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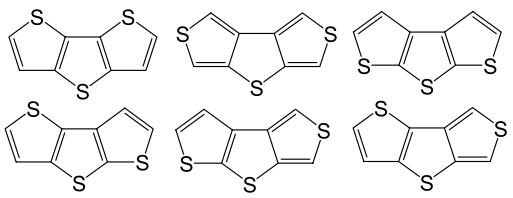
Tetrahedron

Tetrahedron Vol. 61, No. 47, 2005

