conjugates.[4,7–10] The conjugate of a synthetic hydroxamate-biscatechol siderophore with Lorabid®, for example, was found to be about 2000 times more active in vitro against certain *Acinetobacter* strains than Lorabid® itself.[9] Ampicillin conjugates with natural pyoverdins showed activity against multi-resistant *Pseudomonas aeruginosa*, an opportunistic bacterium responsible for frequently lethal hospital infections.[10]

In this paper we report on the synthesis of new iron triscatechol chelators as mimics of natural siderophores such as protochelin and agrobactin and also of hydroxamate-biscatechol chelators resembling semisynthetic siderophores such as spermexatol **1**[11] (Fig. 1). Those hydroxamate-biscatechol ligands showing siderophoric properties were then covalently linked to methyl 6-aminopenicillanate. The resulting



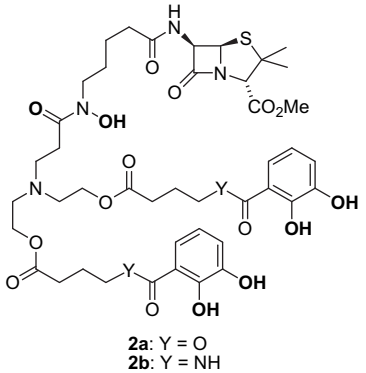


Figure 1.

Keywords: β-Lactams; Siderophores; Phosphorus ylides; Conjugates.
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doi:10.1016/j.tet.2006.05.056

conjugates **2** were tested for siderophoric activity. The synthesis of both the siderophore precursors and their conjugates with methyl penicillanate was based on the use of ketenylidenetriphenylphosphorane, Ph_3PCCO **3**[12] as an acylating C_2 building block.

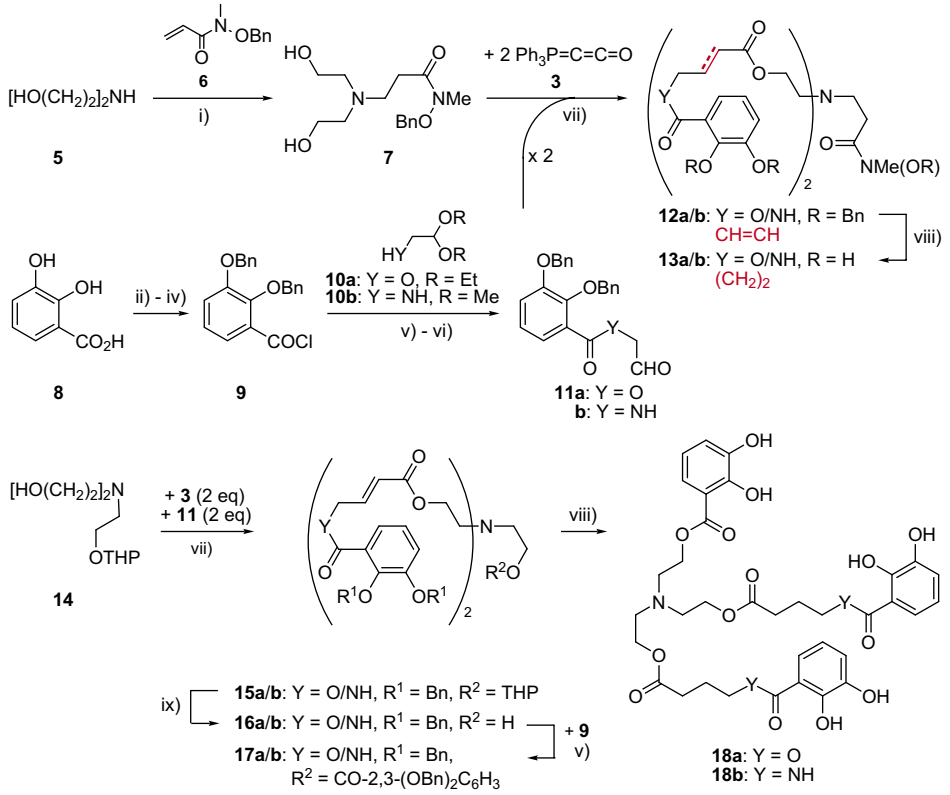
2. Results and discussion

As shown in Figure 1, the siderophores were attached to the 6-amino group of methyl 6-amino-penicillanate [6-APA(OMe)] **4** via an amide bond, which we reckoned would probably survive internalization and enzymatic dismanteling of the siderophore–iron complex. A diethanolamine fragment served as the hub of the siderophore moiety. It carried two catechol appendages optionally linked via ester (Y═O) or amide (Y═NH) bonds and a third chelate ligand (a hydroxamate in case of the conjugates **2**) as part of the tether leading to the penicillin. In modelling studies we ascertained that a strainfree octahedral coordination of Fe^{3+} would be possible for these tris-bidentate ligands. Although it is a well-known fact that a free carboxylic acid functionality at C-3 is required for a penicillin to exhibit antimicrobial activity, we prepared only conjugates of the methyl penicillanate. At this point we just wanted to see whether the ferriconjugate complexes are still being recognized by the receptors, internalized and broken down in order to release growth-promoting ferric ions. The *Escherichia coli* mutant strain H5596 on which we tested all chelators and conjugates lacks own siderophores yet possesses fully functional receptors. If kept under iron limitation, these bacteria depend on external siderophoric substances. Like many *E. coli* strains it is, however, relatively insensitive towards β-lactam antibiotics. Once the siderophoric properties of the herein described siderophore–penicillinate conjugates are proven, tests for antibiotic activity will have to be carried out with the analogues featuring a free carboxylic acid at C-3 of the penicillin on other more susceptible bacteria with similar receptors. Only this would make sure that any growth inhibition originates not from iron starvation but from a genuine penicillin effect.

2.1. Synthesis of the iron chelators

We first prepared chelators that did not provide an anchor for linkage to the penicillin and tested them for siderophoric properties (Scheme 1).

To construct biscatechol-hydroxamate chelators of type **13**, diethanolamine **5** was added to acryl amide **6** to give the monoprotected triol **7**. Compound **6** was obtained from reaction of acryl chloride and *N*-methyl-*O*-benzylhydroxylamine, which in turn was prepared from commercial hydroxylamine hydrochloride as described by Grigg et al.[13] The catechol residues were attached to the diethanolamine hub via an *E*-α,β-unsaturated ester linkage generated by a three-component reaction[14] between diol **7** and 2 equiv each of a suitable aldehyde **11** and the ylide Ph_3PCCO **3**. In this domino process the OH-groups of alcohol **7** added across the central C═C bond of the ylide **3** to form a stabilized ester ylide, which in turn Wittig-alkenated the aldehyde group in compounds **11** to leave the pentabenzylated, bisunsaturated pre-chelators **12**. Then, simultaneously, the olefinic double



Scheme 1. Reagents and conditions: (i) EtOH, rt, 16 h, 77%; (ii) BnBr, K_2CO_3, acetone, reflux, 16 h; (iii) NaOH (2 M), MeOH, rt, 1.5 h, then aq HCl; (iv) $SOCl_2$, CH_2Cl_2, rt, 3 h; (v) CH_2Cl_2, Py, rt, 3 h; (vi) HCl (15%), acetone/THF, rt, 16 h, 80–90%; (vii) THF, rt, 6–12 h, 60–80%; (viii) H_2, Pd/C, MeOH, 6 h, 99%; (ix) *p*-TsOH, toluene, 60 °C, 16 h, ca. 80%.

bonds were saturated and the benzyl protecting groups were removed with hydrogen gas at palladium on charcoal to afford the ligands **13** as colourless or pale yellow solids.

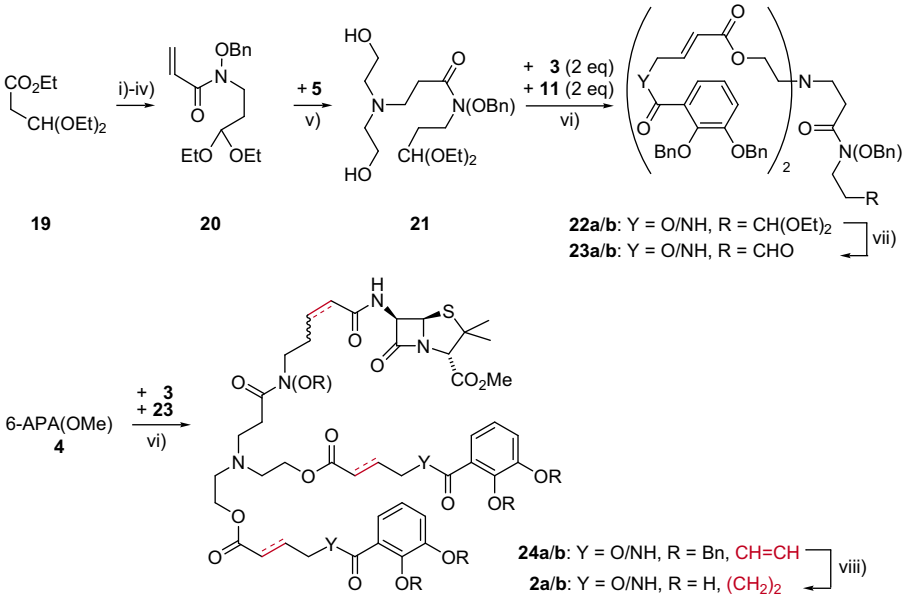
In a similar way we also built up ligands **18** featuring the prominent triscatechol siderophore motif. The mono-THP-protected trisethanolamine **14**[15] was submitted to a three-component reaction with ylide **3** and the appropriate aldehyde **11** to furnish the branched bis-bidentate precursor ligands **15**. Removal of the THP protecting group of **15** with *para*-toluenesulphonic acid in toluene at 60 °C for 16–32 h yielded alcohol **16**, which was subsequently acylated with dibenzoxybenzoyl chloride **9**. Catalytic hydrogenation of **17**, again with palladium (5%) on charcoal, left the free triscatechol compounds **18** as colourless solids. Acid chloride **9** was readily accessible in three steps from dihydroxybenzoic acid **8**, namely by perbenzylation with benzyl bromide, saponification of the intermediate benzyl dibenzoxybenzoate with aqueous NaOH in methanol and treatment of the resulting dibenzoxybenzoic acid with thionyl chloride in dichloromethane. It is worthy of note that conducting the saponification step on a prepurified sample of benzyl dibenzoxybenzoate under less drastic conditions than those described by Gardner et al.[16] (2 M NaOH, 1.5 h, rt instead of 5 M NaOH, 3 h, reflux) improved the yield and purity of the product considerably. Acid chloride **9** was also used to prepare the catechol substituted aldehydes **11** by coupling with the hydroxy or amino substituted acetaldehyde acetals **10** followed by acidic hydrolysis.

2.2. Synthesis of penicillinate–siderophore conjugates

In a previous paper[17] we introduced an expeditious one-pot protocol for the acylation of the 6-amino group of 6-APA or its esters with Ph_3PCCO **3** and different aldehydes. To apply this method to the synthesis of penicillin–siderophore conjugates **2**, the above described chelators **13** had to be fitted at some stage with an additional formyl anchor group. With only slight adaptations to the synthetic pathway outlined in the top half of Scheme 1, we prepared congeners of the biscatechol-hydroxamate ligands **13** that bore a 3-oxopropanyl instead of the methyl group on the hydroxamate nitrogen atom (Scheme 2). Compound **20**, the chain-lengthened analogue of benzoxamate **6** was obtained in four steps from ethyl 3,3-diethoxypropionate **19**. Selective ester reduction with 1 equiv of DIBAL-H[18] in diethyl ether at −78°C furnished the corresponding malonic aldehyde semiacetal, which was transferred into its benzyl protected oxime in an exothermic, quantitative reaction using *O*-benzylhydroxylamine in THF. Reduction[19] with $Na(CN)BH_3$ in dry ethanol/acetic acid gave the corresponding amine in ca. 70% yield, which in turn was added to acryl chloride. The benzoxamate **20** was then linked to diethanolamine in a further Michael-type addition, the resulting diol **21** was fused with the catechol aldehydes **11** in a three-component reaction with ylide **3** as described. The product compounds **22** were treated with aqueous HCl (10%) in acetone to yield the aldehydes **23**. The conjugates **2** were assembled by yet another three-component reaction between ylide **3**, the aldehydes **23** and 6-APA(OMe) **4**, which gave the fully protected conjugates **24** in ca. 60% yield. Their hydrogenolysis (H_2, Pd/charcoal, methanol/dioxane) finally afforded the target conjugates **2a** and **2b** as pale yellow solids.

2.3. Siderophoric activity

The chelators **13** and **18** were screened for siderophoric properties by applying cellulose discs containing small defined doses of them to agar dishes inoculated with *E. coli* strain H5596. This mutant strain lacks own siderophores yet possesses fully functional receptors. As summarized in Table 1, both the hydroxamate-biscatechols **13** and the triscatechols **18** exhibited distinct siderophoric growth-promoting activity with the amides **b** (Y=NH) markedly more so than the esters **a** (Y=O) in either case. The effect is comparable to that of the natural trishydroxamate



Scheme 2. Reagents and conditions: (i) DIBAL-H, Et_2O,−78 °C, 1 h; (ii) H_2NOBn, THF, rt, 2 h; (iii) $Na(CN)BH_3$, EtOH/AcOH, 0 °C to rt, 12 h, 70%; (iv) HC=CHCOCl, pyridine/$CHCl_3$, 0 °C to rt, 1 h; (v) EtOH, rt, 24 h, 85%; (vi) THF, rt, 16 h, 55–62%; (vii) 10% aq HCl, acetone, rt, 1 h, 90%; (viii) H_2, Pd/C (5%), MeOH, rt, 12 h, 60–64%.

Table 1. Promotion of growth of siderophore-deficient *E. coli* mutant H5596 under iron limitation by chelators **13**, **18**, penicillin–chelator conjugates **2** and ferrichrome as a standard[a,b]

Applied quantities (μg)	**13a**	**13b**	**18a**	**18b**	**2a**	**2b**	Ferrichrome
150	25 (0.23)	29 (0.23)	26 (0.21)	30 (0.21)	19 (0.15)	25 (0.15)	—
75	21 (0.12)	26 (0.12)	23 (0.10)	26 (0.10)	16 (0.08)	22 (0.08)	—
38	17 (0.06)	20 (0.06)	19 (0.05)	21 (0.05)	12 (0.04)	17 (0.04)	—
15	12 (0.02)	13 (0.02)	15 (0.02)	15 (0.02)	0 (0.015)	13 (0.015)	17 (0.02)

[a] Agar plates (Mueller–Hinton II medium, 100 μg mL^{-1} EDDA) inoculated with 100 μL of an *E.* coli H5596 suspension were covered with 6 mm cellulose discs containing 15 μL of an ethanolic solution (10, 5, 2.5 or 1 mg mL^{-1}) of the respective compound. The diameters (in mm) of the resulting growth zones were determined after 24 h of incubation at 36 °C and are cited here. The applied quantities in micromolars for each compound are given in parentheses.
[b] Compounds **25** and **26** proved inactive (Ø=0 mm) and are not listed here.

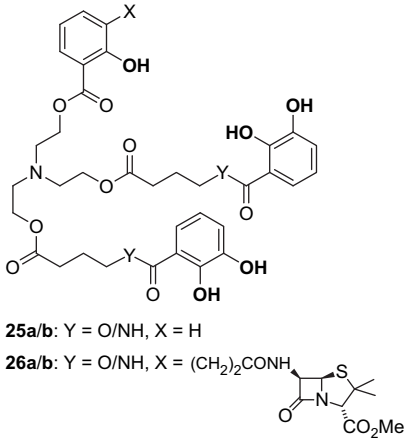


Figure 2. Pentadentate ligands lacking siderophore activity.

siderophore ferrichrome.[4,5] The siderophore–β-lactam ester conjugates **2a** and **2b** also effected normal growth of the bacteria indicating an active transport of iron from the medium into the cells. Interestingly, deleting just one of the six donor atoms required for an octahedral coordination of the metal ion resulted in complete loss of siderophoric activity regardless of whether or not a penicillin is attached. For example, neither the biscatechol-salicylate chelators **25**[20] nor their conjugates **26**[21] were effective in overcoming the iron deprivation of *E. coli* H5596 caused by treatment with ethylenediamine bis(*o*-hydroxyphenyl)acetic acid, EDDA (Fig. 2).

In conclusion we have demonstrated that chelators of the biscatechol-hydroxamate type and conjugates thereof with methyl penicillanate can be prepared in few steps by extensive use of three-component reactions between appropriate aldehydes, amines or alcohols and the cumulated phosphorus ylide Ph_3PCCO. We have also established that the conjugates are still being recognized and internalized by the pertinent receptors and hence exhibit siderophore activity as long as donor atoms are available to maintain the characteristic pattern of an octahedral ligand sphere. We are currently synthesizing the corresponding conjugates featuring a free penicillanic acid moiety in order to test them for antimicrobial activity against susceptible germs.

3. Experimental

3.1. General

Melting points were determined with a Gallenkamp apparatus and are uncorrected. IR-spectra were recorded on spectrophotometers Perkin–Elmer One FTIR and Perkin–Elmer 1600 Series FTIR. Magnetic resonance (NMR) spectra were recorded under conditions as indicated on a Bruker Avance 300 spectrometer. Chemical shifts (δ) are given in parts per million downfield from TMS as internal standard. Mass spectra were recorded using a Varian MAT 311A (EI). Elemental analyses were carried out with a Perkin–Elmer 2400 CHN elemental analyser. Optical rotations were determined at 589 nm with a Perkin–Elmer 343 polarimeter. For column chromatography Merck silica gel 60 (230–400 mesh) was used. Solvents were dried and distilled (THF, diethyl ether and dioxane over Na/Ph_2CO, CH_3OH over CaO, acetone over K_2CO_3, CH_2Cl_2 and $CHCl_3$ over P_2O_5) and stored under argon. Starting compounds were purchased from the usual sources and were used without further purification.

3.1.1. Synthesis of the iron chelators 13 and 18.

3.1.1.1. *N*-Benzyloxy-*N*-methyl 3-[bis-(2′-hydroxyethyl)amino]propionamide 7. A solution of diethanolamine **5** (0.74 g, 7.0 mmol) and *N*-benzoxy-*N*-methylacrylamide **6** (1.34 g, 7.0 mmol), as obtained in 90% yield from *N*-methyl-*O*-benzyl hydroxylamine[13] and acryl chloride in chloroform/pyridine, in ethanol (20 mL) was stirred at room temperature for 16 h. The solvent was evaporated and the residue filtered over silica gel 60 (ethyl acetate/methanol 4:1) and dried on an oil pump to give **7** as a pale yellow viscous oil (1.60 g, 77%); ν_{max}/cm^{-1} 3395, 2941, 1645, 1454, 1389; δ_H (300 MHz; $CDCl_3$) 2.40–2.55 (6H, m, NCH_2C–O, O=CCH_2), 2.71 (2H, t, ^3J=6.3 Hz, NCH_2CC=O), 3.10 (3H, s, CH_3), 3.48 (4H, t, ^3J=5.4 Hz, $NCCH_2OH$), 3.84 (2H, s, OH), 4.76 (2H, s, CH_2Ph), 7.25–7.35 (5H, m); δ_C (75 MHz; $CDCl_3$) 30.1, 33.2, 48.7, 55.9, 59.2, 76.0, 128.5, 128.7, 129.0, 134.1, 174.1. Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.8; H, 8.2; N, 9.5. Found: C, 60.6; H, 8.1; N, 9.5%.

3.1.1.2. 2,3-Dibenzoxybenzoyl chloride 9. Perbenzylation of dihydroxybenzoic acid **8** (10.0 g, 64.9 mmol) was carried out as described in literature[16] yielding crude benzyl 2,3-dibenzoxybenzoate as an orange oil. This was dissolved in diethyl ether and washed with saturated aqueous $NaHCO_3$ and water. Drying (Na_2SO_4) and removal of all volatiles left a yellowish oil, which was extracted with hexane several times to remove excess benzyl bromide. The pure product (26.7 g, 62.9 mmol) was obtained as a colourless solid upon storage at −18 °C over night. Selective saponification with 2 M NaOH for 1–1.5 h at room temperature afforded 2,3-dibenzoxybenzoic acid (20.6 g, 61.6 mmol) as a colourless solid in 95% overall yield. Treating it with thionyl chloride (29.7 g, 250 mmol) in CH_2Cl_2 in the presence of

catalytic amounts of DMF and evaporation of the solvent left **9** (21.7 g, 61.6 mmol) as a pale yellow, waxy solid, which was used for the following reactions without further purification.

3.1.1.3. Formylmethyl 2,3-dibenzoxybenzoate 11a. 2′,2′-Diethoxyethyl 2,3-dibenzoxybenzoate. A solution of **9** (3.70 g, 10.5 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a solution of 2,2-diethoxyethanol **10a** (1.60 g, 11.9 mmol) in CH_2Cl_2 (20 mL) containing pyridine (1.58 g, 20 mmol). The mixture was stirred for 3 h, then poured into cold satd aqueous $NaHCO_3$. The organic phase was washed with satd $NaHCO_3$, aqueous HCl and water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel 60, cyclohexane/ethyl acetate 2:1 v/v, R_f 0.62) giving 2′,2′-diethoxyethyl 2,3-dibenzoxybenzoate as a pale yellow oil (3.64 g, 77%); ν_{max}/cm^{-1} 2976, 1728, 1579, 1474, 1456; δ_H (300 MHz; $CDCl_3$) 1.22 (6H, t, ^3J=7.1 Hz, CH_3), 3.45–3.70 (4H, m, $MeCH_2$), 4.31 (2H, d, ^3J=5.4 Hz, CH_2CO_2), 4.75 (1H, t, ^3J=5.4 Hz, CHO_2), 5.12 (2H, s, CH_2Ph), 5.14 (2H, s, CH_2Ph), 7.00–7.15 (2H, m), 7.25–7.50 (11H, m); δ_C (75 MHz; $CDCl_3$) 15.2, 62.4, 64.4, 71.1, 75.5, 99.6, 118.0, 122.9, 123.9, 126.6, 127.4, 127.8, 128.0, 128.2, 128.7, 136.5, 137.5, 148.3, 152.7, 165.7; *m/z* (EI, 70 eV) 450 (M^+, 3%), 405 (6%), 314 (11%), 242 (33%), 91 (100%).

Formylmethyl 2,3-dibenzoxybenzoate **11a**. 2′,2′-Diethoxyethyl 2,3-dibenzoxybenzoate (3.62 g, 8.0 mmol) dissolved in acetone/THF 3:1 (v/v, 40 mL) was treated with aqueous HCl (15%, 20 mL) for 16–20 h (TLC control). The pH value was adjusted to 7 by addition of aqueous NaOH, most of the solvent was evaporated and ethyl acetate (100 mL) was added. The organic phase was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (silica gel 60, cyclohexane/ethyl acetate 1:1 v/v, R_f 0.28) to leave **11a** as a colourless, highly viscous oil (2.49 g, 82%); ν_{max}/cm^{-1} 2934, 2877, 1733, 1721, 1579, 1474; δ_H (300 MHz; $CDCl_3$) 4.74 (2H, s, CH_2CHO), 5.11 (2H, s, CH_2Ph), 5.14 (2H, s, CH_2Ph), 7.10–7.20 (3H, m), 7.25–7.45 (10H, m), 9.60 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 68.9, 71.2, 75.7, 118.6, 122.8, 124.1, 125.3, 127.9, 128.1, 128.3, 128.6, 136.4, 137.3, 148.7, 152.8, 165.4, 196.0; *m/z* (EI, 70 eV) 376 (M^+, 6%), 285 (18%), 225 (26%), 181 (33%), 91 (100%). HR-EIMS calcd for $C_{23}H_{20}O_5$: *m/z* 376.1311. Found: 376.1313.

3.1.1.4. *N*-Formylmethyl 2,3-dibenzoxybenzamide 11b. *N*-(2′,2′-Dimethoxyethyl) 2,3-dibenzoxybenzamide. Analogously to 2′,2′-diethoxyethyl 2,3-dibenzoxybenzoate (Section 3.1.1.3), *N*-(2′,2′-dimethoxyethyl) 2,3-dibenzoxybenzamide (3.36 g, 70%) was obtained as a yellowish oil from **9** (4.01 g, 11.4 mmol) and **10b** (1.35 g, 12.9 mmol); R_f 0.54 (cyclohexane/ethyl acetate 1:2 v/v); ν_{max}/cm^{-1} 3384, 2933, 1654, 1576, 1532, 1455; δ_H (300 MHz; $CDCl_3$) 3.25 (6H, s, OMe), 3.48 (2H, t, ^3J=5.5 Hz, NCH_2), 4.36 (1H, t, ^3J=5.5 Hz, CHO_2), 5.07 (2H, s, CH_2Ph), 5.14 (2H, s, CH_2Ph), 7.05–7.15 (2H, m), 7.25–7.45 (11H, m), 7.70–7.80 (1H, m), 8.16 (1H, t, ^3J=5.5 Hz, NH); δ_C (75 MHz; $CDCl_3$) 41.1, 53.9, 71.1, 75.9, 102.3, 116.8, 123.1, 124.3, 127.1, 127.6, 127.7, 128.2, 128.5, 128.7, 129.8, 136.2, 146.6, 151.7, 165.1; *m/z* (EI, 70 eV) 421 (M^+, 8%), 298 (55%), 225 (21%), 208 (58%), 91 (100%).

N-Formylmethyl 2,3-dibenzoxybenzamide **11b**. Analogously to **11a** (Section 3.1.1.3), compound **11b** (2.23 g, 76%) was obtained from the acetal precursor (3.30 g, 7.83 mmol) as a colourless solid of mp 88–89 °C; R_f 0.38 (cyclohexane/ethyl acetate 1:4 v/v); ν_{max}/cm^{-1} 3377, 2928, 2872, 1728, 1654, 1576, 1523; δ_H (300 MHz; $CDCl_3$) 4.03 (2H, d, ^3J=5.2 Hz, NCH_2), 5.08 (2H, s, CH_2Ph), 5.13 (2H, s, CH_2Ph), 7.00–7.10 (2H, m), 7.20–7.50 (11H, m), 7.68 (1H, dd, ^3J=7.2, ^4J=2.5 Hz, H^{ar}), 8.52 (1H, t, ^3J=5.2 Hz, NH), 9.49 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 50.2, 71.3, 76.0, 118.4, 124.4, 125.3, 126.7, 128.3, 128.5, 128.7, 128.8, 129.0, 136.3, 137.0, 147.0, 151.7, 165.5, 196.8; *m/z* (EI, 70 eV) 375 (M^+, 7%), 284 (10%), 225 (8%), 181 (11%), 91 (100%). HR-EIMS calcd for $C_{23}H_{21}NO_4$: *m/z* 375.1471. Found: 376.1472.

3.1.1.5. Perbenzylated biscatechol-hydroxamate 12a—typical procedure for the three-component reaction with ylide 3. A solution of **7** (72 mg, 0.24 mmol), **3** (175 mg, 0.58 mmol) and **11a** (200 mg, 0.53 mmol) in dry THF (20 mL) was stirred at room temperature for 6 h. The solvent was removed in vacuum and the residue was purified by column chromatography (silica gel 60, cyclohexane/ethyl acetate 1:2 v/v, R_f 0.40) to give **12a** as a pale yellow foamy solid (166 mg, 63%); ν_{max}/cm^{-1} 2950, 1731, 1716, 1638, 1577, 1474; δ_H (300 MHz; $CDCl_3$) 2.47 (2H, t, ^3J=7.0 Hz, $OCCH_2$), 2.77 (4H, t, ^3J=6.2 Hz, NCH_2CO), 2.88 (2H, t, ^3J=7.0 Hz, NCH_2CCO), 3.16 (3H, s, CH_3), 4.15 (4H, t, ^3J=6.2 Hz, $NCCH_2O$), 4.79 (2H, s, $NOCH_2Ph$), 4.86 (4H, dd, ^3J=4.5, ^4J=1.8 Hz, $CH_2C{=}C$), 5.11 (4H, s, CH_2Ph), 5.13 (4H, s, CH_2Ph), 6.08 (2H, dt, $^3J_{trans}$=15.9, ^4J=1.8 Hz, $C{=}CHC{=}O$), 6.95 (2H, dt, $^3J_{trans}$=15.9, ^3J=4.5 Hz, $HC{=}CC{=}O$), 7.05–7.20 (4H, m), 7.30–7.50 (27H, m); δ_C (75 MHz; $CDCl_3$) 30.5, 50.1, 52.6, 62.6, 62.9, 71.1, 75.5, 76.1, 118.1, 122.0, 122.7, 123.9, 126.0, 127.3, 127.8, 128.0, 128.1, 128.5, 128.6, 128.9, 129.2, 134.3, 136.4, 137.1, 141.4, 148.3, 152.7, 165.2, 165.5. Anal. Calcd for $C_{65}H_{64}N_2O_{14}$: C, 71.2; H, 5.9; N, 2.6. Found: C, 69.9; H, 6.1; N, 2.7%.

3.1.1.6. Perbenzylated biscatechol-hydroxamate 12b. Analogously to **12a** (Section 3.1.1.5), **12b** (139 mg, 32%) was obtained from **7** (120 mg, 0.40 mmol), **3** (290 mg, 0.96 mmol) and **11b** (330 mg, 0.88 mmol); R_f 0.38 (cyclohexane/ethyl acetate 1:4 v/v); ν_{max}/cm^{-1} 2948, 1733, 1656, 1638, 1471, 1373; δ_H (300 MHz; $CDCl_3$) 2.41 (2H, t, ^3J=6.6 Hz, $OCCH_2$), 2.73 (4H, t, ^3J=6.0 Hz, NCH_2CO), 2.80 (2H, t, ^3J=6.6 Hz, NCH_2CCO), 3.16 (3H, s, CH_3), 3.90–4.00 (4H, m, $CH_2C{=}C$), 4.10 (4H, t, ^3J=6.0 Hz, $NCCH_2O$), 4.77 (2H, s, $NOCH_2Ph$), 5.08 (4H, s, CH_2Ph), 5.15 (4H, s, CH_2Ph), 5.78 (2H, dt, $^3J_{trans}$=16.2, ^4J=1.7 Hz, $C{=}CHCO$), 6.80 (2H, dt, $^3J_{trans}$=16.2, ^3J=5.7 Hz, $HC{=}CCO$), 7.05–7.15 (4H, m), 7.20–7.50 (25H, m), 7.70–7.80 (2H, m), 8.11 (2H, t, ^3J=5.5 Hz, NH); δ_C (75 MHz; $CDCl_3$) 31.0, 36.5, 40.2, 49.9, 52.5, 62.5, 68.4, 71.3, 76.1, 117.4, 123.5, 124.4, 126.7, 127.5, 128.3, 128.7, 128.9, 129.1, 129.3, 130.0, 133.2, 135.8, 136.0, 144.2, 146.9, 151.0, 162.5, 165.7, 169.8. Anal. Calcd for $C_{65}H_{66}N_4O_{12}$: C, 71.3; H, 6.1; N, 5.1. Found: C, 71.1; H, 6.3; N, 5.0%.

3.1.1.7. Biscatechol-THP ether 15a. Analogously to **12a** (Section 3.1.1.5), **15a** (981 mg, 69%) was obtained from **14**[15] (320 mg, 1.38 mmol), **3** (997 mg, 3.30 mmol) and **11a** (1.14 g, 3.03 mmol); R_f 0.54 (cyclohexane/ethyl acetate 1:1 v/v); ν_{max}/cm^{-1} 2944, 1731, 1720, 1579, 1473, 1453; δ_H (300 MHz; $CDCl_3$) 1.45–1.80 (6H, m, CH_2), 2.80–2.95 (6H, m, NCH_2), 3.40–3.55 (2H, m, NCC*H*HOTHP, OC*H*H), 3.70–3.85 (2H, m, NCCH*H*OTHP, OCH*H*), 4.21 (4H, t, ^3J=6.1 Hz, $NCCH_2O$), 4.57 (1H, t, ^3J=2.8 Hz, CH), 4.88 (4H, dd, ^3J=4.7, ^4J=1.8 Hz, $OCH_2C{=}C$), 5.11 (4H, s, CH_2Ph), 5.15 (4H, s, CH_2Ph), 6.05 (2H, dt, $^3J_{trans}$=15.8, ^4J=1.9 Hz, OCCH=C), 6.78 (2H, dt, $^3J_{trans}$=15.8, ^3J=4.7 Hz, OCC=CH), 7.05–7.20 (6H, m), 7.25–7.50 (20H, m); δ_C (75 MHz; $CDCl_3$) 19.4, 25.3, 30.6, 53.4, 54.4, 62.1, 62.7, 63.0, 66.0, 71.1, 75.6, 98.9, 118.2, 122.1, 122.8, 124.0, 126.1, 127.5, 127.9, 128.0, 128.2, 128.5, 136.4, 137.2, 141.3, 148.4, 152.8, 165.3, 165.6; *m/z* (EI, 70 eV) 917 (5%), 602 (10%), 518 (32%), 317 (8%), 225 (12%), 181 (45%), 91 (100%). Anal. Calcd for $C_{61}H_{63}NO_{14}$: C, 70.9; H, 6.1; N, 1.4. Found: C, 70.7; H, 6.3; N, 1.4%.

3.1.1.8. Biscatechol-THP ether 15b. Analogously to **12a** (Section 3.1.1.5), **15b** (953 mg, 60%) was obtained from **14**[15] (360 mg, 1.54 mmol), **3** (1.12 g, 3.70 mmol) and **11b** (1.27 g, 3.39 mmol); R_f 0.28 (cyclohexane/ethyl acetate 1:1 v/v); ν_{max}/cm^{-1} 2945, 1719, 1657, 1576, 1526, 1454; δ_H (300 MHz; $CDCl_3$) 1.40–1.75 (6H, m, CH_2), 2.70–2.90 (6H, m, NCH_2), 3.40–3.55 (2H, m, NCC*H*HOTHP, OC*H*H), 3.70–3.85 (2H, m, NCCH*H*OTHP, OCH*H*), 3.92 (4H, m, NCH_2), 4.18 (4H, t, ^3J=6.0 Hz, $NCCH_2O$), 4.50–4.55 (1H, m, CH), 5.07 (4H, s, CH_2Ph), 5.14 (4H, s, CH_2Ph), 5.81 (2H, dt, $^3J_{trans}$=15.7, ^4J=1.7 Hz, OCCH=C), 6.78 (2H, dt, $^3J_{trans}$=15.7, ^3J=5.2 Hz, OCC=CH), 7.05–7.15 (4H, m), 7.20–7.50 (18H, m), 7.65–7.75 (4H, m), 8.14 (2H, t, ^3J=5.8 Hz, NH); δ_C (75 MHz; $CDCl_3$) 19.2, 25.2, 30.4, 40.1, 53.2, 54.1, 62.0, 62.5, 65.8, 71.1, 76.4, 98.7, 117.1, 121.4, 123.2, 124.3, 126.5, 127.5, 128.1, 128.5, 128.7, 135.9, 136.2, 143.9, 146.7, 151.5, 164.9, 165.6; *m/z* (EI, 70 eV) 916 (4%), 559 (30%), 517 (11%), 399 (14%), 317 (49%), 225 (52%), 91 (100%). Anal. Calcd for $C_{61}H_{65}N_3O_{12}$: C, 71.0; H, 6.4; N, 4.1. Found: C, 70.8; H, 6.6; N, 4.0%.

3.1.1.9. Alcohol 16a. A solution of **15a** (970 mg, 0.94 mmol) and *p*-toluenesulphonic acid hydrate (200 mg) in toluene (30 mL) was stirred at 60 °C for 24 h. Ethyl acetate (50 mL) was added and the mixture was washed with $NaHCO_3$ solution and water. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel 60, cyclohexane/ethyl acetate 1:1 v/v, R_f 0.23) to yield **16a** as a yellow oil (722 mg, 81%); ν_{max}/cm^{-1} 3495, 2949, 1730, 1715, 1579; δ_H (300 MHz; $CDCl_3$) 2.72 (2H, t, ^3J=5.2 Hz, NCH_2COH), 2.83 (4H, t, ^3J=5.8 Hz, NCH_2COR), 3.51 (2H, t, ^3J=5.2 Hz, $NCCH_2OH$), 4.18 (4H, t, ^3J=5.8 Hz, $NCCH_2OR$), 4.80–4.90 (4H, dd, ^3J=5.3, ^4J=1.8 Hz, $OCH_2C{=}C$), 5.11 (8H, s, CH_2Ph), 6.08 (2H, dt, $^3J_{trans}$=15.9, ^4J=1.8 Hz, OCCH=C), 6.90 (2H, dt, $^3J_{trans}$=15.9, ^3J=5.3 Hz, OCC=CH), 7.10–7.20 (4H, m), 7.25–7.50 (22H, m); δ_C (75 MHz; $CDCl_3$) 52.8, 56.6, 58.8, 62.3, 62.9, 71.1, 75.5, 118.1, 121.8, 122.7, 123.9, 126.0, 127.4, 127.8, 128.0, 128.5, 128.7, 136.3, 137.1, 141.7, 148.3, 152.7, 165.2, 165.5; *m/z* (EI, 70 eV; +MSTFA) 1021 (M^+, 1%), 931 (2%), 918 (13%), 590 (10%), 518 (10%), 181 (11%), 91 (100%). Anal. Calcd for $C_{56}H_{55}NO_{13}$: C, 70.8; H, 5.8; N, 1.5. Found: C, 71.0; H, 5.8; N, 1.4%.

3.1.1.10. Alcohol 16b. Analogously to **16a** (Section 3.1.1.9), **16b** (656 mg, 76%) was obtained from **15b** (940 mg, 0.91 mmol); R_f 0.28 (cyclohexane/ethyl acetate 1:4 v/v); ν_{max}/cm^{-1} 3388, 2952, 1717, 1654, 1576, 1527; δ_H (300 MHz; $CDCl_3$) 2.70 (2H, t, ^3J=5.3 Hz, NCH_2COH), 2.81 (4H, t, ^3J=5.7 Hz, NCH_2COR), 3.49 (2H, t, ^3J=5.3 Hz, $NCCH_2OH$), 3.90–4.00 (4H, m, NCH_2), 4.16 (4H, t, ^3J=5.7 Hz, $NCCH_2OR$), 5.08 (4H, s, CH_2Ph), 5.16 (4H, s, CH_2Ph), 5.79 (2H, dt, $^3J_{trans}$=15.7, ^4J=1.8 Hz, OCCH=C), 6.81 (2H, dt, $^3J_{trans}$=15.7, ^3J=5.2 Hz, OCC=CH), 7.05–7.15 (4H, m), 7.20–7.50 (20H, m), 7.65–7.75 (2H, m), 8.15 (2H, t, ^3J=5.9 Hz, NH); δ_C (75 MHz; $CDCl_3$) 40.2, 52.8, 56.6, 58.9, 62.2, 71.2, 76.5, 117.2, 121.3, 123.2, 124.4, 126.7, 127.5, 128.2, 128.6, 128.7, 128.9, 136.1, 132.3, 144.5, 146.8, 151.6, 165.0, 165.7; *m/z* (EI, 70 eV, +MSTFA) 1019 (M^+, 1%), 929 (1%), 916 (5%), 559 (18%), 17 (11%), 317 (16%), 225 (23%), 181 (18%), 91 (100%). Anal. Calcd for $C_{56}H_{57}N_3O_{11}$: C, 70.9; H, 6.1; N, 4.4. Found: C, 70.6; H, 6.0; N, 4.6%.

3.1.1.11. Triscatechol 17a. A solution of **16a** (370 mg, 0.39 mmol) and pyridine (0.2 mL) in dry CH_2Cl_2 (10 mL) was slowly treated with a solution of **9** (152 mg, 0.43 mmol) in CH_2Cl_2 (5 mL) by means of a syringe. The mixture was stirred for 2–3 h, washed with diluted HCl (pH 3), satd $NaHCO_3$ and water and then dried over Na_2SO_4. The solvent was removed in vacuum and the residue was purified by column chromatography (silica gel 60, cyclohexane/ethyl acetate 1:1 v/v, R_f 0.41) leaving **17a** as a colourless foamy solid (283 mg, 61%); ν_{max}/cm^{-1} 2957, 1730, 1701, 1577, 1471, 1453; δ_H (300 MHz; $CDCl_3$) 2.75–2.85 (6H, m, NCH_2), 4.15 (4H, t, ^3J=6.0 Hz, $NCCH_2OR$), 4.27 (2H, t, ^3J=6.1 Hz, $NCCH_2OR'$), 4.83 (4H, dd, ^3J=4.3, ^4J=1.9 Hz, $OCH_2C{=}C$), 5.08 (8H, s, CH_2Ph), 5.13 (4H, s, CH_2Ph), 6.05 (2H, dt, $^3J_{trans}$=15.8, ^4J=1.9 Hz, OCCH=C), 6.94 (2H, dt, $^3J_{trans}$=15.8, ^3J=4.3 Hz, OCC=CH), 7.05–7.20 (8H, m), 7.25–7.45 (31H, m); δ_C (75 MHz; $CDCl_3$) 53.1, 62.7, 63.0, 63.1, 67.1, 71.2, 71.3, 75.5, 75.7, 117.9, 118.3, 122.1, 122.7, 123.9, 124.0, 126.1, 126.6, 127.5, 127.7, 127.9, 128.0, 128.2, 128.4, 128.7, 128.9, 129.1, 136.1, 136.5, 137.3, 137.7, 141.5, 146.3, 152.8, 165.0, 165.6, 166.1. Anal. Calcd for $C_{77}H_{71}NO_{16}$: C, 73.0; H, 5.7; N, 1.1. Found: C, 72.7; H, 5.9; N, 1.1%.

3.1.1.12. Triscatechol 17b. Analogously to **17a** (Section 3.1.1.11), **17b** (231 mg, 55%) was obtained from **16b** (315 mg, 0.33 mmol) and **9** (128 mg, 0.36 mmol); R_f 0.42 (cyclohexane/ethyl acetate 1:2 v/v); ν_{max}/cm^{-1} 2952, 1739, 1718, 1652, 1575, 1468; δ_H (300 MHz; $CDCl_3$) 2.75–2.90 (6H, m, NCH_2), 3.90–4.00 (4H, m, $NHCH_2$), 4.14 (4H, t, ^3J=5.9 Hz, $NCCH_2OR$), 4.27 (2H, t, ^3J=6.1 Hz, $NCCH_2OR'$), 5.10 (6H, s, CH_2Ph), 5.13 (2H, s, CH_2Ph), 5.18 (4H, s, CH_2Ph), 5.77 (2H, dt, $^3J_{trans}$=15.9, ^4J=1.6 Hz, OCCH=C), 6.80 (2H, dt, $^3J_{trans}$=15.9, ^3J=5.3 Hz, OCC=CH), 7.00–7.15 (3H, m), 7.20–7.50 (34H, m), 7.65–7.75 (2H, m), 8.10 (2H, t, ^3J=5.8 Hz,

NH); δ_C (75 MHz; $CDCl_3$) 40.2, 53.1, 62.5, 62.9, 71.1, 71.2, 71.4, 75.5, 76.5, 117.2, 117.9, 118.9, 121.4, 122.7, 123.3, 123.9, 124.3, 126.2, 126.7, 127.4, 127.7, 127.8, 128.0, 128.2, 128.3, 128.5, 128.6, 128.7, 128.9, 129.2, 136.1, 136.3, 136.5, 137.5, 144.1, 146.8, 151.6, 152.7, 165.0, 165.7, 165.9. Anal. Calcd for $C_{77}H_{73}N_3O_{14}$: C, 73.1; H, 5.8; N, 3.3. Found: C, 72.9; H, 6.0; N, 3.4%.

3.1.1.13. Biscatechol-hydroxamate 13a—typical procedure for the hydrogenolytic debenzylation. Compound **12a** (145 mg, 0.13 mmol) was dissolved in freshly distilled methanol/dioxane (3:1 v/v, 10 mL), 5% Pd/charcoal catalyst (75 mg) was added and the resulting mixture was flashed with and kept under an atmosphere of hydrogen gas (1 bar) for 6 h while stirring (TLC control). After filtration, the solvent was removed in vacuum. The pale yellow residue was precipitated from CH_2Cl_2 to yield **13a** (77 mg, 90%) as a colourless solid of mp 126–127 °C; ν_{max}/cm^{-1} 3334, 2943, 1745, 1683, 1631, 1468; δ_H (300 MHz; MeOD-d_3) 1.80–1.95 (4H, m, $OCCCH_2C$), 2.46 (4H, t, ^3J=7.0 Hz, $OCCH_2CC$), 2.58 (2H, t, ^3J=6.7 Hz, $OCCH_2$), 2.70–2.85 (6H, m, NCH_2), 3.12 (3H, s, CH_3), 4.10 (4H, t, ^3J=6.1 Hz, $NCCH_2OR$), 4.41 (4H, t, ^3J=5.9 Hz, $OCCCCH_2$), 6.71 (2H, t, ^3J=8.1 Hz, H^{ar}), 6.92 (2H, dd, ^3J=8.1, ^4J=1.6 Hz, H^{ar}), 7.17 (2H, dd, ^3J=8.1, ^4J=1.6 Hz, H^{ar}); δ_C (75 MHz; MeOD-d_3) 26.4, 30.8, 31.9, 36.3, 52.9, 54.2, 62.6, 64.7, 117.9, 118.5, 119.4, 125.7, 147.8, 151.0, 169.2, 171.6, 174.8. Anal. Calcd for $C_{30}H_{38}N_2O_{14}$: C, 55.4; H, 5.9; N, 4.3. Found: C, 55.2; H, 5.9; N, 4.2%.

3.1.1.14. Biscatechol-hydroxamate 13b. Analogously to **13a** (Section 3.1.1.13), **13b** (53 mg, 82%) was obtained from **12b** (110 mg, 0.10 mmol) as a pale yellow solid of mp 131–133 °C; ν_{max}/cm^{-1} 3316, 2941, 1738, 1680, 1633, 1469; δ_H (300 MHz; MeOD-d_3) 1.80–1.95 (4H, m, $NCCH_2$), 2.42 (4H, t, ^3J=7.1 Hz, $NCCCH_2$), 2.57 (2H, t, ^3J=6.7 Hz, $OCCH_2$), 2.77 (4H, t, ^3J=6.0 Hz, NCH_2COR), 2.80 (2H, t, ^3J=6.4 Hz, NCH_2CCO), 3.05–3.20 (7H, m, CH_3, $NHCH_2$), 4.11 (4H, t, ^3J=6.0 Hz, $NCCH_2OR$), 6.71 (2H, t, ^3J=7.8 Hz, H^{ar}), 6.92 (2H, dd, ^3J=7.8, ^4J=1.2 Hz, H^{ar}), 7.18 (2H, dd, ^3J=7.8, ^4J=1.2 Hz, H^{ar}); δ_C (75 MHz; MeOD-d_3) 25.8, 31.7, 32.6, 36.3, 39.9, 52.2, 54.0, 63.9, 116.9, 118.8, 119.5, 119.7, 147.6, 150.7, 171.0, 171.8, 175.1. Anal. Calcd for $C_{30}H_{40}N_4O_{12}$: C, 55.6; H, 6.2; N, 8.6. Found: C, 55.3; H, 6.3; N, 8.4%.

3.1.1.15. Triscatechol 18a. Analogously to **13a** (Section 3.1.1.13), **18a** (142 mg, 90%) was obtained from **17a** (280 mg, 0.22 mmol) as a colourless solid of mp 133–134 °C; ν_{max}/cm^{-1} 3368, 2930, 1738, 1689, 1590, 1468; δ_H (300 MHz; MeOD-d_3) 1.95–2.10 (4H, m, $OCCCH_2$), 2.41 (4H, t, ^3J=7.0 Hz, $OCCH_2C$), 2.75–2.95 (6H, m, NCH_2), 4.08 (4H, t, ^3J=5.5 Hz, $NCCH_2OR$), 4.25–4.40 (6H, m, $NCCH_2OR'$, $OCCCCH_2$), 6.65–6.85 (6H, m, H^{ar}), 6.95–7.10 (3H, m, H^{ar}); δ_C (75 MHz; MeOD-d_3) 26.4, 35.3, 54.3, 54.6, 61.1, 63.2, 63.9, 113.8, 116.7, 117.0, 119.5, 120.0, 125.8, 125.9, 146.8, 147.4, 150.0, 151.6, 170.3, 171.6, 174.2. Anal. Calcd for $C_{35}H_{39}NO_{16}$: C, 57.6; H, 5.4; N, 1.9. Found: C, 57.8; H, 5.2; N, 2.0%.

3.1.1.16. Triscatechol 18b. Analogously to **13a** (Section 3.1.1.13), **18b** (107 mg, 86%) was obtained from **17b** (220 mg, 0.17 mmol) as a colourless solid of mp 138–139 °C; ν_{max}/cm^{-1} 3364, 2932, 1736, 1644, 1586, 1462; δ_H (300 MHz; MeOD-d_3) 1.80–1.90 (4H, m, $OCCCH_2$), 2.38 (4H, t, ^3J=6.9 Hz, $OCCH_2C$), 2.85–3.00 (6H, m, NCH_2), 3.25–3.35 (4H, m, $NHCH_2$), 4.22 (4H, t, ^3J=5.5 Hz, $NCCH_2OR$), 4.53 (2H, t, ^3J=5.4 Hz, $NCCH_2OR'$), 6.70–6.95 (6H, m, H^{ar}), 7.10–7.25 (3H, m, H^{ar}); δ_C (75 MHz; MeOD-d_3) 25.8, 32.4, 39.7, 54.5, 54.7, 62.4, 63.1, 113.9, 116.9, 118.7, 119.8, 120.4, 121.6, 122.1, 147.0, 147.4, 150.3, 151.4, 171.4, 171.8, 174.8. Anal. Calcd for $C_{35}H_{41}N_3O_{14}$: C, 57.8; H, 5.7; N, 5.8. Found: C, 57.8; H, 5.8; N, 5.7%.

3.1.2. Synthesis of the penicillinate–biscatechol-hydroxamate conjugates 24 and 2.

3.1.2.1. *N*-Benzyloxy-*N*-(3,3-diethoxypropyl) acrylamide 20. 3,3-Diethoxypropanal *O*-benzyloxime. To a solution in THF (50 mL) of malonic aldehyde semiacetal (2.63 g, 22.7 mmol), obtained from **19** in 85% according to literature,[18] a solution of *O*-benzyl-hydroxylamine (3.08 g, 25.0 mmol) in THF (10 mL) was added dropwise. The mixture was stirred for 3 h, the solvent was largely evaporated, ethyl acetate (50 mL) was added and the resulting mixture was washed with diluted HCl (pH 3) and water. The organic phase was dried over Na_2SO_4, the solvent was removed in vacuum and the remaining yellow oil was bulb-to-bulb distilled (130–135 °C, 0.1 Torr) to give 3,3-diethoxypropanal *O*-benzyloxime as a colourless liquid (4.86 g, 85%); *E*/*Z* ca. 2:1; ν_{max}/cm^{-1} 2676, 1704, 1496, 1454; δ_H (300 MHz; $CDCl_3$) *E*-isomer: 1.10–1.25 (6H, m, CH_3), 2.53 (2H, t, ^3J=5.8 Hz, CH_2C=N), 3.45–3.75 (6H, m, $MeCH_2$), 4.59 (1H, t, ^3J=5.8 Hz, $CH(OEt)_2$), 5.06 (2H, s, CH_2Ph), 7.20–7.40 (5H, m, H^{ar}), 7.51 (1H, t, ^3J=5.8 Hz, CH=N); *Z*-isomer: 1.10–1.25 (6H, m, CH_3), 2.72 (2H, t, ^3J=5.6 Hz, CH_2C=N), 3.45–3.75 (6H, m, $MeCH_2$), 4.68 (1H, t, ^3J=5.6 Hz, $CH(OEt)_2$), 5.12 (2H, s, CH_2Ph), 6.78 (1 H, t, ^3J=5.6 Hz, CH=N), 7.20–7.40 (5H, H^{ar}); δ_C (75 MHz; $CDCl_3$; mixture of isomers) 15.1, 15.3, 30.9, 34.4, 61.6, 61.7, 75.5, 75.7, 99.7, 100.6, 127.4, 127.6, 127.9, 128.1, 128.7, 129.0, 137.6, 137.9, 147.3, 147.5; *m*/*z* (EI, 70 eV) 251 (M^+, 4%), 206 (14%), 103 (73%), 91 (100%).

3,3-Diethoxypropylbenzoxyamine. 3,3-Diethoxypropanal *O*-benzyloxime (4.80 g, 19.1 mmol) was reduced with $Na(CN)BH_3$ (1.44 g, 22.9 mmol) following a literature procedure;[19] pale yellow oil (3.53 g, 73%) after purification by column chromatography (silica gel 60, cyclohexane/ethyl acetate 1:1 v/v, R_f 0.54); ν_{max}/cm^{-1} 2975, 1738, 1453; δ_H (300 MHz; $CDCl_3$) 1.15 (6H, t, ^3J=6.8 Hz, CH_3), 1.80–1.90 (2H, m, CH_2CNH), 2.93 (2H, t, ^3J=6.5 Hz, CH_2N), 3.45–3.70 (4H, m, CH_2Me), 4.53 (1H, t, ^3J=5.6 Hz, CHO_2), 4.65 (2H, CH_2Ph), 5.75 (1H, br, NH), 7.20–7.40 (5H, m, H^{ar}); δ_C (75 MHz; $CDCl_3$) 15.3, 31.2, 47.9, 61.2, 76.0, 101.7, 127.6, 128.2, 128.3, 138.1; *m*/*z* (EI, 70 eV) 253 (M^+, 2%), 207 (18%), 136 (16%), 91 (100%).

N-Benzyloxy-*N*-(3,3-diethoxypropyl) acrylamide **20**. A solution of 3,3-diethoxypropyl-benzoxyamine (3.50 g, 13.8 mmol) and pyridine (1.58 g, 20 mmol) in dry $CHCl_3$ (50 mL) was slowly treated at 0 °C with a solution of acryl chloride (1.37 g, 15.2 mmol) in the same solvent (10 mL) by means of a syringe. The mixture was stirred for 1 h while coming to room temperature, washed with satd $NaHCO_3$, aqueous HCl (pH 3) and water and finally dried over

Na_2SO_4. Removal of the solvent left a yellow oil, which was purified by column chromatography (silica gel 60, cyclohexane/ethyl acetate 2:1 v/v, R_f 0.32) yielding **20** as a pale yellow liquid (3.47 g, 82%); ν_{max}/cm^{-1} 2974, 1620, 1442, 1413, 1372; δ_H (300 MHz; $CDCl_3$) 1.17 (6H, t, ^3J=7.0 Hz, CH_3), 1.90–2.00 (2H, m, $CH_2C(OEt)_2$), 3.40–3.65 (4H, m, CH_2Me), 3.73 (2H, t, ^3J=7.0 Hz, NCH_2), 4.51 (1H, t, ^3J=5.5 Hz, CHO_2), 4.77 (2H, CH_2Ph), 5.56 (1H, dd, $^3J_{cis}$=10.3, ^2J=2.1 Hz, C=C*H*H), 6.33 (1H, dd, $^3J_{trans}$=17.1, ^2J=2.1 Hz, C=CH*H*), 6.65 (1H, dd, $^3J_{cis}$=10.3, $^3J_{trans}$=17.1 Hz, C*H*=CH_2), 7.25–7.40 (5H, m, H^{ar}); δ_C (75 MHz; $CDCl_3$) 15.1, 31.1, 41.9, 61.3, 76.8, 100.7, 126.2, 128.5, 128.6, 128.8, 129.1, 134.1, 166.3; *m/z* (EI, 70 eV) 307 (M^+, 1%), 262 (16%), 216 (8%), 171 (41%), 154 (23%), 91 (100%). Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.4; H, 8.2; N, 4.6. Found: C, 66.2; H, 8.1; N, 4.8%.

3.1.2.2. *N*-Benzyloxy-*N*-(3′,3′-diethoxypropyl) 3-[bis-(2″-hydroxyethyl)amino]propionamide 21. Analogously to **7** (Section 3.1.1.1), **21** (3.89 g, 85%) was obtained after 32 h stirring as a pale yellow oil from **5** (1.17 g, 11.1 mmol) and **20** (3.40 g, 11.1 mmol); ν_{max}/cm^{-1} 3412, 2975, 1645, 1453; δ_H (300 MHz; $CDCl_3$) 1.12 (6H, t, ^3J=7.1 Hz, CH_3), 1.80–1.95 (2H, m, $CH_2C(OEt)_2$), 2.40–2.55 (6H, NCH_2), 2.74 (2H, t, ^3J=5.9 Hz, O=CCH_2), 3.30–3.60 (10H, m, CH_2Me, CH_2OH), 3.69 (2H, t, ^3J=6.8 Hz, CH_2NOBn), 4.48 (1H, t, ^3J=5.6 Hz, CHO_2), 4.78 (2H, s, CH_2Ph), 7.30–7.40 (5H, m, H^{ar}); δ_C (75 MHz; $CDCl_3$) 15.2, 30.3, 31.0, 48.7, 56.0, 59.4, 61.3, 76.2, 100.7, 128.5, 128.8, 129.0, 134.2, 173.9. Anal. Calcd for $C_{21}H_{36}N_2O_6$: C, 61.1; H, 8.8; N, 6.8. Found: C, 61.3; H, 8.6; N, 6.9%.

3.1.2.3. Perbenzylated biscatechol-hydroxamate 22a. Analogously to **12a** (Section 3.1.1.5), **22a** (0.85 g, 62%) was obtained as yellowish, highly viscous oil from **21** (0.47 g, 1.15 mmol), **3** (0.83 g, 2.75 mmol) and **11a** (0.95 g, 2.53 mmol); R_f 0.56 (cyclohexane/ethyl acetate 1:2 v/v); ν_{max}/cm^{-1} 2974, 1722, 1663, 1580, 1453; δ_H (300 MHz; $CDCl_3$) 1.15 (6H, t, ^3J=6.5 Hz, CH_3), 1.80–1.95 (2H, m, $CH_2C(OEt)_2$), 2.48 (2H, t, ^3J=6.7 Hz, O=CCH_2), 2.70–2.90 (6H, m, NCH_2), 3.40–3.75 (6H, m, CH_2Me, BnONCH_2), 4.12 (4H, t, ^3J=6.2 Hz, $NCCH_2OR$), 4.47 (1H, t, ^3J=5.5 Hz, CHO_2), 4.77 (2H, s, N–O–CH_2Ph), 4.87 (4H, dd, ^3J=4.6, ^4J=1.8 Hz, CH_2C=C), 5.12 (8H, s, C–O–CH_2Ph), 6.05 (2H, dt, $^3J_{trans}$=15.8, ^4J=1.8 Hz, O=CCH=C), 6.99 (2H, dt, $^3J_{trans}$=15.8, ^3J=4.6 Hz, O=CC=CH), 7.10–7.25 (6H, m), 7.30–7.55 (25H, m); δ_C (75 MHz; $CDCl_3$) 15.2, 30.7, 31.1, 50.2, 52.6, 61.1, 62.6, 63.0, 70.8, 71.2, 75.6, 76.2, 100.8, 118.3, 122.0, 122.7, 124.4, 125.3, 126.1, 127.2, 127.5, 127.7, 128.0, 128.8, 136.4, 137.2, 141.3, 151.3, 152.9, 163.0, 163.7, 165.5. Anal. Calcd for $C_{71}H_{76}N_2O_{16}$: C, 70.3; H, 6.3; N, 2.3. Found: C, 70.4; H, 6.1; N, 2.2%.

3.1.2.4. Perbenzylated biscatechol-hydroxamate 22b. Analogously to **12a** (Section 3.1.1.5), **22b** (0.79 g, 55%) was obtained as a yellowish, highly viscous oil from **21** (0.49 g, 1.20 mmol), **3** (0.86 g, 2.86 mmol) and **11b** (1.00 g, 2.65 mmol); R_f 0.44 (cyclohexane/ethyl acetate 1:4 v/v); ν_{max}/cm^{-1} 2974, 1718, 1659, 1577, 1524, 1454; δ_H (300 MHz; $CDCl_3$) 1.16 (6H, t, ^3J=7.0 Hz, CH_3), 1.80–1.95 (2H, m, $CH_2C(OEt)_2$), 2.46 (2H, t, ^3J=6.6 Hz, O=CCH_2), 2.72 (4H, t, ^3J=6.2 Hz, NCH_2COR), 2.84 (2H, t, ^3J=6.4 Hz, NCH_2CCO), 3.40–3.75 (6H, m, CH_2Me, BnONCH_2), 3.85–3.95 (4H, m, NHCH_2), 4.11 (4H, t, ^3J=6.2 Hz, $NCCH_2OR$), 4.49 (1H, t, ^3J=5.6 Hz, CHO_2), 4.78 (2H, s, N–O–CH_2Ph), 5.08 (4H, s, C–O–CH_2Ph), 5.13 (4H, s, C–O–CH_2Ph), 5.78 (2H, dt, $^3J_{trans}$=15.7, ^4J=1.7 Hz, O=CCH=C), 6.78 (2H, dt, $^3J_{trans}$=15.7, ^3J=4.6 Hz, O=CC=CH), 7.05–7.15 (4H, m), 7.30–7.55 (25H, m), 7.70–7.80 (2H, m), 8.12 (2H, t, ^3J=6.0 Hz, NH); δ_C (75 MHz; $CDCl_3$) 15.3, 29.7, 29.8, 31.1, 40.3, 50.2, 52.7, 61.3, 62.4, 71.3, 76.3, 76.5, 100.9, 117.3, 121.5, 123.4, 124.4, 126.7, 127.7, 128.2, 128.7, 128.9, 129.3, 130.0, 136.1, 136.3, 144.2, 146.9, 151.6, 165.1, 165.7. Anal. Calcd for $C_{71}H_{78}N_4O_{14}$: C, 70.4; H, 6.5; N, 4.6. Found: C, 70.2; H, 6.4; N, 4.7%.

3.1.2.5. Aldehyde 23a. To a solution of **22a** (0.90 g, 0.75 mmol) in acetone (15 mL) at 0 °C aqueous HCl (10 mL, 10%) was added. The mixture was stirred for 3 h while warming up to room temperature. The pH was adjusted to 7 by addition of aqueous NaOH and most of the solvent was removed under reduced pressure. Ethyl acetate (20 mL) was added and the organic phase was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (silica gel 60, cyclohexane/ethyl acetate 1:2 v/v, R_f 0.48) to give aldehyde **23a** (0.74 g, 88%) as a pale yellow, highly viscous mass; ν_{max}/cm^{-1} 2931, 1722, 1663, 1581, 1454; δ_H (300 MHz; $CDCl_3$) 2.50 (2H, t, ^3J=6.3 Hz, O=CCH_2), 2.55–2.65 (2H, m, CH_2CHO), 2.75–2.95 (6H, m, NCH_2), 3.89 (2H, t, ^3J=5.8 Hz, BnONCH_2), 4.18 (4H, t, ^3J=6.1 Hz, $NCCH_2OR$), 4.73 (2H, s, N–O–CH_2Ph), 4.86 (4H, dd, ^3J=4.8, ^4J=1.9 Hz, CH_2C=C), 5.11 (8H, s, C–O–CH_2Ph), 6.08 (2H, dt, $^3J_{trans}$=15.9, ^4J=1.9 Hz, O=CCH=C), 7.02 (2H, dt, $^3J_{trans}$=15.9, ^3J=4.8 Hz, O=CC=CH), 7.10–7.30 (6H, m), 7.35–7.55 (25H, m), 9.71 (1H, d, ^3J=2.5 Hz, CHO); δ_C (75 MHz; $CDCl_3$) 30.7, 41.2, 50.0, 52.6, 62.5, 70.8, 71.2, 75.5, 76.3, 118.2, 122.7, 123.8, 125.3, 126.1, 127.2, 127.5, 127.7, 128.0, 128.2, 128.7, 136.3, 137.0, 141.2, 150.8, 152.6, 163.1, 163.9, 165.4, 200.0. Anal. Calcd for $C_{67}H_{66}N_2O_{15}$: C, 70.6; H, 5.8; N, 2.5. Found: C, 70.4; H, 6.0; N, 2.4%.

3.1.2.6. Aldehyde 23b. Analogously to **23a** (Section 3.1.2.5), **23b** (0.63 g, 90%) was obtained as a pale yellow foamy mass from **22b** (0.75 g, 0.63 mmol); R_f 0.34 (cyclohexane/ethyl acetate 1:4 v/v); ν_{max}/cm^{-1} 2957, 1718, 1654, 1576, 1526, 1476; δ_H (300 MHz; $CDCl_3$) 2.55–2.70 (4H, m, CH_2CHO, O=CCH_2,), 2.80–3.05 (6H, m, NCH_2), 3.85 (2H, t, ^3J=6.3 Hz, BnONCH_2), 3.90–4.00 (4H, m, NHCH_2), 4.21 (4H, t, ^3J=6.0 Hz, $NCCH_2OR$), 4.76 (2H, s, N–O–CH_2Ph), 5.07 (4H, s, C–O–CH_2Ph), 5.13 (4H, s, C–O–CH_2Ph), 5.78 (2H, dt, $^3J_{trans}$=15.7, ^4J=1.7 Hz, O=CCH=C), 6.79 (2H, dt, $^3J_{trans}$=15.7, ^3J=4.7 Hz, O=CC=CH), 7.05–7.15 (4H, m), 7.25–7.50 (25H, m), 7.70–7.80 (2H, m), 8.14 (2H, t, ^3J=6.0 Hz, NH), 9.70 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 31.2, 40.2, 41.1, 49.9, 52.5, 62.8, 71.2, 76.4, 76.6, 117.2, 123.2, 124.4, 126.6, 127.5, 127.7, 128.0, 128.3, 128.6, 128.8, 129.1, 129.4, 134.0, 136.1, 136.3, 144.3, 147.8, 151.6, 163.8, 165.0, 165.4, 200.0. Anal. Calcd for $C_{67}H_{68}N_4O_{13}$: C, 70.8; H, 6.0; N, 4.9. Found: C, 70.5; H, 5.8; N, 4.8%.

3.1.2.7. Pentabenzylated conjugate 24a. A solution of methyl 6-aminopenicillanate **4** (110 mg, 0.48 mmol), **3** (174 mg, 0.58 mmol), **23a** (705 mg, 0.48 mmol) and a catalytic amount of benzoic acid in THF (20 mL) was stirred at room temperature over night. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel 60, cyclohexane/ethyl acetate 1:2 v/v, R_f 0.33) to yield **24a** (415 mg, 62%) as a colourless foamy solid; ν_{max}/cm^{-1} 2926, 1785, 1723, 1653, 1581, 1474; δ_H (300 MHz; $CDCl_3$) 1.46 (3H, s, CH_3), 1.61 (3H, s, CH_3'), 2.45–2.55 (4H, m, O=CCH_2, BnONCCH_2), 2.70–2.90 (6H, m, NCH_2), 3.71 (2H, t, ^3J=5.9 Hz, BnO–N–CH_2), 3.77 (3H, s, OCH_3), 4.12 (4H, t, ^3J=6.2 Hz, $NCCH_2OR$), 4.39 (1H, s, CHCO_2Me), 4.76 (2H, s, N–O–CH_2Ph), 4.83 (4H, dd, ^3J=4.8, ^4J=1.8 Hz, OCH_2C=C), 5.06 (4H, s, C–O–CH_2Ph), 5.12 (4H, s, C–O–CH_2Ph), 5.52 (1H, d, ^3J=4.3 Hz, SCH), 5.72 (1H, dd, ^3J=4.3, ^3J=7.1 Hz, SCHCH), 5.85 (1H, d, $^3J_{trans}$=16.0 Hz, NCOCH=C), 6.06 (2H, dt, $^3J_{trans}$=15.9, ^4J=1.8 Hz, OCOCH=C), 6.31 (1H, d, ^3J=7.1 Hz, NH), 6.80 (1H, dt, $^3J_{trans}$=16.0, ^3J=4.6 Hz, NCOC=CH), 6.93 (2H, dt, $^3J_{trans}$=15.9, ^3J=4.8 Hz, OCOC=CH), 7.05–7.20 (6H, m), 7.30–7.55 (25H, m); δ_C (75 MHz; $CDCl_3$) 27.0, 29.6, 30.9, 31.4, 50.3, 52.4, 52.7, 58.6, 62.7, 63.0, 64.8, 68.1, 70.5, 71.0, 71.3, 75.6, 76.4, 118.3, 122.7, 123.8, 125.0, 126.2, 126.8, 127.1, 127.4, 127.7, 128.0, 128.1, 128.5, 136.1, 136.4, 137.0, 141.5, 149.9, 152.8, 163.5, 164.0, 165.6, 168.1, 170.7, 173.8. Anal. Calcd for $C_{78}H_{82}N_4O_{18}S$: C, 67.1; H, 5.9; N, 4.0. Found: C, 66.8; H, 6.1; N, 4.1%.

3.1.2.8. Pentabenzylated conjugate 24b. Analogously to **24a** (Section 3.1.2.7), **24b** (298 mg, 51%) was obtained as a pale yellow foamy solid from **4** (97 mg, 0.42 mmol), **3** (154 mg, 0.51 mmol) and **23b** (610 mg, 0.42 mmol); R_f 0.30 (cyclohexane/ethyl acetate 1:4 v/v); ν_{max}/cm^{-1} 2928, 1783, 1719, 1661, 1576, 1524; δ_H (300 MHz; $CDCl_3$) 1.44 (3H, s, CH_3), 1.62 (3H, s, CH_3'), 2.40–2.55 (4H, m, O=CCH_2, BnONCCH_2), 2.73 (4H, t, ^3J=6.2 Hz, NCH_2COR), 2.86 (2H, t, ^3J=6.4 Hz, NCH_2CCO), 3.67 (2H, t, ^3J=5.8 Hz, BnO–N–CH_2), 3.71 (3H, s, OCH_3), 3.90–4.00 (4H, m, NHCH_2), 4.11 (4H, t, ^3J=6.2 Hz, $NCCH_2OR$), 4.35 (1H, s, CHCO_2Me), 4.74 (2H, s, N–O–CH_2Ph), 5.06 (4H, s, C–O–CH_2Ph), 5.13 (4H, s, C–O–CH_2Ph), 5.51 (1H, d, ^3J=4.2 Hz, SCH), 5.70–5.85 (3H, m, SCHCH, OCOCH=C), 5.79 (1H, d, $^3J_{trans}$=15.8 Hz, NCOCH=C), 6.46 (1H, d, ^3J=7.3 Hz, NH), 6.65–6.80 (3H, m, NCOC=CH, OCOC=CH), 7.05–7.15 (4H, m), 7.25–7.50 (25H, m), 7.90–8.00 (2H, m), 8.13 (2H, t, ^3J=7.1 Hz, NH); δ_C (75 MHz; $CDCl_3$) 27.0, 32.1, 32.3, 34.8, 40.2, 49.7, 52.3, 52.6, 58.1, 58.2, 62.4, 64.6, 68.8, 70.5, 71.3, 76.4, 76.6, 117.3, 121.5, 123.3, 124.3, 126.6, 127.2, 127.5, 128.0, 128.4, 128.6, 128.7, 128.8, 129.0, 136.1, 136.3, 137.5, 144.1, 146.8, 152.6, 161.2, 163.8, 165.1, 165.8, 170.6, 174.0. Anal. Calcd for $C_{78}H_{84}N_6O_{16}S$: C, 67.2; H, 6.1; N, 6.0. Found: C, 66.9; H, 6.2; N, 5.9%.

3.1.2.9. Conjugate 2a. Analogously to **13a** (Section 3.1.1.13), **2a** (161 mg, 60%) was obtained after a 24 h reaction period as a colourless solid of mp 154–156 °C from **24a** (400 mg, 0.29 mmol), $[\alpha]_D^{20}$ 48 (*c* 1.0, EtOH); ν_{max}/cm^{-1} 3358, 2930, 1785, 1738, 1681, 1635; δ_H (300 MHz; MeOD-d_3) 1.38 (3H, s, CH_3), 1.55 (3H, s, CH_3'), 1.55–1.70 (4H, m, $ONCH_2(CH_2)_2$), 2.05–2.25 (6H, m, $OCOCCH_2$, NH(CO)CH_2), 2.65 (2H, t, ^3J=6.1 Hz, ON(CO)CH_2), 2.80–3.00 (6H, m, NCH_2), 3.25 (4H, t, ^3J=5.9 Hz, $OCOCH_2$), 3.67 (2H, t, ^3J=5.8 Hz, $ONCH_2$), 3.70 (3H, s, OCH_3), 4.12 (4H, t, ^3J=6.0 Hz, $NCCH_2OR$), 4.35–4.45 (5H, m, $OCOCH_2$, CHCO_2Me), 5.50 (1H, d, ^3J=4.6 Hz, SCH), 5.70–5.80 (1H, m, SCHCH), 6.73 (2H, t, ^3J=8.1 Hz, H^{ar}), 6.93 (2H, dd, ^3J=8.1, ^4J=1.7 Hz, H^{ar}), 7.20 (2H, dd, ^3J=8.1, ^4J=1.7 Hz, H^{ar}); δ_C (75 MHz; MeOD-d_3) 23.7, 26.3, 27.1, 27.4, 30.8, 31.3, 31.8, 33.9, 48.0, 52.5, 52.7, 54.3, 58.2, 62.8, 63.4, 64.5, 70.4, 76.1, 117.8, 118.6, 119.2, 125.9, 147.8, 151.2, 168.1, 169.2, 171.5, 172.0, 174.6, 175.6. Anal. Calcd for $C_{43}H_{56}N_4O_{18}S$: C, 54.4; H, 6.0; N, 5.9. Found: C, 54.0; H, 5.8; N, 6.1%.

3.1.2.10. Conjugate 2b. Analogously to **13a** (Section 3.1.1.13), **2b** (118 mg, 64%) was obtained after a 24 h reaction period as a faintly yellow solid of mp 160–163 °C from **24b** (280 mg, 0.20 mmol), $[\alpha]_D^{20}$ 46 (*c* 1.0, EtOH); ν_{max}/cm^{-1} 3356, 2928, 1782, 1741, 1680, 1642, 1584; δ_H (300 MHz; MeOD-d_3) 1.40 (3H, s, CH_3), 1.59 (3H, s, CH_3'), 1.60–1.75 (4H, m, $ONC(CH_2)_2$), 2.10–2.25 (4H, m, $NHCH_2CH_2$), 2.24 (2H, t, ^3J=6.1 Hz, $NCOCH_2$), 2.69 (2H, t, ^3J=6.0 Hz, $ONCOCH_2$), 2.80–3.00 (6H, m, NCH_2), 3.23 (4H, t, ^3J=5.8 Hz, $OCOCH_2$), 3.68 (3H, s, OCH_3), 3.70–3.90 (6H, m, NHCH_2, HONCH_2), 4.14 (4H, t, ^3J=6.1 Hz, $NCCH_2OR$), 4.33 (1H, s, CHCO_2Me), 5.48 (1H, d, ^3J=4.4 Hz, SCH), 5.75–5.85 (1H, m, Hz, SCHCH), 6.70 (2H, t, ^3J=8.0 Hz, H^{ar}), 6.92 (2H, dd, ^3J=8.0, ^4J=1.5 Hz, H^{ar}), 7.21 (2H, dd, ^3J=8.0, ^4J=1.5 Hz, H^{ar}), 8.02 (2H, t, ^3J=7.3 Hz, NH); δ_C (75 MHz; MeOD-d_3) 23.5, 25.8, 27.0, 27.2, 31.5, 31.9, 32.4, 33.8, 40.0, 48.3, 52.4, 52.5, 54.0, 58.1, 63.3, 63.6, 71.3, 76.1, 117.3, 118.8, 119.6, 119.9, 148.0, 150.5, 165.7, 168.8, 170.1, 170.7, 172.0, 174.9. Anal. Calcd for $C_{43}H_{58}N_6O_{16}S$: C, 54.5; H, 6.2; N, 8.9. Found: C, 54.7; H, 6.1; N, 8.7%.

3.1.3. Chelators 25[20] and 26[21] lacking siderophore activity.

3.1.3.1. Biscatechol-salicylate 25a. Colourless solid of mp 107–108 °C; ν_{max}/cm^{-1} 3362, 2930, 1734, 1692, 1588; δ_H (300 MHz; MeOD-d_3) 1.95–2.10 (4H, m, $OCOCCH_2$), 2.42 (4H, t, ^3J=7.1 Hz, $OCOCH_2C$), 2.75–2.95 (6H, m, NCH_2), 4.08 (4H, t, ^3J=5.6 Hz, $NCCH_2OR$), 4.25–4.40 (6H, m, $NCCH_2OR'$, $OCCCCH_2$), 6.75–6.85 (2H, m, H^{ar}), 6.90–7.05 (4H, m, H^{ar}), 7.20–7.35 (4H, m, H^{ar}); δ_C (75 MHz; MeOD-d_3) 25.1, 32.8, 54.4, 54.6, 64.1, 64.7, 65.8, 113.8, 119.2, 120.5, 121.4, 128.8, 129.6, 131.2, 136.9, 146.8, 147.2, 151.6, 162.8, 171.7, 174.6, 175.3. Anal. Calcd for $C_{35}H_{39}NO_{15}$: C, 58.9; H, 5.5; N, 2.0. Found: C, 58.6, H, 5.4, N, 2.1%.

3.1.3.2. Biscatechol-salicylate 25b. Colourless solid of mp 111–113 °C; ν_{max}/cm^{-1} 3363, 2928, 1737, 1642, 1583, 1460; δ_H (300 MHz; MeOD-d_3) 1.85–1.95 (4H, m, $OCCCH_2$), 2.39 (4H, t, ^3J=7.0 Hz, $OCCH_2C$), 2.80–2.95 (6H, m, NCH_2), 3.30–3.40 (4H, m, NHCH_2), 4.17 (4H, t, ^3J=5.6 Hz, $NCCH_2OR$), 4.51 (2H, t, ^3J=5.5 Hz, $NCCH_2OR'$), 6.65–6.85 (4H, m, H^{ar}), 7.00–7.30 (6H, m, H^{ar}); δ_C (75 MHz; MeOD-d_3) 25.5, 32.0, 39.6, 54.4, 54.5, 62.8, 63.6, 113.5, 117.1, 118.6, 120.3, 121.4, 121.9, 122.2, 128.0, 136.6, 148.2, 151.4, 161.3, 171.0, 171.7, 174.6. Anal. Calcd for $C_{35}H_{41}N_3O_{13}$: C, 59.1; H, 5.8; N, 5.9. Found: C, 58.7; H, 6.0; N, 5.7%.

3.1.3.3. Conjugate 26a. Pale yellow solid of mp 141–143 °C; $[\alpha]_D^{20}$ 62 (*c* 1.0, EtOH); ν_{max}/cm^{-1} 3365, 2938, 1780, 1732, 1694, 1636, 1453; δ_H (300 MHz; $CDCl_3$) 1.42 (3H, s, CH_3), 1.56 (3H, s, CH_3'), 1.95–2.10 (4H, m, $OCOCCH_2$), 2.35–2.45 (4H, m, $OCOCH_2C$), 2.75–3.00 (8H, m, NCH_2, $NH(CO)CH_2$), 3.11 (2H, t, ^3J=6.5 Hz, $NH(CO)CCH_2$), 3.74 (3H, s, OCH_3), 4.13 (4H, t, ^3J=5.7 Hz, $NCCH_2OR$), 4.30–4.45 (6H, m, $NCCH_2OR'$, $OCCCCH_2$), 4.39 (1H, s, $CHCO_2Me$), 5.48 (1H, d, ^3J=4.3 Hz, SCH), 5.71 (1H, dd, ^3J=4.3 Hz, ^3J=7.0 Hz, SCHCH), 6.32 (1H, d, ^3J=7.0 Hz, NH), 6.80–6.90 (2H, m, H^{ar}), 6.95–7.10 (3H, m, H^{ar}), 7.20–7.40 (4H, m, H^{ar}), 10.90 (5H, br, OH); δ_C (75 MHz; $CDCl_3$) 23.6, 25.2, 26.2, 29.7, 32.5, 35.3, 52.4, 54.5, 54.6, 58.2, 61.8, 63.9, 64.3, 64.7, 65.7, 70.1, 113.8, 116.3, 119.1, 120.3, 126.8, 127.3, 130.0, 131.2, 136.8, 146.6, 151.0, 162.4, 169.2, 171.1, 171.6, 172.1, 174.6, 175.5. Anal. Calcd for $C_{46}H_{55}N_3O_{18}S$: C, 57.0; H, 5.7; N, 4.3. Found: C, 56.6; H, 5.5; N, 4.5%.

3.1.3.4. Conjugate 26b. Pale yellow solid of mp 146–148 °C; $[\alpha]_D^{20}$ 57 (*c* 1.0, EtOH); ν_{max}/cm^{-1} 3360, 2932, 1781, 1741, 1675, 1639, 1585; δ_H (300 MHz; MeOD-d_3) 1.41 (3H, s, CH_3), 1.58 (3H, s, CH_3'), 1.85–1.95 (4H, m, $OCCCH_2$), 2.30–2.40 (4H, m, $OCCH_2C$), 2.80–3.05 (8H, m, NCH_2, $NH(CO)CH_2$), 3.08 (2H, t, ^3J=6.6 Hz, $NH(CO)CCH_2$), 3.30–3.45 (4H, m, $NHCH_2$), 3.72 (3H, s, OCH_3), 4.15 (4H, t, ^3J=5.6 Hz, $NCCH_2OR$), 4.50 (2H, t, ^3J=5.7 Hz, $NCCH_2OR'$), 4.35 (1H, s, $CHCO_2Me$), 5.50 (1H, d, ^3J=4.4 Hz, SCH), 5.70–5.80 (1H, m, SCHCH), 6.80–6.95 (3H, m, H^{ar}), 7.05–7.35 (6H, m, H^{ar}); δ_C (75 MHz; MeOD-d_3) 24.2, 25.6, 26.4, 29.8, 32.0, 35.3, 39.7, 52.2, 54.5, 54.7, 58.1, 62.8, 63.5, 64.1, 65.6, 69.6, 116.3, 118.2, 118.5, 119.6, 120.2, 127.4, 132.5, 135.0, 136.6, 148.2, 151.5, 161.8, 168.9, 171.2, 171.7, 172.1, 174.8, 175.6. Anal. Calcd for $C_{46}H_{57}N_5O_{16}S$: C, 57.1; H, 5.9; N, 7.2. Found: C, 56.8; H, 5.7; N, 7.0%.

3.1.4. Growth promotion assay. Siderophore activities of the chelators **13**, **18** and **25** of the conjugates **2** and **26**, and of ferrichrome were determined by measuring their ability to stimulate growth of bacterial strain *E. coli* H5596 kept under iron limitation by treatment with ethylenediamine bis(*o*-hydroxyphenyl)acetic acid (EDDA).

Agar plates containing 20 mL of Mueller–Hinton II medium (BD-Diagnostics, Heidelberg) with or without EDDA (LaboTest OHG, Niederschöna) at 100 μg mL^{-1} were inoculated with 100 μL of an *E. coli* H5596 suspension in liquid broth (opacity: Mc Farland 0.5) using a Drigalski spatula. Test samples were prepared as solutions of the respective compound in ethanol at 10, 5, 2.5 and 1 mg mL^{-1} and 15 μL of each solution was applied onto sterile 6 mm cellulose discs (CT 0998 B, Oxoid, Wesel). The ethanol was allowed to evaporate and the discs were placed upon the inoculated agar plate. The diameters in millimetre of the resulting growth zones were determined after 24 h of incubation at 36 °C.

Acknowledgements

We are indebted to Professor Klaus Hantke, Institute of Microbiology, University of Tübingen for kindly providing us with various *E. coli* mutant strains and siderophores.

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20. Prepared analogously to **18** by replacing **9** with 2-benzoxybenzoyl chloride; details are available from the authors upon request.
21. Prepared from **16**, which was esterified with 2-benzoxy-3-formylbenzoic acid to give an aldehyde. The latter was reacted with **3** and **4** and the resulting product amide was exhaustively hydrogenated to leave compound **26**. Details are available from the authors upon request.

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A brief and stereoselective synthesis of limonoid models, with antifeedant activity against *Locusts migratoria*

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Received 8 March 2006; revised 23 May 2006; accepted 24 May 2006
Available online 12 June 2006

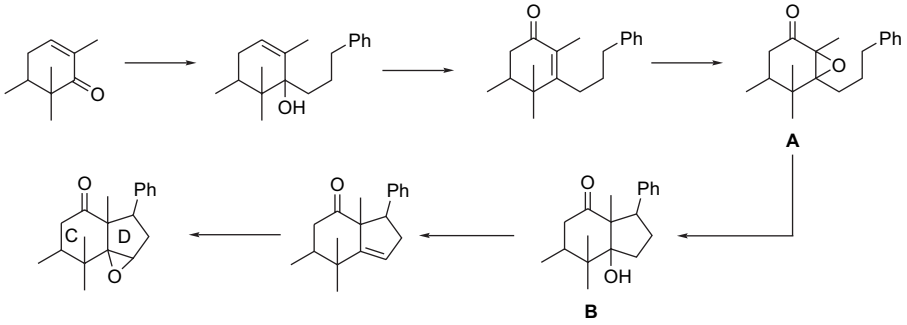
Abstract—A short stereoselective preparation of havanensin-type limonoid models is reported. The synthesis is based on a radical domino reaction of an epoxyketone to a bicyclic hydroxyketone, and is achieved in six and nine steps from simple cyclohexenones. The epoxyhavanensin derivatives show significant antifeedant activity against *Spodoptera littoralis* and *Spodoptera frugiperda*, and the epoxyketone **21** shows potent antifeedant activity against *Locusts migratoria*.

1. Introduction

The hydrindane structural unit is ubiquitous in biologically active molecules such as triterpenoids, steroids and related natural products. Limonoids are a family of degraded triterpenoids with a wide range of biological properties, that contains a structural unit of hydrindane bonded to a heterocycle, constituting the C, D and E rings. Work focused on the hydrindane angular methyl group is relatively limited, with few modes of access to a functionalized ring C, particularly on carbon C-12. Limonoids with an oxygenated function at position C-12 are among the most active of this family of natural products.[1] In connection with synthetic studies directed to the CDE structural fragments of limonoids,[2] we have delineated a new approach directed towards the synthesis of 12-oxo-14,15-epoxy havanensin derivatives, depicted in Scheme 1.

Our strategy is based on a stereoselective construction of ring D by a radical domino sequence from epoxyketone **A** to hydroxyketone **B**, in which the oxygenated functions are situated in the right position and the relative orientation of the methyl and phenyl substituents is the same as in natural limonoids. We have carried out a synthesis of two-keto epoxy limonoid analogues, that differs only on a *gem*-dimethyl group, following the sequence in the Scheme 1.

For the first synthesis, the readily available 2-methylcyclohexenone **1** was selected as the starting material.[3] Conversion of enone **1** into the key intermediate epoxyenone **4**



Scheme 1.

Keywords: Limonoids; Antifeedant; Radical domino cyclization.
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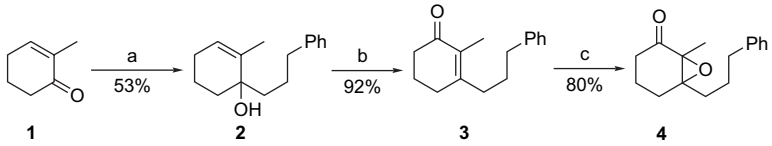
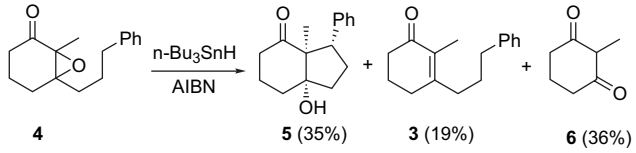
doi:10.1016/j.tet.2006.05.059



Scheme 2. Reaction conditions: (a) $BrCH_2CH_2CH_2Ph$, Li, THF, 25 °C; (b) PCC, CH_2Cl_2, 25 °C and (c) H_2O_2, NaOH, 20 °C.

was achieved in a three-step sequence. Thus, a Barbier reaction[4] of enone **1** with 1-bromo-3-phenylpropane and lithium furnished the allylic alcohol **2** in 53% yield. Oxidation of alcohol **2** using PCC in CH_2Cl_2 afforded the unsaturated ketone **3** in quantitative yield,[5] which was subsequently converted into epoxyketone **4** by treatment with alkaline hydrogen peroxide in 80% yield (Scheme 2).[6]

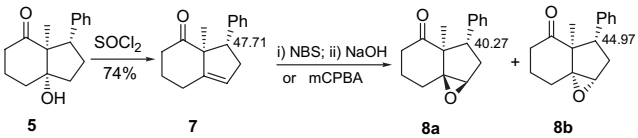
The radical domino reaction of epoxyketone **4** was carried out with AIBN and tributyltin hydride in toluene at reflux. The reaction rate of the epoxyketone **4** was slower as compared to the demethyl derivative in the literature.[7] After 8 h, a 70% conversion of the starting material was achieved (Scheme 3).



Scheme 3.

The expected bicyclic hydroxyketone **5** was obtained in 35% yield, together with another two compounds: the deoxygenation product, enone **3** (19%) and the side-chain fragmentation product, diketone **6** (36%). Other reaction conditions, longer times and several AIBN/*n*-Bu_3SnH/substrate ratios, furnish poorer yields of **5**. The structure assigned to **5** was based on the ^1H NMR signal: the methyl group at 0.78 ppm appears highly shielded by the phenyl ring, and the hydrogen geminal to the phenyl ring at 4.09 ppm as a quartet is deshielded by the nearby carbonyl group.

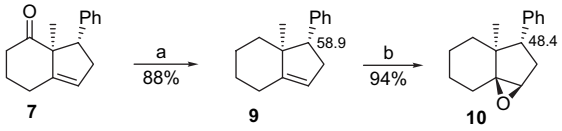
Although the yield of the hydroxyketone **5** in the latter domino reaction was not very high, the sequence is short, easy and stereoselective, and would be competitive with respect to other classic methods. In addition, the two side-products from the domino reaction could be readily recycled. Fortunately, the dehydration of hydroxyketone **5** with thionyl chloride at 0 °C was totally regioselective, affording the desired unsaturated ketone **7** in 74% yield (Scheme 4). The epoxidation of hydrindenone **7** was achieved by two methods, which respectively afforded the two different diastereomers. Treatment of **7** with NBS in water followed by NaOH addition afforded epoxyketone **8b** in 63% yield. In other way, treatment of **7** with *m*-CBPA at 20 °C furnished epoxyketone **8a** in 94% yield.



Scheme 4.

The structural assignation of the epoxides was based on experience gained with analogous compounds described by us elsewhere, in which oxidation with *m*-CBPA afforded always the *endo*-epoxide isomer **8a**.[2a,c,g,j,l,m] Additionally, the γ effect in ^{13}C NMR was considered.[2a,c,g,j,l,m] The difference in the chemical displacement of benzylic carbon between **8a** and **7** (7.5 ppm) was enhanced with respect to the pair **8b** and **7** (2.7 ppm). The shielding effect of the phenyl ring on the protons of the angular methyl group determined the cis relationship between both groups in diastereomers **8a** and **8b,** which appear in ^1H NMR at 0.97 and 0.81, respectively. The benzylic proton is observed to a lower field for **8b** (4.30 ppm) than for isomer **8a** due to deshielding effect of carbonyl group. The δ values in ^{13}C NMR of the isomer **8a** are in agreement with those *endo*-epoxides described by us elsewhere.[2a,c,g,j,l,m] The oxirane carbon (CH) chemical shift for the isomer **8b** are at a lower field (64.3 ppm) than the value observed for *endo*-epoxides,[2a,c,g,j,l,m] which are in the range 56–60 ppm.

For studies of structure–activity relationships (SAR) we obtained deoxoderivative **10** from **7**, following the sequence depicted in (Scheme 5).

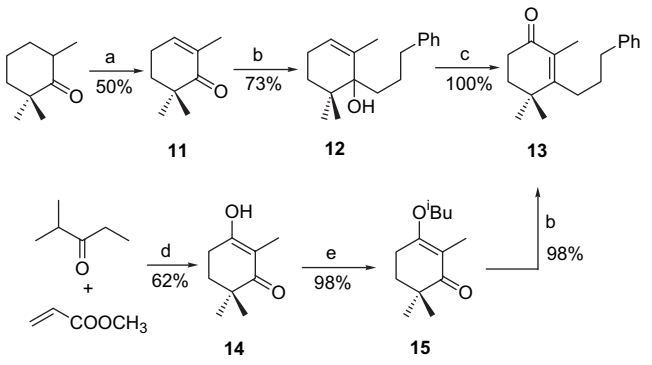


Scheme 5. Reaction conditions: (a) diethylene glycol, Na, N_2H_4 and (b) *m*-CPBA, CH_2Cl_2.

Synthesis of the trimethyl epoxyketone **21** was achieved in two parallel ways through epoxyketone **16**. The first method started with the readily available 2,6,6-trimethylcyclohexenone and comprised four steps: bromination followed by dehydrobromination introduced the required double bond. Addition of the side chain in **11** was done by the Barbier reaction with 1-bromo-3-phenylpropane and lithium. Finally oxidation of the allylic alcohol **12** with PCC/SiO_2 afforded enone **13** in 36% overall yield.

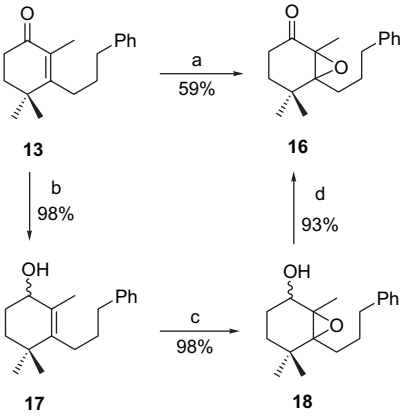
The alternative procedure is easier than the previous one, and only required three steps from 2-methyl-3-pentanone and methyl acrylate: double condensation with sodium methoxide following the M.P. Sammes conditions[8] afforded diketone **14**. Selective ketone protection through enol ether formation[9] to **15** followed by Barbier reaction afforded, after hydrolysis, the required enone **13** in 59% overall yield (Scheme 6).

Epoxidation of enone **13** was accomplished using two alternative methods: the direct one with alkaline water peroxide, which afforded epoxyketone **16** in 59% yield, and the longer indirect route through the allylic alcohol **17**, followed by



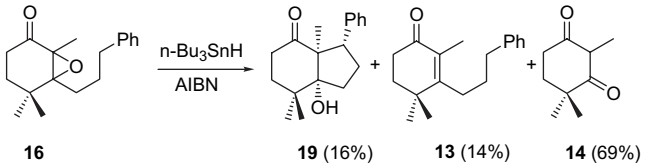
Scheme 6. Reaction conditions: (a) i. NBS, CCl_4 and ii. Li_2CO_3, 25 °C; (b) $BrCH_2CH_2CH_2Ph$, Li, THF, 25 °C; (c) PCC, CH_2Cl_2, 25 °C; (d) NaOMe, xylene, 25 °C and (e) ^{i}BuOH, *p*-TsOH, benzene, 80 °C.

epoxidation with *m*-CPBA and Jones oxidation, in a 89% overall yield (Scheme 7).



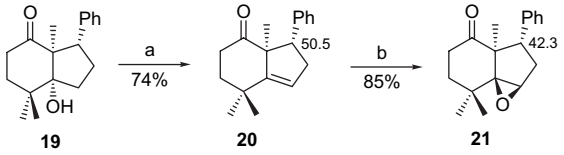
Scheme 7. Reaction conditions: (a) H_2O_2, NaOH, 25 °C; (b) $LiAlH_4$, diethyl ether, 25 °C; (c) *m*-CPBA, CH_2Cl_2, 25 °C and (d) Jones reagent, acetone 0 °C.

After 8 h, the domino reaction of epoxyketone **16** carried out under the same conditions as the demethyl analogue **4**, afforded a mixture of the expected hydroxyketone **19** (16%), the unsaturated ketone **13** (14%) and the diketone **14** (69%). On comparing the results of the domino reaction of epoxyketones **4** and **16**, we observed low conversion for the trimethylketone **16** with respect to the monomethylketone **4**, together an increase in the product arising from the side-chain cleavage. From these results it may be inferred that an increase in substituents around the oxirane slows down the radical reaction and promotes fragmentation of the alkoxyl radical before the 1,5 hydrogen transfer. In spite of these negative aspects, the reaction has other positive aspects such as brevity and stereoselectivity. Additionally, the byproducts could be recycled (Scheme 8).



Scheme 8.

In order to obtain the CDE 12-oxo-14,15-epoxyazadirone fragment **21** from hydroxyketone **19**, only two steps were needed. Dehydration of **19** with thionyl chloride at 0 °C afforded the unsaturated ketone **20** almost quantitatively. Epoxidation of **20** with *m*-CPBA finally afforded the target compound **21** in 85% yield (Scheme 9).



Scheme 9. Reaction conditions: (a) $SOCl_2$, CH_2Cl_2, 0 °C and (b) *m*-CPBA, CH_2Cl_2, −10 °C.

2. Biological results

Larvae of the African leafworms *Spodoptera littoralis* and *Spodoptera frugiperda* were used to assess the antifeedant activity of our molecular fragments.[10] In the series of model compounds related to havanensin, the racemic β-epoxide **8a** was slightly more active than α-epoxide **8b**, and less active than the racemic trimethyl derivative **21** against *S. littoralis* and *S. frugiperda*. The deoxo β-epoxide **10** was the most active of the series.

The 12-oxo-14,15-epoxy havanensin derivative **21** was found to be a very potent antifeedant against *Locusts migratoria*. The larvae died when they had ingested some of the epoxyketone **21**; this is a species of locusts that does not find azadirachtin a very potent insect antifeedant (Table 1).

Table 1. Antifeedant index of the compounds tested in choice bioassays

	Antifeedant index at 100 ppm[a]	
	S. littoralis	*S. frugiperda*
8a	22 (5.7)	22 (3.7)
8b	20 (5.7)	14 (7.6)
10	43 (4.9)	23 (6.8)
21	30 (3.6)	21 (5.4)

[a] Antifeedant index=$[(C-T)/(C+T)]$% of compounds tested in choice bioassays with glass fibre discs (control (C) vs treatment (T)) (n=20).

3. Experimental

3.1. General

Commercial reagents were used as received. Dichloromethane and pyridine were distilled under nitrogen over calcium hydride. Ether and THF were distilled from sodium. Acetone, benzene and hexane were distilled before use. Melting points were determined on a hot-stage apparatus and are not corrected. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 and 50 MHz, respectively. IR spectra were obtained as films. Mass spectra were obtained on a VG-TS 250 instrument. All reactions were carried out under an atmosphere of nitrogen in glassware dried overnight and cooled under nitrogen. TLC monitored reactions. Column chromatography was performed on using silica gel 60 (0.040–0.063 mm, Merck). Organic extracts

were washed with saturated NaCl solution, dried with anhydrous Na_2SO_4 and concentrated under reduced pressure with the aid of rotary evaporator.

3.1.1. 2-Methyl-1-(3-phenyl-propyl)-cyclohex-2-enol 2. A solution of 2-methylcyclohex-2-enone **1** (15.5 g, 137 mmol) and 1-bromo-3-phenylpropane (41 g, 206 mmol) in THF (13 mL) was added via a dropping funnel to a stirred suspension of lithium (3.4 g, 480 mmol) in THF (152 mL) at room temperature under argon. The reaction mixture was vigorously stirred for 7 h. The mixture was filtered to remove excess lithium and the solvent was evaporated at reduced pressure. The residue was hydrolyzed with hydrochloric acid, and the two-phase system was extracted with ether. The combined ethereal extracts were washed with aqueous $NaHCO_3$ (5%) and brine. Removal of the solvent afforded a crude residue, which was purified by chromatography. Eluting with hexane–ethyl acetate (9:1) furnished enone **1** (1 g, 7%), as a colourless oil. Eluting with hexane–ether (8:2) afforded the unsaturated alcohol **2** (8 g, 53%), as a colourless oil: IR 3408, 2941, 1086 cm^{-1}; ^1H NMR δ: 1.65 (3H, s), 1.3–1.7 (8H, m), 1.95 (2H, m), 2.61 (2H, m), 5.52 (1H, br s), 7.1–7.2 (5H, m) ppm; ^{13}C NMR δ: 17.5 (CH_3), 18.9 (CH_2), 25.5 (CH_2), 25.9 (CH_2), 35.2 (CH_2), 38.2 (CH_2), 38.6 (CH_2), 71.8 (C), 125.5 (CH), 126.1 (CH), 128.1 (2CH), 128.2 (2CH), 137.1 (C), 142.2 (C) ppm; MS *m*/*z* (relative intensity) 212 (11, M^+-18), 121 (49), 11 (58), 93 (80), 91 (100), 79 (52), 65 (42), 55 (31); HRMS (ESI): 231.1768 (M^++H, $C_{16}H_{23}O$), calcd 231.1744.

3.1.2. 2-Methyl-3-(3-phenyl-propyl)-cyclohex-2-enone 3. To a stirred suspension of PCC (9.97 g, 46.2 mmol) and silica (10 g) in CH_2Cl_2 (300 mL) was added dropwise a solution of the alcohol **2** (7 g, 30.4 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was vigorously stirred at room temperature under argon for 1 h. The resulting dark brown slurry was filtered through a short column of silica and eluted with CH_2Cl_2. Removal of the solvent afforded cyclohexenone **3** (6.9 g, 98%), as a colourless oil: IR 2950, 1661, 1450 cm^{-1}; ^1H NMR δ: 1.73 (3H, s), 1.7–2.0 (4H, m), 2.35 (6H, m), 2.65 (2H, m), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 9.8 (CH_3), 21.8 (CH_2), 28.2 (CH_2), 30.1 (CH_2), 34.1 (CH_2), 35.2 (CH_2), 37.0 (CH_2), 125.3 (CH), 127.6 (4CH), 130.3 (C), 140.9 (C), 157.6 (C), 198.2 (C) ppm; MS *m*/*z* (relative intensity) 228 (3, M^+), 124 (49), 104 (100), 91 (69), 65 (39), 53 (51); HRMS (ESI): 229.1542 (M^++H, $C_{16}H_{21}O$), calcd 229.1587.

3.1.3. 1-Methyl-6-(3-phenyl-propyl)-7-oxa-bicyclo-[4.1.0]heptan-2-one 4. To a stirred solution of enone **3** (6.1 g, 26.7 mmol) in methanol (232 mL) at 0 °C under argon, were added dropwise H_2O_2 (40 mL, 30%) and a solution of NaOH (14 mL, 6 N). This resulting solution was stirred for 6 h at room temperature, and then poured into a solution of $Na_2S_2O_3$ (10%). The methanol was evaporated off and the aqueous solution was extracted with ether. The organic extracts were washed with brine, dried and filtered. Removal of the solvent afforded a crude residue, which was purified by chromatography. Eluting with hexane–ethyl acetate (8:2) furnished epoxyketone **4** (5.2 g, 80%), as a colourless oil: IR 3027, 2961, 1710, 1459 cm^{-1}; ^1H NMR δ: 1.36 (3H, s), 1.6–2.2 (10H, m), 2.60 (2H, m), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 11.3 (CH_3), 17.6 (CH_2), 26.8 ($2CH_2$), 33.0 (CH_2), 35.5 (CH_2), 35.9 (CH_2), 64.4 (C), 68.5 (C), 125.7 (CH), 128.1 (4CH), 141.3 (C), 207.1 (C) ppm; MS *m*/*z* (relative intensity) 244 (2, M^+), 104 (35), 91 (100), 77 (25), 65 (38), 55 (46); HRMS (ESI): 245.1512 (M^++H, $C_{16}H_{21}O_2$), calcd 245.1536.

3.1.4. Cyclization of the epoxyketone 4 with *n*-Bu_3SnH. A solution of tributyltin hydride (1.7 mL, 6.3 mmol) in benzene (85 mL) was added via a dropping funnel to a refluxing solution of the epoxyketone **4** (5.1 g, 20.9 mmol) and AIBN (1.04 mmol) in benzene (700 mL) under argon. The reaction mixture was refluxed for 8 h. Removal of the solvent afforded a crude residue, which was purified by chromatography. Eluting with hexane–ethyl acetate (9:1) furnished epoxyketone **4** (1.5 g, 30%), as a colourless oil. Eluting with hexane–ethyl acetate (8:2) furnished enone **3** (605 mg, 19%), as a colourless oil. Eluting with hexane–ethyl acetate (1:1) furnished 7a-hydroxy-3a-methyl-3-phenyl-octahydro-inden-4-one **5** (1.25 g, 35%), as a colourless oil: IR 3440, 2865, 1710 cm^{-1}; ^1H NMR δ: 0.79 (3H, s), 1.6–2.4 (8H, m), 2.47 (1H, m), 2.61 (1H, m), 4.07 (1H, t, J=9 Hz), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 14.3 (CH_3), 21.3 (CH_2), 27.0 (CH_2), 34.7 (CH_2), 37.4 (CH_2), 37.6 (CH_2), 48.5 (CH), 62.9 (C), 85.2 (C), 126.4 (CH), 127.9 (2CH), 129.1 (2CH), 141.1 (C), 213.6 (C) ppm; MS *m*/*z* (relative intensity) 244 (4, M^+), 170 (91), 155 (51), 115 (94), 91 (100), 77 (63), 65 (37), 55 (83); HRMS (ESI): 245.1571 (M^++H, $C_{16}H_{21}O_2$), calcd 245.1536. Eluting with ethyl acetate furnished 2-methyl-1,3-cyclohexanodione **6** (0.66 g, 36%), as a white solid identified by comparison with a standard.

3.1.5. 3a-Methyl-3-phenyl-2,3,3a,5,6,7-hexahydro-inden-4-one 7. To a solution of the hydroxyketone **5** (1.13 g, 4.65 mmol) in dry CH_2Cl_2 (23 mL) at 0 °C under argon were gradually added pyridine (1.3 mL) and $SOCl_2$ (0.67 mL, 9.3 mmol). The mixture was stirred at 0 °C for 20 min and then poured into ice water. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with $NaHCO_3$ (5%) and brine, and then dried (Na_2SO_4). Evaporation of the solvent left a crude, which was purified by flash chromatography. Elution with hexane–ethyl acetate (93:7) afforded the unsaturated ketone **7** (774 mg, 74%), as a colourless oil: IR 2950, 1711 cm^{-1}; ^1H NMR δ: 0.92 (3H, s), 1.63 (1H, m), 2.10 (1H, m), 2.2–2.8 (6H, m), 4.06 (1H, t J= 9.5 Hz), 5.46 (1H, s), 7.1–7.6 (5H, m) ppm; ^{13}C NMR δ: 19.9 (CH_3), 25.7 (CH_2), 26.3 (CH_2), 34.9 (CH_2), 38.6 (CH_2), 47.7 (CH), 63.5 (C), 121.92 (CH), 126.0 (CH), 127.7 (2CH), 129.8 (2CH), 141.0 (C), 146.5 (C), 214.0 (C) ppm; MS *m*/*z* (relative intensity) 226 (82, M^+), 211 (58), 169 (100), 155 (81), 115 (70), 91 (81), 77 (56), 65 (930), 55 (41); HRMS (ESI): 227.1439 (M^++H, $C_{16}H_{19}O$), calcd 227.1431.

3.1.6. 3a-Methyl-3-phenyl-hexahydro-1-oxa-cyclopropa-[*c*]inden-4-one 8. To a stirred solution of ketone **7** (210 mg, 0.9 mmol) in acetone (5 mL) and water (0.5 mL) at 0 °C under argon was added NBS (739 mg, 4.1 mmol). The resulting mixture was gradually warmed to room temperature and then, stirred for 1 h, after this hours was poured into water (3 mL) and extracted three times with ether. The combined extracts were washed with brine and then dried (Na_2SO_4). The solvent was evaporated off at reduced

pressure to afford a colourless residue (276 mg), which was dissolved in THF (3 mL). To this stirred solution, at 0 °C, under argon was added NaOH (0.5 mL, 5 M). The reaction mixture was stirred for 45 min, and then H_2O was added, and extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography over silica gel (hexane–ether, 80:20) gave epoxyketone **8b** (133 mg, 63%), as a white solid: mp 109 °C; IR 3023, 2955, 1707, 1460 cm^{-1}; ^1H NMR δ: 0.81 (3H, s), 1.71 (2H, m), 2.0–2.6 (6H, m), 3.41 (1H, s), 4.30 (1H, dd, J=6 Hz, J'=5.5 Hz), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 18.0 (CH_3), 21.2 (CH_2), 26.0 (CH_2), 34.1 (CH_2), 37.2 (CH_2), 44.9 (CH), 61.0 (C), 64.3 (CH), 71.0 (C), 125.8 (CH), 127.7 (2CH), 130.4 (2CH), 143.6 (C), 211.9 (C) ppm; Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.30; H, 7.49. Found: C, 79.39; H, 7.38; MS m/z (relative intensity) 242 (23, M^+), 227 (59), 199 (43), 169 (37), 143 (49), 128 (59), 115 (78), 104 (44), 91 (93), 77 (74), 65 (39), 55 (100); HRMS (ESI): 243.1404 (M^++H, $C_{16}H_{19}O_2$), calcd 243.1380. The second compound, epoxyketone **8a** (45 mg, 22%), was a white solid: mp 120–121 °C; IR 3022, 1707 cm^{-1}; ^1H NMR δ: 0.97 (3H, s), 1.55 (1H, m), 2.0–2.8 (7H, m), 3.60 (1H, dd, J=7.5 Hz, J'=11.5 Hz), 3.66 (1H, s), 7.1–7.5 (5H, m) ppm; ^{13}C NMR δ: 17.2 (CH_3), 23.9 (CH_2), 24.5 (CH_2), 30.0 (CH_2), 37.9 (CH_2), 40.2 (CH), 56.7 (C), 60.5 (CH), 73.3 (C), 126.2 (CH), 127.8 (2CH), 129.7 (2CH), 138.9 (C), 211.6 (C) ppm; Anal. calcd for $C_{16}H_{18}O_2$: C, 79.30; H, 7.49. Found: C, 79.69; H, 7.78; MS m/z (relative intensity) 242 (20, M^+), 169 (100), 155 (26), 141 (34), 115 (44), 91 (50), 77 (37), 65 (20), 55 (41).

3.1.7. 3a-Methyl-3-phenyl-hexahydro-1-oxa-cyclopropa-[*c*]inden-4-one 8a. To a stirred solution of ketone **7** (200 mg, 0.88 mmol) in CH_2Cl_2 (10 mL), under argon, were added catalytic Na_2CO_3 and *m*-CPBA (150 mg, 0.88 mmol). The reaction mixture was stirred for 7 h at room temperature. Then, a 5% solution of $Na_2S_2O_3$ was added and the resulting heterogeneous mixture was stirred for 15 min. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$, water and brine and then dried (Na_2SO_4). Evaporation of the solvent and purification by flash chromatography over silica gel (hexane–ether, 80:20) gave the epoxyketone **8b** (5 mg, 2%) and epoxyketone **8a** (188 mg, 94%).

3.1.8. 7a-Methyl-1-phenyl-2,4,5,6,7,7a-hexahydro-1*H*-indene 9. To anhydrous diethylene glycol (17 mL), under an atmosphere of argon, was added sodium metal (561 mg) and the mixture was stirred until all of the sodium had reacted. Anhydrous hydrazine (prepared by refluxing hydrazine hydrate over sodium hydroxide) was distilled directly into the resulting solution until the latter refluxed freely at 165 °C. The solution was cooled and the bicyclic ketone **7** (350 mg, 1.55 mmol) was added. The mixture was refluxed for 14 h and excess hydrazine was distilled from the mixture until the internal temperature of the latter reached 210 °C. Refluxing was then continued for an additional 8 h. The mixture was cooled, combined with the distillate (see above), and poured into water. The resulting mixture was extracted with hexane. The combined extracts were washed with water and dried over Na_2SO_4. Removal of the solvent gave the bicyclic olefin **9** (300 mg, 88%), as a colourless oil: IR 2928, 2868, 1654, 772 cm^{-1}; ^1H NMR δ: 0.61 (3H, s), 1.2–2.1 (6H, m), 2.42 (2H, m), 2.72 (2H, m), 3.18 (1H, dd, J=8 Hz, J'=10.7 Hz), 5.34 (1H, br s), 7.2–7.4 (5H, m) ppm; ^{13}C NMR δ: 18.2 (CH_3), 22.5 (CH_2), 26.9 (CH_2), 27.0 (CH_2), 33.9 (CH_2), 41.0 (CH_2), 48.1 (C), 58.9 (CH), 118.4 (CH), 126.0 (CH), 127.8 (2CH), 128.7 (2CH), 141.6 (C), 148.3 (C) ppm; HRMS (ESI): 213.1697 (M^++H, $C_{16}H_{21}$), calcd 213.1638.

3.1.9. 3a-Methyl-3-phenyl-octahydro-1-oxa-cyclopropa-[*c*]indene 10. To a stirred solution of alquene **9** (130 mg, 0.6 mmol) in CH_2Cl_2 (10 mL) at room temperature, under argon, were added catalytic Na_2CO_3 and *m*-CPBA (110 mg, 0.6 mmol). The reaction mixture was stirred for 10 min. Then, a 5% solution of $Na_2S_2O_3$ was added and the resulting heterogeneous mixture was stirred for 15 min. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$, water and brine, and then dried (Na_2SO_4). Evaporation of the solvent afforded the epoxyketone **10** (130 mg, 94%) as a colourless oil: IR 2943, 2870, 2454, 758 cm^{-1}; ^1H NMR δ: 0.58 (3H, s), 1.2–2.2 (10H, m), 2.80 (1H, dd, J=7 Hz, J'=11 Hz), 3.55 (1H, s), 7.0–7.4 (5H, m) ppm; ^{13}C NMR δ: 16.1 (CH_3), 21.3 (CH_2), 25.9 (CH_2), 23.6 (CH_2), 25.9 (CH_2), 34.3 (CH_2), 41.8 (C), 48.4 (CH), 60.9 (CH), 70.4 (C), 126.0 (CH), 127.9 (2CH), 128.9 (2CH), 139.6 (C) ppm; HRMS (ESI): 229.1619 (M^++H, $C_{16}H_{21}O$), calcd 229.1587.

3.1.10. 2,6,6-Trimethyl-1-(3-phenyl-propyl)-cyclohex-2-enol 12. A solution of 2,6,6-trimethyl-cyclohex-2-enone (1.27 g, 10.2 mmol) and 1-bromo-3-phenylpropane (3.06 g, 15.4 mmol) in THF (3 mL) was added via a dropping funnel to a stirred suspension of lithium (250 mg, 35.8 mmol) in dry THF (12 mL), at room temperature under argon. The reaction mixture was vigorously stirred for 5 h. The mixture was filtered to remove excess lithium and the solvent was evaporated at reduced pressure. The residue was hydrolyzed with hydrochloric acid, and the two-phase system was extracted with ether. The combined ethereal extracts were washed with aqueous $NaHCO_3$ (5%) and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–ether (8:2) afforded the alcohol **12** (1.93 g, 73%), as a colourless oil: IR 3499, 2951 cm^{-1}; ^1H NMR δ: 0.93 (3H, s), 0.94 (3H, s), 1.3–1.8 (6H, m), 1.65 (3H, s), 1.95 (2H, m), 2.56 (2H, m), 5.40 (1H, s), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 18.9 (CH_3), 22.4 (CH_2), 23.1 (CH_3), 24.1 (CH_3), 27.6 (CH_2/C), 34.0 (CH_2), 36.9 (CH_2), 37.2 (CH_2), 77.2 (C), 123.5 (CH), 125.5 (CH), 128.8 (2CH), 128.2 (2CH), 137.2 (C), 142.2 (C) ppm; MS m/z (relative intensity) 240 (5, M^+-18), 202 (7), 139 (27), 121 (31), 91 (100), 77 (22), 65 (26), 55 (20); HRMS (ESI): 259.2111 (M^++H, $C_{18}H_{27}O$), calcd 259.2057.

3.1.11. 2,4,4-Trimethyl-3-(3-phenyl-propyl)-cyclohex-2-enone 13. To a stirred suspension of PCC (1.8 g, 8.4 mmol) and silica (1 equiv of PCC) in dry CH_2Cl_2 (53 mL) was added a solution of the alcohol **12** (1.4 g, 5.6 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was vigorously stirred at room temperature under argon for 2 h. The resulting dark brown slurry was filtered though a short

column of silica gel and eluted with CH_2Cl_2. Removal of the solvent afforded unsaturated cyclohexenone **13** (1.4 g, 100%), as a colourless oil: IR 2957, 1667, 1352 cm^{-1}; ^1H NMR δ: 1.11 (6H, s), 1.70 (3H, s), 1.77 (4H, m), 2.15 (2H, m), 2.44 (2H, m), 2.70 (2H, t, J=7.4 Hz), 7.15–7.35 (5H, m) ppm; ^{13}C NMR δ: 11.1 (CH_3), 28.8 ($2CH_3$), 30.1 ($2CH_2$), 34.0 (CH_2), 35.9 (C), 36.3 (CH_2), 37.2 (CH_2), 125.7 (CH), 128.1 (4CH), 130.5 (C), 141.2 (C), 164.1 (C), 198.2 (C) ppm; MS *m/z* (relative intensity) 256 (4, M^+), 137 (29), 104 (100), 91 (98), 77 (32), 65 (33), 55 (29); HRMS (ESI): 257.1936 (M^++H, $C_{18}H_{25}O$), calcd 257.1900.

3.1.12. 2,4,4-Trimethyl-cyclohexane-1,3-dione 14. A mixture of 2-methyl-pentan-3-one (30 g, 300 mmol) and methyl acrylate (25.8 g, 300 mmol) was added dropwise at room temperature under argon to a stirred solution of NaOMe (65 mL, 360 mmol) in MeOH (5.5 M) and xylene (180 mL). The resulting mixture was stirred for 30 min at 25 °C. The solution was concentrated in vacuo to remove methanol and the residue was then acidified with HCl 6 N. The organic phase was separated and the aqueous layer was extracted with ether. The organic extracts were washed with brine, dried and concentrated. The residue was chromatographed over silica gel, eluting with AcOEt furnished the diketone **14** (28.4 g, 62%): IR 3208, 2965, 1711, 1092 cm^{-1}; ^1H NMR δ: 1.13 (6H, s), 1.71 (3H, s), 1.79 (2H, t, J=6.3 Hz), 2.49 (2H, t, J=6.3 Hz) ppm.

3.1.13. 3-Isobutoxy-2,6,6-trimethyl-cyclohex-2-enone 15. Diketone **14** (20.6 g, 133.7 mmol), ^{t}BuOH (24.6 mL, 267.6 mmol) and *p*-TsOH (168 mg, 0.9 mmol) in benzene (126 mL) were heated at reflux under argon for 9 h with a Dean and Stark apparatus. The solvent was distilled under reduced pressure, and the residue was diluted with ether and washed with aqueous Na_2CO_3 (10%) and brine, dried, and evaporated in vacuo to afford the ketone **15** (27.6 g, 98%), as a colourless oil: IR 2963, 1736, 1620, 1379 cm^{-1}; ^1H NMR δ: 0.91 (3H, d, J=6.6 Hz), 0.98 (3H, d, J=6.8 Hz), 1.08 (6H, s), 1.70 (3H, s), 1.80 (2H, t, J=6 Hz), 2.00 (1H, m), 2.55 (1H, t, J=6 Hz), 3.74 (2H, d, J=6.5 Hz) ppm; MS *m/z* (relative intensity) 210 (20, M^+), 155 (7), 127 (12), 99 (100), 83 (30), 70 (25), 57 (32); HRMS (ESI): 211.1704 (M^++H, $C_{13}H_{23}O_2$), calcd 211.1693.

3.1.14. 2,4,4-Trimethyl-3-(3-phenyl-propyl)-cyclohex-2-enone 13. A solution of the ketone **15** (18 g, 85.7 mmol) and 1-bromo-3-phenylpropane (25.5 g, 128.5 mmol) in THF (13 mL) was added via a dropping funnel to a stirred suspension of lithium (2.1 g, 300 mmol) in THF (108 mL) at room temperature under argon. The reaction mixture was vigorously stirred for 60 h. The mixture was filtered to remove excess lithium and the solvent was evaporated at reduced pressure. The residue was hydrolyzed with HCl 6 N, and the two-phase system was extracted with ether. The combined ethereal extracts were washed with aqueous $NaHCO_3$ (5%) and brine. The solvent was evaporated under reduced pressure to afford the enone **13** (21.4 g, 98%).

3.1.15. 1,5,5-Trimethyl-6-(3-phenyl-propyl)-7-oxa-bicyclo[4.1.0]heptan-2-one 16. To a stirred solution of enone **13** (14 g, 54.67 mmol) in methanol (491 mL) at 0 °C under argon were added dropwise H_2O_2 (112 mL, 30%) and NaOH (27 mL, 6 N). This resulting solution was stirred for 48 h at room temperature, and then poured into a solution of $Na_2S_2O_3$ (10%). The methanol was evaporated off and the aqueous solution was extracted with ether. The solution was washed with brine, dried and filtered. Evaporation of the solvent left a crude, which was purified by chromatography. Eluting with hexane–ether (9:1) furnished epoxyketone **16** (4.6 g, 59%) as a colourless oil: IR 2961, 1703, 1452 cm^{-1}; ^1H NMR δ: 0.98 (3H, s), 1.10 (3H, s), 1.21 (2H, m), 1.30 (3H, s), 1.74 (4H, m), 2.62 (2H, m), 2.89 (2H, m), 7.1–7.5 (5H, m) ppm; ^{13}C NMR δ: 12.5 (CH_3), 23.7 (CH_3), 25.9 (CH_3), 27.4 (CH_2), 27.7 (CH_2), 32.4 (CH_2), 33.6 (CH_2), 35.4 (C), 38.1 (CH_2), 65.7 (C), 73.2 (C), 125.9 (CH), 128.3 (4CH), 141.8 (C), 207.9 (C) ppm; MS *m/z* (relative intensity) 254 (2, M^+-18), 229 (6), 211 (5), 147 (10), 104 (42), 91 (100), 83 (28), 65 (19), 55 (36); HRMS (ESI): 273.1843 (M^++H, $C_{18}H_{25}O_2$), calcd 273.1849. Eluting with hexane–ether (8:2) furnished enone **13** (234 mg, 47%).

3.1.16. 2,4,4-Trimethyl-3-(3-phenyl-propyl)-cyclohexen-2-ol 17. Lithium aluminium hydride (892 mg, 23.46 mmol) was added to a solution of **13** (6 g, 23.46 mmol) in dry diethyl ether (216 mL) cooled to 0 °C. The mixture was vigorously stirred under argon for 1 h. Then, $Na_2SO_4\cdot 10H_2O$ was added and the resulting mixture was stirred for 30 min. The resulting mixture was filtered and the solvent was concentrated under reduced pressure to afford a solid identified as alcohol **17** (5.9 g, 98%): mp 55–60 °C; IR 3374, 2940, 1454 cm^{-1}; ^1H NMR δ: 0.93 (3H, s), 1.00 (3H, s), 1.34 (2H, m), 1.68 (3H, s), 1.5–2.1 (6H, m), 2.64 (2H, m), 3.87 (1H, m), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 16.6 (CH_3), 27.0 (CH_3), 28.4 (CH_3), 28.5 (CH_2), 28.8 (CH_2), 31.4 (CH_2), 34.7 (CH_2), 35.2 (C), 36.6 (CH_2), 70.1 (CH), 125.6 (CH), 128.1 (2CH), 128.3 (2CH), 128.7 (C), 142.1 (C), 142.1 (C) ppm; MS *m/z* (relative intensity) 240 (15, M^+-H_2O), 139 (14), 121 (45), 91 (100), 77 (27), 51 (12); HRMS (ESI): 259.2007 (M^++H, $C_{18}H_{27}O$), calcd 259.2057.

3.1.17. 1,5,5-Trimethyl-6-(3-phenyl-propyl)-7-oxa-bicyclo[4.1.0]heptan-2-ol 18. To a stirred solution of alcohol **17** (5.9 g, 23.2 mmol) in CH_2Cl_2 (357 mL) at −10 °C under argon, were added catalytic Na_2CO_3 and *m*-CPBA (4 g, 23.2 mmol). The reaction mixture was gradually warmed to room temperature, and stirred for 25 min. Then, a 5% solution of $Na_2S_2O_3$ was added and the resulting heterogeneous mixture was stirred for 15 min. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$, water and brine, and then dried (Na_2SO_4). Evaporation of the solvent afforded the epoxy alcohol **18** (6 g, 98%): IR 3455, 2947, 1452 cm^{-1}; ^1H NMR δ: 1.00 (3H, s), 1.01 (3H, s), 1.35 (3H, s), 1.4–1.9 (8H, m), 2.61 (2H, m), 3.72 (1H, br s), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 18.6 (CH_3), 24.9 (CH_3), 25.7 (CH_3), 27.1 (CH_2), 28.1 (CH_2), 28.3 (CH_2), 31.7 (CH_2), 34.3 (C), 36.3 (CH_2), 66.1 (C), 69.1 (CH), 72.6 (C), 125.7 (CH), 128.2 (2CH), 128.3 (2CH), 141.8 (C) ppm; MS *m/z* (relative intensity) 256 (1, M^+-18), 190 (12), 147 (14), 104 (95), 91 (100), 77 (21), 65 (30), 55 (49); HRMS (ESI): 275.2019 (M^++H, $C_{18}H_{27}O_2$), calcd 275.2006.

3.1.18. 1,5,5-Trimethyl-6-(3-phenyl-propyl)-7-oxa-bicyclo[4.1.0]heptan-2-one 16. Jones reagent was added

dropwise with stirring to a solution of **18** (6 g, 21.89 mmol) in acetone (253 mL) at 0 °C. The resulting mixture was stirred at this temperature for an additional 30 min. Then, isopropilic alcohol was added. The solvent was evaporated under reduced pressure to afford a residue, which was dissolved in water and extracted with ether. The extracts were washed with brine, dried and evaporated to afford the epoxyketone **16** (5.5 g, 93%).

3.1.19. Cyclization of the epoxyketone 16 with *n*-Bu_3SnH. A solution of tributyltin hydride (2.8 mL, 10.5 mmol) in benzene (300 mL) was added via a dropping funnel (4.3 mmol/h) to a refluxing solution of the epoxyketone **16** (9.5 g, 34.9 mmol) and AIBN (1.7 mmol) in benzene (700 mL) under argon. The reaction mixture was refluxed for 8 h. Removal of the solvent afforded a crude residue, which was purified by chromatography. Eluting with hexane–ethyl acetate (9:1) furnished epoxyketone **16** (4.7 g, 50%), as a colourless oil. Eluting with hexane–ethyl acetate (8:2) furnished enone **13** (625 mg, 14%), as a colourless oil. Eluting with hexane–ethyl acetate (8:2) furnished 7a-hydroxy-3a,7,7-trimethyl-3-phenyl-octahydro-inden-4-one **19** (709 mg, 16%), as a colourless oil: IR 3518, 2965, 1694 cm^{-1}; ^1H NMR δ: 0.76 (3H, s), 1.06 (6H, s), 1.7–2.2 (6H, m), 2.61 (2H, m), 3.67 (1H, dd, J=6.8 Hz, J'=11.3 Hz), 7.1–7.3 (5H, m) ppm; ^{13}C NMR δ: 17.5 (CH_3), 22.4 (CH_3), 25.9 (CH_3), 28.4 (CH_2), 32.6 (CH_2), 34.2 (CH_2), 36.1 (CH_2), 37.6 (C), 51.0 (CH), 62.5 (C), 87.6 (C), 126.3 (CH), 127.8 (2CH), 129.5 (2CH), 141.0 (C), 214.5 (C) ppm; MS *m/z* (relative intensity) 254 (53, M^+-18), 198 (60), 173 (64), 159 (100), 115 (56), 91 (83), 70 (48), 55 (90); HRMS (ESI): 273.1858 (M^++H, $C_{18}H_{25}O_2$), calcd 273.1849. Eluting with ethyl acetate furnished 2-methyl-1,3-cyclohexanodione **14** (1.8 g, 69%), as a white solid identified by comparison with a standard.

3.1.20. 3a,7,7-Trimethyl-3-phenyl-2,3,3a,5,6,7-hexahydro-inden-4-one 20. To a solution of the hydroxyketone **19** (200 mg, 0.7 mmol) in dry CH_2Cl_2 (3.5 mL) at 0 °C under argon were gradually added pyridine (0.2 mL) and $SOCl_2$ (0.1 mL, 1.5 mmol). The mixture was stirred at 0 °C for 2 h and then poured into ice water. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with $NaHCO_3$ (5%) and brine, and then dried (Na_2SO_4). Evaporation of the solvent left a crude, which was purified by flash chromatography. Elution with hexane–ethyl acetate (93:7) afforded unsaturated ketone **20** (516 mg, 74%), as a white solid, mp 70–71 °C; IR 2926, 1717, 1458, 1377 cm^{-1}; ^1H NMR δ: 1.03 (3H, s), 1.23 (3H, s), 1.31 (3H, s), 1.65 (1H, m), 1.90 (1H, m), 2.32 (1H, m), 2.50 (1H, m), 2.72 (2H, m), 3.80 (1H, dd, J=8.4 Hz, J'=10.8 Hz), 5.63 (1H, dd, J=1.6 Hz, J'=3.2 Hz), 7.1–7.6 (5H, m) ppm; ^{13}C NMR δ: 21.0 (CH_3), 29.4 (CH_3), 30.2 (CH_3), 33.6 (C), 34.5 (CH_2), 36.2 (CH_2), 38.3 (CH_2), 50.5 (CH), 61.6 (C), 122.7 (CH), 126.2 (CH), 127.7 (2CH), 130.2 (2CH), 140.5 (C), 154.5 (C), 215.1 (C) ppm; MS *m/z* (relative intensity) 254 (30, M^+), 239 (12), 198 (100), 183 (40), 115 (45), 91 (84), 77 (53), 65 (24), 55 (63); HRMS (ESI): 255.1741 (M^++H, $C_{18}H_{23}O$), calcd 255.1744.

3.1.21. 3a,7,7-Trimethyl-3-phenyl-hexahydro-1-oxacyclopropa[*c*]inden-4-one 21. To a stirred solution of ketone **20** (41 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) at −10 °C under argon, were added catalytic Na_2CO_3 and *m*-CPBA (28 mg, 0.16 mmol). The reaction mixture was gradually warmed to room temperature, and stirred for 3 h at room temperature. Then, a 5% solution of $Na_2S_2O_3$ was added and the resulting heterogeneous mixture was stirred for 15 min. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$, water and brine, and then dried (Na_2SO_4). Evaporation of the solvent afforded the epoxyketone **21** (30 mg, 85%) as a colourless solid: mp 97–100 °C; IR 2924, 1711, 1458 cm^{-1}; ^1H NMR δ: 0.94 (3H, s), 1.01 (3H, s), 1.35 (3H, s), 1.93 (2H, m), 2.11 (1H, m), 2.21 (1H, m), 2.46 (1H, m), 2.61 (1H, m), 3.44 (1H, dd, J=7 Hz, J'=11.4 Hz), 3.57 (1H, br s), 7.1–7.4 (5H, m) ppm; ^{13}C NMR δ: 17.8 (CH_3), 26.5 (CH_3), 27.6 (CH_3), 30.7 (CH_2), 32.7 (C), 36.6 (CH_2), 36.7 (CH_2), 42.3 (CH), 56.1 (C), 56.7 (CH), 74.1 (C), 126.3 (CH), 127.7 (2CH), 130.4 (2CH), 138.6 (C), 213.2 (C) ppm; Anal. Calcd for $C_{16}H_{22}O_2$: C, 79.30; H, 7.49. Found: C, 79.69; H, 7.78; MS *m/z* (relative intensity) 255 (25, M^+-15), 197 (100), 156 (66), 115 (46), 91 (67), 77 (46), 55 (52); HRMS (ESI): 271.1690 (M^++H, $C_{18}H_{23}O_2$), calcd 271.1693.

Acknowledgements

Financial support for this work from the Ministerio de Ciencia y Tecnología of Spain (PPQ2002-00290) and the Junta de Castilla y León (SA027/03) is gratefully acknowledged.

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Tetrahedron 62 (2006) 7817–7823
Tetrahedron

The interaction of solvatochromic pyridiniophenolates with cyclodextrins

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Received 16 March 2006; revised 22 May 2006; accepted 23 May 2006
Available online 9 June 2006

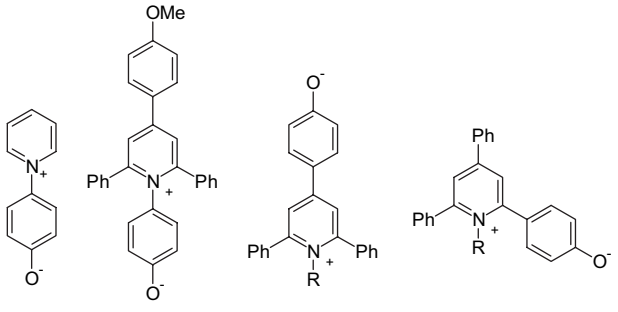
Abstract—The interactions of six solvatochromic pyridiniophenolate dyes with α- and β-cyclodextrins were investigated with the aid of UV–vis and ^{1}H NMR spectroscopies, and molecular dynamics simulations. The deduced mode of encapsulation of these dyes within the hydrophobic host cavity was employed as a measure of the relative contributions of the donor and acceptor moieties to their solvatochromic properties.

1. Introduction

Cyclodextrin inclusion complexes have been widely studied. One reason for this interest is their potential use as carriers of hydrophobic organic compounds in biological media.[1,2] Besides this major application, the increasing number of publications on CD complexation has also reflected a growing interest in more basic aspects of these host–guest interactions. Their study has profited from a variety of analytical methods, like Raman,[3] UV–vis and fluorescence spectroscopies,[4–7] nuclear magnetic resonance,[8,9] calorimetry,[4] and diffusion measurements,[10,11] which provide evidence for the stoichiometry and the arrangements of these complexes in solution. Molecular dynamics simulations have provided a valuable theoretical tool for a more detailed study of these interactions, shedding light on various solvation contributions to the stability of these complexes in aqueous solutions.[6–8,12–14]

Our interest in the interactions of solvatochromic dyes with cyclodextrins originated from the fact that these natural oligomers constitute convenient and well understood heterogeneous microenvironments in aqueous solution. Partial insertion of a solvatochromic dye composed of a donor and an acceptor fragment into the hydrophobic CD cavity locates these two moieties in different microenvironments. The spectral changes observed in the resulting solutions might then be attributed to the changes in the microenvironments that surround each fragment. Simulation studies might be employed for more detailed descriptions of the host–guest interactions and their effect on the observed spectral changes. We have recently followed this protocol in a study of CD encapsulation of two solvatochromic dyes derived from *N*,*N*-dimethylbarbituric acid.[15]

Pyridiniophenolates constitute one of the most popular families of solvatochromic probes.[16] Since their introduction nearly half a century ago, interest in their properties and applications has not declined. It seemed therefore natural to investigate the interactions of this family of dyes with cyclodextrins, with a view to disentangling the contributions of the donor phenolate and the acceptor pyridinium moieties to the solvatochromic behavior of these compounds in a microheterogeneous milieu. We chose compound **1** as a starting point for our studies, because of its simplicity. In addition, compounds **2–6** allowed a comparison to be made among structures that exhibit different patterns of coupling of the phenoxide donor and the pyridinium acceptor fragments.



1 **2** R = Me (**3**), R = *p*-MeOPh (**4**) R = Me (**5**), R = Ph (**6**)

Keywords: Solvatochromic pyridiniophenolates; Cyclodextrins; Molecular dynamics simulation.
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doi:10.1016/j.tet.2006.05.053

2. Results

2.1. Spectroscopic measurements

The UV–vis spectrum of compound **1** in water/methanol (99:1) showed a charge-transfer band at 366 nm. Cyclodextrin did not absorb at this wavelength, so that the observed variations of this CT band were ascribed to the free and complexed forms of compound **1**. Addition of increasing concentrations of α-cyclodextrin caused bathochromic and hypochromic shifts of this band. A Job's plot established a 1:1 stoichiometry for the inclusion complex. The 1:1 association constant was determined by recording absorbance values of a constant concentration of dye **1** ($[D]_o$), upon additions of a large excess of α-CD ([CD]). Under these circumstances, Eq. 1 allowed the determination of K_{assoc} from a Benesi–Hildebrand plot of $[CD][D]_o/\Delta A$ versus [CD],

$$[CD][D]_o/\Delta A = 1/\Delta\varepsilon \cdot K_{assoc} + [CD]/\Delta\varepsilon \quad (1)$$

where $\Delta A = A - A_o$, A_o being the absorbance reading of the pure dye and $\Delta\varepsilon = \varepsilon_{complex} - \varepsilon_{dye}$ is the difference in absorptivity between the complex and the dye.

A similar behavior was observed for dyes **3** and **4** in the presence of α-CD with 1:1 association constants of 79 and 185 M^{-1}, respectively (Fig. 1)

Contrary to the behavior observed for these compounds, UV–vis spectra of betaine **2** did not exhibit changes when increasing amounts of α-CD were added to an aqueous solution of the dye. For the derivatives **5** and **6**, association with α-CD was negligible, according to the observed UV–vis spectral changes. Such changes were evident for β-cyclodextrin, which also formed 1:1 association complexes with dyes **5** and **6**.

All the obtained association constants are given in Table 1.

2.2. ^{1}H NMR measurements

The mode of insertion of dye **1** into the CD cavity was investigated by comparing the ^{1}H NMR spectra of **1** in the absence and presence of the host molecule (Fig. 2). In the presence of a 30-fold excess of α-CD, compound **1** exhibited shifts at 38.4 and 19.2 Hz for the aromatic protons *ortho* and *meta* to the phenoxide oxygen, respectively. The pyridinium ring protons exhibited comparatively smaller shifts: the signals assigned to the α and β protons shifted 10.4 and 6.8 Hz, respectively.

Table 1. Association constants (1:1) for complexes of betaines **1**-**6** and α- or β-cyclodextrin, determined from UV–vis spectroscopic measurements

Betaine	K_{assoc}, M^{-1}	
	α-Cyclodextrin	β-Cyclodextrin
1	160±24	—[a]
2	—[b]	—[a]
3	79±18	—[a]
4	185±28	—[a]
5	—[b]	161±50
6	—[b]	74±11

[a] Not measured.
[b] Not determined, due to negligible spectral changes.

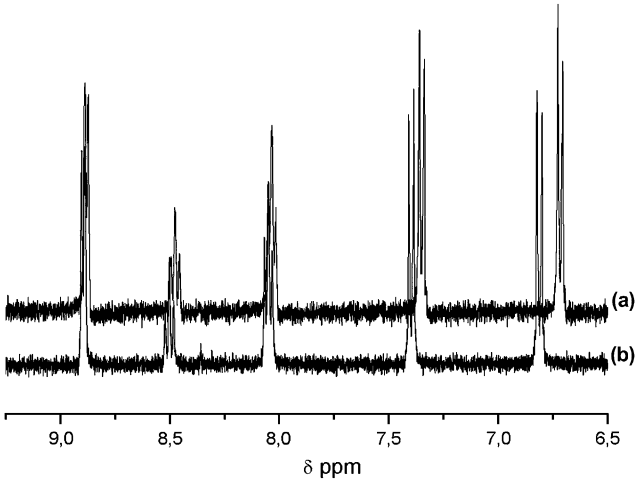

Figure 2. ^{1}H NMR spectra of dye **1** in D_2O/CD_3OD in the (a) absence and (b) presence of a 30-fold excess of α-CD. Signals at δ 6.7 and 7.4, correspond to the AA′BB′ system of the phenoxide group. The pyridinium ring protons appear at δ 8.0 (H-3,5), 8.5 (H-4), and 8.8 (H-2,6).

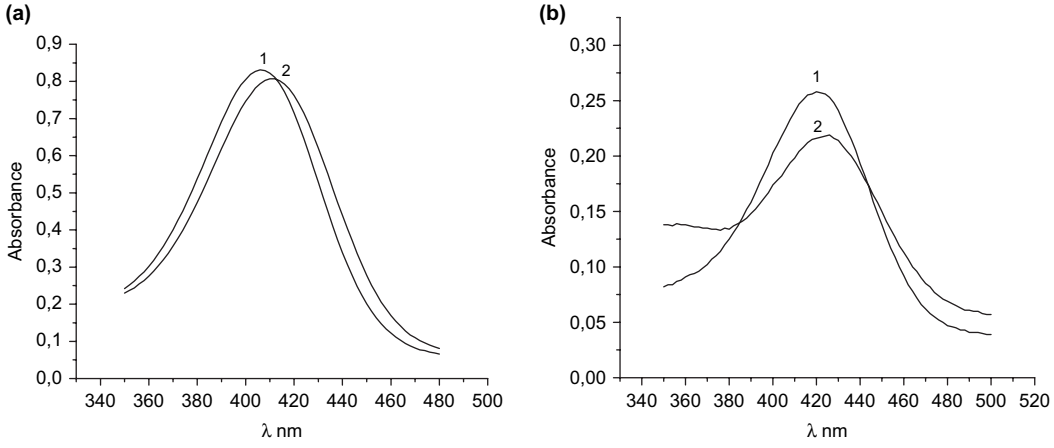

Figure 1. (a) UV–vis spectra of **3** ($c=1.9\times10^{-5}$ M) in water/methanol (99:1) in the (1) absence and (2) presence of α-CD ($c=1\times10^{-2}$ M); (b) UV–vis spectra of **4** ($c=2.3\times10^{-5}$ M) in water/methanol (99:1) in the (1) absence and (2) presence of α-CD ($c=1\times10^{-2}$ M).

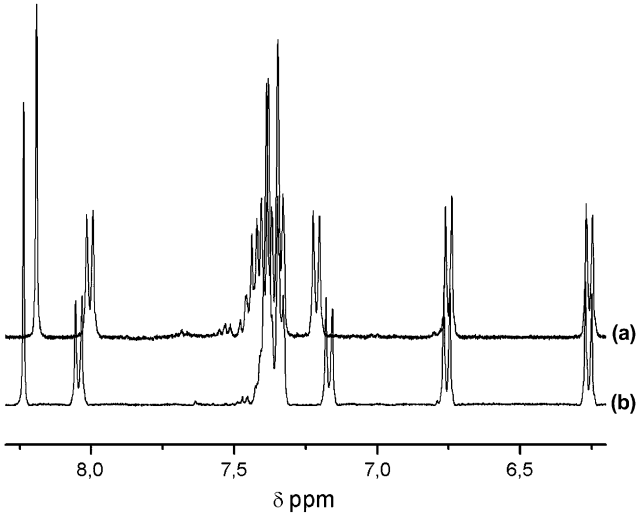

Figure 3. ^{1}H NMR spectra of dye **2** in D_2O/CD_3OD in the (a) absence and (b) presence of a 10-fold excess of α-CD. Signals at δ 7.2 and 8.1 correspond to the AA′BB′ system of the MeO–C_6H_4 group, those at δ 6.3 and 6.7 to the phenoxide group. The pyridinium ring protons appear as a singlet at δ 8.2.

The interaction of dye **2** with α-CD was also investigated by ^{1}H NMR spectroscopy. Figure 3 shows the variations in the spectra of **2** in D_2O/CD_3OD in the presence of cyclodextrin. Signals corresponding to the methoxyphenyl substituent and to the adjacent pyridinium ring protons exhibited significant shifts, in contrast with those of the *N*-phenoxy substituent.

The spectra of betaine **3** in the absence and presence of a 10-fold excess of α-cyclodextrin are shown in Figure 4. Protons *ortho* and *meta* to the phenoxide oxygen shifted by 4.4 and 2.8 Hz, respectively. The other aromatic protons exhibited somewhat smaller shifts. The pyridinium ring protons shifted by 2.8 Hz.

Figure 5 compares the spectra of dye **4** in the absence and presence of a 10-fold excess of α-CD. The signals *ortho* (δ 6.80) and *meta* (δ 7.02) to the OMe group exhibited larger

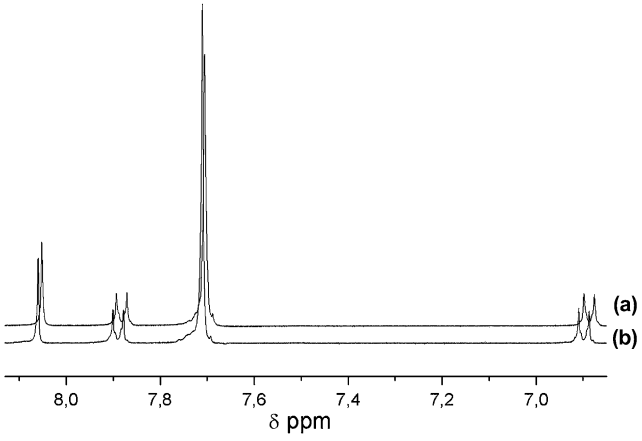

Figure 4. ^{1}H NMR spectra of dye **3** in D_2O/CD_3OD in the (a) absence and (b) presence of a 10-fold excess of α-CD. Signals at δ 6.9 and 7.9 correspond to the AA′BB′ system of the phenoxide group. The pyridinium ring protons appear as a singlet near δ 8.1.

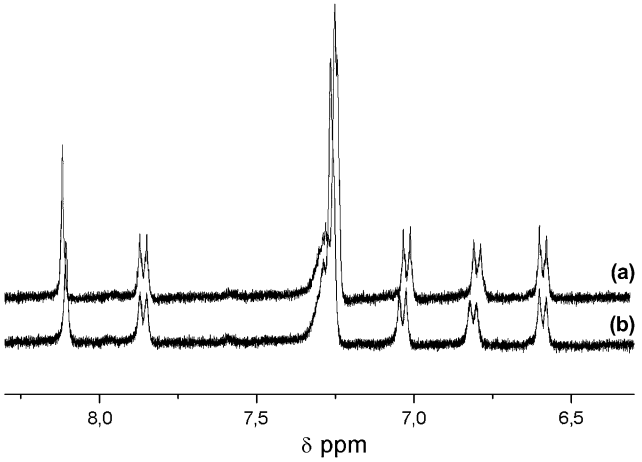

Figure 5. ^{1}H NMR spectra of dye **4** in D_2O/CD_3OD in the (a) absence and (b) presence of a 10-fold excess of α-CD. Signals at δ 6.8 and 7.0 correspond to the AA′BB′ system of the MeO–C_6H_4 group, and those at δ 6.6 and 7.8 to the phenoxide group.

shifts than those observed for protons *ortho* (δ 6.59) and *meta* (δ 7.86) to the phenoxide oxygen.

In the case of the 1:1 complex formed between betaine **5** and β-cyclodextrin, the spectrum of the pure dye was compared with that in the presence of a four-fold excess of β-CD. Addition of the host molecule shifted the signals of the phenoxide ring protons *ortho* and *meta* to the oxygen atom by 15.2 and 10 Hz, respectively. The pyridinium ring protons were less affected, with shifts of 9.6 Hz, corresponding to the hydrogen atom nearer to the phenoxide group, and of 6.8 Hz, for the other hydrogen atom. The N–Me singlet was similarly affected by 6.8 Hz.

A similar behavior was shown by the spectra of betaine **6** in the presence of β-cyclodextrin. The spectra are compared in Figure 6, where the addition of the host brought about shifts of the signals assigned to the 2-phenoxide substituent.

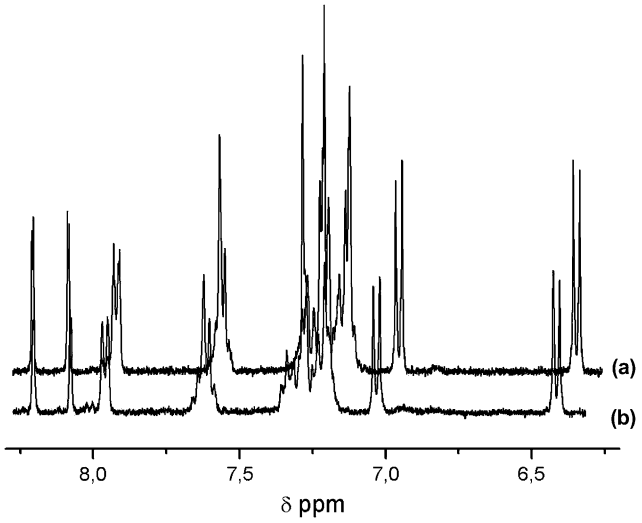

Figure 6. ^{1}H NMR spectra of dye **6** in D_2O/CD_3OD in the (a) absence and (b) presence of a four-fold excess of β-CD. Signals at δ 6.3 and 6.9 correspond to the AA′BB′ system of the phenoxide group. Signals at δ 7.1–7.3, 7.6, and 7.9 correspond to protons from the phenyl substituents. The pyridinium ring protons appear as two singlets at δ 8.1 and 8.2.

2.3. Molecular dynamics simulations

A theoretical support to the experimental evidence gathered from the ^{1}H NMR experiments was obtained by molecular dynamics simulations of all of the 1:1 complexes in water.

Betaine **1** was docked into the cavity of α-cyclodextrin and the resulting structure was soaked into a sphere of 1150 water molecules. After a 200-ps dynamics simulation the system attained equilibrium, as shown by an average variation of less than 10% of the total energy of the system during the acquisition period. The resulting structure of the 1:1 complex is shown in Figure 7a. The molecule is encapsulated by the hydrophobic cavity so that both aromatic rings experience a microenvironment different from that of pure water. As a result, all aromatic protons should exhibit shifts upon the addition of the host molecule, in agreement with the observations from the ^{1}H NMR experiments.

Compound **2** was docked into the α-CD cavity, yielding a complex with preferential insertion of methoxyphenyl group. This result, reasonable in terms of steric considerations, is fully supported by the NMR spectra shown in Figure 3.

The structure of the 1:1 complex of betaine **3** with α-CD is shown in Figure 7b. A similar mode of insertion, with the phenoxide group inside the hydrophobic cavity of the guest, was obtained for the complex between dye **4** and α-CD.

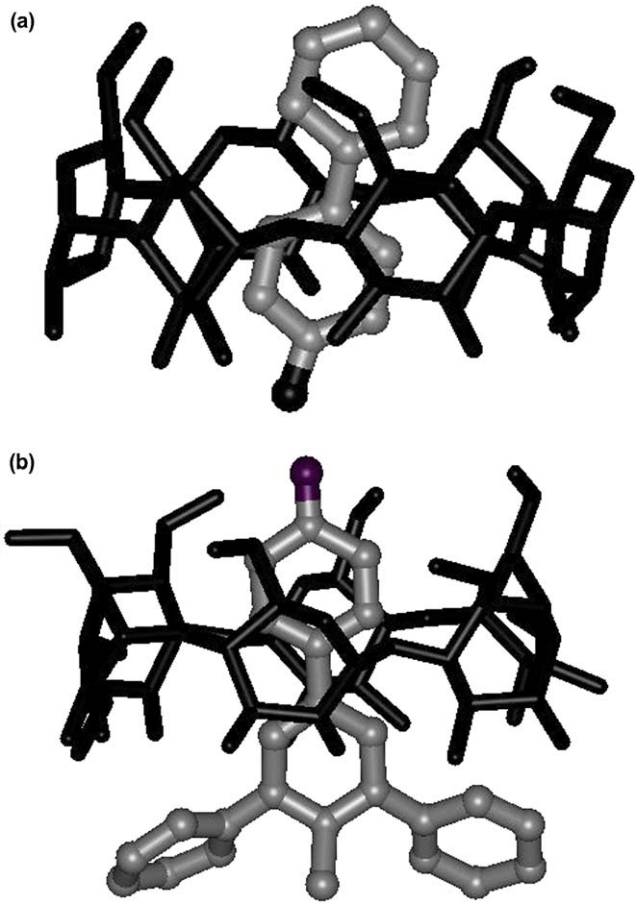

Figure 7. Structures of the 1:1 complexes formed between α-CD and betaines (a) **1** and (b) **3** after dynamics simulation in water. For the sake of clarity all solvent molecules and the hydrogen atoms of the complexes are omitted.

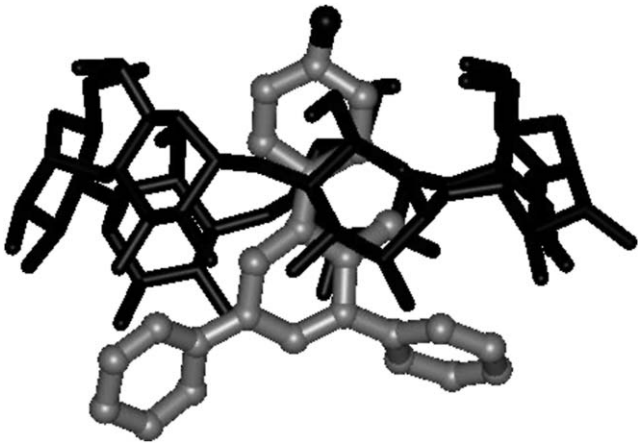

Figure 8. Structure of the 1:1 complex formed between betaine **5** and β-CD after dynamics simulation in water. For the sake of clarity all solvent molecules and the hydrogen atoms of the complex are omitted.

Figure 8 depicts the complex formed between betaine **5** and β-CD, showing the preferential insertion of the phenoxide group. Preliminary docking of **5** into the host cavity yielded an equally stable structure with preferential insertion of the less hindered 4-phenyl group of the betaine.

Finally, docking of dye **6** into β-CD yielded two possible forms of insertion for the complex. The most stable structure corresponded to the insertion of phenyl group at the 4-position of the pyridinium ring of the dye. A second, less stable structure, involved insertion of the phenoxide and the *N*-phenyl groups into the cyclodextrin cavity. The NMR spectra obtained for dye **5** and for the analogous betaine **6** (Fig. 6) revealed significant shifts of the phenoxide protons upon addition of cyclodextrin, in agreement with an insertion of this group, as shown in Figure 8.

3. Discussion

The above results may now be analyzed. Firstly, we will be concerned with the forms of encapsulation of dyes **1**–**6** within the hydrophobic cavities of cyclodextrins. Secondly, we will discuss the effects of the cyclodextrin microenvironment on the donor and acceptor moieties of the pyridiniophenolate systems and the resulting solvatochromic shifts.

Because of its small size, α-CD was employed as a selective host in the formation of 1:1 complexes with the studied dyes. UV–vis spectral changes were observed for complexes formed between α-CD and dyes **1**, **3**, and **4**. All of these compounds had a sterically free phenoxide substituent, so that the observed spectral changes might be attributed to the encapsulation of this substituent inside the host cavity. The obtained structures from the theoretical simulations lent support to this interpretation. Further support was provided by the lack of spectral changes for the interactions between α-CD and dyes **2**, **5**, and **6**. In these compounds, the phenoxide substituent is sterically hindered by one or more adjacent phenyl groups, thus limiting the access of the host to this part of the molecule. In the case of compound **2**, insertion of another less hindered substituent took place, as suggested by NMR evidence (Fig. 3). In the case of dyes **5** and **6**,

encapsulation of the less hindered phenoxide substituent was possible with the larger β-CD host, and the observed UV–vis spectral variations were an indication of this. As shown in Figure 8, this interpretation was supported by the results from simulations.

Some features of Table 1 may be explained by invoking steric effects. The smaller value of the association constant of the β-CD/dye **6** complex, when compared with its analog **5**, reflects the greater steric hindrance of the phenoxide group in the former betaine. Because of its larger cavity, we assumed that the behavior of β-CD with the less hindered systems **1**–**4** would simply parallel that of α-CD. For this reason, our interest in associations of β-CD with the studied systems was restricted to the more sterically hindered guests **5** and **6**, for which there was no UV–vis spectroscopic evidence of associations with α-CD. For the series of compounds **1**, **3**, and **4**, all of which had a common free phenoxide group encapsulated by α-CD, association is probably determined by the guest hydrophobicity. The virtual insolubility of **1** in water prevented recording its UV–vis spectrum in this solvent, and is probably responsible for its comparatively large K_{assoc} value. Of the two vinylogous 4-pyridones **3** and **4**, the latter is more hydrophobic and consequently exhibits a larger K_{assoc} value.

The use of a selective host such as α-CD allowed a comparison of the affinities of different aryl substituents for the host molecule. Both aryl substituents of the small betaine **1** lodged inside the CD cavity. Simulations indicated that the charged oxygen protruded out of the host cavity, and hydrogen-bonded with the external water molecules (Fig. 7a).

In all other complexes between α-CD and dyes **2**, **3**, and **4**, the host molecule exhibited a greater affinity for the substituted phenyl group than for the unsubstituted phenyl groups. This is in-line with the observed trends in the values of association constants between α-CD and various 4-substituted phenols.[17] Association increased in the following order for 4-substituents: NH_3^+<H<F<Me≈OMe<CN<NO_2<Cl<I.[18] Polarizable, hydrophobic substituents favored association, in contrast with hydrophilic groups like NH_3^+. 4-Hydroxyphenol exhibited a slightly smaller association constant than phenol itself,[19] in agreement with the hydrophilic nature of the OH group. However, this situation was reversed in basic media. Comparison of three substituted phenols (4-I, 4-NO_2, and 4-CN) with the corresponding phenolates showed that α-CD had a greater affinity for the latter in all cases.[20,21] This is probably a consequence of the greater internal charge-transfer that occurs in phenolates, when compared with phenols, and of the enhanced dipole moments of the former molecules. Dipole–dipole interactions seem to be the main contributors stabilizing complex orientation with cyclodextrins.[22,23]

We may thus conclude that, among similarly hindered substituents, a cyclodextrin host will show greater affinity for a phenoxy, or a 4-methoxyphenyl, than for a phenyl group.

The evidence provided by the NMR experiments agrees in most cases with what might be expected from the UV–vis spectral changes, steric considerations, and the results from dynamics simulations. This is the case of the complexes formed between α-CD and dyes **1** or **3** and between β-CD and dyes **5** or **6**. In all cases, significant shifts of the signals attributed to the phenoxide protons upon addition of cyclodextrin could be taken as an indication of the encapsulation of this substituent by the hydrophobic host cavity. In the case of dye **2**, in spite of the lack of UV–vis spectral changes, this interaction was confirmed by NMR evidence (see Fig. 3). The situation was less clear for the interaction between α-CD and dye **4**.The poor sensitivity shown by the phenoxide protons to the addition of the host (Fig. 5) casts doubts on the suggestion that this substituent is encapsulated by the host cavity. Instead, according to the NMR evidence gathered in Figure 5, encapsulation of the sterically hindered *N*-methoxyphenyl group should take place in this case.

This last interpretation relies on the assumption that large shift variations should be an indication of a direct interaction between the host molecule and a given substituent. This should be true in the absence of any other effects that is capable of indirectly causing significant shifts at sites not enclosed by the host cavity. Some of these indirect changes may have a conformational origin. A comparison of the NMR spectra of the two isomeric betaines **2** and **4** reveals the importance of 2,6-diphenyl substituents to the chemical shifts of the *N*-aryl group. Anisotropic shielding of AA'BB′ system of the methoxyphenyl group shifts these signals upfield by 0.4–1.1 ppm, in compounds **2** and **4**. Thus, protons *ortho* and *meta* to OMe appear at δ 7.2 and 8.1 in the spectrum of **2** and at δ 6.8 and 7.0 in **4**, respectively. A similar effect is observed for the phenoxy group (see Figs. 3 and 5). Deformations in these guest molecules, caused by complexation with cyclodextrin, may lead to significant chemical shift variations of protons not directly enclosed by the host cavity. Such variations may reflect changes in anisotropic shielding by neighboring phenyl groups, or in the coplanarity of donor–acceptor fragments, and their resulting through-conjugation, masking the direct interaction between the host and the encapsulated substituent.

We may now summarize our conclusions based on the arguments presented above. The structure of the complex formed between dye **1** and α-CD, obtained by simulation and shown in Figure 7a, is supported by UV–vis and NMR spectral evidence. Encapsulation of the 4-methoxyphenyl substituent of **2** by α-CD is supported by steric considerations, absence of UV–vis spectral changes upon addition of the host, and by NMR evidence. Encapsulation of the phenoxide group of dye **3** is clearly established by all spectral and theoretical evidences. Considerations based on steric factors, on the UV–vis spectra, and on the simulation results favor the insertion of a phenoxide substituent of dye **4**, in spite of its NMR spectra, which suggest the insertion of the sterically crowded 4-methoxyphenyl substituent. This latter piece of evidence may be reconciled with the former results by invoking other effects responsible for the chemical shift variations, arising from conformational changes in the complex. Finally, the same considerations support the preferential encapsulation of the phenoxide substituent of dyes **5** and **6** by the β-CD host. The absence of UV–vis spectral changes on addition of α-CD to these dyes may either be taken as an indication of no binding or of encapsulation of a less hindered phenyl group by the smaller host molecule. Since no ^{1}H NMR experiments were carried out with dyes **5** or **6** and α-CD,

we cannot rule out some interaction between these dyes and this smaller host. Nevertheless, our results suggest that when encapsulation of the phenoxide group is prevented by steric hindrance, UV–vis spectra of the dye are not altered by the addition of the host.

The second object of our analysis is the effect of cyclodextrin microenvironment on the donor and acceptor moieties of the pyridiniophenolate systems. It is clear that the UV–vis spectra of these betaines are mostly affected when the donor phenoxide group is encapsulated within the host cavity, a form of insertion observed for the majority of the complexes. This is to be expected in view of the dominant role played by this group in the solvatochromism of pyridiniophenolates and reflects the importance of hydrogen-bonds between the phenoxide oxygen and the protic solvent.

Other aryl substituents on the pyridinium ring are less important, at least in the aqueous medium. The encapsulation of the 4-methoxyphenyl group of **2** within the hydrophobic cavity of α-CD, confirmed by NMR evidence, had no effect on the spectra of this dye in water. Our results thus confirm the overwhelming importance of the solvent acidity to the solvatochromism of pyridiniophenolates in protic media.[24] In water this effect overshadows other solvent contributions associated with the charge distribution over the whole molecule. Substituents on the donor and acceptor rings should affect this charge distribution. The relative insensitivity of dye **2** to the different microenvironment provided by a cyclodextrin host points to a secondary role played by the aryl substituents on the acceptor pyridinium fragment.

4. Experimental

Melting points were obtained with an Electrothermal capillary melting point apparatus and were not corrected. IR spectra were obtained with a Perkin–Elmer 750 equipment. ^{1}H NMR spectra were recorded with a Bruker Avance 400 equipment, employing tetramethylsilane as an internal standard. UV–vis spectra were recorded with an Unicam UV-4 spectrophotometer.

Compound **1** was prepared as described previously.[25] Dye **2** was obtained by in situ treatment of the corresponding *N*-hydroxyphenyl pyridinium perchlorate[26] with base, and the proton assignations of its ^{1}H NMR spectrum in D_2O/CD_3OD (1:1) were deduced from an HMBC experiment: δ 3.93 (3H, s, OMe); 6.25 (2H, d, J=8.8 Hz, Ar–H *ortho* to O^-); 6.74 (2H, d, J=8.8 Hz, Ar–H *meta* to O^-); 7.20 (2H, d, J=8.8 Hz, Ar–H *ortho* to OMe); 7.32–7.53 (10H, m, Ph–H); 7.99 (2H, d, J=8.8 Hz, Ar–H *meta* to OMe); 8.19 (2H, s, py–H).

Similar treatment of the corresponding perchlorate salt yielded compound **4**, for which an HMBC experiment confirmed the proton assignations reported previously.[27] Betaines **5** and **6**, generated by in situ treatment of the corresponding perchlorate salts[28] with base, yielded the following ^{1}H NMR spectra in D_2O/CD_3OD (1:1): compound **5**, δ 4.01 (3H, s, N–CH_3); 6.83 (2H, d, J=8.0 Hz, Ar–H *ortho* to O^-); 7.52 (2H, d, J=8.4 Hz, Ar–H *meta* to O^-); 7.66–7.70 (3H, m, Ar–H); 7.74–7.79 (5H, m, Ar–H); 7.98–8.02 (2H, m, Ar–H); 8.03 (1H, d, J=2.4 Hz, py–H); 8.17 (1H, d, J=2.0 Hz, py–H); compound **6**, δ 6.34 (2H, d, J=8.8 Hz, Ar–H *ortho* to O^-); 6.95 (2H, d, J=8.9 Hz, Ar–H *meta* to O^-); 7.10–7.30 (11H, m, Ar–H); 7.55–7.58 (2H, m, Ar–H); 7.91 (2H, d, J=6.4 Hz, Ar–H); 8.08 (1H, d, J=2.1 Hz, py–H); 8.20 (1H, d, J=2.4 Hz, py–H).

Betaine **3** was obtained following a procedure adapted from literature,[29] from its precursor *N*-methyl-4-(hydroxyphenyl)-2,6-diphenylpyridinium fluoroborate. To a stirred suspension of 4-(4-hydroxyphenyl)-2,6-diphenylpyrylium perchlorate[27] (817 mg, 2 mmol) and methylamine hydrochloride (134 mg, 2 mmol) in CH_2Cl_2 (7 mL), was added dropwise triethylamine (0.6 mL, 5 mmol). The resulting deeply colored solution was stirred at 25 °C until decolorization to a pale red occurred (30 min). The solution was then washed with 10% fluoroboric acid (10 mL) and then with water, the organic solvent was rotary evaporated and the residue was treated with diethyl ether, filtered, and dried to give 610 mg (72% yield) of *N-methyl-4-(hydroxyphenyl)-2,6-diphenylpyridinium fluoroborate*, recrystallized in ethanol, mp 205–208 °C. Anal. Calcd for $C_{24}H_{20}BF_4NO$: C, 67.79; H, 4.74; N, 3.29%; found C, 67.32; H, 4.23; N 2.86%. IR (KBr) ν_{max}: 3400 (OH), 1600, 1280, 1220, 1170 and 1060 (broad, BF_4^-) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 3.69 (3H, *s*, N^+–CH3), 6.94 (2H, *d*, J=8.9 Hz, Ar–H *ortho* to OH), 7.67 (6H, *m*, C_6H_5), 7.82 (4H, *m*, C_6H_5), 8.15 (2H, *d*, J=8.9 Hz, Ar–H *meta* to OH), 8.29 (2H, *s*, py–H). ^{13}C NMR (DMSO-d_6) δ 45.8, 117.1, 124.0, 124.3, 129.7, 130.1, 131.4, 131.6, 133.9, 154.4, 156.7, and 162.5.

The *N*-methyl-4-(hydroxyphenyl)-2,6-diphenylpyridinium fluoroborate (200 mg, 0.47 mmol) was dissolved in methanol and a 2 M KOH methanolic solution was added (0.3 mL). The resulting deep red solution was filtered and rotary evaporated to dryness. The residue was triturated with diethyl ether and filtered to give 130 mg (82% yield) of the betaine **3**, crystallized from acetonitrile in the form of red needles that melted at 180–182 °C. Anal. Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15%; found C, 84.95; H, 5.19; N 3.78%. ^{1}H NMR (DMSO-d_6) δ 3.52 (3H, s, N^+–CH3), 6.54 (2H, d, J=8.9 Hz, Ar–H *ortho* to phenoxide oxygen), 7.64 (6H, m, C_6H_5), 7.78 (4H, m, C_6H_5), 7.94 (2H, d, J=8.9 Hz, Ar–H *meta* to phenoxide oxygen), 7.95 (2H, s, py–H). ^{13}C NMR (DMSO-d_6) 44.6, 117.2, 119.8, 120.9, 129.6, 130.0, 131.2, 131.5, 134.4, 153.5, 155.3, and 172.3.

For the investigation by ^{1}H NMR of dye–CD association, spectra were recorded in 1:1 volume mixtures of D_2O/CD_3OD (99+at %, Aldrich). The residual solvent signal for CD_3OD (δ 3.31 referred to TMS) was employed as internal reference for all observed chemical shifts in these mixtures.

Molecular dynamics simulations were performed with the CHARMM27 force field[30] employing the crystallized α-CD (PDB/ACX)[31] and β-CD (PDB/BCD)[32] structures. The structures of betaines **1**, **3**, **4**, and **5** were generated with InsightII[33] and optimized with the AM1 basis set. The partial atomic charges of the molecules were calculated using the restrained electrostatic potential (RESP) fitting procedure. Electrostatic potentials were generated at the Hartree–Fock/6-31G* level. The dyes were docked into the corresponding CD cavity using Autodock v 3.0 and the most

stable conformation chosen as starting point for simulations in water. The structures were soaked into a 20-Å-radius sphere built with the TIP3P water model.[34] After an initial minimization, followed by a 600-step heating to 300 K, the systems were allowed to reach equilibrium through 500 steps, followed by an acquisition period of 200 ps. During data collection, all systems showed potential-energy fluctuations smaller than 10%. All calculations were done using a cutoff value of 10 Å.

Acknowledgements

We are grateful to grants from FONDECYT project no. 1040001 and MECESUP USA-0007 and to Dr. Fernando González-Nilo for computational facilities.

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Tetrahedron 62 (2006) 7824–7837
Tetrahedron

Radical dearomatization of arenes and heteroarenes

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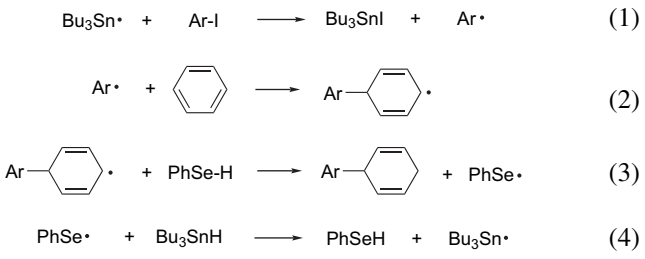
Received 24 March 2006; revised 18 May 2006; accepted 22 May 2006
Available online 15 June 2006

Abstract—The stannane-mediated benzeneselenol-catalyzed addition of aryl iodides to a range of arenes and aromatic hetereocycles has been studied. With furan, thiophene, and several carbocyclic arenes, the addition takes place with quenching of the adduct radical by the catalytic selenol leading to moderate yields of aryl-dihydroarenes. With nitrogen heterocycles, on the other hand, it was not possible to suppress aromatization of the adduct radical and fully aromatized products were isolated. Aryl iodides bearing hydrogen bond donating groups in the *ortho*-position add to nitrogen heterocycles with high selectivity *ortho*- to the nitrogen, affording a simple one-step synthesis of potential chelating ligands. While 2-iodophenol is an excellent aryl radical source in these reactions, the homologous 1-iodo-2-naphthol fails owing to its reaction with diphenyl diselenide, which gives 1-phenylseleno-2-naphthol in high yield.

1. Introduction

A recurring theme in our laboratory in recent years has been the reductive radical arylation of benzene leading to the formation of 3-arylcyclohexa-1,4-dienes, and the application of this reaction in total synthesis. In this chemistry, aryl radicals add rapidly to arenes to give cyclohexadienyl radicals substituted with aryl groups at the 6-position, which undergo hydrogen atom transfer from catalytic benzeneselenol, yielding the reaction product and a benzeneselenyl radical.[1] The benzeneselenyl radical then abstracts hydrogen from tributyltin hydride,[2,3] the stoichiometric reductant, thereby regenerating the catalytic selenol and the stannyl radical necessary for formation of the aryl radical from the aryl iodide. Overall, a four propagation step radical chain sequence is involved (Scheme 1).[1] The catalytic benzeneselenol is necessary because, under typical preparative radical chain conditions, the intermediate cyclohexadienyl radical is insufficiently reactive to propagate the radical chain by hydrogen atom abstraction from stannane or silane hydrogen atom donors. Although the Sn–H and Se–H bond dissociation energies are very similar,[4–6] the selenol traps alkyl radicals some 500 times faster than the stannane,[7–9] because of the operation of a polarity effect.[10] The interrupted propagation in the absence of selenol results in the formation of rearomatized biaryls and the need for large quantities of radical initiator.[11] Similarly, the intramolecular version of simple stannane-mediated, cyclizations of aryl radical onto arenes, is marked by the formation of fully re-oxidized products and the application of copious amounts of initiator.[12] Indeed, the azo-type initiators are now seen to serve the important function of oxidant for the cyclohexadienyl radical in addition to their more obvious planned function.[13–16]



Scheme 1. Mechanism of dearomatizing aryl radical addition to arenes.

The benzeneselenol-catalyzed chemistry is rendered practical by the rapid in situ reduction of diphenyl diselenide to benzeneselenol by the stannane, which enables the direct handling of the air-sensitive selenol to be avoided (Scheme 2).[3]

Scheme 2. In situ selenol generation.

In the reductive radical arylation of benzene (Scheme 1) regiochemistry is not an issue in the addition step, and only becomes a concern in the hydrogen atom transfer step to the cyclohexadienyl radical when formation of the skipped diene is preferred over that of the conjugated diene because of the higher spin density on the central carbon. However, in

Keywords: Radical; Arylation; Cyclohexadienyl; Dearomatization.
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0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.05.051

additions to aromatic heterocycles and other simple arenes the question of regioselectivity also arises in the initial addition reaction, resulting in potentially complex reaction mixtures.[17] In spite of this concern, we were motivated to investigate the use of a broader range of arenes and of aromatic heterocycles as substrates in this chemistry, and report here in full on our explorations.[18]

2. Results and discussion

2.1. Nitrogen heterocycles

Our attention was first directed at pyridine as substrate in view of its ready availability, convenient boiling point, and its well-established free addition radical chemistry, especially that of pyridinium salts.[12,19] The addition of aryl radicals to pyridine and substituted pyridines was studied some 40 years ago using diazonium salts as radical precursors in the Gomberg–Hey reaction, and it was determined that the relative rate of addition of the 4-bromophenyl radical to pyridine with respect to benzene was 0.87.[20,21] Relative rates of addition of phenyl radicals, generated by decomposition of benzoyl peroxide, to alkylpyridines and benzene were also known and of a comparable magnitude.[22–24] The photolysis of triphenylbismuth had also been employed as a means of generating phenyl radicals for addition to pyridine.[25] All of the early work on aryl radical addition to pyridine indicated a small preference for attack at the *ortho*-position, the extent of which was found to depend on the nature of the *ortho*-substituent on the attacking aryl radical, with attack at the pyridine *para*-position being the least favored.[20,21,25–27] Much more recently, and while this work was in progress, Alvarez-Builla and co-workers reported on the tris(trimethylsilyl)silane-mediated addition of aryl bromides to pyridine and obtained mixtures of the fully aromatic biaryl products, in which the isomer arising from attack at the pyridine 2-position predominated (2-aryl:3-aryl:4-aryl∼4:1:1).[28]

On the basis of this literature precedent, the success of the selenol-mediated reductive arylations of benzene, and the common occurrence of dihydropyridines in both nature and the laboratory,[29,30] we were surprised to find that the reaction of various aryl iodides with tributyltin hydride and AIBN, catalyzed by diphenyl diselenide yielded, not the anticipated aryl dihydropyridines, but rather the fully aromatic aryl pyridines (Table 1). Dihydropyridines were not formed in these reactions, as determined by inspection of the crude reaction mixtures by NMR spectroscopy; presumably, the azacyclohexadienyl radical intermediates are too stable to propagate the chain by hydrogen atom abstraction from the selenol. Nevertheless, the diphenyl diselenide/benzeneselenol had a beneficial effect on these reactions as significantly lower conversions were obtained in its absence. For example, heating of **2** with tributyltin hydride and AIBN in pyridine in the absence of diphenyl diselenide, but under otherwise standard conditions, gave **13**, **14**, and **15** in 9, 4, and 1% yield, respectively, along with 47% of recovered substrate. The beneficial effect of the selenide is also apparent from comparison with the Alvarez-Builla tris(trimethylsilyl)silane-mediated additions to pyridine,[28] which were conducted with greater than stoichiometric AIBN as opposed to the 20 mol % used in our study. It is not clear at the present time how the selenol/diselenide is achieving catalysis: one possibility is the quenching of the azacyclohexadienyl radical by diphenyl diselenide to give an aryl phenylselenyl azacyclohexadiene, which spontaneously eliminates benzeneselenol to give the final product. Another possibility is the oxidation of the electron-rich azacyclohexadienyl radical to the corresponding cation by an organoselenium species, such as diphenyl diselenide, or tributylstannyl phenyl selenide.

With *N*-methoxycarbonyl-*o*-iodoaniline **1** as substrate 38% of the *ortho*-substitution product **11** was obtained, along with 3% of the *meta*-isomer **12** (Table 1, entry 1). Likewise, *o*-iodophenol **2**, *o*-iodoaniline **7**, and *o*-iodo-*N*-methylaniline **8** all afforded predominantly the *ortho*-products (Table 1, entries 2, 7, and 8). In contrast, with methyl *o*-iodobenzoate **3**, *p*-bromoiodobenzene **4**, 2-iodothiophene **5**, and *o*-iodoanisole **9** the *ortho*:*para* ratio of products was much lower (Table 1, entries 3, 4, 5, and 9). In most cases, minor amounts of the *para*-isomers were also isolated (Table 1). The improved ratios in favor of the *ortho*-substituted product seen with **1**, **2**, **7**, and **8** are attributed to hydrogen bonding of the substrate to pyridine resulting in both an activating and a directing effect. The exception, *o*-iodovanillin **6**, is explained by preferential intramolecular hydrogen bonding to the methoxy group.

In the nitrogen heterocycles, we also briefly investigated additions to quinoline, isoquinoline, benzothiazole, and pyrrole with varying degrees of success (Table 2). In accordance with the literature for the addition of benzoyl peroxide-generated phenyl radicals to quinoline, when phenylation at all positions was found,[31,32] a complex reaction mixture was obtained when *o*-iodophenol was heated to reflux in benzene in the presence of 30 equiv of quinoline, catalytic diphenyl diselenide, and tributyltin hydride. Only one product was isolated pure from this reaction mixture and that in very low yield (Table 2, entry 1). With isoquinoline on the other hand, a much cleaner reaction was observed and one very predominant product **39**, resulting from attack at the 1-position, was obtained in 44% yield. The only other product **40** isolated in low yield was that of substitution at the 3-position (Table 2, entry 2). The formation of the 1-arylisoquinoline as the major product is in accord with earlier work on the addition of phenyl radicals, generated either by photolysis of phenylthallium bis(trifluoroacetate) or by decomposition of the benzenediazonium cation, to isoquinoline.[33] However, the selectivity is greater than would have been anticipated on the basis of those earlier studies. Furthermore, the formation of the 3-arylisoquinoline as the second most abundant product does not agree with the earlier phenylation studies, when the 3-position was found to be one of the least reactive. As with the additions to pyridine, we invoke hydrogen bonding of the heterocycle with the *o*-iodophenol substrate as the factor increasing the selectivity for attack at both the 1- and the 3-positions.

A brief investigation of aryl radical addition to pyrrole under our standard conditions was unsatisfactory, resulting in the isolation of only one major product, the *ortho*-substituted product **41**, in low yield (Table 2, entry 3). With 20 equiv of benzothiazole in benzene the major product **42** was that

Table 1. Aryl radical additions to pyridine

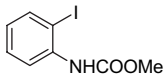
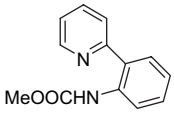
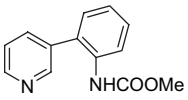
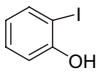
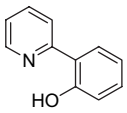
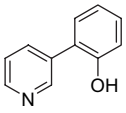
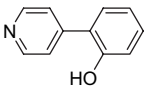
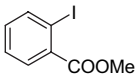
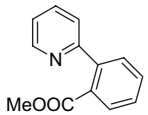
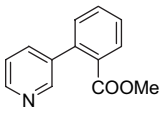
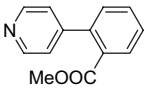
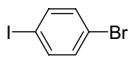
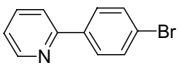
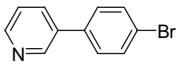
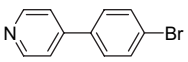
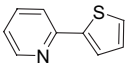
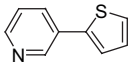
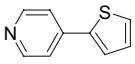
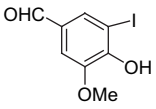
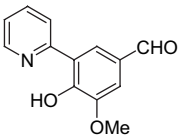
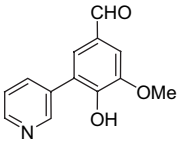
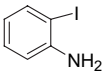
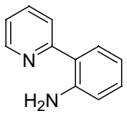
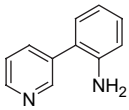
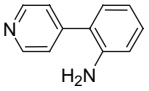
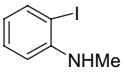
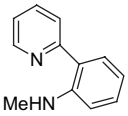
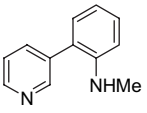
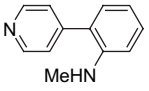
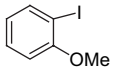
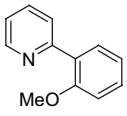
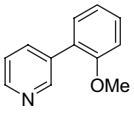
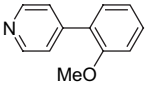
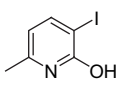
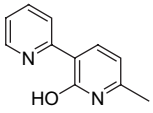
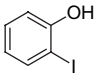
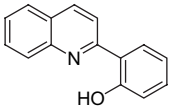
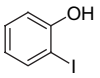
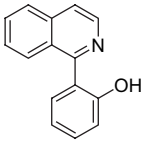
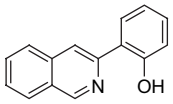
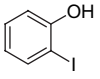
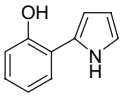
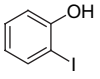
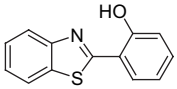
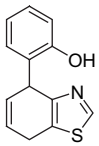
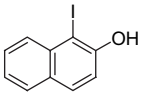
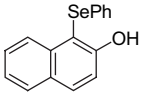
Entry	Substrate	Products (yield)		
1	 **1**	 **11** (38%)	 **12** (3%)	
2	 **2**	 **13** (36%)	 **14** (16%)	 **15** (10%)
3	 **3**	 **16** (20%)	 **17** (22%)	 **18** (9%)
4	 **4**	 **19** (18%)	 **20** (12%)	 **21** (5%)
5	 **5**	 **22** (19%)	 **23** (24%)	 **24** (7%)
6	 **6**	 **25** (17%)	 **26** (17%)	
7	 **7**	 **27** (18%)	 **28** (4%)	 **29** (4%)
8	 **8**	 **30** (25%)	 **31** (7%)	 **32** (5%)
9	 **9**	 **33** (20%)	 **34** (23%)	 **35** (10%)
10	 **10**		 **36** (13%)	

Table 2. Aryl radical addition to other nitrogen heterocycles

Entry	Heterocycle	Substrate	Products (yield)
1	Quinoline	 **2**	 **38** (5%)
2	Isoquinoline	 **2**	 **39** (44%)  **40** (4%)
3	Pyrrole	 **2**	 **41** (17%)
4	Benzothiazole	 **2**	 **42** (19%)  **43** (7%)
5	Isoquinoline	 **37**	 **44** (88%)[a]

[a] Based on diphenyl diselenide.

of attack in the heterocyclic ring, with rearomatization. However, a minor product **43** was also obtained, which resulted from attack on the benzenoid ring at the 4-position, whose structure was established crystallographically.[†] The predominant attack at the benzothiazole 2-position, with that at the 4-position being the second most important, is in agreement with the earlier literature on the radical phenylation of this heterocycle with benzoyl peroxide.[34]

The clean and successful addition of *o*-iodophenol to isoquinoline prompted an investigation of 1-iodo-2-naphthol **37** in this reaction, with a view to a short synthesis of 1-(2-hydroxy-1-naphthyl)isoquinoline.[35] Contrary to our expectations, a complex reaction mixture was obtained from which we were unable to isolate the desired product, but from which we obtained 1-phenylselenyl-2-naphthol[36] **44** in 88% yield based on diphenyl diselenide (Table 2, entry 5). Blank reactions in which **44** was formed in high yield from the reaction of diphenyl diselenide with **37** in benzene at reflux, in the absence of isoquinoline, stannane and AIBN, indicate that the failure of the radical reaction in this case is the result of consumption of the catalyst in an unanticipated reaction with the β-naphthol.

2.2. Oxygen and sulfur heterocycles

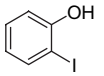
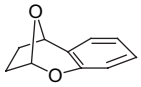
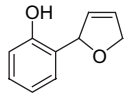
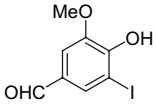
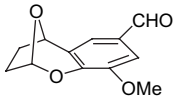
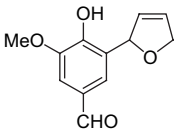
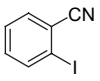
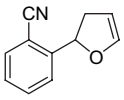
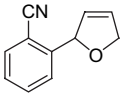
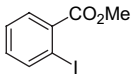
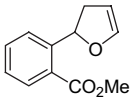
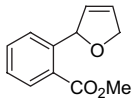
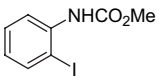
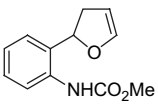
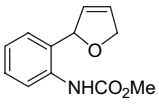
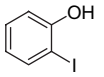
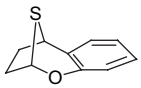
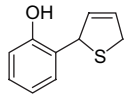
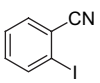
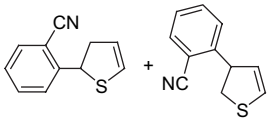
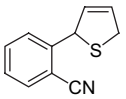
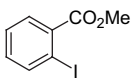
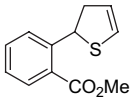
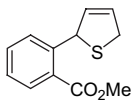
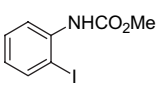
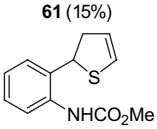
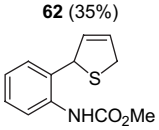
With furan and thiophene as aryl radical trap, the chemistry reverted to the pattern established with benzene, with efficient trapping of the adduct radical, and good chain propagation in the presence of catalytic benzeneselenol. Aryl radical addition to furan and thiophene had been previously studied, with aryl radicals derived from the thermolysis of phenylazotriphenylmethane, and from the metal catalyzed decomposium of the benzenediazonium ion.[37,38] With phenylazotriphenylmethane dearomatized products were obtained, owing to the combination of the initial adduct radical with the triphenylmethyl radical,[37] but the presence of the triphenylmethyl group obviously detracts from the synthetic utility of this method.[38] As expected, rearomatized products were obtained with diazonium salt-derived phenyl radicals. A series of competition reactions revealed the relative rates of addition of the phenyl radical to furan, thiophene, and benzene to be 11.5:2.6:1.[37]

A practical problem faced in the additions to furan was that of initiation. Use of our standard initiator, AIBN, with its half life of 2 h at 80 °C, suitable for reactions in benzene,[39]

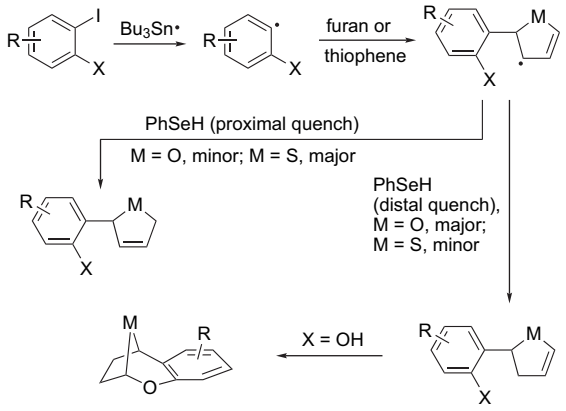
[†] CCDC 607627 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

resulted in no observable reaction at the boiling point (32 °C) of furan. A solution to this problem was found with 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70), which is reported to have a half life of 10 h at 30 °C in toluene,[40,41] for the commercial ±/*meso*-isomer. With this initiator, the benzeneselenol-catalyzed, stannane-mediated addition of aryl iodides to furan took place smoothly, giving yields of isolated products (Table 3, entries 1–5) comparable to those for addition to benzene. Likewise, additions to thiophene (bp 84 °C) proceeded smoothly with V-70 as initiator when the reactions were carried out at an oil bath temperature of 50 °C (Table 3, entries 6–9). In the additions to furan attack of the aryl radical at the 2-position was very strongly favored, in keeping with the previous literature observations.[37] Similarly, the additions to thiophene yielded very predominantly the product of reaction at the 2-position, with only a minor amount of a product from attack at the 3-position isolated in one example (Table 3, entry 7). In the case of furan, the intermediate oxyallyl radical was quenched preferentially at the distal terminus

Table 3. Aryl radical addition to furan and thiophene

Entry	Heterocycle	Substrate	2,3-Dihydro products (yield)	2,5-Dihydro products (yield)
1	Furan	 **2**	 **46** (45%)	 **47** (14%)
2	Furan	 **6**	 **48** (51%)	 **49** (14%)
3	Furan	 **45**	 **50** (45%)	 **51** (22%)
4	Furan	 **3**	 **52** (32%)	 **53** (10%)
5	Furan	 **1**	 **54** (43%)	 **55** (19%)
6	Thiophene	 **2**	 **56** (4%)	 **57** (32%)
7	Thiophene	 **45**	 **58** + **59** (13%) 1.4:1	 **60** (25%)
8	Thiophene	 **3**	 **61** (15%)	 **62** (35%)
9	Thiophene	 **1**	 **63** (11%)	 **64** (31%)

to the oxygen atom, giving the 2,3-dihydro-2-arylfurans, with a preference over the 2,5-dihydro-2-aryl isomers varying between 2:1 and 3.6:1. With thiophene, this preference was reversed with proximal quenching of the 1-thioallyl radical being preferred and the 2,5-dihydro-2-arylthiophenes the major product (Scheme 3). We attribute the differences in regioselectivity of hydrogen atom abstraction between the furan and thiophene series to a change in spin delocalization in the intermediate heteroatom-substituted allyl radicals as the heteroatom is changed from oxygen to sulfur. Indeed, electron spin resonance hyperfine splitting constants indicate that, in the 1-*tert*-butylthioallyl and 1-*tert*-butoxyallyl radicals, the alkylthio group is more effective at localizing spin than the alkoxy group.[42–45] As the recommended C–H bond strengths in methanol, methylamine, and methanethiol are very close,[46] the likelihood that the change in regioselectivity results from any differences in exothermicity of the quenching step is considered small.



Scheme 3. Aryl addition to furan and thiophene.

The use of *o*-iodophenols as substrates in the additions to furan resulted in the immediate cyclization of the 2,3-dihydro-2-aryl adducts to give 2,3,4,5-tetrahydro-2,5-epoxy-1-benzoxepins as the isolated products (Table 3, entries 1 and 2). Presumably, either the phenol itself, or the benzeneselenol catalyst, promotes cyclization directly in the reaction mixture as the initial adducts could not be detected by NMR spectroscopy of the crude reaction mixtures. The analogous cyclization also occurred in the thiophene series (Table 3, entry 6), but much more slowly enabling detection of the intermediate 2,3-dihydro-2-arylthiophene in the crude reaction mixture.

2.3. Carbocyclic arenes

In classical work on the oxidative addition of aryl radicals to arenes it was established that phenyl radicals, obtained on decomposition of *N*-nitrosoacetanilides, add to anisole with a slight preference for the *ortho*-position, over the *para*- and *meta*-positions (3.5:1.5:0.9), and that addition to the *ortho*-position was some three and a half times more rapid than the corresponding addition to benzene.[17,47,48] Under our conditions, with the radical derived from *o*-iodophenol, the main isolated product (Table 4, entry 1) was the methoxytetrahydrodibenzofuran **66**, arising from initial attack at the *ortho*-position. The biphenyl **67** from *ortho*-attack was also obtained, as was a minor amount of the biphenyl **68** from reaction at the *para*-position. Similar results were obtained with *o*-iodobenzoic acid (Table 4, entry 2), and with *o*-iodoaniline (Table 4, entry 3) as the source of aryl radical, except that in the last case only the fully aromatized products were obtained. The *cis*-fused nature of the ring junction in **66** is assigned based on a NOESY cross peak between the bridgehead hydrogen and the pseudoaxial, homoallylic hydrogen adjacent to the methoxy group. The assignment of the *trans*-fused ring junction in **69** follows from the NOESY cross peaks involving the two homoallylic hydrogens, one of which correlates with the bridgehead hydrogen, and the other with the methoxy hydrogens.

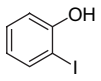
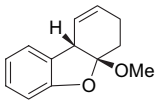
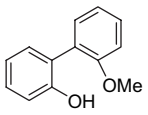
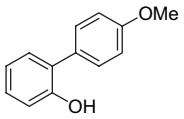
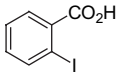
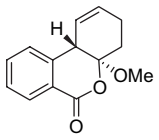
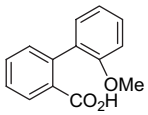
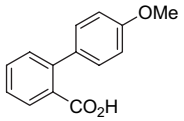
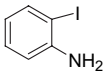
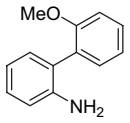
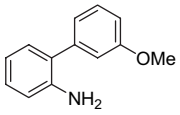
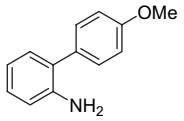
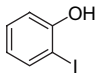
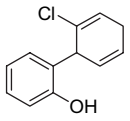
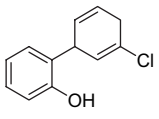
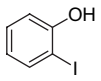
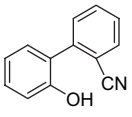
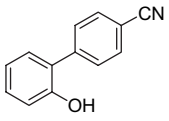
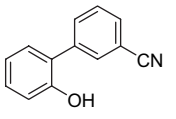
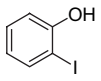
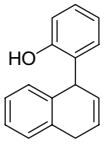
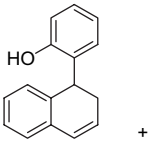
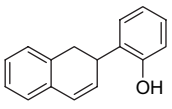
The absolute rate constant for the addition of phenyl radicals to chlorobenzene at 25 °C has been determined to be $1.18\times10^{6}\ M^{-1}\ s^{-1}$, by a laser flash photolytic technique, and so approximately 2.5 times than the comparable addition to benzene.[49,50] Earlier studies found an approximately 1.5:1 preference for the addition of phenyl radicals to the *ortho*-position of chlorobenzene, over addition to the *para*-position (*o*-:*m*-:*p*-=3.1:1:1.5).[47,51] Under the benzeneselenol-catalyzed conditions, two major products were formed in the approximate ratio of 3:1, which was altered in favor of the major isomer on silica gel chromatography owing to the more rapid decomposition of the minor isomer (Table 4, entry 4). Presumably, the more stabilized 3-chloro-6-aryl-1,4-cyclohexadienyl radical arising from attack *para*- to the chlorine did not propagate the radical chain with the selenol, and led to decomposition products. The regiochemistry of **75** and **76** is based on the coupling, in the ^{1}H NMR spectra, of the benzylic hydrogen with a single olefinic hydrogen in **75**, and with two olefinic hydrogens in **76**.

With benzonitrile, previously reported to undergo radical phenylation some 3.9 times faster than benzene,[50] and with a 6:1:3 selectivity for the *ortho*-position over the *meta*- and *para*-positions,[52] we obtained a mixture of three adducts containing approximately equal proportions of the *ortho*- and *para*-adducts, with less of the *meta*-adduct (Table 4, entry 5). Unfortunately, we were unable to suppress rearomatization in these reactions and the products were obtained as the fully aromatic biphenyl derivatives.

Finally, we investigated addition to naphthalene, employed as a solution in benzene. Literature reports on the radical phenylation of naphthalene suggested a strong preference, varying between 3:1 and >8:1, for attack at the 1-position over the 2-position.[53,54] Working with *o*-iodophenol, we found a ratio of 2.8:1 in favor of the adduct at the 1-position (Table 4, entry 6). While quenching of the benzocyclohexadienyl radical derived from addition of the aryl at the 1-position was efficient, enabling isolation of the 1-phenyl dihydronaphthalenes, it was not regioselective and gave an approximately 1:1 mixture of the two regioisomers.

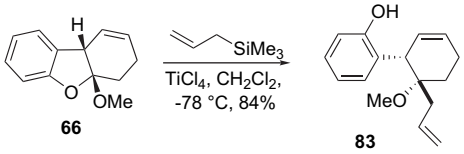
Interestingly, when the methoxytetrahydrodibenzofuran **66** was allowed to react with allyltrimethylsilane in the presence of titanium tetrachloride at −78 °C in dichloromethane the tertiary ether **83** was formed in high yield (Scheme 4). This product, whose stereochemical assignment is based on the NOESY cross peaks of the two homoallylic hydrogens with the benzylic hydrogen and the methoxy hydrogens, arises from Lewis acid-induced cleavage of the

Table 4. Aryl radical additions to carbocyclic arenes

Entry	Arene	Substrate	Products (yield)		
1	Anisole	 **2**	 **66** (20%)	 **67** (12%)	 **68** (5%)
2	Anisole	 **65**	 **69** (19%)	 **70** (7%)	 **71** (2%)
3	Anisole	 **7**	 **72** (21%)	 **73** (4%)	 **74** (5%)
4	Chlorobenzene	 **2**	 **75** (17%)[a]	 **76** (3%)[a]	
5	Benzonitrile	 **2**	 **77** (10%)	 **78** (9%)	 **79** (5%)
6	Naphthalene	 **2**	 **80**	 **81** +  **82**	
				(40%) **80**:**81**:**82** = 1.4:1.4:1	

[a] In the crude reaction mixture, the ratio of **75**:**76** was 3:1. The higher ratio of isolated products is a function of the more rapid decomposition of **76** in the course of the isolation.

endocyclic acetal bond followed by nucleophilic attack on the more open face of the subsequent oxacarbenium ion.



Scheme 4. Reaction of **66** with allyltrimethylsilane and $TiCl_4$.

3. Conclusion

Benzeneselenol catalyzes the addition of aryl radicals, derived from aryl iodides by the action of tributyltin hydride, to a wide range of arenes and hetereoarenes. The ability to isolate arylated dihydroarenes and heteroarenes is strongly system dependent, with nitrogen heterocycles giving only fully aromatic products, but furan and thiophene giving predominantly 2-aryl dihydro systems. Aryl iodides bearing hydrogen bond donating groups in the *ortho*-position add to nitrogen heterocycles with good selectivity *ortho*- to nitrogen, thereby providing a facile synthesis of potential chelating ligands.

4. Experimental

4.1. General

All solvents were dried and distilled by standard procedures. ^1H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, in $CDCl_3$ with chemical shifts (δ) downfield from tetramethylsilane.

4.2. General protocol for aryl radical addition to nitrogen heterocycles

A solution of aryl iodide (1 mmol), diphenyl diselenide (62 mg, 0.2 mmol), and solvent (20 mL) was sparged with argon for 45 min, followed by heating at 95 °C with stirring. A solution of AIBN (33 mg, 0.2 mmol) and Bu_3SnH (0.47 mL, 1.75 mmol) in degassed solvent (10 mL) was added via syringe pump over 16 h, after which heating was continued for 1 h, before the reaction mixture was cooled to room temperature and concentrated. The residue was taken up in 20% EtOAc in hexane (50 mL) and extracted with 2 N HCl (50 mL), (except Table 2, entries 4 and 5, which were purified without acidic workup). The aqueous phase was neutralized with 3 M NaOH and extracted (EtOAc). The extracts were washed with brine, dried (Na_2SO_4), concentrated, and purified by silica gel chromatography (eluent: EtOAc/hexane).

4.2.1. 2-(2-Pyridyl)methoxycarbamoylbenzene (11). Reaction solvent: pyridine; white solid; mp 32–34 °C; ^{1}H NMR δ: 3.76 (s, 3H), 7.12 (dt, J=7.0, 1.0 Hz, 1H), 7.26 (ddd, J=7.5, 4.5, 1.0 Hz, 1H), 7.40 (dt, J=8.0, 1.5 Hz, 1H), 7.63 (dd, J=7.5, 1.5 Hz, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.81 (dt, J=8.0, 2.0 Hz, 1H), 8.33 (br d, J=8.5 Hz, 1H), 8.65 (br d, J=6.0 Hz, 1H), 11.52 (br s, 1H); ^{13}C NMR δ: 52.0, 120.4, 121.8, 122.6, 122.9, 125.3, 128.9, 130.1, 137.6, 137.8, 147.6, 154.5, 158.2; Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30. Found: C, 68.37; H, 5.19.

4.2.2. 2-(3-Pyridyl)methoxycarbamoylbenzene (12). Reaction solvent: pyridine; white solid; mp 108–110 °C; ^{1}H NMR δ: 3.71 (s, 3H), 6.52 (br s, 1H), 7.20 (m, 2H), 7.41 (m, 2H), 7.70 (d, J=7.5 Hz, 1H), 8.05 (br s, 1H), 8.63 (m, 2H); ^{13}C NMR δ: 52.4, 120.9, 123.8, 124.1, 129.4, 130.3, 134.1, 135.0, 136.9, 149.0, 150.0, 154.0; Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30. Found: C, 68.24; H, 5.20.

4.2.3. 2-(2-Hydroxyphenyl)pyridine (13). Reaction solvent: pyridine; colorless oil; spectroscopic data identical to literature values;[55] ^{1}H NMR δ: 6.92 (dt, J=8.0, 1.0 Hz, 1H), 7.06 (dd, J=8.0, 1.0 Hz, 1H), 7.19–7.22 (m, 1H), 7.32 (dt, J=7.0, 1.5 Hz, 1H), 7.77–7.80 (m, 2H), 7.88 (d, J=8.5 Hz, 1H), 8.48 (d, J=4.5 Hz, 1H).

4.2.4. 3-(2-Hydroxyphenyl)pyridine (14). Reaction solvent: pyridine; white solid; mp 162–163 °C, lit.[56] 171–172 °C; ^{1}H NMR δ: 4.93 (br s, 1H), 6.91–6.94 (m, 2H), 7.21 (dt, J=9.0, 1.5 Hz, 1H), 7.28 (dd, J=7.5, 1.5 Hz, 1H), 7.43–7.45 (m, 1H), 8.03 (td, J=7.5, 2.5 Hz, 1H), 8.41 (dd, J=4.5, 1.5 Hz, 1H), 8.73 (dd, J=2.0, 0.5 Hz, 1H).

4.2.5. 4-(2-Hydroxyphenyl)pyridine (15). Reaction solvent: pyridine; white solid; mp 208–210 °C, lit.[57] 213–215 °C; spectroscopic data identical to literature values;[57] ^{1}H NMR δ: 4.91 (br s, 1H), 6.92 (m, 2H), 7.24 (dt, J=7.5, 1.0 Hz, 1H), 7.37 (dd, J=7.5, 1.5 Hz, 1H), 7.69 (dd, J=5.5, 1.5 Hz, 2H), 8.50 (dd, J=5.0, 1.5 Hz, 2H).

4.2.6. Methyl 2-(2-pyridyl)benzoate (16). Reaction solvent: pyridine; colorless oil; spectroscopic data identical to literature values;[58] ^{1}H NMR δ: 3.67 (s, 3H), 7.24 (m, 1H), 7.44–7.48 (m, 2H), 7.55 (dd, J=5.0, 1.0 Hz, 2H), 7.74 (dt, J=8.0, 2.0 Hz, 1H), 7.81 (d, J=7.5 Hz, 1H), 8.63 (qd, J=4.0, 1.0 Hz, 1H).

4.2.7. Methyl 2-(3-pyridyl)benzoate (17). Reaction solvent: pyridine; colorless oil; spectroscopic data identical to literature values;[59] ^{1}H NMR δ: 3.66 (s, 3H), 7.32 (dd, J=7.5, 0.5 Hz, 1H), 7.37 (br m, 1H), 7.46 (dt, J=7.5, 0.5 Hz, 1H), 7.56 (dt, J=7.5, 1.0 Hz, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.93 (dd, J=8.0, 1.5 Hz, 1H), 8.71 (br s, 2H).

4.2.8. Methyl 2-(4-pyridyl)benzoate (18). Reaction solvent: pyridine; colorless oil; spectroscopic data identical to literature values;[57] ^{1}H NMR δ: 3.67 (s, 3H), 7.23 (dd, J=4.5, 1.5 Hz, 2H), 7.32 (td, J=8.0, 0.5 Hz, 1H), 7.49 (dt, J=7.5, 1.5 Hz, 1H), 7.58 (dt, J=8.0, 1.5 Hz, 1H), 7.93 (dd, J=7.5, 1.5 Hz, 1H), 8.63 (dd, J=6.0 Hz, 2H).

4.2.9. 2-(4-Bromophenyl)pyridine (19). Reaction solvent: pyridine; colorless oil; spectroscopic data identical to literature values;[60] ^{1}H NMR δ: 7.24 (m, 1H), 7.60 (d, J=8.5 Hz, 2H), 7.69 (d, J=7.5 Hz, 1H), 7.74 (dt, J=7.5, 1.0 Hz, 1H), 7.86 (d, J=6.5 Hz, 2H), 8.68 (td, J=4.5, 1.0 Hz, 1H).

4.2.10. 3-(4-Bromophenyl)pyridine (20). Reaction solvent: pyridine; colorless oil; spectroscopic data identical to literature values;[21] ^{1}H NMR δ: 7.36 (m, 1H), 7.44 (d, J=8.5 Hz, 2H), 7.60 (d, J=8.5 Hz, 2H), 7.83 (td, J=8.0, 1.5 Hz, 1H), 8.60 (d, J=3.5 Hz, 1H), 8.80 (s, 1H).

4.2.11. 4-(4-Bromophenyl)pyridine (21). Reaction solvent: pyridine; white solid; mp 129.5 °C, lit.[61] 130 °C; spectroscopic data identical to literature values;[61] ^{1}H NMR δ: 7.47 (dd, J=4.5, 1.5 Hz, 2H), 7.51 (d, J=7.0 Hz, 2H), 7.61 (d, J=7.0 Hz, 2H), 8.67 (dd, J=4.5, 1.5 Hz, 2H).

4.2.12. 2-(2-Thienyl)pyridine (22). Reaction solvent: pyridine; white solid; mp 61.5 °C, lit.[62] 61–62 °C; spectroscopic data identical to literature values;[62] ^{1}H NMR δ: 7.13 (m, 2H), 7.39 (dd, J=5.0, 1.0 Hz, 1H), 7.58 (dd, J=4.0, 1.0 Hz, 1H), 7.66 (m, 2H), 8.56 (d, J=4.5 Hz, 1H).

4.2.13. 3-(2-Thienyl)pyridine (23). Reaction solvent: pyridine; colorless oil; spectroscopic data identical to literature values;[63] ^{1}H NMR δ: 7.12 (dd, J=5.0, 4.0 Hz, 1H), 7.30 (m, 1H), 7.35 (d, J=4.0 Hz, 2H), 7.86 (td, J=8.0, 1.5 Hz, 1H), 8.52 (br s, 1H), 8.89 (br s, 1H).

4.2.14. 4-(2-Thienyl)pyridine (24). Reaction solvent: pyridine; colorless oil; spectroscopic data identical to literature values;[64] ^{1}H NMR δ: 7.14 (dd, J=5.0, 4.0 Hz, 1H), 7.42 (d, J=5.0 Hz, 1H), 7.51 (m, 3H), 8.61 (br s, 2H).

4.2.15. 5-(2-Pyridyl)vanillin (25). Reaction solvent: pyridine; yellowish solid; mp 160–161 °C; ^{1}H NMR δ: 3.96 (s, 3H), 7.32 (ddd, J=7.5, 5.0, 1.0 Hz, 1H), 7.39 (d, J=1.5 Hz, 1H), 7.90 (dt, J=7.5, 1.5 Hz, 1H), 7.94 (d, J=2.0 Hz, 1H), 8.0 (d, J=8.5 Hz, 1H), 8.52 (ddd, J=5.3, 2.0, 0.5 Hz, 1H), 9.85 (s, 1H); ^{13}C NMR δ: 56.2, 110.2, 117.9, 119.4, 122.4, 123.7, 127.4, 138.4, 145.4, 150.3, 156.6, 156.8, 190.6; Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84. Found: C, 67.83; H, 4.70.

4.2.16. 5-(3-Pyridyl)vanillin (26). Reaction solvent: pyridine; yellowish solid; mp 162–163 °C; ^{1}H NMR δ: 3.99 (s, 3H), 7.39 (dd, J=8.3, 5.0 Hz, 1H), 7.44 (d, J=2.0 Hz, 1H), 7.50 (d, J=2.0 Hz, 1H), 7.98 (td, J=8.0, 2.0 Hz, 1H), 8.58 (dd, J=5.0, 1.5 Hz, 1H), 8.87 (d, J=2.5 Hz, 1H), 9.87 (s, 1H); ^{13}C NMR δ: 56.5, 108.3, 123.3, 124.1, 128.0, 129.4, 132.5, 136.7, 147.7, 148.4, 149.2, 149.6, 190.7; ESIHRMS, calcd for $C_{13}H_{11}NO_3$: 230.0817 (M+H$^+$), found: 230.0815.

4.2.17. 2-(2-Aminophenyl)pyridine (27). Reaction solvent: pyridine; yellowish oil; spectroscopic data identical to literature values;[65] ^{1}H NMR δ: 5.48 (br s, 2H), 6.78 (m, 2H), 7.18 (m, 2H), 7.51 (dd, J=7.5, 1.0 Hz, 1H), 7.56 (d, J=8.0 Hz, 1H), 7.76 (dt, J=8.0, 2.0 Hz, 1H), 8.61 (td, J=5.0, 0.5 Hz, 1H).

4.2.18. 3-(2-Aminophenyl)pyridine (28). Reaction solvent: pyridine; yellowish oil; spectroscopic data identical to literature values;[66] ^{1}H NMR δ: 3.51 (br s, 2H), 6.78 (d, J=8.0 Hz, 1H), 6.86 (dt, J=7.5, 0.5 Hz, 1H), 7.10 (dd, J=7.5, 2.0 Hz, 1H), 7.21 (dt, J=7.0, 1.0 Hz, 1H), 7.38 (m, 1H), 7.82 (td, J=8.0, 1.5 Hz, 1H), 8.60 (dd, J=4.5, 1.0 Hz, 1H), 8.71 (d, J=2.5 Hz, 1H).

4.2.19. 4-(2-Aminophenyl)pyridine (29). Reaction solvent: pyridine; yellowish oil; spectroscopic data identical to literature values;[57] ^{1}H NMR δ: 3.73 (br s, 2H), 6.77 (d, J=8.0 Hz, 1H), 6.85 (dt, J=8.5, 1.0 Hz, 1H), 7.13 (dd, J=7.5, 1.5 Hz, 1H), 7.21 (tt, J=8.0, 1.0 Hz, 1H), 7.43 (dd, J=5.5, 2.0 Hz, 2H), 8.67 (dd, J=5.5, 1.5 Hz, 2H).

4.2.20. 2-[2-(*N*-Methylamino)phenyl]pyridine (30). Reaction solvent: pyridine; yellowish oil; ^{1}H NMR δ: 2.93 (s, 3H), 6.75 (m, 2H), 7.17 (m, 1H), 7.32 (m, 1H), 7.56 (d, J=7.5 Hz, 1H), 7.67 (dd, J=8.0, 1.0 Hz, 1H), 7.75 (m, 1H), 8.02 (br s, 1H), 8.60 (dd, J=5.0, 1.0 Hz, 1H); ^{13}C NMR δ: 30.0, 110.8, 115.6, 120.8, 121.4, 122.4, 129.4, 130.4, 136.9, 147.5, 148.6, 159.8; ESIHRMS, calcd for $C_{12}H_{12}N_2$: 185.1079 (M+H$^+$), found: 185.1075.

4.2.21. 3-[2-(*N*-Methylamino)phenyl]pyridine (31). Reaction solvent: pyridine; white solid; mp 71–73 °C; ^{1}H NMR δ: 2.80 (s, 3H), 3.80 (br s, 1H), 6.72 (d, J=8.5 Hz, 1H), 6.80 (dt, J=7.5, 1.0 Hz, 1H), 7.07 (dd, J=7.5, 2.0 Hz, 1H), 7.31 (dt, J=8.5, 2.0 Hz, 1H), 7.37 (dd, J=4.5, 1.0 Hz, 1H), 7.76 (td, J=7.5, 2.0 Hz, 1H), 8.59 (dd, J=5.0, 2.0 Hz, 1H), 8.67 (d, J=2.0 Hz, 1H); ^{13}C NMR δ: 30.7, 110.1, 117.1, 123.6, 129.6, 130.3, 135.2, 137.0, 146.3, 148.5, 150.4; ESIHRMS, calcd for $C_{12}H_{12}N_2$: 185.1079 (M+H$^+$), found: 185.1084.

4.2.22. 4-[2-(*N*-Methylamino)phenyl]pyridine (32). Reaction solvent: pyridine; white solid; mp 133–135 °C; ^{1}H NMR δ: 2.82 (s, 3H), 3.93 (br s, 1H), 6.71 (d, J=8.0 Hz, 1H), 6.80 (dt, J=7.5, 1.0 Hz, 1H), 7.09 (dd, J=7.5, 2.0 Hz, 1H), 7.32 (dt, J=7.5, 1.5 Hz, 1H), 7.39 (dd, J=6.0, 2.0 Hz, 2H), 8.66 (dd, J=6.0, 2.0 Hz, 2H); ^{13}C NMR δ: 30.7, 110.3, 117.1, 124.2, 124.4, 129.8, 130.0, 145.8, 147.7, 150.3; ESIHRMS, calcd for $C_{12}H_{12}N_2$: 185.1079 (M+H$^+$), found: 185.1075.

4.2.23. 2-(2-Methoxyphenyl)pyridine (33). Reaction solvent: pyridine; colorless oil; spectroscopic data identical to literature values;[67] ^{1}H NMR δ: 3.84 (s, 3H), 7.00 (d, J=8.5 Hz, 1H), 7.08 (t, J=7.0 Hz, 1H), 7.20 (m, 1H), 7.37 (dt, J=8.5, 2.0 Hz, 1H), 7.69 (dt, J=7.5, 2.0 Hz, 1H), 7.75 (dd, J=7.5, 2.0 Hz, 1H), 7.81 (d, J=8.0 Hz, 1H), 8.70 (d, J=4.5 Hz, 1H).

4.2.24. 3-(2-Methoxyphenyl)pyridine (34). Reaction solvent: pyridine; colorless oil; spectroscopic data identical to literature values;[66] ^{1}H NMR δ: 3.82 (s, 3H), 6.99 (d, J=8.5 Hz, 1H), 7.06 (dt, J=7.5, 1.0 Hz, 1H), 7.30–7.39 (m, 3H), 7.86 (tt, J=8.5, 2.5 Hz, 1H), 8.55 (dd, J=5.0, 2.0 Hz, 1H), 8.77 (dd, J=2.5, 1.0 Hz, 1H).

4.2.25. 4-(2-Methoxyphenyl)pyridine (35). Reaction solvent: pyridine; colorless oil; spectroscopic data identical to literature values;[57] ^{1}H NMR δ: 3.83 (s, 3H), 7.00 (dd, J=8.5, 1.0 Hz, 1H), 7.06 (dt, J=7.0, 0.5 Hz, 1H), 7.34 (dd, J=7.5, 1.5 Hz, 1H), 7.40 (dt, J=8.0, 1.5 Hz, 1H), 7.47 (dd, J=4.5, 2.0 Hz, 2H), 8.62 (dd, J=4.5, 1.5 Hz, 2H).

4.2.26. 6-(2-Pyridyl)-2-picolin-5-ol (36). Reaction solvent: pyridine; yellowish solid; mp 47–48 °C; ^{1}H NMR δ: 2.53 (s, 3H), 7.08 (d, J=9.0 Hz, 1H), 7.23 (d, J=9.0 Hz, 1H), 7.31 (ddd, J=11.5, 5.0, 1.5 Hz, 1H), 7.89 (dt, J=7.5, 2.0 Hz, 1H), 8.50 (dd, J=5.0, 1.0 Hz, 1H), 8.63 (d, J=8.0 Hz, 1H), 14.01 (br s, 1H); ^{13}C NMR δ: 23.7, 120.8, 122.8, 125.6, 126.2, 135.3, 137.8, 145.4, 148.1, 154.4, 158.3; Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41. Found: C, 70.89; H, 5.39.

4.2.27. 2-(2-Hydroxyphenyl)quinoline (38). Reaction solvent: benzene (30 equiv of quinoline in benzene); white solid; mp 110–112 °C, lit.[68] 109.8–110.7 °C; spectroscopic data identical to literature values;[68] ^{1}H NMR δ: 6.96 (tt, J=8.0, 1.5 Hz, 1H), 7.11 (d, J=7.5 Hz, 1H), 7.26 (d, J=1.5 Hz, 1H), 7.37 (dt, J=8.5, 1.0 Hz, 1H), 7.54 (dt, J=7.0, 1.5 Hz, 1H), 7.74 (dt, J=8.0, 1.0 Hz, 1H), 7.80 (d, J=8.0 Hz, 1H), 7.94 (d, J=7.5 Hz, 1H), 8.02 (dd, J=8.0, 2.0 Hz, 1H), 8.24 (d, J=8.5 Hz, 1H), 15.27 (br s, 1H).

4.2.28. 1-(2-Hydroxyphenyl)isoquinoline (39). Reaction solvent: benzene (30 equiv of isoquinoline in benzene); white solid; mp 160–162 °C, lit.[69] 166–168 °C; spectroscopic data identical to literature values;[69] ^{1}H NMR δ: 7.02 (dt, J=7.5, 1.0 Hz, 1H), 7.20 (dd, J=8.5, 1.0 Hz, 1H), 7.39 (dt, J=8.5, 1.5 Hz, 1H), 7.59–7.63 (m, 2H), 7.71–7.75 (m, 2H), 7.88 (d, J=8.0 Hz, 1H), 8.45 (m, 2H), 11.82 (br s, 1H).

4.2.29. 3-(2-Hydroxyphenyl)isoquinoline (40). Reaction solvent: benzene (30 equiv of isoquinoline in benzene); white solid; mp 112–113 °C; ^{1}H NMR δ: 6.96 (dt, J=7.0, 1.0 Hz, 1H), 7.06 (d, J=7.0 Hz, 1H), 7.32 (tt, J=7.0, 1.5 Hz, 1H), 7.60 (dt, J=8.0, 1.0 Hz, 1H), 7.74 (dt, J=7.0, 1.5 Hz, 1H), 7.89 (d, J=8.0 Hz, 1H), 7.92 (d, J=6.0 Hz, 1H), 8.00 (d, J=8.0 Hz, 1H), 8.22 (s, 1H), 9.19 (s, 1H), 14.05 (br s, 1H); ^{13}C NMR δ: 115.4, 118.7, 119.1, 119.5, 126.2, 126.9, 127.1, 127.4, 127.9, 130.9, 131.4, 137.0, 149.0, 151.2, 159.3; Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01. Found: C, 81.39; H, 5.00.

4.2.30. 2-(2-Hydroxyphenyl)-1*H*-pyrrole (41). Reaction solvent: pyrrole; yellowish oil; spectroscopic data identical to literature values;[70] ^{1}H NMR δ: 5.52 (s, 1H), 6.33 (d, J=3.0 Hz, 1H), 6.58 (s, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.89 (s, 1H), 6.97 (t, J=7.0 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H),

7.55 (d, J=8.0 Hz, 1H), 9.42 (br s, 1H); ^{13}C NMR δ: 106.2, 109.2, 116.3, 118.6, 119.6, 121.5, 127.0, 127.2, 128.8, 151.0.

4.2.31. 2-(2-Hydroxyphenyl)benzothiazole (42). Reaction solvent: benzene (20 equiv of benzothiazole in benzene); white solid; mp 130–131 °C, lit.[71] 130–132 °C; ^{1}H NMR δ: 6.96 (tt, J=7.5, 1.0 Hz, 1H), 7.12 (dd, J=8.5, 1.0 Hz, 1H), 7.37–7.42 (m, 2H), 7.50 (dt, J=8.5, 1.5 Hz, 1H), 7.69 (dd, J=8.5 Hz, 1.5 Hz, 1H), 7.89 (d, J=8.5 Hz, 1H), 7.99 (dd, J=8.0, 1.0 Hz, 1H), 12.53 (s, 1H).

4.2.32. 4-(2-Hydroxyphenyl)-4,7-dihydrobenzothiazole (43). Reaction solvent: benzene (20 equiv of benzothiazole in benzene); white solid; mp 210–212 °C; ^{1}H NMR δ: 3.57–3.59 (m, 2H), 5.12–5.15 (m, 1H), 6.07–6.11 (m, 1H), 6.22–6.26 (m, 1H), 6.89 (dt, J=7.5, 1.5 Hz, 1H), 7.05 (dd, J=8.0, 1.5 Hz, 1H), 7.15–7.19 (m, 2H), 8.67 (s, 1H), 10.10 (br s, 1H); ^{13}C NMR δ: 25.4, 37.8, 119.3, 120.7, 124.6, 125.5, 126.9, 127.4, 128.4, 130.3, 150.7, 151.2, 155.5; EIHRMS, calcd for $C_{13}H_{11}NOS$: 229.0561 (M^+), found: 229.0557.

4.3. Reaction of diphenyl diselenide with 1-iodo-2-naphthol (44)

A solution of 1-iodo-2-naphthol (1.0 mmol) and diphenyl diselenide (62.0 mg, 0.2 mmol) in degassed benzene was heated to reflux for 4 h. The solvent was evaporated off under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane) afforded compound **44** in quantitative yield. White solid; mp 79 °C, lit.[36] 77–78 °C; ^{1}H NMR δ: 7.14–7.17 (m, 6H), 7.37–7.40 (m, 2H), 7.51 (dt, J=7.0 Hz, 1.0 Hz, 1H), 7.82 (d, J=8.0 Hz, 1H), 7.90 (d, J=9.0 Hz, 1H), 8.29 (d, J=8.5 Hz, 1H).

4.4. General protocol for aryl radical addition to oxygen and sulfur heterocycles

A solution of aryl iodide (1.0 mmol), diphenyl diselenide (62.0 mg, 0.2 mmol), and freshly distilled furan (thiophene) (20 mL) was sparged with argon for 45 min, followed by heating at 50 °C (bath temperature) with stirring. A solution of 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) (62.0 mg, 0.2 mmol) and Bu_3SnH (0.47 mL, 1.75 mmol) in degassed furan (thiophene) (10 mL) was added via syringe pump over 16 h, after which heating was continued for 1 h, before the reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was taken up in acetonitrile (75 mL) and washed with hexane (4×25 mL). The acetonitrile phase was concentrated and purified by silica gel column chromatography (eluent: EtOAc/hexane).

4.4.1. 2,3,4,5-Tetrahydro-2,5-epoxy-1-benzoxepin (46).[72] Colorless oil; ^{1}H NMR δ: 2.19–2.28 (m, 4H), 5.12 (d, J=4.5 Hz, 1H), 5.94 (m, 1H), 6.75 (d, J=8.5 Hz, 1H), 6.84 (dt, J=7.5, 1.5 Hz, 1H), 6.94 (dd, J=7.0, 2.0 Hz, 1H), 7.15 (dt, J=7.5, 2.0 Hz, 1H); ^{13}C NMR δ: 33.4, 35.7, 77.2, 100.4, 116.1, 120.1, 124.4, 127.2, 128.7, 150.0.

4.4.2. 2-(2,5-Dihydrofuran-2-yl)phenol (47). Colorless oil; ^{1}H NMR δ: 4.79 (m, 1H), 4.86 (m, 1H), 6.07 (m, 3H), 6.86 (m, 2H), 7.02 (ddd, J=7.5, 2.0, 1.0 Hz, 1H), 7.17 (dt, J=7.5, 1.5 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR δ: 75.5, 87.2, 117.1, 119.9, 124.8, 126.5, 126.6, 128.8, 129.0, 155.2; ESIHRMS, calcd for $C_{10}H_{10}O_2$: 185.0579 (M+Na), found: 185.0570.

4.4.3. 9-Methoxy-2,3,4,5-tetrahydro-2,5-epoxy-1-benzoxepin-7-carbaldehyde (48). White solid; mp 100–102 °C (EtOAc/hexane); ^{1}H NMR δ: 2.25–2.35 (m, 4H), 3.90 (s, 3H), 5.20 (d, J=5.5 Hz, 1H), 6.09 (d, J=4.0 Hz, 1H), 7.14 (d, J=1.0 Hz, 1H), 7.30 (d, J=1.5 Hz, 1H), 9.79 (s, 1H); ^{13}C NMR δ: 34.0, 35.3, 56.1, 77.0, 101.5, 109.7, 121.1, 127.8, 129.1, 145.2, 148.5, 190.6; Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.36; H, 5.57.

4.4.4. 3-(2,5-Dihydrofuran-2-yl)-4-hydroxy-5-methoxybenzaldehyde (49). Colorless oil; ^{1}H NMR δ: 3.95 (s, 3H), 4.83 (dd, J=12.0, 3.5 Hz, 1H), 4.92 (dd, J=14.0, 6.5 Hz, 1H), 6.03 (s, 2H), 6.16 (q, J=4.5 Hz, 1H), 6.70 (s, 1H), 7.35 (d, J=2.0 Hz, 1H), 7.47 (d, J=1.5 Hz, 1H), 9.82 (s, 1H); ^{13}C NMR δ: 56.3, 75.8, 82.6, 107.7, 124.7, 126.7, 128.0, 128.4, 129.3, 147.1, 148.4, 191.1; ESIHRMS, calcd for $C_{12}H_{12}O_4$: 243.0634 (M+Na), found: 243.0627.

4.4.5. 2-(2,3-Dihydrofuran-2-yl)benzonitrile (50). Colorless oil; ^{1}H NMR δ: 2.53 (m, 1H), 3.30 (m, 1H), 4.99 (q, J=2.0 Hz, 1H), 5.83 (dd, J=11.0, 7.5 Hz, 1H), 6.48 (q, J=2.5 Hz, 1H), 7.38 (dt, J=7.0, 2.0 Hz, 1H), 7.59 (m, 2H), 7.65 (dd, J=7.5, 1.0 Hz, 1H); ^{13}C NMR δ: 37.8, 79.8, 99.2, 109.6, 117.3, 125.8, 127.9, 132.9, 133.1, 145.2, 147.3; ESIHRMS, calcd for $C_{11}H_9NO$: 194.0582 (M+Na), found: 194.0590.

4.4.6. 2-(2,5-Dihydrofuran-2-yl)benzonitrile (51). Colorless oil; ^{1}H NMR δ: 4.84 (m, 1H), 4.98 (m, 1H), 5.92 (m, 1H), 6.10 (m, 2H), 7.37 (dt, J=7.5, 1.5 Hz, 1H), 7.50 (dd, J=8.0, 1.0 Hz, 1H), 7.58 (dt, J=7.5, 1.5 Hz, 1H), 7.66 (dd, J=7.5, 1.0 Hz, 1H); ^{13}C NMR δ: 76.5, 86.1, 110.1, 117.4, 127.1, 127.8, 128.1, 133.0, 133.3, 146.2; ESIHRMS, calcd for $C_{11}H_9NO$: 194.0582 (M+Na), found: 194.0577.

4.4.7. Methyl 2-(2,3-dihydrofuran-2-yl)benzoate (52). Colorless oil; eluent: 1:1 (hexane/benzene with 0.5% EtOAc); ^{1}H NMR δ: 2.34–2.40 (ddt, J=15.5, 10.5, 2.0 Hz, 1H), 3.31–3.37 (ddt, J=15.5, 10.5, 2.5 Hz, 1H), 3.90 (s, 3H), 4.90 (app. q, J=2.5 Hz, 1H), 6.26 (dd, J=11.5, 7.5 Hz, 1H), 6.51 (q, J=3.0 Hz, 1H), 7.33 (dt, J=8.0, 1.5 Hz, 1H), 7.54 (dt, J=7.5, 1.0 Hz, 1H), 7.63 (dd, J=7.5, 1.0 Hz, 1H), 7.98 (dd, J=7.5, 1.0 Hz, 1H); ^{13}C NMR δ: 38.6, 52.1, 79.7, 99.0, 125.5, 126.8, 126.9, 130.7, 132.7, 145.1, 145.8, 167.2; ESIHRMS, calcd for $C_{12}H_{12}O_3$: 227.0684 (M+Na), found: 227.0691.

4.4.8. Methyl 2-(2,5-dihydrofuran-2-yl)benzoate (53). Colorless oil; eluent: 1:1 (hexane/benzene with 1.5% EtOAc); ^{1}H NMR δ: 3.90 (s, 3H), 4.85 (m, 1H), 4.95 (m, 1H), 5.92 (m, 1H), 6.04 (m, 1H), 6.50 (m, 1H), 7.31 (dt, J=7.5, 1.0 Hz, 1H), 7.53 (dt, J=7.5, 1.5 Hz, 1H), 7.63 (dd, J=7.0, 1.0 Hz, 1H), 7.92 (dd, J=8.0, 1.0 Hz, 1H); ^{13}C NMR δ: 52.1, 76.2, 85.4, 125.5, 126.6, 127.0, 127.3, 130.2, 130.9, 132.8, 145.1, 167.5; ESIHRMS, calcd for $C_{12}H_{12}O_3$: 227.0684 (M+Na), found: 227.0686.

4.4.9. Methyl [2-(2,3-dihydrofuran-2-yl)phenyl]carbamate (54). Colorless oil; eluent: 1.5:1 (hexane/chloroform with 1.5% EtOAc); ^{1}H NMR δ: 2.78 (m, 1H), 2.92 (m,

1H), 3.77 (s, 3H), 5.15 (q, J=2.5 Hz, 1H), 5.53 (t, J=10.5 Hz, 1H), 6.45 (q, J=2.5 Hz, 1H), 7.08 (t, J=7.5 Hz, 1H), 7.23 (d, J=7.0 Hz, 1H), 7.34 (dt, J=7.5, 1.5 Hz, 1H), 7.38 (br s, 1H), 7.95 (br s, 1H); ^{13}C NMR δ: 35.0, 52.4, 82.8, 101.4, 121.9, 123.7, 127.7, 129.1, 129.3, 136.6, 144.6, 154.3; ESIHRMS, calcd for $C_{12}H_{13}NO_3$: 242.0793 (M+Na), found: 242.0794.

4.4.10. Methyl [2-(2,5-dihydrofuran-2-yl)phenyl]carbamate (55). Colorless oil; ^{1}H NMR δ: 3.77 (s, 3H), 4.79 (m, 2H), 5.89 (m, 1H), 6.04 (m, 1H), 6.13 (m, 1H), 7.04 (t, J=8.0 Hz, 1H), 7.12 (dd, J=7.5, 1.5 Hz, 1H), 7.31 (dt, J=9.0, 1.5 Hz, 1H), 7.82 (br s, 1H), 7.93 (br s, 1H); ^{13}C NMR δ: 52.3, 75.3, 85.9, 121.4, 123.4, 127.0, 127.7, 128.1, 128.9, 129.2, 137.1, 154.3; ESIHRMS, calcd for $C_{12}H_{13}NO_3$: 220.0974 (M+H), found: 220.0967.

4.4.11. 2,3,4,5-Tetrahydro-2,5-epithio-1-benzoxepin (56). Colorless oil; eluent: 1:1:1 (benzene/chloroform/hexane); ^{1}H NMR δ: 2.26–2.53 (m, 4H), 4.36 (d, J=5.0 Hz, 1H), 6.19 (d, J=4.5 Hz, 1H), 6.81 (m, 2H), 6.99 (dd, J=7.5, 2.0 Hz, 1H), 7.13 (dt, J=7.5, 1.5 Hz, 1H); ^{13}C NMR δ: 38.0, 40.4, 49.9, 86.9, 117.6, 120.1, 126.0, 128.6, 129.5, 151.3; ESIHRMS, calcd for $C_{10}H_{10}OS$: 179.0531 (M+H), found: 179.0536.

4.4.12. 2-(2,5-Dihydrothiophen-2-yl)phenol (57). White solid; mp 67–68 °C (EtOAc/hexane); ^{1}H NMR δ: 3.95 (m, 2H), 5.57 (m, 1H), 5.85 (m, 1H), 6.03 (m, 1H), 6.40 (br s, 1H), 6.85 (d, J=8.5 Hz, 1H), 6.88 (dt, J=7.5, 1.0 Hz, 1H), 7.15 (dd, J=7.5, 2.0 Hz, 1H), 7.19 (dt, J=7.0, 1.5 Hz, 1H); ^{13}C NMR δ: 39.6, 56.0, 117.2, 120.7, 126.1, 129.2, 129.2, 129.4, 132.5, 155.0; Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65. Found: C, 67.16; H, 5.44.

4.4.13. 2-(2,3-Dihydrothiophen-2-yl)benzonitrile (58) and 2-(2,3-dihydrothiophen-3-yl)benzonitrile (59). Compounds **58** and **59** were obtained as a 1.4:1 inseparable mixture with ESIHRMS, calcd for $C_{11}H_9NS$: 210.0354 (M+Na), found: 210.0352. Compound **58** was characterized by ^{1}H NMR δ: 2.89 (m, 1H), 3.35 (m, 1H), 5.27 (dd, J=10.0, 5.5 Hz, 1H), 5.58 (m, 1H), 6.25 (m, 1H), 7.36 (m, 1H), 7.62 (dd, J=7.5, 1.0 Hz, 1H), 7.75 (d, J=8.0 Hz, 1H), 7.26–7.66 (1H). Compound **59** was characterized by ^{1}H NMR δ: 3.13 (ddd, J=11.0, 6.5, 2.0 Hz, 1H), 3.83 (dt, J=11.5, 2.0 Hz, 1H), 4.73 (m, 1H), 5.65 (m, 1H), 6.47 (m, 1H), 7.35 (t, J=7.0 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.57 (t, J=8.0 Hz, 1H), 7.66 (d, J=7.5 Hz, 1H). Compounds **58** and **59** ^{13}C NMR δ: 39.5, 43.6, 49.3, 51.0, 111.1, 111.7, 117.5, 117.8, 120.1, 123.9, 125.4, 127.6, 127.6, 127.7, 129.3, 132.7, 133.0, 133.32, 133.36, 146.6, 147.5.

4.4.14. 2-(2,5-Dihydrothiophen-2-yl)benzonitrile (60). White solid; mp 80–81 °C (EtOAc/hexane); ^{1}H NMR δ: 3.93 (m, 1H), 4.03 (m, 1H), 5.70 (m, 1H), 5.78 (m, 1H), 6.08 (m, 1H), 7.32 (dt, J=8.0, 1.5 Hz, 1H), 7.48 (dd, J=7.5, 1.0 Hz, 1H), 7.55 (dt, J=7.5, 1.5 Hz, 1H), 7.62 (dd, J=7.5, 1.5 Hz, 1H); ^{13}C NMR δ: 40.3, 56.5, 111.5, 117.4, 127.7, 128.9, 130.6, 130.9, 133.1, 133.1, 147.3; Anal. Calcd for $C_{11}H_9NS$: C, 70.55; H, 4.84. Found: C, 70.47; H, 4.88.

4.4.15. Methyl 2-(2,3-dihydrothiophen-2-yl)benzoate (61). Colorless oil; eluent: 1:1 (hexane/benzene); ^{1}H NMR δ: 2.89 (m, 1H), 3.31 (m, 1H), 3.91 (s, 3H), 5.58 (m, 1H), 5.69 (dd, J=10.0, 4.5 Hz, 1H), 6.23 (m, 1H), 7.29 (dt, J=7.5, 1.5 Hz, 1H), 7.49 (dt, J=7.5, 1.5 Hz, 1H), 7.76 (dd, J=8.0, 1.0 Hz, 1H), 7.85 (dd, J=8.0, 1.5 Hz, 1H); ^{13}C NMR δ: 43.3, 47.9, 52.2, 120.4, 125.5, 126.9, 127.8, 128.2, 130.2, 132.6, 145.3, 167.9; ESIHRMS, calcd for $C_{12}H_{12}O_2S$: 221.0636 (M+H), found: 221.0635.

4.4.16. Methyl 2-(2,5-dihydrothiophen-2-yl)benzoate (62). Colorless oil; eluent: 1:1 (hexane/benzene); ^{1}H NMR δ: 3.81–3.93 (m, 2H), 3.90 (s, 3H), 5.85 (m, 1H), 6.05 (m, 1H), 6.13 (m, 1H), 7.27 (dt, J=6.5, 1.5 Hz, 1H), 7.48 (m, 2H), 7.85 (d, J=9.0 Hz, 1H); ^{13}C NMR δ: 39.1, 52.2, 54.8, 126.9, 128.7, 128.7, 129.5, 130.2, 132.5, 132.5, 144.9, 167.8; ESIHRMS, calcd for $C_{12}H_{12}O_2S$: 221.0636 (M+H), found: 221.0636.

4.4.17. Methyl [2-(2,3-dihydrothiophen-2-yl)phenyl]carbamate (63). Colorless oil; eluent: 1:1 (hexane/benzene with 2% EtOAc); ^{1}H NMR δ: 2.97 (m, 1H), 3.17 (m, 1H), 3.77 (s, 3H), 5.09 (dd, J=10.5, 8.0 Hz, 1H), 5.68 (m, 1H), 6.23 (m,1H), 7.06 (t, J=7.0 Hz, 1H), 7.15 (br s, 1H), 7.29 (m, 2H), 7.81 (br s, 1H); ^{13}C NMR δ: 41.8, 50.2, 52.5, 122.3, 123.3, 124.4, 124.9, 128.5, 129.0, 132.0, 136.0, 154.5; ESIHRMS, calcd for $C_{12}H_{13}NO_2S$: 258.0565 (M+Na), found: 258.0558.

4.4.18. Methyl [2-(2,5-dihydrothiophen-2-yl)phenyl]carbamate (64). Colorless oil; ^{1}H NMR δ: 3.75 (s, 3H), 3.94 (br m, 2H), 5.50 (br s, 1H), 5.81 (m, 1H), 6.03 (m, 1H), 7.08 (t, J=7.0 Hz, 1H), 7.20 (d, J=7.5 Hz, 1H), 7.22 (br s, 1H), 7.27 (dt, J=9.5, 2.0 Hz, 1H), 7.73 (br s, 1H); ^{13}C NMR δ: 39.8, 52.4, 56.7, 123.5, 124.6, 128.6, 129.4, 129.5, 132.2, 136.2, 154.5; ESIHRMS, calcd for $C_{12}H_{13}NO_2S$: 258.0565 (M+Na), found: 258.0568.

4.5. General protocol for aryl radical addition to carbocyclic arenes

A solution of aryl iodide (1.0 mmol), diphenyl diselenide (62.0 mg, 0.2 mmol), and freshly distilled solvent (20 mL) was sparged with argon for 45 min, followed by heating at 90 °C (bath temperature) with stirring. A solution of AIBN (33.0 mg, 0.2 mmol) and Bu_3SnH (0.47 mL, 1.75 mmol) in degassed solvent (10 mL) was added via syringe pump over 16 h, after which heating was continued for 1 h, before the reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was taken up in acetonitrile (75 mL) and washed with hexane (4×25 mL) (except Table 4 entries 1 and 4, which were purified without acetonitrile/hexane workup). The acetonitrile phase was concentrated and purified by silica gel chromatography.

4.5.1. (±)-(4a*R,9b*S**)-4a-Methoxy-3,4,4a,9b-tetrahydrodibenzofuran (66).** Reaction solvent: anisole; colorless oil; eluent: 1:4 (hexane/benzene); ^{1}H NMR δ: 1.82–1.88 (m, 1H), 2.14–2.18 (m, 2H), 2.42–2.46 (td, J=13.0, 4.5 Hz, 1H), 3.39 (s, 3H), 3.71 (s, 1H), 5.73–5.79 (m, 2H), 6.86 (d, J=8.0 Hz, 1H), 6.90 (t, J=8.0 Hz, 1H), 7.16 (t, J=8.0 Hz, 1H), 7.20 (d, J=7.5 Hz, 1H); ^{13}C NMR δ: 22.0, 27.8, 47.3, 49.5, 110.1, 111.6, 121.1, 124.3, 126.4, 126.9, 128.1, 130.3, 157.6; EIHRMS, calcd for $C_{13}H_{14}O_2$: 202.0994 (M^+), found: 202.0999.

4.5.2. 2-(2-Methoxyphenyl)phenol (67). Reaction solvent: anisole; white solid; mp 72 °C, lit.[73] 73–74 °C; spectroscopic data identical to literature values;[73] ^{1}H NMR δ: 3.91 (s, 3H), 6.29 (s, 1H), 7.02–7.08 (m, 3H), 7.14 (dt, J=7.5, 1.0 Hz, 1H), 7.29 (dd, J=8.0, 1.5 Hz, 1H), 7.32 (dt, J=8.5, 1.5 Hz, 1H), 7.37 (dd, J=8.0, 1.5 Hz, 1H), 7.42 (dt, J=8.0, 1.5 Hz, 1H).

4.5.3. 2-(4-Methoxyphenyl)phenol (68). Reaction solvent: anisole; white solid; mp 60–62 °C, lit.[74] 65–66 °C; spectroscopic data identical to literature values;[74] ^{1}H NMR δ: 3.87 (s, 3H), 5.23 (s, 1H), 6.97–7.00 (m, 2H), 7.03 (d, J=9.0 Hz, 2H), 7.22–7.26 (m, 2H), 7.40 (d, J=9.0 Hz, 2H).

4.5.4. (±)-(4a*R,10b*S**)-4a-Methoxy-3,4,4a,10b-tetrahydro-4*H*-dibenzo[*b*,*d*]pyran-6-one (69).** Reaction solvent: anisole; colorless oil; eluent: 1:9 (EtoAc/hexane); ^{1}H NMR δ: 1.68–1.74 (ddd, J=17.5, 11.0, 6.0 Hz, 1H), 2.26–2.32 (m, 1H), 2.40–2.47 (m, 1H), 2.54–2.58 (ddd, J=13.5, 6.0, 2.0 Hz, 1H), 3.40 (s, 3H), 3.67 (m, 1H), 5.37–5.40 (qd, J=10.0, 2.0 Hz, 1H), 5.73–5.77 (m, 1H), 7.31 (dd, J=7.5, 1.0 Hz, 1H), 7.38 (dt, J=7.5, 1.0 Hz, 1H), 7.59 (dt, J=7.5, 1.0 Hz, 1H), 8.10 (dd, J=7.5, 1.0 Hz, 1H); ^{13}C NMR δ: 23.5, 28.0, 43.7, 49.3, 103.7, 123.3, 126.7, 126.8, 127.5, 128.0, 130.0, 134.5, 141.3, 164.2; ESIHRMS, calcd for $C_{14}H_{14}O_3$: 231.1016 (M+H), found: 231.1015.

4.5.5. 2-(2-Methoxyphenyl)benzoic acid (70). Reaction solvent: anisole; white solid; mp 150–152 °C, lit.[75] 149–152 °C; spectroscopic data identical to literature values;[75] ^{1}H NMR δ: 3.71 (s, 3H), 6.88 (d, J=8.0 Hz, 1H), 7.05 (dt, J=7.5, 1.0 Hz, 1H), 7.28 (dd, J=7.0, 1.5 Hz, 1H), 7.32–7.36 (m, 2H), 7.42 (dt, J=8.0, 1.5 Hz, 1H), 7.59 (dt, J=7.5, 1.5 Hz, 1H), 7.94 (dd, J=8.0, 1.5 Hz, 1H).

4.5.6. 2-(4-Methoxyphenyl)benzoic acid (71). Reaction solvent: anisole; white solid; mp 140–141 °C, lit.[76] 140–143 °C; spectroscopic data identical to literature values;[76] ^{1}H NMR δ: 3.85 (s, 3H), 6.93 (d, J=9.0 Hz, 2H), 7.28 (d, J=9.0 Hz, 2H), 7.35 (dd, J=8.0, 2.0 Hz, 1H), 7.40 (dt, J=8.0, 1.0 Hz, 1H), 7.54 (dt, J=8.5, 1.0 Hz, 1H), 7.93 (dd, J=8.5, 1.5 Hz, 1H).

4.5.7. 2-(2-Methoxyphenyl)aniline (72). Reaction solvent: anisole; yellowish solid; mp 65–67 °C, lit.[77] 80 °C; spectroscopic data identical to literature values;[77] ^{1}H NMR δ: 3.52 (br s, 2H), 3.82 (s, 3H), 6.80 (dd, J=8.5, 1.5 Hz, 1H), 6.85 (dt, J=7.0, 1.0 Hz, 1H), 7.01 (d, J=9.0 Hz, 1H), 7.05 (dt, J=7.5, 1.0 Hz, 1H), 7.12 (dd, J=7.5, 1.5 Hz, 1H), 7.18 (dt, J=8.0, 2.0 Hz, 1H), 7.27 (dd, J=7.5, 2.0 Hz, 1H), 7.37 (dt, J=8.5, 2.0 Hz, 1H).

4.5.8. 2-(3-Methoxyphenyl)aniline (73). Reaction solvent: anisole; yellowish oil; eluent: 1:19 (EtoAc/hexane); ^{1}H NMR δ: 3.83 (s, 3H), 6.80 (d, J=7.5 Hz, 1H), 6.85 (dt, J=7.0, 1.0 Hz, 1H), 6.90 (ddd, J=8.5, 2.5, 1.0 Hz, 1H), 7.00 (t, J=2.0 Hz, 1H), 7.05 (td, J=7.5, 1.0 Hz, 1H), 7.14–7.19 (m, 2H), 7.36 (t, J=8.0 Hz, 1H); ^{13}C NMR δ: 55.3, 113.0, 114.5, 115.9, 118.9, 121.4, 127.8, 128.6, 129.8, 130.3, 140.8, 142.9, 159.9; ESIHRMS, calcd for $C_{13}H_{13}NO$: 200.1070 (M+H), found: 200.1069.

4.5.9. 2-(4-Methoxyphenyl)aniline (74). Reaction solvent: anisole; colorless oil; spectroscopic data identical to literature values;[78] ^{1}H NMR δ: 3.84 (s, 3H), 6.79 (dd, J=8.0, 0.5 Hz, 1H), 6.84 (dt, J=7.5, 1.0 Hz, 1H), 6.99 (d, J=8.5 Hz, 2H), 7.11–7.16 (m, 2H), 7.38 (d, J=9.0 Hz, 2H).

4.5.10. 1-(2-Hydroxyphenyl)-2-chloro-cyclohexa-2,5-diene (75). Reaction solvent: chlorobenzene; colorless oil; eluent: 2:1:1 (hexane/benzene/chloroform); ^{1}H NMR δ: 2.93–2.98 (m, 2H), 4.42–4.45 (m, 1H), 5.12 (s, 1H), 5.74–5.78 (m, 1H), 5.82–5.85 (m, 1H), 6.05 (m, 1H), 6.82 (d, J=8.5 Hz, 1H), 6.93 (t, J=7.0 Hz, 1H), 7.15–7.18 (m, 2H); ^{13}C NMR δ: 28.2, 43.2, 116.4, 121.2, 122.9, 123.5, 127.1, 127.4, 128.5, 130.2, 131.9, 153.9; EIHRMS, calcd for $C_{12}H_{11}ClO$: 206.0498 (M^+), found: 206.0508.

4.5.11. 1-(2-Hydroxyphenyl)-3-chloro cyclohexa-2,5-diene (76). Reaction solvent: chlorobenzene; colorless oil; eluent: 2:1:1 (hexane/benzene/chloroform); ^{1}H NMR δ: 3.02–3.05 (m, 2H), 4.41–4.45 (m, 1H), 5.03 (br s, 1H), 5.78–5.81 (m, 1H), 5.83–5.86 (m, 1H), 5.90–5.91 (m, 1H), 6.77–6.78 (dd, J=8.0, 1.0 Hz, 1H), 6.90–6.93 (dt, J=7.5, 1.5 Hz, 1H), 7.10–7.15 (m, 2H); ^{13}C NMR δ: 33.1, 39.3, 115.9, 121.2, 123.8, 124.8, 126.7, 128.2, 128.3, 129.5, 129.9, 153.4; ESIHRMS, calcd for $C_{12}H_{11}ClO$: 205.0420 (M−H), found: 205.0411.

4.5.12. 2-(2-Hydroxyphenyl)benzonitrile (77). Reaction solvent: benzonitrile; white solid; mp 92–93 °C, lit.[79] 71–73 °C, eluent: 1:19 (EtOAc/hexane); spectroscopic data identical to literature values; ^{1}H NMR δ: 7.32–7.38 (m, 2H), 7.48 (dt, J=8.5, 1.5 Hz, 1H), 7.58 (dt, J=8.0, 0.5 Hz, 1H), 7.82 (dt, J=8.0, 1.5 Hz, 1H), 8.06 (dd, J=7.5, 1.0 Hz, 1H), 8.12 (d, J=8.0 Hz, 1H), 8.40 (dd, J=7.5, 1.0 Hz, 1H); ^{13}C NMR δ: 117.8, 118.1, 121.3, 121.7, 122.8, 124.6, 128.9, 130.5, 130.6, 134.8, 134.7, 151.3, 161.2; ESIHRMS, calcd for $C_{13}H_9NO$: 196.0757 (M+H), found: 196.0756.

4.5.13. 4-(2-Hydroxyphenyl)benzonitrile (78). Reaction solvent: benzonitrile; white solid; mp 111–113 °C, lit.[80] 111–112 °C; spectroscopic data identical to literature values; ^{1}H NMR δ: 5.13 (s, 1H), 6.95 (dd, J=8.0, 0.5 Hz, 1H), 7.04 (t, J=8.0 Hz, 1H), 7.26–7.32 (m, 2H), 7.67 (d, J=8.5 Hz, 2H), 7.74 (d, J=8.5 Hz, 2H).

4.5.14. 3-(2-Hydroxyphenyl)benzonitrile (79). Reaction solvent: benzonitrile; colorless oil; spectroscopic data identical to literature values;[79] ^{1}H NMR δ: 4.99 (s, 1H), 6.95 (dd, J=8.0, 1.0 Hz, 1H), 7.04 (dt, J=7.5, 1.0 Hz, 1H), 7.25–7.31 (m, 2H), 7.56 (t, J=8.0 Hz, 1H), 7.66 (tt, J=8.0, 1.5 Hz, 1H), 7.78 (tt, J=7.5, 1.5 Hz, 1H), 7.85 (t, J=2.0 Hz, 1H).

4.5.15. 1-(2-Hydroxyphenyl)-1,4-dihydronaphthalene (80). Reaction solvent: benzene (80 equiv of naphthalene in benzene); colorless oil; eluent: 1:1 (hexane/benzene); ^{1}H NMR δ: 3.53–3.58 (m, 2H), 4.86 (m, 1H), 5.00 (s, 1H), 5.98–6.01 (m, 1H), 6.11–6.14 (m, 1H), 6.79 (dd, J=8.0, 1.5 Hz, 1H), 6.90 (dt, J=7.0, 1.0 Hz, 1H), 7.05 (d, J=8.0 Hz, 1H), 7.10–7.19 (m, 5H); ^{13}C NMR δ: 29.7, 41.3, 116.6, 120.9, 125.3, 126.6 (2C), 128.1, 128.3, 128.4, 129.0, 130.6, 130.7, 133.3, 136.0, 153.8; ESIHRMS, calcd for $C_{16}H_{14}O$: 221.0966 (M−H), found: 221.0961.

4.5.16. 1-(2-Hydroxyphenyl)-1,2-dihydronaphthalene (81) and 2-(2-hydroxyphenyl)-1,2-dihydronaphthalene (82). Compounds **81** and **82** were obtained as a 1.4:1 mixture. Reaction solvent: benzene (80 equiv of naphthalene in benzene); eluent: 1:1 (hexane/benzene); Characteristic ^{1}H NMR peaks of compound **81** δ: 2.61–2.71 (m, 2H), 4.47–4.51 (dd, J=10.5, 8.0 Hz, 1H), 4.81 (s, 1H), 6.03–6.07 (m, 1H), 6.57 (d, J=10.0 Hz, 1H); Characteristic ^{1}H NMR peaks of compound **82** δ: 3.03 (dd, J=16.0, 12.0 Hz, 1H), 3.13 (dd, J=15.5, 7.5 Hz, 1H), 4.09–4.13 (m, 1H), 4.96 (s, 1H), 6.09–6.11 (dd, J=9.5, 3.5 Hz, 1H), 6.68–6.70 (dd, J=9.5, 2.5 Hz, 1H); **81** and **82** ^{1}H NMR δ: 6.80–6.81 (dd, J=8.0, 0.5 Hz, 1H), 6.84–6.85 (dd, J=8.0, 1.0 Hz 1H), 6.90–6.93 (m, 3H), 7.06–7.26 (m, 11H); ^{13}C NMR δ: 30.0, 34.6, 35.3, 38.4, 115.8, 116.1, 121.05, 121.08, 126.2, 126.4, 126.7, 127.2, 127.3, 127.5, 127.6, 127.7, 127.81, 127.83, 127.88, 127.89, 129.0, 129.1, 129.8, 130.24, 130.28, 131.2, 133.3, 134.4, 134.6, 136.2, 153.2, 153.3; ESIHRMS, calcd for $C_{16}H_{14}O$: 221.0966 (M−H), found: 221.0961.

4.6. (±)-(3*S**,4*R**)-Allyl-3-(2-hydroxyphenyl)-4-methoxycyclohexene (83)

To a solution of compound **66** (50 mg, 0.25 mmol) and allyltrimethylsilane (0.039 mL, 0.25 mmol) in CH_2Cl_2 (3.0 mL) under argon at −78 °C was added $TiCl_4$ (0.027 mL, 0.25 mmol). The reaction mixture was quenched with saturated $NaHCO_3$ after 15 min of stirring and extracted with diethyl ether (3×20 mL). The combined organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane) afforded compound **83** in 84%, yield. Colorless oil; ^{1}H NMR δ: 1.78–1.83 (m, 1H), 1.90–1.95 (m, 1H), 2.11–2.16 (m, 1H), 2.23–2.30 (m, 1H), 2.36–2.48 (dq, J=14.0, 7.5 Hz, 2H), 3.28 (s, 3H), 3.63 (t, J=2.5 Hz, 1H), 5.13–5.19 (m, 2H), 5.50–5.53 (qd, J=7.5, 2.5 Hz, 1H), 5.84–5.89 (m, 2H), 6.83 (dt, J=7.5, 1.5 Hz, 1H), 6.90 (dd, J=8.0, 1.0 Hz, 1H), 7.09 (dd, J=7.5, 2.0 Hz, 1H), 7.17 (dt, J=8.0, 2.5 Hz, 1H), 8.34 (br s, 1H); ^{13}C NMR δ: 22.9, 26.3, 38.8, 48.0, 48.8, 79.7, 118.0, 119.1, 119.6, 126.8, 127.6, 127.8, 128.5, 132.4, 133.2, 156.5; EIHRMS, calcd for $C_{16}H_{20}O_2$: 244.1463 (M^+), found: 244.1460.

Acknowledgements

We thank the NSF (CHE 9986200) for partial support of this work and Bhushan Surve for the X-ray crystal structure.

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Synthesis of *N*-alkyl substituted bioactive indolocarbazoles related to Gö6976

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Received 17 March 2006; revised 17 May 2006; accepted 19 May 2006
Available online 19 June 2006

Abstract—The syntheses of new nitrile and amide analogues of 7-keto Gö6976 are described. The amide analogue **22** was formed via the condensation with a new functionalized indoleacetic acid derivative **25** to overcome the solubility problem during the coupling reaction.

1. Introduction

Cell cycle checkpoints are activated in response to DNA damage thereby delaying cell cycle progression in order to provide more time for DNA repair. Cell cycle arrest in G1 or S phase prevents replication of damaged DNA, while arrest in G2 prevents damaged chromosomes from being segregated in mitosis; thus preventing the propagation of genetic abnormalities. Inhibition of the G2 checkpoint has attracted widespread interest because most cancer cells have an inoperative G1 checkpoint. The activity of the G1 checkpoint is dependent on the p53 tumor suppressor protein, which is deleted or mutated in more than 50% of all cancers. Although cells with defective p53 are unable to activate the G1 checkpoint in response to DNA damage, they retain the ability to arrest in S and G2. This provides the cells with an opportunity to repair their DNA and thereby survive and grow. The S and G2 checkpoints are regulated by various kinases among which checkpoint kinase 1 (Chk1) plays a major role. Inhibitors of Chk1 preferentially abrogate cell cycle arrest in p53-defective cells and selectively sensitize cancer cells with mutated p53 to killing by DNA-damaging agents. Therefore, combining a Chk1 inhibitor with a DNA-damaging agent should selectively drive p53-defective cells into a premature and lethal mitosis.[1]

Several small molecules that inhibit checkpoint proteins have been described in the literature, the first of which were the purine alkaloids caffeine (**1**) and pentoxifylline (**2**), which inhibit two upstream kinases, ATM and ATR (Fig. 1).[2]

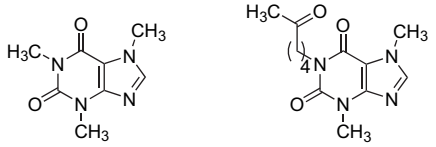

Figure 1.

However, caffeine cannot be used to inhibit this pathway in human beings as the doses required cause central nervous system and cardiac toxicities.

UCN-01 (**3**), one member of the indolocarbazole family,[3] generated considerable interest in our laboratory when it was found to be a potent inhibitor of DNA damage-induced S and G2 cell cycle checkpoints, which led to increased killing of tumor cells (Fig. 2).[4] Although UCN-01 is well recognized as a protein kinase C inhibitor,[5] this checkpoint inhibition was attributed to its ability to inhibit Chk1.[6] Unfortunately, UCN-01 binds avidly to human serum proteins thereby compromising its potential therapeutic activity.[7] Subsequent research identified other Chk1 inhibitors such as staurosporine (**4**),[2] granulatimide (**5**), and isogranulatimide (**6**),[8] but their nonselectivity and/or their weak inhibitory activity justifies the search for new selective Chk1 inhibitors. Accordingly, we initiated a synthetic program to develop novel analogues rationally designed to overcome the obstacles observed with the other analogues and with improved therapeutic potential.

Initially, a K252a (**7**) analogue, ICP-1 (**8**), was synthesized and tested, and was found to overcome the problem of protein binding but it has considerably reduced potency (Fig. 3).[9]

Keywords: Indolocarbazoles; Bisindolylmaleimide; Gö6976; UCN-01; Checkpoint inhibitors.
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doi:10.1016/j.tet.2006.05.049

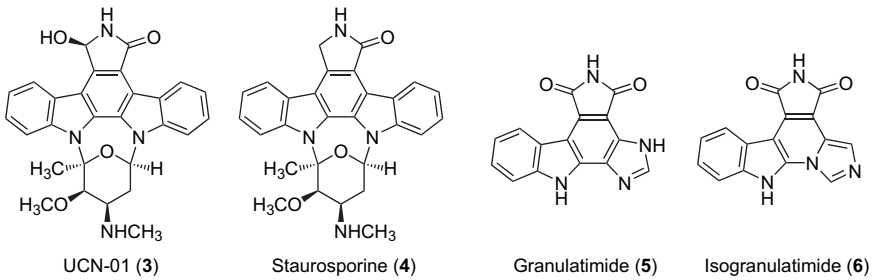


Figure 2.

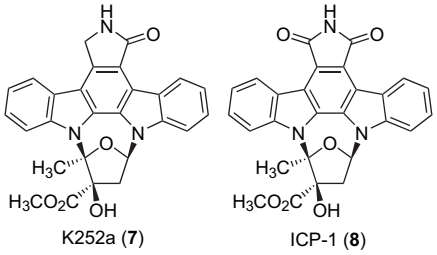


Figure 3.

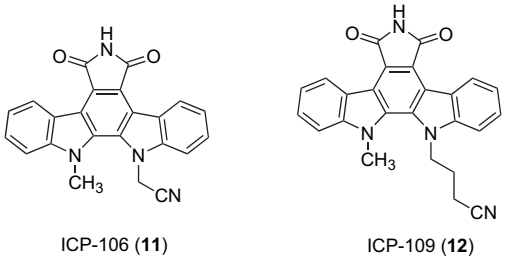


Figure 5.

More recently, we found that Gö6976 (**9**) is a very potent checkpoint inhibitor even in the presence of human serum,[10] and this has also been attributed to the inhibition of Chk1 (Fig. 4).[11] Additionally, Gö6976 abrogated S and G2 arrest at a concentration substantially lower than that required to inhibit PKC. Interestingly, UCN-01 (**3**) did not demonstrate this selectivity for checkpoint inhibition. As a consequence, we have begun a structure–activity study of analogues of Gö6976 (**9**). During our screening to identify novel inhibitors of Chk1 related to Gö6976, we found that ICP-103 (**10**) is also a potent checkpoint inhibitor.[12] Therefore, we have focused our investigation on this class of molecules as potential inhibitors of Chk1. Our initial objective was to investigate the effect of the nitrile chain-length on Chk1 activity, and we now report our results.

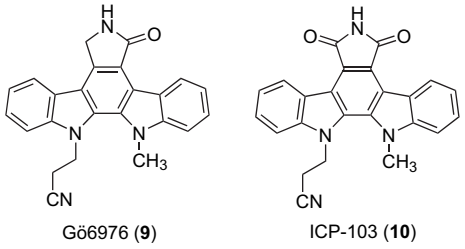


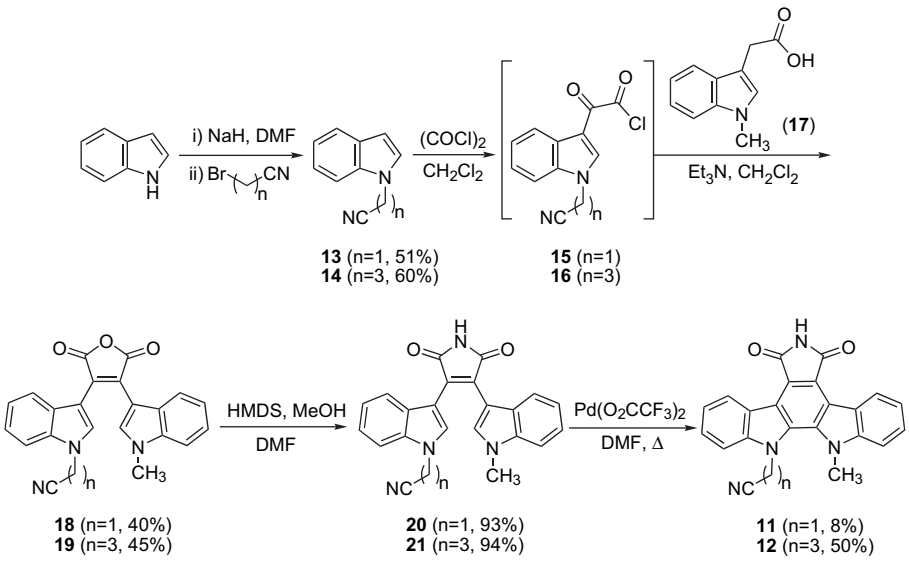
Figure 4.

2. Results and discussion

In the course of our structure–activity relationship studies on ICP-103 analogues, we have synthesized and tested two new nitrile homologues, ICP-106 (**11**) and ICP-109 (**12**) (Fig. 5).

Thus, for the synthesis of **11** and **12**, we alkylated the indole nitrogen with bromoacetonitrile and 4-bromobutyronitrile in the presence of NaH to furnish indole-1-acetonitrile (**13**) and indole-1-butanenitrile (**14**), respectively. Compound **13** was obtained in 51% yield and compound **14** was obtained in 60% yield (Scheme 1). Similar N-alkylation of indole-3-acetic acid using methyl iodide in the presence of excess NaH gave 1-methylindole-3-acetic acid (**17**) in 94% yield. Indole-1-acetonitrile (**13**) was then treated with oxalyl chloride in dichloromethane to furnish the glyoxylyl chloride **15**, which was immediately treated with 1-methylindole-3-acetic acid (**17**) in the presence of triethylamine to produce anhydride **18** in 40% yield in two steps from **13**.[13] Similarly, indole-1-butanenitrile (**14**) furnished **19** in 45% yield via the intermediate glyoxylyl chloride **16**. Due to the potentially labile nitrile functionality, ammonia was generated in situ from 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and methanol and these conditions were used to convert anhydrides **18** and **19** to imides **20** and **21**, respectively, at rt.[14] During our synthesis of ICP-103 (**10**), we found that the final oxidative cyclization was quite challenging for the bisindolylmaleimide with substituents present on both *N*-12 and *N*-13.[12,15,16] However, heating bisindolylmaleimide **20** and **21** in DMF in the presence of palladium(II) trifluoroacetate gave the target compounds **11** and **12** in 8 and 50% yields, respectively. The lower yield of **11** may be a consequence of the strong inductive electron withdrawing effect of the cyano group that retards the (electrophilic) oxidative addition of Pd(II) to bisindolylmaleimide **20**.

In work to be reported separately, we find that ICP-106 (**11**) and ICP-109 (**12**) are less potent than ICP-103 (**10**) at abrogating DNA damage-induced cell cycle arrest. In an assay using flow cytometry analysis,[10] ICP-106 and ICP-109 were found to abrogate S phase arrest at 3 μM and 10 μM, respectively, whereas ICP-103 (**10**) was effective at 100 nM. These values can be compared to the efficacy of Gö6976 (**9**) of 30 nM in the same assay.[10] For drugs to be used in patients, it is also essential that they do not elicit undesirable toxicities. In this regard, the breast cancer MDA-MB-231 cell line was used in an assay of growth inhibition. Cells were



Scheme 1.

incubated with the compounds for 24 h, and the cell number assessed after 7 days. The concentration that inhibited 50% of growth was: Gö6976, 6 μM; ICP-103, 2.5 μM; ICP-106, >10 μM; ICP-109, 2 μM. Accordingly, the concentrations that inhibit growth do not correlate with those that overcome cell cycle arrest, and Gö6976 and ICP-103 are clearly active as checkpoint inhibitors at noncytotoxic concentrations.

From this activity data for the nitrile analogues **10**, **11**, and **12**, it was found that two methylene groups provide maximum activity. Therefore, we attempted to synthesize a novel amide analogue of ICP-103, ICP-112 (**22**), bearing the same number of carbons in the amide arm (Fig. 6). We wanted to further explore the SAR by replacing the nitrile with an amide.

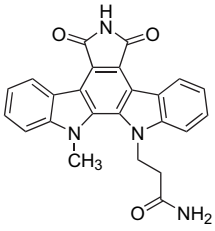
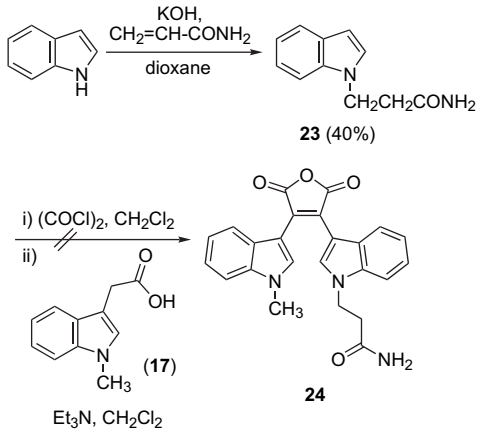


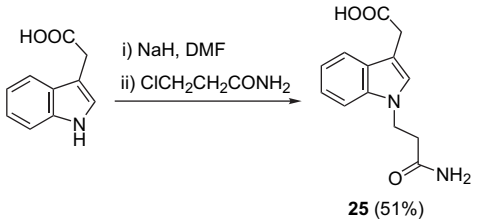
Figure 6.

For the synthesis of ICP-112 (**22**), we initially proceeded through the same route that we used for the nitrile compounds. For this purpose, indole-1-propionamide (**23**) was synthesized from indole and acrylamide in the presence of KOH in 40% yield (Scheme 2). We then treated **23** with oxalyl chloride to prepare the corresponding glyoxylyl chloride that was to be coupled with 1-methylindole-3-acetic acid (**17**) in the presence of triethylamine. To our surprise, the desired anhydride **24** was not formed. The coupling reaction failed probably due to the highly insoluble nature of the glyoxylyl chloride intermediate bearing the polar amide functionality. Use of more polar solvents, such as 1,2-dichloroethane, THF, and DMF, also failed to furnish the desired coupling product **24**.

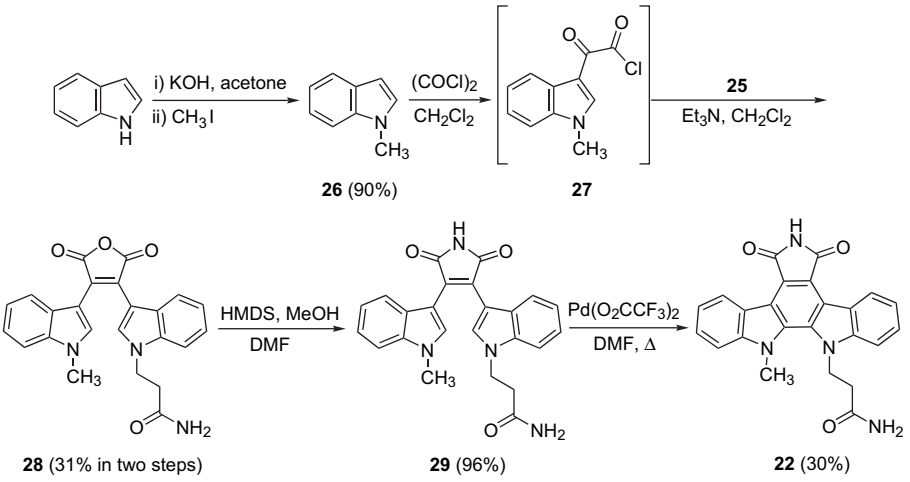


Scheme 2.

To possibly circumvent this solubility issue in the coupling reaction, we decided to attach the amide-chain on the indole-3-acetic acid fragment. Although there does not appear to be literature precedent for these compounds, we were able to synthesize 1-(2-carbamoyl-ethyl)indole-3-acetic acid (**25**) from indole-3-acetic acid in one step, using 3-chloropropionamide as an alkylating agent in the presence of excess NaH (51% yield) (Scheme 3).



Scheme 3.



Scheme 4.

Compound **25** was treated with 1-methylindole-3-glyoxylyl chloride (**27**), derived from the reaction between 1-methylindole (**26**) and oxalyl chloride, to form the desired anhydride **28** in 31% yield over the two steps (Scheme 4). Anhydride **28** was treated with HMDS and methanol to give imide **29** in 96% yield. Heating **29** in DMF with palladium(II) trifluoroacetate afforded the target compound ICP-112 (**22**) in 30% yield. An alternative oxidative cyclization of **29** using ultraviolet light in the presence of a catalytic amount of iodine in THF:acetonitrile (1:1) yielded **22** only in 5% yield.[17]

The new indolocarbazole ICP-112 (**22**) abrogated S phase arrest at 1–3 μM. This value should be compared to the 100 nM efficacy observed with the nitrile analogue, ICP-103 (**10**). Accordingly, it appears that the nitrile is the preferred structure for further study. Our detailed biological activity data will be reported separately.

3. Conclusion

In summary, we have explored one aspect of the structure–activity relationships (SARs) of Gö6976 and discovered that a three-carbon nitrile chain seems essential for optimal activity. Also, we find that a nitrile is the more desirable functionality than an amide for activity. Work is in progress in our laboratory with other nitrogen-bearing functionalities and these will be reported in due course.

4. Experimental

4.1. General experimental procedures

Melting points were determined with a Mel-Temp Laboratory Device apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 600 series FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian XL-300 or 500 Fourier-transform NMR spectrometer. Both low- and high-resolution mass spectra were carried out at the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois at Urbana Champaign. Anhydrous THF and CH_2Cl_2 were prepared by a solvent purification system; anhydrous DMF and Et_3N were purchased from Aldrich.

4.1.1. 1*H*-Indole-1-acetonitrile (13). To a stirred suspension of NaH (600 mg, 15 mmol, 60% dispersion in mineral oil) in DMF (35 mL) at 0 °C was added dropwise a solution of indole (1.17 g, 10 mmol) in DMF (15 mL). After stirring the mixture for 30 min at 0 °C, a solution of bromoacetonitrile (1.1 mL, 15 mmol) in DMF (15 mL) was added dropwise. The mixture was allowed to slowly reach rt and continued to stir overnight. The mixture was poured into cold water (100 mL) and extracted with ether (3×50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (3:1 hexane:ethyl acetate) to give the desired product (796 mg, 51%) as a colorless oil, which solidified after prolonged drying: mp 75–77 °C (lit.[18] 74–75 °C); IR (thin film) 3097, 2978, 2941, 2252, 1611, 1462, 1317 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.75–7.71 (m, 1H), 7.44–7.35 (m, 2H), 7.31–7.25 (m, 1H), 7.13 (d, 1H, J=3.4 Hz), 6.67 (dd, 1H, J=3.2 Hz, 0.7 Hz), 4.99 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 129.1, 127.3, 123.1, 121.7, 121.0, 114.6, 109.0, 104.3, 34.4.

4.1.2. 1*H*-Indole-1-butanenitrile (14). To a stirred suspension of NaH (600 mg, 15 mmol, 60% dispersion in mineral oil) in DMF (35 mL) at 0 °C was added dropwise a solution of indole (1.17 g, 10 mmol) in DMF (15 mL). After stirring the mixture for 30 min at 0 °C, a solution of bromobutyronitrile (1.6 mL, 15 mmol) in DMF (15 mL) was added dropwise. The mixture was allowed to slowly reach rt and continued to stir overnight. The mixture was poured into cold water (100 mL) and extracted with ethyl acetate (3×50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (2:1 hexane: ethyl acetate) to give the desired product (1.1 g, 60%) as a colorless oil:[19] IR (thin film) 3051, 2939, 2246, 1610, 1512, 1463, 1314 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.77–7.74 (m, 1H), 7.45–7.42 (m, 1H), 7.37–7.31 (m, 1H), 7.27–7.22 (m, 1H), 7.17 (d, 1H, J=3.2 Hz), 6.63 (dd, 1H, J=3.2 Hz, 0.7 Hz), 4.35–4.31 (m, 2H), 2.27–2.18 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 135.8, 128.8, 127.8, 122.0, 121.3, 119.8, 118.9, 109.2, 102.1, 44.4, 26.0, 14.6.

4.1.3. 1-Methyl-1*H*-indole-3-acetic acid (17). To a stirred suspension of NaH (6.0 g, 150 mmol, 60% dispersion in mineral oil) in THF (125 mL) at 0 °C was added a solution of indole-3-acetic acid (5.25 g, 30 mmol) in THF (50 mL). After stirring the mixture for 30 min at 0 °C, a solution of methyl iodide (14.2 g, 100 mmol) in THF (50 mL) was added dropwise. The mixture was allowed to slowly reach rt and continued to stir for 16 h. The reaction mixture was then cooled to 0 °C and excess hydride was carefully destroyed by slow addition of MeOH (5 mL) with vigorous stirring followed by cold water until a clear yellow solution resulted. Ether (100 mL) was added. The aqueous phase was separated, acidified with 6 N HCl, and extracted with dichloromethane (3×100 mL). The combined dichloromethane extracts were dried (Na_2SO_4) and concentrated to about 40–50 mL. Pet ether was then added slowly until a brownish colored solid completely precipitated out. The crude solid was recrystallized from ethanol to give the desired product (5.33 g, 94%) as a pale brown solid: mp 127–128 °C (lit.[20] 127–129 °C); IR (thin film) 3059, 2933, 1699, 1617, 1474 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.64–7.62 (m, 1H), 7.34–7.26 (m, 2H), 7.19–7.15 (m, 1H), 7.07 (s, 1H), 3.83 (s, 2H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 178.8, 137.0, 128.1, 127.7, 122.0, 119.5, 119.1, 109.5, 106.2, 32.9, 31.2.

4.1.4. 3-[2,5-Dihydro-4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-3-furanyl]-1*H*-indole-1-acetonitrile (18). To a stirred solution of indole-1-acetonitrile (683 mg, 4.37 mmol) in dichloromethane (45 mL) at 0 °C was added dropwise oxalyl chloride (594 mg, 4.68 mmol). The mixture was stirred at 0 °C for 2 h and again oxalyl chloride (0.5 mL) was added. The mixture was further stirred at 0 °C for 3 h and allowed to slowly reach rt and continued to stir for 8 h. Oxalyl chloride (1 mL) was again added and stirred for 1 h at rt. The solvent was removed in vacuo. The residue was redissolved in dichloromethane (60 mL) and added dropwise to a stirred solution of 1-methylindole-3-acetic acid (827 mg, 4.37 mmol) and triethylamine (885 mg, 8.74 mmol) in dichloromethane (15 mL). The mixture was stirred overnight and concentrated in vacuo. The residue was purified by column chromatography on silica gel (97:3 dichloromethane:methanol) to give the desired product (666 mg, 40%) as an orange-red solid: mp 231–233 °C; IR (thin film) 3119, 1816, 1750, 1629, 1531, 1255 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.04 (s, 1H), 7.92 (s, 1H), 7.63 (d, 1H, J=8.3 Hz), 7.49 (d, 1H, J=8.3 Hz), 7.24–7.19 (m, 1H), 7.13–7.08 (m, 1H), 7.01 (d, 1H, J=7.8 Hz), 6.89–6.84 (m, 1H), 6.74–6.66 (m, 2H), 5.66 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 166.4, 166.3, 136.9, 135.6, 135.0, 132.3, 130.1, 126.0, 125.7, 125.1, 123.2, 122.4, 121.7, 121.4, 121.0, 120.4, 116.1, 110.7, 110.4, 106.2, 103.9, 34.2, 33.2; LRMS (EI): m/z 381 (M^+), 223, 203, 168, 156, 144, 141, 116, 91, 77, 62 (100%); HRMS (EI) calcd for $C_{23}H_{15}N_3O_3$: 381.1113, found: 381.1108.

4.1.5. 3-[2,5-Dihydro-4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-3-furanyl]-1*H*-indole-1 butanenitrile (19). To a stirred solution of indole-1-butyronitrile (829 mg, 4.5 mmol) in dichloromethane (45 mL) at 0 °C was added dropwise oxalyl chloride (600 mg, 4.73 mmol). After stirring the mixture for 1 h at 0 °C, the solvent was removed in vacuo. The residue was redissolved in dichloromethane (45 mL) and added dropwise to a stirred solution of 1-methylindole-3-acetic acid (851 mg, 4.5 mmol) and triethylamine (911 mg, 9 mmol) in dichloromethane (15 mL). The mixture was stirred overnight at rt and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (97:3 dichloromethane:methanol) to give the desired product (829 mg, 45%) as a red solid: mp 89–91 °C (dec); IR (thin film) 3052, 2941, 2247, 1816, 1750, 1628, 1529, 1255 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.98 (s, 1H), 7.80 (s, 1H), 7.56 (d, 1H, J=8.3 Hz), 7.49 (d, 1H, J=8.1 Hz), 7.15–7.09 (m, 2H), 7.05 (d, 1H, J=7.8 Hz), 6.83 (t, 1H, J=7.6 Hz), 6.74–6.70 (m, 2H), 4.30 (t, 2H, J=6.8 Hz), 3.87 (s, 3H), 2.41 (t, 2H, J=7.3 Hz), 2.02 (qn, 2H, J=7.1 Hz); ^{13}C NMR (DMSO-d_6): δ 166.5, 166.3, 136.9, 135.9, 134.6, 132.8, 128.5, 126.8, 125.7, 124.9, 122.5, 122.3, 121.7, 121.5, 120.3, 120.2, 120.0, 110.7, 110.5, 104.7, 103.9, 44.7, 33.1, 25.6, 13.8; LRMS (EI): m/z 409 (M^+), 380, 355, 203, 144 (100%), 62; HRMS (EI) calcd for $C_{25}H_{19}N_3O_3$: 409.1426, found: 409.1424.

4.1.6. 3-[2,5-Dihydro-4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-1*H*-pyrrol-3-yl]-1*H*-indole-1-acetonitrile (20). To a stirred solution of anhydride **18** (381 mg, 1 mmol) in DMF (4 mL) was added 1,1,1,3,3,3-hexamethyldisilazane (1.61 g, 10 mmol) followed by methanol (0.16 g, 5 mmol). The tightly closed reaction mixture was stirred for 24 h at rt. The mixture was then poured into water (25 mL) and extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with water (50 mL). The separated organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (93:7 dichloromethane:methanol) to give the desired product (354 mg, 93%) as an orange-red solid: mp 278–280 °C; IR (thin film) 3311, 1692, 1628, 1532, 1329 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.02 (s, 1H), 7.91 (s, 1H), 7.83 (s, 1H), 7.58 (d, 1H, J=8.4 Hz), 7.42 (d, 1H, J=8.4 Hz), 7.15 (t, 1H, J=7.7 Hz), 7.07–7.01 (m, 1H), 6.92 (d, 1H, J=7.7 Hz), 6.78 (t, 1H, J=7.5 Hz), 6.68–6.60 (m, 2H), 5.63 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 172.8, 172.7, 136.6, 135.4, 133.6, 131.3, 129.2, 126.5, 125.6, 125.4, 122.6, 121.8, 121.4, 121.0, 120.5, 119.7, 116.2, 110.2, 110.0, 107.0, 104.4, 34.1, 32.9; LRMS (EI): m/z 380 (M^+, 100%), 340, 297, 269, 176, 135, 121, 62; HRMS (EI) calcd for $C_{23}H_{16}N_4O_2$: 380.1273, found: 380.1272.

4.1.7. 3-[2,5-Dihydro-4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-1*H*-pyrrol-3-yl]-1*H*-indole-1-butanenitrile (21). To a stirred solution of anhydride **19** (409 mg, 1 mmol) in DMF (4 mL) was added 1,1,1,3,3,3-hexamethyldisilazane (1.61 g, 10 mmol) followed by methanol (0.16 g, 5 mmol). The tightly closed reaction mixture was stirred for 24 h at rt. The mixture was then poured into water (25 mL) and extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with water (50 mL). The separated organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (93:7 dichloromethane:methanol) to give the desired product (384 mg, 94%) as a red solid: mp 249–251 °C; IR (thin film) 3281, 2246, 1756, 1704, 1610, 1532, 1334 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.95 (s, 1H), 7.86 (s, 1H), 7.68 (s, 1H), 7.50 (d, 1H, J=8.4 Hz), 7.43 (d, 1H, J=8.4 Hz), 7.10–6.98 (m, 3H), 6.75 (t, 1H, J=7.7 Hz), 6.68–6.61 (m, 2H), 4.27 (t, 2H, J=6.8 Hz), 3.85 (s, 3H), 2.38 (t, 2H, J=7.3 Hz), 2.01 (qn, 2H, J=7.0 Hz); ^{13}C NMR

(DMSO-d_6): δ 172.9, 172.8, 136.6, 135.7, 133.3, 131.6, 128.0, 126.6, 126.1, 125.4, 121.9, 121.7, 121.4, 121.1, 119.9, 119.7, 119.5, 110.2, 110.0, 105.5, 104.4, 44.4, 32.9, 25.6, 13.7; LRMS (EI): *m/z* 408 (M^+, 100%), 380, 354, 297, 283, 269, 204, 142, 121, 62; HRMS (EI) calcd for $C_{25}H_{20}N_4O_2$: 408.1586, found: 408.1595.

4.1.8. 5,6,7,13-Tetrahydro-13-methyl-5,7-dioxo-12*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-12-acetonitrile (11). A mixture of maleimide **20** (19 mg, 0.05 mmol) and palladium(II) trifluoroacetate (83 mg, 0.25 mmol) in DMF (3 mL) was heated at 90 °C for 9 h. The reaction mixture was then cooled, diluted with ethyl acetate (25 mL), and washed with 0.5 N HCl (50 mL). The organic phase was dried (Na_2SO_4) and filtered through Hyflo. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (97:3 dichloromethane:methanol) to give the desired product (1.5 mg, 8%) as a fluorescent yellow solid: mp >250 °C (dec); IR (thin film) 3201, 2919, 2615, 2282, 1696 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.26 (s, 1H), 9.14–9.11 (m, 2H), 7.95 (d, 1H, *J*=8.1 Hz), 7.82 (d, 1H, *J*=8.6 Hz), 7.75–7.68 (m, 2H), 7.53 (t, 1H, *J*=7.4 Hz), 7.45 (t, 1H, *J*=7.7 Hz), 5.87 (s, 2H), 4.29 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 171.2, 170.5, 144.4, 144.3, 132.8, 128.3, 123.4, 122.3, 121.4, 120.3, 119.7, 118.9, 116.3, 112.7, 111.4, 38.5, 35.6; LRMS (EI): *m/z* 378 (M^+), 272, 239, 229, 213, 161, 149 (100%), 133, 119, 109, 104, 95, 91, 83, 78, 69, 62; HRMS (EI) calcd for $C_{23}H_{14}N_4O_2$: 378.1117, found: 378.1119.

4.1.9. 5,6,7,13-Tetrahydro-13-methyl-5,7-dioxo-12*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-12-butanenitrile (12). A mixture of maleimide **21** (20 mg, 0.05 mmol) and palladium(II) trifluoroacetate (83 mg, 0.25 mmol) in DMF (3 mL) was heated at 90 °C for 2 h. The reaction mixture was then cooled, diluted with ethyl acetate (25 mL), and washed with 0.5 N HCl (50 mL). The organic phase was dried (Na_2SO_4) and filtered through Hyflo. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (97:3 dichloromethane:methanol) to give the desired product (10 mg, 50%) as a fluorescent yellow solid: mp >200 °C (dec); IR (thin film) 3201, 2245, 1748, 1710, 1695, 1317 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.14 (s, 1H), 9.14 (d, 1H, *J*=7.8 Hz), 9.11 (d, 1H, *J*=7.8 Hz), 7.89 (d, 1H, *J*=8.3 Hz), 7.77 (d, 1H, *J*=8.3 Hz), 7.67–7.63 (m, 2H), 7.44–7.40 (m, 2H), 4.86 (t, 2H, *J*=7.6 Hz), 4.24 (s, 3H), 2.26 (t, 2H, *J*=7.1 Hz), 1.85 (qn, 2H, *J*=7.3 Hz); ^{13}C NMR (DMSO-d_6): δ 171.5, 171.4, 145.5, 144.1, 133.8, 132.5, 128.3, 128.1, 125.5, 125.2, 123.6, 122.5, 122.1, 121.8, 121.7, 120.8, 120.5, 120.1, 119.4, 112.9, 112.0, 47.6, 37.4, 24.6, 14.3; LRMS (EI): *m/z* 406 (M^+), 378, 338, 239, 211, 161, 149, 133, 130, 119, 109, 104, 97, 91, 83, 77, 71, 69, 62 (100%); HRMS (EI) calcd for $C_{25}H_{18}N_4O_2$: 406.1430, found: 406.1436.

4.1.10. 1*H*-Indole-1-propanamide (23). To a stirred solution of indole (2.93 g, 25 mmol) in dioxane (75 ml) at 0 °C was added acrylamide (2.67 g, 37.5 mmol) and freshly powdered KOH (1.4 g, 25 mmol). The reaction mixture was slowly allowed to come to rt and stirred for 24 h. The solution was filtered to remove the insoluble materials and the solvent was removed in vacuo. The residue was purified with column chromatography on silica gel (15:1 chloroform:methanol) to give the desired product (1.88 g, 40%) as a white solid: mp 101–102 °C (lit.[21] 90–92 °C); IR (thin film) 3446, 3358, 3190, 1668, 1611, 1462, 1402, 1314 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.54–7.53 (m, 1H), 7.49–7.48 (m, 1H), 7.39 (s, 1H), 7.31 (d, 1H, *J*=3.2 Hz), 7.15–7.11 (m, 1H), 7.03–7.00 (m, 1H), 6.92 (s, 1H), 6.41–6.40 (m, 1H), 4.39 (t, 2H, *J*=6.9 Hz), 2.57 (t, 2H, *J*=6.8 Hz); ^{13}C NMR (DMSO-d_6): δ 171.9, 135.5, 128.6, 128.1, 121.0, 120.4, 119.0, 109.8, 100.5, 41.8, 35.8.

4.1.11. (2-Carbamoyl-ethyl)-1*H*-indole-3-acetic acid (25). To a stirred suspension of NaH (1 g, 25 mmol, 60% dispersion in mineral oil) in DMF (10 mL) at 0 °C was added dropwise a solution of indole-3-acetic acid (1.7 g, 10 mmol) in DMF (10 mL). After the addition, the solution was allowed to warm to rt and stirred for 1 h. It was then cooled to 0 °C and a solution of 3-chloropropionamide (1.2 g, 11 mmol) was added dropwise. The solution was allowed to warm to rt and stirred for 8 h. It was then stirred at 70 °C for 17 h and 90 °C for 2 h. The mixture was cooled to rt and the solvent was evaporated. Ether (50 mL) was slowly added to the oily-residue and excess sodium hydride was destroyed by the dropwise addition of water. The solution was acidified with 1 N HCl (50 mL) and extracted with ethyl acetate (2×100 mL). The combined organic phase was washed with water (100 mL) and dried (Na_2SO_4). Solvent was evaporated and the residue was purified by column chromatography on silica gel (90:10 dichloromethane:methanol) to yield the desired product (1.25 g, 51%) as a yellowish oil, which solidified upon extensive drying: mp 141–143 °C; IR (thin film) 3333, 2359, 1660 cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.22 (br s, 1H), 7.50 (d, 1H, *J*=7.6 Hz), 7.45 (d, 1H, *J*=8.2 Hz), 7.40 (br s, 1H), 7.22 (s, 1H), 7.15–7.12 (m, 1H), 7.02 (t, 1H, *J*=7.5 Hz), 6.91 (br s, 1H), 4.34 (t, 2H, *J*=6.7 Hz), 3.62 (s, 2H), 2.55 (t, 2H, *J*=6.9 Hz); ^{13}C NMR (DMSO-d_6): δ 173.0, 171.9, 135.7, 127.6, 127.2, 121.2, 118.9, 118.6, 109.7, 107.2, 41.6, 35.8, 30.9; LRMS (EI): *m/z* 246 (M^+), 201 (100%), 130, 115; HRMS (EI) calcd for $C_{13}H_{14}N_2O_3$: 246.1004, found: 246.1003.

4.1.12. 1-Methyl-1*H*-indole (26). To a stirred solution of indole (4.68 g, 40 mmol) in acetone (120 mL) at 0 °C was added freshly powdered potassium hydroxide (11.22 g, 200 mmol). After stirring the mixture for 30 min at 0 °C, methyl iodide (11.35 g, 80 mmol) was added dropwise with vigorous stirring. The mixture was allowed to slowly reach rt and continued to stir for 18 h. The mixture was filtered to remove the insoluble materials and concentrated in vacuo. The residue was distilled at a reduced pressure (bp 123–125 °C/22–25 Torr) to give the desired product (4.72 g, 90%) as a colorless oil: (lit.[22] bp 118–120 °C/20 Torr); ^1H NMR ($CDCl_3$): δ 7.86–7.83 (m, 1H), 7.49–7.39 (m, 2H), 7.35–7.29 (m, 1H), 7.17 (d, 1H, *J*=3.2 Hz), 6.69–6.67 (m, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 136.8, 128.9, 128.6, 121.6, 120.9, 119.3, 109.3, 100.9, 32.8.

4.1.13. 3-[2,5-Dihydro-4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-3-furanyl]-1*H*-indole-1-propanamide (28). To a stirred solution of 1-methylindole (656 mg, 5 mmol) in dichloromethane (50 mL) at 0 °C was added dropwise oxalyl chloride (635 mg, 5 mmol). After stirring the mixture for 1 h at 0 °C, the solvent was removed in vacuo. The residue was redissolved in dichloromethane (50 mL) and added dropwise

to a stirred solution of **25** (1.23 g, 5 mmol) and triethylamine (1.01 g, 10 mmol) in dichloromethane (20 mL). The mixture was stirred overnight at rt and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (90:10 dichloromethane:methanol) to give the desired product (640 mg, 31%) as a red solid: mp 218–220 °C; IR (thin film) 3194, 1816, 1749, 1673, 1612, 1529, 1257 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.96 (s, 1H), 7.83 (s, 1H), 7.55 (d, 1H, J=8.2 Hz), 7.48 (d, 1H, J=8.2 Hz), 7.42 (br s, 1H), 7.12–7.07 (m, 2H), 6.96 (br s, 1H), 6.91–6.88 (m, 1H), 6.76–6.69 (m, 3H), 4.46 (t, 2H, J=6.7 Hz), 3.89 (s, 3H), 2.58 (t, 2H, J=6.7 Hz); ^{13}C NMR (DMSO-d_6): δ 171.6, 166.5, 166.4, 136.7, 135.7, 134.4, 133.2, 127.9, 126.9, 125.7, 125.3, 122.3, 122.2, 121.5, 121.4, 120.3, 120.1, 110.6, 110.5, 104.4, 104.1, 42.4, 35.4, 33.1; LRMS (EI): m/z 413 (M^+), 260, 201 (100%), 158, 130, 72; HRMS (EI) calcd for $C_{24}H_{19}N_3O_4$: 413.1376, found: 413.1368.

4.1.14. 3-[2,5-Dihydro-4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-1*H*-pyrrol-3-yl]-1*H*-indole-1-propanamide (29). To a stirred solution of anhydride **28** (265 mg, 0.64 mmol) in DMF (3 mL) was added a 1,1,1,3,3,3-hexamethyldisilazane (1.03 g, 6.4 mmol) followed by methanol (102 mg, 3.2 mmol). The tightly closed mixture was stirred for 30 h at rt. The mixture was then poured into water (25 mL) and extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with water (50 mL). The separated organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (90:10 dichloromethane:methanol) to give the desired product (253 mg, 96%) as a red solid: mp >230 °C (dec); IR (thin film) 3189, 3044, 1750, 1701, 1661, 1606, 1530, 1336 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.94 (s, 1H), 7.84 (s, 1H), 7.73 (s, 1H), 7.50 (d, 1H, J=8.2 Hz), 7.42–7.40 (m, 2H), 7.04–7.01 (m, 2H), 6.96 (br s, 1H), 6.82 (d, 1H, J=7.9 Hz), 6.67–6.63 (m, 3H), 4.44 (t, 2H, J=6.7 Hz), 3.85 (s, 3H), 2.58 (t, 2H, J=6.7 Hz); ^{13}C NMR (DMSO-d_6): δ 173.0, 172.9, 171.8, 136.5, 135.5, 133.1, 132.0, 127.6, 126.7, 126.2, 125.8, 121.8, 121.7, 121.2, 121.1, 119.8, 119.6, 110.3, 110.1, 105.1, 104.7, 42.3, 35.6, 33.0; LRMS (ESI): m/z 413 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{21}N_4O_3$ [M+H]: 413.1614, found: 413.1596.

4.1.15. 5,6,7,13-Tetrahydro-13-methyl-5,7-dioxo-12*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-12-propanamide (22). A mixture of maleimide **29** (21 mg, 0.05 mmol) and palladium(II) trifluoroacetate (83 mg, 0.25 mmol) in DMF (3 mL) was heated at 90 °C for 2 h. The reaction mixture was then cooled, diluted with ethyl acetate (25 mL), and washed with 0.5 N HCl (50 mL). The organic phase was dried (Na_2SO_4) and filtered through Hyflo. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (90:10 dichloromethane: methanol) to give the desired product (6 mg, 30%) as a fluorescent yellow solid: mp >250 °C (dec); IR (thin film) 2921, 2853, 1715, 1645, 1254 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.14 (s, 1H), 9.14 (t, 2H, J=8.2 Hz), 7.91 (d, 1H, J=8.2 Hz), 7.82 (d, 1H, J=8.2 Hz), 7.68–7.63 (m, 2H), 7.45–7.41 (m, 2H), 7.24 (s, 1H), 6.80 (s, 1H), 5.01 (t, 2H, J=7.6 Hz), 4.26 (s, 3H), 2.41 (t, 2H, J=7.6 Hz); ^{13}C NMR (DMSO-d_6): δ 171.3, 170.8, 170.7, 144.7, 143.6, 133.2, 131.9, 127.6, 127.4, 124.7, 124.5, 122.9, 121.8, 121.3, 121.1, 120.8, 120.0, 119.4, 118.6, 112.3, 111.3, 44.7, 36.8, 33.7; LRMS (ESI): m/z 411 $[M+H]^+$; HRMS (ESI) calcd for $C_{24}H_{19}N_4O_3$ [M+H]: 411.1457, found: 411.1448.

Acknowledgements

This investigation was supported in part by the donors of the Petroleum Research Fund (PRF), administered by the American Chemical Society, the National Institutes of Health (CA 82220), and Wyeth.

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Tetrahedron 62 (2006) 7846–7853
Tetrahedron

Synthesis of tetra-oligothiophene-substituted calix[4]arenes and their optical and electrochemical properties

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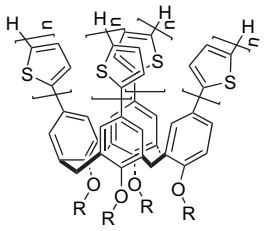
Received 3 April 2006; revised 17 May 2006; accepted 18 May 2006
Available online 9 June 2006

Abstract—A facile and efficient approach to synthesize tetra-oligothiophene-substituted calix[4]arenes, **Calix-OT(*n*)** with *n* up to 4 using palladium-catalyzed Kumada coupling of thienylmagnesium bromide and bromo-substituted calix[4]arene as a key step has been developed. The close proximity of the tetra-oligothiophenes constructed within a calix[4]arene assembly leads to peak/band broadening, spectral shifting, i.e., blue-shift in absorption and red-shift in emission spectra as well as fluorescence quantum yield quenching as compared to those of monomers indicating the existence of chromophoric interaction. We have shown that the intra-chromophoric interaction lowers the first ionization (raises HOMO level) of an oligothiophene within an assembly. It also stabilizes the formation of a radical cation, which results in an increase in the subsequent voltammetric oxidation and the occurrence of the higher oxidation states as compared to the monomeric counterparts. This assembly can serve as a model for the investigation of molecular interaction of π-conjugated systems.

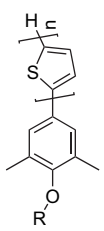
1. Introduction

Oligothiophenes are an important class of π-conjugated organic materials that have been extensively investigated and explored as active materials for (opto)electronic device applications such as field-effect transistors, light emitting diodes, photovoltaic cells, and sensors in the last few years.[1] Tuning the molecular properties of oligothiophenes by means of chemical and structural modifications has been successfully much achieved in recent years.[2] However, the ultimate bulk performance of an oligothiophene-based material relies greatly on the molecular/chain arrangement in the solid-state and/or morphology of the material.[3] For example, ordered close packing of sexithiophenes in the solid-state leads to low photoluminescence efficiency due to excitonic coupling of proximate oligomers.[4] On the other hand, proper molecular alignment results in better charge transport and lowers operating voltages in field-effect transistor applications.[5] As a result, structural studies of oligothiophenes and morphological investigations of these materials are important issues related to their applications. Toward this end, it is of great interest to investigate well-defined multi-oligothiophene-based molecular assemblies, in which thiophene oligomers are preorganized and preoriented within a molecular framework, within which studies would provide insight into the effect of through-space interactions of oligomeric and polymeric chains. Several cyclophane-based oligothiophene assemblies have been synthesized and investigated for π-stacking effects.[6] In addition, the intramolecular interaction and corporation effect of the proximate chromophores could give rise to novel or enhanced functional and structural/morphological properties of resulting materials.[7]

Calixarenes are one of the most useful building platforms for constructing supramolecular systems and have been widely used in the preparation of artificial receptors for neutral and ionic molecules.[8] One of the unique features of these calix[4]arene derivatives is that they can exist in a relatively rigid and stable cone structure, in which four functionalized phenolic units, oriented in the same direction are linked at their *ortho*-positions by methylene bridges. With oligothiophenes built onto such frameworks, the arrangement and orientation of oligothiophenes will be predefined and preorganized with the oligothiophene units close enough to interact. Thus, the effect of coupling interactions on various functional properties of such assemblies could readily be probed. We herein report the facile and efficient synthesis and optical and electrochemical properties of a novel series



Calix-OT(*n*), *n* = 1-4



M-OT(*n*), *n* = 1-4

Keywords: Tetra-oligothiophene-substituted calix[4]arene; Intra-chromophoric interaction; Kumada coupling.
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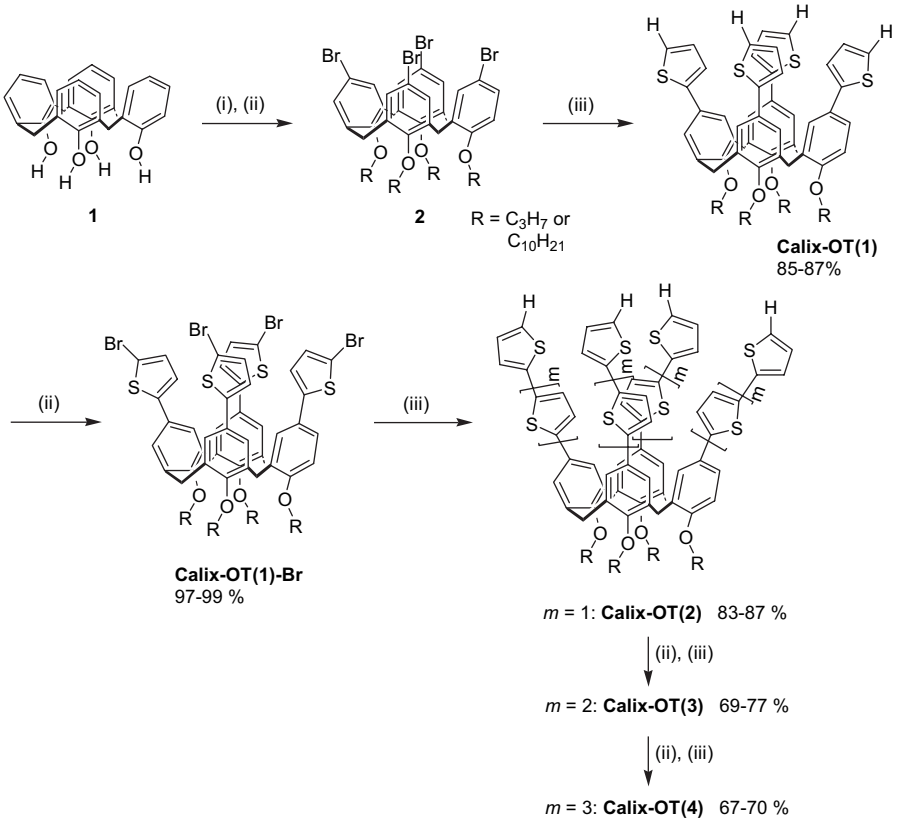
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.05.050

of monodisperse and well-defined π-conjugated tetra-oligothiophene-substituted calix[4]arene assemblies, **Calix-OT(*n*)** where n=1–4.

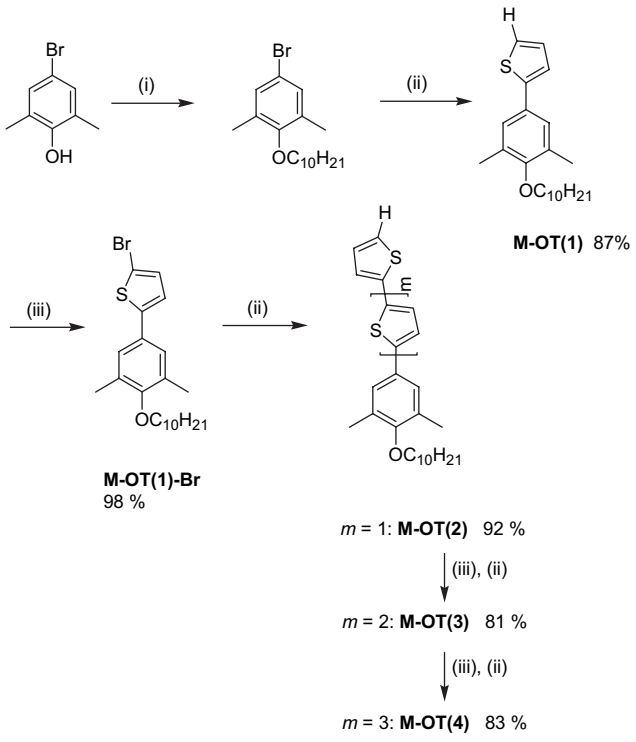
2. Results and discussion

Recently, various oligophenylene-substituted calix[4]arenes have been efficiently synthesized by palladium-catalyzed Suzuki cross-coupling reactions;[7b,c] however, such protocols were found to be not useful for the synthesis of tetra-oligothiophene-substituted calix[4]arenes, **Calix-OT(*n*)**. Even though bis(dithienyl)-substituted calix[4]arenes were previously prepared by Stille cross-coupling reaction,[1e] we find that palladium-catalyzed Kumada cross-coupling is more efficient and useful for the synthesis of tetra-oligothiophene-substituted calix[4]arenes. Since the preparations of oligothienylmagnesium bromides were non-trivial and inefficient, the use of convergent approach to synthesize the higher homologous was not practical. As a result, the tetra-oligothienyl chains were constructed onto the calix[4]arene framework by a divergent approach using palladium-catalyzed Kumada cross-coupling of thienylmagnesium bromide and tetrabromo(oligothienyl)-calix[4]arene as a key step for chain length extension. The synthetic route is outlined in Scheme 1. To stabilize the cone conformation, calix[4]arene **1** was alkylated with either bromopropane or bromodecane using NaH as a base in DMF.[9] Bromination of tetraalkoxycalix[4]arene with NBS in refluxing $CHCl_3$ afforded the tetrabromocalix[4]arene **2**.[7a] Cross-coupling of freshly prepared thienylmagnesium bromide and **2** in the presence of $PdCl_2$(dppf) as a catalyst afforded tetrathienylcalix[4]arene, **Calix-OT(1)** in a good yield (85–87%). Bromination of tetrathienylcalix[4]arene with NBS in refluxing CH_2Cl_2 gave tetrabromothienylcalix[4]arene, **Calix-OT(1)-Br** in an excellent yield (90–93%). Subsequent cross-coupling reaction of **Calix-OT(1)-Br** with thienylmagnesium bromide afforded tetrakis-(bithienyl)calix[4]arene, **Calix-OT(2)** in 83–87% yield. By repeating such a sequence of bromination and cross-coupling reactions, a higher homologue series of oligothiophene-substituted calix[4]arenes including **Calix-OT(3)** and **Calix-OT(4)** were readily synthesized. The MALDI-TOF mass spectra of **Calix-OT(3)** and **Calix-OT(4)** showed a base peak at m/z 1970.6421 and 2299.6157, corresponding to $[M^+]$ and $[M^+{+}H]$, respectively. In addition to low/high-resolution mass spectroscopy, all the newly synthesized oligothiophene-substituted calix[4]arenes were fully characterized by ^{1}H NMR, ^{13}C NMR, and/or elemental analyses and found to be in good agreement with the expected structures. For properties comparison, their corresponding monomers oligothiophene-substituted 4-alkyoxy-3,5-dimethylbenzenes, **M-OT(*n*)** with n up to 4 were also synthesized using the same strategy as shown in Scheme 2.

Figure 1 shows the single crystal X-ray structure of **Calix-OT(2)**, which adopts a pinched cone structure similar to other arylene-substituted calix[4]arenes.[10] In contrast to the biphenylene counterparts, all the bithiophene units are in an *anti* coplanar conformation except there is a twist



Scheme 1. Synthesis of oligothiophene-substituted calix[4]arene assemblies, **Calix-OT(*n*)**, n=1–4. Reagents and conditions: (i) NaH, C_3H_7Br or $C_{10}H_{21}Br$, DMF, 50 °C; (ii) NBS, $CHCl_3$ or CH_2Cl_2, reflux; (iii) (a) 2-bromothiophene, Mg, THF, reflux and (b) $PdCl_2$(dppf), reflux.



Scheme 2. Synthesis of monomeric oligothiophenes, **M-OT(*n*)**, n=1–4. Reagents and conditions: (i) NaH, $C_{10}H_{21}Br$, DMF, 50 °C; (ii) (a) 2-bromothiophene, Mg, THF, reflux and (b) $PdCl_2$(dppf), reflux; (iii) NBS, $CHCl_3$ or CH_2Cl_2, reflux.

between the aryl ring of calix[4]arene skeleton and bithiophene. Although the two parallel bithiophene units are leaned toward each other, the distal terminal thiophene rings do not pack in a co-facial arrangement owing to the *anti* conformation of bithiophene.

The thermal behavior and stability of these oligothiophene-substituted calix[4]arenes were investigated by DSC and TGA analyses, respectively. The results are summarized in Table 1. In general, **Calix-OT(*n*)** shows an excellent and enhanced thermal stability with T_d>400 °C than that of the corresponding **M-OT(*n*)**. All the oligothiophene-substituted

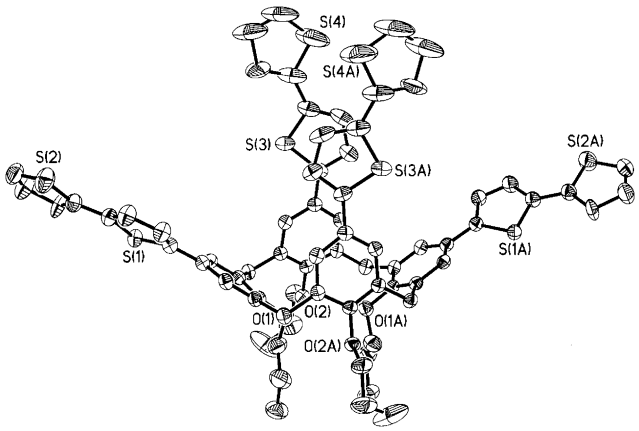


Figure 1. ORTEP drawings of **Calix-OT(2)** (25% probability). All hydrogen atoms are omitted for clarity.

calix[4]arenes are highly soluble in common organic solvents except **Calix-OT(4)**.

The electronic absorption and emission spectra of all the oligomers, **M-OT(*n*)** and assemblies, **Calix-OT(*n*)** were recorded in chloroform and their results are summarized in Table 1. In general, there is a sequential increase in the absorption maxima with a concomitant increase in molar absorptivity and the emission maxima in both series as the thienyl unit increases. However, in addition to the peak broadening, the absorption spectra of oligothiophene-substituted calix[4]arenes are relatively blue-shifted (Δ=3–8 nm) whereas their emission spectra are shifted to the longer wavelengths (Δ=12–14 nm) as compared to those of corresponding monomer (Fig. 2). In contrast to the monomeric series, the moderate increase in the fluorescence quantum yield as the chain length extends was not observed in oligothiophene-substituted calix[4]arene series. All these phenomena suggest the occurrence of the chromophoric interaction of proximate tetra-thiophene oligomers constructed within the calix[4]arene framework. The blue-shift in absorption spectra can be explained in terms of the excited state splitting due to the exciton coupling of the proximate chromophores within the assembly in which the singlet–singlet transitions

Table 1. Summaries of physical measurements of **Calix-OT(*n*)** and **M-OT(*n*)** series

	λ_{max}^{abs} [a]/nm ($\varepsilon_{max}\times10^4$/M^{-1} cm^{-1})	λ_{max}^{em} [a,b]/nm	Φ_{FL} [a,c]	FL lifetime in solution/ns[a,d]	E_{ox} [e]/V	T_m [f] (T_d [g])/°C
M-OT(1)	286 (1.97)	385, 402	[h]	1.03	0.87 (ir, 1e)	(292)
M-OT(2)	348 (2.71)	396, 414	0.07	1.19	0.63 (ir, 1e)	63 (352)
M-OT(3)	384 (3.54)	442, 469	0.15	1.17	0.47 (r, 1e), 0.76 (q, 1e)	112 (396)
M-OT(4)	414 (4.64)	477, 510	0.31	1.36	0.37 (r, 1e), 0.67 (r, 1e)	177 (427)
Calix-OT(1)	288 (8.02)	402, 425	[h]	1.20	0.75 (ir, 1e)	239 (412)
Calix-OT(2)	342 (8.80)	427	0.08	1.87	0.47 (ir, 1e), 0.61 (ir, 1e)	241 (409)
Calix-OT(3)	381 (12.9)	454, 482	0.11	1.77	0.44 (ir, 1e). 0.87 (q, 2e)	200 (431)
Calix-OT(4)	406 (14.8)	489, 524	0.11	1.50	0.38 (q, 1e), 0.73 (q, 2e)	227 (421)

[a] Measured in $CHCl_3$.
[b] Excited at the absorption maxima.
[c] Using quinine in 0.1 M H_2SO_4 (Φ_{365}=0.54) as a standard.
[d] Estimated using an iterative fitting procedure from the measured fluorescence decayed excited by nitrogen laser.
[e] E_{ox} estimated by CV method using platinum disc electrode as a working electrode, platinum wire as a counter electrode, and SCE as a reference electrode with an agar salt bridge connecting to the oligomer solution and all the potentials were calibrated with ferrocene, which was also used as an internal standard, $E_{1/2}$ (Fc/Fc^+)=0.49 V versus SCE with a scan rate of 100 mV/s.
[f] Determined by differential scanning calorimeter with a heating rate of 10 °C/min under N_2.
[g] Determined by thermal gravimetric analyzer with a heating rate of 10 °C/min under N_2.
[h] Less than 0.01.

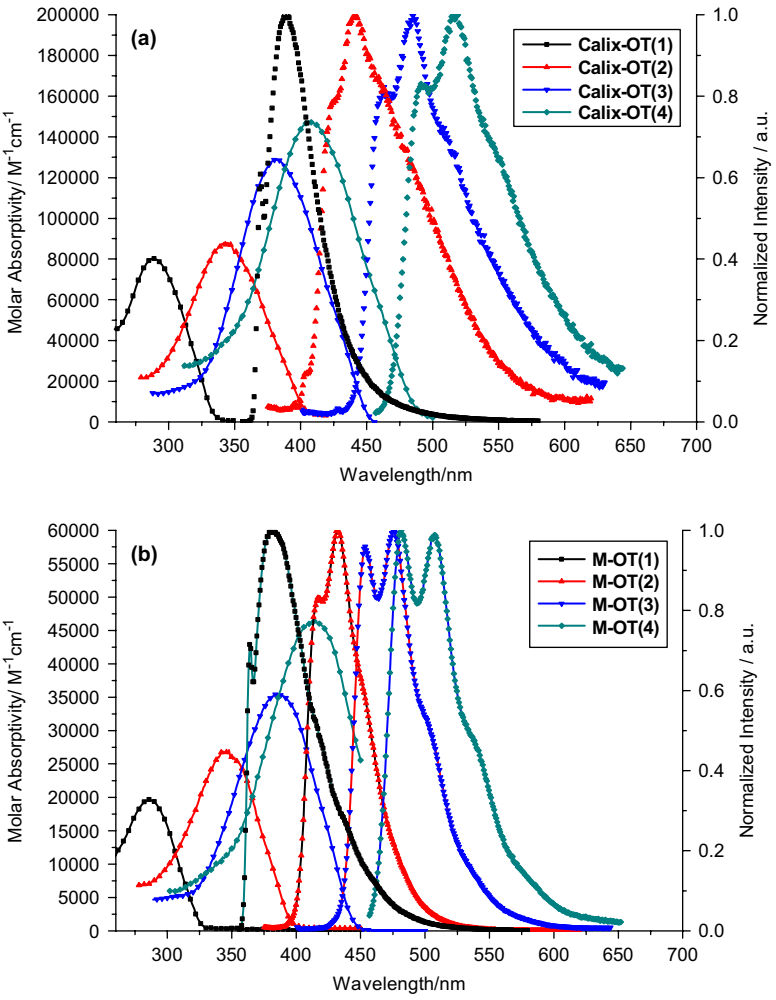


Figure 2. Absorption and emission spectra of (a) **Calix-OT(*n*)** and (b) **M-OT(*n*)** series.

from the ground state to the lowest coupled excited state are forbidden but to the second excited state are allowed.[11] Because of the through-space interaction and/or the steric shielding imposed by proximate oligomers, the oligothiophene-substituted calix[4]arenes exhibit slightly longer fluorescence lifetimes (1.20–1.87 ns) than the corresponding monomeric counterparts (1.03–1.36 ns).

The redox properties of **M-OT(*n*)** and **Calix-OT(*n*)** were studied by cyclic voltammetry, which was carried out in a three-electrode cell set-up with 0.1 M of Bu_4NPF_6 as supporting electrolyte in $CHCl_3$. All the potentials reported are internally referenced to Fc/Fc^+ standard and the results are tabulated in Table 1. **M-OT(1)** exhibits an irreversible one-electron oxidation with E_{pa} at 0.87 V in $CHCl_3$ corresponding to the formation of monocation. When repeated cycling of the electrode between 0 and 1.8 V, an appearance of solid films on the electrode surface and a growing broad wave at a lower potential associated with an increased peak current were observed indicating the occurrence of electrochemical dimerization/polymerization. As the thienyl unit increases, the first oxidation potential decreases progressively. Furthermore, there is an improvement in reversibility of the voltammetric wave and instability toward electrochemical reactions as the chain length increases. In contrast to **M-OT(1)** and **M-OT(2)**, the voltammetric wave of **M-OT(3)** and **M-OT(4)** also exhibits two one-electron oxidation waves corresponding to the sequential formation of monocation and dication. The second oxidation potential also decreases with an increase in thienyl unit. All these evolution/changes are attributed to the stabilizing effect of the enhanced π-conjugation of the longer homologues.

Even though there were several reports on the electrochemical studies of polythiophene–calixarene hybrid materials,[1e,12] the electrochemical properties of tetra-oligothiophene–calixarene molecules are not known. The influence of intramolecular chromophoric interaction on the electrochemical properties of **Calix-OT(*n*)** is profound. Even though **Calix-OT(1)** exhibits an irreversible one-electron oxidation similar to **M-OT(1)**, its oxidation potential (E_{pa}=0.75 V) is substantially lower than that of **M-OT(1)** (E_{pa}=0.87 V). The lowering of the first oxidation potential of **Calix-OT(*n*)**s relative to **M-OT(*n*)**s is consistently observed throughout the series. This phenomenon suggests that the cation formed is stabilized by the proximate thiophene oligomers within the assembly. In addition, the intra-chromophoric stabilization leads to the exhibition of two well-resolved one-electron oxidation waves of **Calix-OT(2)** corresponding to the sequential formation of monocation and dication whereas

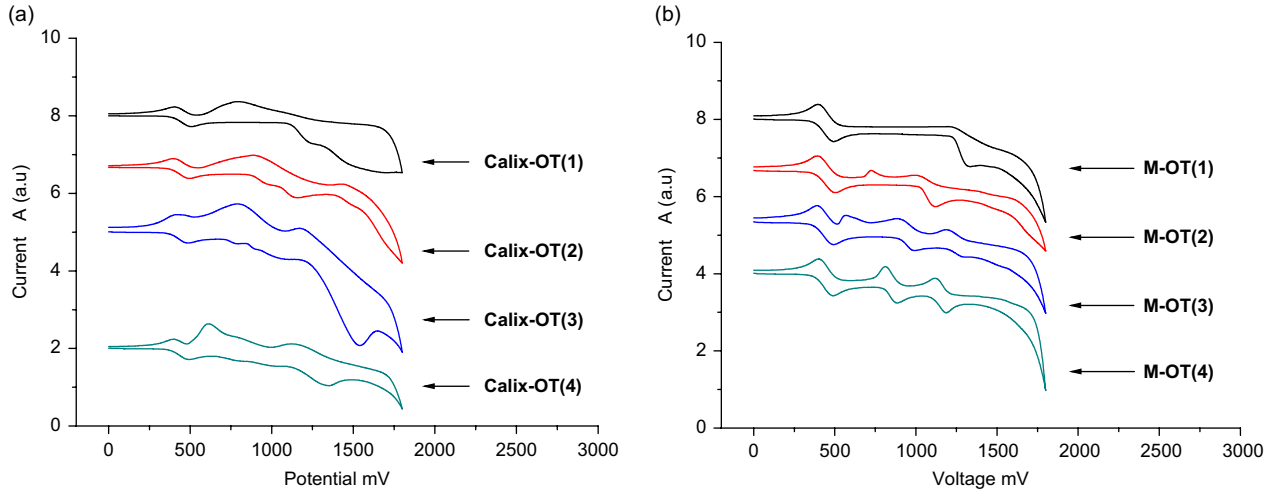


Figure 3. CV traces of (a) **Calix-OT(*n*)** and (b) **M-OT(*n*)** series with ferrocene were used as an internal standard, $E_{1/2}$ (Fc/Fc$^+$)=0.49 V versus SCE with a scan rate of 100 mV/s.

M-OT(2) only exhibits a single one-electron oxidation (Fig. 3). The stabilizing effect imposed by proximate oligomers and chain length extension also leads to the exhibition of the higher oxidation states in **Calix-OT(3)** and **Calix-OT(4)**. There are small steps appearing in the oxidation waves of the higher homologues, which are attributed to the micro-environment difference for each thiophene oligomer within an assembly. Such a difference is likely created by the relatively slow interconversion of two conformationally mobile C_{2v} 'pinched or flattened' cone conformers in solution for the higher homologues within CV time scale. On the other hand, **Calix-OT(3)** appears to have a higher second oxidation potential than that of **Calix-OT(2)**, which is attributed to one more electron involved in the second oxidation of **Calix-OT(3)**. For **Calix-OT(4)**, the second oxidation potential drops again. Since the number of electrons involved in the second oxidation of **Calix-OT(3)** and **Calix-OT(4)** is more, their second oxidation generally occurs at a higher potential than that of the corresponding **M-OT(*n*)**. Electro-polymerization also occurs readily for the **Calix-OT(*n*)** series upon repeated anodic scans.

3. Conclusions

In summary, we have developed a divergent approach to synthesize a novel series of tetra-oligothiophene-substituted calix[4]arenes, **Calix-OT(*n*)** with n up to 4 by means of a facile and efficient palladium-catalyzed Kumada coupling of thienylmagnesium bromide and bromo-substituted calix[4]arene as the key step. In addition to the spectral widening, blue-shift of absorption spectra, red-shift of emission spectra, and increased quenching in fluorescence quantum yields, the intramolecular coupling/interaction leads to lowering of the first oxidation potential of an oligothiophene stabilizing the formation of radical cation and exhibiting higher oxidation states in higher homologues of the tetra-oligothiophene-substituted calix[4]arenes assembly. These assemblies can serve as a model in the intermolecular interaction of π-conjugated molecules/polymers. Our studies also provide an insight into the influence of intermolecular interaction on the positive charge in the condensed phase.

4. Experimental

4.1. General

All the solvents were dried by the standard methods wherever needed. ^{1}H NMR spectra were recorded using a 270 MHz or 400 MHz FT-NMR spectrometer and are referenced to the residual $CHCl_3$ 7.24 ppm. ^{13}C NMR spectra were recorded using a 270 MHz or 400 MHz FT-NMR spectrometer and are referenced to the $CDCl_3$ 77 ppm. High-resolution mass spectroscopy (HRMS) measurement was carried using MALDI-TOF method. The fluorescence decay curves were recorded on PTI fluorescence Master 2M1 Luminescence Spectrophotometer using PTI G2-3300 Nitrogen Laser as excitation. The lifetimes were estimated from the measured fluorescence decay using iterative fitting procedure. $E_{1/2}$ (E_{pa}) versus Fc$^+$/Fc was estimated by cyclic voltammetric method using platinum disc electrode as a working electrode, platinum wire as a counter electrode, and SCE as a reference electrode with an agar salt bridge connecting to the oligomer solution (1 mM) dissolved in $CHCl_3$ using 0.1 M of Bu_4NPF_6 as a supporting electrolyte with a scan rate of 100 mV/s and all the potentials were calibrated and referenced with ferrocene ($E_{1/2}$ (Fc/Fc$^+$)=0.49 V vs SCE) as an internal standard.

4.1.1. 5,11,17,23-Tetrakis(thienyl)-25,26,27,28-tetrapropoxycalix[4]arene Calix-OT(1). To a flame dried 100-mL two-necked flask containing 2-bromothiophene (0.7 g, 4.3 mmol) in 20 mL anhydrous THF were added Mg turnings (0.12 g, 5 mmol) at room temperature under N_2. The solution mixture was stirred vigorously. After the boiling had stopped, the reaction mixture was heated to reflux for 3 h. After cooling to room temperature, tetrabromocalix[4]arene **2** (0.2 g, 0.22 mmol) and $PdCl_2$(dppf) (9 mg, 5 mmol %) were added and allowed to reflux overnight. After cooling, the reaction mixture was quenched with 50 mL of water, acidified with 6 M HCl to pH 4–5 and then extracted with DCM (3×20 mL). The combined organic solvent was washed with brine and dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by flash silica gel column chromatography using petroleum

ether as eluent affording the title compound as a white solid (0.17 g, 85% yield). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 6.98 (t, J=3.2 Hz, 4H), 6.92 (s, 8H), 6.78 (d, J=3.5 Hz, 8H), 4.47 (d, J=13.2 Hz, 4H), 3.89 (t, J=7.6 Hz, 8H), 3.20 (d, J=13.2 Hz, 4H), 1.96–1.94 (m, 8H), 1.00 (t, J=4.9 Hz, 12H). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 156.1, 144.4, 135.0, 128.5, 127.5, 125.9, 123.4, 121.8, 76.9, 31.1, 23.3, 10.5. MS (FAB) m/z 920.6 [M$^+$]. Anal. Calcd for $C_{56}H_{56}O_4S_4$: C, 73.01; H, 6.13. Found: C, 72.89; H, 6.12.

4.1.2. 5,11,17,23-Tetrakis(5-bromothienyl)-25,26,27,28-tetrapropoxycalix[4]arene Calix-OT(1)-Br. To a stirred solution of **Calix-OT(1)** (0.22 g, 0.24 mmol) in 30 mL CH_2Cl_2 in a 100-mL round-bottomed flask was added NBS (0.17 g, 0.96 mmol). The solution mixture was heated to reflux overnight. After evaporating the solvent, the residue was purified by flash silica gel column chromatography using CH_2Cl_2 as eluent affording a white solid (0.27 g 90% yield). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 6.81–6.79 (m, 12H), 6.55 (d, J=3.8 Hz, 4H), 4.45 (d, J=13.2 Hz, 4H), 3.86 (t, 8H), 3.16 (d, J=13.2 Hz, 4H), 1.93–1.88 (m, 8H), 0.99 (t, 12H). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 156.4, 145.7, 135.2, 130.5, 127.7, 125.3, 121.9, 77.2, 31.1, 23.3, 10.4. MS (FAB) m/z 1236.2 [M$^+$]. HRMS (MALDI-TOF) Calcd for $C_{56}H_{53}Br_4O_4S_4$: 1236.9527. Found: 1236.9569 [M$^+$+H].

4.1.3. 5,11,17,23-Tetrakis(dithienyl)-25,26,27,28-tetrapropoxycalix[4]arene Calix-OT(2). The coupling procedure described above was followed using 2-bromothiophene (0.8 g, 4.9 mmol), Mg turnings (0.14 g, 5.8 mmol), **Calix-OT(1)-Br** (0.3 g, 0.24 mmol), and $PdCl_2$(dppf) (9 mg, 5 mmol %). The crude product was purified by flash silica gel column chromatography using CH_2Cl_2/petroleum ether (v/v=1/3) as eluent affording a pale yellow solid (0.25 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.10 (d, J=1.2 Hz, 4H), 7.01 (d, J=3.6 Hz, 4H), 6.93 (s, 8H), 6.92–6.89 (m, 4H), 6.80 (d, J=3.6 Hz, 4H), 6.71 (d, J=3.2 Hz, 4H), 4.49 (d, J=13.6 Hz, 4H), 3.90 (t, J=7.2 Hz, 8H), 3.22 (d, J=13.6 Hz, 8H), 1.99–1.93 (m, 8H), 1.02 (t, J=7.2 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 156.4, 143.3, 137.8, 135.3, 135.2, 128.3, 127.6, 125.6, 124.4, 123.6, 123.0, 122.5, 76.9, 31.0, 23.2, 10.3. MS (FAB) m/z 1248.8 [M$^+$]. Anal. Calcd for $C_{72}H_{64}O_4S_8$: C, 69.19; H, 5.16. Found: C, 69.08; H, 5.14.

4.1.4. 5,11,17,23-Tetrakis(5′-bromodithienyl)-25,26,27,28-tetradecyloxycalix[4]arene Calix-OT(2)-Br. The bromination procedure described above was followed using **Calix-OT(2)** (0.16 g, 0.1 mmol) and NBS (69.5 mg, 0.4 mmol). The crude product was purified by flash silica gel column chromatography using CH_2Cl_2/petroleum ether (v/v=1/3) as eluent affording a white solid with a quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 6.91 (s, 8H), 6.87 (d, J=3.2 Hz, 4H), 6.77 (s, 4H), 6.74 (d, J=3.6 Hz, 8H), 4.48 (d, J=13.2 Hz, 4H), 3.93 (t, J=7.2 Hz, 4H), 3.21 (d, J=13.2 Hz, 4H), 1.93–1.92 (m, 8H), 1.39–1.29 (m, 56H), 0.89 (t, J=6.4 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 156.6, 143.8, 139.2, 135.3, 134.4, 130.4, 128.0, 125.6, 124.5, 122.9, 122.5, 110.2, 75.5, 32.0, 31.0, 30.3, 30.0, 29.9, 29.8, 29.5, 26.4, 22.7, 14.1. MS (FAB) m/z 1956.6 [M$^+$]. HRMS (MALDI-TOF) Calcd for $C_{100}H_{117}Br_4O_4S_8$: 1959.3425. Found: 1959.3488 [M$^+$+H].

4.1.5. 5,11,17,23-Tetrakis(terthienyl)-25,26,27,28-tetradecyloxycalix[4]arene Calix-OT(3). The coupling procedure described above was followed using **Calix-OT(2)-Br** (2 g, 1 mmol), 2-bromothiophene (3.26 g, 20 mmol), Mg turnings (3.9 g, 0.16 mmol), and $PdCl_2$(dppf) (16 mg, 2 mmol %) affording a dark yellow solid (1.54 g, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.26 (d, J=8 Hz, 4H), 7.15 (d, J=4.8 Hz, 4H), 7.05–7.04 (m, 20H), 6.85 (s, 4H), 6.76 (s, 4H), 4.49 (d, J=13.2 Hz, 4H), 3.94 (t, J=6.8 Hz, 8H), 3.23 (d, J=13.2 Hz, 4H), 1.95 (s, 8H), 1.41–1.29 (m, 56H), 0.9 (t, J=6.8 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 156.5, 143.5, 137.3, 136.6, 135.5, 135.3, 135.1, 128.2, 127.8, 125.6, 124.4, 124.2, 124.0, 123.6, 123.4, 122.6, 75.5, 32.0, 31.1, 30.3, 30.0, 29.9, 29.8, 29.5, 26.4, 22.7, 14.1. MS (FAB) m/z 1969.7 [M$^+$]. HRMS (MALDI-TOF) Calcd for $C_{116}H_{128}O_4S_{12}$: 1970.6484. Found: 1970.6421 [M$^+$].

4.1.6. 5,11,17,23-Tetrakis(5″-bromoterthienyl)-25,26,27,28-tetradecyloxycalix[4]arene Calix-OT(3)-Br. The bromination procedure described above was followed using **Calix-OT(3)** (0.61 g, 0.3 mmol) and NBS (0.2 g, 1.2 mmol) affording a dark yellow solid (0.66 g, 96% yield). ^{1}H NMR (270 MHz, $CDCl_3$, δ) 6.93 (s, 8H), 6.87–6.80 (m, 16H), 6.73 (d, J=5.4 Hz, 8H), 4.47 (d, J=13.2 Hz, 4H), 3.92 (t, J=5.4 Hz, 8H), 3.21 (d, J=13.2 Hz, 4H), 1.94 (s, 8H), 1.39–1.28 (m, 56H), 0.87 (t, J=5.4 Hz, 12H). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ) 156.4, 143.6, 138.6, 136.9, 135.2, 134.8, 134.2, 130.5, 128.0, 125.6, 124.4, 124.2, 123.4, 123.1, 122.5, 110.6, 75.4, 32.1, 31.1, 30.4, 30.09, 30.07, 29.9, 29.5, 26.5, 22.8, 14.2. HRMS (MALDI-TOF) Calcd for $C_{116}H_{124}Br_4O_4S_{12}$: 2286.2859. Found: 2286.2850 [M$^+$].

4.1.7. 5,11,17,23-Tetrakis(quaterthienyl)-25,26,27,28-tetradecyloxycalix[4]arene Calix-OT(4). The coupling procedure described above was followed using **Calix-OT(3)-Br** (0.63 g, 0.28 mmol), 2-bromothiophene (0.9 g, 5.6 mmol), Mg (0.16 g, 6.7 mmol), and $PdCl_2$(dppf) (11 mg, 5 mmol %) to afford a dark yellow solid (0.4 g, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.17 (d, J=5.2 Hz, 8H), 7.06 (d, J=3.6 Hz, 8H), 6.96–6.86 (m, 20H), 6.79 (s, 8H), 4.49 (d, J=13.2 Hz, 8H), 3.94 (s, 8H), 3.23 (d, J=13.2 Hz, 8H), 1.96–1.94 (m, 8H), 1.41–1.25 (m, 56H), 0.89 (t, J=6.0 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 156.5, 143.6, 142.1, 136.55, 136.51, 136.4, 135.4, 135.2, 131.3, 128.7, 128.2, 125.7, 124.3, 124.2, 124.1, 123.7, 123.5, 122.6, 75.5, 32.0, 31.4, 30.4, 29.8, 29.5, 29.0, 28.6, 26.4, 22.7, 14.1. HRMS (MALDI-TOF) Calcd for $C_{132}H_{137}O_4S_{16}$: 2299.6073. Found: 2299.6157 [M$^+$+H]. Anal. Calcd for $C_{132}H_{136}O_4S_{16}$: C, 68.95; H, 5.96. Found: C, 69.14; H, 5.93.

Crystal data for **Calix-OT(2)**: $C_{72}H_{64}O_4S_8$, M_w=1249.71, crystal size=0.34×0.22×0.20 mm^3, monoclinic, space group $C2/c$, a=21.6040(14), b=22.1252(15), c=17.1240(11) Å, β=125.4460(10)°, V=6668.1(8) Å^3, Z=4, μ(Mo Kα)=0.315 mm^{-1}. Intensity data were measured on a Bruker-AXS CCD area-detector diffractometer with graphite monochromated Mo Kα (λ=0.71073 Å) radiation, 15,702 reflections measured, 5670 unique, R(int)=0.0252. Final R=0.0594 and $wR2$=0.1568 for 3457 observed reflections with $I>2\sigma(I)$ and GOF=1.005.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre with supplementary publication no. CCDC 606338. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.1.8. 1-Decyloxy-2,6-dimethyl-4-thienylbenzene M-OT(1). The coupling procedure described in the paper was followed using 1-decyloxy-2,6-dimethyl-4-bromobenzene (1 g, 2.9 mmol), 2-bromothiophene (2.5 g, 0.015 mol), Mg (0.45 g, 0.019 mol), and $PdCl_2$(dppf) (10 mg, 0.5 mmol %) affording a colorless liquid (0.88 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.22–7.20 (m, 2H), 7.03 (dd, J=4.8, 2.0 Hz, 1H), 3.76 (t, 2H), 2.30 (s, 6H), 1.84–1.77 (m, 2H), 1.52–1.48 (m, 2H), 1.38–1.28 (m, 12H), 0.89 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 155.8, 144.4, 131.4, 129.8, 127.8, 126.4, 124.1, 122.4, 72.5, 31.9, 30.4, 29.6, 29.57, 29.55, 29.3, 26.1, 22.7, 16.4, 14.1. MS (FAB) m/z 344.3 [M^+]. HRMS (MALDI-TOF) Calcd for $C_{22}H_{32}OS$: 344.2173. Found: 344.2177.

4.1.9. 1-Decyloxy-2,6-dimethyl-4-(5-bromothienyl)benzene M-OT(1)-Br. The bromination procedure described in the paper was followed using **M-OT(1)** (1.17 g, 3.4 mmol) and NBS (0.6 g, 3.4 mmol) affording a blue sticky solid (1.4 g, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.15 (s, 2H), 6.98 (d, J=3.2 Hz, 1H), 6.93 (d, J=3.2 Hz, 1H), 3.75 (t, 2H), 2.30 (s, 6H), 1.82–1.78 (m, 2H), 1.51–1.48 (m, 2H), 1.33–1.28 (m, 12H), 0.88 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 156.2, 145.9, 131.6, 130.6, 129.0, 126.1, 122.5, 110.4, 72.5, 31.9, 30.4, 29.61, 29.57, 26.1, 22.7, 16.4, 14.1. MS (FAB) m/z 422.2 [M^+]. HRMS (MALDI-TOF) Calcd for $C_{22}H_{31}BrOS$: 424.1255. Found: 424.1253 [M^+].

4.1.10. 1-Decyloxy-2,6-dimethyl-4-dithienylbenzene M-OT(2). The coupling procedure described in the paper was followed using **M-OT(1)-Br** (0.57 g, 1.34 mmol), 2-bromothiophene (1.1 g, 6.7 mmol), Mg (0.2 g, 8.3 mmol), and $PdCl_2$(dppf) (11 mg, 0.1 mmol %) affording a blue solid (0.53 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.24 (s, 2H), 7.20 (dd, J=4.2, 1.2 Hz, 1H), 7.17 (dd, J=4.2, 1.2 Hz, 1H), 7.12 (s, 2H), 7.02 (dd, J=4.8, 3.2 Hz, 1H), 3.77 (t, J=6.4 Hz, 2H), 2.31 (s, 6H), 1.83–1.77 (m, 2H), 1.52–1.48 (m, 2H), 1.38–1.24 (m, 12H), 0.89 (t, J=6.8 Hz, 3H). ^{13}C NMR (66 MHz, $CDCl_3$, δ) 155.8, 143.0, 137.5, 135.8, 131.4, 129.3, 127.7, 126.0, 124.4, 124.0, 123.2, 123.0, 72.5, 32.0, 30.5, 29.69, 29.66, 29.63, 29.4, 26.2, 22.8, 16.5, 14.2. MS (FAB) m/z 426.3 [M^+]. HRMS (MALDI-TOF) Calcd for $C_{26}H_{34}OS_2$: 426.2051. Found: 426.2057.

4.1.11. 1-Decyloxy-2,6-dimethyl-4-(5′-bromodithienyl)-benzene M-OT(2)-Br. The bromination procedure described in the paper was followed using **M-OT(2)** (0.53 g, 1.24 mmol) and NBS (0.22 g, 1.24 mmol) affording a yellow solid (0.6 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.23 (s, 2H), 7.09 (dd, J=3.6, 1.6 Hz, 1H), 7.03 (dd, J=4.0, 1.6 Hz, 1H), 6.96 (dd, J=3.6, 1.6 Hz, 1H), 6.90 (dd, J=3.6, 1.6 Hz, 1H), 3.76 (t, J=6.8 Hz, 2H), 2.30 (s, 6H), 1.82–1.79 (m, 2H), 1.52–1.48 (m, 2H), 1.33–1.28 (m, 12H), 0.89 (t, J=6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 156.1, 143.8, 139.1, 134.9, 131.6, 130.6, 129.2, 126.1, 124.8, 123.4, 123.0, 110.6, 72.5, 31.9, 30.4, 29.6, 29.58, 29.55, 29.3, 26.1, 22.7, 16.4, 14.1. MS (FAB) m/z 506.1 [M^+]. HRMS (MALDI-TOF) Calcd for $C_{26}H_{33}BrOS_2$: 506.1132. Found: 506.1134 [M^+].

4.1.12. 1-Decyloxy-2,6-dimethyl-4-terthienylbenzene M-OT(3). The coupling procedure described in the paper was followed using **M-OT(2)-Br** (0.47 g, 0.93 mmol), 2-bromothiophene (0.76 g, 4.7 mmol), Mg (0.13 g, 5.6 mmol), and $PdCl_2$(dppf) (11 mg, 0.15 mmol %) affording a yellow solid (0.4 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.25 (s, 2H), 7.21 (dd, J=5.2, 1.2 Hz, 1H), 7.17 (dd, J=3.6, 1.2 Hz, 1H), 7.12 (dd, J=6.4, 4 Hz, 2H), 7.08 (dd, J=5.2, 3.6 Hz, 2H), 7.02 (dd, J=4.8, 3.6 Hz, 1H), 3.77 (t, J=6.4 Hz, 2H), 2.31 (s, 6H), 1.85–1.78 (m, 2H), 1.54–1.49 (m, 2H), 1.34–1.28 (m, 12H), 0.89 (t, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 156.1, 143.4, 137.2, 136.4, 135.9, 135.7, 131.6, 129.3, 127.9, 126.1, 124.47, 124.43, 124.4, 123.9, 123.6, 123.1, 72.6, 31.9, 30.4, 29.6, 29.57, 29.56, 29.3, 26.1, 22.7, 16.4, 14.1. MS (FAB) m/z 508.3 [M^+]. HRMS (MALDI-TOF) Calcd for $C_{30}H_{36}OS_3$: 508.1928. Found: 508.1926.

4.1.13. 1-Decyloxy-2,6-dimethyl-4-(5″-bromoterthienyl)-benzene M-OT(3)-Br. The bromination procedure described in the paper was followed using **M-OT(3)** (0.3 g, 0.6 mmol) and NBS (0.11 g, 0.6 mmol) affording a yellow solid (0.34 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.24 (s, 2H), 7.11 (dd, J=6.8, 4 Hz, 2H), 7.05 (d, J=3.6 Hz, 1H), 7.0 (d, J=4 Hz, 1H), 6.97 (d, J=3.6 Hz, 1H), 6.90 (d, J=3.6 Hz, 1H), 3.77 (t, J=6.8 Hz, 2H), 2.30 (s, 6H), 1.84–1.77 (m, 2H), 1.52–1.48 (m, 2H), 1.35–1.28 (m, 12H), 0.89 (t, J=6.8 Hz, 3H). ^{13}C NMR (66 MHz, $CDCl_3$, δ) 155.9, 143.4, 138.5, 136.8, 135.2, 134.6, 131.4, 130.5, 129.1, 125.9, 124.5, 124.4, 123.7, 123.4, 123.0, 110.8, 72.5, 32.0, 30.5, 29.70, 29.67, 29.63, 29.40, 26.2, 22.8, 16.5, 14.2. MS (FAB) m/z 588.2 [M^+]. HRMS (MALDI-TOF) Calcd for $C_{30}H_{35}BrOS_3$: 588.1009. Found: 588.1005 [M^+].

4.1.14. 1-Decyloxy-2,6-dimethyl-4-quaterthienylbenzene M-OT(4). The coupling procedure described in the paper was followed using **M-OT(3)-Br** (0.4 g, 0.68 mmol), 2-bromothiophene (0.55 g, 3.37 mmol), Mg (0.1 g, 4.2 mmol), and $PdCl_2$(dppf) (11 mg, 2 mmol %) affording a yellow solid (0.34 g, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.25 (s, 2H), 7.22 (d, J=5.2 Hz, 1H), 7.18 (d, J=3.6 Hz, 1H), 7.12, (dd, J=6.0, 3.6 Hz, 2H), 7.08 (dd, J=5.2, 4 Hz, 2H), 7.02 (dd, J=4.8, 3.6 Hz, 1H), 3.77 (t, J=6.4 Hz, 2H), 2.37 (s, 6H), 1.83–1.79 (m, 2H), 1.52–1.48 (m, 2H), 1.34–1.28 (m, 12H), 0.89 (t, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 156.1, 143.5, 137.1, 136.6, 136.3, 135.9, 135.6, 131.6, 129.3, 127.9, 126.1, 124.5, 124.4, 124.3, 124.2, 123.9, 123.7, 123.2, 72.5, 31.9, 30.4, 29.6, 29.59, 29.56, 29.3, 26.2, 22.7, 16.4, 14.1. MS (FAB) m/z 590.3 [M^+]. HRMS (MALDI-TOF) Calcd for $C_{34}H_{38}OS_4$: 590.1805. Found: 590.1829.

Acknowledgements

This work was supported by Earmarked Research Grant (HKBU2019/02P) from Research Grants Council, Hong

Kong. We gratefully acknowledge Dr. K.K. Shiu for his advice on the electrochemical measurements.

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Tetrahedron 62 (2006) 7854–7865

Shaping the cavity of calixarene architecture for molecular recognition: synthesis and conformational properties of new azocalix[4]arenes

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Received 28 January 2006; revised 27 April 2006; accepted 18 May 2006
Available online 21 June 2006

Abstract—A series of new azocalix[4]arenes containing one, two, three, and four free phenolic groups have been synthesized through the reaction of 4-nitro- and 2,4-dinitrophenylhydrazines with flexible calix[4]arene diquinones as well as through diazocoupling reactions of calix[4]arenes. Characterization of synthesized compounds by spectroscopic methods and X-ray diffraction revealed that azocalix[4]arenes adopt a cone conformation if they contain at least one free phenolic group. Partial cone or 1,3-alternate conformers of azocalix[4]arenes result only when they are devoid of free phenolic groups. The results can be utilized to shape calix[4]arene architecture for ionic and molecular recognition.

1. Introduction

Calix[*n*]arenes (*n*=4–20) are phenolic $[1]_n$-metacyclophanes,[1] which can be synthesized through acid or base catalyzed condensation of *p*-substituted phenols and formaldehyde. They possess easily functionalizable hydrophobic upper rim and hydrophilic lower rim to encompass a hollow cavity, the dimensions of which depend upon their conformation and appended functional groups.[2] The observed diversity of calix[*n*]arenes essentially lies in their conformational isomerism due to rotation of Ar–CH_2–Ar bonds or molecular rotation through the annulus.[3] Different stable conformers of calix[4]arenes have different capabilities for ionic and molecular recognition.[4]

Though X-ray structure analysis is the final diagnosis for the determination of conformation of calix[*n*]arenes, it has now been established that ^{1}H NMR and ^{13}C NMR spectral analysis can be effectively employed for conformational analysis. For instance, when the phenolic units around each methylene unit are in a *syn* orientation, the methylene carbon appears around δ 31 when phenolic units are in an *anti* orientation with respect to each other, the methylene carbon appears around δ 37[5] in the ^{13}C NMR spectrum of calix[4]arenes.

Introduction of azo groups into the calix[*n*]arene framework confers chromogenicity to their molecular architecture, which can be utilized for development of specific molecular diagnostics and sensor materials.

A number of azocalix[*n*]arenes have recently been examined for metal ion recognition.[6] Apparently, azocalix[4]arenes devoid of the possibility of intramolecular hydrogen bonding have not been examined to a great extent, as deprotonation of phenolic hydroxyls to elicit shift in the UV–vis spectra as an analytical signal (Fig. 1)[7] is not possible in such cases. Mere involvement of intramolecular hydrogen bonding to explain the observed role of hydrophobic cavity and its size and shape in molecular and ionic recognition needs to be explored further.[8] In order to understand the recognition characteristics of azocalix[*n*]arenes better, one is required to develop rational methods for obtaining cone, partial cone or alternate conformations of chromogenic calixarenes to examine their differential host–guest interaction to arrive at conclusions, which may define the role of weak interaction in the ionic recognition by azocalix[4]arenes. In this paper, we report our exploration in the role of hydrogen bonding in shaping the cavity of azocalixarenes and methods to achieve their different conformers. The choice of pyridylazo- and nitrophenylazo- groups as chromogens was motivated by the assumption that these functions when present in cone, partial cone, and 1,3-alternate conformations would allow better sensing capability for cations and neutral organic guests even in the absence of free phenolic hydroxyls. Assignment of the conformational structure of synthesized azocalix[4]arenes has been inferred from examination of their NMR splitting patterns and structure determination through single crystal X-ray diffraction.

Keywords: Calix[*n*]arenes; Diazotization; Conformation; Hydrogen bond.
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doi:10.1016/j.tet.2006.05.040

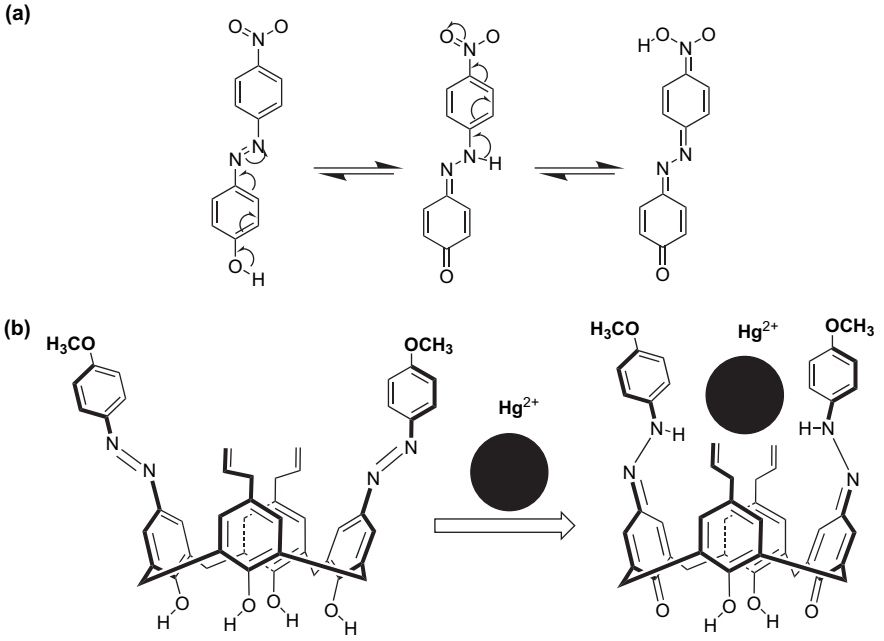


Figure 1. (a) Suggested mechanism of conversion of azo phenol moiety to quinoidal form; (b) an example of ionic recognition through azo quinoidal form.

2. Results and discussion

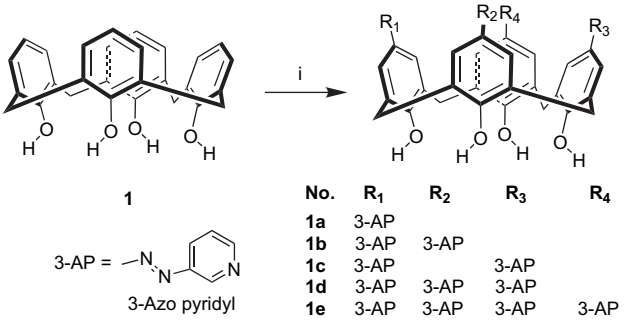
2.1. Results and characterization of the products

Calix[*n*]arenes bearing *p*-nitrophenylazo- and pyridylazo-chromogens containing one, two, three or four free phenolic groups in calix[4]arenes were synthesized either through the diazocoupling reaction of corresponding diazotized amines with calix[4]arene derivatives or through the reaction of nitrosubstituted phenyl hydrazines with calix[4]arene diquinones. Some of the derivatives were afforded through acylation or benzoylation of calix[4]arene derivatives. The choice of calix[4]arene diquinones as the starting materials for affording some of the derivatives was based upon their conformational flexibility and possible availability of partial cone conformation. Reaction conditions described in the Section 4 allowed the isolation of compounds, which were identified by examination of their ^{1}H and ^{13}C NMR and FAB mass spectra, NOESY experiments and X-ray diffraction analysis (for **3b** and **12a**).

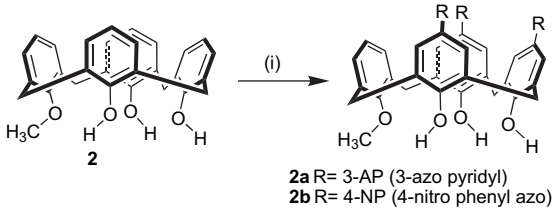
Azocalix[4]arene containing four free phenolic groups (**1a**–**e**) were synthesized by the diazonium coupling reaction of diazotized aromatic amines and calix[4]arene (**1**) by employing the method reported earlier[9] (Scheme 1). The identity of purified products was confirmed by comparison with authentic samples and analysis of their spectral data (IR, NMR).

Azocalix[4]arenes containing three free phenolic groups (**2a**, **2b**) were obtained by the diazonium coupling reaction of pyridyl or 4-nitrophenyl diazonium chloride and monomethoxy-calix[4]arene at 0–5 °C in DMF/methanol (8:5) in the presence of sodium acetate (pH 7–9) (Scheme 2). The products were isolated as red powders, which were characterized as **2a** and **2b** by spectral measurements.

The synthesis of azocalix[4]arenes containing two free phenolic groups (**3a**–**6a**, Scheme 3) was achieved in moderate



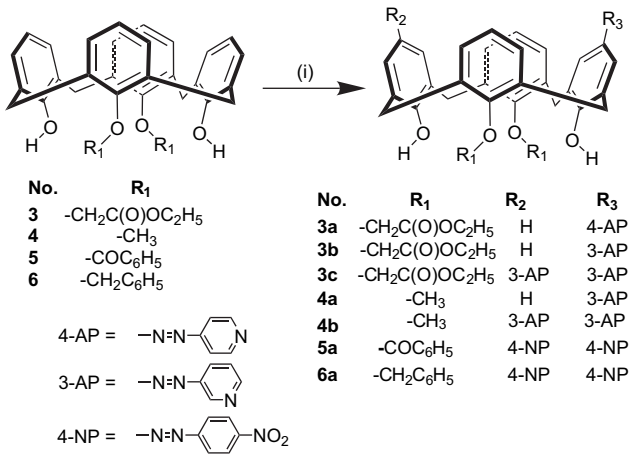
Scheme 1. Synthesis of azocalix[4]arenes with four free phenolic groups. Reagents and conditions (i) diazonium salt obtained from 3-aminopyridine, DMF/MeOH, CH_3COONa, 0–5 °C, 3 h.



Scheme 2. Synthesis of azocalix[4]arenes with three free phenolic groups. Reagents and conditions (i) diazonium salt obtained from respective amine, DMF/MeOH, CH_3COONa, 0–5 °C, 3 h.

yields (21–56%) by reacting dialkylated calix[4]arenes at 0–5 °C with 3 equiv of diazonium salt obtained from the corresponding amine in DMF/methanol (8:5) in the presence of sodium acetate as a base for adjustment of pH of the reaction (pH 7–9).

^{13}C NMR spectra of the synthesized derivatives revealed that their methylene carbon appears at δ 31.0 indicating that the synthesized compounds were in their cone conformation in accordance with the earlier findings on conformational assignment in calix[4]arenes.[5] It was interesting to note that



Scheme 3. Synthesis of dialkyl azocalix[4]arenes with two free phenolic groups. Reagents and conditions (i) diazonium salt obtained from respective amine, DMF/MeOH, CH_3COONa, 0–5 °C, 3 hr.

the diester derivative **3a** and **3b** displayed a quartet or a pair of doublet for the –OCH_2CO– protons at δ 4.71 and 4.75, respectively, in their ^1H NMR spectra as against the expected singlet for these protons (Supplementary data, 1). This is perhaps due to molecular dissymmetry, which then induces a diastereomeric relationship. This conclusion was confirmed by recording the single crystal X-ray (discussed later) and NOESY spectrum[10] of **3b** (Fig. 2b), which revealed the presence of cross peaks for these protons as indicated by arrows in Figure 2a.

A non-diazocoupling route was also used to synthesize azocalix[4]arene derivatives containing two free phenolic groups. Accordingly, dibenzoylated and dibenzylated calix[4]arene diquinones (**7**, **8**) were prepared by oxidation of dibenzoylated and dibenzylated calix[4]arenes (**5**, **6**) with ClO_2, which were treated with 4-nitro- and 2,4-dinitrophenylhydrazine in $CHCl_3$/EtOH mixture in the presence of H_2SO_4 to give bis(nitrophenylazophenol) derivatives in 78–84% yields. These derivatives were characterized as **5a**, **6a**, **7a**, and **8a** by spectral measurements as given in the Section 4 (Scheme 4).

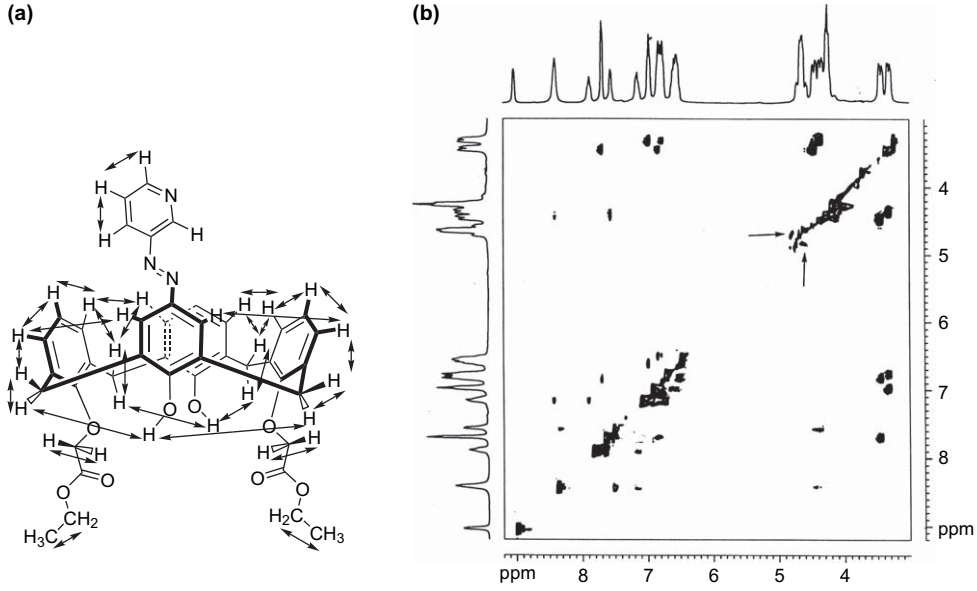
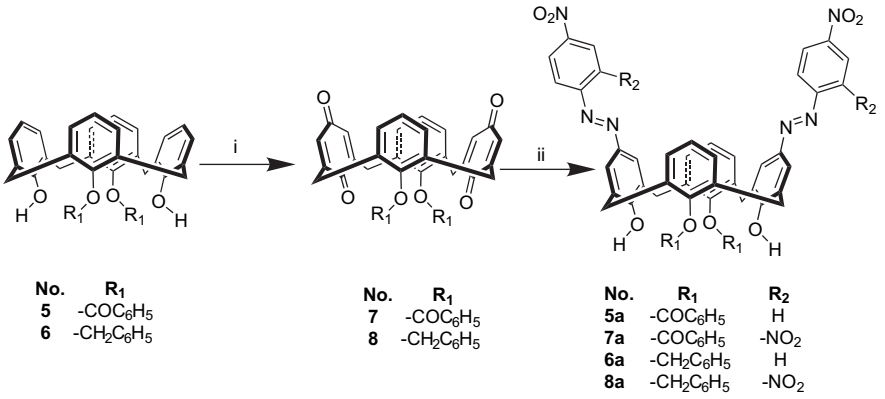


Figure 2. (a) Molecular structure of **3b** and observed correlations in its NOESY spectrum; (b) correlation of aromatic and methylene protons in the NOESY spectrum of **3b** in $CDCl_3$ at 25 °C and 300 MHz.



Scheme 4. Synthesis of dialkyl azocalix[4]arenes with two free phenolic groups via a diquinone route. Reagents and conditions (i) ClO_2, room temperature; (ii) chloroform/ethanol, nitrosubstituted phenyl hydrazines, concn H_2SO_4, 4 h, room temperature.

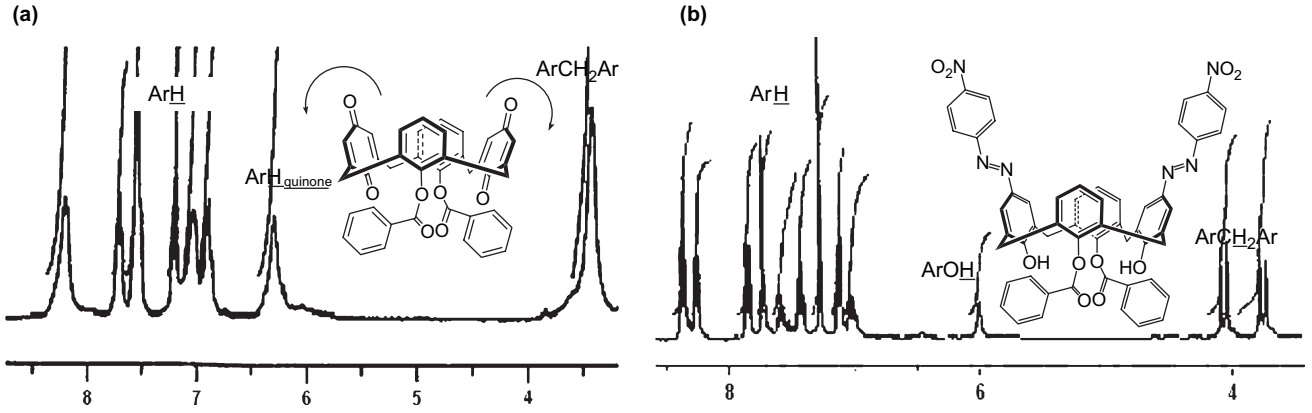
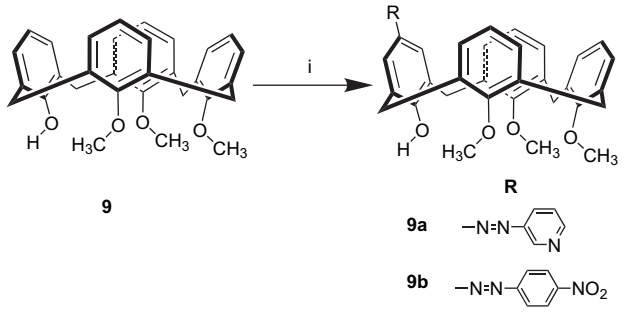


Figure 3. (a) Molecular structure and ^{1}H NMR spectra of dibenzoylcalix[4]diquinone **7**; (b) molecular structure and ^{1}H NMR spectra of 5,17-bis(4′-nitrophenylazo)-25,27-di(benzyloxy)-26,28-dihydroxycalix[4]arene **5a**.

The synthesized dibenzoylcalix[4]arene diquinones exhibited characteristic methylene bridge protons as a broad singlet in their ^{1}H NMR spectrum to reveal their flexible conformational constitution. On conversion into *p*-nitrophenylazocalix[4]arene dibenzoyl derivative, the broad singlet for methylene bridge protons got split into a pair of doublet for azocalix[4]arenes (**6a**, **7a**, and **8a**) indicating that they were present in their cone conformations (Fig. 3).

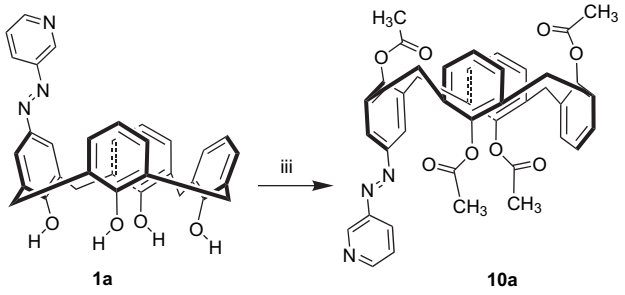
Trimethylated-calix[4]arenes **9** (i.e., containing only one free phenolic group) when reacted with 3 equiv of corresponding diazonium chlorides at 0–5 °C in DMF/methanol (8:5) using sodium acetate (pH 7–9) as a base gave **9a**,**b**.

Examination of the ^{1}H NMR and ^{13}C NMR spectra of tri-*O*-substituted azocalix[4]arenes having only one hydroxyl group (Scheme 5, **9a**, **9b**) indicated that they were also present in their cone conformation albeit the cone conformation was flattened and deviated from its perfect cone structure as revealed by X-ray diffraction analysis.[11]



Scheme 5. Synthesis of azocalix[4]arenes with one free phenolic group. Reagents and conditions (i) diazonium salt obtained from respective amine, DMF/MeOH, CH_3COONa, 0–5 °C, 3 h.

2.1.1. Acylation and benzoylation of azocalix[4]arenes: conformational outcome. When **1a** was reacted with acetic anhydride and pyridine in dichloromethane at room temperature, it gave **10a** as a major product (Scheme 6), which exhibited a singlet and a pair of doublet (1:1) for methylene protons in its ^{1}H NMR spectrum suggesting it to have a partial cone or 1,3-alternate conformation. This dichotomy of ^{1}H NMR spectral interpretation was resolved by the ^{13}C NMR spectrum (DEPT-135) in which methylene carbons appeared at δ 37.5 and 37.4 to reveal its 1,3-alternate conformation. Since no signal was observed at around δ 30, the possibility of a partial cone conformation was not considered on the basis of literature precedents.[5]

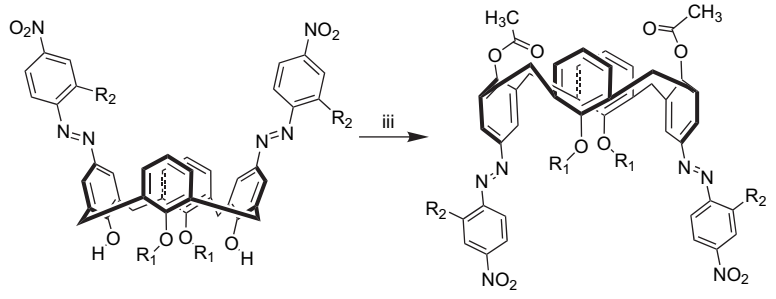


Scheme 6. Synthesis of tetra-alkyl azocalix[4]arenes with one azo substituent. Reagents and conditions (iii) acetic anhydride, dichloromethane/pyridine (10:1), room temperature, 24 h.

When azocalix[4]arenes with two free phenolic groups present in the cone conformation (**5a**–**8a**) were subjected to acetylation in the presence of acetic anhydride and pyridine in dichloromethane at room temperature, they gave **11a**–**12b** in 67–75% yield (Scheme 7), which exhibited a pair of doublet in the ^{1}H NMR spectrum (Supplementary data, 2). The methylene carbons in **11a** and **12a** appeared at δ 37.2 and δ 37.4, respectively, in their ^{13}C NMR spectrum could be attributed to 1,3-alternate conformations that were confirmed by X-ray crystallographic analysis of **12a** (discussed later).

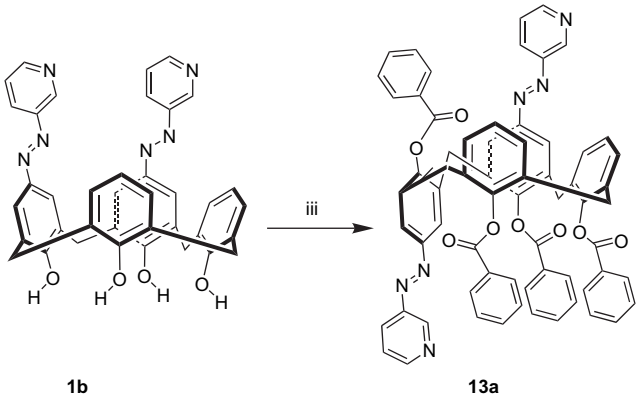
Room temperature benzoylation of **1b** with benzoyl chloride and pyridine in dichloromethane yielded **13a** (Scheme 8) in which methylene protons appeared as a multiplet in its ^{1}H NMR spectrum. The exact conformation for **13a** therefore was difficult to infer from its ^{1}H NMR spectrum, but methylene carbons in its ^{13}C NMR spectrum appeared as four signals at δ 37.8, 36.9, 30.2, 29.6 (Supplementary data, 3), which were possible only if azocalix[4]arenes (**13a**) had a partial cone conformation.

Similarly, room temperature acylation of **2a**,**b** with acetic anhydride and pyridine in dichloromethane yielded **14a**,**b** (Scheme 9). The synthesized derivatives exhibited multiplets for methylene protons in their ^{1}H NMR spectrum, which made it difficult to infer exact information about the conformation. However, ^{13}C NMR spectrum (DEPT-135)



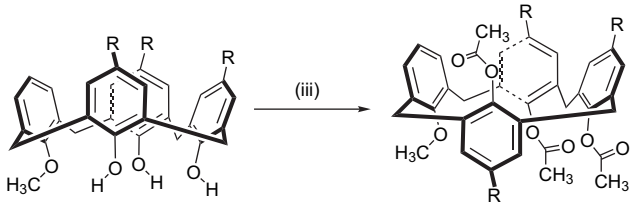
No.	R_1	R_2
11a	$-COC_6H_5$	H
11b	$-CH_2C_6H_5$	H
12a	$-COC_6H_5$	$-NO_2$
12b	$-CH_2C_6H_5$	$-NO_2$

Scheme 7. Synthesis of tetra-alkyl azocalix[4]arenes with two distal azo substituents. Reagents and conditions (iii) acetic anhydride, dichloromethane/pyridine (10:1), room temperature, 24 h.



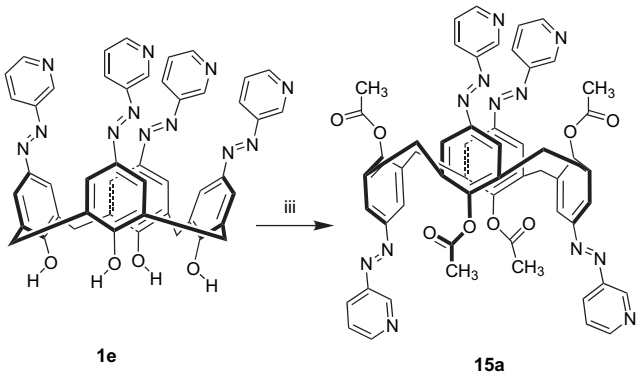
Scheme 8. Synthesis of tetra-alkyl azocalix[4]arenes with two proximal azo substituent. Reagents and conditions (iii) benzoyl chloride, dichloromethane/pyridine (10:1), room temperature, 24 h.

of **14a** revealed the presence of four signals at δ 38.4, 37.8, 31.7, 30.4 for methylene carbons and three signals at δ 21.2, 20.6, 20.2 for –CO*C*H$_3$ carbon suggesting the formation of a partial cone conformer with one azophenol moiety near the anisole unit in the *anti* disposition.



Scheme 9. Synthesis of tetra-alkyl azocalix[4]arenes without free phenolic groups. Reagents and conditions (iii) acetic anhydride, dichloromethane/pyridine (10:1), room temperature, 24 h.

Acetylation of **1e** in the presence of acetic anhydride and pyridine at room temperature resulted in **15a** (Scheme 10), which exhibited a singlet for methylene bridge protons in its ^{1}H NMR spectrum and methylene carbon at δ 38.2 in its ^{13}C NMR spectrum to suggest that it is present in the 1,3-alternate conformation.



Scheme 10. Synthesis of tetra-alkyl azocalix[4]arenes without free phenolic groups. Reagents and conditions (iii) acetic anhydride, dichloromethane/pyridine (10:1), room temperature, 24 h.

A summary of the splitting patterns observed in the ^{1}H NMR spectra, chemical shift values of methylene carbons in their ^{13}C NMR spectra, and the assigned conformation of the synthesized new azocalix[4]arene analogs is given in Table 1.

2.2. X-ray crystallographic analysis

2.2.1. X-ray crystallographic analysis of 3b. An ORTEP diagram of **3b** is shown in Figure 4a. It appears that **3b** crystallizes with chloroform. The torsion angles φ and χ around Ar—CH_2—Ar bonds about C7, C14, C21, and C28 show a −+, −+, −+, −+ pattern, which is consistent with the cone conformation.[12] The inter planer angles between ring A (C1—C6) and its distally positioned ring C (C15—C20) is 34.36° while the inter planer angle between ring B (C8—C13) and D (C22—C27) is 75.90°. This suggests that rings A and C are almost parallel while rings B and D are almost perpendicular to each other. The azopyridyl group has been found to be disordered. The corresponding hydroxyl substituents O1, O2, O3, and O4 are directed inwards the cavity of the calixarene architecture. Both the O2–C33–C34–O7 and O4–C29–C30–O5 are cis thereby

Table 1. Conformational assignment of synthesized azocalix[*n*]arenes. ^{1}H NMR splitting pattern for methylene protons and ^{13}C NMR data for methylene carbons (δ, 300 MHz, 25 °C) in different azocalix[4]arenes

No	^{1}H NMR splitting pattern of methylene protons (ratio of protons)	^{13}C NMR values for methylene carbons	Conformation
2a	Two pair of doublet (1:1:1:1)	31.2, 33.3	Cone
2b	Two pair of doublet (1:1:1:1)	—	Cone
3a	Two pair of doublet (1:1:1:1)	31.3, 29.6	Cone
3b	Two pair of doublet (1:1:1:1)	31.3, 29.6	Cone
3c	One pair of doublet (1:1)	31.4	Cone
4a	One triplet and one pair of doublet (2:1:1)	31.0, 29.5	Cone
4b	One pair of doublet (1:1)	31.1	Cone
5a	One pair of doublet (1:1)	32.9	Cone
6a	One pair of doublet (1:1)	—	Cone
7a	One pair of doublet (1:1)	—	Cone
8a	One pair of doublet (1:1)	—	Cone
9b	Two pair of doublet (1:1:1:1)	—	Cone
10a	One singlet and one pair of doublet (1:1)	38.7, 37.5	1,3-Alternate
11a	One pair of doublet	37.2	1,3-Alternate
11b	One pair of doublet	—	1,3-Alternate
12a	One pair of doublet	37.4	1,3-Alternate
12b	One pair of doublet	—	1,3-Alternate
13a	Multiplet	37.8, 36.9, 30.2, 29.6	Partial cone
14a	Multiplet	38.4, 37.8, 31.7, 30.4	Partial cone
14b	Multiplet	—	Partial cone
15a	One singlet	38.2	1,3-Alternate

making both the carbonyl groups *endo* with respect to the calix cavity.

A significant intramolecular hydrogen bonding has been observed amongst hydroxyl groups and proximal oxygens (O1–H1—O2=1.939 Å, O3–H3—O4=1.970 Å). There is a prominent C–H$\cdots\pi$ interaction among C10–H10$\cdots$ring A (with H$\cdots\pi$ distance 3.395 Å) that brings two phenyl rings much closer thereby resulting in the formation of a dimer. A prominent intermolecular interaction exists between the pyridyl ring and hydrogen of the ester chain to result in a dimeric columnar packing (Fig. 4b). These dimeric columns run parallel and are associated with each other through weak intermolecular hydrogen bonds (C36–H36B$\cdots$N2X–= 2.650 Å) and C–H$\cdots\pi$ interaction among C35–H35A$\cdots$ring A (with H$\cdots\pi$ distance 3.016 Å). The molecular packing of **3b** along the axis *a* is shown in Figure 4b.

2.2.2. X-ray crystallographic analysis of 12a. An ORTEP diagram for **12a** is shown in Figure 5a. Torsion angles φ and χ around Ar—CH_2—Ar bonds about C7, C14, C21, and C28 showing ++, −−, ++, −− are consistent with 1,3-alternate conformation.[13] The inter planar angles between rings A (C1—C6) and its distally positioned ring C (C15—C20) is 25.04° while between ring B (C8—C13) and D (C22—C27) is 20.76°, which suggest that these are almost parallel to each other. Phenyl rings of the benzoyl group are perpendicular to the respective calixaryl aromatic ring plane. The oxygen of the carbonyl group remains *exo* to the cavity. The dihedral angle between the phenylazo group plane (C29–C34) and ring A (C1–C6) is 7.41°, which corroborates that one phenylazo ring is parallel and the other phenylazo ring (C42–C47) is perpendicular to ring C (C15—C20) showing a dihedral angle 70.01° with the nitro group (*ortho* to azo), which remains outward of the calixarene cavity. There are prominent intramolecular C–H$\cdots\pi$ interactions among C34–H34$\cdots$Phenyl ring (C36–C41) and C47–H47$\cdots$Phenyl ring (C49–C54) with H$\cdots\pi$ distance 3.484 Å and 3.493 Å, respectively. This brings the substituted phenylazo group much closer to the adjacent benzoyl ring (Fig. 5b). The molecular packing of **12a** along the axis *a* is shown in Figure 5c.

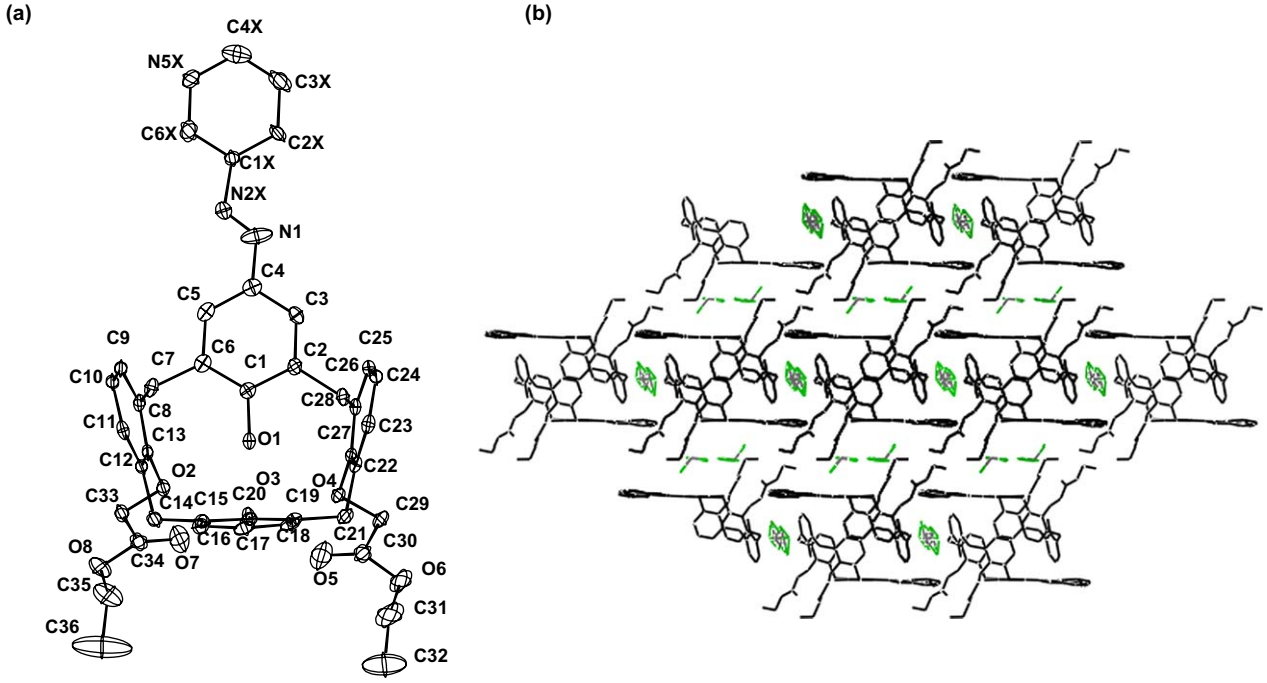


Figure 4. (a) ORTEP diagram of **3b** (hydrogens, solvent molecules, and disordered part have been omitted for clarity); (b) view of the molecular packing along the axis *a*.

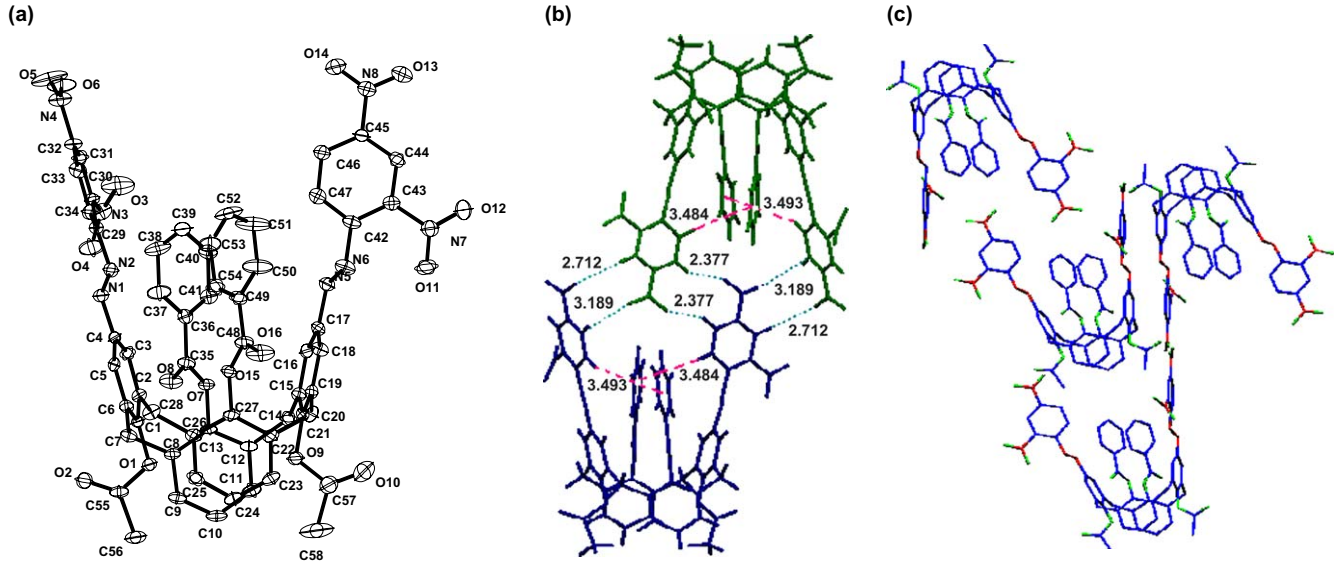


Figure 5. (a) ORTEP diagram showing labeling of atoms in **12a** with 30% probability factor (hydrogen atoms have been omitted for clarity); (b) intermolecular hydrogen bonds and CH–π interactions; (c) view of the molecular packing along the axis *a*.

3. Discussion

The conformational flexibility of calixarene compounds has often been explained by the presence of intramolecular hydrogen bonds, which is directly correlated with the number of free phenolic hydroxyls present in the calix[4]arene. Accordingly, azocalix[4]arenes with four free phenolic groups at the lower rim (**1a**–**e**, Scheme 1) adopt a cone conformation in accordance with the earlier reports.[14] When the number of phenolic groups is decreased, it is apparently expected to exert a profound effect on the conformational outcome. Present investigations however indicate that mono alkyl azocalix[4]-arenes (**2a**–**2d**, Scheme 2) bearing three phenolic hydroxyl groups and the dialkyl azocalix[4]arenes (**3a**–**6a**, Scheme 3) bearing two phenolic hydroxyl groups also exist in their cone conformation.

The use of an alternate route for the synthesis of azocalix[4]-arenes with two free phenolic groups through dialkylcalix[4]arene diquinones, which are known to be present in their cone and partial cone conformations in equilibrium with each other[15] also resulted in azocalix[4]arenes in their cone conformation. This revealed that the route adopted or the conformation of the starting material does not have any bearing on the conformational outcome of the azocalix[4]arenes.

Examination of spectral characteristics of tri-*O*-substituted azocalix[4]arenes possessing one free phenolic group (**9a**,**b**, Scheme 5) indicate that they were also present in their flattened cone conformation as revealed by their single crystal X-ray diffraction analysis.[11] The flattened cone conformation probably results because these compounds are conformationally flexible due to loss of stabilization owing to decreased strength of intramolecular hydrogen bonding. Nonetheless, it is important to note that even when only one phenolic hydroxyl is present, synthesized azocalix[4]arene is present in the cone conformation.

When free phenolic groups at the lower rim in azocalix-arenes are completely absent, the diazo coupled product may lead to the 1,3-alternate or partial cone conformer. It has been determined that in such cases the 1,3-alternate conformation predominates particularly when the number of azo substituents is one (Scheme 2) or when they are symmetrically positioned at the upper rim (Schemes 7 and 10). However, it seems that in the event, when free phenolic groups at the lower rim were absent and when they possess more than two unsymmetrically positioned azo substituents (Schemes 8 and 9) at the upper rim, a partial cone conformation has been found to be the major conformer.

In conclusion, we report that one can obtain the cone conformation of azocalix[4]arenes if at least one free phenolic groups present at their lower rim. 1,3-alternate and partial cone conformations are only obtained when free phenolic groups are absent. The conformational outcome in azocalix[4]arenes is also dictated by the symmetric disposition of azo substituent at the upper rim.

4. Experimental

4.1. General

All the reagents used in the study were purchased from Sigma–Aldrich or Merck and were chemically pure. The solvents used were distilled (for diazotization reaction) and dried (for acetylation or benzoylation reaction). Column chromatography was performed on silica gel (60–120 mesh) obtained from Merck. ^{1}H NMR, ^{13}C NMR, DEPT-135, and NOESY spectra were recorded on a 300 MHz Bruker DPX 300 instrument at room temperature using tetramethylsilane (TMS) at 0.00 as an internal standard. IR spectra were recorded on a Nicolet Protégé 460 spectrometer in KBr disks while X-ray data was recorded using a Bruker SMART CCD single crystal diffractometer. UV–vis spectra were

obtained on a Perkin–Elmer (Lambda-3B) recording spectrophotometer. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 Mass spectrometer/Data System using argon/xenon (6 kV, 10 mA) as the FAB gas. Melting points were determined on an electrothermal Toshniwal melting point apparatus and were uncorrected.

4.2. General procedure for the synthesis

p-tert-Butylcalix[4]arene and calix[4]arene were synthesized by the method described by Gutsche.[16] Compound **1–10** were synthesized as described in the literature[17] while **1a–e** and **9a** were previously synthesized by our group.[9,11]

4.2.1. Synthesis of azocalix[*n*]arenes through the diazotization reaction (compounds 1a–e, 2a–b, 3a–c, 4a,b, 5a, 6a, 9a, 9b). The pyridyl diazonium chloride solutions were prepared by the addition of an aqueous solution of sodium nitrite (2 equiv of amine) into solution of respective amines in concn HCl (10–20 equiv) and distilled water (5–10 ml) at 0–5 °C. The diazotized solution was slowly added (in standardized 1.5 molar ratio with respect to each free phenolic group in the corresponding calix[*n*]arenes) into an ice-cold (0–5 °C) solution of corresponding calix[*n*]arenes (*n*=4) in DMF/methanol (8:5), sodium acetate (pH 7–9) with constant stirring to give yellow to dark red suspension. The reaction mixture was stirred for 3 h at 0–5 °C and then for 30 min at room temperature. The suspension was poured into water, acidified with concn HCl to give a yellow to dark red precipitate, which was filtered to give a product or a mixture of products. The mixture of products was then separated by column chromatography (silica gel) to give substituted azocalix[*n*]arene derivatives.

4.2.2. Synthesis of azocalix[*n*]arenes through the reaction between quinones and hydrazines (compounds 5a, 6a, 7a, 8a). To a solution of disubstituted-calix[4]arene diquinones (**7**, **8**) in $CHCl_3$ was added ethanol, nitrosubstituted phenyl hydrazines in presence of concn H_2SO_4. The reaction mixture was stirred for 4 h at room temperature and treated with cold water and extracted with chloroform. The organic phase was separated and dried with sodium sulfate and evaporated in vacuo to give orange powder, which was purified by recrystallization from chloroform/methanol.

4.2.3. Synthesis of substituted azocalix[*n*]arenes through the acetylation or benzylation reaction (compounds 10a, 11a,b, 12a,b, 13a, 14a, 14b, 15a). The synthesized azocalix[4]arenes (**1a**, **1b**, **1e**, **5a**, **6a**, **7a**, **8a**) and acetic anhydride (for acetylation) or benzoyl chloride (for benzoylation) (20 equiv) in dichloromethane/pyridine (10:1) were stirred at room temperature for a period of 24 h. The reaction mixture was poured into cold water, washed with 1 M HCl and water, and evaporated in vacuo to give a yellow solid.

4.2.4. 5,11,17-Tris(3′-pyridylazo)-25-(methoxy)-26,27,28-trihydroxycalix[4]arene, 2a. Afforded as an orange solid. Yield: 90%, mp>200 °C (decomposed). IR (KBr pellet, cm^{-1}): 3416, 1580, 1459, 1423. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): δ 9.12 (s, 2H, Py*H*), 9.00 (s, 1H, Py*H*), 8.60 (s, 2H, Py*H*), 8.52 (s, 1H, Py*H*), 8.06 (d, *J*=6.9 Hz, 2H, Py*H*), 7.96 (d, *J*=6.9 Hz, 1H, Py*H*), 7.81 (s, 4H, Ar*H*), 7.69 (s, 2H, Ar*H*), 7.38 (br s, 3H, Py*H*), 6.86 (br s, 2H, Ar*H*), 6.65 (br s, 1H), 4.52 (d, *J*=11.7 Hz, 2H, ArCH_2Ar), 4.39 (d, *J*=12.6 Hz, 2H, ArCH_2Ar), 3.93 (s, 3H, ArOCH_3), 3.64 (d, *J*=12.6 Hz, 2H, ArCH_2Ar), 3.53 (d, *J*=11.7 Hz, 2H, ArCH_2Ar). ^{13}C NMR (300 MHz, $CDCl_3$): 150.3, 149.7, 148.0, 146.4, 132.0, 130.4, 129.7, 128.9, 126.4, 125.4, 124.5, 123.7, 123.1 (Ar*C*H and Ar*C*), 63.6 (ArO*C*H_3), 33.5, 30.4 (Ar*C*H_2Ar). FABMS *m/z*: 754 (M^+). Anal. Calcd for $C_{44}H_{35}N_9O_4$: C, 70.11; H, 4.68; N, 16.72. Found: C, 70.35; H, 4.70; N, 16.65.

4.2.5. 5,11,17-Tris(4′-nitrophenylazo)-25-(methoxy)-26,27,28-trihydroxycalix[4]arene, 2b. Afforded as a red solid. Yield: 94%, mp>200 °C (decomposed). IR (KBr pellet, cm^{-1}): 3423, 1593, 1519, 1467, 1341. ^1H NMR (300 MHz, $CDCl_3$): δ 8.35 (d, *J*=8.7 Hz, 4H, NO_2–Ar*H*), 8.22 (d, *J*=8.4 Hz, 2H, NO_2–Ar*H*), 7.96 (d, *J*=8.7 Hz, 4H, NO_2–Ar*H*), 7.90 (d, *J*=8.4 Hz, 2H, NO_2–Ar*H*), 7.86 (s, 2H, Ar*H*), 7.85 (s, 2H, Ar*H*), 7.82 (s, 2H, Ar*H*), 7.14 (d, *J*=6.9 Hz, 2H, ArH_{meta}), 6.91 (t, *J*=6.9 Hz, 1H, ArH_{para}), 4.47 (t, *J*=13.5 Hz, 4H, ArCH_2Ar), 4.15 (s, 3H, ArOCH_3), 3.77 (d, *J*=13.5 Hz, 2H, ArCH_2Ar), 3.67 (d, *J*=13.2 Hz, 2H, ArCH_2Ar). FABMS *m/z*: 886 (M^+). Anal. Calcd for $C_{47}H_{35}N_9O_{10}$: C, 63.73; H, 3.98; N, 14.23. Found: C, 63.58; H, 4.00; N, 14.17.

4.2.6. 5-(4′-Pyridylazo)-25,27-di(ethoxycarbonyl methoxy)-26,28-dihydroxycalix[4]arene, 3a. Purified by column chromatography using hexane/ethyl acetate (7:3) as the eluent, orange solid. Yield: 10%, mp>230 °C (decomposed). IR (KBr pellet, cm^{-1}): 3262, 1750, 1652, 1584, 1464. ^1H NMR (300 MHz, $CDCl_3$): δ 8.72 (br s, 2H, Py*H*), 8.56 (br s, 1H, D_2O exchangeable, ArO*H*), 7.71 (s, 2H, Ar*H*), 7.62 (br s, 2H, Py*H*), 7.57 (s, 1H, D_2O exchangeable, ArO*H*), 7.00 (d, *J*=7.5 Hz, 2H, ArH_{meta}), 6.92 (d, *J*=7.5 Hz, 2H, ArH_{meta}), 6.89 (d, *J*=7.5 Hz, 2H, ArH_{meta}), 6.73 (t, *J*=7.5 Hz, 2H, ArH_{para}), 6.61 (t, *J*=7.5 Hz, 1H, ArH_{para}), 4.75 (dd, *J*=15.3, 15.9 Hz, 4H, ArOCH_2), 4.50 (d, *J*=13.5 Hz, 2H, ArCH_2Ar), 4.39 (d, *J*=13.2 Hz, 2H, ArCH_2Ar), 4.32 (q, *J*=6.9 Hz, 4H, –OCH_2CH$_3$), 3.48 (d, *J*=13.5 Hz, 2H, ArCH_2Ar), 3.37 (d, *J*=12.9 Hz, 2H, ArCH_2Ar), 1.32 (t, *J*=7.2 Hz, 6H, –OCH$_2$CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 166.5, 157.9, 152.8, 152.2, 151.0, 134.5, 133.2, 129.5, 129.2, 128.8, 128.5, 127.8, 125.7, 124.7, 119.2, 116.1 (Ar*C*H and Ar*C*), 72.4 (ArO*C*H_2), 61.4 (–O*C*H_2CH$_3$), 31.3, 29.6 (Ar*C*H_2Ar), 14.0 (–OCH$_2$*C*H$_3$). ESMS *m/z*: 702.61 (M^++1). Anal. Calcd for $C_{41}H_{39}N_3O_8$: C, 70.17; H, 5.60; N, 5.99. Found: C, 69.99; H, 5.56; N, 5.97. UV (λ_{max}, MeOH): 261, 379 nm.

4.2.7. 5-(3′-Pyridylazo)-25,27-di(ethoxycarbonyl methoxy)-26,28-dihydroxycalix[4]arene, 3b. Purified by column chromatography using hexane/chloroform (6:4) as the eluent, orange solid. Yield: 35%, mp>230 °C (decomposed). IR (KBr pellet, cm^{-1}): 3448, 1754, 1633, 1586, 1471. ^1H NMR (300 MHz, $CDCl_3$): δ 9.04 (s, 1H, Py*H*), 8.43 (br s, 2H, 1H–D_2O exchangeable, Py*H* and ArO*H*), 7.90 (d, *J*=7.2 Hz, 1H, Py*H*), 7.69 (s, 2H, Ar*H*), 7.56 (s, 1H, D_2O exchangeable, ArO*H*), 7.17 (dd, *J*=4.5, 3.3 Hz, 1H, Py*H*), 6.99 (d, *J*=6.9 Hz, 2H, ArH_{meta}), 6.84 (d, *J*=7.2 Hz, 2H, ArH_{meta}), 6.79 (d, *J*=7.2 Hz, 2H, ArH_{meta}), 6.59–6.52 (m, 3H, ArH_{para}), 4.71 (dd, *J*=15.0, 15.6 Hz, 4H, ArOCH_2), 4.47 (d, *J*=13.2 Hz, 2H, ArCH_2Ar), 4.38 (d, *J*=12.9 Hz, 2H, ArCH_2Ar), 4.27 (q, *J*=6.9 Hz, 4H, –OCH_2CH$_3$), 3.46

(d, J=13.2 Hz, 2H, ArCH_2Ar), 3.34 (d, J=12.9 Hz, 2H, ArCH_2Ar), 1.28 (t, J=6.9 Hz, 6H, –OCH$_2$CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 168.6, 157.2, 152.8, 152.1, 150.4, 148.1, 146.6, 145.5, 133.0, 132.1, 130.7, 129.4, 129.1, 128.5, 127.8, 126.6, 125.6, 124.1, 123.8, 119.1 (Ar*C*H and Ar*C*), 72.3 (ArOCH$_2$), 61.4 (–OCH$_2$CH$_3$), 31.3, 29.6 (ArCH$_2$Ar), 14.0 (–OCH$_2$CH$_3$). ESMS *m*/*z*: 702.61 (M^++1). Anal. Calcd for $C_{41}H_{39}N_3O_8$: C, 70.17; H, 5.60; N, 5.99. Found: C, 70.01; H, 5.57; N, 5.94. UV (λ_{max}, MeOH): 263, 372 nm.

4.2.8. 5,17-Bis(3′-pyridylazo)-25,27-di(ethoxycarbonyl methoxy)-26,28-dihydroxycalix[4]arene, 3c. Purified by column chromatography using $CHCl_3$/MeOH (9.9:0.1) as the eluent, red solid. Yield: 25%, mp>230 °C (decomposed). IR (KBr pellet, cm^{-1}): 3374, 1730, 1601, 1466. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.06 (s, 2H, Py*H*), 8.56 (br s, 2H, Py*H*), 8.39 (br s, 2H, D_2O exchangeable, ArO*H*), 8.01 (d, J=6.9 Hz, 2H, Py*H*), 7.70 (s, 4H, Ar*H*), 7.33 (dd, J=4.5, 3.3 Hz, 2H, Py*H*), 6.97 (d, J=6.9 Hz, 4H, ArH_{meta}), 6.76 (t, J=7.2 Hz, 2H, ArH_{para}), 4.69 (s, 4H, ArOCH_2), 4.47 (d, J=12.9 Hz, 4H, ArCH_2Ar), 4.31 (q, J=6.9 Hz, 4H, –OCH_2CH$_3$), 3.51 (d, J=12.9 Hz, 4H, ArCH_2Ar), 1.33 (t, J=6.6 Hz, 6H, –OCH$_2$CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 168.7, 157.2, 152.2, 150.5, 148.2, 146.7, 145.7, 132.4, 129.6, 128.5, 126.7, 125.9, 124.2, 123.8 (ArCH and ArC), 72.4 (ArOCH_2), 61.5 (–OCH_2CH$_3$), 31.4 (ArCH_2Ar), 14.1 (–OCH$_2$CH_3). FABMS *m*/*z*: 806 (M^+). Anal. Calcd for $C_{46}H_{42}N_6O_8$: C, 68.47; H, 5.25; N, 10.42. Found: C, 68.35; H, 5.20; N, 10.34. UV (λ_{max}, MeOH): 257, 370 nm.

4.2.9. 5-(3′-Pyridylazo)-25,27-dimethoxy-26,28-dihydroxycalix[4]arene, 4a. Purified by column chromatography using $CHCl_3$/MeOH (9.95:0.05) as the eluent, yellow solid. Yield: 40%, mp 180 °C. IR (KBr pellet, cm^{-1}): 3274, 1653, 1590, 1470. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.14 (s, 1H, Py*H*), 8.64 (d, J=3.6 Hz, 1H, Py*H*), 8.51 (br s, 1H, D_2O exchangeable, ArO*H*), 8.09 (d, J=8.1 Hz, 1H, Py*H*), 7.78 (s, 2H, Ar*H*), 7.76 (s, 1H, D_2O exchangeable, ArO*H*), 7.40 (dd, J=4.2, 4.2 Hz, 1H, Py*H*), 7.10 (d, J=7.2 Hz, 2H, ArH_{meta}), 6.95 (d, J=7.2 Hz, 2H, ArH_{meta}), 6.90 (d, J=7.5 Hz, 2H, ArH_{meta}), 6.74–6.70 (m, 3H, ArH_{para}), 4.37 (t, J=12.9 Hz, 4H, ArCH_2Ar), 4.00 (s, 6H, ArOCH_3), 3.57 (d, J=13.2 Hz, 2H, ArCH_2Ar), 3.44 (d, J=13.2 Hz, 2H, ArCH_2Ar). ^{13}C NMR (300 MHz, $CDCl_3$): 157.2, 153.0, 150.4, 148.1, 146.6, 145.5, 132.7, 131.8, 129.3, 129.0, 128.5, 127.7, 126.5, 125.3, 124.1, 123.7, 119.1 (Ar*C*H and Ar*C*), 63.5 (ArOCH_3), 31.0, 29.5 (ArCH_2Ar). FABMS *m*/*z*: 558 (M^+). Anal. Calcd for $C_{35}H_{31}N_3O_4$: C, 75.38; H, 5.60; N, 7.54. Found: C, 75.25; H, 5.58; N, 7.51. UV (λ_{max}, MeOH): 260, 369 nm.

4.2.10. 5,17-Bis(3′-pyridylazo)-25,27-dimethoxy-26,28-dihydroxycalix[4]arene, 4b. Purified by column chromatography using $CHCl_3$/MeOH (9.9:0.1) as the eluent, orange solid. Yield: 22%, mp>230 °C (decomposed). IR (KBr pellet, cm^{-1}): 3382, 1630, 1586, 1473. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.14 (s, 2H, Py*H*), 8.64 (br s, 2H, Py*H*), 8.50 (br s, 2H, D_2O exchangeable, ArO*H*), 8.10 (d, J=7.8 Hz, 2H, Py*H*), 7.79 (s, 4H, Ar*H*), 7.43 (dd, J=4.5, 3.3 Hz, 2H, Py*H*), 7.00 (d, J=7.5 Hz, 4H, ArH_{meta}), 6.80 (t, J=7.2 Hz, 2H, ArH_{para}), 4.37 (d, J=13.2 Hz, 4H, ArCH_2Ar), 4.03 (s, 6H, ArOCH_3), 3.60 (d, J=13.2 Hz, 4H, ArCH_2Ar). ^{13}C NMR (300 MHz, $CDCl_3$): 157.2, 153.1, 150.6, 148.1, 146.7, 145.7, 132.1, 129.4, 128.5, 126.6, 125.5, 124.1, 123.8 (ArCH and ArC), 63.8 (ArOCH_3), 31.1 (ArCH_2Ar). FABMS *m*/*z*: 662 (M^+). Anal. Calcd for $C_{40}H_{34}N_6O_4$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.35; H, 5.14; N, 12.62. UV (λ_{max}, MeOH): 258, 372 nm.

4.2.11. 5,17-Bis(4′-nitrophenylazo)-25,27-dibenzoyloxy-26,28-dihydroxycalix[4]arene, 5a. Obtained as a red solid. Yield: 78%, mp>270 °C (decomposed). IR (KBr pellet, cm^{-1}): 3500, 1729, 1655, 1595, 1518, 1461, 1343, 1262. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (d, J=9 Hz, 4H, NO_2–Ar*H*), 8.25 (d, J=7.5 Hz, 4H, *o*-Ar′*H*), 7.84 (d, J=8.7 Hz, 4H, NO_2–Ar*H*), 7.71 (s, 4H, Ar*H*), 7.60 (m, 4H, *m*-Ar′*H*), 7.44 (t, J=7.8 Hz, 2H, *p*-Ar′*H*), 7.12 (d, J=7.2 Hz, 4H, ArH_{meta}), 7.02 (t, J=7.5 Hz, 2H, ArH_{para}), 5.98 (br s, 2H, D_2O exchangeable, ArO*H*), 4.07 (d, J=14.4 Hz, 4H, ArCH_2Ar), 3.71 (d, J=14.4 Hz, 4H, ArCH_2Ar). ^{13}C NMR (300 MHz, $CDCl_3$): 134.0, 133.8, 132.8, 132.0, 130.5, 130.0, 129.7, 128.9, 128.4, 126.9, 126.1, 125.2, 124.6, 123.0 (Ar*C*H and Ar*C*), 32.9 (Ar*C*H$_2$Ar). FABMS *m*/*z*: 930 (M^+). Anal. Calcd for $C_{54}H_{38}N_6O_{10}$: C, 69.67; H, 4.11; N, 9.03. Found: C, 69.65; H, 4.09; N, 9.01.

4.2.12. 5,17-Bis(4′-nitrophenylazo)-25,27-dibenzyloxy-26,28-dihydroxycalix[4]arene, 6a. Obtained as a red solid. Yield: 78%, mp>240 °C (decomposed). IR (KBr pellet, cm^{-1}): 3378, 1588, 1519, 1463, 1262. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (br s, 2H, D_2O exchangeable, ArO*H*), 8.29 (d, J=8.7 Hz, 4H, NO_2–Ar*H*), 7.89 (d, J=8.7 Hz, 4H, NO_2–Ar*H*), 7.73 (s, 4H, Ar*H*), 7.58 (d, J=5.4 Hz, 4H, *o*-Ar′*H*), 7.35 (m, 6H, *m*-Ar′*H* and *p*-Ar′*H*), 6.94 (d, J=7.5 Hz, 4H, ArH_{meta}), 6.75 (t, J=7.5 Hz, 2H, ArH_{para}), 5.05 (s, 4H, Ar′CH_2), 4.30 (d, J=13.2 Hz, 4H, ArCH_2Ar), 3.42 (d, J=13.2 Hz, 4H, ArCH_2Ar). FABMS *m*/*z*: 902 (M^+). Anal. Calcd for $C_{54}H_{42}N_6O_8$: C, 71.83; H, 4.69; N, 9.31. Found: C, 71.81; H, 4.67; N, 9.29.

4.2.13. 5,17-Bis(2′,4′-dinitrophenylazo)-25,27-dibenzoyloxy-26,28-dihydroxycalix[4]arene, 7a. Obtained as a red solid. Yield: 84%, mp>250 °C (decomposed). IR (KBr pellet, cm^{-1}): 3506, 1732, 1660. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.91 (br s, 2H, D_2O exchangeable, ArO*H*), 8.75 (s, 2H, NO_2–Ar*H*), 8.43 (dd, J=2.1, 2.1 Hz, 4H, NO_2–Ar*H*), 8.23 (d, J=7.2 Hz, 4H, *o*-Ar′*H*), 7.77 (s, 4H, Ar*H*), 7.57 (m, 4H, *m*-Ar′*H*), 7.38 (t, J=8.7 Hz, 2H, *p*-Ar′*H*), 7.04 (d, J=8.2 Hz, 4H, ArH_{meta}), 6.95 (t, J=7.5 Hz, 2H, ArH_{para}), 4.04 (d, J=15.3 Hz, 4H, ArCH_2Ar), 3.73 (d, J=15.3 Hz, 4H, ArCH_2Ar). FABMS *m*/*z*: 1020 (M^+). Anal. Calcd for $C_{54}H_{36}N_8O_{14}$: C, 63.53; H, 3.55; N, 10.98. Found: C, 63.50; H, 3.52; N, 10.96.

4.2.14. 5,17-Bis(2′,4′-dinitrophenylazo)-25,27-dibenzyloxy-26,28-dihydroxycalix[4]arene, 8a. Obtained as a red solid. Yield: 81%, mp>280 °C (decomposed). IR (KBr pellet, cm^{-1}): 3206, 1598, 1531, 1461, 1345. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.93 (br s, 2H, D_2O exchangeable, ArO*H*), 8.76 (s, 2H, NO_2–Ar*H*), 8.50 (dd, J=2.4, 2.4 Hz, 4H, NO_2–Ar*H*), 7.84 (d, J=9 Hz, 4H, *o*-Ar′*H*), 7.78 (s, 4H, Ar*H*), 7.64 (m, 4H, *m*-Ar′*H*), 7.43 (d, J=6.3 Hz, 2H, *p*-Ar′*H*), 7.00 (d, J=7.5 Hz, 4H, ArH_{meta}), 6.86 (t, J=7.2 Hz, 2H, ArH_{para}), 5.12 (s, 4H, Ar′CH_2), 4.35 (d, J=13.2 Hz, 4H, ArCH_2Ar), 3.53 (d, J=13.2 Hz, 4H, ArCH_2Ar).

FABMS *m/z*: 992 (M^+). Anal. Calcd for $C_{54}H_{40}N_8O_{12}$: C, 65.32; H, 4.06; N, 11.29. Found: C, 65.30; H, 4.04; N, 11.26.

4.2.15. 5-(4′-Nitrophenylazo)-25,26,27-trimethoxy-28-hydroxycalix[4]arene, 9b. Obtained as a yellow solid. Yield: 12%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, J=8.7 Hz, 2H, NO_2–ArH), 7.90 (d, J=8.7 Hz, 2H, NO_2–Ar*H*), 7.90 (d, J=8.7 Hz, 2H, NO_2–Ar*H*), 7.73 (s, 2H, Ar*H*), 7.30 (d, J=6.9 Hz, 2H, Ar*H*), 7.11 (d, J=6.9 Hz, 2H, Ar*H*), 6.95–6.39 (m, 7H, Ar*H*), 4.33 (t, J=13.2 Hz, 4H, ArCH_2Ar), 3.90 (s, 3H, OCH_3), 3.79 (s, 6H, OCH_3), 3.45 (d, J=13.8 Hz, 2H, ArCH_2Ar), 3.23 (d, J=13.8 Hz, 2H, ArCH_2Ar). FABMS *m/z*: 616 (M^+). Anal. Calcd for $C_{37}H_{33}N_3O_6$: C, 72.18; H, 5.40; N, 6.83. Found: C, 71.93; H, 5.37; N, 6.76.

4.2.16. 5(3′-Pyridylazo)-25,26,27,28-tetracetyloxy-calix[4]arene, 10a. Obtained as a yellow solid. Yield: 72%, mp>230 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.16 (s, 1H, Py*H*), 8.73 (br s, 1H, Py*H*), 8.32 (d, 1H, J=6.9 Hz, Py*H*), 7.71 (s, 2H, Ar*H*), 7.48 (br m, 1H, Py*H*), 7.10–6.61 (m, 9H, Ar*H*), 3.88 (d, J=14.1 Hz, 2H, ArCH_2Ar), 3.76 (s, 4H, ArCH_2Ar), 3.60 (d, J=14.1 Hz, 2H, ArCH_2Ar), 2.38 (s, 3H, –COCH_3), 1.78 (s, 3H, –COCH_3), 1.68 (s, 6H, –COCH_3). DEPT-135 NMR (300 MHz, $CDCl_3$): 152.4, 147.7, 129.5, 127.3, 126.1, 125.9, 125.2, 124.4, 124.1, 119.6 (Ar*C*H), 37.5, 37.4 (Ar*C*H_2Ar), 21.5, 20.7, 20.6 (–CO*C*H_3). FABMS *m/z*: 698 (M^+). Anal. Calcd for $C_{41}H_{35}N_3O_8$: C, 70.58; H, 5.06; N, 6.02. Found: C, 70.78; H, 5.08; N, 5.98.

4.2.17. 5,17-Bis(4′-nitrophenylazo)-25,27-diacetyloxy-26,28-benzoyloxycalix[4]arene, 11a. Obtained as an orange solid. Yield: 76%, mp>320 °C. IR (KBr pellet, cm^{-1}): 1754, 1731, 1601, 1521, 1458, 1345. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, J=8.4 Hz, 4H, NO_2–Ar*H*), 7.58 (d, J=7.5 Hz, 4H, *o*-Ar′*H*), 7.40 (d, J=8.7 Hz, 4H, NO_2–Ar*H*), 7.28 (s, 4H, Ar*H*), 7.12 (m, 8H, *m*-Ar′*H* and ArH_{meta}), 6.96 (t, J= 7.5 Hz, 4H, *p*-Ar′*H* and ArH_{para}), 3.80 (d, J=15.6 Hz, 4H, ArCH_2Ar), 3.63 (d, J=15.6 Hz, 4H, ArCH_2Ar), 2.00 (s, 6H, –COCH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 148.3, 134.5, 133.3, 132.9, 130.5, 130.2, 128.3, 125.6, 124.9, 124.4, 123.2 (Ar*C*H and Ar*C*), 37.2 (Ar*C*H_2Ar), 21.0 (CO*C*H_3). FABMS *m/z*: 1014 (M^+). Anal. Calcd for $C_{58}H_{42}N_6O_{12}$: C, 68.63; H, 4.17; N, 8.28. Found: C, 68.61; H, 4.13; N, 8.23.

4.2.18. 5,17-Bis(4′-nitrophenylazo)-25,27-diacetyloxy-26,28-benzyloxycalix[4]arene, 11b. Obtained as an orange solid. Yield: 69%, mp 180 °C. IR (KBr pellet, cm^{-1}): 1750, 1589, 1521, 1460, 1341. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (d, J=8.1 Hz, 4H, NO_2–Ar*H*), 7.98 (d, J=8.4 Hz, 4H, NO_2–Ar*H*), 7.78 (s, 4H, Ar*H*), 7.29 (m, 10H, Ar′*H*), 6.87 (m, 6H, Ar*H*), 5.08 (s, 4H, Ar′CH_2), 4.80 (d, J=12 Hz, 4H, ArCH_2Ar), 4.73 (d, J=12 Hz, 4H, ArCH_2Ar), 2.15 (s, 6H, –COCH_3). FABMS *m/z*: 986 (M^+). Anal. Calcd for $C_{58}H_{46}N_6O_{10}$: C, 70.58; H, 4.70; N, 8.51. Found: C, 70.56; H, 4.67; N, 8.50.

4.2.19. 5,17-Bis(2′,4′-dinitrophenylazo)-25,27-diacetyloxy-26,28-benzoyloxycalix[4]arene, 12a. Obtained as an orange solid. Yield: 67%, mp>270 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 2H, NO_2–Ar*H*), 8.36 (dd, J=3, 3 Hz, 4H, NO_2–Ar*H*), 7.52 (s, 4H, Ar*H*), 7.24–6.94 (m, 16H, Ar*H* and Ar′*H*), 3.83 (d, J=15.6 Hz, 4H, ArCH_2Ar), 3.70 (d, J=15.6 Hz, 4H, ArCH_2Ar), 1.94 (s. 6H, –COCH_3). ^{13}C NMR (300 MHz, $CDCl_3$): 148.5, 134.7, 134.1, 133.4, 131.6, 126.3, 125.6, 124.9, 124.6, 123.0 (Ar*C*H and Ar*C*), 37.4 (Ar*C*H_2Ar), 21.2 (CO*C*H_3). FABMS *m/z*: 1104 (M^+). Anal. Calcd for $C_{58}H_{40}N_8O_{16}$: C, 63.04; H, 3.65; N, 10.14. Found: C, 63.01; H, 3.62; N, 10.11.

4.2.20. 5,17-Bis(2′,4′-dinitrophenylazo)-25,27-diacetyloxy-26,28-benzyloxycalix[4]arene, 12b. Obtained as an orange solid. Yield: 71%, mp>250 °C (decomposed). IR (KBr pellet, cm^{-1}): 1743, 1728, 1603, 1537, 1456, 1347. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (s, 2H, NO_2–Ar*H*), 8.56 (dd, J=2.2, 2.2 Hz, 4H, NO_2–Ar*H*), 7.71 (s, 4H, Ar*H*), 7.51 (d, J=9 Hz, 4H, *o*-Ar′*H*), 7.23 (m, 6H, *m*-Ar′*H* and *p*-Ar′*H*), 6.77 (d, J=7.2 Hz, 4H, ArH_{meta}), 6.69 (t, J= 8.7 Hz, 2H, ArH_{para}), 4.78 (s, 4H, Ar′CH_2), 4.72 (d, J=10.5 Hz, 4H, ArCH_2Ar), 4.64 (d, J=10.5 Hz, 4H, ArCH_2Ar), 1.94 (s, 6H, –COCH_3). FABMS *m/z*: 1076 (M^+). Anal. Calcd for $C_{58}H_{44}N_8O_{14}$: C, 64.68; H, 4.12; N, 10.40. Found: C, 64.63; H, 4.10; N, 10.44.

4.2.21. 5,11-Bis(3′-pyridylazo)-25,26,27,28-tetrabenzyloxycalix[4]arene, 13a. Obtained as an orange solid. Yield: 72%, mp>230 °C (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.81–6.40 (m, 38H, Ar*H* and Py*H*), 4.09–3.45 (m, 8H, ArCH_2Ar). ^{13}C NMR (300 MHz, $CDCl_3$): 163.7, 152.0, 151.5, 148.1, 147.3, 146.8, 135.4, 133.8, 133.6, 133.3, 132.9, 131.3, 130.6, 129.8, 129.4, 129.1, 128.7, 128.2, 127.9, 126.9, 126.6, 126.0, 125.7, 125.0, 123.6, 122.3 (Ar*C*H and Ar*C*), 37.8, 36.9, 30.2, 29.6 (Ar*C*H_2Ar). FABMS *m/z*: 1051 (M^+). Anal. Calcd for $C_{66}H_{46}N_6O_8$: C, 75.42; H, 4.41; N, 8.00. Found: C, 75.25; H, 4.43; N, 8.05.

4.2.22. 5,11,17-Tris(3′-pyridylazo)-25,26,27-tri-acetyloxy-28-methoxycalix[4]arene, 14a. Obtained as an orange solid. Yield: 70%, mp 155 °C. IR (KBr pellet, cm^{-1}): 1753, 1648, 1575, 1462. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.25 (s, 1H, Py*H*), 9.17 (s, 1H, Py*H*), 9.06 (s, 1H, Py*H*), 8.75–8.67 (m, 3H, Py*H*), 8.21–6.66 (m, 15H, Py*H* and Ar*H*), 4.17–3.42 (m, 11H, ArCH_2Ar and ArOCH_3), 2.27 (s, 3H, –COCH_3), 1.85 (s, 3H, –COCH_3), 1.50 (s, 3H, –COCH_3). DEPT-135 NMR (300 MHz, $CDCl_3$): 152.3, 151.2, 147.7, 147.1, 130.6, 130.2, 128.4, 127.3, 127.0, 126.0, 125.7, 124.6, 124.4, 123.6, 120.3, 120.1 (Ar*C*H), 61.7 (ArO*C*H_3), 38.4, 37.8, 31.7, 30.4 (Ar*C*H_2Ar), 21.2, 20.6, 20.2 (–CO*C*H_3). FABMS *m/z*: 880 (M^+). Anal. Calcd for $C_{50}H_{41}N_9O_7$: C, 68.25; H, 4.70; N, 14.33. Found: C, 68.11; H, 4.71; N, 14.29.

4.2.23. 5,11,17-Tris(4′-nitrophenylazo)-25,26,27-tri-acetyloxy-28-methoxycalix[4]arene, 14b. Obtained as an orange solid. Yield: 83%, mp 162 °C. IR (KBr pellet, cm^{-1}): 1756, 1595, 1522, 1462, 1342. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37–6.60 (m, 21H, Py*H* and Ar*H*), 4.09–3.20 (m, 11H, ArCH_2Ar and ArOCH_3), 2.37 (s, 3H, –COCH_3), 1.91 (s, 3H, –COCH_3), 1.49 (s, 3H, –COCH_3). FABMS *m/z*: 1012 (M^+). Anal. Calcd for $C_{53}H_{41}N_9O_{13}$: C, 62.91; H, 4.08; N, 12.46. Found: C, 62.63; H, 4.10; N, 12.38.

4.2.24. 5,11,17,23-Tetrakis(3′-pyridylazo)-25,26,27,28-tetracetyloxycalix[4]arene, 15a. Obtained as an orange solid. Yield: 92%, mp 180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.14 (s, 4H, Py*H*), 8.63 (d, J=4.2 Hz, 1H, Py*H*), 8.03 (d, J=7.8 Hz, 1H, Py*H*), 7.68 (s, 8H, Ar*H*), 7.39 (dd,

J=4.8, 4.2 Hz, 4H, Py*H*), 3.92 (s, 8H, ArCH_2Ar), 3.76 (s, 4H, ArCH_2Ar), 3.60 (d, J=14.1 Hz, 2H, ArCH_2Ar), 1.50 (s, 12H, –COCH_3). DEPT-135 NMR (300 MHz, $CDCl_3$): 149.4, 144.6, 129.4, 126, 125.2 (Ar*C*H), 38.2 (Ar*C*H_2Ar), 21.0 (–CO*C*H_3). FABMS *m/z*: 1013 (M^+). Anal. Calcd for $C_{56}H_{44}N_{12}O_8$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.63; H, 4.38; N, 16.64.

4.3. X-ray Structure Determination of 3b

Crystal data: $C_{41}H_{35}N_3O_8\times 2CCl_3$; M=934; triclinic; a=10.2509(18) Å, b=14.302(3) Å, c=14.672(3) Å; α=93.644(3)°, β=97.642(3)°, γ=106.115(3)°; V=2036.7(6) Å^3; Z=2; Dc=1.427 g cm^{-3}; μ=0.381 mm^{-1}; space group=P1. Intensity data were collected up to θ=47.4° by using 2θ scanning mode with graphite filtered Mo Kα radiation (λ=0.71073) on a 0.249×0.116×0.072 mm^3 crystal at 100(2) K. A total of 15,324 reflections were measured, 7481 were independent and of which 5532 [I>2(I)] were considered observed. Final R indices [I>2σ(I)] R1=0.0856, wR2=0.2265, and R indices (all data) R1=0.1093, wR2=0.2436 was found for 7481 observed reflections, 0 restraints, and 605 parameters. The apparent high R values are possibly due to the disorder found in azopyridyl unit and the solvent molecules. The structure was solved by direct methods and refined by full matrix least-square techniques on F^2 using SHELXTL. All the nonhydrogen atoms were refined anisotropically. C–H hydrogen atoms were placed in geometrically calculated positions by using a riding model. SADABS was applied for absorption correction. Torsion angles and H-bonding were calculated using PARST. Crystal data have been deposited with the Cambridge Crystallographic Data Center, under reference CCDC 281637.

4.4. X-ray Structure Determination of 12a

Crystal data: $C_{58}H_{40}N_8O_{16}$; M=1104.98; triclinic; a=11.229(3) Å, b=14.397(4) Å, c=17.555(5) Å; α=103.152(5)°, β=102.341(5)°, γ=101.175(6)°; V=2610.6(12) Å^3; Z=2; Dc=1.406 g cm^{-3}; μ=0.105 mm^{-1}; space group=P1. Intensity data were collected up to θ=45° by using 2θ scanning mode with graphite filtered Mo Kα radiation (λ=0.71073) on a 0.219×0.109×0.105 mm^3 crystal at 298(2) K. A total of 20,423 reflections were measured, 6806 were independent and of which 4938 [I>2(I)] were considered observed. The structure was solved by direct methods and refined by full matrix least-square techniques on F^2 using SHELXTL. All the nonhydrogen atoms were refined anisotropically. C–H hydrogen atoms were placed in geometrically calculated positions by using a riding model. SADABS was applied for absorption correction. Final R indices [I>2σ(I)] R1=0.0929, wR2=0.1830, and R indices (all data) R1=0.1303, wR2=0.1996 was found for 6806 observed reflections, 0 restraints, and 741 parameters. Torsion angles and H-bonding were calculated using PARST. Crystal data have been deposited with the Cambridge Crystallographic Data Center, under reference CCDC No. 294509.

Acknowledgements

We thank the Council for Scientific and Industrial Research for a senior research fellowship (to SPS) and Department of Science and Technology and Department of Biotechnology, Govt. of India for financial assistance. We also thank Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow for the mass spectra reported in this paper. DST-FIST grant for single crystal X-ray facility available at the Indian Institute of Technology, New Delhi is thankfully acknowledged.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.05.040.

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Solvent induced folding of conformationally bistable helical imide triads

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Received 20 January 2006; revised 24 April 2006; accepted 18 May 2006
Available online 19 June 2006

Abstract—Foldamer population of imide triads derived from (*R*,*R*)-1,2-diaminocyclohexane was studied with the use of ^{1}H NMR and CD spectroscopy, as well as computational modeling. Two stable foldamers of *C* and *S* shape, having correspondingly *M* and *P* helicity, are found to differ very little in energy. However, their interaction with the solvent results in significant shift of the equilibrium. For the interaction with aromatic solvent molecules a sandwich-type donor–acceptor model, stabilizing the *S* foldamer, is proposed. The limitations of the NMR and CD methods for studying the foldamer equilibrium in solution are discussed, pointing to the inadequacy of static computational models of CD spectra, not including the effect of rotation of the imide chromophores in the dynamic model of real molecules.

1. Introduction

Polymerization of monomers leads to macromolecules having new properties and capable of playing important roles, for example, as skeletal material of organisms or biocatalysts for the reactions in the cell (proteins), as the storage and transduction of genetic information (nucleic acids), and as the constituents of plant and animal tissues (oligosaccharides).[1] The structure and function of these highly functional biopolymers is determined to a large extent by intra- or intermolecular interactions, involving hydrogen bonding and stacking of planar aromatic (heterocyclic) rings.

In recent years, there has been increasing interest in basic studies of the structure and properties of artificial oligomers, which may or may be not directly related to the structure of biopolymers. The purpose of such studies is to uncover fundamental relationships between monomer structure (constitution, configuration) and oligomer conformation as well as its interaction with other molecules and ultimately to develop new lead structures for applications in materials science.

One of the basic themes of oligomer studies is their folding, i.e., the formation of ordered helical or non-helical structures, as well as their aggregation in solution. Ultimately the outcome of such studies would be predictability of oligomer folding and knowledge of the factors with which one could then tune their desired secondary structure. A particularly fascinating aspect of oligomer folding is programming of their helical structure.[2,3] Oligomer helical enantiodifferentiation may be achieved by cooperative interactions between subunits, leading to amplification of helical discrimination due to chiral substituents.[4]

The term foldamer has been coined to encompass a broad group of oligomers of well-defined bent/helical structure. In his manifesto[5] Gellman described foldamers as "polymers with a strong tendency to adopt a specific compact conformation". Moore et al. in their in-depth review[6] provided a more rigorous definition of a foldamer as "any oligomer that folds into a conformationally ordered state in solution, the structures of which are stabilized by a collection of noncovalent interactions between nonadjacent monomer units".

The most intensively studied foldamer types include oligoamides with unnatural peptide backbones,[7,8] either aromatic[9–12] or of β-peptidomimetic type.[13–15] Their secondary structure is primarily determined by the network of intramolecular hydrogen bonds.[16] Oligomers of this type are capable of creating nanocavities with tunable sizes.[17] Other foldamers of growing interest are helical strands based on heterocyclic oligomers[18] as well as *m*-phenylene ethynylene oligomers,[19] showing solvophobically driven π-stacking[20] and receptor properties.[21]

Heterogeneous backbone foldamers (i.e., those composed of two or more types of molecules) have, to date, received less

Keywords: Circular dichroism; *trans*-1,2-Diaminocyclohexane; Foldamers; Host–guest complexes; Imides; Dipole–dipole interactions.
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doi:10.1016/j.tet.2006.05.039

attention. Prominent examples are aedaomers (*a*romatic *e*lectron *d*onor–*a*cceptor *o*ligo*mers*) in which the aromatic diimide and 1,5-dialkoxynaphthalene units are linked with chiral aminoacid derivatives. Oligomers of such structure and of sufficient length adopt well-defined pleated structures in solution, stabilized by donor–acceptor interactions.[22]

Imide triads **1a**–**1c**, **2a**–**2c** described in this paper represent a set of carefully chosen, structurally minimalistic foldamers, having all the characteristics of such molecules.[6] They are chain oligomers of aromatic imides and *trans*-1,2-diaminocyclohexane and their structure (in solution) can be described as a dynamic process, involving two stable foldamers, *C* and *S* of opposite helicity; for (*R*,*R*)-diaminocyclohexane derivatives, respectively, of *M* and *P* helicity.[23] The two diastereoisomers differ little in steric energy, as the two halves of the molecule obtained by dissection of the central diimide molecule can be considered identical (Fig. 1).

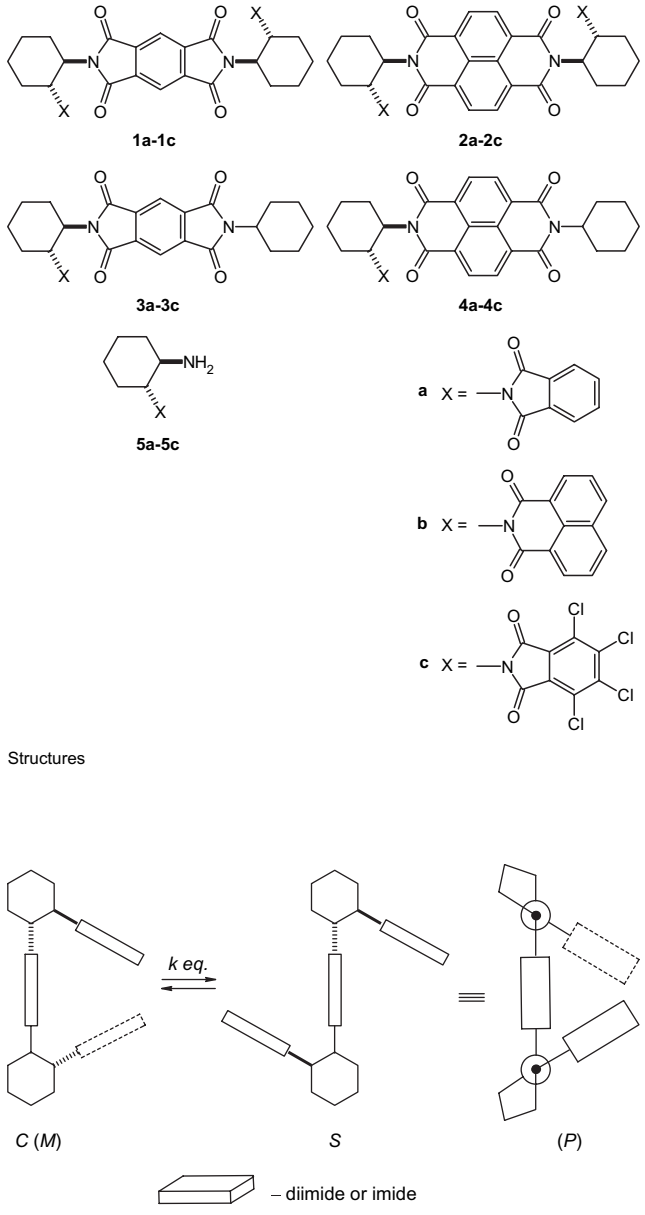

Figure 1. The two stable foldamers of imide triads with the (*R*,*R*)-1,2-diaminocyclohexane linkers.

Therefore the bistable imide triads **1a**–**1c**, **2a**–**2c** can be seen as sensitive probes for the interaction with the environment, in particular with the solvent. Although the general and important issue of foldamer stabilization by solvation has been addressed in numerous reports and accounts, much less is known about solvent effect on foldamer populations, i.e., on the role of the solvent in the folding process of a chain molecule, otherwise determined by noncovalent interactions between nonadjacent monomer units. For example, the solvent effect on conformational equilibrium of oligo(*m*-phenylene ethynylene) oligomers has been addressed by Moore[20] with the conclusion that solvent can play a dramatic role in modulating the strength of the interactions in π-stacked structures. Folding dynamics of (*m*-phenylene ethynylene)12-*mer* in various solvents has been recently analyzed by the application of Markov state model techniques.[24] Here we will show that the folding of chiral imide triads **1a**–**1c**, **2a**–**2c** can be significantly influenced by the solvent used.

2. Results and discussion

2.1. Synthesis

Imide triads **1a**–**1c**, **2a**–**2c** were obtained by condensation of 1,2,4,5-benzenetetracarboxylic dianhydride or 1,4,5,8-naphthalenetetracarboxylic dianhydride, respectively, with readily available monoprotected (*R*,*R*)-*trans*-1,2-diaminocyclohexane derivatives **5a**–**5c**.[25] We have found that the thermal condensation reaction proceeds with much higher yields (**1a**, 44%; **1c**, 48%) in refluxing acetic acid, compared to the reactions carried out in *N*,*N*-dimethylformamide at 120 °C (**1a**, 18%; **1c**, 12% yield). Dyads **3a**–**3c**, **4a**–**4c** were prepared by the condensation of monoanhydrides of either *N*-cyclohexyl-1,2,4,5-benzenetetracarboxymonoimide or *N*-cyclohexyl-1,4,5,8-naphthalenetetracarboxymonoimide,[26] respectively, with **5a**–**5c** in DMF at 120 °C, in moderate yields (32–58%).

2.2. Computational modeling

The lowest-energy structures of triads **1a**–**1c**, **2a**–**2c** as well as dyads **3a**–**3c**, **4a**–**4c** were obtained by a computational search using PM3 method, followed by DFT (b3lyp/6-31g(d)) optimization. A potential energy surface (PES) was obtained for each molecule as a function of torsion angles α_1 and α_2 (C(O)–N–CH(N)–CH_2). For example, two stable conformers, *C* and *S*, were found for triad **2b** (Fig. 2). These two low energy conformers are characterized by α_1=63°, α_2=62° and α_1=−118°, α_2=62°, respectively (Fig. 2).

In general, two stable foldamers, *C* and *S*, of close energies were obtained for each triad and one stable foldamer was found for each dyad. The common features and structural differences between these foldamers are listed in Table 1.

The foldamers of the triads can also be characterized by the dihedral angle N1–C1/C2′–N2′, involving the two outermost C–N bonds: for the *C* foldamers this angle is in the range −61 to −85° whereas it is in the range 104–122° for the *S* foldamers. *C* and *S* foldamers also differ in the

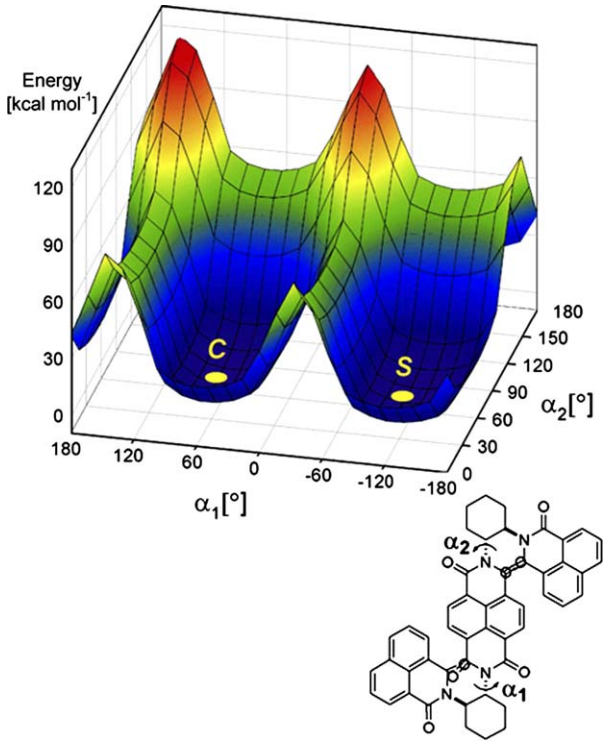

Figure 2. PM3 calculated PES and the two minima corresponding to the stable *C* and *S* conformers of **2b**.

magnitude of the computed dipole moments. The dipole moments of *C* foldamers are higher, compared to those of *S*, whereas the magnitudes of the dipole moments of *S* foldamers are slightly higher than those of the corresponding dyads. It appears that the energy differences between C and *S* conformers of imide A–B–A triads to a large extent are due to dipole–dipole interactions between the A imide components. The calculated dipole moments for *N*-methyl-1,8-naphthalenedicarboximide, *N*-methylphthalimide, and *N*-methyltetrachlorophthalimide are correspondingly 4.30 D, 2.49 D, and 0.05 D; therefore dipole–dipole interactions significantly stabilize *S* foldamers and destabilize *C* foldamers of triads **1a**, **1b**, **2a**, and **2b**. It should be noted that the energies of these dipole–dipole interactions are at the level of 0.1 kcal mol^{-1}, according to standard calculations (see Supplementary data) and can be even less significant in a high dielectric constant environment.

Table 1. Characterization of the stable foldamers of triads **1a**–**1c**, **2a**–**2c** by DFT computation (b3lyp 6-31g(d))

Triad	Foldamer	ΔE (kcal mol^{-1})	N1–C1/C2′–N2′ dihedral angle	Dipole moment (*D*)
1a	C	0.10	−73.4	3.38
	S	0.0	+110.1	2.35
1b	C	0.12	−84.8	6.06
	S	0.0	+109.8	4.09
1c	C	0.0	−66.6	0.92
	S	0.05	+104.7	0.65
2a	C	0.0	−60.7	3.40
	S	0.0	+119.2	1.98
2b	C	0.13	−61.4	6.21
	S	0.0	+117.7	3.96
2c	C	0.0	−64.9	3.90
	S	0.12	+122.5	1.89

The local conformation of the imide moieties, determined by the magnitude of the torsion angle H–C–N–C(=O), is similar in either foldamer of the triad, as well as in dyads, and is described as synperiplanar, with the torsion angle in the range 0 to −10°. This corresponds to the previously established minimum-energy structures of imides attached to a cyclohexane ring.[27]

The conclusion emerging from the computational study of isolated imide triads is quite simple: there is little energy difference between the corresponding *C* and *S* foldamers of the triads and it is in favor of the latter, except triads **1c** and **2c**. The significant differences in the magnitudes of the dipole moments of *C* and *S* foldamers of the triads do not seem to contribute significantly to destabilization of the *C* foldamers. In fact, dipole–dipole interactions appear to account fully for any energy difference between *C* and *S* foldamers. Therefore the conformationally bistable triads appear to be good candidates for studying the effect of the solvent on the mode of their folding.

2.3. ^{1}H NMR studies

Since the computational studies for isolated triad molecules do not reveal any significant bias toward either *C* or *S* foldamer there remains an intriguing question whether in solution one can observe a shift of the equilibrium between the populations of triad foldamers. To answer this question, we used the ^{1}H NMR spectra of triads in which the diimide proton signals show anisochrony, i.e., separate signals due to the diimide protons in each foldamer will appear in the spectra (Table 2).

In $CDCl_3$ solution, these signals appear conveniently in the 8.1–8.7 ppm spectral window. In the case of **2b** the 1,8-naphthalimide and 1,4,5,8-naphthalenedicarboximide signals overlap. Complete assignment of the signals in the aromatic portion of the spectrum was possible with the use of ^{1}H–^{1}H correlation NMR spectra. The two singlets (*S*) and doublets (*C*) of the diimide fragment, due to the two foldamers, were found at 8.36, 8.59 and 8.45, 8.53 ppm, respectively (Fig. 3).

Other ^{1}H NMR signals of the triads are not resolved at room temperature. This applies to the CH(N) signals, which appear in the range 5.0–5.9 ppm. Their position is dependent on the size of the imide ring and can be readily calculated using simple additivity of the shielding effect.[25] Thus in the case of triads **1a** and **1c** with two five-membered imide rings the CH(N) signals appear at ca. 5.0 ppm, whereas two six-membered imide rings (**2b**) shift the signal to ca. 6.4 ppm. Mixed type imides (**1b**, **2a**, **2c**) are characterized by two CH(N) signals at ca. 5.5 and 5.9 ppm (see Supplementary data).

The imide triads are poorly soluble in certain solvents (e.g., acetone, methanol), nevertheless we were able to obtain the NMR spectra in deuterated chloroform, benzene, hexafluorobenzene, and dimethyl sulfoxide (Table 3).

Table 2. Diastereotopic diimide proton signals in triads[28]

Diimide	Foldamer *C*	Foldamer *S*
1,2,4,5-Benzenedicarboxydiimide	One singlet	Two singlets
1,4,5,8-Naphthalenedicarboxydiimide	Two doublets	Two singlets

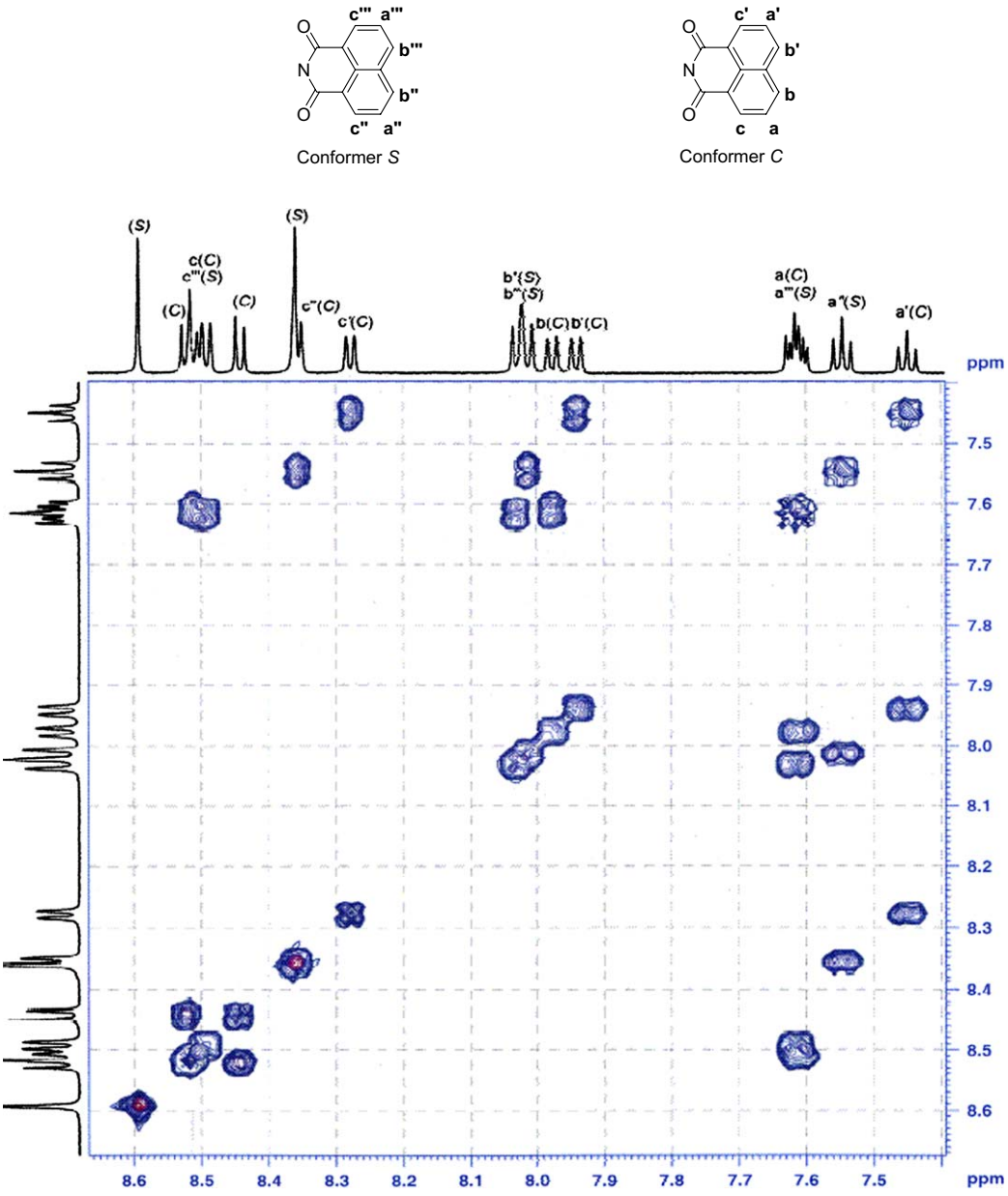

Figure 3. Aromatic protons region of ^{1}H–^{1}H correlation NMR spectrum of triad **2b**.

Another factor, limiting the analysis of the spectra, is a slow exchange of the diimide signals of pyromellitdiimides in **1a**–**1c** at room temperature, leading to broad, structureless signals. However, on lowering the temperature separate signals due to *C* and *S* foldamers could be obtained. Inspection of the data of Table 3 disclosed the preference for *C* foldamer in $CDCl_3$ solution. This preference increases upon lowering the temperature, up to the ratio *C*:*S*=67:33 for **1b** at 223 K. The only exception is triad **2b** for which a small preference for the *S* foldamer (*C*:*S*=45:55) was observed at 293 K. This could be due to the bulkiness of the naphthalene-based imide components of **2b**, destabilizing the *C* conformer.

Table 3. Ratio of *C*:*S* atropisomers of imide triads **1a**–**1c**, **2a**–**2c** in various solvents[a]

Triad	$CDCl_3$ (293 K)	$CDCl_3$, (273 K)	$CDCl_3$ (223 K)	C_6D_6 (293 K)	C_6F_6 (293 K)	$(CD_3)_2SO$ (293 K)
1a	[b]	54:46	60:40	[b]	[b]	[b]
1b	[b]	60:40	67:33	[b]	[b]	[b]
1c	[b]	50:50	56:44	[b]	[b]	[b]
2a	53:47	55:45	56:44	25:75	51:49	51:49
2b	45:55	46:54	47:53[c]	17:83	38:62	37:63
2c	52:48	54:46	55:45	[d]	[d]	58:42

[a] From integration of diimide ^{1}H NMR signals.
[b] Unresolved diimide ^{1}H NMR signals.
[c] At 253 K.
[d] Low solubility.

2.4. Circular dichroism study

Imide triads **1a**–**1c**, **2a**–**2c** are chiral trichromophoric systems whose CD spectra result primarily from exciton coupling of the allowed electronic transitions of component chromophores. Thus, the CD of a trichromophoric system can be treated as a sum of Cotton effects due to exciton coupling of the electronic transitions in each of the three chromophoric pairs. Therefore, the CD spectrum of a triad of

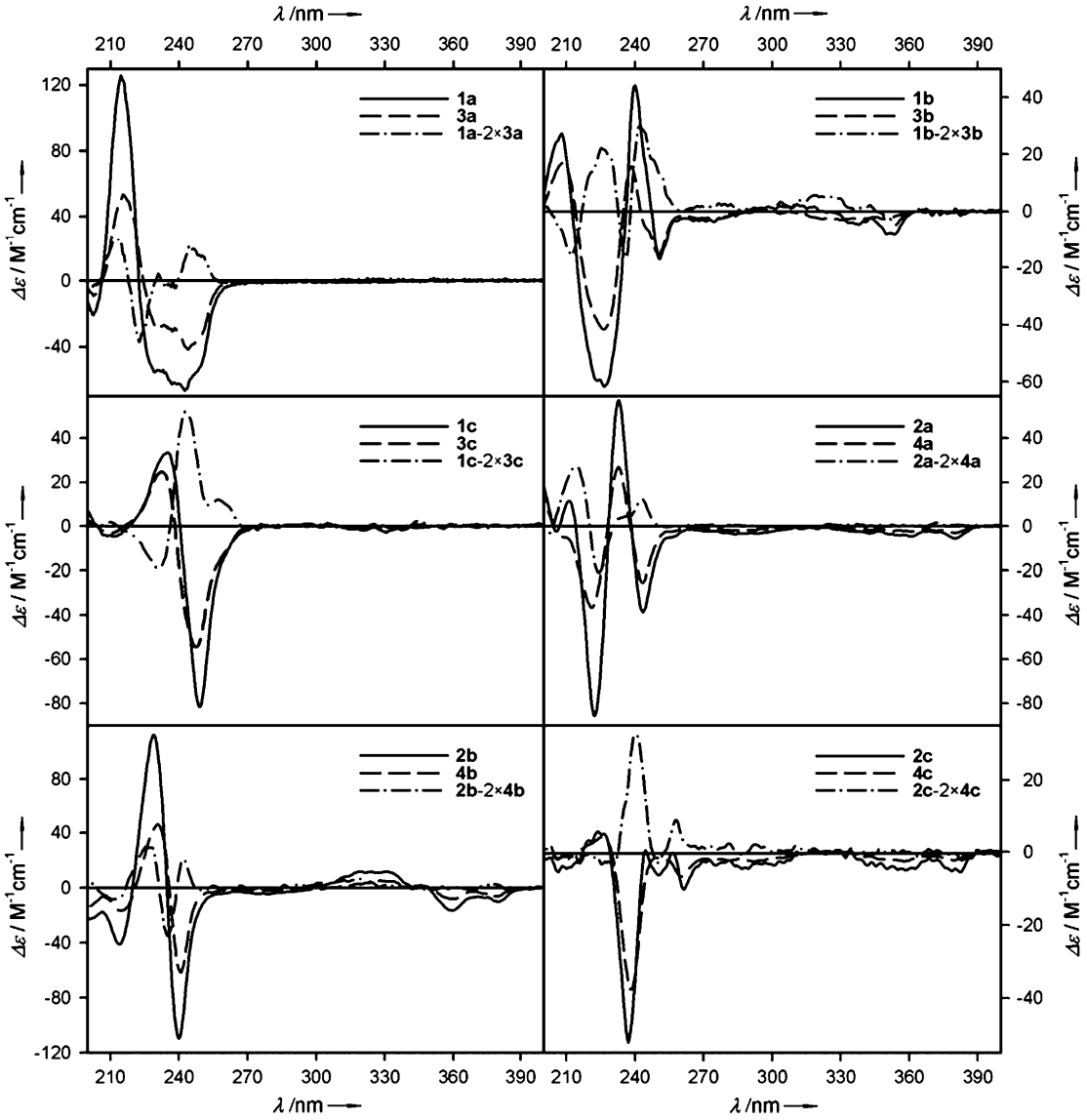

Figure 4. CD spectra of triads (——), the corresponding dyads (– – –) and the differential CD spectra: triad−2×dyad (· – · –), in acetonitrile solution.

the A–B–A type (**1a**–**1c**, **2a**–**2c**) can be considered as a sum of the two CD spectra of the corresponding dyads A–B (**3a**–**3c**, **4a**–**4c**) and the CD contribution due to exciton coupling of the two outer chromophores (A/A), Eq. 1.

$$\mathrm{CD(A-B-A)} \approx 2 \times \mathrm{CD(A-B)} + \mathrm{CD(A/A)} \qquad (1)$$

The CD contribution due to A/A coupling should be sensitive to triad conformation and it should change sign and/or magnitude with the change of the triad conformation between the stable *C* and *S* foldamers. Thus, by subtracting the experimental double CD spectrum of a dyad from the experimental CD spectrum of a triad one should get the differential CD spectrum reflecting the contribution due to the dominant foldamer of the triad. This approximation was found to work well with the triad **1a** and dyad **3a**. The differential CD spectrum indicated a strong negative exciton Cotton effect due to the phthalimide 220 nm transition and hence it was concluded that the *C* foldamer of **1a** was the dominant one in acetonitrile solution.[23]

We extended this approach to the other imide triads and dyads. Figure 4 shows their CD spectra in acetonitrile solution, as well as the corresponding differential CD spectra according to Eq. 1.

In addition, the validity of this experimental approach was checked (see Supplementary data) by comparison of the UV spectra of chromophores A of the triads A–B–A with the differential UV spectra obtained according to Eq. 2:

$$\mathrm{UV(A-B-A)} - \mathrm{UV(A-B)} \approx \mathrm{UV(A)} \qquad (2)$$

Within the exciton coupling approach, satisfactory results of comparison of the UV spectra were obtained.

In order to get a better understanding of the relation between the CD spectra and conformation of the imide triads we carried out computational simulation of the CD spectra within the semiempirical ZINDO/S method. The CD and UV spectra were calculated for the previously computed

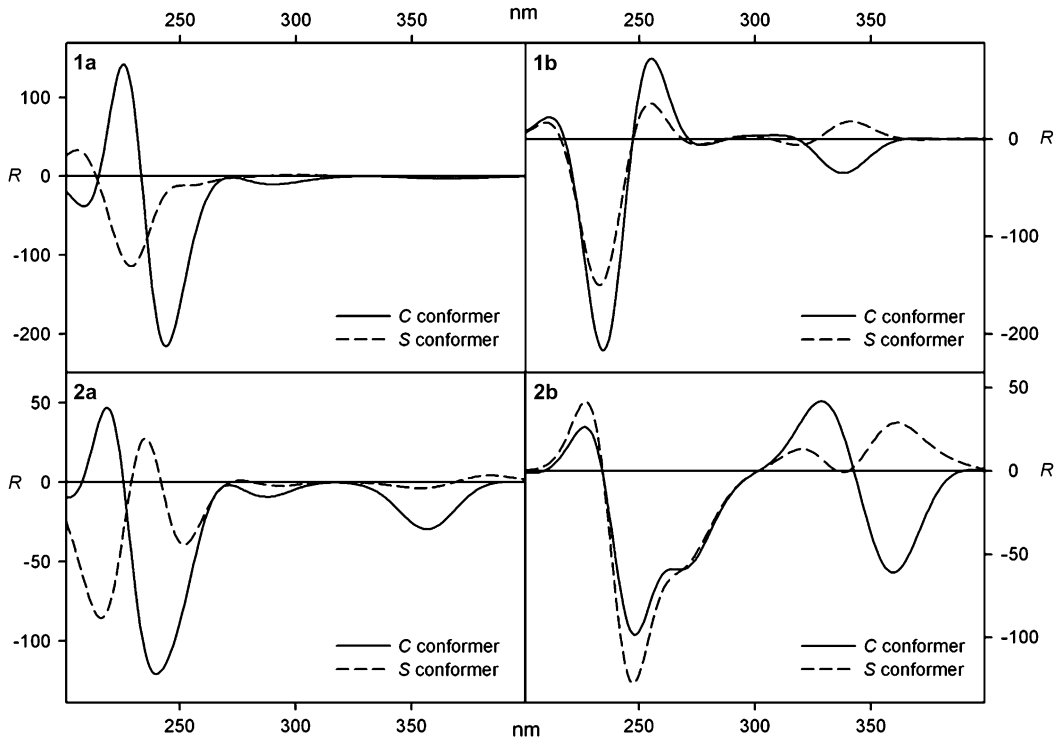

Figure 5. Calculated by ZINDO/S method CD spectra of C and S foldamers of triads **1a**, **1b**, **2a** and **2b**.

lowest-energy conformers of triads **1a**, **1b**, **2a**, **2b**. It was found that each CD and UV contour band of the calculated spectra is composed of several transitions of varying intensity (see Supplementary data). The shapes of the computed CD spectra of the *C* and *S* foldamers of triads **1a** and **2a** are different; in fact for the diagnostic 210–240 nm electronic transitions region of the phthalimide (PHT) chromophore system a strong negative exciton Cotton effect is obtained for the *C* foldamer, whereas a moderate, opposite-sign exciton Cotton effect is calculated for the *S* foldamer (Fig. 5).

This can be predicted on the basis of consideration of the relative orientation of the electronic dipole transition moments for the long axis polarized transitions of the PHT chromophores in **1a** and **2a**. Note that the computations are carried out for the lowest-energy foldamers of the triads, whereas in real molecules the conformers due to the rotation of the imide chromophores about the C–N axis will contribute significantly to the experimental CD spectrum. This occurs because the Cotton effects due to coupling of the electronic transitions polarized in the direction of the C–N bond axes will be independent of the imide chromophore rotation whereas those due to transitions polarized perpendicularly to the C–N bond axes will be averaged by rotation (weak contribution to the CD spectrum). The latter case refers to the transitions located at 240 nm in PHT, 248 nm in PYR, 231 nm in NDC and 239 nm in NTC chromophores (Fig. 6).

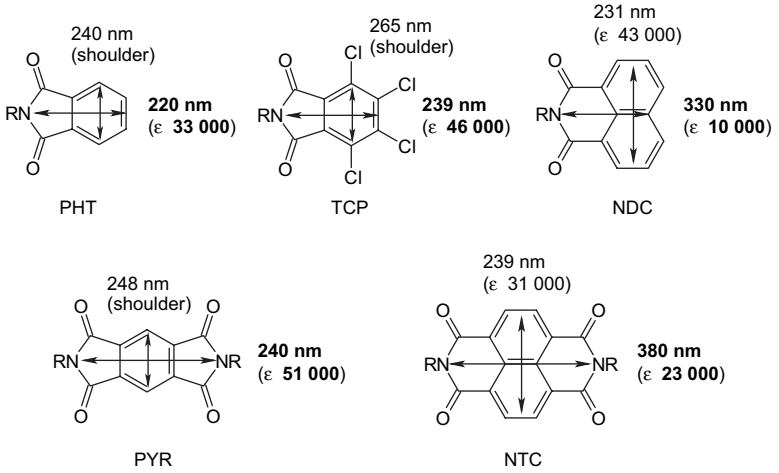

Figure 6. Most intense in-plane polarized π–π* transitions of aromatic mono- and diimides in the region 380–220 nm (data from Refs. 26, 27). The data for the diagnostic transitions, polarized in the direction of the R–N bond, are shown in bold.

For this reason, the calculated CD spectra of either foldamer of **1a** and **2a** in Figure 5 show significant (negative) CD contributions around 250 nm (in the case of foldamer *S* of **1a** a canceling effect of the positive long-wavelength part of the exciton Cotton effect due to the long axis polarized transition with the negative Cotton effect of the perpendicularly polarized transition was observed).

A less clear situation was found in the case of the CD spectra of triads **1b** and **2b**, having 1,8-naphthalimide chromophores. Here (Fig. 5) the calculated CD spectra of the *C* and *S* foldamers differ only in their magnitudes in the range of the most intense transitions (210–250 nm). However, opposite-sign Cotton effects are clearly seen in the region 330–370 nm, corresponding to the naphthalimide transition polarized along the imide rotation axis (Fig. 6). Thus, for the *C* foldamers of **1b** and **2b** a negative and for the *S* foldamers a positive long-wavelength Cotton effect is obtained, as anticipated for the transitions not affected by rotation of the chromophore.

These computational results demonstrate that reliable differentiation of the *C* and *S* foldamers of imide triads can only be achieved by the analysis of Cotton effects due to electronic transitions polarized in the direction of the imide rotational axis, as the rotatory strength in this case is independent of rotation. In the case of electronic transitions polarized perpendicularly to the axis of rotation the Cotton effects are evidently highly sensitive to the imide rotamer population (dynamic model) and the calculation of the rotational strength for a single 'frozen' rotamer of the triad (static model) does not reflect the situation found in real molecules.

Returning to the experimental CD spectra of the triads, we note that despite their complexity, useful information could be obtained from the analysis of Cotton effects resulting from coupling of the transitions polarized in the direction of imide rotational axis. As expected, both triad **1a** and dyad **3a** display a negative exciton Cotton effect centered at 215–220 nm, due to coupling of the long axis polarized transitions of PHT and PYR (Fig. 4). The differential CD spectrum also shows a negative exciton Cotton effect ($\Delta\varepsilon$ −37.0 at 223 nm, +25.6 at 213 nm). This can be interpreted as the effect of the dominant *C* foldamer of triad **1a**. Such a conclusion should be taken with caution since the CD contributions of each *C* and *S* foldamer are of opposite sign but not of the same magnitudes.

The CD spectrum of triad **2a** displays several Cotton effects in the region below 300 nm. In contrast, the differential CD spectrum of **2a**−2×**4a** (Fig. 4) is quite simple, resembling that of **1a**−2×**3a**. Thus, besides a positive CD maximum at 245 nm a negative exciton Cotton effect is found in the region of PHT absorption ($\Delta\varepsilon$ −36.2 at 223 nm, +25.6 at 214 nm). As in the case of **1a**, this can be interpreted as a characteristic spectral signature of the *C* foldamer of **2a**.

A similar analysis can be carried out for triad **1c** and dyad **3c**, as well as for **2c** and **4c**, where the principal role in exciton coupling can be ascribed to the long axis polarized transitions of the TCP chromophores. Whereas **1c** and **3c** as well as **2c** and **4c** show the expected negative exciton Cotton effect centered at ca. 240 nm, the differential CD spectra feature positive exciton Cotton effects ($\Delta\varepsilon$ +51.9 at 243 nm, −19.3 at 231 nm for **1c** and +32.7 at 241 nm, −3.3 at 226 nm for **2c**). This is a strong indication of the dominant *S* foldamer of triads **1c** and **2c**, contrasting with the preference of *C* foldamer in non-chlorinated analogs **1a** and **2a**, in acetonitrile solution.

Rather complex experimental CD spectra characterize the triads and dyads incorporating the naphthalene-based imide chromophores (NDC, NTC). For example, at least four Cotton effects can be seen in the CD spectra of imide triad **1b** and dyad **3b** in the region 210–260 nm. We therefore use for the conformational analysis the long-wavelength Cotton effects due to the coupling of the NDC chromophore transitions. Since the experimental long-wavelength Cotton effects of **1b** as well as **2b** are negative we conclude that in both cases the more stable foldamer in acetonitrile solution is *C*.

In short, the analysis of the CD spectra of imide triads is highly complicated and hindered by the inadequacy of currently available computational protocols to provide exact results including the effect of rotation of the chromophores. A comparison of experimental and calculated CD spectra of triads and dyads shows that foldamer *C* is the dominant one for all non-chlorinated imide triads **1a**, **1b**, **2a** and **2b** whereas foldamer *S* is the preferred one in the case of **1c** and **2c** in acetonitrile solution.

2.5. Crystal structure of triad 2a inclusion compound

We were able to obtain crystals suitable for X-ray diffraction analysis for triads **1a** and **2a**. X-ray data for **1a** have already been published[23] while those for **2a** are the subject of this presentation. Both compounds crystallize with planar aromatic molecules as guests, with the host to guest ratio 1:2, and both adopt the extended *S* conformation. Although the two crystal structures differ in the mode the host and guest molecules pack in the crystal, one can define two basic supramolecular motifs that are common for both crystal structures. One of these motifs, which might be described as tri-aromatic stack, consists of a host diimide molecule surrounded on both sides by planar aromatic solvent molecules (pyridine in **1a** and benzene in **2a**). The three molecules (i.e., two guest and one host) are engaged in face-to-face stacking interactions. This is illustrated for **2a** in Figure 7a,b.

The distance from the center of the diimide moiety to the centers of the two benzene rings amounts to 3.749 and 3.835 Å and the rings are parallel to within 5°. The other supramolecular motif that is common for the crystal structures of **1a** and **2a** involves the host molecules that are engaged in C–H(cyclohexane)$\cdots\pi_c$(PHT) pair-wise interactions [π_c(PHT) describes the center of the benzene ring that is a part of the phthalimide moiety]. These interactions are responsible for joining the host molecules into infinite chains. In the crystal of **2a**, the chains run parallel to [101] direction and the H$\cdots\pi_c$(PHT) distances and C–H$\cdots\pi_c$(PHT) angles amount to 2.95 and 2.92 Å and 158 and 156°, respectively. The host–host interactions in the crystal structure of **2a** are further supplemented by the C–H(cyclohexane)$\cdots$O=C hydrogen bonds (2.47 Å and 140° for H$\cdots$O distance and C–H$\cdots$O angle, respectively) by which the [101] molecular chains are extended into the (010) layers. The benzene guest

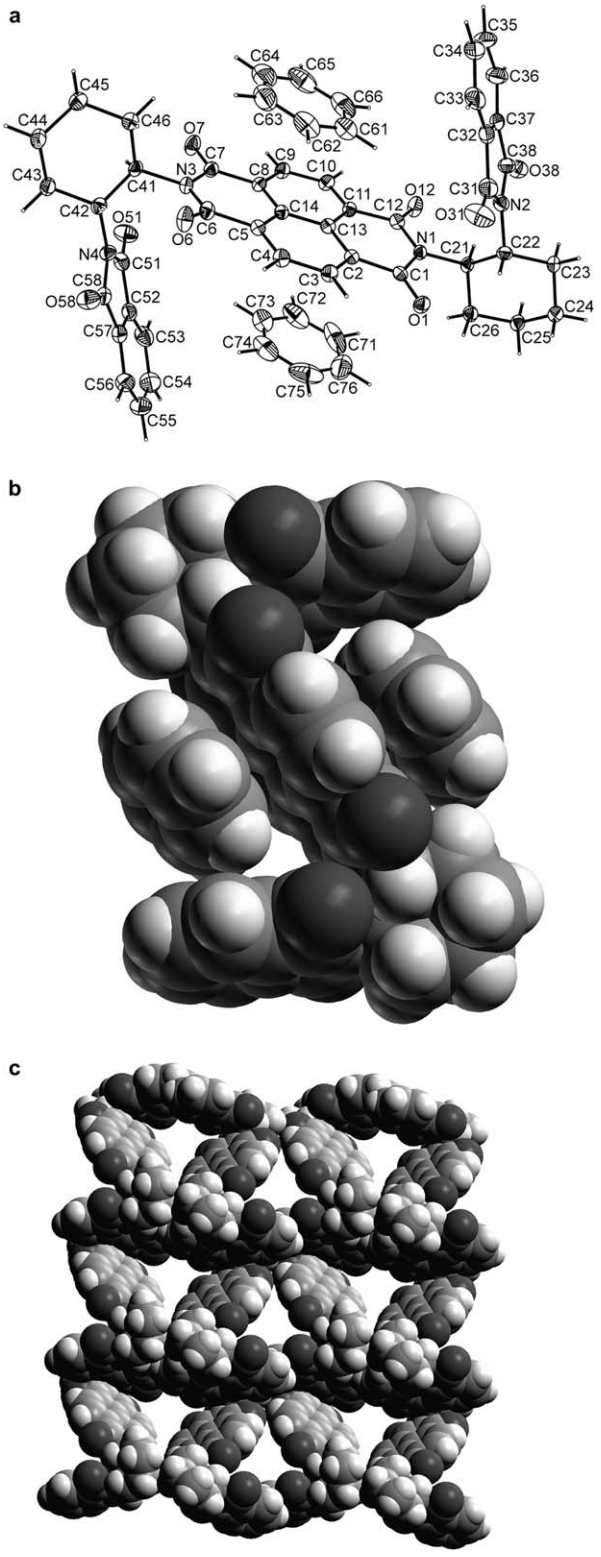

Figure 7. (a) Perspective view of the content of the independent part of the unit cell. Thermal ellipsoids are drawn at 40% probability level and give a graphical representation of atomic displacements at 150 K; (b) the basic supramolecular motif—the imide triad **2a** and the two benzene molecules—glued together by face-to-face stacking interactions; (c) view along the *c*-direction illustrating the porosity of the crystal structure. Host molecules are represented as van der Waals spheres, guest molecules are omitted.

molecules in the crystal of **2a** are arranged in channels running along the *c*-direction (Fig. 7c). There are two such channels per unit cell, related to each other by the two-fold screw axis. The guest accessible volume per unit cell amounts to 594 Å^3, which means that approximately 27% of the crystal volume is available for including guests.[29] A term 'porosity' has been used in the literature when referring to the latter value. Unlike the pyridine guest molecules in **1a**, which engage in stacking interactions between themselves, the benzene guest molecules in **2a** seem to be involved solely in the face-to-face stacking interactions with the host.

The inherently preferred synperiplanar conformation of the cyclic imide moiety with respect to the attached cyclohexane, established by the theoretical calculations (vide supra), and described by the magnitude of the torsion angle H–C–N–C(=O), is also observed in the presented crystal structure of **2a**. However, as the molecule does not utilize its C_2 symmetry in the crystal lattice, the torsion angle values differ significantly at the two ends of the molecule: the H22–C22–N2–C31 and H21–C21–N1–C12 torsion angles amount to −5 and 5°, respectively, while the H41–C41–N3–C7 and H42–C42–N4–C58 angles adopt the values of 25 and 21°, respectively. A CSD search (2005 release)[30] carried out for cyclic imides attached to cyclohexane (17 observations) revealed that in the solid state the magnitudes of the H–C–N–C(=O) torsion angles vary from 0 to 23°. Nonetheless, the fact that imide group prefers the synperiplanar orientation for one of its carbonyl bonds with respect to the cyclohexane C–H bond must be due to additional attractive interactions. We see this in 1,3-(C=O)/(H–C) antiparallel dipole–dipole interactions and/or in intramolecular C–H···O=C hydrogen bonds that close both 5- and 6-membered rings.

3. Conclusions

Imide triads, derived from *trans*-1,2-diaminocyclohexane and aromatic anhydrides, can exist in the dynamic equilibrium of two diastereomeric folded structures of *C* and *S* shape. This equilibrium reflects the process of helix *M*–helix *P* transition for each triad. Whereas the calculated energy difference between the foldamers is low (<0.1 kcal mol^{-1}) the equilibrium in solution can be significantly altered. For example, the *C*:*S* ratio is 2:1 for triad **1b** in $CDCl_3$ solution at 223 K, whereas the ratio 1:5 was measured for **2b** in C_6D_6 solution at 293 K. The effect of aromatic solvent molecules stabilizing *S* foldamer of the triad can be adequately explained by a truncated model emphasizing the donor–acceptor interactions (Fig. 8).

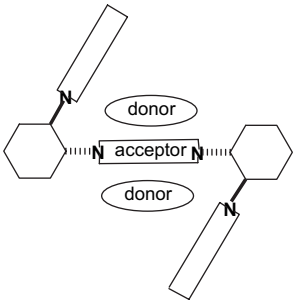

Figure 8. A model for the donor–acceptor interaction between *S* foldamer of the imide triad and donor solvent molecules.

This sandwich-type model is based on the X-ray determined structures of **2a**×2 benzene (present work) and **1a**×2 pyridine clathrates.[23] Both ^{1}H NMR and CD spectroscopy are potentially useful for studying the foldamer population in solution, with the limitations intrinsic for each method. For the NMR method, the rate of exchange between the folded *C* and *S* structures is of paramount importance and the signal separation could be observed for aromatic protons of the 1,2,4,5-benzenetetracarboxydiimide core in triads **1a**–**1c** at lowered temperatures only. The helical *C* and *S* structures feature signature CD spectra, according to ZINDO/S calculations. However, the analysis of the CD spectra is of only limited use because of the complex nature of the experimental CD spectra and inadequacy of the static computational models, not including the rotation of the imide chromophores in real molecules, to reproduce correctly the chiroptical properties of the foldamers. Nevertheless, by carefully choosing the CD spectral window, corresponding to electronic transitions polarized in the direction of the axis of rotation, the estimation of the preferred foldamer in the equilibrium was possible. Such an analysis indicated the preference of *S* foldamer of the triads **1c** and **2c**, containing the tetrachlorophthalimide fragments, in acetonitrile solution.

4. Experimental

4.1. General

NMR spectra were recorded on Varian XL300 or Bruker Avance DRX 600 instruments and are reported in parts per million with respect to TMS as a reference. CD and UV spectra were measured on a JASCO 810 spectropolarimeter in acetonitrile solution. MS were recorded with a AMD 604 Intectra or AMD 402 Intectra spectrometers. FTIR spectra were taken in KBr pellets on a Bruker IFS 113v spectrometer. Elemental analyses were performed with a Perkin–Elmer 2400 CHNS/O analyzer. Melting points are uncorrected. TLC plates (silica gel on alumina foil) were developed with hexane–ethyl acetate (3:1); R_f values were ca. 0.6 for triads **1a**–**1c**, **2a**–**2c** and 0.85 for dyads **3a**–**3c**, **4a**–**4c**.

4.2. Preparation of triads 1a–1c, 2a–2c

4.2.1. Method A. A mixture of appropriate DACH derivative **5a**, **5b** or **5c**[25] (2 mmol) and 1,4,5,8-naphthalenetetracarboxylic dianhydride (268 mg, 1 mmol) or pyromellitic dianhydride (218 mg, 1 mmol) in DMF (10 ml) was stirred at 90 °C until homogeneous solution was obtained. After that, stirring at 120–130 °C was continued for 6 h. The solution was evaporated in vacuo. The product was purified by column chromatography on silica gel using mixtures of CH_2Cl_2 and AcOEt as eluent, followed by crystallization.

4.2.1.1. Triad 1a. Yield 18%, mp 342–344 °C; ^{1}H NMR δ 1.50–1.66 (m, 6H, $CH_{cycl.}$), 1.89–1.91 (m, 6H, $CH_{cycl.}$), 2.41–2.44 (m, 4H, $CH_{cycl.}$), 4.97 (m, 4H, CH–N), 8.2 (br s, 10H, CH_{Ar}); ^{13}C NMR δ 24.83, 24.86, 50.77, 53.40, 118.4, 123.31, 131.01, 133.98, 136.84, 136.05, 136.84, 165.76, 167.97; CD (acetonitrile) $\Delta\varepsilon$ (nm) −66.9 (243), +125.6 (215), −20.7 (202); UV (acetonitrile) ε (nm) 4800 (297), 65,900 (235), 103,900 (220); IR ν (cm^{-1}) 3080, 3066, 2937, 2859, 1772, 1720, 1380, 1110, 872, 730, 631; FABHRMS: calcd for $C_{38}H_{31}O_8N_4$ (M+1): 671.2142, found: 671.2142.

4.2.1.2. Triad 1b. Yield 13%, mp>360 °C; ^{1}H NMR δ 1.48–1.67 (m, 5H, $CH_{cycl.}$), 1.8–2.0 (m, 7H, $CH_{cycl.}$), 2.34–2.7 (m, 4H, $CH_{cycl.}$), 5.49 (dt, *J*=3.3, 11.5 Hz, 2H, CH–N), 5.81 (dt, *J*=3.82, 11.5 Hz, 2H, CH–N), 7.15–7.62 (m, 2H, CH_{Ar}), 7.69 (t, *J*=7.7 Hz, 3H, CH_{Ar}), 8.10 (t, *J*=7.7 Hz, 5H, CH_{Ar}), 8.35 (br s, 2H, CH_{Ar}), 8.54 (d, *J*=7.1 Hz, 2H, CH_{Ar}); ^{13}C NMR δ 25.03, 25.26, 28.51, 29.46, 29.67, 50.88, 53.23, 118.20, 121.97, 122.63, 126.77, 127.02, 128.05, 128.30, 131.21, 131.29, 131.63, 133.61, 133.75, 135.98, 136.68, 164.26, 164.45, 165.94; CD (acetonitrile) $\Delta\varepsilon$ (nm) −7.9 (355), −4.5 (338), −17.0 (251), +44.1 (240), −61.7 (226), −59.5 (224), +27.3 (208); UV (acetonitrile) ε (nm) 20,300 (343), 22,700 (333), 19,800 (324), 17,600 (251), 106,100 (233), 45,400 (208); IR ν (cm^{-1}) 3096, 2932, 2868, 1770, 1714, 1664, 1586, 1356, 1237, 1108, 780; Anal. Calcd for $C_{46}H_{34}N_4O_8$: C, 71.69; H, 4.45; N, 7.27. Found: C, 71.58; H, 4.40; N, 7.26.

4.2.1.3. Triad 1c. Yield 12%, mp>360 °C; ^{1}H NMR δ 1.17–1.80 (m, 6H, $CH_{cycl.}$), 1.90–1.93 (m, 6H, $CH_{cycl.}$), 2.17–2.70 (m, 4H, $CH_{cycl.}$), 4.96 (m, 4H, CH–N), 8.15 (br s, 2H, CH_{Ar}); ^{13}C NMR δ 23.80, 24.74, 24.78, 28.81, 28.88, 51.29, 51.75, 118.75, 126.63, 127.14, 128.31, 129.74, 136.29, 140.36, 163, 14, 165.72; CD (acetonitrile) $\Delta\varepsilon$ (nm) −81.5 (249), +33.4 (235), −4.6 (212); UV (acetonitrile) ε (nm) 177,400 (238): IR ν (cm^{-1}) 3478, 2936, 2865, 1770, 1728, 1345, 1111, 825, 734; Anal. Calcd for $C_{38}H_{22}N_4O_8Cl_8$: C, 48.24; H, 2.34; N, 5.92. Found: C, 48.20; H, 2.53; N, 5.88.

4.2.1.4. Triad 2a. Yield 16%, mp>360 °C; ^{1}H NMR δ 1.18–1.60 (m, 4H, $CH_{cycl.}$), 1.90–2.1 (m, 8H, $CH_{cycl.}$), 2.47–2.67 (m, 4H, $CH_{cycl.}$), 5.42 (dt, *J*=4.6, 11.8 Hz, 2H, CH–N), 5.87 (tt, *J*=3.1, 8.1 Hz, 2H, CH–N), 7.19–7.64 (br s, 8H, CH_{Ar}), 8.46 (s, 1H), 8.53 (d, *J*=7.4 Hz, 1H, CH_{Ar}), 8.61 (d, *J*=7.4 Hz, 1H, CH_{Ar}), 8.70 (s, 1H, CH_{Ar}); ^{13}C NMR δ 25.21, 25.25, 25.43, 25.46, 28.66, 29.60, 29.73, 29.78, 50.33, 123.01, 123.13, 125.81, 125.89, 126.76, 126.85, 130.60, 130.88, 130.99, 131.28, 131.48, 133.58, 133.66, 162.73, 162.98, 163.03, 167.91, 168.03; CD (acetonitrile) $\Delta\varepsilon$ (nm) −5.3 (381), −3.2 (343), −3.6 (284), −38.7 (244), +57.0 (233), −85.6 (223), +11.4 (211), −2.1 (206), +20 (200); UV (acetonitrile) ε (nm) 26,800 (381), 21,900 (360), 7000 (300), 4500 (233), 78,600 (221); IR ν (cm^{-1}) 2956, 2875, 1775, 1710, 1680, 1663, 1380, 1330, 1245, 1110, 887, 725; FABMS: *m*/*z* 721.3 [M+H]; Anal. Calcd for $C_{42}H_{32}N_4O_8$: C, 69.99; H, 4.47; N, 7.77. Found: C, 70.18; H, 4.46; N, 7.79.

4.2.1.5. Triad 2b. Yield 13%, mp>360 °C; ^{1}H NMR δ 1.25–1.69 (m, 4H, $CH_{cycl.}$), 2.05–2.18 (m, 8H, $CH_{cycl.}$), 2.63–2.67 (m, 4H, $CH_{cycl.}$), 6.30 (m, 4H, CH–N), 7.46 (t, *J*=7.7 Hz, 1H, CH_{Ar}), 7.55 (t, *J*=7.7 Hz, 1H, CH_{Ar}), 7.63 (t, *J*=7.4 Hz, 2H, CH_{Ar}), 7.94 (d, *J*=9.3 Hz, 1H, CH_{Ar}), 8.03 (d, *J*=6.2 Hz, 2H, CH_{Ar}), 8.05 (d, *J*=6.2 Hz, 1H, CH_{Ar}), 8.27 (d, *J*=6.3 Hz, 1H, CH_{Ar}), 8.36 (d, *J*=6.2 Hz, 2H, CH_{Ar}), 8.37 (s, 1H, CH_{Ar}), 8.48 (d, *J*=7.7 Hz, 1H, CH_{Ar}), 8.49 (d, *J*=6.2 Hz, 1H, CH_{Ar}), 8.52 (d, *J*=6.1 Hz, 1H, CH_{Ar}), 8.59 (s, 1H, CH_{Ar}); ^{13}C NMR δ 25.65, 29.34,

29.413, 29.78, 53.06, 53.19, 53.81, 122.26, 122.33, 123.13, 123.19, 125.90, 126.24, 126.44, 126.61, 126.70, 126.78, 127.97, 130.39, 130.57, 130.74, 130.87, 130.96, 131.12, 131.17, 131.23, 131.34, 133.11, 133.19, 133.31; CD (acetonitrile) $\Delta\varepsilon$ (nm) −9.9 (381), −16.4 (359), +1.80 (346), +11.8 (331), −4.8 (279), −111.2 (240), −42.5 (214); UV (acetonitrile) ε (nm) 24,200 (380), 32,900 (341), 19,800 (324), 100,900 (231); IR ν (cm^{-1}) 2926, 2853, 1704, 1672, 1587, 1342, 1237, 1106, 780; FABMS: *m/z* 821.3 [M+H]; Anal. Calcd for $C_{50}H_{36}N_4O_8$: C, 73.16; H, 4.42; N, 6.83. Found: C, 72.58; H, 4.40; N, 6.86.

4.2.1.6. Triad 2c. Yield 14%, mp>360 °C; ^{1}H NMR δ 1.49–1.65 (m, 6H, $CH_{cycl.}$), 1.85–2.0 (m, 6H, $CH_{cycl.}$), 2.4–2.68 (m, 4H, $CH_{cycl.}$), 5.46 (dt, *J*=3.8, 11.5 Hz, 2H, CH–N), 5.83 (dt, *J*=3.3, 11.3 Hz, 2H, CH–N), 8.56 (s, 1H, CH_{Ar}), 8.61 (d, *J*=7.1 Hz, 1H, CH_{Ar}), 8.67 (d, *J*=7.24 Hz, 1H, CH_{Ar}), 8.73 (s, 1H, CH_{Ar}); ^{13}C NMR δ 25.37, 28.69, 29.12, 29.45, 51.21, 53.79, 54.45, 125.58, 126.36, 126.47, 126.91, 127.06, 129.43, 130.50, 130.78, 130.99, 131.33, 139.85, 162.78, 162.93, 163.11; UV (acetonitrile) ε (nm) 23,200 (380), 19,100 (360), 14,300 (340), 5200 (271), 85,400 (237); CD (acetonitrile) $\Delta\varepsilon$ (nm) −5.52 (383), −4.9 (359), −10.2 (261), −52.2 (237), +5.5 (224); IR ν (cm^{-1}) 2931, 2856, 1776, 1722, 1666, 1579, 1452, 1345, 1190, 1104; Anal. Calcd for $C_{42}H_{24}N_4O_8Cl_8$: C, 50.64; H, 2.43; N, 5.62. Found: C, 50.82; H, 2.41; N, 5.58.

4.2.2. Method B. A mixture of **5a** (488 mg, 2 mmol) or **5c** (764 mg, 2 mmol) and pyromellitic anhydride (218 mg, 1 mmol) was stirred under reflux in glacial acetic acid (5 ml) for 6 h. The solution was evaporated in vacuo. The product was purified as in method A. Yield **1a**: 44%, **1c**: 48%.

4.3. Preparation of dyads 3a–3c, 4a–4c

Monoanhydride of *N*-cyclohexyl-1,4,5,8-naphthalenetetracarboxymonoimide (349 mg, 1 mmol) or monoanhydride of *N*-cyclohexyl-1,2,4,5-benzenetetracarboxymonoimide (299 mg, 1 mmol)[26] and appropriate DACH derivative **5a**, **5b** or **5c**[25] (1 mmol) in DMF (10 ml) was heated with stirring at 120–130 °C for 5 h. The solution was evaporated in vacuo. The product was purified by column chromatography on silica gel, using hexane–CH_2Cl_2 and CH_2Cl_2 as eluents, followed by crystallization.

4.3.1. Dyad 3a. Yield 42%, mp 233–236 °C; ^{1}H NMR δ 1.28–1.30 (m, 3H, $CH_{cycl.}$), 1.53–1.57 (m, 3H, $CH_{cycl.}$), 1.67–1.70 (m, 3H, $CH_{cycl.}$), 1.90–2.2 (m, 6H, $CH_{cycl.}$), 2.13–2.15 (m, 2H, $CH_{cycl.}$), 2.42–2.45 (m, 1H, $CH_{cycl.}$), 4.11 (m, 1H, CH–N), 5.01 (m, 2H, CH–N), 8.2 (br s, 6H, CH_{Ar}); CD (acetonitrile) $\Delta\varepsilon$ (nm) −41.7 (244), +53.4 (216), −8.5 (203); UV (acetonitrile) ε (nm) 3200 (304), 59,900 (237), 64,700 (220); FABHRMS: calcd for $C_{30}H_{28}O_6N_3$ (M+1): 526.1978, found: 526.1956.

4.3.2. Dyad 3b. Yield 38%, mp>360 °C; ^{1}H NMR δ 1.18–1.39 (m, 4H, $CH_{cycl.}$), 1.61–1.67 (m, 6H, $CH_{cycl.}$), 1.81–2.13 (m, 6H, $CH_{cycl.}$), 2.15–2.72 (m, 2H, $CH_{cycl.}$), 4.07 (dt, *J*=3.3, 11.3 Hz, 1H, CH–N), 5.59 (dt, *J*=3.5, 11.6 Hz, 1H, CH–N), 5.89 (dt, *J*=3.8, 11.5 Hz, 1H, CH–N), 7.59 (t, *J*=7.4 Hz, 1H, CH_{Ar}), 7.75 (t, *J*=7.5 Hz, 1H, CH_{Ar}), 8.1 (br s, 2H, CH_{Ar}), 8.15 (t, *J*=7.4 Hz, 2H, CH_{Ar}), 8.43 (d, *J*=7.7 Hz, 1H, CH_{Ar}), 8.43 (d, *J*=7.7 Hz, 1H, CH_{Ar}); CD (acetonitrile) $\Delta\varepsilon$ (nm) −2.6 (332), −2.6 (276), −15.1 (251), +15.7 (239), −41.6 (227), +16.9 (209); UV (acetonitrile) ε (nm) 10,600 (342), 12,100 (333), 21,100 (251), 81,500 (234), 38,700 (214); Anal. Calcd for $C_{34}H_{29}N_3O_6$: C, 70.95; H, 4.99; N, 7.46. Found: C, 70.95; H, 5.08; N, 7.32.

4.3.3. Dyad 3c. Yield 58%, mp 162–165 °C; ^{1}H NMR δ 1.22–1.53 (m, 5H, $CH_{cycl.}$), 1.72–1.85 (m, 3H, $CH_{cycl.}$), 1.9–1.93 (m, 6H, $CH_{cycl.}$), 2.1–2.22 (m, 2H, $CH_{cycl.}$), 2.36–2.45 (m, 2H, $CH_{cycl.}$), 4.12 (tt, *J*=3.6, 11.7 Hz, 1H, CH–N), 4.39–5.01 (m, 2H, CH–N), 8.15 (br s, 2H, CH_{Ar}); CD (acetonitrile) $\Delta\varepsilon$ (nm) −54.5 (248), +24.5 (234), −3.3 (211); UV (acetonitrile) ε (nm) 102,700 (237). Elemental analysis: calcd for $C_{30}H_{23}N_3O_6Cl_4$: C, 54.32; H, 3.49; N, 6.33%; obtained: C, 54.26; H, 3.53; N, 6.30%.

4.3.4. Dyad 4a. Yield 32%, mp 165–170 °C; ^{1}H NMR δ 1.27–1.87 (m, 9H, $CH_{cycl.}$), 1.86–1.96 (m, 5H, $CH_{cycl.}$), 2.43–2.70 (m, 4H, $CH_{cycl.}$), 4.97 (dt, *J*=3.6, 12.1 Hz, 1H, CH–N), 5.46 (dt, *J*=3.6, 11.5 Hz, 1H, CH–N), 5.91 (dt, *J*=4.1, 11.5 Hz, 1H, CH–N), 7.28–7.61 (m, 4H, CH_{Ar}), 8.59 (s, 2H, CH_{Ar}), 8.68 (d, *J*=7.7 Hz, 1H, CH_{Ar}), 8.74 (d, *J*=7.7 Hz, 1H, CH_{Ar}); CD (acetonitrile) $\Delta\varepsilon$ (nm) −3.0 (380), −2.1 (371), −2.5 (362), −25.4 (243), +26.8 (233), −34.5 (223); UV (acetonitrile) ε (nm) 26,400 (380), 21,800 (360), 38,100 (235), 49,800 (221). EIHRMS: calcd for $C_{34}H_{29}O_6N_3$ (M): 575.2056, found: 575.2072.

4.3.5. Dyad 4b. Yield 42%, mp>360 °C; ^{1}H NMR δ 1.25–2.06 (m, 12H, $CH_{cycl.}$), 2.04–2.49 (m, 3H, $CH_{cycl.}$), 2.68–2.72 (m, 3H, $CH_{cycl.}$), 4.93 (tt, *J*=3.6, 12.3 Hz, 1H, CH–N), 6.32 (dt, *J*=4.1, 11.0 Hz, 1H, CH–N), 6.39 (dt, *J*=3.9, 11.0 Hz, 1H, CH–N), 7.56 (t, *J*=7.4 Hz, 1H, CH_{Ar}), 7.64 (t, *J*=7.4 Hz, 1H, CH_{Ar}), 8.05 (t, *J*=7.3 Hz, 2H, CH_{Ar}), 8.39 (d, *J*=7.1 Hz, 1H, CH_{Ar}), 8.46–8.55 (m, 1H, CH_{Ar}), 8.53 (s, 2H, CH_{Ar}), 8.61 (d, *J*=7.7 Hz, 1H, CH_{Ar}), 8.70 (d, *J*=7.7 Hz, 1H, CH_{Ar}); CD (acetonitrile) $\Delta\varepsilon$ (nm) −6.2 (380), −8.2 (360), +5.0 (332), −63.4 (240), +47.1 (230), −16.1 (216); UV (acetonitrile) ε (nm) 24,000 (379), 23,000 (341), 63,300 (232); Anal. Calcd for $C_{38}H_{30}N_3O_6$: C, 73.07; H, 4.84; N, 6.73. Found: C, 72.95; H, 4.82; N, 6.67.

4.3.6. Dyad 4c. Yield 48%, mp 177–180 °C; ^{1}H NMR δ 0.88–0.9 (m, 2H, $CH_{cycl.}$), 1.25–1.95 (m, 12H, $CH_{cycl.}$), 2.42–2.68 (m, 4H, $CH_{cycl.}$), 4.98 (dt, *J*=3.8, 8.5 Hz, 1H, CH–N), 5.50 (dt, *J*=4.0, 11.8 Hz, 1H, CH–N), 5.86 (dt, *J*=3.8, 11.5 Hz, 1H, CH–N), 8.63 (s, 2H, CH_{Ar}), 8.69 (d, *J*=7.6 Hz, 1H, CH_{Ar}), 8.74 (d, *J*=7.4 Hz, 1H, CH_{Ar}); CD (acetonitrile) $\Delta\varepsilon$ (nm) −2.3 (380), −6.8 (261), −37.7 (239), +4.0 (225); UV (acetonitrile) ε (nm) 21,900 (379), 10,900 (366), 17,600 (359), 11,700 (340), 64,900 (237); Anal. Calcd for $C_{34}H_{25}N_3O_6Cl_4$: C, 57.25; H, 3.53; N, 5.89. Found: C, 57.13; H, 3.54; N, 5.77.

5. X-ray structure determination of 2a

Triad **2a** crystallized from benzene as an inclusion compound with the formula $C_{42}H_{32}N_4 \cdot 2C_6H_6$, M_r=876.93, *T*=150 K. Crystal system: monoclinic. Space group: $P2_1$.

Unit cell dimensions: a=11.354(2), b=16.712(3), c=11.413(2) Å, β=90.50(3)°; V=2165.5(7) Å^3; Z=2; ρ_{cal}=1.345 Mg m^{-3}; Mo Kα (λ=0.71073, ω-scan); μ=0.091 mm^{-1}. Final R value 0.0560 for 3370 observed reflections [$I>2\sigma(I)$]. Crystal size: 0.3×0.4×0.3 mm^3. Data was collected with a KM4CCD kappa-geometry diffractometer[31] equipped with graphite monochromator. Theta range for data collection was 4.17–25.03° and the *hkl* ranges were −13/13, −19/9, −13/13, respectively. Of the 10,777 reflections collected, 3884 were unique (R_{int}=0.0510) and 3370 were considered as observed with $I>2\sigma(I)$. The intensity data were corrected for *Lp* effects. No absorption correction was applied.

Data reduction and analysis were carried out with the CrysAlisRED.[31] The structure was solved by direct methods using SHELXS-97,[32,33] and refined by the full matrix least-squares techniques with SHELXL-97.[34] Non-hydrogen atoms were refined anisotropically. The positions of all H atoms attached to carbon atoms were calculated geometrically (C–H= 0.96 Å). All H atoms were refined using a riding model and their isotropic displacement parameters were given a value 20% higher than the isotropic equivalent for the atom to which the H atoms were attached. The absolute structure of the crystals was assumed from the known absolute configuration of (*R*,*R*)-1,2-diaminocyclohexane used in synthesis. A Mercury[35] program was used to prepare the drawings.

Atomic coordinates and displacement parameters for **2a** have been deposited at the Cambridge Crystallographic Data Center (CCDC) and allocated the deposition number CCDC 29,2051.

6. Computational details

Geometry optimizations were performed with the use of b3lyp hybrid functional and split-valence 6-31g(d) basis set.[36] For all structures, frequency calculations were carried out at the b3lyp/6-31g(d) level of theory to establish that the conformations are stable. In our computations all excited-state calculations have been performed based upon the ground state geometries of single molecules with the use of a Gaussian program package and semiempirical ZINDO/S method.[36] Thus the results correspond to vertical transitions, and the excitation energies can be compared with the band maxima in the experimental spectra. Rotatory strengths were calculated using length and velocity representations. In the present study the differences between the length and velocity calculated values of rotatory strengths were quite small, thus only velocity representations were taken under further considerations. The CD spectra were simulated by overlapping Gaussian functions for each transition according to the procedure described by Grimme and Diedrich.[37] No correlation for the medium dielectric constant was implemented.

All conformers of triads **1a**–**1c**, **2a**–**2c** are of C_2 symmetry.

Acknowledgements

We thank Dr. B. Nowak-Wydra for running some of the NMR experiments. This work was supported by the Committee of Scientific Investigations, grants no. 3T 09A 183 27 (to M.K.) and 4T 09A 185 25 (to U.R.). All calculations were performed at Poznań Supercomputing and Networking Center.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.05.039.

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Tetrahedron 62 (2006) 7878–7886
Tetrahedron

Mesitylene based azo-coupled chromogenic tripodal receptors—a visual detection of Ag(I) in aqueous medium

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Received 25 November 2005; revised 3 May 2006; accepted 18 May 2006
Available online 12 June 2006

Abstract—A series of novel tripodal ligands **3a–d**, based on a mesitylene anchor, containing aza-thioethers as donor atoms and coupled with 4-(4/3/2-nitrophenyl)azophenol or 4-(2-chlorophenyl)azophenol have been synthesized as chromogenic receptors, which are highly selective for silver(I). The complexation behavior of **3a–d** with various metal ions has been evaluated by UV–vis spectrometry in dioxane/water (1:9/v:v) solution at 25 °C. The UV–vis spectra show that the complexation of **3a–c** with Ag^+ have pronounced bathochromic shifts accompanied by a unique color change in the solution from yellow to red, which is visible with the naked eye. The ligands do not show any significant change on addition of other metal ions like Li^+, Na^+, K^+, Sr^{2+}, Ca^{2+}, Cd^{2+}, Zn^{2+}, Hg^{2+}, Pb^{2+}, Ni^{2+}, and Cu^{2+} and thus are highly specific and selective for Ag^+ in the aqueous medium.

1. Introduction

Chromogenic sensors provide an informative signal due to the specific color change of a ligand upon metal complexation. This change can be utilized in analyte-sensing systems[1–3] and finds widespread use in environmental and biomedical applications.[4] Receptors specifically designed for sensing purposes are generally called chemosensors.[5] Many of these chemosensors are optical in nature, working on a binding site-signaling subunit approach[6] and usually employ the unspecific interactions with the indicator dyes to generate signal changes.[7] Using this approach a wide variety of cation sensing chemosensors based on crown ethers,[2] calixarenes,[8] azacrown-calixarenes,[9] spherands,[10] cryptands,[11] and podands[3,12] have been reported in literature. This strategy has led to a significant development of a number of chromogenic systems sensing anions,[13] neutral analytes,[14] nucleic acids,[15] and oligonucleotides.[15] As far as metal ion sensing is concerned, the chemosensors may be grouped into three broad categories.[1b] The first category consists of those, which show a color change upon complexation in a totally organic medium. It includes neutral and some anionic species and also those chromoionophores, which work on the basis of skeletal isomerization. The second category comprises anionic species, which are used for metal extraction photometry. The third category includes those chromosensors, which are specially developed for metal photometry in aqueous media. This type of photometry eliminates the use of toxic and volatile organic solvents and also eliminates the phase separation step required in extraction photometry.

Heavy metal ions like Ag^+, Hg^{2+} are environmental pollutants for water resources, so their recognition and selective removal forms an important part of chemical research. The existing chemical sensors for the detection of heavy metals include devices based on their films of gold,[16] environmentally sensitive organic molecules,[17] polymeric materials,[18] and bio-composites.[19] These devices have their own limitations. There are numerous reported examples for fluroionophores,[20] which show excellent selectivity for heavy metals. However, the fluorescence quenching nature of the paramagnetic transition metal species via enhancing spin-orbital coupling[21] poses a disadvantage in high signal output upon complexation. The techniques that are available for Ag^+ detection are very tedious[22] and involve extraction of Ag^+ from aqueous to organic phase.[23] While it is possible to detect other transition metal ions in the aqueous samples by using dithizones in the presence of nonionic surfactants (Triton X-100), Ag^+ forms secondary dithizonates, which find no real application in spectroscopic analysis.[24] The development of an optical sensor having high selectivity and sensitivity for Ag^+, transducing a visual signal, in the environment friendly aqueous medium, is thus highly desirable.

The above mentioned binding site-signaling subunit[6] approach has been extended to modify one of our acyclic receptors **1**. These chromogenic studies were initiated because such thioether-imine based receptors[25] have been

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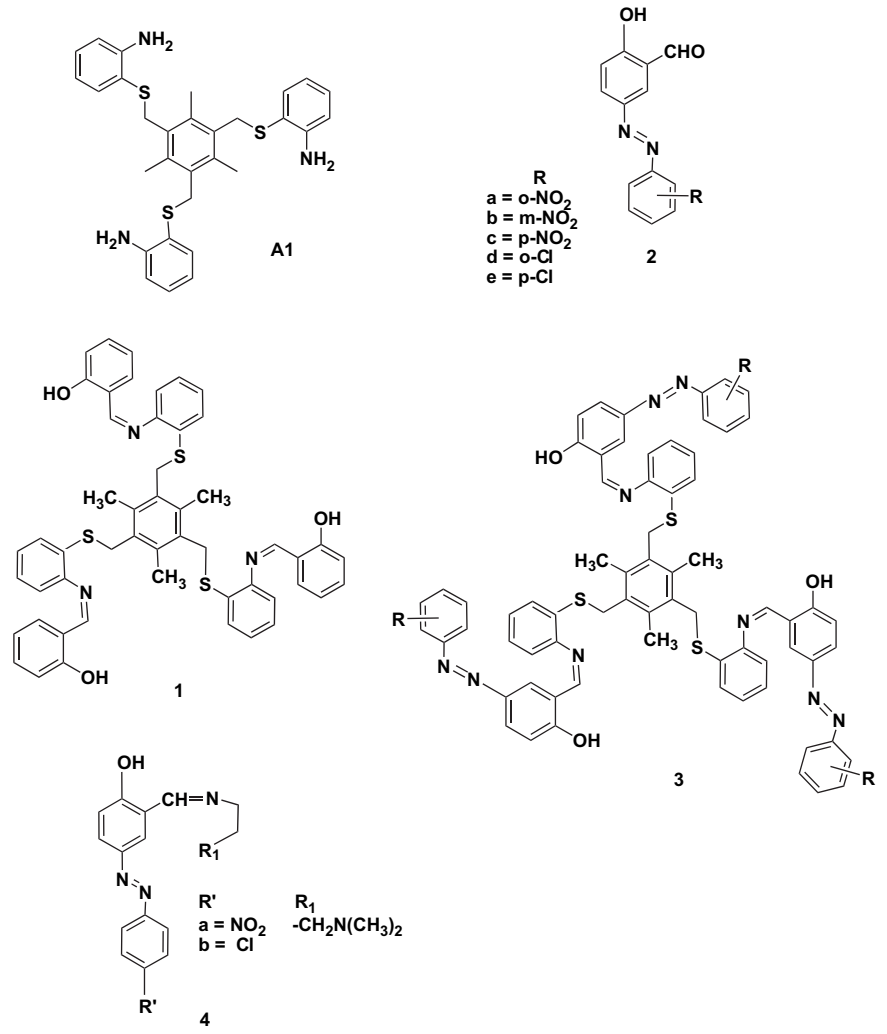
doi:10.1016/j.tet.2006.05.047

seen to be highly responsive toward Ag^+. In order to optically sense this binding of Ag^+, a sensing unit **2** was introduced to the receptor **1**. The idea was to check whether the former transduces the chemical change brought about by the interaction of the latter with the metal ion. The appendage of the signaling unit to the lower part of the receptor **1** is shown in Scheme 1, gives new chromogenic receptors **3**. While various 1,3,5-substituted 2,4,6-ethylbenzene based tripodands have been used[26] in IDA (indicator displacement assays) and as anion receptors, to the best of our knowledge there have been hardly any reports where mesitylene based tripodands have been used as binding units transmitting optical signals to show metal recognition. We report here the synthesis of **3** possessing multiple chromogenic donors and the binding ability for Li^+, Na^+, K^+, Sr^{2+}, Ca^{2+}, Cd^{2+}, Zn^{2+}, Hg^{2+}, Pb^{2+}, Ni^{2+}, Cu^{2+}, and Ag^+ metal ions.



Scheme 1.

2. Results and discussion

Compounds **2a–e** were prepared by the literature method[8v] while **A1** and **1** were prepared as already reported by us.[25a] Compounds **3a–d** were prepared by the reaction of 1 mmol of **A1** in dry acetonitrile with 3 mmol aldehydes **2a–d** in chloroform (see Section 4). Compounds **4a**,**b** were synthesized by reacting **2c** and **2e** with *N*,*N*′-dimethylethylenediamine and characterized by ^1H and ^{13}C NMR (Supplementary data). Compounds **3a–d** were characterized by various spectroscopic techniques. A band around 1613–1625 cm^{-1} characterized the presence of imine linkages in IR spectra. The ^1H NMR spectra of **3a–d** either show two clear peaks each (in the intensity ratio 2:1) for the methyl, methylene, and OH protons or relatively broad signals corresponding to them. In ^{13}C NMR spectra also there are two peaks corresponding to methylene carbons. This shows that the conformation of the ligands[27] is II, i.e., cis, trans, trans instead of I, i.e., cis, cis, cis conformation as found in **1** in the solution form[25a] (Fig. 1). The imine units were characterized from signals lying in the range ~ δ 8.43–8.60 in the ^1H NMR spectrum and at ~ δ 160 in the ^{13}C NMR spectra and also from the absence of any signal at ~ δ 10.0 in the ^1H NMR, which corresponds to the aldehyde group. The FAB mass spectra and CHN data are also in accordance with the molecular formulae.

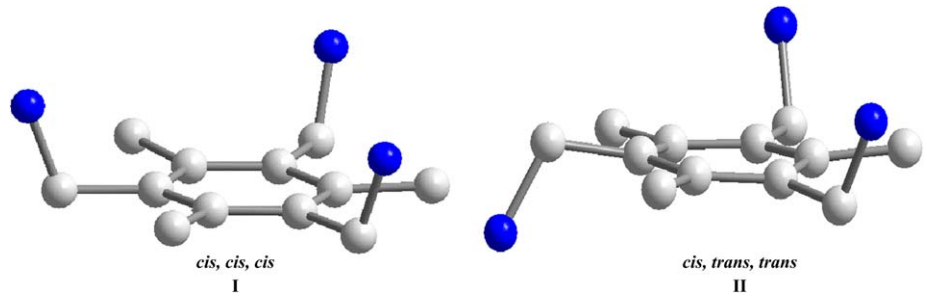


Figure 1. Two possible conformations of mesitylene based tripodands.

Most of the phenolic chromoionophores, including azobenzene based molecules, show the role of the phenolic groups in metal–ligand interaction.[28] Therefore, for investigation of the chromogenic behavior of **3** and to find out the origin of the color change, pH dependent UV–vis spectral titrations were performed in the presence of 0.1 M potassium nitrate (to maintain a constant ionic strength). The spectral changes obtained on titration of an acidic solution of **3c** with alkali are shown in Figure 2a. At pH 1.6 the ligand shows a band at ~ λ_{max} 387 nm, which was assigned as an internal charge-transfer transition of the chromophore from OH to electron withdrawing nitro group. The absorption value of this band increases gradually as the pH is raised from 1.6 to 6.9. After which an increase of pH from 7.0 to 7.5 brings about a slight decrease in absorption of this band. Further increase of 1 unit of pH is accompanied by a slight red shift (~9 nm) in this band and simultaneous appearance of a new band at λ_{max}~510 nm. Any further increase in the pH produces a gradual increase in the absorption of the latter band. Deprotonation of the phenolic group in the basic conditions causes a charge density shift in the direction of the acceptor nitro substituents of the chromogenic receptor. This increases the dipole moments, which ultimately leads to a bathochromic shift[29] due to the stabilization of the photoexcited state more than the ground state. These spectral changes are completely reversible, i.e., by titrating an alkaline solution of **3c** with an acid similar changes were observed in the reverse direction as shown in Figure 2b and are brought about by the protonation of the phenolic group.

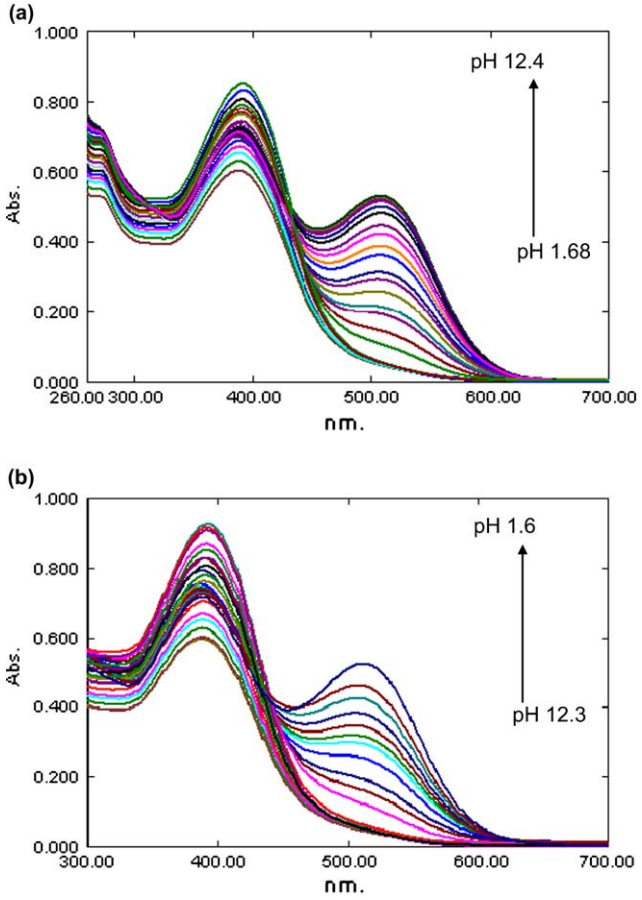


Figure 2. Changes in the UV–vis spectra of **3c** upon pH titration of (a) an acidic solution of **3c** with alkali and (b) an alkaline solution of **3c** with acid.

To obtain a quantitative insight into the metal affinity of the chromogenic tripodal ligands, the wavelength changes upon complexation of various metal ions were determined. The solvent system used was dioxane/water in 1:9 (V:V) ratio, so that all the studies were performed virtually in an aqueous system at 25 °C at neutral pH. Typically, receptor **3c** shows a band at λ_{max}=371 nm (ε=17,000 M^{-1} cm^{-1}) in chloroform/acetonitrile (9:1) and at λ_{max}=384 nm (ε=16,500 M^{-1} cm^{-1}) in water/dioxane (9:1). Figure 3 shows the changes in λ_{max} upon addition of various metal ions. It was found that there were no significant changes in the spectra upon addition of Li^+, Na^+, K^+, Sr^{2+}, Ca^{2+}, Cd^{2+}, Zn^{2+}, Hg^{2+}, Pb^{2+}, Ni^{2+}, and Cu^{2+} metal ion solutions. However, there is a marked change in λ_{max} on addition of Ag^+ ion solution to the chromogenic receptor **3c** where the band at 384 nm splits into two at 394 and 510 nm. One of them showing slight and other one a marked bathochromic shift. The latter is responsible for the distinct color change (Fig. 4) of the solution from yellow (λ_{max}=384 nm) to red

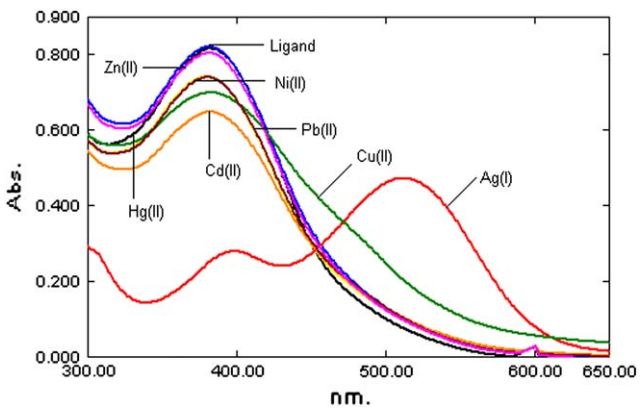


Figure 3. Changes in λ_{max} of **3c** upon addition of metal ions.

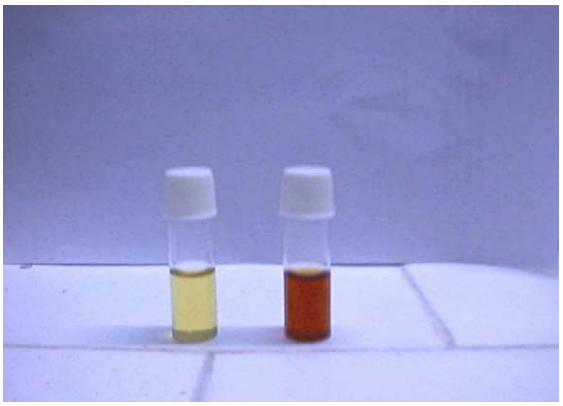


Figure 4. A visual change in color upon addition of Ag^+ salt.

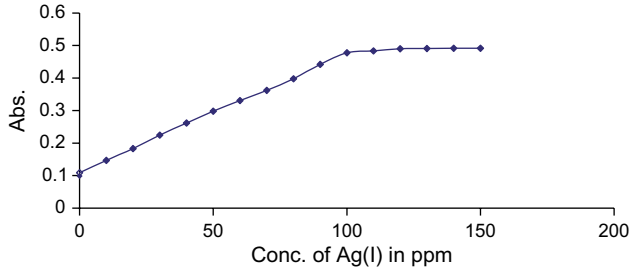


Figure 5. A mole-ratio plot for **3c** showing changes in absorption intensity at λ_{max}=510 nm upon addition of increased amounts of Ag^+ in water samples.

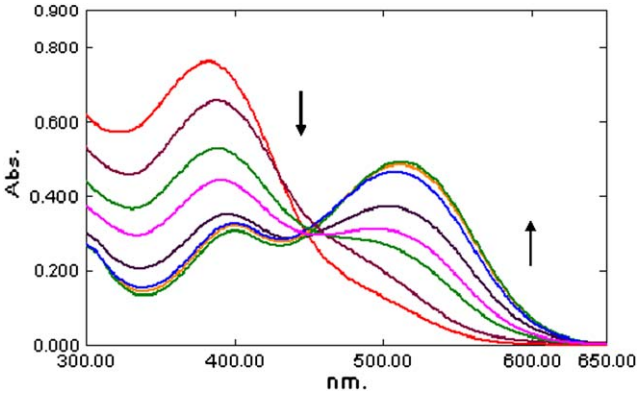


Figure 6. Gradual addition of Ag^+ into a solution of receptor **3c** shows decrease in the intensity of band at 384 nm and a new peak at 510 nm intensifies leading to an isobestic point at 450 nm.

(λ_{max}=510 nm) upon addition of Ag(I), which is visible even with the naked eye.

Table 1 gives an account of the changes in $\lambda_{max.}$ in different ligands **3a–d** with various metal ions. It shows that the results for the recognition of Ag^+ are spectacular in the cases of ortho- and para-substituted **3a** and **3c** products and relatively less pronounced in **3b** and **3d**. These changes in the spectra have been interpreted as a consequence of 1:1 complex formation between the ligands **3** and the Ag(I) ion. The stoichiometry of the **3c** complex was determined by a titration method. The plot between absorption and concentration of Ag(I) reaches a maximum when *L*/*M* ratio is 1:1. Further addition of Ag^+ does not cause any change in the absorption (Fig. 5).

A gradual decrease in the intensity of band at 384 nm with a simultaneous increase in the intensity at 510 nm was seen (Fig. 6) when the concentration of metal ion solution was increased stepwise to a solution of **3c**, giving an isobestic point at 450 nm. The association constant K_s for the inclusion complexes of **3** and **4** with different metal ions was determined on the basis of Benesi–Hilderbrand plots[8a,30] for 1:1 stoichiometry and are given in Table 2. The K_as have not been determined with some of the metal ions because their metal ion-induced absorption changes were too small to be evaluated. It is worth noting that for receptors **3**, especially for **3c**, the association constants were the highest. This is in agreement with the observation that their metal ion-induced changes in the spectra are maximum with Ag^+, in the form of a new band at 510 nm. The measurements for K_as of Ag complexes were made at λ_{max}~500 nm. On the other hand, no other metal ion shows the appearance of any such new band with **3**. Some of them, however, show changes only in the absorption values of the band at λ_{max}~400 nm. Their association constants were determined from measurements at these wavelengths. This shows that the ligands (**3a** and **3c**) are highly selective in their response to Ag^+ in comparison to other metal ions at λ_{max}~500 nm. Thus they may be used for selective recognition of Ag^+, which is even visually realized with these chromogenic compounds. By using these chromogenic receptors, Ag^+ may be detected spectrophotometrically at a low concentration of 1×10^{-5}M and up to a concentration of 5×10^{-5}M visually from the color change. More important, however, is the fact that these studies are performed in aqueous solution. On decomplexation of Ag^+ by thiourea the spectral changes were be totally reversible as shown in Figure 7. This suggests the reusability of the compound as a reversible chemosensor for Ag(I). The system was further extended to estimate Ag^+ in the presence of other soft metal ions, which cause interference in the estimation of Ag^+. Experiments were performed

Table 1. Optical response of ligands **3a–d**, **4a–b** (10^{-4} M) to different metal nitrate salts (10^{-3} M) in 1:9 dioxane/water

Compd	λ_{max} (nm)	ε (l cm^{-1} mol^{-1})	Ag^+	Cu^{2+}	Ni^{2+}	Zn^{2+}	Cd^{2+}	Hg^{2+}	Pb^{2+}	Li^+	Na^+	K^+	Ca^{2+}	Sr^{2+}	Co^{2+}
3a	394	10.9×10^3	+66	+6	+3	+7	−1	0	−2	−1	+2	0	0	+1	—
3b	425	6.2×10^3	+57	+18	+19	+3	+14	+5	−20	0	+1	0	0	0	—
3c	384	8.2×10^3	+126	+2	−5	−1	+1	−1	−4	+2	+3	−1	0	0	—
3d	364	13.2×10^3	+9	+2	+3	+1	−1	−22	+1	0	0	0	0	0	—
4a	400	17.6×10^3	−10	−15	−45	—	—	—	—	—	—	—	—	—	−20
4b	397	18.2×10^3	−3	−5.0	−10	—	—	—	—	—	—	—	—	—	−5

(+) and (−) in wavelength changes denote red and blue shifts. Samples were prepared by mixing 1 ml of 10^{-3} M ligand solution in dioxane and 1 ml of 10^{-2} M metal nitrate solution in water and making 10.0 ml of the total solution.

Table 2. Association constants (K_s, M^{-1}) of various metal nitrates with different ligands

Receptor	Ag^+	Cu^{2+}	Ni^{2+}	Zn^{2+}	Cd^{2+}	Hg^{2+}	Pb^{2+}	Na^+	Co^{2+}
3a	2.7×10^3	8.9×10^2	1.12×10^2	3.8×10^2	—	—	—		—
3b	1.2×10^3	8.3×10^2	8.15×10^2	—	5.8×10^2	—	8.5×10^2	—	—
3c	1.8×10^4	3.2×10^2	—	—	—	—	3.5×10^1	2.3×10^2	—
3d	4.2×10^2	2.9×10^2	2.4×10^2	—	—	6.6×10^2	—	—	—
4a	4.1×10^2	—	1.4×10^3	—	—	—	—	—	9.9×10^2
4b	—	2.5×10^2	5.7×10^2	—	—	—	—	—	—

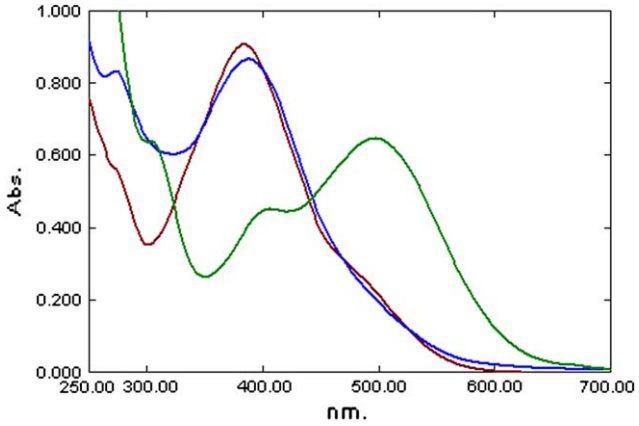


Figure 7. UV–vis spectra of **3c** before and after addition of Ag(I) and reversed changes upon addition of thiourea. Blue [**3c** (0.1 mM)], green [**3c**+Ag(I) (both 0.1 mM)], brown [**3c**+Ag(I) (both 0.1 mM)+thiourea (excess)].

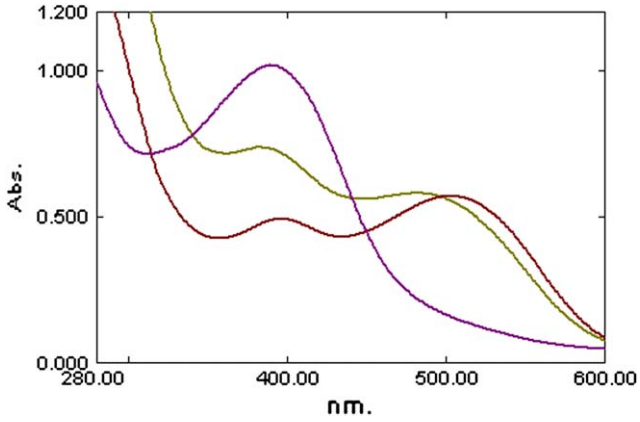


Figure 9. Spectra of ligand **3c**·**Ag** at different pH: purple (pH 1.6), brown (pH 7), dark green (pH 12). The aqueous phase of pH 1 and 12 was adjusted by HCl and triethylamine, respectively.

to measure absorption in the UV–vis spectra of a series of solutions containing **3c**, different amounts of Ag(I) and one other metal ion having concentrations 100–500 times more than Ag(I). The plot of absorption vs concentration of Ag(I) (Fig. 8) shows that Cd^{2+}, Zn^{2+}, Hg^{2+}, Pb^{2+}, Ni^{2+} do not make any difference in the absorption value for the band at 510 nm. Hence, these metal ions do not cause any interference in the estimation of Ag^+, even when they are present in a concentration 500 times larger than Ag^+, except for Cu^{2+}, which causes a small interference when water samples contain Ag^+ at very low concentrations (less than 50 μM) and $[Cu^{2+}]/[Ag^+]$ ratio is 500.

To see the effect of pH on the metal–ligand complex the spectra of the ligand **3c** in the presence of Ag^+ were taken at three different pH values as shown in Figure 9. At pH 7 the complex showed two bands of different intensities, at 396 and 503 nm, just as was found for the free ligand at basic pH. In basic conditions, i.e., at pH 12, both the free ligand as well as the complex showed two bands at 384 and 484 nm, having different absorption values. The bathochromic shift at pH 12 is as expected since the phenolate ions produced in the basic conditions result in stronger interaction between **3** and Ag^+ leading to the absorption at 484 nm. Also two bands at different $\lambda_{max.}$ values, are indicative of two types of phenolic groups both in the free ligand (in alkaline pH) as well as in the complex (in neutral and alkaline pH). Such a band splitting has earlier been reported in the chromogenic azo-coupled calix[4]crown compounds[9a,d] with two types of -oxy units, having nonequivalent interactions with the metal ion. From this it may be inferred that the complexation does not entail complete deprotonation of all the phenolic groups to form an ion pair but is more of covalent in nature. This is in accordance with suggestions[31] made by Takagi that less basic, more charge-delocalized phenolates preferentially bind to large metal ions (with low charge densities) by forming intramolecular complexes similar to ion pairs whereas more basic, less charge-delocalized phenolates extract smaller ions (with high charge densities) preferentially by forming covalent complexes. In contrast, the UV–vis absorption peaks in the acidic solution (pH∼1) remain almost invariant (∼390 nm) both in the free ligand as well as in the complex. It may be concluded from above that there is a metal ion-induced deprotonation of the phenolic group at neutral pH in the presence of Ag(I) ions.

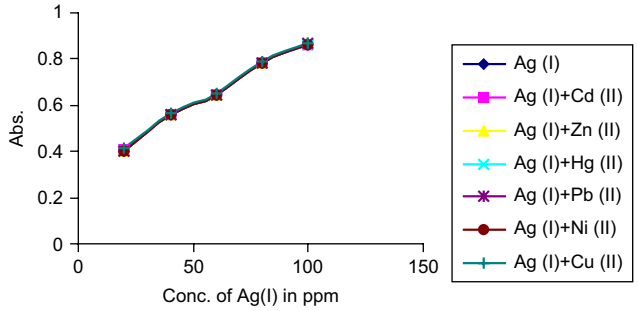


Figure 8. Changes in absorption intensity when Ag^+ is present along with other interfering cations.

The mode of binding by the receptors was inferred from the ^1H NMR spectra of **3a** and **3a**·Ag^+ taken in DMSO since ligand as well as metal ion are soluble in it. Though the peaks are broader, they showed clear and significant shifts in the chemical shift values on complexation. NMR spectra of

the complex also showed that the ligand is in conformation II as found in the free ligand. An upfield shift of $\Delta\delta$ 0.186, 0.022 in imine, 0.151 in OH, 0.016, 0.064 in methyl protons, and a downfield shift of 0.122, 0.173 in methylene protons, respectively, indicate participation of S, imine N, and hydroxyl group in coordination toward Ag^+ ion. The color changes accompanying interactions of **3** with Ag^+, demonstrate a significant chromogenic effect taking place on metal-induced cooperative binding by the phenol group. In both free state and the complex, the ligand is found in conformation II, hence one of the phenolic groups, which is pointing in the other direction may be participating cooperatively in coordination with the metal ion. This also explains the splitting of the 384 nm band of the free ligand into two bands (Fig. 3) at 394 and 510 nm in the UV–vis spectrum. Thus the observed chromogenic effect could be explained in terms of the protonable receptors undergoing complete or partial, metal-induced deprotonation of the phenolic groups. On addition of an aqueous solution of Ag^+ to the solution of receptor **3c**, the coordination of Ag^+ occurs through soft donors S and imine nitrogens and is further facilitated by cooperative binding from a polar OH group. Such cooperative, sidearm binding by phenolic groups has been seen in all phenolic chromoionophores.[28]

It has been seen that the availability of a 2-dimensional pseudo-cavity provided by soft S and imine N of the tripodal ligands in conformation II, augmented by chelation through –OH group, has an important role in cation binding and selectivity. Both are working cooperatively with each other and one would not show the chromogenic behavior in the absence of other. This was inferred by making similar UV–vis studies on **4** in 1:9 (v/v) mixture of dioxane and water. The responses in the electronic spectra of **4** for Co^{2+}, Ni^{2+}, Cu^{2+}, and Ag^+ were studied (Table 1). It was seen that **4a** shows a considerable shift of 45 nm with Ni^{2+} whereas Ag^+ shows only a small shift, both of which are hypsochromic in nature. On the other hand, **4b** hardly shows any response toward any of these metal ions. As the binding sites available in **4a** are more appropriate for the borderline transition metal ions than softer Ag^+, it shows better response toward Ni^{2+} ion. The strong electron withdrawing nitro group at the para position to the hydroxyl group facilitates deprotonation of the latter resulting in chelation to the metal ion. The sensing units **2** (aldehydes of the dye component) do not show any significant change in their electronic spectra with Ag^+ ions at neutral pH (Supplementary data). This suggests that the chelation by the podand molecule, having metal specific soft binding sites and favorable disposition of the signaling unit helping in ionization of hydroxyl group, is required for the efficient chromogenic response of these chemosensors toward Ag(I) ions.

3. Conclusions

Silver ion selectivity and specificity of the binding unit of Schiff base **1** was optically transduced by the sensing unit **2**. Appendage of **2** to **1** has resulted in a fully reversible, chromogenic response to the binding of Ag(I) metal ion. The metal ion recognition is detectable spectrophotometrically up to a metal ion concentration of 1×10^{-5} M and visually up to a concentration of 5×10^{-5} M. The results are highly useful as these chromogenic compounds are developed for metal photometry in environment friendly aqueous medium. The compounds are highly Ag(I) selective and do not show any interference from common contaminants even when they are present in concentrations 500 times larger than Ag(I) ion, except for Cu^{2+}, which shows small interference when water samples contain Ag(I) at a very low concentration, i.e., less that 50 μM.

4. Experimental

4.1. General

Melting points are uncorrected. Most chemicals were purchased from Aldrich Co. and used as received without further purification. Organic solvents were purified by standard procedures. The elemental analyses were performed on a Flash EA 1112 elemental analyzer and FAB mass spectra were recorded at RSIC at Central Drug Research Institute, Lucknow, India. The ^1H and ^{13}C NMR were taken on a 200 MHz Bruker or a 300 MHz JEOL spectrometers using TMS as a standard reference. IR spectra were recorded on a PYE Unicam IR spectrometer for the compounds in the solid state as KBr discs or as neat samples. UV–vis absorption spectra were taken on a Shimadzu Pharamaspec UV-1700 UV–vis spectrophotometer. The compounds **2a–e** were prepared by the literature method.[8v] The tripodal amine **A1** was prepared as already reported by us.[25a]

4.2. General method of preparation

Compounds **3a–d** were prepared by taking tripodal amine **A1** (531 mg, 1.0 mmol) in dry acetonitrile and the aldehyde **2a–c** (1.084 g, 4.0 mmol) or **2d** (1.020 g, 4.0 mmol) in chloroform. The two solutions were mixed and the reaction mixture refluxed for 2 h. The progress of the reaction was monitored by TLC. At completion the solvent was evaporated and the product recrystallized in methanol to give reddish orange solids.

4.2.1. Compound 3a. Yield=64%; mp=160 °C; IR (KBr, cm^{-1}) 1622; FABMS $[M+1]^+$=1291; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.24 (s, –OH of solvent methanol), 1.56 (br s, $-CH_3$ of solvent methanol), 1.99, 2.14 (s, 9H, $-CH_3$), 3.69, 3.74 (br s, 6H, $-CH_2$); 7.04 (d, 3H, Ar, J=8.0 Hz), 7.14–7.29 (m, 6H, Ar), 7.41–7.52 (m, 6H, Ar), 7.59–7.66 (m, 6H, Ar), 7.68–7.83 (m, 6H, Ar), 7.87–7.97 (m, 6H, Ar) 8.50 (s, 3H, CH=N), 14.03 (s, 3H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.61 (CH_3), 29.68 (CH_2), 118.13 (Ar), 118.39 (Ar), 118.58 (Ar), 119.05 (Ar), 123.94 (Ar), 124.12 (Ar), 127.70 (Ar), 128.09 (Ar), 128.57 (Ar), 129.91 (Ar), 130.31 (Ar), 131.32 (Ar), 132.33 (Ar), 132.88 (Ar), 145.25 (Ar), 146.95 (Ar), 147.42 (Ar), 160.75 (–CH=N), 165.49 (ArOH); Anal. Calcd $C_{69}H_{54}N_{12}O_9S_3$: C 64.18, H 4.18, N 13.02, S 7.44; found: C 63.89, H 4.38, N 13.64, S 6.98.

4.2.2. Compound 3b. Yield=63%; mp=185 °C; IR (KBr, cm^{-1}) 1616; FABMS $[M+1]^+$=1291; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.26 (s, –OH of solvent methanol), 1.57 (br s, $-CH_3$ of solvent methanol), 2.00, 2.17 (s, 9H, $-CH_3$), 3.72,

3.97 (s, 6H, –CH_2), 7.06 (d, 3H, Ar, J=8.0 Hz), 7.09–7.30 (m, 12H, Ar), 7.33–7.40 (m, 3H, Ar), 7.62–7.66 (m, 6H, Ar), 7.95–8.55 (m, 9H, Ar), 8.55–8.60 (m, 3H, CH═N), 13.87, 13.98 (s, 3H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ15.65 (CH_3), 15.79 (CH_3), 29.68 (CH_2), 33.64 (CH_2), 116.61 (Ar), 118.13 (Ar), 118.60 (Ar), 119.05 (Ar), 124.35 (Ar), 127.27 (Ar), 127.67 (Ar), 128.05 (Ar), 129.05 (Ar), 129.25 (Ar), 129.84 (Ar), 130.64 (Ar), 131.28 (Ar), 132.42 (Ar), 136.46 (Ar), 144.88 (Ar), 146.93 (Ar), 148.94 (Ar), 152.89 (Ar), 160.79 (CH═N), 165.28 (ArOH); Anal. Calcd $C_{69}H_{54}N_{12}O_9S_3$: C 64.18, H 4.18, N 13.02, S 7.44; found: C 63.78, H 3.97, N 12.89, S 6.89.

4.2.3. Compound 3c. Yield=63%; mp=210 °C; IR (KBr, cm^{-1}) 1625; FABMS $[M+1]^+$=1291; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (s, –OH of solvent methanol), 1.58 (br s, –CH_3 of solvent methanol), 2.01 (br s, 9H, –CH_3), 3.71–3.79 (m, 6H, –CH_2), 6.91–7.46 (m, 18H, Ar), 7.57 (d, 3H, Ar, J=8.0 Hz), 7.94 (d, 3H, Ar, J=8.0 Hz), 8.07 (s, 3H, Ar), 8.29–8.37 (m, 6H, Ar), 8.43–8.56 (m, 3H, –CH═N), 13.17, 14.07 (s, 3H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.60 (CH_3), 26.99 (CH_2), 29.67 (CH_2), 117.27 (Ar), 118.07 (Ar), 119.03 (Ar), 123.12 (Ar), 124.70 (Ar), 125.45 (Ar), 127.37 (Ar), 128.15 (Ar), 129.94 (Ar), 130.36 (Ar), 131.38 (Ar), 132.35 (Ar), 136.52 (Ar), 146.90 (Ar), 147.42 (Ar), 160.75 (CH═N), 165.58 (ArOH); Anal. Calcd $C_{69}H_{54}N_{12}O_9S_3$: C 64.18, H 4.18, N 13.02, S 7.44; found: C 64.56, H 4.56, N 12.88, S 6.93.

4.2.4. Compound 3d. Yield=64%; mp=165 °C; IR (KBr, cm^{-1}) 1614; FABMS $[M+1]^+$=1258, 1260 (isotopic peaks); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (s, –OH of solvent methanol), 1.59 (br s, –CH_3 of solvent methanol), 2.00, 2.14 (s, 9H, –CH_3), 3.74, 3.95 (s, 6H, –CH_2), 7.07 (d, 3H, Ar, J=8.0 Hz), 7.16–7.33 (m, 12H, Ar), 7.40–7.56 (m, 6H, Ar), 7.60–7.66 (m, 6H, Ar), 8.00–8.06 (m, 6H, Ar), 8.53 (s, 3H, –CH═N), 13.89 (s, 3H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.62 (CH_3), 29.73 (CH_2), 33.66 (CH_2), 117.52 (Ar), 118.20 (Ar), 118.32 (Ar), 119.05 (Ar), 127.21 (Ar), 127.90 (Ar), 128.10 (Ar), 128.19 (Ar), 130.08 (Ar), 130.57 (Ar), 130.70 (Ar), 131.98 (Ar), 132.10 (Ar), 134.02 (Ar), 136.44 (Ar), 145.61 (Ar), 147.24 (Ar), 148.57 (Ar), 161.05 (CH═N), 164.64 (ArOH); Anal. Calcd $C_{69}H_{54}N_9O_3S_3Cl_3$: C 65.87, H 4.29, N 10.02, S 7.63; found: C 65.32, H 4.53, N 10.37, S 7.97.

4.3. Stability constant determination

Fifteen measuring flasks were taken each containing 1 ml of ligand solution (1×10^{-3} M, in dioxane) along with varied amounts (0.1–1.5 ml) of metal nitrate solution (1×10^{-3} M, in water). Then the measuring flasks were filled to make 10 ml, with a stock solution of a commercially available buffer of pH 7 and 1 M KNO_3. The measurements for Ag(I) were made at λ_{max}~510 nm and for the remaining metals at λ_{max}~400 nm.

4.4. Mole-ratio method

Fifteen solutions were made by varying *L*/*M* ratio and keeping the total volume of the solution constant as 10 ml in water/dioxane 9:1. The concentration of the receptor was kept at 10^{-4} M in all the solutions, while the metal ion concentration was varied from 1×10^{-5} to 1.5×10^{-4} M in different solutions. A stock solution of a commercially available buffer solution of pH 7 and 1 M KNO_3 was used to maintain a constant pH and ionic strength. The absorption was measured at 510 nm as it showed the maximum and the cleanest variation upon addition of Ag^+.

4.5. Ion interference studies

For every interfering ion, five 10 ml measuring flasks each containing 1 ml of ligand solution (1×10^{-3} M, in dioxane) were taken. To these varied amounts of water solution of Ag^+ (0.20–1.0 ml of 1×10^{-3} M) were added. Then 1 ml solution of one interfering metal ion (1×10^{-1} M) was added to all of them. The measuring flasks were then filled up to the mark with buffered solution of pH 7 and 1 M KNO_3 in water so as to keep the composition of solution in each flask as constant. The respective flasks thus contained interfering metal ion in concentrations 100–500 times more than Ag(I). The absorption of each solution was recorded at λ_{max}=510 nm.

Acknowledgements

G.H. is thankful to the CSIR, India for research grant No. 01(1796)/02/EMR-II, N.S. and V.K.B. are thankful to the CSIR for research fellowship.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.05.047.

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Tetrahedron 62 (2006) 7887–7891

Aerobic photo-oxidation of alcohols in the presence of a catalytic inorganic bromo source

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Received 27 February 2006; accepted 17 May 2006
Available online 9 June 2006

Abstract—Alcohols were found to be oxidized to the corresponding carboxylic acid in the presence of a catalytic inorganic bromo source, for example, lithium bromide, bromine, and hydrobromic acid, under photo-irradiation.

1. Introduction

Oxidation of alcohols is the foundation of synthetic chemistry, and has been the subject of study by many researchers; however, these reactions essentially involved the use of large quantities of heavy metals and complex organic compounds, which generate large amounts of waste, and were not at all environmentally benign.[1] With this background in mind, we examined a new oxidation method with the catalysis of alkali metal halides[2] and molecular oxygen. Molecular oxygen has recently received much attention in the field of synthetic organic chemistry, since it is photosynthesized by plants and is an effective oxidant of larger atom efficiency than that of other oxidants.[3] In the course of our study of photo-oxidation, we have found that alcohols were oxidized directly to the corresponding carboxylic acids in the presence of catalytic lithium bromide in an oxygen atmosphere under irradiation by a high-pressure mercury lamp.[4] This new form of oxidation reaction is interesting in keeping with the notion of Green Chemistry due to non-use of heavy metals, waste reduction, use of molecular oxygen, and inexpensive acquisition of reagents.[5,6] We believe that this oxidation proceeds only if a catalytic amount of a bromo radical is generated in situ.[7] This is the driving force of our continued studies on this oxidation with a new inorganic bromo source, which is inexpensive, safe, and easily separable from the reaction mixture by extraction, and we have found that bromine, which is more reactive than lithium bromide, and hydrobromic acid, which is less expensive than lithium bromide, are also suitable for this purpose. Herein, we report our detailed study on the generality of this photo-oxidation of alcohols in the presence of a catalytic inorganic bromo source, such as lithium bromide, bromine, and hydrobromic acid.

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doi:10.1016/j.tet.2006.05.048

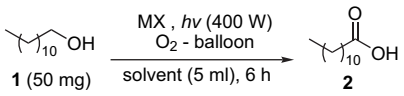
2. Results and discussion

2.1. Aerobic photo-oxidation of alcohols in the presence of catalytic amount of lithium bromide

Table 1 shows the results of the study of reaction conditions conducted with **1** (50 mg, 0.269 mmol) as a test substrate under 6 h external irradiation by a 400-W high-pressure mercury lamp in an oxygen atmosphere. The temperature of the final stage of this reaction was about 50 °C. We do not have any direct evidence; however, we believe an effective wavelength of the light is 365 nm, which is an emission line of the strongest and longest wavelength in an ultraviolet region irradiated from a high-pressure mercury lamp, since passing through water, a test tube and a cooling jacket, which are made from Pyrex glass, and air is necessary for the light to effect this reaction. Among the alkali metal halides and solvents examined, only lithium bromide and ethyl acetate were found to afford most efficiently the corresponding carboxylic acid **2**. We were surprised to find, however, reduction in the yield of **2** regardless of increase or decrease in the amount of lithium bromide used, and obtained the best results from our tests when using 0.3 equiv of lithium bromide (entries 1–6). That no oxidation proceeded without either irradiation of UV or the addition of lithium bromide shows the necessity of both for this reaction. Furthermore, from the fact that yields of the target substance were reduced substantially when the reaction was conducted under the flow of argon, we can assume that the actual oxidant in this reaction is molecular oxygen.

Table 2 shows the results of the photo-oxidation reaction using several alcohols in the presence of cat. lithium bromide. Both benzyl and aliphatic alcohols, in general, afford the corresponding carboxylic acids in good yields, although there is a difference in reaction times.

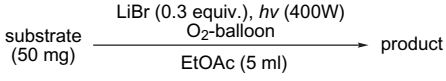
Table 1. Study of reaction conditions of aerobic photo-oxidation in the presence of cat. LiBr

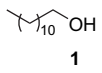
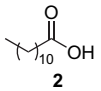
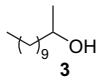
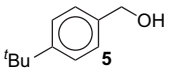
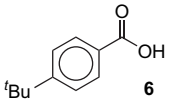
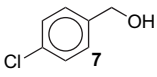
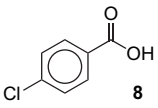
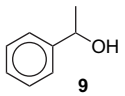
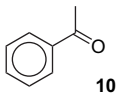


Entry	MX	(Equiv)	Solvent	Yield of **2** (%)[a]
1	LiBr	0.1	EtOAc	66
2	LiBr	0.2	EtOAc	76
3	LiBr	0.3	EtOAc	82
4	LiBr	0.4	EtOAc	63
5	LiBr	0.5	EtOAc	10
6	LiBr	1.0	EtOAc	Trace
7	LiBr	0.3	Acetone	0
8	LiBr	0.3	MeCN	0
9	LiBr	0.3	THF	Trace
10	LiBr	0.3	Benzene	12
11	LiBr	0.3	H_2O	0
12	LiCl	0.3	EtOAc	0
13	NaBr	0.3	EtOAc	0
14	KBr	0.3	EtOAc	0

[a] All yields are for pure, isolated products.

Table 2. Aerobic photo-oxidation for various alcohol substrates in the presence of cat. LiBr



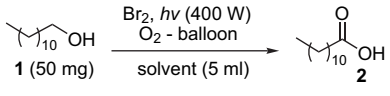
Entry	Substrate	*t* (h)	Product	Yield (%)[a]
1	 **1**	6	 **2**	82
2	 **3**	15	 **4**	75
3	 **5**	2	 **6**	83
4	 **7**	5	 **8**	89
5	 **9**	9	 **10**	82

[a] All yields are for pure, isolated products.

2.2. Aerobic photo-oxidation of alcohols in the presence of catalytic amount of bromine

Although lithium bromide is undoubtedly an inexpensive and safe reagent, it is not necessarily easy to handle because of its hygroscopic property. Table 3 shows our initial study of the reaction conditions of the aerobic photo-oxidation, which was carried out using **1** with bromine in various solvents. Among the solvents and the amounts of bromine examined, acetonitrile and 0.07 equiv of bromine were found to be suitable for the reaction. Bromine is a more

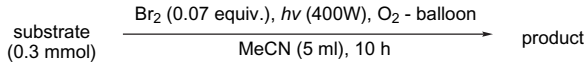
Table 3. Study of reaction conditions of aerobic photo-oxidation in the presence of cat. bromine

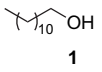
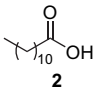
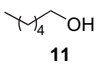
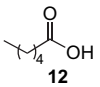
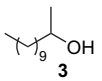
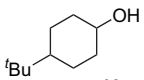
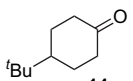
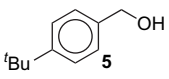
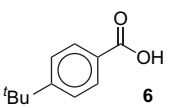
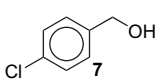
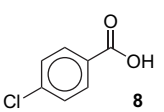
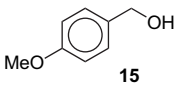
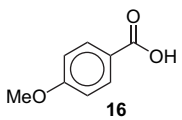


Entry	Br_2 (equiv)	Solvent	*t* (h)	Yield of **2** (%)[a]
1	0.07	MeCN	4	47
2	0.07	MeCN	6	46
3	—	MeCN	10	0
4	1.4×10^{-4}	MeCN	10	0
5	1.4×10^{-3}	MeCN	10	18
6	0.007	MeCN	10	65
7	0.07	MeCN	10	85
8	0.07	MeCN	10	0[b]
9	0.07	MeCN	10	0[c]
10	0.14	MeCN	10	68
11	0.21	MeCN	10	33
12	0.35	MeCN	10	9
13	0.07	EtOAc	10	59
14	0.07	CH_2Cl_2	10	13
15	0.07	AcOH	10	64
16	0.07	Hexane	10	0
17	0.07	THF	10	0
18	0.07	MeOH	10	0

[a] All yields are for pure, isolated products.
[b] The reaction was carried out in the dark.
[c] The reaction was carried out in an argon atmosphere.

Table 4. Aerobic photo-oxidation in the presence of cat. bromine



Entry	Substrate	Product	Yield (%)[a]
1	 **1**	 **2**	95
2	 **11**	 **12**	80
3	 **3**	 **4**	61
4	 **13**	 **14**	15[b]
5	 **5**	 **6**	99
6	 **7**	 **8**	100
7	 **15**	 **16**	80

[a] The reaction was carried out for 20 h.
[b] All yields are for pure, isolated products.

effective catalyst than lithium bromide since the amount of bromine required for carrying out this oxidation smoothly is much smaller than that of lithium bromide previously reported.[4] That no oxidation proceeded without either irradiation of UV, or the addition of bromine or molecular oxygen shows the necessity of all for this reaction (entries 3, 8 and 9).

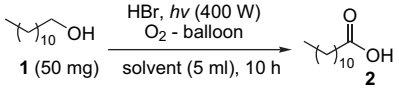
Table 4 shows the results for the oxidation of several substrates (0.3 mmol) under the reaction conditions outlined above. Although in general primary alcohols, including benzyl alcohols, were oxidized to the corresponding carboxylic acids in high yields, secondary alcohols afforded the product in modest yield due to recovery of the starting materials.

2.3. Aerobic photo-oxidation of alcohols in the presence of catalytic amount of hydrobromic acid

Although bromine was found to be more effective than lithium bromide, it is difficult to say that bromine is a good reagent because of its intractable and toxic properties. Then, hydrobromic acid was examined for this oxidation reaction. Table 5 shows the results of study of reaction conditions conducted with **1** under the conditions of 10 h external irradiation by a 400-W high-pressure mercury lamp in an oxygen atmosphere. Among the solvents examined, acetonitrile was found to afford most efficiently the corresponding carboxylic acid **2** (entries 9–14). We also found that reduction in the yield of **2** was observed regardless of increase or decrease in the amount of hydrobromic acid used, and obtained the best result among our tests when using 0.14 equiv or 0.20 equiv of hydrobromic acid (entries 2–5 and 8). That no oxidation proceeded without either the addition of hydrobromic acid or irradiation of UV or molecular oxygen shows the necessity of all for this reaction (entries 1, 6 and 7).

Table 6 shows the generality of this oxidation reaction using a variety of 0.3 mmol of alcohols in the presence of

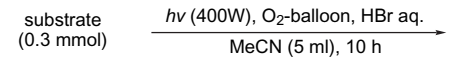
Table 5. Study of conditions for photo-oxidation of **1** in the presence of cat. hydrobromic acid

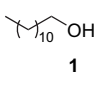
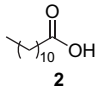
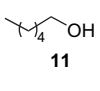
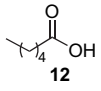
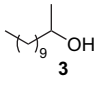
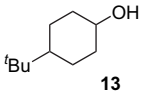
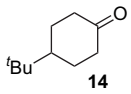
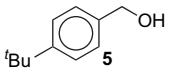
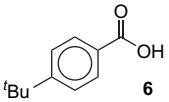
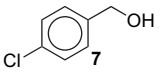
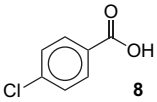
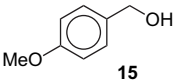
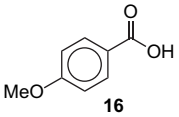
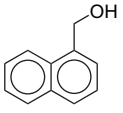
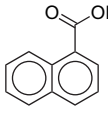
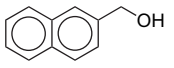
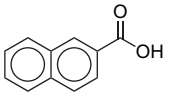
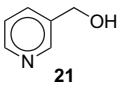
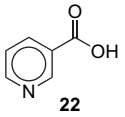
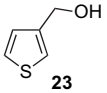
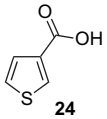


Entry	HBr (equiv)	Solvent	Yield of **2** (%)[a]
1	—	MeCN	0
2	1.4×10^{-3}	MeCN	0
3	0.035	MeCN	62
4	0.07	MeCN	70
5	0.14	MeCN	81
6	0.14	MeCN	0[b]
7	0.14	MeCN	0[c]
8	0.20	MeCN	77
9	0.70	MeCN	0
10	0.07	EtOAc	56
11	0.07	Acetone	50
12	0.07	Hexane	15
13	0.07	MeOH	0
14	0.07	H_2O	0

[a] All yields are for pure, isolated products.
[b] The reaction was carried out in the dark.
[c] The reaction was carried out in an argon atmosphere.

Table 6. Aerobic photo-oxidation of alcohols in the presence of cat. hydrobromic acid



Entry	Substrate	HBr aq (equiv)	Product	Yield (%)[a]
1	 **1**	0.14	 **2**	69
2	 **11**	0.20	 **12**	66
3	 **3**	0.20	 **4**	57
4	 **13**	0.20	 **14**	27[b]
5	 **5**	0.20	 **6**	99
6	 **7**	0.20	 **8**	100
7	 **15**	0.20	 **16**	92
8	 **17**	0.20	 **18**	81
9	 **19**	0.20	 **20**	94
10	 **21**	0.20	 **22**	100
11	 **23**	0.20	 **24**	83

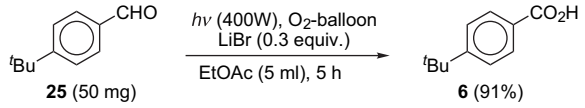
[a] All yields are pure, isolated products.
[b] The reaction was carried out for 20 h.

0.14 equiv or 0.20 equiv of hydrobromic acid. Aliphatic primary alcohols, in general, afford the corresponding carboxylic acids in moderate yields; however, aliphatic secondary

alcohols were less reactive than primary alcohols (entries 1–4). The corresponding benzoic acids were obtained in high yield regardless of an electron-donating or electron-withdrawing group at the aromatic nucleus when using benzyl alcohols (entries 5–7). Compounds 1- and 2-naphthalenemethanols (**17** and **19**) also afforded the corresponding naphthoic acids (**18** and **20**) in high yields. Furthermore, heterocyclic compounds, such as 3-pyridinemethanol (**21**) and 3-thiophenemethanol (**23**), afforded the corresponding carboxylic acids **22** and **24**, respectively, in high yields.

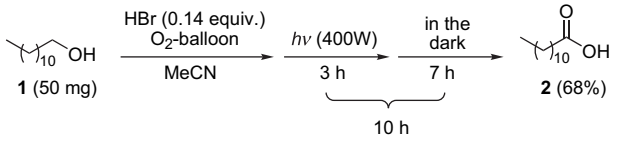
2.4. Mechanism

In order to examine the mechanism of this reaction, at first, aldehyde **25**, which is presumed to be an intermediate, was subjected to similar aerobic photo-oxidation conditions, and **6** was obtained in 91% yield. Thus, this reaction is thought to proceed through the aldehyde as an intermediate (Scheme 1).



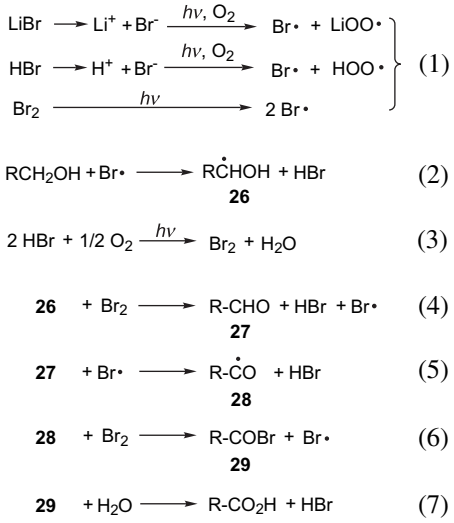
Scheme 1. Aerobic photo-oxidation of aldehyde.

Also, lowering of the yield (68%) under the condition whereby **1** was reacted under irradiation for 3 h with a 400-W high-pressure mercury lamp and then reacted in the dark for 7 h, shows the necessity of continuous irradiation to complete this oxidation, and this reaction does not involve an auto-oxidation path (Scheme 2).



Scheme 2. Study of auto-oxidation path.

Furthermore, ethyl acetate or acetonitrile is thought to be suitable for liberating the 'naked' bromo anion due to its solvation effect to the corresponding counter cation by the oxygen or nitrogen atom. We present in Scheme 3 what we assume is a plausible path of this oxidation, which is postulated by considering all of the results mentioned above, and the necessity of a catalytic amount of an inorganic bromo source and of molecular oxygen in this reaction.[6] The radical species **26** is thought to be generated by abstraction of a hydrogen radical with a bromo radical, formed by continuous aerobic photo-oxidation of the bromo anion from the inorganic bromo source (Eqs. 1 and 2). Bromine, then, was formed by aerobic photo-oxidation of hydrogen bromide, which is generated in Eq. 2 (Eq. 3). Aldehyde **27** was afforded by abstraction of a hydrogen radical with bromine (Eq. 4), and the re-generated bromo radical abstracted a hydrogen radical from **27** to give radical species **28**, which was transformed to acyl bromide **29** (Eqs. 5 and 6). The carboxylic acid was formed by reaction with water (Eq. 7).



Scheme 3. Plausible path of aerobic photo-oxidation of alcohols.

3. Conclusion

As mentioned above, photo-oxidation with molecular oxygen of alcohols in the presence of a catalytic amount of an inorganic reagent, lithium bromide, bromine, and hydrogen bromide, was studied, and the corresponding carboxylic acid was obtained in good yield. Especially, among the reagents examined, hydrobromic acid is inexpensive, safe, and easy to handle due to its non-hygroscopic property, and thus, this oxidation is a facile and convenient method in the view point of synthetic organic chemistry.

4. Experimental

4.1. General

Methylene chloride was freshly distilled from CaH_2 under nitrogen. THF was freshly distilled from Na metal/benzophenone ketyl. All other dry solvents were obtained from Kanto Kagaku Co., Ltd. Other chemicals used were of reagent grade and were obtained from Aldrich Chemical Co., Tokyo Kasei Kogyo Co., Ltd and Wako Pure Chemical Industries, Ltd. All reactions were carried out in a Pyrex test tube equipped with an O_2-balloon, which was set up from the center of 400-W high-pressure mercury lamp to the distance of 37.5 mm. All of the products are known compounds. ^{1}H NMR spectra were recorded on JEOL 400-MHz spectrometer (EX-400 and AL-400) using TMS as an internal standard or solvent peak as a standard. ^{13}C NMR spectrum was recorded on JEOL EX-400 (100 MHz) spectrometer using TMS as an internal standard. Mass spectrometric data were collected on a JEOL JMS-SX 102A mass spectrometer.

4.1.1. Oxidation of primary alcohols in the presence of cat. LiBr, bromine, or hydrobromic acid. A typical procedure is as follows: in a Pyrex test tube with an O_2-balloon, a solution (5 mL) of the substrate and catalytic bromo source in dry solvent was stirred and irradiated at room temperature with a 400-W high-pressure mercury lamp, which was equipped with a cooling jacket, externally for the indicated time. The reaction mixture was concentrated under reduced

pressure, and 10% NaOH aqueous solution was added. The aqueous solution was washed with diethyl ether, and then acidified with 2 N HCl aqueous solution, which was extracted with diethyl ether. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated under reduced pressure. The product was pure without further purification.

4.1.2. Oxidation of secondary alcohols in the presence of cat. LiBr, bromine, or hydrobromic acid. A typical procedure is as follows: in a Pyrex test tube with an O_2-balloon, a solution (5 mL) of the substrate and catalytic bromo source in dry solvent were stirred and irradiated at room temperature with a 400-W high-pressure mercury lamp, which was equipped with a cooling jacket, externally for the indicated time. The reaction mixture was concentrated under reduced pressure, and 10% NaOH aqueous solution was added. The aqueous solution was washed with diethyl ether and the organic layer was concentrated, and the residue was purified by preparative tlc.

4.1.3. Dodecanoic acid (2). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.32 (t, J=7.4 Hz, 2H, –CH_2–COOH), 1.60 (m, 2H, –CH_2–CH_2–COOH), 1.23 (m, 16H), 0.86 (t, J=6.8 Hz, 3H, –CH_3). MS: m/z=200.

4.1.4. 2-Dodecanone (4). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.35 (t, J=7.4 Hz, 2H, –CH_2–CO–), 2.07 (s, 3H, CH_3–CO–), 1.50 (m, 2H, –CH_2–CH_2–CO–), 1.20 (m, 14H), 0.82 (t, J=6.8 Hz, 3H, –CH_3). MS: m/z=184.

4.1.5. 4-*tert*-Butylbenzoic acid (6). ^{1}H NMR (400 MHz, acetone-d_6): δ=7.96 (d, J=8.7 Hz, 2H, C2 and C6-H), 7.54 (d, J=8.7 Hz, 2H, C3 and C5-H), 1.34 (s, 9H, *t*-Bu). MS: m/z=163.

4.1.6. 4-Chlorobenzoic acid (8). ^{1}H NMR (400 MHz, acetone-d_6): δ=8.03 (d, J=8.7 Hz, 2H, C2 and C6-H), 7.55 (d, J=8.7 Hz, 2H, C3 and C5-H). MS: m/z=139.

4.1.7. Acetophenone (10). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.94 (d, J=7.2 Hz, 2H, C2 and C6-H), 7.54 (t, J=7.2 Hz, 1H, C4-H), 7.44 (t, J=7.2 Hz, 2H, C3 and C5-H), 2.59 (s, 3H). MS: m/z=120.

4.1.8. Hexanoic acid (12). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.35 (t, J=7.6 Hz, 2H, –CH_2–CO_2H), 1.64 (quin, J=7.4 Hz, 2H, –CH_2–CH_2–CO_2H), 1.36–1.29 (m, 4H), 0.90 (t, J=7.1 Hz, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=180.2, 34.0, 31.2, 24.3, 22.3, 13.9.

4.1.9. 4-*tert*-Butylcyclohexanone (14). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.42–2.26 (m, 4H), 2.17–2.05 (m, 2H), 1.53–1.39 (m, 3H), 0.92 (s, 9H, *t*-Bu). MS: m/z=154.

4.1.10. 4-Anisic acid (16). ^{1}H NMR (400 MHz, CD_3OD): δ=7.98 (d, J=8.7 Hz, 2H, C2 and C6-H), 7.01 (d, J=8.7 Hz, 2H, C3 and C5-H), 3.87 (s, 3H, –OCH_3). MS: m/z=152.

4.1.11. 1-Naphthoic acid (18). ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.07 (d, J=8.0 Hz, 1H, C8-H), 8.40 (dd, J=7.3, 1.5 Hz, 1H, C2-H), 8.08 (d, J=8.0 Hz, 1H, C4-H), 7.91 (dd, J=8.0, 0.7 Hz, 1H, C5-H), 7.65 (ddd, J=8.5, 7.0, 1.5 Hz, 1H, C7-H), 7.58 (m, 2H, C3 and C6-H). MS: m/z=172.

4.1.12. 2-Naphthoic acid (20). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.70 (s, 1H, C1-H), 8.10 (dd, J=8.7, 1.5 Hz, 1H, C-H), 7.98 (d, J=7.8 Hz, 1H, C-H), 7.90 (m, 2H, C-H), 7.62 (dd, J=7.0, 1.3 Hz, 1H, C5-H), 7.58 (dd, J=7.7, 1.3 Hz, 1H, C6-H), 7.55 (dd, J=6.8, 1.2 Hz, 1H, C7-H). MS: m/z=172.

4.1.13. Nicotinic acid (22). ^{1}H NMR (400 MHz, CD_3OD): δ=9.12 (s, 1H, C2-H), 8.73 (dd, J=5.0, 1.5 Hz, 1H, C6-H), 8.42 (ddd, J=6.0, 1.9, 1.9 Hz, 1H, C4-H), 7.57 (ddd, J=7.2, 5.0, 0.7 Hz, 1H, C5-H). MS: m/z=123.

4.1.14. 3-Thiophene carboxylic acid (24). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.17 (dd, J=2.9, 1.5 Hz, 1H, C2-H), 7.50 (dd, J=5.3, 1.5 Hz, 1H, C4-H), 7.27 (dd, J=5.3, 2.9 Hz, 1H, C5-H). MS: m/z=128.

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Tetrahedron 62 (2006) 7892–7901
Tetrahedron

A new method for generation of non-stabilized α-amino-substituted carbanions by the reaction of magnesium carbenoids with *N*-lithio arylamines: their reactivity and a new synthesis of α-amino acid derivatives

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Received 25 April 2006; accepted 16 May 2006
Available online 15 June 2006

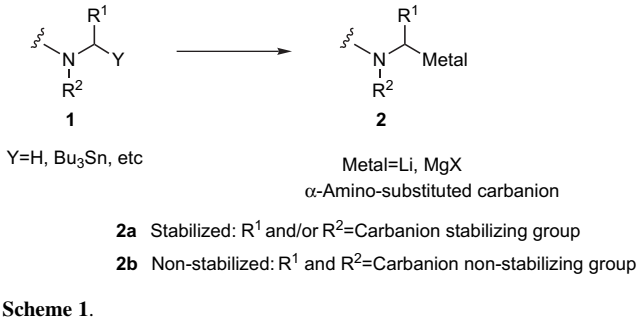
Abstract—Magnesium carbenoids were generated from aryl 1-chloroalkyl sulfoxides with *i*-PrMgCl in THF at low temperature in quantitative yields. The magnesium carbenoids were found to be reactive with *N*-lithio alkylamines to afford an olefin, which was derived from dimerization of the magnesium carbenoid, in moderate yield. On the other hand, reaction of the magnesium carbenoids with *N*-substituted *N*-lithio arylamines gave non-stabilized α-amino-substituted carbanions in good yields. Reactivity of the α-amino-substituted carbanions with some electrophiles was investigated and it was found that ethyl chloroformate reacted to give α-amino acid derivatives in good yields. As a whole, a new method for one-pot, three-component combined synthesis of α-amino acid derivatives from aryl 1-chloroalkyl sulfoxides was realized.

1. Introduction

α-Amino-substituted carbanions **2** are quite interesting reactive intermediates in the synthesis of amines and α-amino acid derivatives.[1–4] They are classified into two categories: stabilized α-amino-substituted carbanions **2a**[1,2] and non-stabilized α-amino-substituted carbanions **2b**.[3,4] The substituent R^1 of the stabilized α-amino-substituted carbanions **2a** is usually an alkyl-, alkenyl-, or aryl group and the substituent R^2 is generally a *tert*-butoxycarbonyl (Boc) group. Generation of **2a** is carried out by hydrogen–lithium (H–Li) exchange reaction or by tin–lithium (Bu_3Sn–Li) exchange reaction from the corresponding **1**.

On the other hand, non-stabilized α-amino-substituted carbanions **2b** are generated from **1** with Bu_3Sn–Li exchange reaction and fewer examples are reported.[4] Only lithium is reported so far as the metal of the α-amino-substituted carbanions **2** (Scheme 1).

Carbenes and carbenoids have been well known as a highly reactive carbon species and are recognized as useful intermediates in organic synthesis.[5] Recently, we have been interested in the generation of magnesium carbenoids from α-halo sulfoxides via sulfoxide–magnesium exchange reaction[6] and applications of the generated magnesium carbenoids to new methods for organic synthesis.[7] In continuation of our interest in the chemistry of the magnesium carbenoids, we recently studied the generation of simple magnesium carbenoids **4** from aryl 1-chloroalkyl sulfoxides **3** with isopropylmagnesium chloride and the reaction of magnesium carbenoids **4** with nitrogen nucleophiles (Scheme 2).



Scheme 1.

Interestingly, the reaction of magnesium carbenoid **4** with *N*-lithio alkylamine gave an olefin **5** (dimerized product of the carbenoid). In sharp contrast to this result, the reaction of **4** with several *N*-lithio *N*-substituted arylamines afforded

Keywords: Sulfoxide–magnesium exchange; Magnesium carbenoid; Dimerization; α-Amino-substituted carbanion; α-Amino acid.
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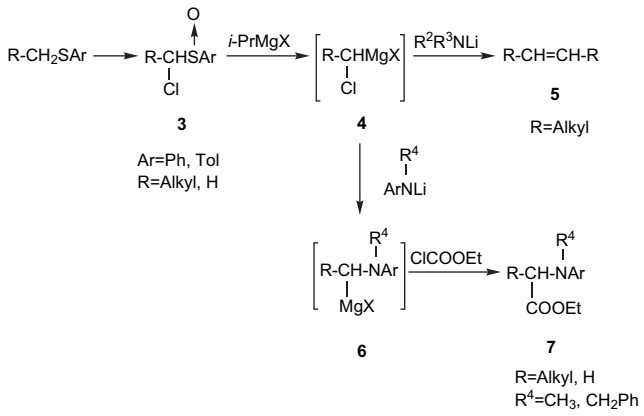
doi:10.1016/j.tet.2006.05.052



Scheme 2.

the non-stabilized α-amino-substituted carbanions **6**. We investigated the reactivity of the α-amino-substituted carbanions **6** with several electrophiles and found that the reaction with ethyl chloroformate gave α-amino acid derivatives **7** in good yields (Scheme 2).[8]

Herein we report in detail the generation of non-stabilized α-amino-substituted carbanions **6** from magnesium carbenoids **4** with *N*-lithio *N*-substituted arylamines and a study of their reactivity with some electrophiles. A new one-pot, three-component combined synthesis of α-amino acid derivatives **7** from **3**, including glycine derivatives, is described.

2. Results and discussion

2.1. Generation of the magnesium carbenoid and the reaction with *N*-lithio alkylamines

At first, 1-chloro-3-(4-methoxyphenyl)propyl phenyl sulfoxide **3a** was synthesized from 3-(4-methoxyphenyl)propyl phenyl sulfide[9] and it was treated with 2.5 equiv of *i*-PrMgCl at −70 °C in THF to give cleanly magnesium carbenoid **4a** in a quantitative yield.[9] To this solution was added 5 equiv of *N*-lithio piperidine (generated from piperidine and *n*-BuLi) through a cannula and the temperature of the reaction mixture was slowly allowed to warm to −40 °C for 1 h.

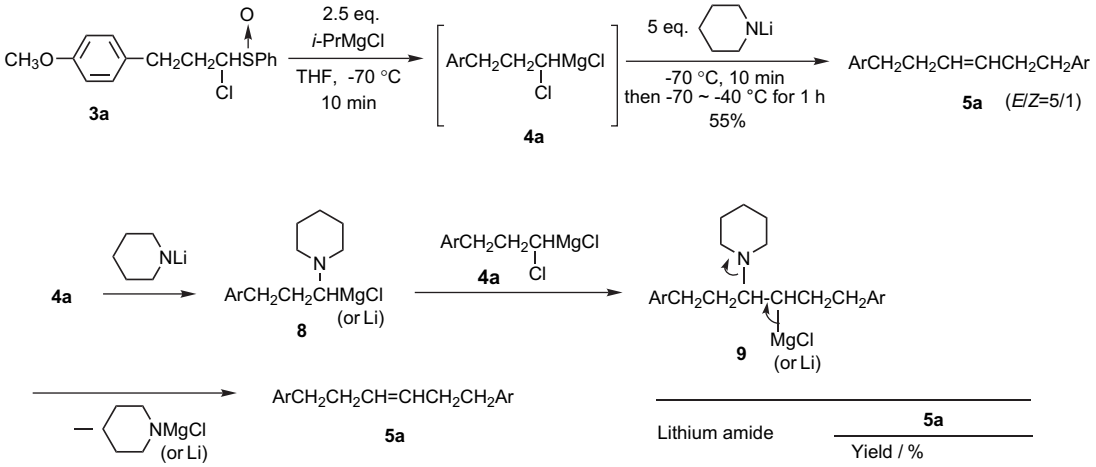
We anticipated the reaction of the carbenoid **4a** with *N*-lithio piperidine would give the *N*-alkylated product; however, unexpectedly, an olefin **5a** (dimer of the carbenoid **4a**) was obtained in 55% yield. The produced olefin **5a** was found to be a mixture of two geometrical isomers (*E*/*Z*=5:1).[10] Quite interestingly, olefin **5a** was not obtained at all from carbenoid **4a** in the absence of *N*-lithio piperidine. Obviously, *N*-lithio piperidine is essential in this olefin formation (Scheme 3).

The reaction of the generated magnesium carbenoid **4a** with lithium diisopropylamide and lithium *tert*-butylamide gave also olefin **5a** in 37% and 46% yield, respectively (see the table in Scheme 3). Again, the product **5a** was a mixture of two geometrical isomers and the ratio of the two isomers was found to be variable by the used lithium amide.

A plausible mechanism for the formation of the olefin **5a** is proposed in Scheme 3. Thus, magnesium carbenoid **4a** reacted with *N*-lithio piperidine to give the α-amino-substituted carbanion **8** (metal was magnesium or lithium), which reacted again with carbenoid **4a** to give **9**. β-Elimination of *N*-magnesio (or lithio) piperidine from **9** afforded olefin **5a**.

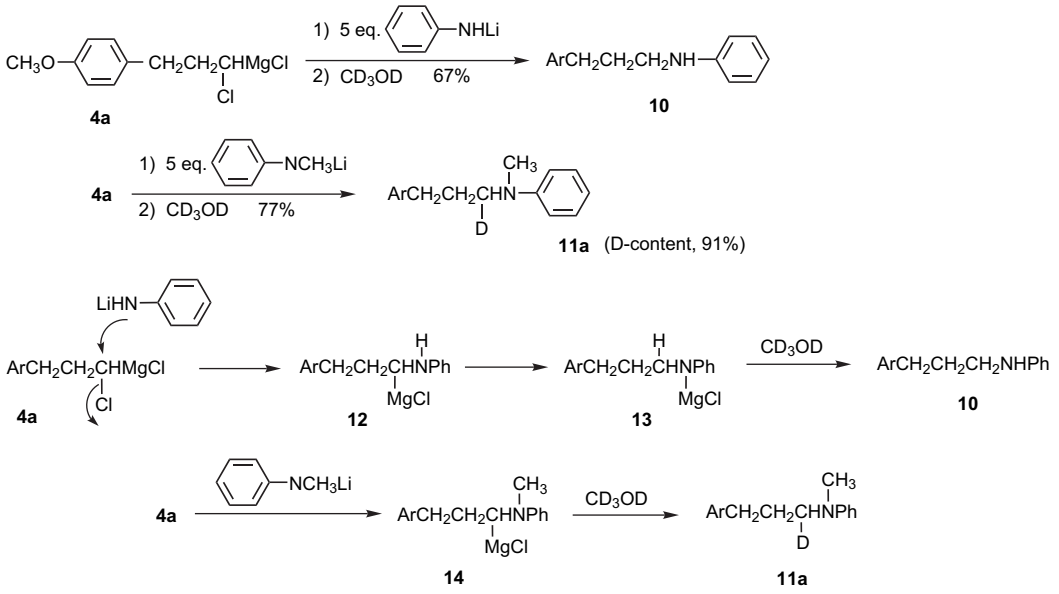
2.2. Reaction of the generated magnesium carbenoids with *N*-lithio arylamines

We next investigated the reaction of magnesium carbenoid **4a** with *N*-lithio arylamines (Scheme 4). In contrast to the reaction of **4a** with *N*-lithio alkylamines, the reaction with *N*-lithio aniline gave *N*-alkylaniline **10** in 67% yield. In order to know if the intermediate of this reaction was α-amino-substituted carbanion **12**, the reaction mixture was quenched with excess CD_3OD; however, no deuterium was incorporated on the α-carbon in the *N*-alkylaniline **10**. Next, magnesium carbenoid **4a** was treated with 5 equiv of



Lithium amide	5a Yield / %	
i-Pr_2NLi	37	*E*/*Z*=4/1
t-BuNHLi	46	*E*/*Z*=2/1

Scheme 3. Treatment of magnesium carbenoid **4a** with *N*-lithio alkylamines to give olefin **5a** and a plausible mechanism for the formation of the olefin.



Scheme 4. Treatment of magnesium carbenoid **4a** with *N*-lithio aniline and *N*-lithio *N*-methylaniline, and a plausible mechanism for the formation of *N*-alkylaniline **10** and *N*-(1-deuterated alkyl)-*N*-methylaniline **11a**.

N-lithio *N*-methylaniline under the same conditions as above, and the reaction mixture was quenched with excess CD_3OD. We obtained the *N*,*N*-dialkylaniline **11a** in 77% yield and the product was deuterated on the α-carbon and the deuterium incorporation was found to be 91% judging from its ^1H NMR spectra. A plausible mechanism of this interesting reaction is shown in Scheme 4.

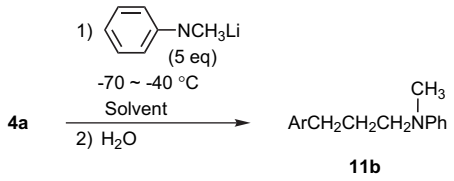
The reaction of the magnesium carbenoid with *N*-lithio aniline gave the desired α-amino-substituted carbanion **12**. As carbanion **12** has an acidic hydrogen on the nitrogen, the carbanion quickly picks up this acidic hydrogen to give **13**. So, as described above, on quenching this reaction with CD_3OD no deuterium was incorporated on the α-carbon. In contrast to this, the reaction of **4a** with *N*-lithio *N*-methylaniline provided the α-amino-substituted carbanion **14**, which has no acidic hydrogen on the nitrogen, to give the product **11a** deuterated at the α-position.

Generation of the non-stabilized α-amino-substituted carbanions is well recognized to be quite difficult from unactivated amines. The results obtained in this study are highly notable as a new method for generation of non-stabilized α-amino carbanions.[3,4]

We investigated the best conditions for the reaction of **4a** with *N*-lithio *N*-methylaniline and the results are summarized in Table 1. As shown in Table 1, DME or HMPA as additive gave almost the same results (entries 2 and 3). Toluene as a solvent gave much lower yield (entry 4). A mixture of toluene–DME and diethyl ether–THF did not show any good result (entries 5 and 6). We decided to use THF as a solvent without any additive throughout this study.

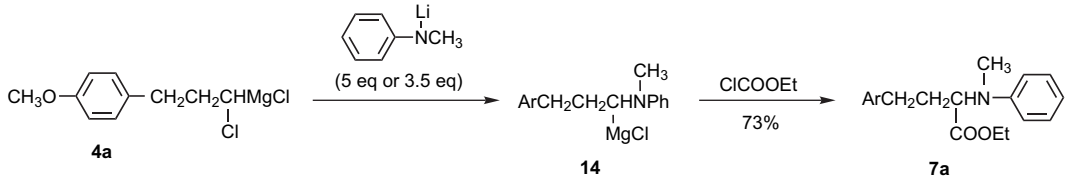
Next, we investigated trapping the generated non-stabilized α-amino carbanion **14** with electrophiles other than deuterium (Scheme 5). After the generation of carbanion **14** at −70 to −40 °C, 5 equiv of aldehydes (benzaldehyde and propionaldehyde), acetophenone, benzoyl chloride, or propionyl chloride were added. Carbanion **14** proved to show quite low reactivity and all these reactions gave only a rather complex mixture with the protonated product **11b**.

Table 1. Reaction of magnesium carbenoid **4a** with *N*-lithio *N*-methylaniline in several solvents



Entry	Solvent	**11b**
		Yield/%
1	THF	77
2	THF+DME (6 equiv)[a]	79
3	THF+HMPA (6 equiv)[a]	78
4	Toluene	47
5	Toluene+DME (6 equiv)[a]	56
6	Diethyl ether+THF (4:1)	49

[a] Corresponding to **4a**.



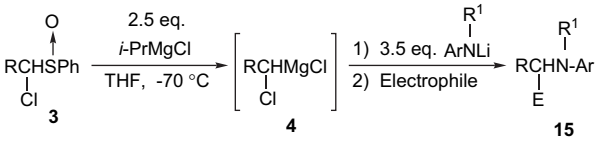
Scheme 5. Treatment of magnesium carbenoid **4a** with *N*-lithio *N*-methylaniline followed by ethyl chloroformate to give α-amino acid derivative **7a**.

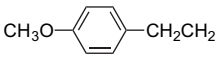
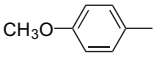
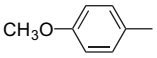
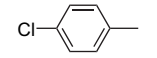
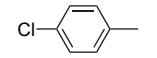
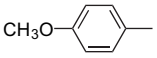
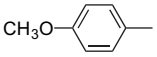
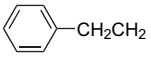
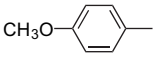
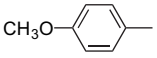
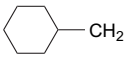
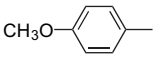
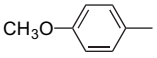
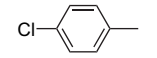
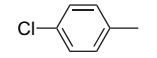
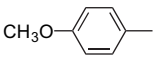
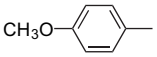
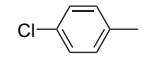
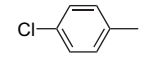
Fortunately, addition of 5 equiv of ethyl chloroformate gave a clean reaction mixture and the desired ethoxycarbonylated product, α-amino acid ester, **7a** was obtained in 73% yield (Scheme 5). After some further investigation for improvement of this reaction, reducing of *N*-lithio *N*-methylaniline to 3.5 equiv was found to be enough to give the same yield. We used 3.5 equiv of *N*-lithio *N*-substituted arylamines and 5 equiv of ethyl chloroformate in this new method for the synthesis of α-amino acid derivatives **7** (vide infra).

2.3. Investigation for generality of the new synthetic method of α-deuterio amines and α-amino acid ethyl esters

Generality of the above-mentioned reaction was investigated using four kinds of 1-chloroalkyl phenyl sulfoxides **3** and *N*-methyl-*p*-anisidine, *N*-benzyl-*p*-anisidine, and *N*-methyl-*p*-chloroaniline. The results are summarized in Table 2.

Table 2. Synthesis of α-deuterio *N*,*N*-dialkyl arylamines and α-amino acid esters from magnesium carbenoids **4** by the reaction with *N*-lithio *N*-substituted arylamines followed by methanol-d_4 or ethyl chloroformate



Entry	3	Ar	R^1	Electrophile	E	15
	R					Yield/%
1	 **3a**		CH_3	CD_3OD	D	**15a** 81%[a]
2	**3a**		CH_3	ClCOOEt	COOEt	**15b** 74%
3	**3a**		CH_3	CD_3OD	D	**15c** 79%[a]
4	**3a**		CH_3	ClCOOEt	COOEt	**15d** 73%
5	**3a**		$PhCH_2$	CD_3OD	D	**15e** 69%[b]
6	**3a**		$PhCH_2$	ClCOOEt	COOEt	**15f** 67%
7	 **3b**		$PhCH_2$	CD_3OD	D	**15g** 73%[c]
8	**3b**		$PhCH_2$	ClCOOEt	COOEt	**15h** 71%
9	 **3c**		CH_3	CD_3OD	D	**15i** 70%[b]
10	**3c**		CH_3	ClCOOEt	COOEt	**15j** 68%
11	**3c**		CH_3	CD_3OD	D	**15k** 72%[c]
12	**3c**		CH_3	ClCOOEt	COOEt	**15l** 68%
13	 **3d**		CH_3	CD_3OD	D	**15m** 48%[d]
14	**3d**		CH_3	ClCOOEt	COOEt	**15n** 48%
15	**3d**		CH_3	CD_3OD	D	**15o** 42%[b]
16	**3d**		CH_3	ClCOOEt	COOEt	**15p** 41%

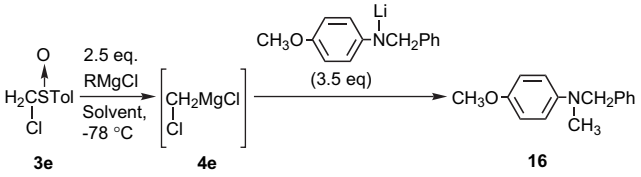
[a] D-content 90%.
[b] D-content 97%.
[c] D-content 95%.
[d] D-content 99%.

Entries 1–6 show that the reaction of the magnesium carbenoid generated from **3a** with three kinds of arylamines, *N*-methyl-*p*-anisidine, *N*-methyl-*p*-chloroaniline, and *N*-benzyl-*p*-anisidine, gave equally good yields (67–81%) of the α-deuterio amines or α-amino acid derivatives. The reaction starting from the sulfoxide having a 2-phenylethyl group as R (**3b**) gave similar results (entries 7 and 8). Entries 9–12 show the reaction starting from sulfoxide **3c** having a cyclohexylmethyl group as R. The results were shown to be almost equal to those described above. Interestingly, the reaction starting from the sulfoxide having a cyclohexyl group as R (**3d**) showed markedly diminished yield of the α-deuterio amines and α-amino acid derivatives (entries 13–16). Steric hindrance or the stability of the generated magnesium carbenoid is thought to be the reason for the lowering of the yield.

2.4. Synthesis of glycine derivatives

We further investigated the generation of magnesium methylidene **4e** from chloromethyl *p*-tolyl sulfoxide **3e** with *i*-PrMgCl at −78 °C and trapping of the carbenoid with *N*-lithio *N*-benzyl-*p*-anisidine (Table 3). Thus, a solution of **3e** in THF was added to a solution of *i*-PrMgCl (2.5 equiv) in THF at −78 °C and after 10 min a solution of *N*-lithio *N*-benzyl-*p*-anisidine was added to the reaction mixture. The temperature of the reaction mixture was slowly allowed to warm to −40 °C. We obtained the desired **16**; however, the yield was only 23% (entry 1).

Table 3. Generation of magnesium carbenoid **4e** from chloromethyl *p*-tolyl sulfoxide **3e** with Grignard reagent and the trapping of **4e** with *N*-lithio *N*-benzyl-*p*-anisidine



Entry	Solvent	RMgCl	Temperature	**16**
				Yield/%
1	THF	*i*-PrMgCl	−78 to −40 °C[a]	23
2	THF	*i*-PrMgCl	−78 to −70 °C[b]	36
3	THF	*i*-PrMgCl	−78 to −40 °C[b]	65
4	THF	*i*-PrMgBr	−78 to −40 °C[b]	32
5	THF	EtMgCl	−78 to −40 °C[b]	15
6	Toluene	*i*-PrMgCl	−78 to −40 °C[b]	20

[a] *N*-Lithio arylamine was added after 10 min.
[b] *N*-Lithio arylamine was added immediately after generation of magnesium carbenoid **4e**.

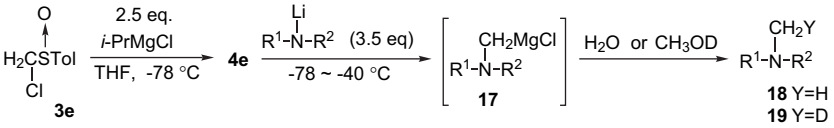
After some investigation, as we found that the generated carbenoid **4e** was fairly unstable, it was immediately treated with *N*-lithio *N*-benzyl-*p*-anisidine to give better yield (entry 2). Finally, the conditions shown in entry 3 were found to be the choice for this reaction. We further investigated other conditions shown in entries 4–6; however, all the trials were ineffective.

Next, magnesium carbenoid **4e** was treated with *N*-lithio amines and the generated α-amino-substituted carbanions **17** were treated with water or methanol-d_1 (Table 4). The reaction of **4e** with *N*-lithio *N*-benzyl-*p*-anisidine followed by CH_3OD gave the deuterated amine **19a** with 96% deuterium incorporation (entry 2). The reaction with *N*-lithio *N*-methyl-*p*-anisidine gave the desired amine **18b** or deuterated amine **19b**; however, the yield was not satisfactory (entries 3 and 4). Interestingly the reaction of the magnesium methylidene **4e** with *N*-lithio alkylamine (dibenzylamine) gave **18c** and **19c** in 31% yield.

Finally, we studied the reaction for the synthesis of glycine derivatives by the trapping of the generated α-amino-substituted carbanions **17** with ethyl chloroformate (Table 5). The reaction of magnesium carbenoid **4e** with *N*-lithio *N*-benzyl-*p*-anisidine followed by ethyl chloroformate gave the desired α-amino acid ester **20a** in 58% yield. Although the yield of the corresponding amine **18b** was 35%, the glycine derivative **20b** was obtained in moderate yield (entry 2). The reaction using *N*-methyl-*p*-chloroaniline and *N*-methylaniline gave the desired amino acid ethyl ester **20c** and **20d**; however, the yields were low (entries 3 and 4). As shown in entry 5, although the yield was low, *N*,*N*-dibenzylglycine ethyl ester **20e** could be synthesized by this method.

In conclusion, we have found a novel and versatile method for generation of non-stabilized α-amino-substituted carbanions by the reaction of magnesium carbenoids with *N*-lithio *N*-alkyl arylamines. Trapping the non-stabilized

Table 4. Generation of magnesium carbenoid **4e** from chloromethyl *p*-tolyl sulfoxide **3e** with Grignard reagent and the trapping of **4e** with *N*-lithio amines followed by water or methanol-d_1



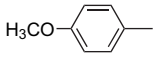
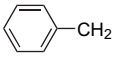
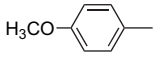
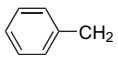
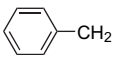
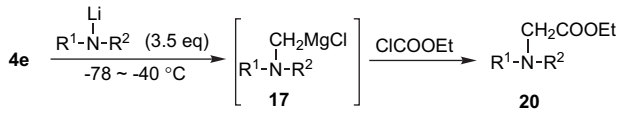
Entry	Amine		Electrophile	**16**, **18** or **19**	
	R^1	R^2		Yield/%	(D content/%)
1			H_2O	**16**	65
2			CH_3OD	**19a**	65 (96)
3		CH_3	H_2O	**18b**	35
4			CH_3OD	**19b**	35 (99)
5			H_2O	**18c**	31
6			CH_3OD	**19c**	31 (99)

Table 5. Synthesis of glycine derivatives **20** from magnesium carbenoid **4e** with *N*-lithio amines followed by ethyl chloroformate



Entry	Amine		**20**
	R^1	R^2	Yield/%
1	H_3CO	CH_2	**20a** 58
2	H_3CO	CH_3	**20b** 61
3	Cl	CH_3	**20c** 30
4		CH_3	**20d** 23
5	CH_2	CH_2	**20e** 25
6			0

α-amino-substituted carbanions with deuterated methanol gave amines having the alkyl group deuterated at the α-position. Trapping the carbanions with ethyl chloroformate gave α-amino acid ethyl esters. As a whole, a novel method for the synthesis of α-amino acid derivatives from three components, aryl 1-chloroalkyl sulfoxide, *N*-alkyl arylamines, and ethyl chloroformate, in one flask was realized.

3. Experimental

3.1. General

^{1}H NMR spectra were measured in a $CDCl_3$ solution with JOEL JNM-LA 500 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. Silica gel 60 (Merck) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry reagent and solvent, THF was distilled from diphenylketyl. Piperidine, diisopropylamine, *tert*-butylamine, and toluene were dried over CaH and distilled before use. HMPA were dried over $CaSO_4$ and distilled before use. 1-Chloroalkyl phenyl sulfoxides **3a–d** were synthesized from the corresponding alcohols (or halides) via the sulfides in the same way as described before.[9,12]

3.1.1. 1,6-Di(4-methoxyphenyl)-3-hexene (5a). To a solution of *i*-PrMgCl (0.5 mmol) in 0.5 mL of dry THF in a flame-dried flask at −70 °C under argon atmosphere was added a solution of **3a**[9] (62 mg; 0.2 mmol) in 0.4 mL of dry THF dropwise with stirring. The reaction mixture was stirred at −70 °C for 10 min. To a solution of the generated magnesium carbenoid **4a** was added a solution of *N*-lithio piperidine [prepared from piperidine (1 mmol) and *n*-BuLi (1.2 mmol) in 2 mL of THF at 0 °C and the solution was cooled to −70 °C] through a cannula with stirring. The reaction mixture was slowly allowed to warm to −40 °C for 1 h and the reaction mixture was quenched with satd aq NH_4Cl. The whole was extracted with $CHCl_3$ and the organic layer was washed with satd aq NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel column chromatography to afford **5a** (33 mg; 55%) as a colorless oil (a mixture of two geometrical isomers; the ratio is about *E*/*Z*=5:1). IR (neat) 3010, 2933, 1611, 1510, 1245, 1037, 757 cm^{-1}; ^{1}H NMR δ 2.24–2.26 (4H, m), 2.52 (0.7H, t, *J*=7.8 Hz), 2.59 (3.3H, t, *J*=7.8 Hz), 3.78 (6H, s), 5.40 (0.3H, t, *J*=4.7 Hz), 5.46 (1.7H, t, *J*=3.7 Hz), 6.81 (4H, d, *J*=8.5 Hz), 7.07 (4H, d, *J*=8.5 Hz). MS *m*/*z* (%) 296 (M^+, 15), 121 (100). Calcd for $C_{20}H_{24}O_2$: M, 296.1774. Found: *m*/*z* 296.1774.

3.1.2. Ethyl 4-(4-methoxyphenyl)-2-(*N*-methyl-*N*-phenylamino)butyrate (7a). To a solution of *i*-PrMgCl (0.5 mmol) in 0.5 mL of dry THF in a flame-dried flask at −70 °C under argon atmosphere was added a solution of **3a** (62 mg; 0.2 mmol) in 0.4 mL of dry THF dropwise with stirring. The reaction mixture was stirred at −70 °C for 10 min. To a solution of the generated magnesium carbenoid **4a** was added a solution of *N*-lithio *N*-methylaniline [prepared from *N*-methylaniline (1 mmol) and *n*-BuLi (1.2 mmol) in 2 mL of THF at 0 °C and the solution was cooled to −70 °C] through a cannula with stirring. The reaction mixture was slowly allowed to warm to −40 °C for 1 h. To a solution of the α-amino-substituted carbanion **14** was added ethyl chloroformate (1 mmol) dropwise at −40 °C with stirring. After 20 min, the reaction mixture was quenched with satd aq NH_4Cl. The whole was extracted with $CHCl_3$ and the organic layer was washed with satd aq NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel column chromatography to afford **7a** (48 mg; 73%) as colorless oil; IR (neat) 2955, 1731 (CO), 1600, 1512, 1301, 1247, 1179, 1036, 751, 693 cm^{-1}; ^{1}H NMR δ 1.21 (3H, t, *J*=7.0 Hz), 2.11–2.18 (1H, m), 2.20–2.28 (1H, m), 2.53–2.59 (1H, m), 2.64–2.70 (1H, m), 2.93 (3H, s), 3.78 (3H, s), 4.09–4.17 (2H, m), 4.31 (1H, dd, *J*=9.3, 5.5 Hz), 6.75 (3H, m), 6.80 (2H, d, *J*=8.6 Hz), 7.05 (2H, d, *J*=8.6 Hz), 7.22 (2H, m). MS *m*/*z* (%) 327 (M^+, 20), 254 (75), 132 (9), 121 (100), 91 (9). Calcd for $C_{20}H_{25}NO_3$: M, 327.1835. Found: *m*/*z* 327.1838.

3.1.3. *N*-[3-(4-Methoxyphenyl)propyl]aniline (10). To a solution of *i*-PrMgCl (0.5 mmol) in 0.5 mL of dry THF in a flame-dried flask at −70 °C under argon atmosphere was added a solution of **3a** (62 mg; 0.2 mmol) in 0.4 mL of dry THF dropwise with stirring. The reaction mixture was stirred at −70 °C for 10 min. To a solution of the generated magnesium carbenoid **4a** was added a solution of *N*-lithio aniline [prepared from aniline (1 mmol) and *n*-BuLi (1.2 mmol) in 2 mL of THF at 0 °C and the solution was cooled to −70 °C] through a cannula with stirring. The reaction mixture was slowly allowed to warm to −40 °C for 1 h. The reaction mixture was quenched with excess CD_3OD. The whole was extracted with $CHCl_3$. The organic layer was washed satd aq NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel column chromatography to afford **10** (32 mg; 67%) as colorless oil; IR (neat) 3404, 2933, 2835, 1604, 1512, 1246, 1178, 1035, 750, 693 cm^{-1}; ^{1}H NMR δ 1.91 (2H, quintet, *J*=7.3 Hz), 2.67 (2H, t, *J*=7.3 Hz), 3.12 (2H, t, *J*=7.3 Hz), 3.59 (1H, s), 3.79 (3H,

s), 6.57 (2H, d, J=8.8 Hz), 6.68 (1H, t, J=7.3 Hz), 6.83 (2H, d, J=8.6 Hz), 7.11 (2H, d, J=8.3 Hz), 7.16 (2H, m). MS m/z (%) 241 (M^+, 50), 148 (37), 121 (13), 106 (100), 93 (11), 77 (16). Calcd for $C_{16}H_{19}NO$: M, 241.1465. Found: m/z 241.1463.

3.1.4. *N*-[1-Deuterio-3-(4-methoxyphenyl)propyl]-*N*-methylaniline (11a). Colorless oil; IR (neat) 2934, 1600, 1511, 1300, 1245, 1177, 1035, 748, 692 cm^{-1}; ^1H NMR δ 1.89 (2H, q, J=7.7 Hz), 2.59 (2H, t, J=7.7 Hz), 2.91 (3H, s), 3.30 (1H, t, J=7.7 Hz), 3.79 (3H, s), 6.63–6.69 (3H, m), 6.83 (2H, d, J=8.6 Hz), 7.10 (2H, d, J=8.6 Hz), 7.18–7.22 (2H, m). MS m/z (%) 256 (M^+, 25), 121 (100), 107 (15), 77 (12). Calcd for $C_{17}H_{20}DNO$: M, 256.1685. Found: m/z 256.1687.

3.1.5. *N*-Methyl-*N*-[3-(4-methoxyphenyl)propyl]aniline (11b). Colorless oil; IR (neat) 2935, 1600, 1511, 1371, 1246, 1178, 1035, 749, 693 cm^{-1}; ^1H NMR δ 1.87 (2H, quintet, J=7.6 Hz), 2.59 (2H, t, J=7.6 Hz), 2.91 (3H, s), 3.32 (2H, t, J=7.6 Hz), 3.79 (3H, s), 6.64–6.69 (3H, m), 6.82 (2H, d, J=8.6 Hz), 7.10 (2H, d, J=8.6 Hz), 7.18–7.22 (2H, m). MS m/z (%) 255 (M^+, 30), 120 (100), 107 (13), 77 (11). Calcd for $C_{17}H_{21}NO$: M, 255.1623. Found: m/z 255.1616.

3.1.6. *N*-[1-Deuterio-3-(4-methoxyphenyl)propyl]-*N*-methyl-*p*-anisidine (15a). Colorless oil; IR (neat) 2932, 1611, 1508, 1243, 1037, 814 cm^{-1}; ^1H NMR δ 1.83 (2H, q, J=7.6 Hz), 2.57 (2H, t, J=7.6 Hz), 2.84 (3H, s), 3.21 (1H, t, J=7.5 Hz), 3.75 (3H, s), 3.79 (3H, s), 6.66 (2H, d, J=9.2 Hz), 6.79–6.84 (4H, m), 7.09 (2H, d, J=8.6 Hz). MS m/z (%) 286 (M^+, 40), 151 (100), 137 (13), 121 (20). Calcd for $C_{18}H_{22}DNO_2$: M, 286.1791. Found: m/z 286.1796.

3.1.7. Ethyl 4-(4-methoxyphenyl)-2-[*N*-(4-methoxyphenyl)-*N*-methylamino]butyrate (15b). Colorless oil; IR (neat) 2936, 1729 (CO), 1612, 1511, 1464, 1299, 1245, 1179, 1037, 818 cm^{-1}; ^1H NMR δ 1.19 (3H, t, J=7.3 Hz), 2.08–2.23 (2H, m), 2.55–2.61 (1H, m), 2.65–2.71 (1H, m), 2.88 (3H, s), 3.76 (3H, s), 3.79 (3H, s), 4.08–4.11 (2H, m), 4.14–417 (1H, m), 6.74 (2H, d, J=8.9 Hz), 6.79–6.82 (4H, m), 7.06 (2H, d, J=8.6 Hz). MS m/z (%) 357 (M^+, 35), 284 (80), 122 (10), 121 (100). Calcd for $C_{21}H_{27}NO_4$: M, 357.1938. Found: m/z 357.1936.

3.1.8. *N*-[1-Deuterio-3-(4-methoxyphenyl)propyl]-*N*-methyl-4-chloroaniline (15c). Colorless oil; IR (neat) 2934, 1596, 1505, 1245, 809 cm^{-1}; ^1H NMR δ 1.84 (2H, q, J=7.6 Hz), 2.58 (2H, t, J=7.6 Hz), 2.88 (3H, s), 3.26 (1H, t, J=7.6 Hz), 3.79 (3H, s), 6.53 (2H, d, J=9.2 Hz), 6.83 (2H, d, J=8.5 Hz), 7.08–7.13 (4H, m). MS m/z (%) 290 (M^+, 40), 155 (100), 141 (20), 121 (10). Calcd for $C_{17}H_{19}DClNO$: M, 290.1294. Found: m/z 290.1292.

3.1.9. Ethyl 2-[*N*-(4-chlorophenyl)-*N*-methylamino]-4-(4-methoxyphenyl)butyrate (15d). Colorless oil; IR (neat) 2956, 1732 (CO), 1597, 1513, 1301, 1247, 1179, 1102, 1036, 812 cm^{-1}; ^1H NMR δ 1.20 (3H, t, J=7.5 Hz), 2.10–2.17 (1H, m), 2.20–2.27 (1H, m), 2.51–2.57 (1H, m), 2.64–2.69 (1H, m), 2.90 (3H, s), 3.79 (3H, s), 4.11–4.17 (2H, m), 4.20–4.23 (1H, m), 6.64 (2H, d, J=7.5 Hz), 6.80 (2H, d, J=6.0 Hz), 7.03 (2H, d, J=6.0 Hz), 7.14 (2H, d, J=7.5 Hz). MS m/z (%) 361 (M^+, 20), 290 (20), 288 (55), 122 (10), 121 (100). Calcd for $C_{20}H_{24}ClNO_3$: M, 361.1443. Found: m/z 361.1442.

3.1.10. *N*-Benzyl-*N*-[1-deuterio-3-(4-methoxyphenyl)-propyl]-*p*-anisidine (15e). Colorless oil; IR (neat) 2933, 1611, 1510, 1452, 1242, 1178, 1037, 814 cm^{-1}; ^1H NMR δ 1.89 (2H, q, J=7.6 Hz), 2.57 (2H, t, J=7.6 Hz), 3.29 (1H, t, J=7.6 Hz), 3.72 (3H, s), 3.78 (3H, s), 4.42 (2H, s), 6.61 (2H, d, J=9.2 Hz), 6.76 (2H, d, J=9.2 Hz), 6.81 (2H, d, J=8.6 Hz), 7.06 (2H, d, J=8.6 Hz), 7.20–7.24 (3H, m), 7.27–7.30 (2H, m). MS m/z (%) 362 (M^+, 60), 227 (70), 137 (15), 121 (20), 91 (100). Calcd for $C_{24}H_{26}DNO_2$: M, 362.2102. Found: m/z 362.2096.

3.1.11. Ethyl 2-[benzyl(4-methoxyphenyl)amino]-4-(4-methoxyphenyl)butyrate (15f). Colorless oil; IR (neat) 2935, 1732 (CO), 1612, 1512, 1454, 1300, 1246, 1178, 1039, 819, 755 cm^{-1}; ^1H NMR δ 1.22 (3H, t, J=7.0 Hz), 2.04–2.12 (1H, m), 2.20–2.26 (1H, m), 2.60–2.73 (2H, m), 3.72 (3H, s), 3.78 (3H, s), 4.12 (2H, q, J=7.0 Hz), 4.25 (1H, t, J=7.2 Hz), 4.51 (1H, d, J=17.1 Hz), 4.57 (1H, d, J=17.1 Hz), 6.73 (4H, s), 6.78 (2H, d, J=8.6 Hz), 6.97 (2H, d, J=8.6 Hz), 7.19–7.21 (1H, m), 7.27–7.32 (4H, m). MS m/z (%) 433 (M^+, 35), 360 (100), 212 (18), 147 (8), 121 (80), 91 (55), 77 (8). Calcd for $C_{27}H_{31}NO_4$: M, 433.2253. Found: m/z 433.2260.

3.1.12. *N*-Benzyl-*N*-(1-deuterio-3-phenylpropyl)-*p*-anisidine (15g). Colorless oil; IR (neat) 2935, 1512, 1453, 1242, 1044, 814, 699 cm^{-1}; ^1H NMR δ 1.93 (2H, q, J=7.6 Hz), 2.62 (2H, t, J=7.6 Hz), 3.31 (1H, t, J=7.6 Hz), 3.72 (3H, s), 4.43 (2H, s), 6.61 (2H, d, J=8.9 Hz), 6.76 (2H, d, J=8.9 Hz), 7.15–7.18 (3H, m), 7.21–7.23 (3H, m), 7.26–7.30 (4H, m). MS m/z (%) 332 (M^+, 50), 269 (10), 227 (70), 137 (10), 91 (100). Calcd for $C_{23}H_{24}DNO$: M, 332.1996. Found: m/z 332.1995.

3.1.13. Ethyl 2-[benzyl(4-methoxyphenyl)amino]-4-phenylbutyrate (15h). Colorless oil; IR (neat) 2935, 1732 (CO), 1604, 1512, 1453, 1244, 1179, 1040, 818, 737, 700 cm^{-1}; ^1H NMR δ 1.22 (3H, t, J=7.0 Hz), 2.08–2.16 (1H, m), 2.23–2.30 (1H, m), 2.66–2.71 (1H, m), 2.73–2.79 (1H, m), 3.72 (3H, s), 4.13 (2H, q, J=7.0 Hz), 4.27 (1H, t, J=7.2 Hz), 4.52 (1H, d, J=17.1 Hz), 4.57 (1H, d, J=17.1 Hz), 6.72–6.76 (4H, m), 7.07 (2H, d, J=7.7 Hz), 7.16–7.22 (2H, m), 7.23–7.25 (2H, m), 7.28–7.33 (4H, m). MS m/z (%) 403 (M^+, 20), 330 (100), 285 (18), 134 (10), 91 (80). Calcd for $C_{26}H_{29}NO_3$: M, 403.2146. Found: m/z 403.2160.

3.1.14. *N*-(1-Deuterio-2-cyclohexylethyl)-*N*-methyl-*p*-anisidine (15i). Colorless oil; IR (neat) 2922, 2851, 1515, 1448, 1244, 1042, 813 cm^{-1}; ^1H NMR δ 0.87–0.98 (2H, m), 1.11–1.27 (4H, m), 1.40 (2H, t, J=7.6 Hz), 1.64–1.74 (5H, m), 2.83 (3H, s), 3.22 (1H, t, J=7.6 Hz), 3.76 (3H, s), 6.69 (2H, d, J=9.2 Hz), 6.83 (2H, d, J=9.2 Hz). MS m/z (%) 248 (M^+, 30), 151 (100), 136 (10), 121 (8). Calcd for $C_{16}H_{24}DNO$: M, 248.1997. Found: m/z 248.2007.

3.1.15. Ethyl 3-cyclohexyl-2-[*N*-(4-methoxyphenyl)-*N*-methylamino]propionate (15j). Colorless oil; IR (neat) 2924, 2852, 1732 (CO), 1514, 1448, 1247, 1182, 1040,

817 cm^{-1}; ^1H NMR δ 0.87–1.02 (2H, m), 1.11–1.16 (2H, m), 1.19 (3H, t, J=7.3 Hz), 1.29–1.38 (1H, m), 1.58–1.78 (8H, m), 2.84 (3H, s), 3.76 (3H, s), 4.07–4.14 (2H, m), 4.30 (1H, t, J=7.6 Hz), 6.77–6.83 (4H, m). MS m/z (%) 319 (M^+, 15), 246 (100), 164 (8), 55 (8). Calcd for $C_{19}H_{29}NO_3$: M, 319.2145. Found: m/z 319.2143.

3.1.16. *N*-(1-Deuterio-2-cyclohexylethyl)-*N*-methyl-4-chloroaniline (15k). Colorless oil; IR (neat) 2923, 2852, 1597, 1505, 1448, 1216, 808, 760 cm^{-1}; ^1H NMR δ 0.90–0.99 (2H, m), 1.13–1.27 (4H, m), 1.41 (2H, t, J=7.3 Hz), 1.64–1.73 (5H, m), 2.87 (3H, s), 3.27 (1H, t, J=7.3 Hz), 6.57 (2H, d, J=8.9 Hz), 7.13 (2H, d, J=8.9 Hz). MS m/z (%) 252 (M^+, 20), 155 (100), 140 (10). Calcd for $C_{15}H_{21}DClN$: M, 252.1502. Found: m/z 252.1505.

3.1.17. Ethyl 2-[*N*-(4-chlorophenyl)-*N*-methylamino]-3-cyclohexylpropionate (15l). Colorless oil; IR (neat) 2925, 2852, 1733 (CO), 1598, 1499, 1188, 1140, 1104, 811 cm^{-1}; ^1H NMR δ 0.87–1.02 (2H, m), 1.14–1.16 (2H, m), 1.21 (3H, t, J=7.3 Hz), 1.26–1.31 (1H, m), 1.56–1.69 (6H, m), 1.77 (2H, t, J=7.3 Hz), 2.87 (3H, s), 4.09–4.16 (2H, m), 4.37 (1H, t, J=7.3 Hz), 6.71 (2H, d, J=8.3 Hz), 7.17 (2H, d, J=8.3 Hz). MS m/z (%) 323 (M^+, 10), 250 (100), 168 (15), 154 (20), 55 (17). Calcd for $C_{18}H_{26}ClNO_2$: M, 323.1650. Found: m/z 323.1648.

3.1.18. *N*-[Cyclohexyl(deuterio)methyl]-*N*-methyl-*p*-anisidine (15m). Colorless oil; IR (neat) 2923, 2851, 1513, 1448, 1245, 1181, 1121, 1042, 811, 757, 692 cm^{-1}; ^1H NMR δ 0.86–0.95 (2H, m), 1.11–1.26 (3H, m), 1.64–1.75 (6H, m), 2.88 (3H, s), 3.00 (1H, d, J=6.7 Hz), 3.75 (3H, s), 6.63 (2H, d, J=8.9 Hz), 6.82 (2H, d, J=8.9 Hz). MS m/z (%) 234 (M^+, 25), 151 (100), 136 (10). Calcd for $C_{15}H_{22}DNO$: M, 234.1841. Found: m/z 234.1844.

3.1.19. Ethyl cyclohexyl[*N*-(4-methoxyphenyl)-*N*-methylamino]acetate (15n). Colorless oil; IR (neat) 2929, 2852, 1731 (CO), 1512, 1449, 1279, 1246, 1176, 1039, 818 cm^{-1}; ^1H NMR δ 0.85–0.93 (1H, m), 0.98–1.06 (1H, m), 1.15–1.34 (3H, m), 1.19 (3H, t, J=7.3 Hz), 1.62–1.81 (5H, m), 1.94–2.02 (1H, m), 2.85 (3H, s), 3.75 (3H, s), 3.86 (1H, d, J=10.7 Hz), 4.10 (2H, q, J=7.3 Hz), 6.81 (4H, s). MS m/z (%) 305 (M^+, 20), 232 (100), 222 (30), 194 (12), 150 (15). Calcd for $C_{18}H_{27}NO_3$: M, 305.1989. Found: m/z 305.1980.

3.1.20. *N*-[Cyclohexyl(deuterio)methyl]-*N*-methyl-4-chloroaniline (15o). Colorless oil; IR (neat) 2924, 2852, 1598, 1505, 1448, 1331, 807 cm^{-1}; ^1H NMR δ 0.88–0.95 (2H, m), 1.12–1.25 (3H, m), 1.65–1.73 (6H, m), 2.92 (3H, s), 3.07 (1H, d, J=6.7 Hz), 6.55 (2H, d, J=9.2 Hz), 7.13 (2H, d, J=9.2 Hz). MS m/z (%) 238 (M^+, 15), 155 (100), 140 (8). Calcd for $C_{14}H_{19}DClN$: M, 238.1346. Found: m/z 238.1346.

3.1.21. Ethyl [*N*-(4-chlorophenyl)-*N*-methylamino]cyclohexylacetate (15p). Colorless oil; IR (neat) 2928, 2853, 1732 (CO), 1597, 1499, 1449, 1176, 1105, 1027, 810, 757 cm^{-1}; ^1H NMR δ 0.81–0.96 (1H, m), 0.99–1.08 (1H, m), 1.14–1.36 (3H, m), 1.21 (3H, t, J=7.3 Hz), 1.63–1.78 (5H, m), 1.97–2.04 (1H, m), 2.89 (3H, s), 3.92 (1H, d, J=10.7 Hz), 4.08–4.16 (2H, m), 6.75 (2H, d, J=8.9 Hz), 7.15 (2H, d, J=8.9 Hz). MS m/z (%) 309 (M^+, 18), 236 (100), 226 (23), 198 (13), 154 (40), 138 (8). Calcd for $C_{17}H_{24}ClNO_2$: M, 309.1494. Found: m/z 309.1498.

3.1.22. *N*-Benzyl-*N*-methyl-*p*-anisidine (16). To a solution of *i*-PrMgCl (0.5 mmol) in 0.5 mL of dry THF in a flame-dried flask at −78 °C under argon atmosphere was added a solution of **3e** (38 mg; 0.2 mmol) in 0.4 mL of dry THF dropwise with stirring. Immediately, to a solution of the generated magnesium carbenoid **4e** was added a solution of *N*-lithio *N*-benzyl-*p*-anisidine [prepared from *N*-benzyl-*p*-anisidine (0.7 mmol) and *n*-BuLi (0.77 mmol) in 2 mL of THF at 0 °C and the solution was cooled to −78 °C] through a cannula with stirring. The reaction mixture was slowly allowed to warm to −40 °C for 1 h. The reaction mixture was quenched with satd aq NH_4Cl. The whole was extracted with $CHCl_3$ and the organic layer was washed with satd aq NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel column chromatography to afford **16** (30 mg; 65%) as a colorless oil.[11]

3.1.23. *N*,*N*-Dimethyl-*p*-anisidine (18b). Colorless oil; IR (neat) 2933, 1515, 1245, 1038, 817 cm^{-1}; ^1H NMR δ 2.86 (6H, s), 3.76 (3H, s), 6.75 (2H, d, J=8.9 Hz), 6.84 (2H, d, J=8.9 Hz). MS m/z (%) 151 (M^+, 65), 136 (100), 108 (12), 65 (8). Calcd for $C_9H_{13}NO$: M, 151.0996. Found: m/z 151.0998.

3.1.24. *N*-Methyldibenzylamine (18c). Colorless oil; IR (neat) 3028, 2786, 1495, 1453, 1366, 1024, 736, 698 cm^{-1}; ^1H NMR δ 2.18 (3H, s), 3.52 (4H, s), 7.21–7.25 (2H, m), 7.29–7.33 (4H, m), 7.35–7.37 (4H, m). MS m/z (%) 211 (M^+, 40), 134 (40), 120 (20), 91 (100). Calcd for $C_{15}H_{17}N$: M, 211.1360. Found: m/z 211.1364.

3.1.25. *N*-Benzyl-*N*-deuteriomethyl-*p*-anisidine (19a). Colorless oil; IR (neat) 2932, 2831, 1509, 1451, 1241, 1040, 813 cm^{-1}; ^1H NMR δ 2.89 (2H, t, J=1.5 Hz), 3.75 (3H, s), 4.42 (2H, s), 6.73 (2H, d, J=8.9 Hz), 6.82 (2H, d, J=8.9 Hz), 7.22–7.32 (5H, m). MS m/z (%) 228 (M^+, 100), 213 (10), 151 (20), 137 (95), 91 (65). Calcd for $C_{15}H_{16}DNO$: M, 228.1372. Found: m/z 228.1375.

3.1.26. *N*-Deuteriomethyl-*N*-methyl-*p*-anisidine (19b). Colorless oil; IR (neat) 2951, 2832, 1512, 1244, 1038, 817 cm^{-1}; ^1H NMR δ 2.84 (2H, t, J=1.8 Hz), 2.86 (3H, s), 3.76 (3H, s), 6.75 (2H, d, J=9.2 Hz), 6.84 (2H, d, J=9.2 Hz). MS m/z (%) 152 (M^+, 70), 137 (100), 109 (10), 65 (10). Calcd for $C_9H_{12}DNO$: M, 152.1060. Found: m/z 152.1062.

3.1.27. *N*-Deuteriomethyldibenzylamine (19c). Colorless oil; IR (neat) 3063, 3028, 2794, 1603, 1495, 1454, 1367, 1028, 735, 698 cm^{-1}; ^1H NMR δ 2.16 (2H, br s), 3.52 (4H, s), 7.22–7.26 (2H, m), 7.29–7.37 (8H, m). MS m/z (%) 212 (M^+, 40), 135 (40), 121 (20), 91 (100), 65 (14). Calcd for $C_{15}H_{16}DN$: M, 212.1423. Found: m/z 212.1425.

3.1.28. Ethyl [benzyl(4-methoxyphenyl)amino]acetate (20a). To a solution of *i*-PrMgCl (0.5 mmol) in 0.5 mL of dry THF in a flame-dried flask at −78 °C under argon atmosphere was added a solution of **3e** (38 mg; 0.2 mmol) in 0.4 mL of dry THF dropwise with stirring. Immediately,

to a solution of the generated magnesium carbenoid **4e** was added a solution of *N*-lithio *N*-benzyl-*p*-anisidine [prepared from *N*-benzyl-*p*-anisidine (0.7 mmol) and *n*-BuLi (0.77 mmol) in 2 mL of THF at 0 °C and the solution was cooled to −78 °C] through a cannula with stirring. The reaction mixture was slowly allowed to warm to −40 °C for 1 h. To a solution of the α-amino-substituted carbanion **17** was added ethyl chloroformate (1 mmol) dropwise at −40 °C with stirring. After 20 min, the reaction mixture was quenched with satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The organic layer was washed with satd aq NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel column chromatography to afford **20a** (35 mg; 58%) as a colorless oil; IR (neat) 2935, 1745 (CO), 1514, 1244, 1187, 1029, 815, 739, 698 cm^{-1}, ^1H NMR δ 1.24 (3H, t, J=7.0 Hz), 3.73 (3H, s), 4.01 (2H, s), 4.18 (2H, q, J=7.0 Hz), 4.58 (2H, s), 6.66 (2H, d, J=8.9 Hz), 6.79 (2H, d, J=8.9 Hz), 7.23–7.35 (5H, m). MS *m*/*z* (%) 299 (M^+, 47), 226 (75), 195 (40), 120 (10), 91 (100). Calcd for $C_{18}H_{21}NO_3$: M, 299.1520. Found: *m*/*z* 299.1519.

3.1.29. Ethyl [*N*-(4-methoxyphenyl)-*N*-methylamino]-acetate (20b). Colorless oil; IR (neat) 2937, 1747 (CO), 1515, 1245, 1188, 1118, 1038, 948, 816 cm^{-1}. ^1H NMR δ 1.23 (3H, t, J=7.0 Hz), 3.01 (3H, s), 3.75 (3H, s), 3.99 (2H, s), 4.16 (2H, q, J=7.0 Hz), 6.68 (2H, d, J=8.9 Hz), 6.82 (2H, d, J=8.9 Hz). MS *m*/*z* (%) 223 (M^+, 28), 150 (100), 135 (15), 120 (10). Calcd for $C_{12}H_{17}NO_3$: M, 223.1207. Found: *m*/*z* 223.1208.

3.1.30. Ethyl [*N*-(4-chlorophenyl)-*N*-methylamino]-acetate (20c). Colorless oil; IR (neat) 2982, 1747 (CO), 1598, 1504, 1370, 1192, 1119, 1029, 811 cm^{-1}. ^1H NMR δ 1.24 (3H, t, J=7.0 Hz), 3.04 (3H, s), 4.03 (2H, s), 4.17 (2H, q, J=7.0 Hz), 6.60 (2H, d, J=9.2 Hz), 7.17 (2H, d, J=9.2 Hz). MS *m*/*z* (%) 227 (M^+, 20), 154 (100), 139 (10). Calcd for $C_{11}H_{14}ClNO_2$: M, 227.0712. Found *m*/*z* 227.0711.

3.1.31. Ethyl (*N*-methyl-*N*-phenylamino)acetate (20d). Colorless oil; IR (neat) 2931, 1748 (CO), 1602, 1508, 1369, 1191, 1029, 749, 691 cm^{-1}. ^1H NMR δ 1.24 (3H, t, J=7.0 Hz), 3.07 (3H, s), 4.05 (2H, s), 4.17 (2H, q, J=7.0 Hz), 6.69 (2H, d, J=7.9 Hz), 6.75 (1H, t, J=7.3 Hz), 7.23 (2H, m). MS *m*/*z* (%) 193 (M^+, 29), 120 (100), 105 (7), 77 (10). Calcd for $C_{11}H_{15}NO_2$: M, 193.1102. Found *m*/*z* 193.1096.

3.1.32. Ethyl (dibenzylamino)acetate (20e). Colorless oil; IR (neat) 2854, 1729 (CO), 1455, 1190, 1029, 746, 698 cm^{-1}. ^1H NMR δ 1.26 (3H, t, J=7.0 Hz), 3.28 (2H, s), 3.81 (4H, s), 4.15 (2H, q, J=7.0 Hz), 7.22–7.26 (2H, m), 7.29–7.32 (4H, m), 7.37–7.41 (4H, m). MS *m*/*z* (%) 283 (M^+, 4), 210 (98), 192 (10), 91 (100). Calcd for $C_{18}H_{21}NO_2$: M, 283.1571. Found *m*/*z* 283.1575.

Acknowledgements

This work was supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan to promote multi-disciplinary research project, which is gratefully acknowledged.

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Tetrahedron 62 (2006) 7902–7910
Tetrahedron

Oxidative cyclization of *N*-alkyl-*o*-methyl-arenesulfonamides to biologically important saccharin derivatives

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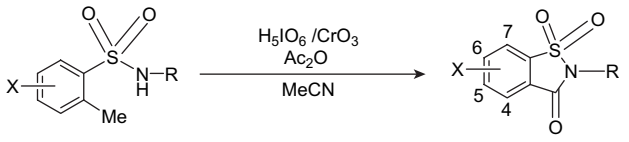
Received 13 March 2006; revised 11 May 2006; accepted 15 May 2006
Available online 19 June 2006

Abstract—Various biologically important saccharin skeletons and their *N*-alkyl derivatives have been efficiently prepared by chromium(VI) oxide catalyzed H_5IO_6 oxidation of *N*-alkyl-*o*-methyl-arenesulfonamides in acetonitrile. *N*-*tert*-Butyl saccharin skeletons were easily prepared by H_5IO_6–CrO_3 oxidation of *N*-*tert*-butyl-*o*-methyl arenesulfonamides in the presence of acetic anhydride. The method that furnished the novel fluoro and trifluoromethyl substituted saccharin skeletons is characterized by two steps, a simple work-up procedure, a single purification and good overall yields from substituted toluene derivatives.

1. Introduction

The H_5IO_6–CrO_3 oxidation system has been used for various C–H oxidations, such as tertiary C–H,[1] benzylic C–H,[2] alcoholic C–H,[3] aromatic C–H.[4] In recent years, our group has been studying the H_5IO_6–CrO_3 oxidation system and reported several novel C–H oxidations by using H_5IO_6–CrO_3 to oxidize *N*-alkylamides to imides,[5] *N*-alkylsulfonamides to sulfonimides,[6] benzylic silyl ethers to aldehydes or ketones.[7] Although the chromium(VI) catalyzed H_5IO_6 oxidation of toluenes to benzoic acids has been described by Yamazaki,[2] the application of this oxidation system to oxidize *N*-alkyl-*o*-methyl-arenesulfonamides to saccharin skeletons has not been reported.



1,2-Benzisothiazole-3-one-1,1-dioxide (saccharin) has been widely incorporated into a variety of biologically active compounds. The saccharin moiety has been identified as an important molecular component in various classes of 5-HT1a antagonists,[7] human leukocyte elastase inhibitors,[8] analgesics,[9] human mast cell tryptase inhibitors,[10] α1a and α1c adrenergic receptor antagonists,[11] aldehyde dehydrogenase inhibitors,[12] and bactericides.[13] To our knowledge, only one method has been reported in the literature for the transformation of *N*-alkyl-*o*-methyl-arenesulfonamides to *N*-alkyl saccharin derivatives.[14] However, this method is limited to *N*-methyl derivatives with electron-withdrawing aryl ring substituents and the yields are fairly low. During our recent study of chromium catalyzed periodic acid oxidations,[5–7,15] we found that *N*-alkyl-*o*-methyl-arenesulfonamides could be efficiently oxidized to saccharin and saccharin *N*-alkyl derivatives with H_5IO_6–CrO_3 in acetonitrile. Herein we report this novel and efficient method for the preparation of various saccharin skeletons.

2. Results

2.1. Direct oxidation of *N*-alkyl-*o*-toluenesulfonamides to saccharin derivatives

The results of oxidation of *N*-alkyl-*o*-methyl-toluenesulfonamides **1** to afford saccharin derivatives **2** are summarized in Table 1. The oxidation of *o*-toluenesulfonamide (**1a**) was incomplete with only 4 equiv of H_5IO_6 either at rt or 85 °C (Table 1, entries 1–3). At least 6 equiv of H_5IO_6 and 10 mol % of CrO_3 were required for complete reaction at 85 °C (Table 1, entry 5). The oxidation was also completed in 1 h by refluxing **1a** with 8 equiv of H_5IO_6 and 5% of CrO_3 in acetonitrile (Table 1, entry 7). Similar results were obtained at rt with 8 equiv of H_5IO_6 but longer reaction time (16 h) or higher catalyst loading (10 mol %) was required.

A competitive oxidation of the α-C–H of the *N*-alkyl group was observed in the oxidation of several *N*-alkyl-*o*-toluenesulfonamides. Oxidation of *N*-methyl-*o*-toluenesulfonamide

Keywords: Saccharin; Sulfonamides; Periodic acid; Chromium trioxide; Oxidation; Oxidative cyclization
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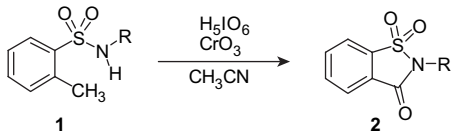
doi:10.1016/j.tet.2006.05.038

Table 1. Direct oxidation of *N*-alkyl-*o*-toluenesulfonamides to saccharin derivatives



Entry	1	R	2	H_5IO_6 (equiv)	CrO_3 (mol %)	Temperature (°C)	Time (h)	Yield (%)[a]
1	**1a**	H	**2a**	4	10	22	16	32
2	**1a**	H	**2a**	4	20	22	16	48
3	**1a**	H	**2a**	4	20	85	1	60
4	**1a**	H	**2a**	6	5	85	1	68
5	**1a**	H	**2a**	6	10	85	1	75
6	**1a**	H	**2a**	8	5	22	16	75
7	**1a**	H	**2a**	8	5	85	1	75
8	**1b**	Me	**2b**	8	5	22	8	35[b]
9	**1c**	Et	**2c**	8	5	22	8	12
10	**1d**	*i*-Pr	**2d**	8	5	22	8	20
11	**1e**	c-Pr	**2e**	8	5	22	16	46
12	**1f**	CF_3CH_2	**2f**	8	5	85	1	94
13	**1f**	CF_3CH_2	**2f**	8	10	22	8	94
14	**1g**	*t*-Bu	**2g**	6	5	22	16	76
15	**1g**	*t*-Bu	**2g**	6	5	22	16	84[c]
16	**1g**	*t*-Bu	**2g**	8	5	22	16	80
17	**1g**	*t*-Bu	**2g**	8	5	22	10	86[d]
18	**1g**	*t*-Bu	**2g**	8	10	22	8	86
19	**1g**	*t*-Bu	**2g**	8	10	22	8	88[d]
20	**1h**	MeO		8	5	22	3	0[e]

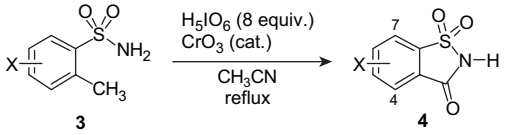
[a] Isolated yields.
[b] Saccharin was also obtained (20%).
[c] The reaction was performed in the presence of 6 equiv of Ac_2O.
[d] The reaction was performed in the presence of 8 equiv of Ac_2O.
[e] Intractable mixture.

(**1b**) (Table 1, entry 8) afforded *N*-methyl saccharin (**2b**) in 35% yield and saccharin (**2a**) was also obtained in 20% yield. Only a 12% yield of *N*-ethyl saccharin (**2c**) was obtained in oxidation of *N*-ethyl-*o*-toluenesulfonamide (**1c**, Table 1, entry 9). The competitive α-C–H oxidation was more significant in oxidation of *N*-isopropyl-*o*-toluenesulfonamide (**1d**) than that of *N*-cyclopropyl-*o*-toluenesulfonamide (**1e**) (Table 1, entries 10 and 11). However, the 2, 2, 2-trifluoroethyl group and *tert*-butyl group were tolerant of the oxidation conditions. Oxidation of *N*-2, 2, 2-trifluoroethyl-*o*-toluenesulfonamide (**1f**) afforded the corresponding saccharin derivative **2f** in 94% either at rt or at reflux (Table 1, entries 12 and 13). The oxidation of *N*-*tert*-butyl-*o*-toluenesulfonamide (**1g**) also gave high yields of the corresponding *N*-*tert*-butyl saccharin (**2g**) at rt (Table 1, entry 14). In addition, the yields of the **2g** were slightly improved when acetic anhydride was added to the reaction mixture to maintain anhydrous conditions (Table 1, entries 15, 17, and 19). Acetic anhydride was selected as a desiccant over molecular sieves or other inorganic reagents because of the heterogeneous character of the reaction mixture. Iodic acid (HIO_3) is formed as a by-product of the oxidation and precipitates from the reaction mixture. The addition of solid desiccant reagents was not desirable since adequate mixing could become difficult. To this end, optimal conditions were realized with 8 equiv of acetic anhydride to yield the *N*-*tert*-butyl saccharin (**2g**) in 88% yield. The presence of acetic anhydride also significantly shortened the reaction time (Table 1, entry 19). In addition, no acetylated products were identified. Attempts to oxidize the *N*-methoxy-*o*-toluenesulfonamide were unsuccessful and only an intractable mixture was obtained.

2.2. Oxidation of various substituted *o*-toluenesulfonamides to saccharin skeletons

To date a number of methods have been reported for the construction of the saccharin ring system.[16–21] However, currently available methods either employ sophisticated reagents or give only moderate yields of saccharin derivatives. A practical and general method for the preparation of saccharin-based compounds is still desirable. The direct oxidation of *o*-methyl arenesulfonamides is the simplest and most straightforward method for the preparation of saccharin skeletons. However, most of the reported oxidations are generally conducted in aqueous acidic or basic solutions affording the product in fairly low yields (40–50%).[16] Some oxidations even use excess CrO_3 as the oxidant but these conditions can lead to the environmental problem of waste metal disposal. Based on our initial results from the direct oxidation of *N*-alkyl-*o*-toluenesulfonamides (Table 1), we developed a practical and general method for the preparation of *N*-unsubstituted saccharin derivatives. As summarized in Table 2, various substituted *o*-toluenesulfonamides **3** were easily oxidized to the corresponding substituted saccharin derivatives **4** by refluxing with 8 equiv of H_5IO_6 and a catalytic amount of CrO_3 in acetonitrile. Higher catalyst loading (10 mol %) of CrO_3 was required for complete oxidation of substrates with strong electron-withdrawing groups. It is noteworthy that *p*-xylenesulfonamide (**3i**) was efficiently oxidized to the 6-CO_2H saccharin derivative **4i** with 10 equiv of H_5IO_6 and 10 mol % of CrO_3 (Table 2, entry 9).

Table 2. Oxidation of substituted *o*-toluenesulfonamides to saccharin skeletons



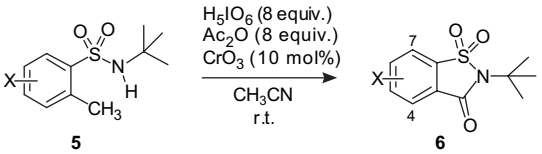
Entry	3	4	Saccharin X	CrO_3 (mol %)	Time (h)	Yield (%)[a]
1	**3a**	**4a**	6-Cl	5.0	1	76
2	**3b**	**4b**	5-Cl	5.0	1	76
3	**3c**	**4c**	4-Cl	5.0	1	74
4	**3d**	**4d**	7-Cl	5.0	1	75
5	**3e**	**4e**	6-Br	5.0	1	76
6	**3f**	**4f**	5-Br	5.0	1	76
7	**3g**	**4g**	6-F	5.0	1.5	74
8	**3h**	**4h**	5-F	5.0	1.5	74
9	**3i**	**4i**	6-CO_2H	10.0	2	75[b]
10	**3j**	**4j**	6-SO_2Me	10.0	2	70
11	**3k**	**4k**	6-$SONH_2$	10.0	3	68
12	**3l**	**4l**	6-NO_2	10.0	3	65

[a] Isolated yield.
[b] Starting material was *p*-xylenesulfonamide and H_5IO_6 (10 equiv).

2.3. Oxidation of *N*-*tert*-butyl-*o*-methyl arenesulfonamides to saccharin derivatives

From the study of *N*-alkyl substituted toluenesulfonamides described above, it was evident the *N*-*tert*-butyl group could be utilized as a protecting group in this system for the preparation of N-protected saccharin derivatives. As summarized

Table 3. Oxidation of *N-tert*-butyl-*o*-methyl arenesulfonamides to saccharin derivatives



5 **6**

Entry	5	6	Saccharin X	Time (h)	Yield (%)[a]
1	**5a**	**6a**	6-*t*-Bu	5	90
2	**5b**	**6b**	6-Cl	8	88
3	**5c**	**6c**	5-Cl	10	86
4	**5d**	**6d**	4-Cl	14	88[b](64)[c]
5	**5e**	**6e**	7-Cl	10	92[b](65)[c]
6	**5f**	**6f**	6-Br	8	90
7	**5g**	**6g**	5-Br	10	88
8	**5h**	**6h**	6-F	10	86
9	**5i**	**6i**	5-F	10	86
10	**5j**	**6j**	6-$MeSO_2$	14	80
11	**5k**	**6k**	6-SO_2NH*t*-Bu	16	76
12	**5l**	**6l**	6-NO_2	20	72
13	**5m**	**6m**	5-NO_2	20	72
14	**5n**	**6n**	7-NO_2	20	88[b](62)[c]
15	**5o**	**6o**	5-Cl-6-Me	4	42

[a] Isolated yield.
[b] Crude yield, >90% purity by ^{1}H NMR.
[c] The product was inseparable by chromatography, the yield was determined after recrystallization from ethanol.

in Table 3, a variety of *N-tert*-butyl-*o*-methyl arenesulfonamides (**5**) were smoothly oxidized to the corresponding N-protected saccharin derivatives (**6**) in good to excellent yields by using 8 equiv of H_5IO_6 and 10 mol % of CrO_3 in the presence of acetic anhydride at rt. The oxidation of *N-tert*-butyl-5-*tert*-butyl-*o*-toluenesulfonamides furnished the corresponding *N-tert*-butyl-6-*tert*-butyl saccharin **6a** in 90% yield (Table 3, entry 1). Longer reaction times were required for substrates with halogen or electron-withdrawing substituents.

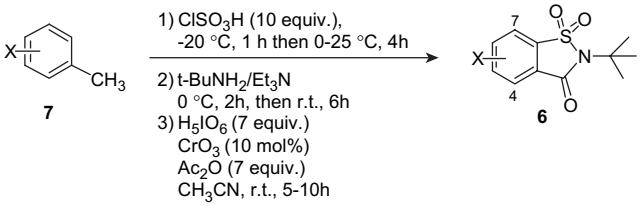
3. Discussion

For benzylic oxidation of substituted toluenes to benzoic acids, Yamazaki reported that only 3.5 equiv of H_5IO_6 was necessary for complete oxidation but 20 mol % CrO_3 was required for a complete oxidation of toluene derivatives with electron-withdrawing groups. Our investigation found that for the oxidation of *o*-toluenesulfonamides lower catalyst loading of only 5–10 mol % could be achieved with 8 equiv of H_5IO_6 in acetonitrile at reflux (Table 2). In addition, the oxidation reaction was significantly accelerated after addition of acetic anhydride. The oxidation of α-C–H of the *N*-alkyl group was identified as a competitive side reaction in oxidation of *N*-alkyl-*o*-methyl-arenesulfonamides, thus limiting the scope of utility of the process. The reactivity of N–α-CH bonds in this side reaction decreased in the following order: secondary>tertiary>primary. Only 12% of *N*-ethyl saccharin was obtained in oxidation of *N*-ethyl-*o*-toluenesulfonamide. For *N*-2, 2, 2-trifluoroethyl and *N-tert*-butyl substituted *o*-toluenesulfonamide, the α-C–H of *N*-alkyl group was not oxidized and high yields of products were obtained.

Chromium(VI) oxide was found to be the most effective catalyst in this oxidative cyclization. Other chromium species such as chromium(III) acetylacetonate, chromium(III) acetate hydroxide or chromium(III) trichloride, while effective for the oxidation of sulfide to sulfones and alcohols and silyl ethers to carbonyl compounds, were inferior as catalysts for the α-C–H oxidation of the *N*-alkyl-*o*-methyl-arenesulfonamides.[7,15]

The *N-tert*-butyl group proved to be a suitable nitrogen-protecting group for the preparation of *N-tert*-butyl saccharin derivatives from *o*-methyl arenesulfonamides. It was found that the *tert*-butyl group could be more easily removed than protective groups (methyl or a *p*-methoxy benzyl) typically used for the preparation of saccharin derivatives.[22,23] In addition, the purification of the substituted saccharin derivatives either by column chromatography or by recrystallization from ethanol was greatly facilitated by the *N-tert*-butyl group. Based upon these results, it was of interest to develop a direct method for the preparation of substituted saccharin derivatives from substituted toluene derivatives that employ the *N-tert*-butyl group as a protecting group for the saccharin nitrogen atom. To this end, the required *N-tert*-butyl-*o*-methyl arenesulfonamides were easily prepared by chlorosulfonation of substituted toluene derivatives **7** with chlorosulfonic acid.[24] The resulting sulfonyl chlorides were treated with *tert*-butyl amine to furnish the *N-tert*-butyl-*o*-toluenesulfonamide derivatives. For toluene and some substituted toluene derivatives (F, Cl, Br, CF_3, *t*-Bu) a mixture of isomers was observed (NMR, TLC) derived from the chlorosulfonation step. The other regioisomers present in small amounts (10–20%) were very difficult to separate from the *N-tert*-butyl-*o*-toluenesulfonamide isomers either by distillation or column chromatography. However, typically the isomeric mixture of *N-tert*-butyl-toluenesulfonamides was carried forward without purification to the oxidation step. Upon H_5IO_6 –CrO_3 oxidation of the mixture, the *N-tert*-butyl-*o*-toluenesulfonamide isomer was converted into the desired saccharin derivative **6** while other *N-tert*-butyl-toluenesulfonamide regioisomers present in the mixture were converted into substituted benzoic acids. The acid derivatives could then be easily removed by washing with saturated sodium bicarbonate solution affording the clean *N-tert*-butyl protected saccharin derivatives in moderate to good yields. As summarized in Table 4, a series of 6- and 5-substituted saccharin

Table 4. Direct preparation of saccharin derivatives from substituted toluene derivatives



7 **6**

Entry	6	X	Yield (%)[a]	Entry	6	X	Yield (%)[a]
1	**2g**	H	45	6	**6g**	5-Br	52
2	**6a**	6-*t*-Bu	56	7	**6h**	6-F	79
3	**6b**	6-Cl	65	8	**6i**	5-F	66
4	**6c**	5-Cl	58	9	**6p**	6-CF_3	58
5	**6f**	6-Br	61	10	**6q**	5-CF_3	38

[a] Isolated yield.

skeletons were easily prepared by this direct method. This one-pot procedure was amenable to the preparation of a variety of substituted saccharin derivatives, some not readily available by other methods. In addition, to our knowledge, this is the first report of the preparation of trifluoromethyl substituted saccharin derivatives **6p** and **6q**.

The mechanism of this novel oxidative cyclization has not been clearly established. Based upon observation in this study and related studies, we believe that this oxidative cyclization is likely to occur through the mechanism illustrated in Scheme 1. Chromium oxo or peroxo species are believed to abstract a benzylic hydrogen atom from the *N*-alkyl-*o*-toluenesulfonamide **1** and form benzylic radical **A**. It is well known that Cr(VI) oxo and peroxo species can abstract activated hydrogen atoms from organic compounds to form alkylradical intermediates.[25] Although the initial catalyst is Cr(VI) other oxidation states of chromium [e.g., Cr(V) and Cr(IV)] may be involved in the oxidative cyclization. The presence of N-dealkylation by-products suggests the possibility of a N-centered radical intermediate formed by intramolecular hydrogen transfer to form radical **B**. The radical **B** could then be easily oxidized to carbonyl diradical **C** that could cyclize quickly to afford the saccharin skeleton **2**. Alternatively, **B** could undergo a second H atom abstraction to give an alkyl diradical species **D**. The intramolecular coupling of the N-centered radical and benzylic radical of **D** would then afford intermediate **E**. Once formed, intermediate **E** could be easily and quickly oxidized to the saccharin skeleton. This reaction pathway is supported by recent studies in our laboratories that have shown that *N*-alkylamides and *N*-alkylsulfonamides are easily oxidized by H_5IO_6–CrO_3 system to give high yields of imide derivatives.[5] In addition, it is not likely that the oxidative cyclization reaction takes place through the dehydration of a benzoic acid intermediate. We have found that 2-carboxy-*N*-alkyl benzenesulfonamides do not cyclize to generate the saccharin skeleton under acidic conditions (aqueous HCl). Therefore, it is believed that the excess H_5IO_6 used in this oxidation is necessary to force the reaction to completion but not for the dehydration. Moreover, benzoic acid intermediates were never observed during the oxidation of *N*-alkyl-*o*-methyl-arenesulfonamides.

4. Conclusion

In conclusion, we have developed a novel and practical method for the preparation of saccharin and saccharin derivatives from substituted toluene derivatives by oxidation with the H_5IO_6–CrO_3 system. This oxidative-cyclization procedure is superior to other methods in both yield and waste metal production for the construction of the saccharin ring system. In addition, this method is tolerant of a variety of functional groups and has allowed the facile preparation of substituted saccharin derivatives that were previously difficult to synthesize.

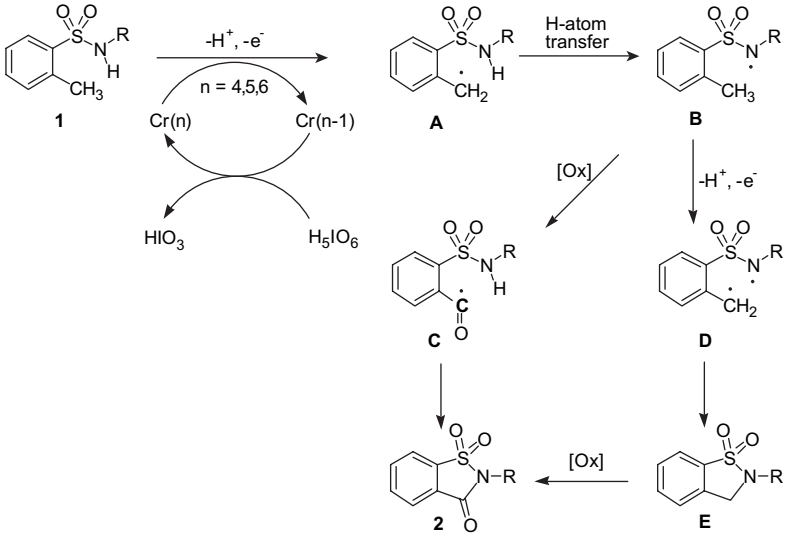
5. Experimental

5.1. General

All known compounds were identified by comparison of NMR spectral and physical data with the data reported in the literature and with the authentic samples when available. All new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. NMR spectra were recorded on a Varian-400 MHz spectrometer at ambient temperature in $CDCl_3$/DMSO-d_6 with TMS as an internal standard. Infra red spectra were recorded with BOMEM Infrared Spectrometer, MB Series. Elemental analyses (C, H, N) were determined by Atlantic Microlabs, Inc., Norcross, GA. Melting points were recorded on a Hoover Mel-Temp apparatus and are uncorrected.

5.2. General procedure for the preparation of *N*-unsubstituted saccharin skeletons (2a and 4a–l)

A mixture of H_5IO_6 (18 g, 80 mmol), CrO_3 (50 mg, 0.5 mmol, 5 mol %) and *o*-methyl arenesulfonamide (10 mmol) in acetonitrile (100 mL) was heated to reflux until the oxidation was complete (monitored by TLC).



Scheme 1.

Isopropyl alcohol (10 mL) was added dropwise. After the addition was complete, the mixture was heated to reflux for an additional 10 min, cooled to rt, filtered and the solids were washed with acetone (2×60 mL). The filtrates were combined and concentrated under reduced pressure. The residue was triturated with 2 N H_2SO_4 solution (30 mL) and the crude product was collected by vacuum filtration. Most products were quite pure based on ^{1}H NMR and melting points. If necessary, further purification was performed by dissolving the crude product in satd Na_2CO_3 solution (40 mL). Any solids were filtered and the filtrate was extracted with EtOAc (40 mL). The aqueous layer was separated and acidified with concentrated HCl solution to pH 1. The resulting precipitate was collected by vacuum filtration to give pure products.

5.3. General procedure for the preparation of *N*-alkyl-*o*-methyl-arenesulfonamide derivatives

A solution of *o*-methylarenesulfonyl chloride (20 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a solution of alkylamine (21 mmol) and triethylamine (21 mmol) in CH_2Cl_2 (80 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then rt for 6 h. The mixture was washed, respectively, with 0.1 N HCl solution (50 mL) and satd $NaHCO_3$ solution (50 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded the *N*-alkyl-*o*-methyl-arenesulfonamides in sufficient purity for further use. If necessary, further purification by flash column chromatography (hexanes/EtOAc, 4:1) furnished the pure *N*-alkyl-*o*-methyl-arenesulfonamide derivatives.

5.3.1. *N*-Cyclopropyl-*o*-toluenesulfonamide (1e). Yellow oil. IR (liquid film) 3285, 3019, 1453, 1312, 1160, 1069, 881 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.87 (d, J=7.6, 1H), 7.53 (t, J=7.6, 1H), 7.38–7.42 (m, 2H), 2.56 (s, 3H), 2.10–2.14 (m, 1H), 0.30–0.45 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.3, 136.5, 132.4, 132.3, 128.9, 126.1, 23.4, 19.7, 5.0. Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.87; H, 6.16; N, 6.63. Found: C, 57.06; H, 6.33; N, 6.62.

5.3.2. *N*-(2,2,2-Trifluoroethyl)-*o*-toluenesulfonamide (1f). Mp 78–80 °C. IR ($CHCl_3$) 3285, 3061, 1540, 1453, 1330, 1270, 1168 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.7 (t, J=6.8, 1H), 7.84 (d, J=8.0, 1H), 7.53 (t, J=7.2, 1H), 7.36–7.42 (m, 2H), 3.69–3.78 (m, 2H), 2.58 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.9, 136.5, 132.7, 132.5, 128.1, 126.3, 122.6, 43.4, 19.7. Anal. Calcd for $C_9H_{10}F_3NO_2S$: C, 42.68; H, 3.95; N, 5.53. Found: C, 42.75; H, 4.04; N, 5.49.

5.3.3. *N*-Methoxy-*o*-toluenesulfonamide (1h). Yellow oil. IR (liquid film) 3283, 3011, 1456, 1318, 1149, 1066, 883 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.5 (s, 1H), 7.85 (d, J=8.4, 1H), 7.58 (t, J=7.6, 1H), 7.48–7.37 (m 2H), 3.62 (s, 3H), 2.60 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.1, 135.6, 133.4, 132.5, 130.0, 126.3, 64.2, 20.1. Anal. Calcd for $C_8H_{11}NO_3S$: C, 47.76; H, 5.47; N, 6.96. Found: C, 47.48; H, 7.02; N, 6.74.

5.3.4. *N-tert*-Butyl-2-methyl-5-*tert*-butylbenzenesulfonamide (5a). Mp 140–142 °C. IR ($CHCl_3$) 3280, 2965, 2873, 1540, 1394, 1311, 1137, 1000 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J=8.4, 1H), 7.35 (d, J=7.6, 1H), 7.36 (s, 1H), 2.57 (s, 3H), 1.26 (s, 9H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.3, 139.5, 136.4, 129.6, 128.6, 123.2, 53.6, 34.9, 31.2, 30.1, 20.3. Anal. Calcd for $C_{15}H_{25}NO_2S$: C, 63.60; H, 8.83; N, 4.94. Found: C, 63.56; H, 8.90; N, 4.86.

5.3.5. *N-tert*-Butyl-2-methyl-5-chlorobenzenesulfonamide (5b). Mp 140–142 °C. IR ($CHCl_3$) 3285, 2969, 1540, 1467, 1320, 1142, 1009 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 7.69 (s, 1H), 7.58 (d, J=8.4, 1H), 7.42 (d, J=8.4, 1H), 2.56 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 144.0, 135.8, 134.7, 132.2, 130.8, 127.9, 53.9, 30.1, 19.4. Anal. Calcd for $C_{11}H_{16}ClNO_2S$: C, 50.47; H, 6.12; N, 5.35. Found: C, 50.18; H, 6.21; N, 5.38.

5.3.6. *N-tert*-Butyl-2-methyl-4-chlorobenzenesulfonamide (5c). Mp 142–144 °C. IR ($CHCl_3$) 3294, 2965, 2878, 1559, 1464, 1312, 1151 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J=8.8, 1H), 7.61 (s, 1H), 7.50 (s 1H), 7.44 (d, J=8.8, 1H), 2.59 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 140.9, 138.9, 136.5, 131.8, 130.2, 126.1, 53.4, 29.7, 19.5. Anal. Calcd for $C_{11}H_{16}ClNO_2S$: C, 50.47; H, 6.12; N, 5.35. Found: C, 50.49; H, 6.15; N, 5.25.

5.3.7. *N-tert*-Butyl-2-methyl-3-chlorobenzenesulfonamide (5d). Mp 146–148 °C. IR ($CHCl_3$) 3280, 2965, 1430, 1311, 1202, 1142, 1000 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J=8.4, 1H), 7.71 (s, 1H), 7.69 (d, J=8.8, 1H), 7.40 (t, J=8.0, 1H), 2.64 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 144.2, 135.6, 134.1, 132.8, 127.4, 127.3, 53.6, 29.7, 16.5. Anal. Calcd for $C_{11}H_{16}ClNO_2S$: C, 50.47; H, 6.12; N, 5.35. Found: C, 50.64; H, 6.19; N, 5.32.

5.3.8. *N-tert*-Butyl-2-methyl-6-chlorobenzenesulfonamide (5e). Mp 162–168 °C. IR ($CHCl_3$) 3308, 2969, 1536, 1449, 1320, 1151, 1005 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (s 1H), 7.47 (d, J=7.6, 1H), 7.42 (d, J=7.6, 1H), 7.34 (d, J=7.2, 1H), 2.63 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 140.3, 139.9, 132.8, 132.7, 132.6, 130.7, 54.0, 29.8, 23.6. Anal. Calcd for $C_{11}H_{16}ClNO_2S$: C, 50.47; H, 6.12; N, 5.35. Found: C, 50.47; H, 6.16; N, 5.29.

5.3.9. *N-tert*-Butyl-2-methyl-5-bromobenzenesulfonamide (5f). Mp 160–162 °C. IR ($CHCl_3$) 3276, 2974, 1540, 1472, 1316, 1137, 1009 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.71 (d, J=8.4, 1H), 7.70 (s, 1H), 7.36 (d, J=8.4, 1H), 2.55 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 144.2, 136.2, 135.1, 135.0, 130.7, 118.8, 53.9, 30.1, 19.5. Anal. Calcd for $C_{11}H_{16}BrNO_2S$: C, 43.13; H, 5.22; N, 4.57. Found: C, 43.20; H, 5.31; N, 4.56.

5.3.10. *N-tert*-Butyl-2-methyl-4-bromobenzenesulfonamide (5g). Mp 146–148 °C. IR ($CHCl_3$) 3285, 2969, 1540, 1316, 1151, 1009 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J=8.4, 1H), 7.64 (s, 1H), 7.57–7.60 (m, 2H), 2.57 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (75 MHz,

DMSO-d_6) δ 141.7, 139.5, 135.1, 130.6, 129.5, 125.9, 53.8, 30.0, 19.8. Anal. Calcd for $C_{11}H_{16}BrNO_2S$: C, 43.13; H, 5.22; N, 4.57. Found: C, 43.11; H, 5.27; N, 4.48.

5.3.11. *N*-*tert*-Butyl-2-methyl-5-fluorobenzenesulfonamide (5h). Mp 118–120 °C. IR ($CHCl_3$) 3299, 2976, 2868, 1490, 1316, 1229, 1142, 1005 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 7.67 (s, 1H), 7.60–7.63 (m, 1H), 7.42–7.45 (m, 1H), 7.33–7.39 (m, 1H), 2.56 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.9, 144.0, 134.8, 133.0, 119.4, 115.5, 53.9, 30.0, 19.2. Anal. Calcd for $C_{11}H_{16}FNO_2S$: C, 53.87; H, 6.53; N, 5.71. Found: C, 53.67; H, 6.60; N, 5.71.

5.3.12. *N*-*tert*-Butyl-2-methyl-4-fluorobenzenesulfonamide (5i). Mp 140–142 °C. IR ($CHCl_3$) 3294, 2978, 2878, 1582, 1476, 1311, 1147, 1005 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 7.90–7.93 (m, 1H), 7.53 (s, 1H), 7.25–7.28 (m, 1H), 7.17–7.21 (m, 1H), 2.59 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.7, 140.6, 138.8, 131.6, 119.3, 113.3, 53.7, 30.1, 20.1. Anal. Calcd for $C_{11}H_{16}FNO_2S$: C, 53.87; H, 6.53; N, 5.71. Found: C, 53.71; H, 6.63; N, 5.69.

5.3.13. *N*-*tert*-Butyl-2-methyl-5-methylsulfonylbenzenesulfonamide (5j). Mp 182–184 °C. IR ($CHCl_3$) 3285, 2976, 1545, 1316, 1147, 1005 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.04 (s, 1H), 7.82 (s, 1H), 7.69 (d, J=7.6, 1H), 3.26 (s, 3H), 2.69 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 143.3, 143.2, 139.3, 134.2, 130.8, 127.0, 54.2, 43.9, 30.1, 20.2. Anal. Calcd for $C_{12}H_{19}NO_4S_2$: C, 47.21; H, 6.22; N, 4.59. Found: C, 47.35; H, 6.22; N, 4.49.

5.3.14. *N*-*tert*-Butyl-2-methyl-5-(*N*-*tert*-butylaminosulfonyl)benzenesulfonamide (5k). Mp 224–226 °C. IR ($CHCl_3$) 3280, 2978, 2878, 1540, 1394, 1325, 1147, 995 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.92 (d, J=8.0, 1H), 7.76 (d, J=5.6, 1H), 7.58 (d, J=8.4, 1H), 2.65 (s, 3H), 1.109 (s, 9H), 1.107 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 142.6, 142.4, 140.6, 133.3, 129.5, 126.4, 53.6, 53.4, 29.79, 29.69, 19.70. Anal. Calcd for $C_{15}H_{26}N_2O_4S_2$: C, 49.72; H, 7.18; N, 7.73. Found: C, 49.71; H, 7.35; N, 7.68.

5.3.15. *N*-*tert*-Butyl-2-methyl-5-nitrobenzenesulfonamide (5l). Mp 127–129 °C. IR ($CHCl_3$) 3294, 2974, 1522, 1353, 1156, 995 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.34 (d, J=8.4, 1H), 7.92 (s, 1H), 7.71 (d, J=8.0, 1H), 2.73 (s, 3H), 1.13 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.4, 144.3, 143.1, 134.0, 126.3, 122.7, 53.7, 29.6, 19.7. Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.88; N, 10.29. Found: C, 48.66; H, 5.94; N, 10.22.

5.3.16. *N*-*tert*-Butyl-2-methyl-4-nitrobenzenesulfonamide (5m). Mp 157–159 °C. IR ($CHCl_3$) 3290, 2978, 2868, 1531, 1320, 1156, 1005 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.20 (d, J=8.8, 1H), 8.13 (d, J=8.8, 1H), 7.92 (s, 1H), 2.71 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.0, 147.5, 138.8, 129.8, 126.9, 121.3, 53.8, 29.7, 19.7. Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.88; N, 10.29. Found: C, 48.76; H, 5.89; N, 10.33.

5.3.17. *N*-*tert*-Butyl-2-methyl-6-nitrobenzenesulfonamide (5n). Mp 181–183 °C. IR ($CHCl_3$) 3290, 2976, 1545, 1330, 1156 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.68–7.62 (m, 3H), 2.68 (s, 3H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.0, 140.0, 135.2, 133.4, 132.9, 122.0, 54.6, 29.7, 20.6. Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.88; N, 10.29. Found: C, 48.77; H, 5.94; N, 10.35.

5.3.18. *N*-*tert*-Butyl-2, 5-dimethyl-4-chlorobenzenesulfonamide (5o). Mp 170–172 °C. IR ($CHCl_3$) 3294, 2974, 1545, 1316, 1142, 1005 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 2.53 (s, 3H), 2.34 (s, 3H), 1.1 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 141.1, 137.0, 136.3, 133.7, 132.6, 131.1, 53.7, 30.1, 19.4, 19.3. Anal. Calcd for $C_{12}H_{18}ClNO_2S$: C, 52.26; H, 6.53; N, 5.08. Found: C, 52.51; H, 6.63; N, 5.01.

5.4. General procedure for the preparation of *N*-alkyl saccharin derivatives

A mixture of H_5IO_6 (18 g, 80 mmol) in acetonitrile (140 mL) was stirred vigorously at rt for 1 h, then CrO_3 (100 mg, 1 mmol, 10 mol %) was added followed by acetic anhydride (8.2 g, 80 mmol). The resulting orange solution was cooled to 0 °C. The *N*-alkyl-*o*-methyl-arenesulfonamide (10 mmol) was then added in one portion. After stirring at 0 °C for 15 min, the reaction mixture was allowed to warm to rt and stirred until the oxidation was complete (monitored by TLC). The solvent was removed at rt under reduced pressure and the residue was extracted with EtOAc (2×80 mL). The combined organic portions were washed with satd $NaHCO_3$ solution (80 mL), satd $Na_2S_2O_3$ solution (60 mL), brine (60 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product. Some of the crude saccharin derivatives were quite pure by ^1H NMR. If necessary, further purification by flash column chromatography (hexanes/EtOAc, 4:1) furnished the pure *N*-alkyl saccharin derivatives.

5.4.1. *N*-Cyclopropyl-1,2-benzisothiazole-3-one-1,1-dioxide (2e). Mp 144–146 °C. IR ($CHCl_3$) 3010, 1737, 1540, 1458, 1320,1183 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J=7.2, 1H), 7.99–8.10 (m, 3H), 2.80–2.81 (m, 1H), 1.02–1.03 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.5, 136.6, 135.8, 135.1, 126.1, 124.9, 121.4, 20.2, 3.74. Anal. Calcd for $C_{10}H_9NO_3S$: C, 53.81; H, 4.04; N, 6.27. Found: C, 53.73; H, 4.07; N, 6.31.

5.4.2. *N*-(2,2,2-Trifluoroethyl)-1,2-benzisothiazole-3-one-1,1-dioxide (2f). Mp 132–134 °C. IR ($CHCl_3$) 3093, 3024, 1756, 1540, 1348, 1247, 1174 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J=8.0, 1H), 8.19 (d, J=7.2, 1H), 8.13 (t, J=7.6, 1H), 8.06 (t, J=8.0, 1H), 4.62–4.69 (q, J=9.2, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.7, 136.7, 136.5, 135.6, 125.7, 125.60, 124.7, 121.9, 40.2. Anal. Calcd for $C_9H_6F_3NO_3S$: C, 40.75; H, 2.26; N, 5.28. Found: C, 40.68; H, 2.29; N, 5.18.

5.4.3. *N*-*tert*-Butyl-6-*tert*-butyl-1,2-benzisothiazole-3-one-1,1-dioxide (6a). Mp 120–122 °C. IR ($CHCl_3$) 2965, 2873, 1719, 1536, 1334, 1252, 1192 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J=7.6, 1H), 8.05 (d,

J=8.4, 1H), 7.97 (s, 1H), 1.69 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.7, 158.6, 134.4, 132.8, 126.3, 120.8, 120.5, 60.2, 35.4, 30.4, 27.2. Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 61.01; H, 7.12; N, 4.74. Found: C, 60.89; H, 7.20; N, 4.72.

5.4.4. *N-tert*-Butyl-6-chloro-1,2-benzisothiazole-3-one-1,1-dioxide (6b). Mp 162–164 °C. IR ($CHCl_3$) 3079, 2974, 1714, 1540, 1330, 1266, 1151 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.02 (s, 2H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.6, 140.5, 138.3, 135.2, 126.3, 124.7, 121.1, 60.6, 27.2. Anal. Calcd for $C_{11}H_{12}ClNO_3S$: C, 48.26; H, 4.38; N, 5.11. Found: C, 48.25; H, 4.40; N, 5.06.

5.4.5. *N-tert*-Butyl-5-chloro-1,2-benzisothiazole-3-one-1,1-dioxide (6c). Mp 141–143 °C. IR ($CHCl_3$) 3088, 2987, 1714, 1540, 1417, 1330, 1174 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, J=9.2, 1H), 8.08 (d, J=7.2, 1H), 8.07 (s, 1H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 139.9, 135.5, 135.4, 128.2, 124.5, 122.6, 60.7, 27.1. Anal. Calcd for $C_{11}H_{12}ClNO_3S$: C, 48.26; H, 4.38; N, 5.11. Found: C, 48.16; H, 4.38; N, 5.09.

5.4.6. *N-tert*-Butyl-4-chloro-1,2-benzisothiazole-3-one-1,1-dioxide (6d). Mp 162–164 °C. IR ($CHCl_3$) 3079, 2974, 1719, 1458, 1330, 1151 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (dd, J=6.0, 2.4, 1H), 7.95–8.00 (m, 2H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.2, 139.2, 136.7, 136.6, 131.5, 122.0, 119.7, 60.7, 27.1. Anal. Calcd for $C_{11}H_{12}ClNO_3S$: C, 48.26; H, 4.38; N, 5.11. Found: C, 48.12; H, 4.42; N, 5.10.

5.4.7. *N-tert*-Butyl-7-chloro-1,2-benzisothiazole-3-one-1,1-dioxide (6e). Mp 72–74 °C. IR ($CHCl_3$) 2987, 1728, 1545, 1453, 1343, 1158 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J=8.8, 1H), 7.9–8.0 (m, 2H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 136.7, 135.9, 133.9, 128.8, 126.2, 123.4, 60.9, 27.1. Anal. Calcd for $C_{11}H_{12}ClNO_3S$: C, 48.26; H, 4.38; N, 5.11. Found: C, 48.31; H, 4.31; N, 5.00.

5.4.8. *N-tert*-Butyl-6-bromo-1,2-benzisothiazole-3-one-1,1-dioxide (6f). Mp 168–170 °C. IR ($CHCl_3$) 3083, 2965, 1714, 1540, 1334, 1151 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.16 (dd, J=8.4, J=1.6, 1H), 7.94 (d, J=7.6, 1H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.8, 138.3, 138.0, 129.2, 126.3, 125.3, 123.7, 60.6, 27.1. Anal. Calcd for $C_{11}H_{12}BrNO_3S$: C, 41.50; H, 3.77; N, 4.40. Found: C, 41.57; H, 3.84; N, 4.38.

5.4.9. *N-tert*-Butyl-5-bromo-1,2-benzisothiazole-3-one-1,1-dioxide (6g). Mp 146–148 °C. IR ($CHCl_3$) 3092, 2992, 1714, 1540, 1417, 1330, 1256, 1169 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16–8.24 (m, 3H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 138.3, 135.7, 128.6, 128.1, 127.3, 122.6, 60.7, 27.1. Anal. Calcd for $C_{11}H_{12}BrNO_3S$: C, 41.50; H, 3.77; N, 4.40. Found: C, 41.33; H, 3.73; N, 4.33.

5.4.10. *N-tert*-Butyl-6-fluoro-1,2-benzisothiazole-3-one-1,1-dioxide (6h). Mp 134–136 °C. IR ($CHCl_3$) 3070, 2978, 1728, 1600, 1485, 1330, 12656, 1151 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (dd, J=7.2, J=2.0, 1H), 8.1 (dd, J=8.4, J=4.4, 1H), 7.82 (dt, J=8.8, J=2.0, 1H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.6, 139.1, 127.7, 122.7, 122.51, 109.1, 60.6, 27.2. Anal. Calcd for $C_{11}H_{12}FNO_3S$: C, 51.36; H, 4.67; N, 5.44. Found: C, 51.27; H, 4.74; N, 5.59.

5.4.11. *N-tert*-Butyl-5-fluoro-1,2-benzisothiazole-3-one-1,1-dioxide (6i). Mp 88–90 °C. IR ($CHCl_3$) 3102, 2983, 1724, 1472, 1279, 1174 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31–8.35 (m, 1H), 7.80–7.91 (m, 2H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3, 133.05, 129.49, 123.9, 123.2, 122.9, 112.1, 60.7, 27.1. Anal. Calcd for $C_{11}H_{12}FNO_3S$: C, 51.36; H, 4.67; N, 5.44. Found: C, 51.53; H, 4.71; N, 5.36.

5.4.12. *N-tert*-Butyl-6-methylsulfonyl-1,2-benzisothiazole-3-one-1,1-dioxide (6j). Mp 194–196 °C. IR ($CHCl_3$) 3102, 2992, 2919, 1714, 1545, 1339, 1183 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.45 (d, J=7.6, 1H), 8.28 (d, J=8.4, 1H), 3.45 (s, 3H), 1.71 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 147.0, 137.4, 133.3, 130.0, 126.1, 120.0, 61.0, 42.6, 27.1. Anal. Calcd for $C_{12}H_{15}NO_5S_2$: C, 45.42; H, 4.73; N, 4.41. Found: C, 45.42; H, 4.77; N, 4.27.

5.4.13. *N-tert*-Butyl-6-(*N-tert*-butylaminosulfonyl)-1,2-benzisothiazole-3-one-1,1-dioxide (6k). Mp 166–168 °C. IR ($CHCl_3$) 3285, 2978, 1728, 1545, 1398, 1339, 1151 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.35 (d, J=8.4, 1H), 8.23 (d, J=7.6, 1H), 7.99 (s, 1H), 1.70 (s, 9H), 1.13 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3, 150.7, 137.4, 132.4, 128.6, 126.1, 118.4, 60.9, 54.0, 29.6, 27.1. Anal. Calcd for $C_{15}H_{22}N_2O_5S_2$: C, 48.12; H, 5.88; N, 7.48. Found: C, 48.33; H, 6.20; N, 7.36.

5.4.14. *N-tert*-Butyl-6-nitro-1,2-benzisothiazole-3-one-1,1-dioxide (6l). Mp 182–184 °C. IR ($CHCl_3$) 3111, 2996, 1733, 1545, 1334, 1270, 1188 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.68 (dd, J=8.4, 1H), 8.26 (d, J=8.0, 1H), 1.71 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.9, 151.7, 137.7, 130.6, 130.0, 126.4, 117.1, 61.2, 27.1. Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.23; N, 9.85. Found: C, 46.65; H, 4.26; N, 9.79.

5.4.15. *N-tert*-Butyl-5-nitro-1,2-benzisothiazole-3-one-1,1-dioxide (6m). Mp 151–153 °C. IR ($CHCl_3$) 3102, 2983, 1728, 1540, 1339, 1266, 1156 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, J=8.4, 1H), 8.58 (s, 1H), 8.52 (d, J=8.4, 1H), 1.71 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.6, 151.5, 140.7, 130.6, 128.0, 122.8, 119.7, 61.2, 27.1. Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.23; N, 9.85. Found: C, 46.59; H, 4.28; N, 9.87.

5.4.16. *N-tert*-Butyl-7-nitro-1,2-benzisothiazole-3-one-1,1-dioxide (6n). Mp 152–154 °C. IR ($CHCl_3$) 3102, 2992, 1719, 1545, 1348, 1197 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, J=8.4, 1H), 8.44 (d, J=7.6, 1H), 8.23 (t, J=8.0, 1H), 1.72 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.5, 141.1, 136.9, 130.7, 130.5, 130.3, 129.2, 61.2, 27.2. Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.23; N, 9.85. Found: C, 46.55; H, 4.25; N, 9.76.

5.4.17. *N-tert*-Butyl-5-chloro-6-methyl-1,2-benzisothiazole-3-one-1,1-dioxide (6o). Mp 205–207 °C. IR ($CHCl_3$) 3001, 2960, 1714, 1545, 1325, 1261, 1165 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.03 (s, 1H), 2.52 (s, 3H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.4, 144.7, 140.1, 135.4, 125.6, 124.6, 122.8, 60.6, 27.1, 20.2. Anal. Calcd for $C_{12}H_{14}ClNO_3S$: C, 50.08; H, 4.87; N, 4.87. Found: C, 50.06; H, 4.85; N, 4.86.

5.5. General procedure for direct preparation of saccharin skeletons from toluenes

Toluene or a substituted toluene derivative (20 mmol) was added portionwise over a period of 30 min to pre-cooled chlorosulfonic acid (0.2 mol) at −20 °C. After addition, the reaction mixture was stirred at −20 °C for 1 h, then gradually allowed warm to rt over 1 h and stirred at rt for additional 4 h. The mixture was poured onto ice (500 g), extracted with Et_2O or CH_2Cl_2 (120×2 mL). The extracts were combined and washed with satd $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was dissolved in dry CH_2Cl_2 (40 mL). The solution was then added dropwise to a solution of *tert*-butyl amine (21 mmol) and triethylamine (21 mmol) in CH_2Cl_2 (80 mL) at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 2 h and then rt for 6 h, washed, respectively, with 0.1 N HCl solution and satd $NaHCO_3$ solution, dried over $MgSO_4$. Removal of the solvent afforded the isomers *N-tert*-butyl-*o*-methyl arenesulfonamides.

A mixture of H_5IO_6 (0.14 mol) in acetonitrile (200 mL) was stirred vigorously at rt for 1 h, then CrO_3 (200 mg, 2 mmol, 10 mol %) was added followed by acetic anhydride (0.14 mol). The resulting orange solution was cooled to 0 °C. To this solution was added the isomers of *N-tert*-butyl-*o*-methyl arenesulfonamides in one portion. After stirring at 0 °C for 30 min, the reaction mixture was allowed to warm to rt and stirred until the oxidation was complete (monitored by TLC). The solvent was removed at rt under reduced pressure and the residue was extracted with EtOAc (2×100 mL). The extracts were collected and washed, respectively, with satd $NaHCO_3$ solution (160 mL), satd $Na_2S_2O_3$ solution (120 mL) and brine, dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product. Some of the crude saccharin derivatives were quite pure by ^1H NMR. If necessary, further purification by flash column chromatography (hexanes/EtOAc, 4:1) or recrystallization from ethanol furnished the pure *N-tert*-butyl saccharin derivatives.

5.5.1. *N-tert*-Butyl-6-trifluoromethyl-1,2-benzisothiazole-3-one-1,1-dioxide (6p). Mp 156–158 °C. IR ($CHCl_3$) 2982, 1732, 1419, 1252, 1152 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.34 (d, J=8.0, 1H), 8.23 (d, J=8.0, 1H), 1.71 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3, 137.7, 135.1, 134.8, 132.1, 129.7, 125.9, 118.9, 60.9, 27.1. Anal. Calcd for $C_{12}H_{12}NF_3O_3S$: C, 46.90; H, 3.90; N, 4.56. Found: C, 46.82; H, 3.85; N, 4.53.

5.5.2. *N-tert*-Butyl-5-trifluoromethyl-1,2-benzisothiazole-3-one-1,1-dioxide (6q). Mp 132–134 °C. IR ($CHCl_3$) 2989, 1723, 1430, 1263, 1130 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J=8.4, 1H), 8.42 (d, J=8.4, 1H), 8.32 (s, 1H), 1.71 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3, 140.1, 135.0, 134.7, 132.8, 127.7, 122.4, 121.9, 60.9, 27.1. Anal. Calcd for $C_{12}H_{12}NF_3O_3S$: C, 46.90; H, 3.90; N, 4.56. Found: C, 46.90; H, 3.87; N, 4.58.

Acknowledgements

We wish to thank Professor Gregory Fu and the Department of Chemistry at MIT for all of the assistance provided H.S. during the evacuation of New Orleans due to Hurricane Katrina.

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Tetrahedron 62 (2006) 7911–7925
Tetrahedron

Enantiodiscrimination of racemic electrophiles by diketopiperazine enolates: asymmetric synthesis of methyl 2-amino-3-aryl-butanoates and 3-methyl-aspartates

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Received 3 April 2006; revised 27 April 2006; accepted 11 May 2006
Available online 19 June 2006

Abstract—Enolates of (*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-*iso*-propylpiperazine-2,5-dione exhibit high levels of enantiodiscrimination in alkylations with (*RS*)-1-aryl-1-bromoethanes and (*RS*)-2-bromoesters, affording substituted diketopiperazines containing two new stereogenic centres in high de. Deprotection and hydrolysis of the resultant substituted diketopiperazines provides a route to the asymmetric synthesis of homochiral methyl 2-amino-3-aryl-butanoates and 3-methyl-aspartates in high de and ee.

1. Introduction

The design and synthesis of novel peptides incorporating conformationally constrained amino acid residues are currently an area of much scientific attention.[1] β-Alkyl-α-amino acids are one class of conformationally constrained amino acids that have been shown to modulate peptide secondary structure and produce beneficial changes in the action of biologically active peptides.[2] These compounds are also non-proteinogenic α-amino acid components of a number of natural products[3] and the asymmetric synthesis of this class of α-amino acid, requiring the stereoselective formation of two contiguous stereogenic centres, is a growing field of research.[4] Although the application of chiral auxiliary strategies for the selective generation of a single stereogenic centre is well established, the application of chiral auxiliaries to discriminate between the enantiomers of racemic electrophiles to afford selectively products containing two contiguous stereogenic centres are less common.[5]

Previous investigations from this laboratory have introduced a diketopiperazine derived chiral auxiliary (*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-*iso*-propylpiperazine-2,5-dione **1** for the asymmetric synthesis of homochiral α-amino acids. Alkylations of the lithium enolate of **1** proceed with high levels of trans-selectivity, affording (*R*)-α-amino acids in homochiral form after *N*-deprotection and hydrolysis.[6] In an extension of this methodology, we report herein our studies directed toward the selective alkylation of the lithium and potassium enolates **2** and **3** of parent diketopiperazine **1**

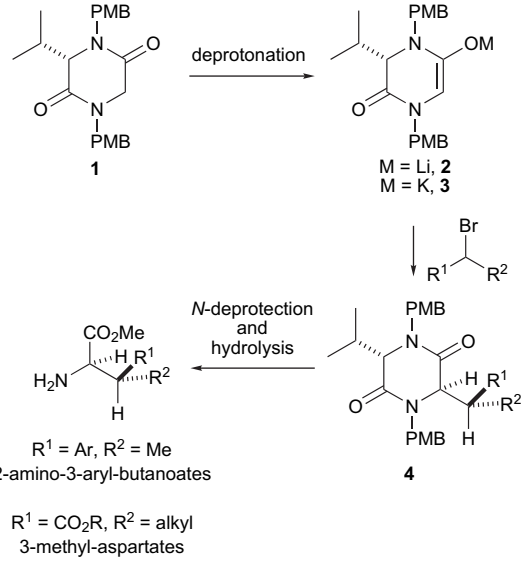

Figure 1. Proposed enantiodiscrimination strategy for the asymmetric synthesis of 2-amino-3-aryl-butanoates and 3-methyl-aspartates.

Keywords: Enantiodiscrimination; Diketopiperazine; 3-Methyl-aspartate.
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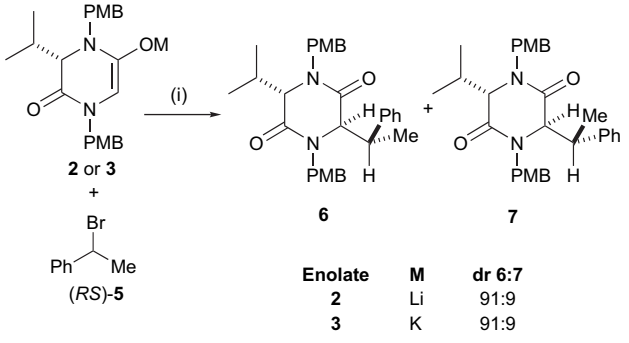
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.05.033

with one enantiomer of (*RS*)-1-aryl-1-bromoethanes and (*RS*)-2-bromoesters. This strategy would allow the formation of two stereogenic centres in a single reaction step, one by asymmetric synthesis and the other by enantiodiscrimination, and facilitate the asymmetric synthesis of methyl 2-amino-3-aryl-butanoates and 3-methyl-aspartates after *N*-deprotection and hydrolysis of intermediates **4** (Fig. 1). Part of this work has been communicated previously.[7]

2. Results and discussion

2.1. Enantiodiscrimination of (*RS*)-1-aryl-1-bromoethanes for the asymmetric synthesis of 2-amino-3-aryl-butanoates

Initial investigations focused upon the reaction of (*RS*)-1-aryl-1-bromoethanes with the lithium enolate **2** of (*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-*iso*-propylpiperazine-2,5-dione **1**. Treatment of lithium enolate **2**[8] with 10 equiv of (*RS*)-1-phenyl-1-bromoethane **5** gave a 91:9 mixture of two diastereoisomers **6** and **7** (82% de). Fractional crystallisation of the crude reaction mixture furnished the major diastereoisomer **6** in 60% yield and >98% de. When lithium enolate **2** was allowed to react with 1 equiv of (*RS*)-**5** for 3 h the reaction proceeded to 56% conversion, and unreacted **5** was recovered in 43% yield. The specific rotation of the recovered **5** {$[\alpha]_D^{21}$ −25.9 (*c* 4.8 in $CHCl_3$); lit.[9] $[\alpha]_D^{23}$ −90.8 (*c* 2.8 in $CHCl_3$) for 81% ee} indicated that it was enriched in the (*S*)-enantiomer (24% ee), consistent with the preferential reaction of enolate **2** with (*R*)-**5** and partial racemisation of the residual electrophile by bromide ion.[10] The diastereoselectivity of this reaction proved to be insensitive to the nature of the enolate metal counterion since treatment of the potassium enolate **3**[11] with 2.2 equiv of (*RS*)-**5** afforded a 91:9 mixture of **6** and **7**, from which the major diastereoisomer **6** was isolated in 57% yield (>98% de) by recrystallisation (Scheme 1).



Scheme 1. Reagents and conditions: (i) (*RS*)-PhCH(Br)Me (2.2 equiv), THF, −78 °C, 12 h.

The C(3) and C(6) trans-relative configuration within both diastereoisomers **6** and **7** was initially assigned by analysis of ^{1}H NMR spectroscopic data, with both diastereoisomers **6** and **7** exhibiting *iso*-propyl group chemical shifts diagnostic for the trans-relative configuration.[12] The (1′*S*)-configuration within the major diastereoisomer **6** was then assigned by consideration of the configuration of the recovered (*S*)-electrophile, assuming the major reaction pathway follows an S_N2 displacement. This assignment was unequivocally confirmed by single crystal X-ray diffraction of the major diastereoisomer **6**, with the absolute (3*S*,6*S*,1′*S*) configuration following from the known configuration of the (*S*)-valine derived stereogenic centre (Fig. 2).

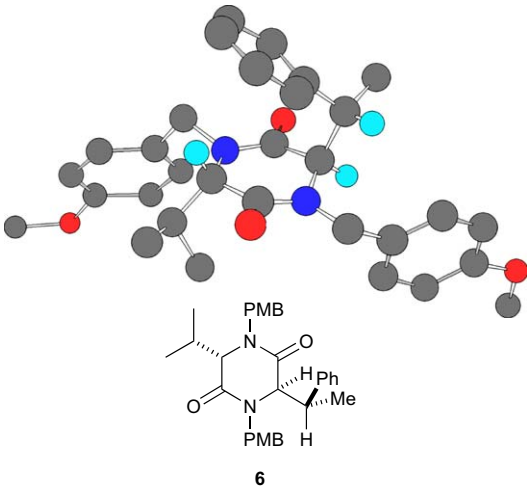
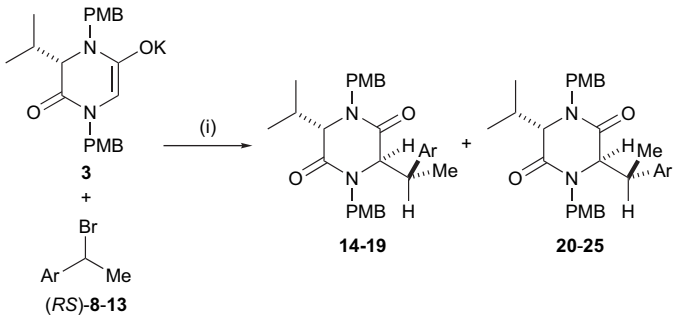


Figure 2. Chem 3D representation of the X-ray crystal structure of **6** (some H atoms omitted for clarity).

The ability of the enolate of **1** to discriminate between the enantiomers of a range of (*RS*)-1-aryl-1-bromoethanes **8**–**13** was next examined. Preliminary studies using lithium enolate **2** afforded low levels of conversion; however, treatment of potassium enolate **3** with 2.2 equiv of racemic electrophiles **8**–**13** afforded diketopiperazines **14**–**25** in 70% de to >95% de, as assessed by ^{1}H NMR spectroscopic analysis of the crude reaction product (Scheme 2). Purification of the crude reaction product in each case by chromatography and/or recrystallisation afforded diketopiperazines **14**–**19** in 45–75% yield, and in >98% de in each case. These results indicate that this enantiodiscrimination protocol is tolerant of both *ortho*- and *para*-substituted aryl groups and for both electron poor and electron rich aryl groups within the 1-aryl-1-bromoethane structure. Notable results within this series indicate that the potassium enolate **3** reacts with lower stereoselectivity with electronically activated (*RS*)-1-(*p*-methoxyphenyl)-1-bromoethane **10** than the parent (*RS*)-1-phenyl-1-bromoethane system, affording **16** in 70% de. However, the potassium enolate **3** reacts with the electronically deactivated (*RS*)-1-(2′-pyridyl)-1-bromoethane **11** to give **17** in 92% de. Furthermore, potassium enolate **3** showed superior levels of enantiodiscrimination in the reactions with the bulky *o*-tolyl-(*RS*)-**9**, 1-naphthyl-(*RS*)-**12** and 2-naphthyl-(*RS*)-**13** electrophiles, affording **15**, **18** and **19** in >95, 91 and 90% de, respectively (Scheme 2).

The (3*R*,6*S*,1′*S*) configuration of the major diastereoisomers **14**–**19** isolated from this protocol was assigned initially by analogy with that determined unambiguously for the alkylation reaction with (*RS*)-1-phenyl-1-bromoethane **5**. In support of this assignment, the relative configuration of 2′-pyridyl-**17** was established by X-ray crystallographic analysis, with the absolute (3*R*,6*S*,1′*S*) configuration following from the (*S*)-valine derived stereogenic centre (Fig. 3).

Having demonstrated the ability of the potassium enolate **3** to discriminate readily between the antipodes of



Electrophile	Ar	Conversion %	dr %[a]	Product	Yield (de) %[b]
5	Ph	85	91:9	**6**	57 (>98)
8	*p*-tolyl	100	91:9	**14**	61 (>98)
9	*o*-tolyl	100	>97.5:<2.5	**15**	69 (>98)
10	*p*-OMeC$_6$H$_4$	100	85:15	**16**	64 (>98)
11	2-pyridyl	100	96:4	**17**	85 (>98)
12	1-naphthyl	55	95.5:4.5	**18**	47 (>98)
13	2-naphthyl	83	95:5	**19**	68 (>98)

Scheme 2. Reagents and conditions: (i) (*RS*)-ArCH(Br)Me (2.2 equiv), THF, −78 °C, 12 h. [[a]As indicated by ^{1}H NMR analysis of the crude reaction product; [b]Purified yield of major diastereoisomer.]

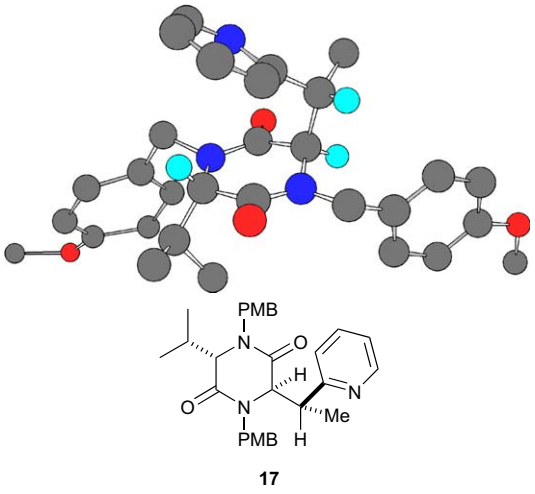
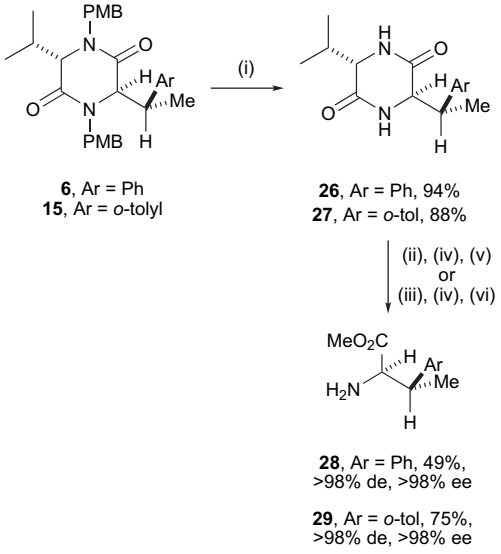


Figure 3. Chem 3D representation of the X-ray crystal structure of **17** (some H atoms omitted for clarity).

(*RS*)-1-aryl-1-bromoethanes **5** and **8**–**13**, the deprotection and hydrolysis of a representative set of substrates to the corresponding 2-amino-3-aryl-butanoates was investigated. *N*-Deprotection of **6** (>98% de) with ceric ammonium nitrate (CAN) afforded diketopiperazine **26** in 94% isolated yield and >98% de, which was hydrolysed by prolonged treatment with 5 M HCl at 100 °C. The resultant mixture of α-amino acid hydrochloride salts was converted to the corresponding methyl esters, with chromatographic purification giving methyl (2*R*,3*R*)-2-amino-3-phenyl-butanoate **28** in 45% overall yield and >98% de (Scheme 3). Following the same protocol, *N*-deprotection of *o*-tolyl-**15** (>98% de) with CAN afforded diketopiperazine **27** in 88% yield and >98% de. Although the hydrolysis of diketopiperazine **27** with hydrochloric acid proved prohibitively slow, treatment with concentrated hydroiodic acid at reflux led to clean hydrolysis within 24 h. Conversion of the resultant crude product mixture of α-amino acid hydroiodide salts to the corresponding methyl esters afforded **29** in 75% yield and >98% de after the volatile (*S*)-valine methyl ester was evaporated (Scheme 3). The enantiomeric excess of **28** was determined as >98% ee by examination of the ^{19}F NMR spectrum of the Mosher's amide derivative and comparison with authentic racemic samples, and the ee of **29** was assigned by analogy.

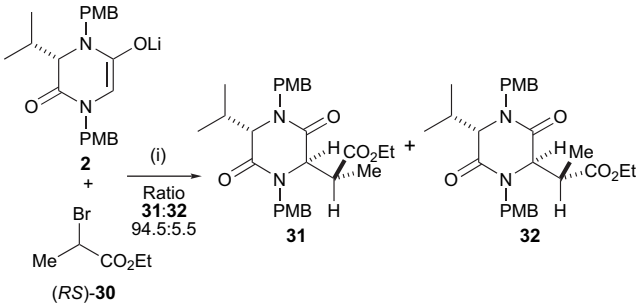


Scheme 3. Reagents and conditions: (i) CAN, MeCN/H_2O (v/v 2:1); (ii) HCl (5 M, aq), reflux, four days; (iii) HI, reflux, 24 h; (iv) MeOH, $SOCl_2$; (v) $NaHCO_3$, then chromatography; (vi) evaporation.

2.2. Enantiodiscrimination of (*RS*)-2-bromoesters for the asymmetric synthesis of 3-methyl-aspartates

Having established that lithium and potassium enolates **2** and **3** effectively discriminate between the enantiomers of (*RS*)-1-aryl-1-bromoethanes, allowing the asymmetric synthesis of methyl 2-amino-3-aryl-butanoates, subsequent investigations focused upon the reaction of lithium enolate **2** with (*RS*)-2-bromoesters. Treatment of lithium enolate **2** with (*RS*)-ethyl 2-bromopropanoate **30** (10 equiv or 2.2 equiv) gave a 94.5:5.5 mixture of **31** and **32**, from which

31 and **32** were isolated in 93 and 3% yield, respectively, as single diastereoisomers after chromatography (Scheme 4). The relative trans-configuration of the C(3) and C(6) diketopiperazine ring substituents within **31** and **32** was supported by the diagnostic *iso*-propyl group chemical shifts that indicate this relative configuration.[12] The configuration of the (2′*R*)-stereogenic centre within major diastereoisomer **31** was preliminarily assigned from analysis of the unreacted electrophile, as ethyl 2-bromopropanoate **30** recovered from reaction of enolate **2** with (*RS*)-**30** (2.2 equiv) was enantiomerically enriched in the (*S*)-enantiomer (16% yield, 34% ee) {$[\alpha]_D^{23}$ −11.1 (*c* 1.1 in $CHCl_3$), lit.[13] for enantiomer $[\alpha]_D^{23}$ +37.0 (*c* 1.0 in $CHCl_3$)}. Assuming an S_N2 process in this reaction, this specific rotation indicates that enolate **2** reacts preferentially with (*R*)-**30**, affording the major diastereoisomer **31** with (2′*R*)-configuration. The 34% ee obtained for the recovered electrophile is lower than the calculated value of 74% ee that is expected given the 94.5:5.5 ratio of alkylation products **31**:**32**; this discrepancy presumably reflects the known capacity of bromide ions to racemise ethyl 2-bromo-propanoate **30**.[14]

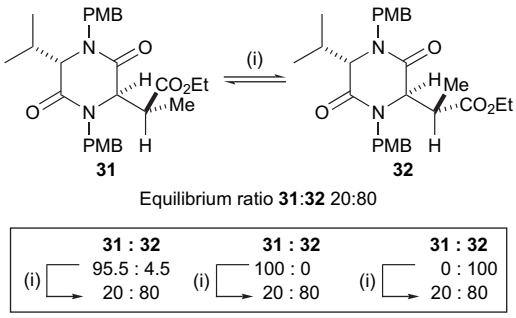


Scheme 4. Reagents and conditions: (i) (*RS*)-**30** (2.2 equiv or 10 equiv), THF, −78 °C, 12 h.

Although the observed major product **31** in this reaction is expected to arise from a stereospecific and enantioselective S_N2 alkylation of the electrophile, it may potentially derive from thermodynamic equilibration of the 2′-stereogenic centre α to the ester functionality of the kinetic product under the basic reaction conditions. In order to establish that the predominant isomer **31** did not derive from equilibration of the kinetic product, the epimerisation of the 2′-stereogenic centre was examined. Treatment of the 94.5:5.5 mixture of **31**:**32** with lithium ethoxide in dry ethanol, in the presence of methyl iodide as an electrophilic scavenger, afforded a 20:80 mixture of **31**:**32**. The highly crystalline **32** was readily isolated via recrystallisation of the crude reaction mixture in 66% yield. The 20:80 ratio of **31**:**32** represents the thermodynamic equilibrium position, since similar treatment of a homochiral sample of either **31** or **32** gave identical 20:80 mixtures of **31**:**32** (Scheme 5).

The relative configuration of **32** was unequivocally confirmed by single crystal X-ray analysis, with the absolute (3*R*,6*S*,2′*S*) configuration determined from the (*S*)-valine derived stereogenic centre (Fig. 4).

The generality of this enantiodiscrimination process was then explored. Variation of the alkyl ester group within the (*RS*)-2-bromopropanoate structure did not markedly affect the level of enantiodiscrimination: alkylation of enolate **2**



Scheme 5. Reagents and conditions: (i) LiHMDS, MeI, anhydrous EtOH.

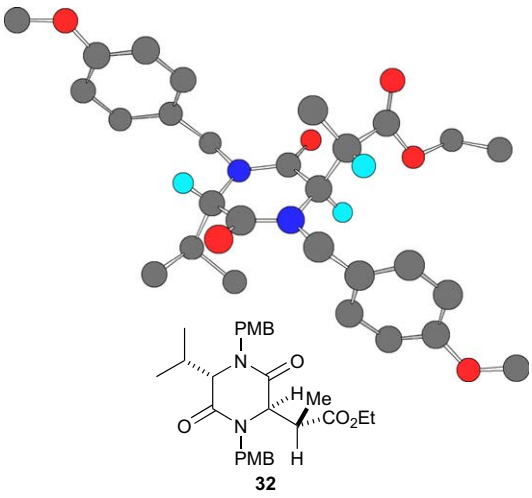
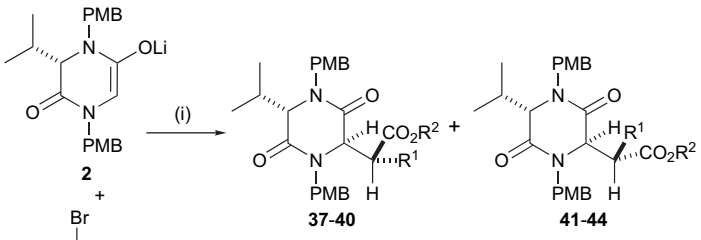


Figure 4. Chem 3D representation of the X-ray crystal structure of **32** (some H atoms omitted for clarity).

with (*RS*)-methyl 2-bromopropanoate **33** gave diketopiperazine **37** in 92% de, and in 87% yield and >98% de after chromatography, while alkylation of **2** with (*RS*)-*tert*-butyl 2-bromopropanoate **34** gave diketopiperazine **38** in 92% de, and in 83% yield and >98% de after chromatography. Enolate **2** was also found to discriminate efficiently between the enantiomers of (*RS*)-ethyl 2-bromobutyrate **35** and (*RS*)-ethyl 2-bromoheptanoate **36** to afford *trans*-alkylated diketopiperazines **39** and **40**, respectively, in 84 and 88% de, which after chromatographic purification gave **39** and **40** in 82 and 86% yield, respectively, and in >98% de in each case. ^{1}H NMR data for the major diastereoisomeric reaction products **37**–**40** were similar in each case to that of **31** derived from alkylation of enolate **2** with (*RS*)-ethyl 2-bromopropanoate **30**, with the absolute (3*R*,6*S*,2′*R*) configuration of these products assigned by analogy to that unambiguously assigned in the related (*RS*)-ethyl 2-bromopropanoate system (Scheme 6).

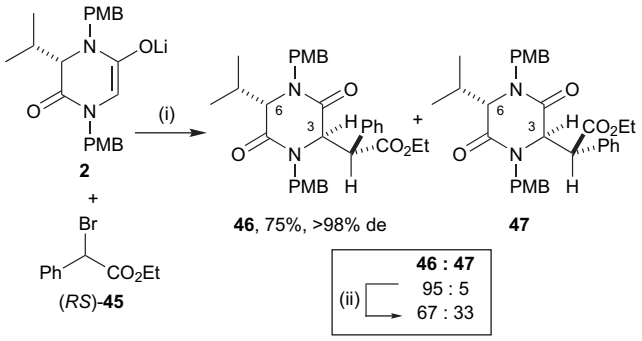
Having observed effective enantiodiscrimination of (*RS*)-2-bromoalkylacetates **5** and **8**–**13** and (*RS*)-1-aryl-1-bromoethanes **30** and **33**–**36** with enolates **2** and **3**, the reaction of enolate **2** with (*RS*)-ethyl 2-bromophenylacetate **45** was undertaken. Treatment of lithium enolate **2** with (*RS*)-**45** gave a 95:5 mixture of **46**:**47** (90% de) from which **46** was isolated in 75% yield and >98% de (Scheme 7). The relative configuration within **46** was established by single crystal X-ray diffraction, while the absolute (3*R*,6*S*,2′*S*) configuration derives from the known (*S*)-valine derived stereocentre



Electrophile	R^1	R^2	dr %[a]	Product	Yield (de) %[b]
30	Me	Et	94.5:5.5	**31**	93 (>98)
33	Me	Me	96:4	**37**	87 (>98)
34	Me	^{t}Bu	96:4	**38**	83 (>98)
35	Et	Et	92:8	**39**	82 (>98)
36	C_5H_{11}	Et	94:6	**40**	86 (>98)

Scheme 6. Reagents and conditions: (i) (*RS*)-$R^1CH(Br)CO_2R^2$ (2.2 equiv), THF, −78 °C. [[a]As indicated by ^{1}H NMR analysis of the crude reaction product; [b]Purified yield of major diastereoisomer.]

(Fig. 5). The major diastereoisomer **46** does not derive from equilibration of the kinetic product since treatment of **46** (>98% de) with lithium ethoxide catalysed regioselective *C*(2′) epimerisation to afford a 67:33 mixture of **46**:**47**. Attempts to establish the thermodynamic equilibrium position in this reaction via prolonged epimerisation were hampered by decomposition of the materials. The identification of **46** as the major diastereoisomer in this reaction is consistent with enolate **2** preferentially reacting with the (*S*)-enantiomer of (*RS*)-ethyl 2-bromophenylacetate **45** in an S_N2 process.



Scheme 7. Reagents and conditions: (i) (*RS*)-**45** (2.2 equiv), THF, −78 °C; (ii) LiHMDS, anhydrous EtOH.

The deprotection and hydrolysis of **31** and **32** to the corresponding 3-methyl-aspartates was then investigated. Attempted *N*-deprotection by treatment of **31** with CAN in $MeCN/H_2O$ afforded diketopiperazine **48** in low yield, possibly due to ester hydrolysis under the acidic reaction conditions. However, *N*-deprotection of **31** was readily achieved by treatment with refluxing TFA, affording diketopiperazine **48** in 60% yield and >98% de. Initial attempts to hydrolyse **48** under strongly acidic conditions led to partial epimerisation at the 2′-stereogenic centre and, in order to circumvent this problem, conversion of **48** to bis-lactim ether **49** was investigated in the expectation that hydrolysis would then proceed readily under mild acid conditions.[15] Treatment of **48** with trimethyloxonium tetrafluoroborate (Me_3OBF_4) in DCM over a period of four days gave a 60:20:20 mixture of the desired bis-lactim ether **49**, and two more polar components, tentatively assigned as the corresponding

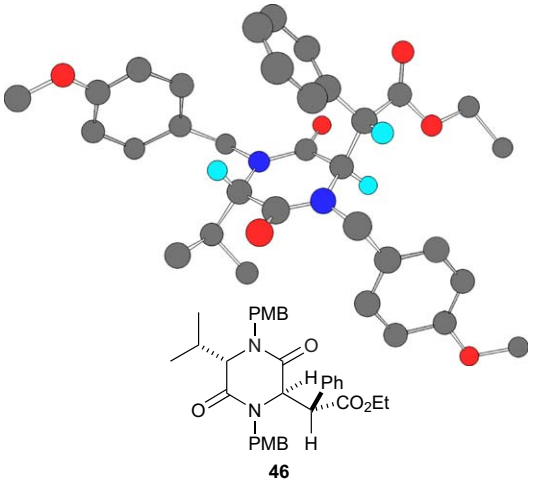
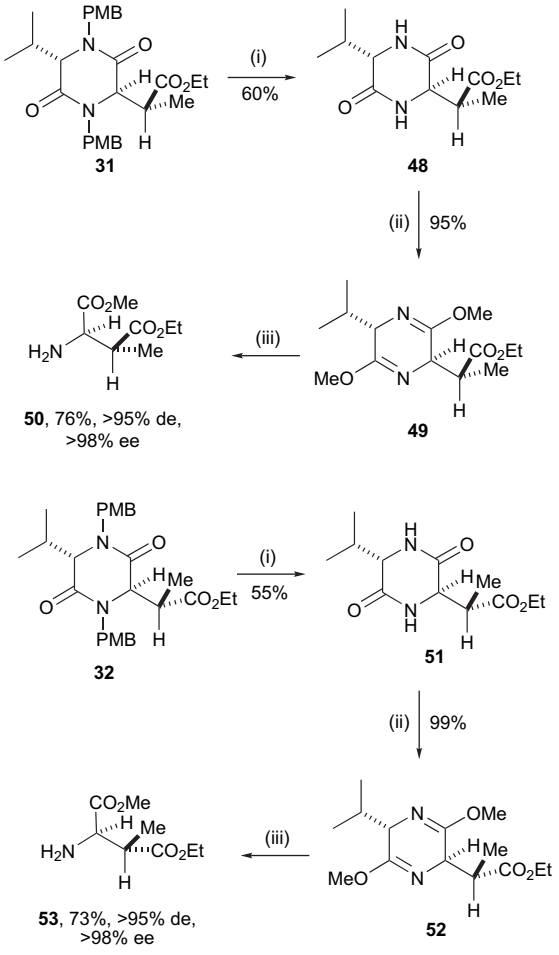


Figure 5. Chem 3D representation of the X-ray crystal structure of **46** (some H atoms omitted for clarity).

mono-lactim ethers of **48**. Attempted chromatographic purification of bis-lactim ether **49** proved difficult, resulting in significant mass loss and low isolated yield (~50%). In order to drive this methylation to completion, treatment of **48** with Me_3OBF_4 in the ionic liquid solvent *N*-butyl-*N*′-methylimidazolium tetrafluoroborate ($Bmim\cdot BF_4$)[16] was followed, affording bis-lactim ether **49** as the sole reaction product in 95% yield. The ionic liquid solvent system presumably serves to stabilise the intermediate hydrotetrafluoroborate salts of the lactim ethers and facilitates the reaction by solvation of both Me_3OBF_4 and charged intermediates that are poorly soluble in organic solvents. Subsequent hydrolysis of bis-lactim ether **49** with 0.5 M aq TFA at rt afforded a mixture of **50** and (*S*)-valine methyl ester as the trifluoroacetate salts, which were converted to free amines and separated by distillation giving **50** in 76% yield, >95% de and >98% ee[17] (Scheme 8). Following the success of this protocol, the deprotection and hydrolysis of **32** by a similar protocol was then investigated. *N*-Deprotection of **32** by treatment with refluxing TFA afforded diketopiperazine **51** in 55% yield and >98% de, with subsequent treatment of **51** with Me_3OBF_4 in $Bmim\cdot BF_4$ affording bis-lactim ether **52** in 99% yield. Hydrolysis of bis-lactim ether **52** afforded **53** and (*S*)-valine methyl ester as the trifluoroacetate salts,

which after conversion to the corresponding free amines and distillation gave **53** in 73% yield, >95% de and >98% ee (Scheme 8).



Scheme 8. Reagents and conditions: (i) TFA, reflux; (ii) Me_3OBF_4 (4 equiv), Bmim·BF_4, four days; (iii) 0.5 M aq TFA, then $NaHCO_3$.

2.3. Models for enantiorecognition

For the reaction of the potassium enolate **3** with (*RS*)-1-aryl-1-bromoethanes **5** and **8**–**13**, the observed enantiodiscrimination must be controlled by steric interactions between the enolate and electrophile in the alkylation transition state. The (3*R*,6*S*,1′*S*) configuration of the major diastereoisomer in each case and the observed specific rotation of the recovered electrophiles from these alkylations indicate that the reaction preferentially proceeds via approach of the (*R*)-electrophile to enolate **3** *anti* to the C(3) *iso*-propyl group. Assuming that this reaction takes place in an S_N2 process and that the substituents of the electrophile are staggered relative to the carbon framework of the enolate, the bromide leaving group will be electronically activated when orientated perpendicular to the adjacent π-system of the aromatic ring.[18] Analysis of the X-ray crystal structures indicates that *trans*-substituted *N*-alkylated diketopiperazines **6**, **17**, **32** and **46** all have a conformational preference in which the small C(1′)*H* substituent occupies the most sterically crowded position adjacent to the *N*(4)-*p*-methoxybenzyl substituent, minimising *syn*-pentane interactions. Assuming

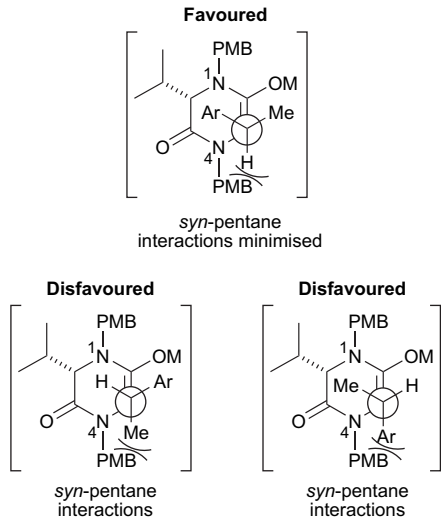


Figure 6. Generic model for enantiodiscrimination.

that the reaction of enolate **3** with (*RS*)-1-aryl-1-bromoethanes **5** and **8**–**13** occurs via a late, product-like transition state, and using this crystal structure analysis of the products as a basis for the transition state, a simple model may be used to predict the more reactive enantiomer of the electrophile. In the transition state, the overriding assumption of this model is that the C(1)*H* of the (*RS*)-1-aryl-1-bromoethane electrophile occupies the sector above the *N*(4)-*p*-methoxybenzyl substituent, minimising *syn*-pentane interactions (Fig. 6).

Following this rationale, in considering the reaction of the two enantiomers of (*RS*)-1-aryl-1-bromoethanes **5** and **8**–**13** with the enolate of **1**, (*R*)-1-aryl-1-bromoethanes approach with the planar aryl group over the diketopiperazine ring with the sp^3 hybridised methyl group oriented away from the diketopiperazine ring; a similar approach of the (*S*)-1-aryl-1-bromoethanes places the sp^3 methyl group in a sterically encumbered position where it suffers steric interactions with the diketopiperazine ring framework, disfavouring reaction of this enantiomer (Fig. 7).

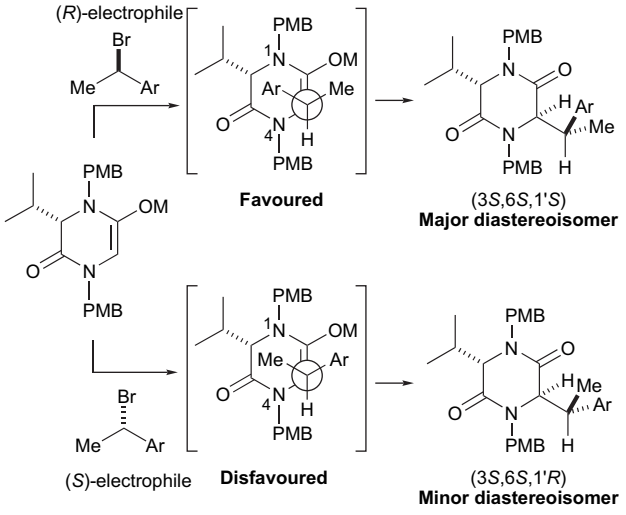


Figure 7. Model for the preferential reaction of enolate **3** with (*R*)-ArCH(Br)Me.

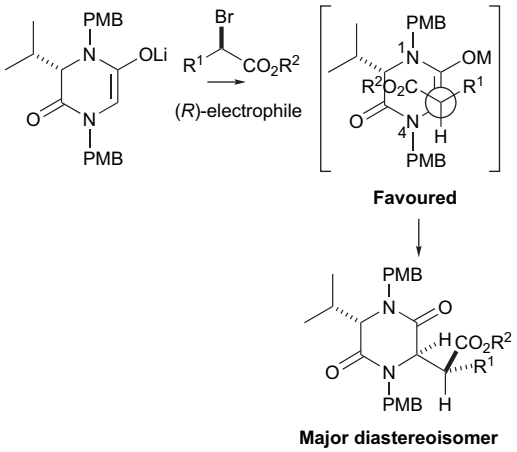


Figure 8. Model for the preferential reaction of enolate **2** with (*R*)-$R^1CH(Br)CO_2R^2$.

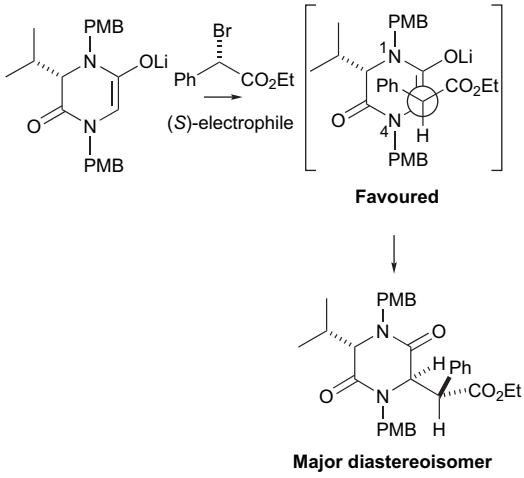


Figure 9. Model for preferential reaction of enolate **2** with (*S*)-$PhCH(Br)CO_2Et$.

For the reactions of lithium enolate **2** with (*RS*)-2-bromoesters **30**, **33**–**36** and **45** the enantiodiscrimination may be controlled either by chelation between the ester group and the enolate counterion or by steric factors similar to those above. Again assuming the overall requirement for the C(2)*H* of the (*RS*)-2-bromoester to occupy the sector above the *N*(4)-*p*-methoxybenzyl substituent, the discrimination reactions involving **30** and **33**–**36** are consistent with the reaction proceeding under steric control[19] with preferential reaction of the (*R*)-electrophile (Fig. 8: planar ester group over ring, sp^3 alkyl group away from ring) while the reaction involving **45** proceeds under chelation control (Fig. 9: planar aryl group over ring, planar ester chelating to enolate counterion).

3. Conclusion

In conclusion, enolates derived from (*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-*iso*-propylpiperazine-2,5-dione **1** exhibit a high degree of enantiodiscrimination in alkylations with a range of (*RS*)-1-aryl-1-bromoethanes **5** and **8**–**13**, and (*RS*)-2-bromoesters **30**, **33**–**36** and **45** to afford trans-alkylated products in high de. The deprotection and hydrolysis of representative recognition products within each series has established the efficacy of this process for the asymmetric synthesis of methyl 2-amino-3-aryl-butanoates and 3-methyl-aspartates and in high de and ee.

4. Experimental

4.1. General

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[20] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in gram per 100 mL. IR spectra were recorded on Bruker Tensor 27 FTIR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometer in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF and were internally calibrated with polyanaline in positive and negative modes, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m×0.25 mm) using amyl acetate as a lock mass.

4.1.1. General procedure 1: alkylation of 1. To a stirred solution of **1** (1.0 equiv) in degassed THF (50 mL g^{-1}) at −78 °C was added a solution of LiHMDS (1.0 M in THF, 1.1 equiv) or KHMDS (0.5 M in PhMe, 0.9 equiv). The resultant solution was allowed to stir at −78 °C for 1 h prior to the addition of the electrophile. The mixture was stirred at −78 °C for 12 h then allowed to warm to rt before NH_4Cl (satd aq) was added. The mixture was partitioned between EtOAc and H_2O. The aqueous phase was extracted twice with EtOAc and the combined organic layers were dried and concentrated in vacuo to yield the crude product.

4.1.1.1. (3*S*,6*S*,1′*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-phenylethyl)piperazine-2,5-dione 6. Compound **1** (200 mg, 0.50 mmol) in THF (10 mL), LiHMDS (1.0 M in THF, 0.55 mL, 0.55 mmol) and (*RS*)-**5** (944 mg, 5.0 mmol) were reacted according to Section 4.1.1 to afford

a crude solid. Recrystallisation from EtOAc gave **6** as colourless blocks (151 mg, 60%); mp 214–216 °C; $[\alpha]_D^{23}$ +43.5 (*c* 1.1 in $CHCl_3$); ν_{max} (KBr) 1655 (C=O); δ_H (400 MHz, $CDCl_3$) 0.64 (3H, d, *J* 6.8, CH_3CHCH_3), 0.98 (3H, d, *J* 6.8, CH_3CHCH_3), 1.50 (3H, d, *J* 7.3, ArCHCH_3), 2.08 (1H, m, C*H*$(CH_3)_2$), 3.03 (1H, d, *J* 2.5, $(CH_3)_2CHCH$), 3.60 (1H, m, PhC*H*CH_3), 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.91 (1H, d, *J* 14.5, NCH_2ArOMe), 4.04 (1H, d, *J* 15.0, NCH_2ArOMe), 4.10 (1H, d, *J* 1.9, C(3)*H*), 4.54 (1H, d, *J* 15.0, NCH_2ArOMe), 5.49 (1H, d, *J* 14.5, NCH_2ArOMe), 6.70–7.40 (13H, m, Ar); δ_C (100 MHz, $CDCl_3$) 15.3, 16.5, 19.2, 30.5, 41.0, 46.2, 47.3, 55.2, 55.3, 62.8, 63.2, 113.8, 114.2, 127.2, 128.3, 128.6, 129.6, 130.4, 140.3, 158.9, 159.4, 165.5, 165.7; *m/z* (CI^+) 501 ($[M+H]^+$, 8%), 121 (100); HRMS (ESI^+) $C_{31}H_{36}N_2NaO_4^+$ ($[M+Na]^+$) requires 523.2567, found 523.2553.

4.1.1.2. X-ray crystal structure determination for 6. Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 124 K. The structure was solved by direct methods (SIR97). All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[21]

Crystal data for **6** $[C_{31}H_{36}N_2O_4]$: M=500.64; monoclinic; space group $P1\,21\,1$, a=7.5802(2) Å, b=28.1447(6) Å, c=12.4766(4) Å; β=94.4890(11)°; V=2653.62 Å^3; Z=4; μ=0.073 mm^{-1}; colourless plate; crystal dimensions= 0.04×0.04×0.26 mm^3. A total of 5600 unique reflections were measured for $3<\theta<27$ and 5598 reflections were used in the refinement. The final parameters were wR_2= 0.1290 and R_1=0.0955 (all data).

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC280792. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.1.1.3. Alkylation of potassium enolate 3 with (*RS*)-5. Compound **1** (2.0 g, 5.0 mmol) in THF (100 mL), KHMDS (0.5 M in PhMe, 9.1 mL, 4.5 mmol) and (*RS*)-**5** (2.03 g, 11.0 mmol) were reacted according to Section 4.1.1, to yield a suspension of colourless solid in a brown oil. Analysis of the high field ^{1}H NMR spectrum of the crude product indicated that the diastereoisomers **6** and **7** were formed in a de of 82%, 85% of the starting **1** being converted to alkylated products. Fractional recrystallisation from EtOAc/hexane led to the isolation of **6** (1.41 g, 57%).

4.1.1.4. Recovery of α-methylbenzyl bromide (*S*)-5. To **1** (500 mg, 1.26 mmol) in degassed THF (20 mL) at −78 °C was added a solution of LiHMDS (1.39 mL, 1 M in THF, 1.39 mmol). The resultant solution was allowed to stir at −78 °C for 1 h prior to the addition of (*RS*)-**5** (233 mg, 1.26 mmol). The mixture was stirred at −78 °C for 3 h, NH_4Cl (satd aq) was added, and the mixture was allowed to warm to rt. The mixture was partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc and the combined organic layers were dried and concentrated in vacuo to yield the crude product. Chromatography (alumina, eluent 30–40° petrol/Et_2O 9:1) gave (*S*)-**5** as a colourless oil (100 mg, 43%); $[\alpha]_D^{23}$ −25.9 (*c* 4.8 in $CHCl_3$); {lit.[9] $[\alpha]_D^{23}$ −90.8 (*c* 2.8 in $CHCl_3$) for 81% ee sample}.

4.1.2. General procedure 2: preparation of (*RS*)-1-aryl-1-bromo-ethanes 8–10. Concentrated HBr (48% in H_2O, 10 mL) was added to alcohol in PhMe (6 mL per 7 mmol) and the resulting mixture was rapidly stirred for 12 h then partitioned between Et_2O and H_2O. The organic phase was washed sequentially with H_2O and $NaHCO_3$ (satd aq), dried and concentrated in vacuo.

4.1.2.1. (*RS*)-1-(1′-Bromoethyl)-4-methyl-benzene (*RS*)-8. 1-(4-Methylphenyl)ethanol (5.0 g, 37 mmol) was treated as described in Section 4.1.2 to give (*RS*)-**8** as a yellow oil (5.7 g, 78%) which was used without further purification; ν_{max} (film) 1514, 1441, 817, 719; δ_H (500 MHz, $CDCl_3$) 2.11 (3H, d, *J* 6.9, ArCHBrCH_3), 2.4 (3H, s, ArCH_3), 5.29 (1H, q, *J* 6.9, ArC*H*$BrCH_3$), 7.22–7.42 (4H, m, Ar); δ_C (125 MHz, $CDCl_3$) 21.2, 26.8, 49.8, 126.7, 129.3, 138.2, 140.3; *m/z* ($APCI^+$) 119 ($[C_9H_{11}]^+$, 100%).

4.1.2.2. (*RS*)-1-(1′-Bromoethyl)-2-methyl-benzene (*RS*)-9. 1-(2-Methylphenyl)ethanol (5.0 g, 37 mmol) was treated as described in Section 4.1.2 to give (*RS*)-**9** as a yellow oil (6.4 g, 87%), which was used without further purification; ν_{max} (film) 1491, 1463, 761, 723; δ_H (400 MHz, $CDCl_3$) 2.10 (3H, d, *J* 6.9, ArCHBrCH_3), 2.43 (3H, s, ArCH_3), 5.45 (1H, q, *J* 6.9, ArC*H*$BrCH_3$), 7.16–7.58 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 19.0, 25.6, 46.1, 125.8, 126.6, 128.2, 130.7, 135.4, 140.8; *m/z* ($APCI^+$) 119 ($[C_9H_{11}]^+$, 100%).

4.1.2.3. (*RS*)-1-(1′-Bromoethyl)-4-methoxy-benzene (*RS*)-10. 1-(4-Methoxyphenyl)ethanol (5.0 g, 33 mmol) was treated as described in Section 4.1.2 to give (*RS*)-**10** as a colourless oil (6.0 g, 84%), which was used without further purification; ν_{max} (film) 1610, 1513, 1252, 831; δ_H (500 MHz, $CDCl_3$) 2.07 (3H, d, *J* 6.9, ArCHBrCH_3), 3.83 (3H, s, OCH_3), 5.27 (1H, q, *J* 6.9, ArC*H*$BrCH_3$), 6.89–7.41 (4H, m, Ar); δ_C (125 MHz, $CDCl_3$) 22.4, 50.0, 55.2, 114.0, 128.0, 135.4, 159.4; *m/z* ($APCI^+$) 135 ($[C_9H_{11}O]^+$, 100%).

4.1.3. General procedure 3: preparation of (*RS*)-1-aryl-1-bromo-ethanes 11–13. The alkyl aromatic substrate (1.0 equiv), NBS (1.1 equiv) and benzoylperoxide (0.01 equiv) were dissolved in CCl_4 (8.0 mL per mmol of aromatic substrate) and then refluxed at 70 °C for 3 h. The solution was filtered, and the filtrate concentrated in vacuo.

4.1.3.1. (*RS*)-2-(1′-Bromoethyl)pyridine (*RS*)-11. 2-Ethylpyridine (10.0 g, 93 mmol), NBS (16.5 g, 102 mmol), benzoylperoxide (200 mg, 0.93 mmol) and CCl_4 (744 mL) were reacted according to Section 4.1.3 to yield a yellow oil, containing a 2:1 mixture of (*RS*)-**11** and 2-(1′,1′-dibromoethyl)pyridine. Chromatography (silica, eluent Et_2O/hexane 1:1) gave (*RS*)-**11** as an oil (7.4 g, 43%) and 2-(1′,1′-dibromoethyl)pyridine as an oil (5.6 g, 23%).

Data for (*RS*)-**11**: ν_{max} (film) 1590, 1571, 787; δ_H (400 MHz, $CDCl_3$) 2.07 (3H, d, *J* 6.9, CHBrCH_3), 5.25 (1H, q, *J* 6.9, C*H*$BrCH_3$), 7.19–8.60 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$)

25.0, 49.2, 121.6, 123.1, 137.2, 149.1, 169.2; *m/z* (CI$^+$) 188 ([M+H]$^+$, ^{81}Br, 42%), 186 (41).

Data for 2-(1′,1′-dibromoethyl)pyridine: ν_{max} (film) 1754, 1787, 1586; δ_H (400 MHz, $CDCl_3$) 3.01 (3H, s, CH_3CBr$_2$), 6.95–8.53 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 39.3, 62.4, 122.5, 123.5, 137.1, 147.5, 162.0; *m/z* (CI$^+$) 268 ([M+H]$^+$, ^{81}Br^{81}Br, 49%), 266 (100), 264 (50), 186 (28), 184 (22), 105 (10).

4.1.3.2. (*RS*)-1-(1′-Bromoethyl)naphthalene (*RS*)-12. 1-Ethylnaphthalene (5.0 g, 32 mmol), NBS (6.3 g, 35 mmol), benzoylperoxide (70 mg, 0.29 mmol) and CCl_4 (256 mL) were reacted according to Section 4.1.3. Trituration with hot pentane and concentration of the supernatant in vacuo gave (*RS*)-**12** as a brown oil (7.0 g, 94%); ν_{max} (film) 1691, 1598, 1511, 775; δ_H (400 MHz, $CDCl_3$) 2.32 (3H, d, *J* 6.9, ArCHBrCH_3), 6.06 (1H, q, *J* 6.9, ArC*H*BrCH$_3$), 7.50–8.31 (7H, m, *Ar*CHBrCH$_3$); δ_C (100 MHz, $CDCl_3$) 25.5, 45.1, 123.6, 123.8, 125.5, 126.0, 126.9, 128.6, 128.7, 130.4, 133.6, 138.0; *m/z* (EI$^+$) 236 ([M]$^+$, ^{81}Br, 10%), 234 (12), 155 (100), 127 (12); HRMS (EI$^+$) $C_{12}H_{10}^{81}Br^+$ ([M+H]$^+$, ^{81}Br) requires 234.9945, found 234.9941; $C_{12}H_{10}^{79}Br^+$ ([M+H]$^+$, ^{79}Br) requires 232.9966, found 232.9961.

4.1.3.3. (*RS*)-2-(1′-Bromoethyl)naphthalene (*RS*)-13. 2-Ethylnaphthalene (5.0 g, 32 mmol), NBS (6.3 g, 35 mmol), benzoylperoxide (70 mg, 33 mmol) and CCl_4 (256 mL) were reacted according to Section 4.1.3. Trituration with hot pentane and concentration of the supernatant in vacuo gave (*RS*)-**13** as a brown solid (7.2 g, 97%); mp 50–53 °C; ν_{max} (KBr) 1691, 1599, 1597, 751; δ_H (400 MHz, $CDCl_3$) 2.17 (3H, d, *J* 6.9, ArCHBrCH_3), 5.43 (1H, q, *J* 6.9, ArC*H*BrCH$_3$), 7.27–8.18 (7H, m, Ar); δ_C (100 MHz, $CDCl_3$) 26.7, 50.1, 125.1, 126.5, 127.9, 128.1, 128.5, 128.7, 131.0, 133.0, 133.1, 140.4; *m/z* (EI$^+$) 235 ([M+H]$^+$, ^{81}Br, 53%), 233 (55), 155 (100), 127 (32).

4.1.3.4. (3*R*,6*S*,1′*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-(4-methylphenyl)ethyl)piperazine-2,5-dione 14. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), KHMDS (0.5 M in PhMe, 1.24 mL, 0.6 mmol) and (*RS*)-**8** (0.17 mL, 1.1 mmol) were reacted according to Section 4.1.1 to afford a brown oil. Chromatography (silica gel, eluent 30–40° petrol/Et_2O 4:1) gave **14** as a colourless solid (160 mg, 61%); mp 133–135 °C; $[\alpha]_D^{21}$ +46.5 (*c* 1.3 in $CHCl_3$); ν_{max} (KBr) 1653, 1515, 1441; δ_H (500 MHz, $CDCl_3$) 0.65 (3H, d, *J* 6.9, CH_3CHCH$_3$), 0.96 (3H, d, *J* 6.9, CH$_3$CHCH_3), 1.49 (3H, d, *J* 7.3, ArCHCH_3), 2.08 (1H, m, (CH$_3$)$_2$C*H*), 2.40 (3H, s, ArCH_3), 3.04 (1H, d, *J* 2.4, (CH_3)$_2$CHC*H*), 3.56 (1H, m, ArC*H*CH$_3$), 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.93 (1H, d, *J* 14.5, NCH_2ArOMe), 4.00 (1H, d, *J* 15.0, NCH_2ArOMe), 4.07 (1H, d, *J* 1.9, C*H*CH(CH$_3$)Ar), 4.61 (1H, d, *J* 15.0, NCH_2ArOMe), 5.49 (1H, d, *J* 14.5, NCH_2ArOMe), 6.72–6.76 (4H, m, Ar), 6.86–6.88 (2H, m, Ar), 7.08–7.14 (6H, m, Ar); δ_C (125 MHz, $CDCl_3$) 15.2, 16.7, 19.8, 21.0, 30.3, 40.3, 46.0, 47.0, 55.2, 55.1, 62.4, 63.1, 113.7, 114.1, 127.0, 127.1, 128.1, 129.1, 129.6, 130.4, 136.7, 136.9, 158.8, 159.3, 165.4, 165.5; *m/z* (APCI$^+$) 515 ([M+H]$^+$, 100%), 121 (45); HRMS (CI$^+$) $C_{32}H_{39}N_2O_4^+$ ([M+H]$^+$) requires 515.2909, found 515.2921.

4.1.3.5. (3*R*,6*S*,1′*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-(2-methylphenyl)ethyl)piperazine-2,5-dione 15. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), KHMDS (0.5 M in PhMe, 1.24 mL, 0.6 mmol) and (*RS*)-**9** (0.17 mL, 1.1 mmol) were reacted according to Section 4.1.1 to afford a brown oil. Chromatography (silica gel, eluent cyclohexane/EtOAc 1:1) gave **15** as a colourless solid (179 mg, 69%); mp 120–122 °C; $[\alpha]_D^{21}$ +80.8 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1652, 1514; δ_H (400 MHz, $CDCl_3$) 0.64 (3H, d, *J* 6.9, CH_3CHCH$_3$), 1.04 (3H, d, *J* 6.9, CH$_3$CHCH_3), 1.40 (3H, d, *J* 7.2, ArCHCH_3), 2.22 (1H, m, (CH$_3$)$_2$C*H*), 2.38 (3H, s, ArCH_3), 3.26 (1H, d, *J* 2.3, (CH$_3$)$_2$CHC*H*), 3.52 (1H, d, *J* 14.5, NCH_2ArOMe), 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.87 (1H, m, ArC*H*CH$_3$), 4.23 (1H, d, *J* 14.9, NCH_2ArOMe), 4.24 (1H, d, *J* 1.4, C*H*CH(CH$_3$)Ar), 4.72 (1H, d, *J* 14.9, NCH_2ArOMe), 5.36 (1H, d, *J* 14.5, NCH_2ArOMe), 6.74–6.81 (4H, m, Ar), 6.83–6.85 (2H, m, Ar), 7.04–7.06 (2H, m, Ar), 7.17–7.32 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 15.3, 15.8, 19.7, 20.2, 30.5, 39.7, 46.4, 47.6, 55.2, 61.7, 62.9, 113.9, 113.9, 126.1, 127.2, 127.3, 127.5, 127.8, 129.6, 130.1, 131.0, 137.3, 139.8, 159.0, 159.2, 165.8, 167.0; *m/z* (APCI$^+$) 515 ([M+H]$^+$, 30%), 121 (100); HRMS (CI$^+$) $C_{32}H_{39}N_2O_4^+$ ([M+H]$^+$) requires 515.2909, found 515.2904.

4.1.3.6. (3*R*,6S,1′*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-(4-methoxyphenyl)ethyl)piperazine-2,5-dione 16. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), KHMDS (0.5 M in PhMe, 1.24 mL, 0.6 mmol) and (*RS*)-**10** (0.17 mL, 1.1 mmol) were reacted according to Section 4.1.1 to afford a brown oil. Chromatography (silica gel, eluent cyclohexane/Et_2O 4:1) gave **16** as a colourless solid (169 mg, 64%); mp 151–153 °C; $[\alpha]_D^{23}$ +34.0 (*c* 1.5 in $CHCl_3$); ν_{max} (KBr) 1650, 1513, 1440, 1247; δ_H (400 MHz, $CDCl_3$) 0.64 (3H, d, *J* 6.9, CH_3CHCH$_3$), 0.97 (3H, d, *J* 6.9, CH$_3$CHCH_3), 1.49 (3H, d, *J* 7.3, ArCHCH_3), 2.08 (1H, m, (CH$_3$)$_2$C*H*), 3.04 (1H, d, *J* 2.4, (CH$_3$)2CHCH), 3.53 (1H, m, NCHC*H*(Ar)CH$_3$), 3.78 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.95 (1H, d, *J* 14.5, NCH_2ArOMe), 4.00 (1H, d, *J* 15.0, NCH_2ArOMe), 4.04 (1H, d, *J* 1.5, C*H*CH(CH$_3$)Ar), 4.60 (1H, d, *J* 15.0, NCH_2ArOMe), 5.50 (1H, d, *J* 14.5, NCH_2ArOMe), 6.70–6.76 (4H, m, Ar), 6.83–8.89 (4H, m, Ar), 7.08–7.16 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 15.3, 17.6, 19.9, 30.3, 39.9, 46.2, 47.0, 55.2, 55.3, 62.6, 63.2, 113.8, 113.8, 114.2, 127.0, 127.1, 128.9, 129.3, 129.6, 130.5, 131.8, 158.9, 158.9, 159.4, 165.5, 165.5; *m/z* (APCI$^+$) 531 ([M+H]$^+$, 45%), 121 (100); HRMS (CI$^+$) $C_{32}H_{39}N_2O_5^+$ ([M+H]$^+$) requires 531.2858, found 531.2867.

4.1.3.7. (3*R*,6*S*,1′*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-(2-pyridyl)ethyl)piperazine-2,5-dione 17. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), KHMDS (0.5 M in PhMe, 1.24 mL, 0.6 mmol) and (*RS*)-**11** (0.17 mL, 1.1 mmol) were reacted according to Section 4.1.1 to afford a brown oil. Chromatography (silica gel, eluent cyclohexane/Et_2O 4:1) gave **17** as a yellow solid (216 mg, 85%); mp 109–112 °C; $[\alpha]_D^{19}$ +22.8 (*c* 1.3 in $CHCl_3$); ν_{max} (film) 1656, 1513, 1439; δ_H (400 MHz, $CDCl_3$) 0.72 (3H, d, *J* 6.9, CH_3CHCH$_3$), 1.04 (3H, d, *J* 6.9, CH$_3$CHCH_3), 1.41 (3H, d, *J* 6.0, ArCHCH_3), 2.25 (1H, m, (CH$_3$)$_2$C*H*), 3.43 (1H, d, *J* 2.7, (CH$_3$)$_2$CHC*H*), 3.70 (1H, d, *J* 14.8, NCH_2ArOMe), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3),

3.95 (1H, d, *J* 14.8, CH_2ArOMe), 4.46 (1H, d, *J* 1.8, C*H*CH(CH_3)Ar), 5.06 (1H, d, *J* 14.8, NCH_2ArOMe), 5.31 (1H, d, *J* 14.8, NCH_2ArOMe), 6.76–6.82 (4H, m, Ar), 6.91–6.95 (2H, m, Ar), 7.01–7.05 (2H, m, Ar), 7.17–7.22 (2H, m, py), 7.60 (1H, m, py), 8.53 (1H, m, C_6H–py); δ_C (100 MHz, $CDCl_3$) 15.1, 16.2, 20.4, 31.7, 44.2, 46.4, 47.3, 55.7, 55.7, 62.8, 63.2, 114.4, 114.4, 122.3, 122.5, 127.9, 128.0, 130.3, 130.5, 137.0, 149.6, 159.5, 162.0, 165.8, 166.8; *m/z* (APCI$^+$) 502 ([M+H]$^+$, 100%), 121 (75); HRMS (CI$^+$) $C_{30}H_{36}N_3O_4^+$ ([M+H]$^+$) requires 502.2706, found 502.2713.

4.1.3.8. X-ray crystal structure determination for 17. Data were collected using a Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR97). All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[21]

Crystal data for **17** [$C_{30}H_{35}N_3O_4$]: M=501.62; monoclinic; space group $P1\,21\,1$; a=7.5984(1) Å, b=28.2598(5) Å, c=12.3274(2) Å; β=94.2499(9)°; V=2639.8 Å^3; Z=4; μ=0.084 mm^{-1}; colourless plate; crystal dimensions 0.1×0.3×0.6 mm^3. A total of 6119 unique reflections were measured for $1<\theta<27$ and 5622 reflections were used in the refinement. The final parameters were wR_2=0.033 and R_1=0.038 (all data).

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC280651. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.1.3.9. (3*R*,6*S*,1′*S*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-(1-naphthyl)ethyl)piperazine-2,5-dione 18. Following Section 4.1.1 using **1** (200 mg, 0.5 mmol), KHMDS (0.5 M in toluene, 1.24 mL, 0.6 mmol), THF (10 mL) and (*RS*)-**12** (0.12 mL, 1.1 mmol) afforded a crude solid containing 55:45 mixture of **18** and **1**. Chromatography (silica gel, eluent 30–40° petrol/Et_2O 9:1) gave **18** as a colourless oil (130 mg, 47%); $[\alpha]_D^{22}$ +60.6 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 1642, 1513, 1454; δ_H (400 MHz, $CDCl_3$) 0.67 (3H, d, *J* 7.0, CH_3CHCH$_3$), 1.11 (3H, d, *J* 7.0, (CH$_3$)CHCH_3), 1.43 (3H, d, *J* 7.1, ArCHCH_3), 2.36 (1H, m, (CH$_3$)$_2$C*H*), 3.18 (1H, d, *J* 14.3, NCH_2ArOMe), 3.62 (3H, s, OCH_3), 3.70 (1H, d, *J* 3.0, (CH$_3$)$_2$CHC*H*), 3.80 (3H, s, OCH_3), 4.03 (1H, d, *J* 14.7, NCH_2ArOMe), 4.61 (1H, m, CH$_3$C*H*Ar), 4.67 (1H, s, C*H*CH(CH$_3$)Ar), 5.14 (1H, d, *J* 14.3, NCH_2ArOMe), 5.31 (1H, d, *J* 14.7, NCH_2ArOMe), 6.15–6.17 (2H, m, Ar), 6.37–6.39 (2H, m, Ar), 6.87–6.90 (2H, m, Ar), 7.19–7.21 (2H, m, Ar), 7.45–8.54 (7H, m, naphthyl); δ_C (100 MHz, $CDCl_3$) 13.4, 15.5, 20.1, 30.7, 41.0, 46.6, 46.7, 55.1, 55.3, 61.8, 62.3, 113.3, 114.2, 123.6, 124.6, 125.2, 125.9, 126.8, 127.0, 127.4, 128.1, 128.7, 130.0, 130.7, 131.9, 134.0, 138.8, 158.7, 159.3, 165.9, 167.6; *m/z* (APCI$^+$) 551 ([M+H]$^+$, 100%), 121 (78); HRMS (CI$^+$) $C_{35}H_{39}N_2O_4^+$ ([M+H]$^+$) requires 551.2909, found 551.2908.

4.1.3.10. (3*R*,6*S*,1′*S*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-(2-naphthyl)ethyl)piperazine-2,5-dione 19. Following Section 4.1.1 using **1** (200 mg, 0.5 mmol), THF (8 mL), KHMDS (0.5 M in toluene, 1.24 mL, 0.6 mmol) and (*RS*)-**13** (259 mg in 2 mL of THF, 1.1 mmol) afforded a brown solid containing 83:17 mixture of **19** and **1**. Chromatography (silica gel, eluent cyclohexane/EtOAc 9:1) gave **19** as a colourless solid (180 mg, 68%); mp 188–191 °C; $[\alpha]_D^{21}$ −48.6 (*c* 1.5 in $CHCl_3$); ν_{max} (KBr) 1654, 1514; δ_H (400 MHz, $CDCl_3$) 0.67 (3H, d, *J* 7.0, CH_3CHCH$_3$), 0.9 (3H, d, *J* 7.0, CH$_3$CHCH_3), 1.64 (3H, d, *J* 7.3, ArCHCH_3), 2.06 (1H, m, (CH$_3$)$_2$C*H*), 3.01 (1H, d, *J* 2.5, (CH$_3$)$_2$CHC*H*), 3.68 (3H, s, OCH_3), 3.80 (1H, m, C*H*(CH$_3$)Ar), 3.79 (1H, d, *J* 14.9, NCH_2ArOMe), 3.82 (3H, s, OCH_3), 4.05 (1H, d, *J* 14.5, NCH_2ArOMe), 4.19 (1H, d, *J* 1.4, C*H*CH(CH$_3$)Ar), 4.71 (1H, d, *J* 14.9, NCH_2ArOMe), 5.56 (1H, d, *J* 14.5, NCH_2ArOMe), 6.27–6.34 (4H, m, Ar), 6.84–6.89 (2H, m, Ar), 7.14–7.16 (2H, m, Ar), 7.32–7.90 (7H, m, naphthyl); δ_C (100 MHz, $CDCl_3$) 15.4, 17.0, 19.7, 30.2, 40.6, 45.7, 45.8, 55.1, 55.3, 61.9, 63.2, 113.6, 114.2, 125.9, 126.3, 126.3, 126.6, 126.9, 126.9, 127.6, 128.1, 128.1, 129.4, 130.6, 132.6, 133.5, 137.6, 158.7, 159.4, 165.3; *m/z* (APCI$^+$) 551 ([M+H]$^+$, 80%), 121 (100); HRMS (CI$^+$) $C_{35}H_{39}N_2O_4^+$ ([M+H]$^+$) requires 551.2909, found 551.2923.

4.1.3.11. (3*R*,6*S*,1′*S*)-6-*iso*-Propyl-3-(1′-phenylethyl)-piperazine-2,5-dione 26. Compound **6** (450 mg, 0.9 mmol) and CAN (1.7 g, 5.4 mmol) in acetonitrile (10 mL) and water (5 mL) were stirred at rt for 12 h. After the addition of satd aq K_2CO_3 (20 mL) the mixture was extracted with dichloromethane and the organic fractions combined, dried and concentrated in vacuo. Trituration of the resultant solid with hexane gave **26** as a colourless solid (218 mg, 94%); mp 253–255 °C; $[\alpha]_D^{21}$ +74.8 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3189, 3056, 1668; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d *J* 7.0, CH_3CHCH$_3$), 1.02 (3H, d, *J* 7.0, CH$_3$CHCH_3), 1.35 (3H, d, *J* 7.1, PhCHCH_3), 2.41 (1H, m, C*H*(CH$_3$)$_2$), 3.70–3.72 (1H, m, PhC*H*CH$_3$), 3.76 (1H, d, *J* 1.6, (CH$_3$)$_2$CHC*H*), 4.17 (1H, d, *J* 1.5, C*H*CH(CH$_3$)Ph), 5.64 (1H, s, N*H*), 6.16 (1H, s, N*H*), 7.27–7.42 (5H, m, Ar); δ_C (100 MHz, $CDCl_3$) 11.9, 15.7, 18.5, 32.1, 41.9, 56.0, 60.2, 127.6, 127.7, 129.2, 140.3, 167.2, 167.5; *m/z* (APCI$^+$) 261 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{15}H_{21}N_2O_2^+$ ([M+H]$^+$) requires 261.1603, found 261.1604.

4.1.3.12. (3*R*,6*S*,1′*S*)-6-*iso*-Propyl-3-(1′-(2-methylphenyl)ethyl)piperazine-2,5-dione 27. Compound **15** (300 mg, 0.6 mmol) and CAN (3.6 mmol) in acetonitrile (3 mL) and water (3 mL) were stirred for 1 h at rt. The organic solvent was evaporated, ether was added (20 mL) and the resultant solid filtered and washed with ether to give **27** as a colourless solid (145 mg, 88%); mp 166–168 °C; $[\alpha]_D^{25}$ +64.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1683; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8, (CH_3)$_2$CH), 1.03 (3H, d, *J* 6.8, (CH_3)$_2$CH), 1.31 (1H, d, *J* 7.0, CH_3CH), 2.40–2.47 (1H, m, (CH$_3$)$_2$C*H*), 2.43 (3H, s, CH_3Ph), 3.87 (1H, br s, (CH$_3$)$_2$CHC*H*), 3.97–4.04 (1H, m, C*H*CH$_3$), 4.04 (1H, br s, C*H*CHCH$_3$), 5.62 (1H, s, N*H*), 6.14 (1H, s, N*H*), 7.19–7.29 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 12.3, 15.8, 18.5, 19.3, 32.2, 37.8, 57.6, 60.0, 126.4, 126.7, 127.4, 131.4, 136.1, 138.5, 167.5; HRMS (CI$^+$) $C_{12}H_{18}NO_2^+$ ([M+H]$^+$) requires 275.1760, found 275.1761.

4.1.3.13. (2*R*,3*S*)-Methyl 2-amino-3-phenyl-butanoate 28. Compound **26** (380 mg, 1.32 mmol) was heated in HCl (5 M aq, 50 mL) at 100 °C for 24 h. After this the volatile material was removed in vacuo and the resulting mixture was subjected to these conditions twice more. The resulting mixture of amino acids was then dissolved in MeOH (20 mL) and $SOCl_2$ (5 mL) added (CARE!) and the mixture then refluxed for 2 h, cooled to rt and the volatile material removed in vacuo. The residue was partitioned between satd aq $NaHCO_3$ (30 mL) and DCM (30 mL), the organic layer washed with satd brine (30 mL), dried and the solvent removed in vacuo. Chromatography (silica, ether/dimethylethylamine 20:1) afforded a mixture of (*S*)-valine methyl ester and **28**. (*S*)-Valine methyl ester was removed in vacuo to give **28** as a colourless oil (126 mg, 49%); $[\alpha]_D^{23}$ −49.9 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 3386, 3311, 3029, 2952, 1740, 1602; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 7.1, CHC*H*$_3$), 1.43 (2H, br s, N*H*$_2$), 3.20 (1H, m, C*H*Ph), 3.62 (3H, s, OC*H*$_3$), 3.64 (1H, d, *J* 5.4, C*H*NH$_2$), 7.20–7.33 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 15.2, 43.8, 52.2, 61.0, 127.2, 128.1, 128.8, 143.4, 175.5; *m*/*z* (APCI$^+$) 194 ([M+H]$^+$, 58%), 133 (100); HRMS (ESI$^+$) $C_{11}H_{16}NO_2^+$ ([M+H]$^+$) requires 194.1181, found 194.1176.

4.1.3.14. (2*R*,3*S*)-2-Amino-3-(2-methylphenyl)-butyric acid methyl ester 29. Compound **27** (100 mg, 0.4 mmol) in hydroiodic acid (57% in water, 15 mL) was refluxed for 24 h then the solvent was evaporated in vacuo to afford a mixture of amino acids, which were dissolved in MeOH (20 mL) and cooled to 0 °C and thionyl chloride (1.0 mL) added. The mixture was subject to reflux overnight then concentrated in vacuo. The mixture of the methyl ester amino hydrochlorides was partitioned between DCM and aq $NaHCO_3$, the organic phase dried and concentrated in vacuo. Removal of (*S*)-valine methyl ester under vacuum gave **29** as a colourless oil (62 mg, 75%); $[\alpha]_D^{25}$ −18.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1738; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 7.1, C*H*$_3$CH), 2.38 (3H, s, C*H*$_3$Ph), 2.69 (2H, br s, N*H*$_2$), 3.51–3.57 (1H, m, C*H*CH$_3$), 3.66 (3H, s, OC*H*$_3$), 3.71 (1H, d, *J* 5.3, C*H*NH$_2$), 7.12–7.27 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 14.7, 19.4, 37.9, 52.0, 58.3, 126.1, 126.6, 126.7, 130.6, 135.6, 140.7, 174.3; *m*/*z* (ES$^+$) 208 ([M+H]$^+$, 100%,); HRMS (CI$^+$) $C_{12}H_{18}NO_2^+$ ([M+H]$^+$) requires 208.1338, found 208.1345.

4.1.3.15. (3*R*,6*S*,2′*R*)- and (3*R*,6*S*,2′*S*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-3-*iso*-propyl-6-(2′-ethylpropanoate)piperazine-2,5-dione 31 and 32. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), LiHMDS (0.55 mL, 1 M in THF, 0.55 mmol) and (*RS*)-**30** (0.64 mL, 5.0 mmol) were reacted according to Section 4.1.1 to give a crude oil from which excess of (*RS*)-**30** was removed under vacuum (1 mmHg, ambient temperature). Chromatography (silica, ether/hexane 1:1) gave **31** as a colourless solid (first to elute, 230 mg, 93%) and **32** as a colourless solid (second to elute, 15 mg, 3%).

Data for **31**: mp 112–114 °C (ether); $[\alpha]_D^{23}$ −13.3 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1730, 1646; δ_H (400 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.9, C*H*$_3$CHCH$_3$), 1.13 (3H, d, *J* 6.9, CH$_3$CHC*H*$_3$), 1.14 (3H, d, *J* 7.2, (EtO$_2$C)CHC*H*$_3$), 1.15 (3H, t, *J* 7.2, OCH$_2$C*H*$_3$), 2.30 (1H, m, CH$_3$C*H*CH$_3$), 3.48 (1H, dq, *J* 1.6, 7.2, (EtO$_2$C)C*H*CH$_3$), 3.69 (1H, d, *J* 15.2, NC*H*$_2$ArOMe), 3.79 (4H, m, OC*H*$_3$ and 6-*H*), 3.80 (3H, s, OC*H*$_3$), 3.89 (1H, d, *J* 14.7, NC*H*$_2$ArOMe), 3.95 (1H, m, OC*H*$_2$CH$_3$), 4.14 (1H, m, OC*H*$_2$CH$_3$), 4.57 (1H, s, 3-*H*), 5.28 (1H, d, *J* 15.2, NC*H*$_2$ArOMe), 5.34 (1H, d, *J* 14.7, NC*H*$_2$ArOMe), 6.84 (4H, m, Ar*H*), 7.18 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 11.8, 14.0, 16.4, 19.8, 31.3, 42.4, 46.0, 47.1, 55.2, 61.2, 113.9, 114.2, 127.4, 127.7, 129.4, 129.9, 159.1, 159.3, 165.7, 165.8, 173.7; *m*/*z* (APCI$^+$) 497 ([M+H]$^+$, 50%), 121 (100); HRMS (CI$^+$) $C_{28}H_{37}N_2O_6^+$ ([M+H]$^+$) requires 497.2645, found 497.2652.

Data for **32**: $C_{28}H_{36}N_2O_6$ requires C, 67.7; H, 7.3; N, 5.6%. Found C, 67.7; H, 7.3; N, 5.6%; mp 136 °C (ethyl acetate/hexane); $[\alpha]_D^{23}$ +62.4 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2984, 2933, 1739, 1640; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.9, C*H*$_3$CHCH$_3$), 0.98 (3H, d, *J* 6.9, CH$_3$CHC*H*$_3$), 1.10 (3H, d, *J* 7.0, (EtO$_2$C)CHC*H*$_3$), 1.26 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 2.30 (1H, m, CH$_3$C*H*CH$_3$), 3.10 (1H, dq, *J* 1.6, 6.9, (EtO$_2$C)C*H*CH$_3$), 3.778 (1H, d, *J* 3.1, 6-*H*), 3.782 (1H, d, *J* 14.7, NC*H*$_2$ArOMe), 3.81 (6H, s, 2×OC*H*$_3$), 3.99 (1H, d, *J* 14.9, NC*H*$_2$ArOMe), 4.14–4.38 (2H, m, OC*H*$_2$CH$_3$), 4.70 (1H, d, *J* 3.2, 3-*H*), 5.27 (1H, d, *J* 14.9, NC*H*$_2$ArOMe), 5.43 (1H, d, *J* 14.7, NC*H*$_2$ArOMe), 6.86–6.88 (4H, m, Ar), 7.14–7.27 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 8.6, 11.8, 14.1, 31.7, 40.0, 46.1 46.2, 55.23, 55.26, 60.0, 60.8, 62.2, 114.0, 114.2, 126.9, 127.3, 130.0, 130.2, 159.3, 159.4, 164.4, 165.8, 172.0; *m*/*z* (APCI$^+$) 497 ([M+H]$^+$, 10%), 121 (100).

4.1.3.16. X-ray crystal structure determination for 32. Data were collected using an Enraf–Nonius Mach 3 diffractometer with graphite monochromated Cu radiation using standard procedures at 193 K. The structure was solved by direct methods (SIR97). All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[21]

Crystal data for **32** [$C_{28}H_{36}N_2O_6$]: *M*=496.6, monoclinic; space group *P*1 21 1; *a*=9.220(2) Å, *b*=12.304(2) Å, *c*=12.354(3) Å; *β*=105.376(18)°; *V*=1351.3 Å^3; *Z*=2; *μ*=0.697 mm^{-1}; colourless plate; crystal dimensions 0.02×0.6×0.6 mm^3. A total of 2892 unique reflections were measured for $19<\theta<23$ and 2789 reflections were used in the refinement. The final parameters were wR_2=0.061 and R_1=0.046 (all data).

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC280790. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.1.3.17. Recovery of ethyl 2-bromopropanoate 30. To **1** (200 mg, 0.5 mmol) in degassed anhydrous THF (10 mL) at −78 °C was added a solution of LiHMDS (1.0 M in THF, 0.55 mL, 0.55 mmol). The resultant solution was allowed to stir at −78 °C for 1 h prior to the addition of (*RS*)-**30** (140 mg, 0.77 mmol). The mixture was stirred at −78 °C for 12 h then allowed to warm to rt when solid NH_4Cl (250 mg) was added. The solvent was removed in vacuo and the residue distilled (1 mmHg, ambient temperature)

to afford (*S*)-**30** (23 mg, 16%); $[\alpha]_D^{23}$ −11.1 (*c* 1.1 in $CHCl_3$); {lit.[13] for enantiomer $[\alpha]_D^{23}$ +37.0 (*c* 1.0 in $CHCl_3$)}.

4.1.3.18. Epimerisation of 31 and 32. LiHMDS (1.6 mL, 1 M in THF, 1.60 mmol) was added to a 94.5:5.5 mixture of **31**:**32** (787 mg, 1.60 mmol) and methyl iodide (100 μL, 1.60 mmol) in anhydrous ethanol (50 mL), and the mixture stirred for 12 h at rt. NH_4Cl (satd aq) was then added and the mixture was partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc and the combined organic layers were dried and concentrated in vacuo to yield a crude solid 20:80 mixture of **31**:**32**. Crystallisation from EtOAc/hexane gave **32** (522 mg, 66%).

4.1.3.19. (3*R*,6*S*,2′*R*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-3-*iso*-propyl-6-(2′-methylpropanoate)piperazine-2,5-dione 37. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), LiHMDS (0.55 mL, 1 M in THF, 0.55 mmol) and (*RS*)-**33** (835 mg, 5.0 mmol) were reacted together according to Section 4.1.1 to give a crude oil from which excess of (*RS*)-**33** was removed under vacuum (1 mmHg, ambient temperature). Chromatography (silica, ether/hexane 1:1) gave **37** as a colourless solid (212 mg, 87%); $[\alpha]_D^{23}$ −10.4 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2958, 1730, 1644; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 1.08 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.15 (3H, d, *J* 7.2, (EtO$_2$C)CHC*H*$_3$), 2.31 (1H, m, CH$_3$C*H*CH$_3$), 3.49 (1H, dq, *J* 1.6, 7.2, (EtO$_2$C)C*H*CH$_3$), 3.59 (3H, s, CO$_2$C*H*$_3$), 3.68 (1H, d, *J* 15.2, NCH$_2$ArOMe), 3.77 (1H, d, *J* 3.4, 6-*H*), 3.79 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 3.88 (1H, d, *J* 14.7, NCH$_2$ArOMe), 4.52 (1H, d, *J* 1.6, 3-*H*), 5.31 (1H, d, *J* 15.2, NC*H*$_2$ArOMe), 5.36 (1H, d, *J* 14.7, NC*H*$_2$ArOMe), 6.82–6.87 (4H, m, Ar), 7.13–7.21 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 12.0, 16.4, 19.8, 26.9, 31.3, 42.1, 45.9, 47.1, 52.1, 55.2, 55.3, 60.2, 62.8, 113.9, 114.2, 127.3, 127.5, 129.6, 129.9, 159.1, 159.3, 165.7, 165.7, 174.1; *m*/*z* (CI^+) 483 ([M+H]$^+$, 40%), 378 (10), 121 (100); HRMS (CI^+) $C_{27}H_{35}N_2O_6^+$ ([M+H]$^+$) requires 483.2495, found 483.2496.

4.1.3.20. (3*R*,6*S*,2′*R*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-3-*iso*-propyl-6-(2′-*tert*-butylpropanoate)piperazine-2,5-dione 38. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), LiHMDS (1.0 M in THF, 0.55 mL, 0.55 mmol) and (*RS*)-**34** (1.04 g, 5.0 mmol) were reacted together according to Section 4.1.1 to give a crude oil. Chromatography (silica, ether/hexane 1:1) gave **38** as a colourless solid (220 mg, 83%); $C_{30}H_{40}N_2O_6$ requires C, 68.7; H, 7.7; N, 5.3%. Found C, 68.2; H, 7.6; N, 5.1%; $[\alpha]_D^{23}$ −10.3 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2965, 1716, 1648; δ_H (400 MHz, $CDCl_3$) 0.65 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 1.01 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.10 (3H, d, *J* 7.3, (^{t}BuO$_2$C)CHC*H*$_3$), 1.42 (9H, s, C(CH$_3$)$_3$), 2.24 (1H, m, CH$_3$C*H*CH$_3$), 3.41 (1H, dq, *J* 1.8, 7.3, (^{t}BuO$_2$C)C*H*CH$_3$), 3.69 (1H, d, *J* 14.8, NCH$_2$ArOMe), 3.72 (1H, d, *J* 3.3, 6-*H*), 3.77 (3H, s, OCH$_3$), 3.78 (3H, s, OCH$_3$), 3.92 (1H, d, *J* 14.8, NCH$_2$ArOMe), 4.61 (1H, d, *J* 1.2, 3-*H*), 5.18 (1H, d, *J* 14.8, NCH$_2$ArOMe), 5.28 (1H, d, *J* 14.8, NCH$_2$ArOMe), 6.81–6.86 (4H, m, Ar), 7.17–7.28 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 12.3, 16.2, 19.8, 27.9, 31.3, 43.4, 46.2, 47.2, 55.2, 55.2, 60.5, 62.9, 81.6, 113.8, 114.1, 127.5, 128.3, 129.8, 130.0, 159.1, 159.2, 165.4, 166.0, 172.8; *m*/*z* (ESI^+) 547 ([M+Na]$^+$, 100%); HRMS (ESI^+) $C_{30}H_{40}N_2NaO_6^+$ ([M+Na]$^+$) requires 547.2784, found 547.2779.

4.1.3.21. (3*R*,6*S*,2′*R*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-3-*iso*-propyl-6-(2′-ethylbutanoate)piperazine-2,5-dione 39. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), LiHMDS (1.0 M in THF, 0.55 mL, 0.55 mmol) and (*RS*)-**35** (975 mg, 5.0 mmol) were reacted together according to Section 4.1.1 to give a crude oil. Chromatography (silica, ether/hexane 1:1) gave **39** as a colourless solid (212 mg, 82%); $[\alpha]_D^{23}$ −28.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2960, 1731, 1657; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 0.86 (3H, t, *J* 7.4, CHCH$_2$C*H*$_3$), 1.07 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.14 (3H, t, *J* 7.2, OCH$_2$C*H*$_3$), 1.49 (1H, m, CHC*H*$_2$CH$_3$), 1.90 (1H, m, CHC*H*$_2$CH$_3$), 2.30 (1H, m, CH$_3$C*H*CH$_3$), 3.12 (1H, m, (EtO$_2$C)C*H*CH$_2$CH$_3$), 3.73 (1H, d, *J* 3.0, 6-*H*), 3.77 (3H, s, OC*H*$_3$), 3.77 (3H, s, OC*H*$_3$), 3.80 (1H, d, *J* 14.4, NC*H*$_2$ArOMe), 3.92 (1H, d, *J* 14.9, NC*H*$_2$ArOMe), 3.96 (1H, m, OC*H*$_2$CH$_3$), 4.11 (1H, m, OC*H*$_2$CH$_3$), 4.34 (1H, d, *J* 2.1, 3-*H*), 5.28 (1H, d, *J* 14.4, NC*H*$_2$ArOMe), 5.31 (1H, d, *J* 14.9, NC*H*$_2$ArOMe), 6.82–6.85 (4H, m, Ar), 7.14–7.20 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 12.7, 14.0, 16.2, 19.9, 21.3, 31.0, 46.0, 47.0, 49.1, 55.2, 58.9, 61.0, 62.8, 114.0, 127.4, 127.4, 129.7, 130.0, 159.2, 159.2, 165.4, 165.6, 172.9; *m*/*z* (ESI^+) 533 ([M+Na]$^+$, 100%); HRMS (ESI^+) $C_{29}H_{38}N_2NaO_6^+$ ([M+Na]$^+$) requires 533.2628, found 533.2622.

4.1.3.22. (3*S*,6*R*,2′*R*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-3-*iso*-propyl-6-(2′-ethylhexanoate)piperazine-2,5-dione 40. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), LiHMDS (0.55 mL, 1 M in THF, 0.55 mmol) and (*RS*)-**36** (1.11 g, 5.0 mmol) were reacted together according to Section 4.1.1 to give a crude oil. Chromatography (silica, ether/hexane 1:1) gave **40** as a colourless oil (233 mg, 86%); $[\alpha]_D^{23}$ −30.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1731, 1658, 1513, 1248; δ_H (400 MHz, $CDCl_3$) 0.78 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 0.84 (3H, t, *J* 7.4, CH$_2$CH$_2$C*H*$_3$), 1.07 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.14 (3H, t, *J* 7.2, OCH$_2$C*H*$_3$), 1.10–1.42 (3H, m, CH$_2$C*H*$_2$CH$_3$ and C*H*$_2$CH$_2$CH$_3$), 1.82 (1H, m, C*H*$_2$CH$_2$CH$_3$), 2.30 (1H, m, CH$_3$C*H*CH$_3$), 3.21 (1H, m, (EtO$_2$C)C*H*(CH$_2$)$_2$CH$_3$), 3.74 (1H, d, *J* 3.2, 6-*H*), 3.77 (3H, s, OC*H*$_3$), 3.78 (3H, s, OC*H*$_3$), 3.79 (1H, d, *J* 14.6, NC*H*$_2$ArOMe), 3.91 (1H, d, *J* 14.6), 3.94 (1H, m, OC*H*$_2$CH$_3$), 4.13 (1H, m, OC*H*$_2$CH$_3$), 4.38 (1H, d, *J* 1.6, 3-*H*), 5.30 (1H, d, *J* 14.6, NC*H*$_2$ArOMe), 5.33 (1H, d, *J* 14.6, NC*H*$_2$ArOMe), 6.81–6.86 (4H, m, Ar), 7.13–7.21 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 13.9, 14.0, 16.3, 19.9, 22.6, 27.5, 30.5, 31.1, 46.0, 47.1, 47.7, 55.2, 59.3, 61.0, 62.8, 114.0, 114.1, 127.4, 127.4, 129.7, 130.0, 159.2, 159.3, 165.5, 165.6, 173.2; *m*/*z* (CI^+) 539 ([M+H]$^+$, 20%) 121 (100); HRMS (CI^+) $C_{31}H_{43}N_2O_6^+$ ([M+H]$^+$) requires 538.3121, found 539.3114.

4.1.3.23. (3*R*,6*S*,1′*S*)-1,4-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1-phenylethylethanoate)piperazine-2,5-dione 46. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), LiHMDS (1.0 M in THF, 0.62 mL, 0.6 mmol) and (*RS*)-**45** (0.14 mL, 1.1 mmol) were reacted together according to Section 4.1.1 to give a brown oil. Chromatography (silica, ether/hexane 1:9) gave **46** as a colourless crystalline solid (210 mg, 75%); $C_{33}H_{38}N_2O_6$ requires C, 70.9; H, 6.9; N, 5.0%. Found C, 70.6; H, 6.9; N, 5.0%; mp 115–118 °C (EtOAc/hexane); $[\alpha]_D^{23}$ +81.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1744, 1645, 1513; δ_H (400 MHz, $CDCl_3$) 0.63 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.95 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.27

(3H, t, *J* 7.1, OCH_2CH_3), 2.09 (1H, m, $(CH_3)_2CH$), 3.10 (1H, d, *J* 2.8, $(CH_3)_2CHCH$), 3.78 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.96 (1H, d, *J* 14.9, NCH_2ArOMe), 4.10 (1H, d, *J* 14.9, NCH_2ArOMe), 4.19–4.34 (3H, m, OCH_2CH_3 and $NCHCH(Ph)CO_2Et$), 4.74 (1H, d, *J* 14.9, NCH_2ArOMe), 5.00 (1H, d, *J* 3.2, $CHCH(CO_2Et)Ph$), 5.48 (1H, d, *J* 14.9, NCH_2ArOMe), 6.76–6.93 (6H, m, Ar), 7.22–7.35 (7H, m, Ar); δ_C (100 MHz, $CDCl_3$) 14.1, 15.7, 19.8, 31.0, 46.1, 47.4, 51.3, 55.2, 55.3, 60.8, 61.3, 62.8, 114.0, 114.2, 126.9, 126.9, 128.1, 128.4, 129.8, 130.5, 130.7, 132.3, 159.1, 159.5, 164.7, 165.4, 169.9; *m/z* ($APCI^+$) 559 ($[M+H]^+$, 95%), 121 (100).

4.1.3.24. X-ray crystal structure determination for 46. Data were collected using an Enraf–Nonius Mach 3 diffractometer with graphite monochromated Cu radiation using standard procedures at 293 K. The structure was solved by direct methods (SIR97). All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[21]

Crystal data for **46** [$C_{33}H_{38}N_2O_6$]: M=558.67; monoclinic; space group $P1\,21\,1$; a=10.612(2) Å, b=12.349(2) Å, c=12.274(2) Å; β=107.82(2)°; V=1531.4 Å^3; Z=2; μ=0.674 mm^{-1}; colourless plate; crystal dimensions 0.06×0.06×0.6 mm^3. A total of 3271 unique reflections were measured for $22<\theta<42$ and 2710 reflections were used in the refinement. The final parameters were wR_2=0.096 and R_1=0.076 (all data).

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC280789. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.1.3.25. (3*R*,6*S*,2′*R*)-3-*iso*-Propyl-6-(2′-ethylpropanoate)piperazine-2,5-dione 48. Compound **31** (400 mg, 0.81 mmol) was stirred in TFA (5 mL) at reflux for 48 h. The mixture was cooled and excess TFA removed in vacuo. Column chromatography (Al_2O_3; ether/hexane 1:1, followed by ethyl acetate/ethanol 3:1) afforded diketopiperazinedione **48** as a colourless solid (124 mg, 60%); mp 204 °C; $[\alpha]_D^{23}$ +88.5 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1741, 1673; δ_H (400 MHz, MeOH-d_4) 0.98 (3H, d, *J* 6.9, CH_3CHCH_3), 1.07 (3H, d, *J* 7.1, CH_3CHCH_3), 1.23 (3H, d, *J* 7.2, $(EtO_2C)CHCH_3$), 1.30 (3H, t, *J* 7.1, OCH_2CH_3), 2.32 (1H, m, CH_3CHCH_3), 3.23 (1H, dq, *J* 2.6, 7.2, $(EtO_2C)CHCH_3$), 3.87 (1H, dd, *J* 3.3, 0.8, 6-*H*), 4.21 (2H, m, OCH_2CH_3), 4.50 (1H, dd, *J* 2.6, 0.8, 3-*H*), 7.18–7.56 (2H, br s, N*H*); δ_C (100 MHz, MeOH-d_4) 11.9, 14.8, 17.4, 19.2, 34.7, 43.7, 57.2, 61.8, 169.5, 170.1, 175.4; *m/z* (CI^+) 257 ($[M+H]^+$, 40%), 211 (100); HRMS (CI^+) $C_{12}H_{21}N_2O_4^+$ ($[M+H]^+$) requires 257.1506, found 257.1501.

4.1.3.26. (3*R*,6*S*,2′*R*)-3-*iso*-Propyl-2,5-dimethoxy-(2′-ethylpropanoate)-3,6-(2*H*)pyrazine 49. Compound **48** (100 mg, 0.39 mmol) and Me_3OBF_4 (230 mg, 1.56 mmol) were stirred in 1-butyl-3-1*H*-methylimidazolium tetrafluoroborate (4 mL) under vacuum (2 mmHg) at rt for four days. The mixture was then poured into satd $NaHCO_3$ (100 mL) and extracted with ether, the organic phase dried and the solvent removed under vacuum to provide **49** as a clear oil (105 mg, 95%); $[\alpha]_D^{23}$ +27.3 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 1738, 1696; δ_H (400 MHz, $CDCl_3$) 0.70 (3H, d, *J* 6.8, CH_3CHCH_3), 0.90 (3H, d, *J* 6.9, CH_3CHCH_3), 1.04 (3H, d, *J* 6.9, $(EtO_2C)CHCH_3$), 1.28 (3H, t, *J* 7.3, OCH_2CH_3), 2.25 (1H, m, CH_3CHCH_3), 3.05 (1H, dq, *J* 4.0, 6.9, $(EtO_2C)CHCH_3$), 3.63 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.97 (1H, t, *J* 3.4, 3.7 Hz, 6-*H*), 4.20 (2H, q, *J* 7.3, OCH_2CH_3), 4.57 (1H, t, *J* 4.0, 3.7, 3-*H*); δ_C (100 MHz, $CDCl_3$) 9.9, 14.2, 16.6, 19.0, 31.8, 42.2, 52.41, 52.46, 57.3, 60.4, 60.8, 161.9, 164.1, 173.9; *m/z* ($APCI^+$) 285 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{14}H_{25}N_2O_4^+$ ($[M+H]^+$) requires 285.1814, found 285.1822.

4.1.3.27. (2*R*,3*R*)-3-Methyl-aspartic acid 4-ethyl-1-methyl diester 50. Bis-lactim ether **49** (200 mg, 0.70 mmol) was stirred in 0.5 M aq TFA (5 mL) and THF (10 mL) at rt for 24 h then the solvent removed and the resultant oil was loaded onto a short column of silica. Elution (ether/dimethylethylamine 20:1) gave a mixture of **50** and (*S*)-valine methyl ester, which were separated by removal of the (*S*)-valine methyl ester under vacuum (0.5 mmHg, ambient temperature) to give **50** as an oil (104 mg, 76%); $[\alpha]_D^{23}$ −8.6 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 3391, 2980, 1732; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 7.1, $(EtO_2C)CHCH_3$), 1.26 (3H, t, *J* 7.1, OCH_2CH_3), 2.15 (2H, br s, NH_2), 2.96 (1H, m, $(EtO_2C)CHCH_3$), 3.75 (3H, s, CO_2CH_3), 3.97 (1H, br s, $CHNH_2$), 4.17 (2H, q, *J* 7.1, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 11.3, 14.1, 42.7, 52.2, 55.8, 60.9, 174.2; *m/z* ($APCI^+$) 190 ($[M+H]^+$, 100%), 116 (89); HRMS (CI^+) $C_8H_{16}NO_4^+$ ($[M+H]^+$) requires 190.1079, found 190.1082.

The diastereoisomeric excess (>95%) and enantiomeric excess (>98%) of **50** were determined from the ^{19}F NMR spectrum of the Mosher's amide derivative.

4.1.3.28. (3*R*,6*S*,2′*S*)-3-*iso*-Propyl-6-(2′-ethylpropanoate)piperazine-2,5-dione 51. Compound **32** (100 mg, 0.20 mmol) was stirred in TFA (2 mL) at reflux for 48 h. The mixture was cooled and excess TFA removed in vacuo. Column chromatography (Al_2O_3; ether/hexane 1:1, followed by ethyl acetate/ethanol 3:1) afforded diketopiperazinedione **51** as a colourless solid (23 mg, 60%); mp 214 °C; $[\alpha]_D^{23}$ −23.8 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1739, 1664; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 7.0, CH_3CHCH_3), 1.05 (3H, d, *J* 7.0, CH_3CHCH_3), 1.24 (3H, t, *J* 7.2, OCH_2CH_3), 1.29 (3H, d, *J* 7.4, EtO_2CCHCH_3), 2.43 (1H, m, CH_3CHCH_3), 3.11 (1H, dq, *J* 3.4, 7.4, $(EtO_2C)CHCH_3$), 3.91 (1H, s, 6-*H*), 4.14 (2H, q, *J* 7.2, OCH_2CH_3), 4.24 (1H, d, *J* 3.4, 3-*H*), 7.26 (1H, br s, N*H*), 7.57 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 12.2, 14.3, 16.0, 31.8, 42.2, 56.7, 60.1, 61.0, 62.1, 167.7, 168.7, 171.9; *m/z* (CI^+) 257 ($[M+H]^+$, 50%), 211 (100); HRMS (ESI^+) $C_{12}H_2N_2NaO_4^+$ ($[M+Na]^+$) requires 279.1321, found 279.1315.

4.1.3.29. (3*R*,6*S*,2′*R*)-3-*iso*-Propyl-2,5-dimethoxy-(2′-ethylpropanoate)-3,6-(2*H*)pyrazine 52. Compound **51** (100 mg, 0.39 mmol) and Me_3OBF_4 (440 mg, 2.97 mmol) were stirred in 1-butyl-3-1*H*-methylimidazolium tetrafluoroborate (2 mL) under vacuum (2 mmHg) at rt for four days. The mixture was then poured into satd $NaHCO_3$ (100 mL) and extracted with ether, the organic phase dried

and the solvent removed under vacuum to provide **52** as a clear oil (110 mg, 99%); $[\alpha]_D^{23}$ −15.0 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1732, 1698; δ_H (400 MHz, $CDCl_3$) 0.71 (3H, d, *J* 7.0, CH_3CHCH_3), 1.04 (3H, d, *J* 7.0, CH_3CHCH_3), 1.12 (3H, d, *J* 7.1, $(EtO_2C)CHCH_3$), 1.22 (3H, t, *J* 7.2, OCH_2CH_3), 2.26 (1H, m, CH_3CHCH_3), 2.99 (1H, dq, *J* 3.2, 6.8, $(EtO_2C)CHCH_3$), 3.67 (6H, s, $2\times OCH_3$), 3.96 (1H, t, *J* 3.8, 6-*H*), 4.12 (2H, m, OCH_2CH_3), 4.36 (1H, t, *J* 3.2, 3-*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 16.7, 18.9, 20.8, 31.9, 43.4, 52.3, 52.4, 57.9, 60.2, 60.9, 162.0, 164.4, 173.3; *m*/*z* (APCI$^+$) 285 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{14}H_{25}N_2O_4^+$ ([M+H]$^+$) requires 285.1814, found 285.1815.

4.1.3.30. (2*R*,3*S*)-3-methyl-aspartic acid 4-ethyl-1-methyl diester 53. Bis-lactim ether **52** (110 mg, 0.39 mmol) was stirred in 0.5 M aq TFA (5 mL) and THF (10 mL) at rt for 24 h then the solvent removed and the resultant oil was loaded onto a short column of silica. Elution (ether/dimethylethylamine 20:1) gave a mixture of **53** and (*S*)-valine methyl ester, which were separated by removal of the (*S*)-valine methyl ester under vacuum (0.5 mmHg, ambient temperature) to give **53** as an oil (55 mg, 73%); $[\alpha]_D^{23}$ −6.8 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3390, 2979, 1738; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 7.2, $(EtO_2C)CHCH_3$), 1.24 (3H, t, *J* 7.2, OCH_2CH_3), 1.87 (2H, br s, NH_2), 2.95 (1H, dq, *J* 5.2, 7.2, $(EtO_2C)CHCH_3$), 3.60 (1H, d, *J* 5.2, $CHNH_2$), 3.73 (3H, s, OCH_3), 4.15 (2H, m, OCH_2CH_3); δ_C (125 MHz, $CDCl_3$) 13.9, 14.1, 43.5, 53.3, 57.0, 60.7, 173.6, 174.5; *m*/*z* (APCI$^+$) 190 ([M+H]$^+$, 95%) 144 (20), 116 (100); HRMS (CI$^+$) $C_8H_{16}NO_4^+$ ([M+H]$^+$) requires 190.1079, found 190.1081.

The diastereoisomeric excess (>95%) and enantiomeric excess (>98%) of **53** were determined from the ^{19}F NMR spectrum of the Mosher's amide derivative.

Acknowledgements

The authors wish to thank the EPSRC for a ROPA award (A.C.G.), and New College, Oxford for a Junior Research Fellowship (A.D.S.).

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Tetrahedron 62 (2006) 7926–7933

Pd/C–Et_3N-mediated catalytic hydrodechlorination of aromatic chlorides under mild conditions

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Received 27 February 2006; accepted 8 May 2006
Available online 23 June 2006

Abstract—A mild and efficient one-pot procedure for the hydrodechlorination of aromatic chlorides using a Pd/C–Et_3N system was developed. A variety of aromatic chlorides could be dechlorinated at room temperature and under ambient hydrogen pressure. Et_3N activates the catalysis and is likely to work as a single electron donor in this system.

1. Introduction

Much study has been devoted to developing new methods for the dehalogenation of aromatic halides from the synthetic[1] and environmental[2] points of view. It is well-known that aromatic chlorides are much less reactive than aromatic bromides and iodides and hence, the dechlorination of aromatic chlorides cannot readily be achieved.[3] Furthermore, the reduction of some persistent chlorinated aromatic pollutants such as DDT and PCB, which are difficult to degrade, has been a global issue. Therefore, the development of efficient dechlorination methods remains a topic of great interest. The dechlorination of aromatic chlorides is an underdeveloped methodology and few effective methods are available.[4] Existing techniques usually utilize hydride reduction,[5] hydrogenation,[3,6] catalytic transfer hydrogenation with formic acid,[7] formic acid salt,[8] or hydrazine,[9] dechlorination using metals,[10] photolysis,[11] oxidation,[12] electrolysis,[13] or supercritical water oxidation.[14] These reactions mostly require high heat, high pressure, radiation, stoichiometric reagents, vast amounts of catalyst, special equipment, and/or strong basic conditions and most of the reactions are frequently incomplete.

We have reported that addition of a nitrogen-containing base (e.g., NH_3, pyridine, ammonium acetate) to a Pd/C-catalyzed hydrogenation system as a weak catalyst poison chemoselectively inhibited the hydrogenolysis of a benzyl ether with smooth hydrogenation of other reducible functionalities such as olefin, Cbz, benzyl ester, azide, and so on. During the course of our further study on the chemoselective hydrogenation using a variety of Pd/C–amine systems, we found that the use of Et_3N remarkably and selectively enhanced the catalytic activity of Pd/C toward the hydrodechlorination of aromatic chlorides,[15] contrary to our expectation.[16] Kaneda et al. also reported a Pd-hydroxyapatite-catalyzed hydrodechlorination of aryl chlorides in the presence of Et_3N in 2004,[17] although our highly referential communications of hydrodechlorination published in 2002 (Refs. 16 and 18) were not properly cited in their paper. In this paper, we describe more details of the general procedure for the Pd/C-catalyzed hydrodechlorination of aromatic chlorides that operates under ambient hydrogen pressure at room temperature, together with the role of Et_3N in the system.

2. Results and discussion

2.1. General procedure for the Pd/C–Et_3N-mediated hydrodechlorination of aromatic chlorides

A control experiment on the Pd/C-catalyzed hydrodechlorination was performed using 4-chlorobiphenyl **1** as a substrate, which contains no reducible functional groups except an aromatic chloride, to investigate the effect of Et_3N as an additive. The hydrodechlorination of **1** using commercial 10% Pd/C (3% of the weight of **1**) and 1.2 equiv of Et_3N in MeOH was smoothly completed within 1 h under ambient hydrogen pressure (balloon) at room temperature to afford biphenyl **2** in 100% conversion yield (GC/MS) and triethylammonium chloride, whereas the dechlorination was incomplete even after 3 days when the reaction was carried out without Et_3N (Fig. 1 and Scheme 1).

To optimize the reaction conditions, a variety of nitrogen-containing bases were investigated (Table 1). The reaction was carried out under ordinary hydrogen pressure (balloon)

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doi:10.1016/j.tet.2006.05.025

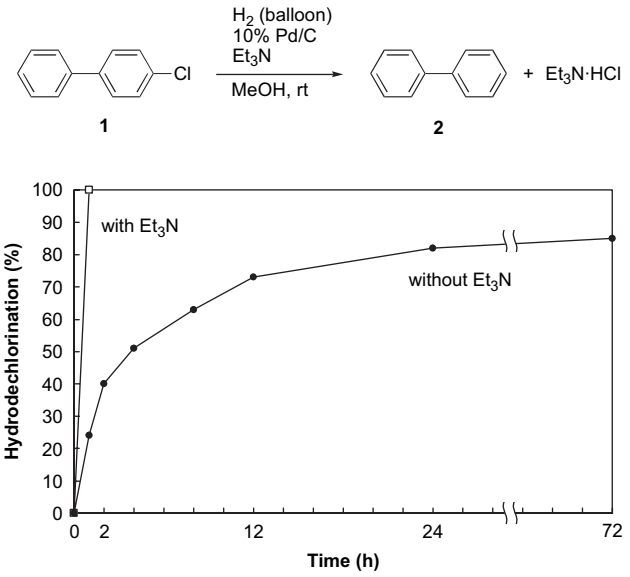


Figure 1. Kinetics plots on the hydrodechlorination of **1** using 10% Pd/C (3% of the weight of **1**) with or without Et_3N (1.2 equiv) in MeOH under ambient hydrogen pressure at room temperature.

using 1.2 equiv of an additive and 10% Pd/C (3% of the weight of **1**) in MeOH at room temperature for 1 h and the products were analyzed by GC/MS and ^1H NMR after simple extraction. Entries 3–10 in Table 1 indicate that the addition of relatively lipophilic amines greatly enhanced the efficiency of the reaction compared with the less lipophilic NH_3 or ethylendiamine (entries 2 and 11). In addition, the amines, which have aromatic substituents such as aniline and *N*,*N*-diethylaniline were effective additives (entries 9 and 10), whereas the aromatized heterocyclic bases such as pyridine or quinoline strongly suppressed the hydrodechlorination and no reaction was observed (entries 12 and 13). The addition of NaOH, an inorganic base, was also effective for the completion of the reaction (entry 15), although concern that the strong basicity and nucleophilicity of NaOH would narrow the applicability of this method excluded NaOH from the candidates.

Table 1. Assessment of bases in the dechlorination of 4-chlorobiphenyl (**1**)[a]

Entry	Additive	Yield of **2** (%)[b]
1	None	24
2	NH_3	67
3	Me_2NH	100
4	Me_3N	100
5	Et_3N	100
6	*i*-Pr_2NEt	100
7	*i*-Pr_3N	100
8	DBU	100
9	$PhNH_2$	100
10	$PhNEt_2$	100
11	$H_2N(CH_2)_2NH_2$	94
12	Pyridine	0
13	Quinoline	0
14	NaOH	100
15	NaOAc	10
16	$Et_3N·HCl$	17

[a] All reactions were carried out under ordinary hydrogen pressure (balloon) using 1.2 equiv of additive and 10% Pd/C (3% of the weight of **1**) in MeOH at room temperature for 1 h.
[b] Yields were determined by GC/MS.

Among the nitrogen-containing bases, which worked well for the hydrodechlorination of **1**, Et_3N was selected as the best candidate for its cost-efficiency and its non-nucleophilicity.

The results of optimization of the solvent for the hydrodechlorination of aromatic chlorides are listed in Table 2. The use of an alcoholic solvent led to the completion of the reaction within an hour (entries 1, 3, and 4). When the reaction in such alcoholic solvent was carried out without hydrogen, no conversion to **2** was observed (entries 2 and 5) indicating that the hydrogen atom of alcoholic solvents cannot be a hydrogen source and hydrogen gas is indispensable for the hydrodechlorination system as a hydrogen donor. Using hexane as a solvent caused difficult stirring of the reaction mixture due to the poor solubility of the resulting $Et_3N·HCl$ accompanied by the reaction progress (entry 8). When H_2O was used as a solvent, no reaction took place since H_2O could not dissolve **1** at all. Therefore, MeOH was chosen as a solvent for the hydrodechlorination.

The use of 10% Pd/C with more than 3% weight of **1** accomplished completion of the hydrodechlorination of **1**, although the reduction in weight of the catalyst to 1% weight of **1** resulted in incompletion of the reaction even after 24 h (Table 3, entries 1 and 2). The hydrodechlorination smoothly took place even under dark conditions (entry 3). Lowering the reaction temperature led to drastic decrease of the reaction efficiency (entry 4) and surprisingly, entirely no reaction was observed under reflux conditions (Table 3, entry 5). Detailed optimization of the reaction conditions eventually revealed that treatment of the methanol solution of **1** with 10% Pd/C

Table 2. Assessment of solvents in the dechlorination of **1**[a]

Entry	Solvent	Yield of **2** (%)[b]
1	MeOH	100
2[c]	MeOH	0
3	EtOH	100
4	*i*-PrOH	100
5[c]	*i*-PrOH	0
6	DMF	3
7	THF	43
8	Hexane	63
9	H_2O	0

[a] Reactions were carried out under ordinary hydrogen pressure (balloon) using 1.2 equiv of Et_3N and 10% Pd/C (3% of the weight of **1**) in a solvent at room temperature for 1 h.
[b] Yields were determined by GC/MS.
[c] Reaction was performed without hydrogen.

Table 3. Assessment of amount of 10% Pd/C and temperature in the dechlorination of **1**[a]

Entry	Amount of Pd/C[b]	Temperature	Yield of **2** (%)[c]
1	3 wt %	rt	100
2[d]	1 wt %	rt	98
3[e]	3 wt %	rt	100
4	3 wt %	−20 °C	4
5	3 wt %	Reflux	0

[a] Reactions were carried out under ordinary hydrogen pressure (balloon) using 1.2 equiv of Et_3N and 10% Pd/C in MeOH for 1 h.
[b] Amount of 10% Pd/C toward the weight of **1**.
[c] Yields were determined by GC/MS.
[d] The reaction was carried out for 24 h.
[e] Under dark conditions.

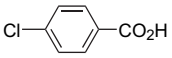
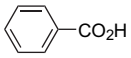
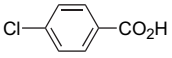
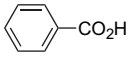
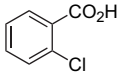
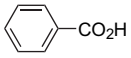
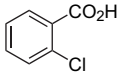
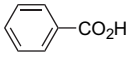
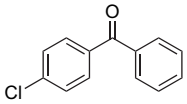
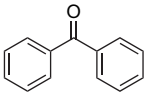
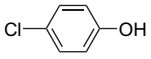
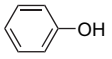
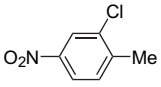
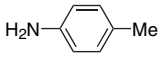
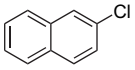
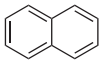
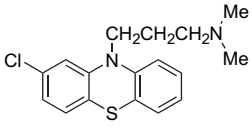
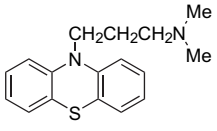
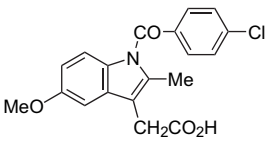
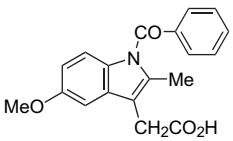
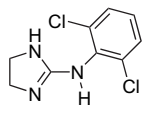
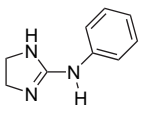
(more than 3% of the weight of **1**) and Et_3N (1.2 equiv) at room temperature under ordinary hydrogen pressure (balloon) is the best reaction conditions for the present hydrodechlorination.

To explore the scope of this method, the hydrodechlorination of a variety of aromatic chlorides was investigated (Table 4). The results shown in entries 1, 3, and 6 demonstrated that the reaction could be carried out in the presence of carboxylic acid and phenolic functionalities in the substrates. Absence of Et_3N in the reaction mixture diminished the efficiency of the hydrodechlorination (entries 2 and 4). Competitive reduction of the nitro moiety of 2-chloro-4-nitrotoluene was observed and 4-toluidine was isolated as the sole product (entry 7), while the aromatic ketone moiety of 4-chlorobenzophenone remained intact and the corresponding benzophenone was quantitatively generated (entry 5). In addition, some medicines (entries 9–15) were efficiently dechlorinated, although prolonged reaction time was required. In the hydrodechlorination of furosemide, the furan ring was competitively reduced to the corresponding tetrahydrofuran ring (entry 15).

2.2. Mechanism analysis of the Pd/C–Et_3N-mediated hydrodechlorination of aromatic chlorides

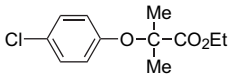
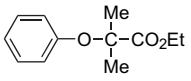
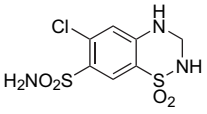
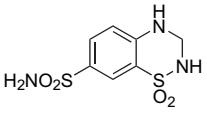
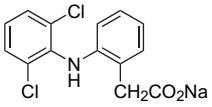
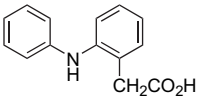
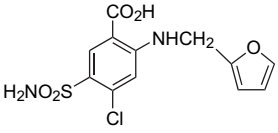
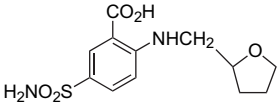
We demonstrated that the efficiency of the hydrodechlorination was greatly affected by the nature of amine. The use of

Table 4. Ten percent Pd/C–Et_3N-mediated dechlorination of aromatic chlorides[a]

Entry	ArCl	Time (h)	Product	Yield (%)[b]
1		6		100 (99)
2[c]		6		50
3		3		100 (100)
4[c]		3		60
5		1		100 (65)
6		3		100 (92)
7		2		100 (90)
8		1		100 (51)[d]
9[e]	 Chlorpromazine	24		100
10	 Indometacin	25		100 (44)
11[e]	 Clonidine	16		100

(*continued*)

Table 4. (*continued*)

Entry	ArCl	Time (h)	Product	Yield (%)[b]
12	 Clofibrate	27		100 (71)
13	 Hydrochlorothiazide	22		100 (85)[f]
14[e]	 Dicrofenac sodium salt	22		100
15[e]	 Furosemide	6		100

[a] Reactions were carried out under ordinary hydrogen pressure (balloon) using Et_3N (1.2 equiv vs the number of chlorine atoms) and 10% Pd/C (3% of the weight of ArCl) in MeOH (ca. 1% solution of ArCl) at room temperature.
[b] Yields were determined by GC/MS and the isolated yields are indicated in parentheses. Hundred percent yield implied that no other products were detected by GC/MS.
[c] The reaction was carried out without Et_3N.
[d] The low isolated yield of the product is due to the low boiling point and volatile nature.
[e] The reaction was carried out using 10% Pd/C with 10% of the weight of ArCl.
[f] Product was contaminated with 10% of $Et_3N\cdot HCl$.

aliphatic amines led to excellent conversion to the corresponding dechlorinated product, whereas the use of aromatized heterocyclic bases led to the complete recovery of the chlorinated starting material. As shown in entry 16 in Table 1, the presence of $Et_3N\cdot HCl$ in the reaction mixture seemed to delay the reaction rate rather than not to affect it in comparison with the absence of any additives (Table 1, entry 1). These results led us to presume that Et_3N does not work just for the removal of the generated HCl, which is suspected as a catalyst poison.

It is well-known that hydrogen chloride, which is generated during the Pd/C-catalyzed hydrodechlorination of aromatic chlorides decreases the efficiency of the reaction.[19] On the contrary, Angel and Benitez showed that the reaction rate of the hydrodechlorination of chlorobenezene in HCl media was boosted using their homemade Pd/C.[6h] To investigate the role of Et_3N in our system, we, first, studied the effect of HCl on the Pd/C-catalyzed hydrodechlorination of 4-chlorobiphenyl (**1**). As shown in Figure 2, HCl dose-dependently impeded the reaction progress. In each case, the hydrodechlorination started with a certain reaction rate, although the reaction rate gradually decreased as the reaction proceeded and eventually reached a plateau. These results suggest that Pd/C was time-dependently poisoned by the exposure to HCl. Furthermore, after pre-stirring of 10% Pd/C in the presence of HCl (1.2 equiv of **1**) in MeOH under hydrogen (balloon) at room temperature for 24 h, no hydrodechlorination of **1** was observed (Table 5, entry 2). On the other hand, the 1-h stirring of **1** under hydrogen atmosphere with the 10% Pd/C that was pre-treated without HCl afforded **2** in 12% yield (Table 5, entry 1). These results prove that HCl, which forms during the hydrodechlorination, time-dependently poisoned the commercial 10% Pd/C. Similar reaction conditions using $Et_3N\cdot HCl$ as an additive in place of HCl led to no hydrodechlorination of **1** (Table 5, entry 3). This result indicates that $Et_3N\cdot HCl$, which forms by neutralization of HCl generated from the reaction mixture, also

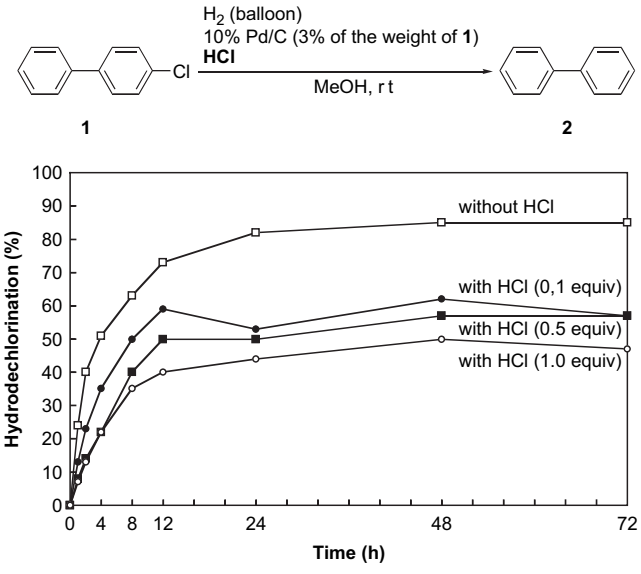
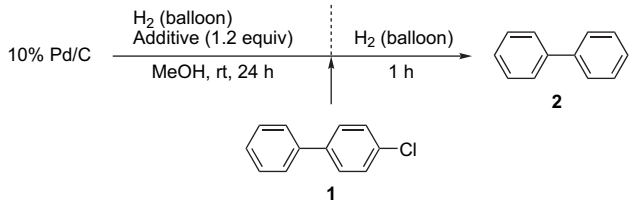


Figure 2. The effect of HCl on the hydrodechlorination of **1**.

Table 5. The effect of HCl and $Et_3N \cdot HCl$ on the hydrodechlorination of **1**[a]



Entry	Additive	Conversion (%)[b]
1	None	12
2	HCl	0
3	$Et_3N \cdot HCl$	0

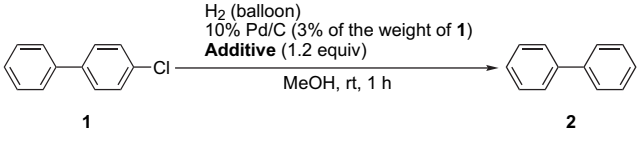
[a] All reactions were carried out by stirring 10% Pd/C (3% of the weight of **1**) with 1.2 equiv of additive in MeOH under ordinary hydrogen pressure (balloon) at room temperature for 24 h followed by the addition of **1**, reintroduction of hydrogen (balloon), and stirring the mixture for 1 h.
[b] Yields were determined by GC/MS.

suppresses the catalyst activity of Pd/C. It, therefore, seems sure that the great acceleration of the hydrodechlorination of aromatic chlorides by the addition of a certain amine is not achieved by just neutralization of HCl with the amine.

We described that the addition of pyridine or quinoline instead of Et_3N completely blocked the hydrodechlorination (Table 1, entries 12 and 13 or Table 6, entries 2 and 3). Furthermore, addition of either pyridine or quinoline to the Pd/C–Et_3N system suppressed the hydrodechlorination efficiency (Table 6, entries 4 and 5), and no reaction was observed when quinoline was added to the reaction mixture (entry 5). There is little doubt that Et_3N is not only an HCl scavenger but also plays some vital role as a strong accelerator in the Pd/C-catalyzed hydrodechlorination process. Moreover, addition of TCNE (tetracyanoethylene) or TCNQ (7,7,8,8-tetracyanoquinodimethane), a single electron capture, to the hydrodechlorination reaction mixture in the presence of Et_3N thoroughly suppressed the reaction (entries 6 and 7), suggesting the participation of a single electron transfer (SET) mechanism in the simple catalytic process.

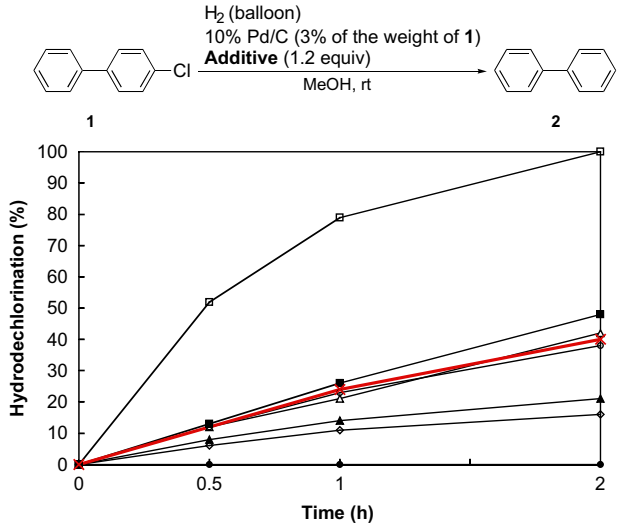
Et_3N has been reported as an initiator (single electron donor) of the photochemical dechlorination of aryl chlorides.[11a–f] It seems reasonable to consider that an SET from aliphatic amines such as Et_3N to aromatic chlorides initiated the hydrodechlorination in our system and each pyridine or quinoline may have worked as an electron acceptor to inhibit the electron transfer to aromatic chlorides. Hydrodechlorination of **1** using pyridine or a variety of substituted pyridines as an additive was investigated (Fig. 3): (1) use of 2-methyl- or 4-methylpyridine caused very sluggish hydrodechlorination of **1**, although use of pyridine caused no hydrodechlorination; (2) use of 2,6-dimethylpyridine, 4-methoxypyridine, or 4-*tert*-butylpyridine allowed the reaction to proceed at a rate similar to that of the reaction without additives; (3) the addition of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) expedited the reaction to completion. Tabner and Yandle reported the half-wave potentials ($E_{1/2}$) of a series of nitrogen-containing heterocyclic compounds in DMF: the potentials of quinoline, pyridine, 2-methylpyridine, 4-methylpyridine, and 2,6-dimethylpyridine are −2.18, −2.76, −2.80, −2.86, and −2.85 V [vs a saturated calomel electrode (SCE)], respectively.[20] The $E_{1/2}$ of 4-chlorobiphenyl (**1**) in DMF was also reported to be −2.37 V (vs SCE).[13b] The $E_{1/2}$ of quinoline is much greater than that of **1**, while the potentials of pyridine analogs are lower than that of **1** and are very close. It is, therefore, reasonable to think quinoline accepted an electron exclusively from Pd(0) or Et_3N to block the hydrodechlorination of **1** (Table 6, entries 3 and 5).[21] On the contrary, both the comparison between pyridines and **1** and the similarity of pyridines in $E_{1/2}$ seem to make it difficult to explain our results in Figure 3 with a simple SET mechanism. We reported that less sterically hindered pyridine inhibited more the hydrogenolysis of aliphatic benzyl ethers[22] and these results suggested some interaction, possibly complexation, between pyridines and palladium metal delayed the reaction rate. Combining the substituent effect on the pyridine ring as a catalyst poison with the SET mechanism, the results in Figure 3 could be rationally explained: (1) pyridine interacted with palladium metal to block the hydrogenation and even in the presence of Et_3N as an additive (the deactivation of catalysis was observed, Table 6, entry 1 vs entry 4); (2) mono-substituted pyridines such as 2-methyl- and

Table 6. The effect of additional additive on the hydrodechlorination of **1**[a]



Entry	Additive	Yield of **2** (%)[b]
1	Et_3N	100
2	Pyridine	0
3	Quinoline	0
4	Et_3N+pyridine	90
5	Et_3N+quinoline	0
6	Et_3N+TCNE	0
7	Et_3N+TCNQ	0

[a] All reactions were carried out under ordinary hydrogen pressure (balloon) using 1.2 equiv of additive and 10% Pd/C (3% of the weight of **1**) in MeOH at room temperature for 1 h.
[b] Yields were determined by GC/MS.

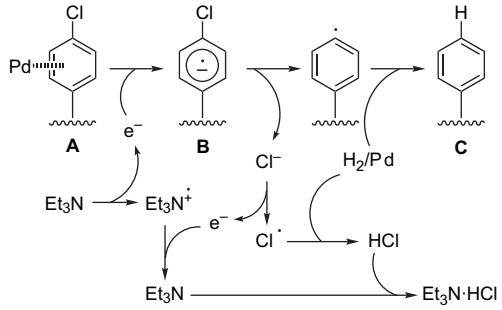


pyridine (●), 2-methylpyridine (◇), 4-methylpyridine (▲), 2,6-dimethylpyridine (○), 4-methoxypyridine (△), 4-*tert*-butylpyridine (■), DTBMP (□), without additive (×)

Figure 3. The effect of substituted pyridine as an additive on the hydrodechlorination of **1**.

4-methylpyridines could interact with palladium metal and deactivated Pd/C less than pyridine; (3) bulky pyridines such as 2,6-dimethylpyridine, 4-methoxypyridine, and 4-*tert*-butylpuridine were hard to interact with palladium metal and did not interfere in the catalyst activity for the hydrodechlorination; (4) the bulkiest DTBMP never interacts with palladium metal, but acts as an electron donor, as well as Et_3N.

These experimental results suggest that an SET mechanism is involved in the dechlorination using the Pd/C–Et_3N system (Scheme 1). Initial single electron transfer from Et_3N to the palladium-activated chlorobenzene ring of **A** affords an anion radical **B**, which then could be converted to the dechlorinated benzene ring of **C** by the elimination of the chloride anion and subsequent hydrogenation of the corresponding benzene radical.



Scheme 1. Proposed mechanism of the hydrodechlorination of aromatic chlorides.

3. Conclusion

We have developed a mild and efficient one-pot method for the hydrodechlorination of aromatic chlorides that proceeds at room temperature and under ordinary hydrogen pressure. The presence of Et_3N is crucial for the reaction and Et_3N works not only as a scavenger of hydrogen chloride but also as an electron donor to expedite the reaction. The reaction is general for a variety of aromatic chlorides. The simplicity and reliability of this method make it an attractive tool for organic and environmental chemists.

4. Experimental[23]

4.1. General

Pd/C (10%) was purchased from Sigma–Aldrich (cat. no. 205699) and Et_3N was purchased from Wako Pure Chemical Industries, Ltd. Analytical thin-layer chromatography (TLC) was carried out on pre-coated Silica Gel 60 F_{254} plates (Merck, Art 5715) and visualized with UV light. Column chromatography was accomplished using Merck Silica Gel 60 (230–400 mesh). For reversed phase column chromatography Waters Sep-Pak® C_{18} cartridge was used. ^1H NMR spectra were recorded on a JOEL JNM EX-400 NMR spectrometer (400 MHz). Chemical shifts (δ) are expressed in parts per million and are internally referenced (0.00 ppm for tetramethylsilane—$CDCl_3$, 4.79 ppm for D_2O, or 3.31 ppm for CD_3OD). Mass spectra and high-resolution mass spectra were taken on a JMS-SX 102A spectrometer at the Mass Spectrometry Laboratory at Gifu Pharmaceutical University.

4.2. General procedure (Fig. 1)

After two vaccum/H_2 cycles to remove air from a round-bottom flask, a suspension of 4-chlorobiphenyl (100 mg, 0.53 mmol), 10% Pd/C (3.0 mg), and Et_3N (89 μL, 0.64 mmol) in MeOH (10 mL) was vigorously stirred using a stir bar under hydrogen atmosphere (balloon) at ambient temperature (ca. 20 °C). At a given time point, the reaction mixture (1 mL) was sampled using a syringe, filtered through a 0.2-μL Millipore membrane filter (Millipore), and concentrated in vacuo. The residue was partitioned between hexanes (10 mL) and H_2O (10 mL) and the organic layer was washed with brine (10 mL), dried ($MgSO_4$), and filtered. An aliquot (1 mL) was taken from the filtrate, diluted with hexanes (19 mL), and analyzed by a Hewlett Packard 5891 series II gas chromatograph equipped with a Hewlett Packard 5972 mass-selective detector (Hewlett Packard) and a Neutrabond-5 capillary column (30 m×0.25 m, 0.4 μm film thickness; GL Science). Helium was employed as carrier gas with a flow rate of 1.0 mL/min. Injector and detector temperatures were 230 and 250 °C, respectively. The column temperature was programmed to ramp from 150 °C (5 min hold) to 250 °C (3 min hold) at a rate of 5 °C/min. The retention times of 4-chlorobiphenyl and biphenyl were 8.86 min and 4.81 min, respectively. The products were identified by their retention times on GC/MS or their ^1H NMR spectra in comparison with those of commercial authentic samples.

4.2.1. Optimization of base for the hydrodechlorination of 4-chlorobiphenyl (1) (Table 1). According to the general procedure, the reaction was carried out for 1 h using another base in place of Et_3N. The reaction mixture was filtered through a 0.2-μL Millipore membrane filter and concentrated in vacuo. The residue was partitioned between hexanes (10 mL) and H_2O (10 mL) and the organic layer was washed with brine (10 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo. An aliquot (1 mg) was taken from the residue, dissolved in hexanes (20 mL), and analyzed as described in Section 4.2.

4.2.2. Optimization of solvent for the hydrodechlorination of 1 (Table 2). According to the general procedure, the reaction was carried out for 1 h using another solvent in place of MeOH. The reaction mixture was treated and analyzed in the same manner as described in Table 1.

4.2.3. Optimization of amount of Pd/C and temperature for the hydrodechlorination of 1 (Table 3). According to the general procedure, the reaction was carried out for 24 h using 1 mg of 10% Pd/C (1% weight of **1**) in place of 3 mg of 10% Pd/C or the reaction was carried out for 1 h at −20 °C or reflux in place of room temperature. Aluminum foil was used for the reaction under dark conditions. The reaction mixture was treated and analyzed in the same manner as described in Table 1.

4.3. Hydrodechlorination of aromatic chlorides (Table 4)

According to the general procedure, the reaction was carried out using 100 mg of a substrate. After the starting chloride

disappeared, the reaction mixture was filtered through a 0.2-μL Millipore membrane filter and concentrated in vacuo. The residue was partitioned between Et_2O (10 mL) and H_2O (10 mL) and the organic layer was washed with brine (10 mL), dried ($MgSO_4$), and filtered. If necessary, the residue was purified by silica gel column chromatography or reversed phase column chromatography.

4.3.1. 10-[3-(Dimethylamino)propyl]phenothiazine [CAS Registry Number 58-40-2] (entry 9).[24] ^{1}H NMR ($CDCl_3$) δ 2.19 (5H, m), 2.42 (6H, s), 2.76 (2H, t, J=6.4 Hz), 4.00 (2H, t, J=6.4 Hz), 6.89–6.96 (4H, m), 7.17 (4H, m); MS (EI) m/z 284 (M^+), 58 (83), 198 (45), 238 (42), 284 (100); HRMS (EI) Calcd for $C_{17}H_{20}N_2S$ (M^+) 284.1347; Found 284.1356.

4.3.2. 1-Benzoyl-5-methoxy-2-methylindole-3-acetic acid [CAS Registry Number 1601-19-0] (entry 10).[25] ^{1}H NMR ($CDCl_3$) δ 2.38 (3H, s), 3.71 (2H, s), 3.83 (3H, s), 6.65 (1H, d, J=9.3 Hz), 6.87 (1H, d, J=9.3 Hz), 6.95 (1H, s), 7.49 (2H, t, J=7.6 Hz), 7.62 (1H, t, J=7.6 Hz), 7.70 (2H, d, J=7.6 Hz); MS (EI) m/z 357 (M^+), 77 (61), 105 (100), 158 (25), 323 (76); HRMS (EI) Calcd for $C_{19}H_{17}NO_4$ (M^+) 323.1158; Found 323.1146.

4.3.3. 2-(Phenylamino)imidazoline [CAS Registry Number 1848-75-5] (entry 11).[26] ^{1}H NMR (D_2O) δ 3.62 (4H, s), 7.18 (2H, s), 7.26 (1H, t, J=7.3 Hz), 7.36 (2H, t, J=7.3 Hz); MS (EI) m/z 161 (M^+), 77 (29), 104 (33), 160 (40); HRMS (EI) Calcd for $C_9H_{11}N_3$ (M^+) 161.0953; Found 161.0949.

4.3.4. Ethyl 2-methyl-2-phenoxypropanoate [CAS Registry Number 18672-04-3] (entry 12).[27] ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J=7.1 Hz), 1.60 (6H, s), 4.23 (2H, q, J=7.1 Hz), 6.84 (2H, d, J=8.0 Hz), 6.98 (1H, t, J=8.0 Hz), 7.24 (2H, t, J=8.0 Hz); MS (EI) m/z 208 (M^+), 77 (18), 94 (100), 135 (54); HRMS (EI) Calcd for $C_{12}H_{16}O_3$ (M^+) 208.1099; Found 208.1101.

4.3.5. 7-Sulfamoyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide [CAS Registry Number 23141-82-4] (entry 13).[28] ^{1}H NMR (CD_3OD) δ 3.46 (2H, s), 4.89 (2H, s), 7.01 (1H, d, J=8.9 Hz), 7.85 (1H, d, J=8.9 Hz), 8.14 (1H, s); MS (EI) m/z 263 (M^+), 171 (58), 187 (36); HRMS (EI) Calcd for $C_7H_9N_3O_4S_2$ (M^+) 263.0034; Found 263.0038.

4.3.6. 2-(Phenylamino)benzeneacetic acid [CAS Registry Number 70172-33-7] (entry 14).[29] ^{1}H NMR (CD_3OD) δ 3.53 (2H, s), 6.70 (1H, t, J=7.6 Hz), 6.77 (2H, d, J=7.6 Hz), 6.87 (1H, t, J=7.6 Hz), 7.05–7.10 (3H, m), 7.13–7.17 (2H, m); MS (EI) m/z 227 (M^+), 167 (10), 180 (100), 209 (54); HRMS (EI) Calcd for $C_{14}H_{13}NO_2$ (M^+) 227.0946; Found 227.0956.

4.3.7. 5-Sulfamoyl-*N*-(tetrahydrofurfuryl)anthranilic acid [CAS Registry Number 4818-84-2] (entry 15).[30] ^{1}H NMR (CD_3OD) δ 1.80–1.93 (1H, m), 1.99–2.10 (2H, m), 3.42–3.49 (2H, m), 3.86 (1H, m), 4.01 (1H, m), 4.23 (1H, m), 6.86 (1H, d, J=8.8 Hz), 7.81 (1H, d, J=8.8 Hz), 8.51 (1H, s); MS (EI) m/z 300 (M^+), 71 (57), 81 (73), 211 (100), 229 (42); HRMS (EI) Calcd for $C_{12}H_{16}N_2O_5S$ (M^+) 300.0780; Found 300.0785.

4.4. Hydrodechlorination of 1 in the presence of HCl (Fig. 2)

According to the general procedure, the reaction was carried out using 0.1 M HCl in MeOH (0, 0.1, 0.5, or 1.0 equiv) in place of Et_3N and analyzed.

4.5. Hydrogenation of 1 after pre-treatment of Pd/C with additive (Table 5)

A suspension of 10% Pd/C (3 mg) and an additive (0.64 mmol) was stirred under hydrogen (balloon) for 24 h. 4-Chlorobiphenyl (100 mg, 0.53 mmol) was added and the mixture was stirred under hydrogen (balloon) for 1 h. The reaction mixture was treated and analyzed in the same manner as described in Table 1.

4.6. Hydrogenation of 1 in the presence of Et_3N and an additional additive (Table 6)

According to the general procedure, the reaction was carried out for 1 h in the presence of Et_3N (89 μL, 0.64 mmol) and an additive (0.64 mmol). The reaction mixture was treated and analyzed in the same manner as described in Table 1.

4.7. Hydrogenation of 1 in the presence of pyridine analog (Fig. 3)

According to the general procedure, the reaction was carried out using a substituted pyridine (0.64 mmol) in place of Et_3N and analyzed.

Acknowledgements

We thank N. E. Chemcat Corp. for the Pd leaching assay. This work was supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of the Japanese Government (No. 13672222), the Research Foundation for Pharmaceutical Sciences, and the Research Foundation for the Electrotechnology of Chubu.

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Tetrahedron 62 (2006) 7934–7939
Tetrahedron

Synthesis of (9*E*)-isoambrettolide, a macrocyclic musk compound, using the effective lactonization promoted by symmetric benzoic anhydrides with basic catalysts

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Received 8 February 2006; revised 14 April 2006; accepted 20 April 2006
Available online 15 June 2006

Abstract—Two alternative methods for the synthesis of (9*E*)-isoambrettolide are established via the rapid lactonization of the free *threo*-aleuritic acid or its protected seco-acid using substituted benzoic anhydrides with basic catalysts. The most efficient lactonization of the *threo*-aleuritic acid is performed using 2-methyl-6-nitrobenzoic anhydride (MNBA) with a catalytic amount of 4-dimethylaminopyridine *N*-oxide (DMAPO).

1. Introduction

Macrocyclic compounds, such as (−)-muscone (**1**), the key odorous component of musk, and civetone (**2**), the key odorous component of civet, have a typical animal-like musk odor (Fig. 1).[1,2] From ancient times, musk obtained from the scent gland of the male musk-deer, *Moschus moschiferus*, and civet obtained from the scent glands of the male and female musk-cat, *Viverra civetta* L, had been used for many famous perfumes as the most important fragrance raw material. However, the supply of these rare natural raw materials has recently become extremely short and difficult due to them being on the endangered species list and their unusual breeding methods. Therefore, the development of practical methods for the syntheses of musk compounds, such as (−)-muscone (**1**)[3] and civetone (**2**),[4] is an important subject in perfume chemistry.

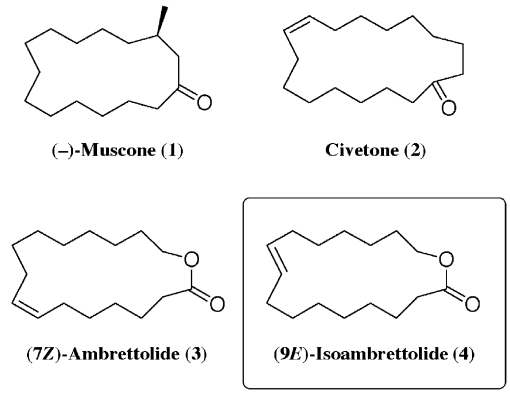

Figure 1. Some macrocyclic perfumed molecules.

On the other hand, some vegetable oils, such as ambrette seed oil, also have a musk-like odor[5] and are frequently used as valuable fragrance raw materials. Interestingly, the odorous key component of the ambrette seed, *Hibiscus abelmochus* L, is a 17-membered ring lactone, (7*Z*)-ambrettolide (**3**),[6] which has an elegant musk odor. Furthermore, (9*E*)-isoambrettolide (**4**) is now a very attractive artificial substrate as an alternative musk resource, and several methods for the synthesis of **4** have been reported.[7–10]

In 1972, Mookherjee reported a protocol for providing macrocyclic lactones involving **4** from cyclohexadeca-l,9-diene via a successive double-epoxidation, non-selective epoxy-opening reduction, Baeyer–Villiger oxidation and dehydration.[7] Although this process gives **4** in only five steps from the starting material, extraction of the desired **4** from the mixture of several isomeric products requires complicated operations and the total yield of the targeted molecule is not sufficient for the industrial production of **4**.

Independently, Bhattacharyya et al.[8] and Tseng[9] developed original methods for the production of **4** starting from

Keywords: (9*E*)-Isoambrettolide; Macrocyclic musk; Lactonization; Benzoic anhydride; MNBA; DMAPO.
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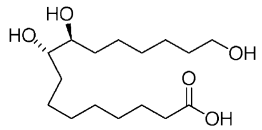
doi:10.1016/j.tet.2006.04.077



threo-Aleuritic acid (**5**)

Figure 2. *threo*-Aleuritic acid (**5**), a naturally occurring trihydroxycarboxylic acid.

threo-aleuritic acid (**5**, depicted in Fig. 2),[11] a major ingredient of the natural shellac produced by *Laccifer lacca*.

In the former case, **5** was first converted to the corresponding tribromide by the substitution of all the hydroxyl groups. Successive reductive double-bond formation of the vicinal dibromide part, hydroxylation of the resulting primary bromide and saponification of the ester moiety produced the intermediate seco-acid. Finally, the non-chemoselective polymerization of the seco-acid using a traditional dehydration condensation method and distillation of the monomeric lactone from the mixture under depolymerization conditions formed **4** in moderate yield. In the latter one, a dioxolane derivative was first prepared from **5** using acidic transacetalization, and the intermediate was then transformed into the corresponding *cis*-olefin by pyrolysis under severe conditions. Finally, consecutive trans-polymerization and depolymerization procedures at high temperature with potassium hydroxide were repeated several times under reduced pressure to afford the desired monomeric lactone **4** in moderate yield.

Furthermore, Villemin developed an improved method for the preparation of **4** by thermolysis of a mixed *N*,*O*-orthoester generated from **5**, followed by polymerization and depolymerization techniques.[10] In this procedure, the desired monomeric lactone **4** was first obtained in 35% yield from the reaction mixture by distillation, and then 30% of **4** was additionally generated from the polymeric mixture by the second thermo-depolymerizing operation.

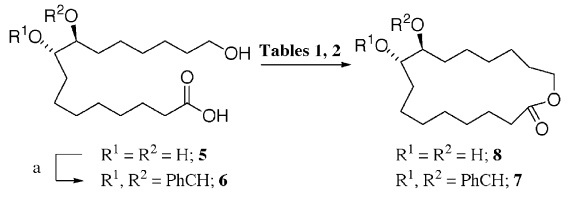
Because very severe conditions and inefficient stepwise procedures were required for the preparation of **4** in the successive polymerization and depolymerization process, it is desirable to develop more effective and facile methods for the synthesis of the monomeric lactone **4** from the corresponding seco-acids.

Recently, we developed a new and rapid lactonization of ω-hydroxycarboxylic acids using symmetric substituted benzoic anhydrides such as 2-methyl-6-nitrobenzoic anhydride (MNBA) as a condensation reagent.[12,3dd] This protocol could be performed by a very simple procedure, and the desired lactones are obtained within a very short time under mild conditions since the reaction quickly proceeds by the promotion of a catalytic amount of basic catalysts such as DMAP or its *N*-oxide (DMAPO). In this paper, we now report a simple method for the synthesis of (9*E*)-isoambrettolide (**4**) from *threo*-aleuritic acid (**5**) using an effective lactonization protocol accelerated by symmetric benzoic anhydrides, as a part of our continuous efforts for the application of the new synthetic methodology to produce useful lactones.[12,13]

2. Results and discussion

2.1. Lactonization of protected seco-acid

The two possible alternative pathways for producing **4** from **5** are as follows (Scheme 1): (i) masking the vicinal dihydroxy unit in **5** with cyclic protective groups, followed by lactonization and successive conversion of the bicyclic compound to the final targeted compound **4**, or (ii) the direct lactonization of trihydroxycarboxylic acid **5** to produce the corresponding dihydroxylactone **8**, a potential intermediate of the lactone **4**, by our effective monomer-selective cyclization using symmetric benzoic anhydrides.



Scheme 1. Reagents and conditions: (a) $PhCH(OMe)_2$, CSA, DMF, 60 °C (66%).

We initially attempted the preparation of the protected lactone **7** via the seco-acid **6** prepared from **5** by treatment with $PhCH(OMe)_2$ and 10-camphorsulfonic acid (CSA). First, optimization of the reaction conditions was carried out for the lactonization of **6** as shown in Table 1. When a solution of **6** in dichloromethane was slowly added to the reaction mixture of 1.2 equiv of MNBA and 2.4 equiv of DMAP in dichloromethane over a 16.5 h period at room temperature, the corresponding monomeric lactone **7** was obtained in 84% yield along with 7% of the dimeric lactide (Entry 1). Further examination to decrease the amount of DMAP to 20 mol% with the use of an excess amount of triethylamine afforded a lower yield of the desired monomer (59%), although the yield of the undesired dimeric compound increased to 21% (Entry 2). On the other hand, when DMAPO, a novel powerful basic catalyst, was employed in Entry 3, the yield of the monomer dramatically increased and reached 77%. The difference between these two reactions indicates that the combination of MNBA and DMAPO is more efficient than that of MNBA and DMAP. Careful monitoring of the reaction mixture by the TLC analysis showed that the rate of the cyclization using DMAPO is apparently faster compared with that using DMAP, therefore, the chemical yields of the lactones and the product-selectivity of the monomer to dimer might be improved in the DMAPO-catalyzed reaction system.

Table 1. Synthesis of 17-membered ring lactone **7** from protected seco-acid **6** using MNBA

Entry	Dehydrating agent	Base	Yield/%	
			Monomer	Dimer
1	MNBA	DMAP (2.4 equiv)	84	7
2	MNBA	DMAP (0.2 equiv), Et_3N (2.2 equiv)	59	21
3	MNBA	DMAPO (0.2 equiv), Et_3N (2.2 equiv)	77	10
4	$(PhCO)_2O$	DMAP (2.4 equiv)	79	10
5	$(PhCO)_2O$	DMAPO (0.2 equiv), Et_3N (2.2 equiv)	60	9

We further examined the effect of the substituents on the aromatic moiety of the symmetric benzoic anhydrides in our mixed anhydride method for the synthesis of lactone **7**. As shown in Entries 4 and 5, the same lactonization of **6** was carried out using the simple benzoic anhydride instead of using MNBA in order to investigate a commercially advanced method for the synthesis of **4**. When the benzoic anhydride was used together with a stoichiometric amount of DMAP for the reaction of **6**, the desired monomeric lactone **7** was obtained in good yield (79%) and the chemoselectivity is similar to the result for Entry 3. From the point of view concerning the economic cost of the dehydrating reagents, the use of cheap benzoic anhydride is also one of the convenient ways to produce the desired compounds in high yields. It is noteworthy that this method seems to be applicable to realize a new industrial production process of the perfume **4**. On the other hand, the catalytic reaction using DMAPO in the presence of the simple benzoic anhydride did not produce a satisfactory yield of **7** (Entry 5).

2.2. Lactonization of non-protected seco-acid and the short-step synthesis of (9*E*)-isoambrettolide

Next, we tried to develop the direct lactonization using *threo*-aleuritic acid (**5**) itself as shown in Table 2. First, the standard reaction conditions (1.2 equiv of MNBA and 2.4 equiv of DMAP) were used for the synthesis of the dihydroxylactone **8**. Since **5** did not completely dissolve in the dichloromethane at room temperature, the entire amount of **5** was added at once to the reaction mixture containing MNBA and DMAP in dichloromethane. By use of this unusual procedure for the chemoselective lactonization, the desired monomeric compound **8** was formed in moderate yield (Entry 1 or 2). Similar results were unfortunately attained using THF as the solvent instead of dichloromethane (Entries 3 and 4), although the solubility of the free carboxylic acid **5** in THF sufficiently increased. Interestingly, the yield of lactone **8** remarkably improved to 77% using the mixed-solvent composed of THF and dichloromethane in the reaction; that is, the starting seco-acid was dissolved in THF prior to use, which was then added to the reaction mixture including MNBA and DMAP in dichloromethane over a 12 h period at room temperature (Entry 5).

Table 2. Synthesis of 17-membered ring lactone **8** from free seco-acid **5** using MNBA

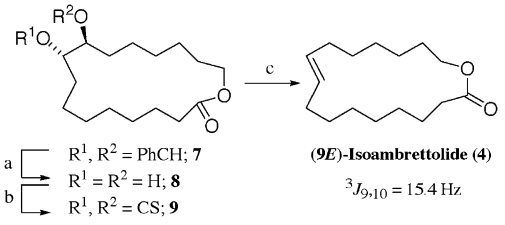
Entry	Base	Solvent	Concn/mM	Method	Yield/%
1	DMAP (2.4 equiv)	CH_2Cl_2	1.8	A[a]	49
2	DMAP (2.4 equiv)	CH_2Cl_2	3.6	A[a]	41
3	DMAP (2.4 equiv)	THF	1.8	A[a]	48
4	DMAP (2.4 equiv)	THF	1.8	B[b]	40
5	DMAP (2.4 equiv)	Mixed[c]	1.9	B[b]	77
6	DMAP (0.2 equiv), Et_3N (2.2 equiv)	Mixed[c]	1.9	B[b]	67
7	DMAPO (0.2 equiv), Et_3N (2.2 equiv)	Mixed[c]	1.9	B[b]	83
8	DMAPO (0.2 equiv), Et_3N (2.2 equiv)	CH_2Cl_2	1.8	A[a]	62
9[d]	DMAP (2.4 equiv)	CH_2Cl_2	1.8	A[a]	40
10[d]	DMAP (2.4 equiv)	Mixed[c]	1.9	B[b]	69
11[d]	DMAPO (0.2 equiv), Et_3N (2.2 equiv)	Mixed[c]	1.9	B[b]	50

[a] Method A: solid **5** was added at once to a solution of reagents.
[b] Method B: A solution of **5** was slowly added to a solution of reagents.
[c] A solution of **5** in THF was added to a solution of reagents in CH_2Cl_2.
[d] Benzoic anhydride was used as a dehydrating agent instead of MNBA.

Based on these results, the reaction was then carried out with 20 mol% of DMAPO and an excess amount of triethylamine in the mixed-solvent at room temperature, and the yield of **8** finally reached 83% as shown in Entry 7. Although we have tried to apply DMAP as a catalyst to this reaction system as shown in Entry 6, the yield of the monomer decreased to 67%. The difference between the yields for Entries 6 and 7 again shows that DMAPO is superior to DMAP for the generation of the desired monomeric lactones in the MNBA cyclization.

Next, a simple benzoic anhydride was used instead of MNBA for the cyclization of the free *threo*-aleuritic acid (**5**). The desired compound was obtained in 40% yield when the reaction was carried out by the total addition of the solid starting material to the solution of promoters (Entry 9), however, the yield increased to 69% by the slow-addition of a solution of the seco-acid in THF to a solution of promoters in dichloromethane (Entry 10). It is also showed that the combination of simple benzoic anhydride and DMAPO as a dehydrating reagent and as a basic catalyst, respectively, is ineffective for the reaction of the free seco-acid **5** (Entry 11) even though the couple of MNBA and DMAPO is an universally suitable combination of the promoters (Entry 7).

The facile deprotection of **7** with $AcOH/H_2O$ was then carried out to produce the *threo*-aleuritic acid lactone (**8**), which is an important synthetic intermediate (9*E*)-isoambrettolide (**4**) as depicted in Scheme 2. The dihydroxylactone **8** prepared by the above-mentioned two methods was in turn converted to the corresponding thiocarbonate **9** by treating with 1,1′-thiocarbonyldiimidazole (TCDI) and DMAP under reflux in toluene. Finally, it was transformed into (9*E*)-isoambrettolide (**4**) using trimethyl phosphite in 87% yield.[14] The geometric structure of **4** was determined from the coupling constants data of olefinic protons using ^1H NMR.



Scheme 2. Reagents and conditions: (a) AcOH, H_2O, rt (93%); (b) TCDI, DMAP, toluene, 130 °C (91%) and (c) $P(OMe)_3$, 140 °C (87%).

2.3. Conclusion

Thus, the substituted benzoic anhydride method was successfully used for the formation of the large-ring lactones having some oxygenated functionalities, which are useful synthetic intermediates of (9*E*)-isoambrettolide (**4**). Through this synthetic study, the protected or unprotected 17-membered ring lactone (**7** or **8**) was consequently prepared from the corresponding masked or free seco-acid (**6** or **5**) using MNBA as the dehydrating reagent with DMAPO, a powerful

basic catalyst. In particular, we revealed that the latter pathway is extremely efficient for the preparation of the synthetic intermediates of **4** since only three steps (83%, 91%, and 87% yields, respectively) are required to produce the artificial perfume compound **4** starting from **5**.

On the other hand, the combination of a simple benzoic anhydride and commercially available DMAP is practically useful for the industrial supply of **4** since inexpensive reagents and facile protocols are employed in this synthetic strategy. Therefore, it is also revealed that the intramolecular dehydration method using symmetric benzoic anhydrides with basic catalysts could be applicable for the plant-scale production of the musk-like lactones as well as the synthesis of other complicated molecules such as multi-oxygenated large- or medium-sized ring lactones.[12]

3. Experimental

3.1. General

All melting points were measured on a Yanaco MP-S3 micro-melting point apparatus. IR spectra were recorded on a Horiba FT-300 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270L, a JEOL JNM-AL300 or a JEOL JNM-LA500 spectrometer with cholorform (in chloroform-*d*) or benzene (in benzene-d_6) as an internal standard. High-resolution mass spectra were recorded on a JEOL JMS-SX102A instrument using 4-nitrobenzyl alcohol as a matrix. Column chromatography was performed on Silica gel 60 (Merck) or Wakogel B5F. Thin layer chromatography was performed on Wakogel B5F.

All reactions were carried out under an argon atmosphere in dried glassware, unless otherwise noted. Dichloromethane was distilled from diphosphorus pentoxide, then calcium hydride, and dried over MS 4 Å, tolune and DMF were distilled from diphosphrous pentoxide, and dried over MS 4 Å, and THF was distilled from sodium/benzophenone immediately prior to use. *threo*-Aleuritic acid (**5**) was purchased from Fulka Chemical Co., Ltd, and used after purification by silica gel chromatography (eluant; chloroform/methanol = 10/1). 2-Methyl-6-nitrobenzoic anhydride (MNBA) was purchased from Tokyo Kasei Kogyo Co., Ltd (TCI, M1439). Other reagents were purchased from Tokyo Kasei Kogyo Co., Ltd, Kanto Chemical Co., Inc. or Aldrich Chemical Co., Inc., and used without further purification unless otherwise noted.

3.2. *threo*-9,10-Benzylidenedioxy-16-hydroxyhexadecanoic acid (6)

To a solution of *threo*-aleuritic acid (**5**) (222 mg, 0.729 mmol) and benzaldehyde dimethylacetal (0.120 mL, 0.800 mmol) in DMF (0.73 mL) at room temperature was added CSA (33.8 mg, 0.146 mmol). After the reaction mixture had been stirred for 5 h at 60 °C and for 10 h at room temperature, triethylamine (0.02 mL) was added. The mixture was concentrated by evaporation of the solvent and then the crude product was purified by column chromatography (eluant; dichloromethane/methanol = 20/1) to afford benzylidene acetal **6** (a mixture of stereoisomeric benzylidene acetals, ca. 1:1, 190 mg, 66%) as a colorless oil. IR (neat): 3420, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.51–7.43 (m, 2H, Ph), 7.41–7.31 (m, 3H, Ph), 5.86 (s, 1H, CHPh), 3.81–3.71 (m, 2H, 9-H, 10-H), 3.65 (t, J=6.2 Hz, 2H, 16-H), 2.34 (t, J=7.0 Hz, 2H, 2-H), 1.74–1.23 (m, 22H, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15-H); ^{13}C NMR (C_6D_6): δ 179.4 (1), 139.6 (Ph), 129.1 (Ph), 128.4 (Ph), 127.1 (Ph), 103.0 (CHPh), [83.0, 83.0] (9 or 10), [81.7, 81.6] (10 or 9), 62.6 (16), [34.4, 34.3] (2), 33.3, 33.3, 32.8, [29.7, 29.7], [29.7, 29.6], [29.4, 29.4], 29.2, [26.5, 26.4], [26.3, 26.3], [26.0, 26.0], 25.1 (3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15). The values in square brackets are the chemical shifts of the identical carbons of two diastereomers. HRMS: calcd for $C_{23}H_{37}O_5$ (M+H$^+$) 393.2641, found 393.2632.

3.3. *threo*-9,10-Benzylidenedioxyheptadecan-16-olide (7)

An experimental procedure is described for the preparation of lactone **7** using MNBA with a catalytic amount of DMAPO (Table 1, Entry 3). To a solution of MNBA (116 mg, 0.337 mmol), triethylamine (62.8 mg, 0.621 mmol), and DMAPO (7.7 mg, 0.056 mmol) in dichloromethane (116 mL) at room temperature was slowly added a solution of benzylidene acetal **6** (110 mg, 0.280 mmol) in dichloromethane (84 mL) with a mechanically driven syringe over a 16.5 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford lactone **7** (a mixture of stereoisomeric benzylidene acetals, ca. 1:1, 77.0 mg, 77%) as a white solid and its dimer (10.3 mg, 10%) as a pale yellow oil. **7**: IR (KBr): 1730 cm^{-1}; ^{1}H NMR (C_6D_6): δ 7.67–7.61 (m, 2H, Ph), 7.23–7.10 (m, 3H, Ph), 5.97 (s, 1H, CHPh), 4.07–3.93 (m, 2H, 16-H), 3.81–3.66 (m, 2H, 9-H, 10-H), 2.22–2.06 (m, 2H, 2-H), 1.88–0.97 (m, 22H, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15-H); ^{13}C NMR (C_6D_6): δ 172.9 (1), 139.6 (Ph), 129.1 (Ph), 128.4 (Ph), 127.1 (Ph), [102.9, 102.8] (CHPh), [82.3, 82.2] (9 or 10), [80.8, 80.7] (10 or 9), 63.9 (16), 34.5 (2), [33.3, 33.1], 32.4, 29.1, 28.8, [28.7, 28.6], 28.3, 27.8, [25.9, 25.8], [25.5, 25.2], [25.0, 24.9], 24.3 (3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15). The values in square brackets are the chemical shifts of the identical carbons of two diastereomers. HRMS: calcd for $C_{23}H_{35}O_4$ (M+H$^+$) 375.2535, found 375.2532.

3.4. *threo*-9,10-Dihydroxyheptadecan-16-olide (8)

3.4.1. From 7. To lactone **7** (9.9 mg, 0.026 mmol) at room temperature were added acetic acid (0.76 mL) and water (0.19 mL). After the reaction mixture had been stirred for 24 h at room temperature, saturated aqueous sodium hydrogencarbonate and solid sodium hydrogencarbonate were successively added at 0 °C. The reaction mixture was stirred for 10 h and then the mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford dihydroxylactone **8** (7.0 mg, 93%) as a white solid. Mp 53.5–54.0 °C; IR (KBr): 3440, 3310, 1730 cm^{-1}; ^{1}H NMR ($CDC1_3$): δ 4.18–4.05 (m, 2H, 16-H), 3.50–3.41 (br m, 2H, 9-H, 10-H), 2.40 (br s, 2H,

9-OH, 10-OH), 2.31 (t, J=6.8 Hz, 2H, 2-H), 1.70–1.22 (m, 22H, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15-H); ^{13}C NMR ($CDC1_3$): δ 174.0 (1), 74.1 (9 or 10), 73.4 (10 or 9), 64.2 (16), 34.6 (2), 32.5, 31.4, 28.6, 28.2, 28.1, 27.7, 27.6, 25.4, 25.0, 23.9, 23.1 (3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15); Anal. calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 66.97; H, 10.54. HRMS: calcd for $C_{16}H_{31}O_4$ ($M+H^+$) 287.2222, found 287.2223.

3.4.2. From 5; direct lactonization of *threo*-aleuritic acid. An experimental procedure is described for the preparation of dihydroxylactone **8** using MNBA with a catalytic amount of DMAPO (Table 2, Entry 7). To a solution of MNBA (165 mg, 0.479 mmol), triethylamine (89.1 mg, 0.881 mmol), and DMAPO (11.1 mg, 0.080 mmol) in dichloromethane (169 mL) at room temperature was slowly added a solution of **5** (118 mg, 0.388 mmol) in THF (40 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford dihydroxylactone **8** (92.0 mg, 83%) as a white solid.

3.5. *threo*-9,10-Thiocarbonyldioxyheptadecan-16-olide (9)

To a solution of dihydroxylactone **8** (80.2 mg, 0.280 mmol) in toluene (14 mL) were added TCDI (499 mg, 2.80 mmol) and DMAP (3.4 mg, 0.028 mmol). After the reaction mixture had been stirred for 4 h at 130 °C, it was cooled down to room temperature. The mixture was concentrated by evaporation of the solvent and then the crude product was purified by thin layer chromatography to afford thiocarbonate **9** (83.8 mg, 91%) as a white solid. Mp 73–74 °C; IR (KBr): 1720, 1280, 1180 cm^{-1}; ^{1}H NMR ($CDC1_3$): δ 4.55–4.43 (m, 2H, 9-H, 10-H), 4.21–4.08 (m, 2H, 16-H), 2.42–2.25 (m, 2H, 2-H), 2.10–1.21 (m, 22H, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15-H); ^{13}C NMR ($CDC1_3$): δ 191.4 (CS), 173.7 (1), 86.1 (9), 86.1 (10), 63.9 (16), 34.4 (2), 32.4, 32.1, 28.7, 28.3, 27.9, 27.9, 27.1, 25.6, 25.0, 23.6, 23.2 (3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15). Anal. calcd for $C_{17}H_{28}O_4S$: C, 62.16; H, 8.59. Found: C, 62.05; H, 8.61. HRMS: calcd for $C_{17}H_{29}O_4S$ ($M+H^+$) 329.1786, found 329.1791.

3.6. (9*E*)-Isoambrettolide (4)

To thiocarbonate **9** (20.4 mg, 0.062 mmol) was added trimethyl phosphite (3 mL) at room temperature. After the reaction mixture had been stirred for 25 h at 140 °C, it was cooled down to room temperature. The mixture was concentrated by evaporation of the solvent and then the crude product was purified by thin layer chromatography to afford (9*E*)-isoambrettolide (**4**) (13.7 mg, 87%) as a colorless oil. IR (neat): 1730 cm^{-1}; ^{1}H NMR (C_6D_6): δ 5.42 (dddd, J=15.4, 9.5, 3.5, 1.6 Hz, 1H, 9-H or 10-H), 5.32 (dddd, J=15.4, 9.5, 3.8, 1.6 Hz, 1H, 10-H or 9-H), 4.08 (t, J=5.4 Hz, 2H, 16-H), 2.19 (t, J=7.0 Hz, 2H, 2-H), 2.12–1.97 (m, 4H, 8-H, 11-H), 1.62–1.50 (m, 2H, 3-H), 1.48–1.34 (m, 2H, 15-H), 1.42–1.13 (m, 14H, 4, 5, 6, 7, 12, 13, 14-H); ^{13}C NMR (C_6D_6): δ 172.9 (1), 131.4 (9 or 10), 130.8 (10 or 9), 64.0 (16), 34.9 (2), 32.2 (8 or 11), 31.8 (11 or 8), 29.2 (15), 29.9, 28.8, 28.3, 28.2, 28.1, 27.2, 27.1 (4, 5, 6, 7, 12, 13, 14), 25.3 (3). HRMS: calcd for $C_{16}H_{29}O_2$ ($M+H^+$) 253.2167, found 253.2165.

Acknowledgements

We would like to express our thanks to Ms. Mari Ohno (Dainippon Ink and Chemicals, Inc.) for elemental analysis. This study was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

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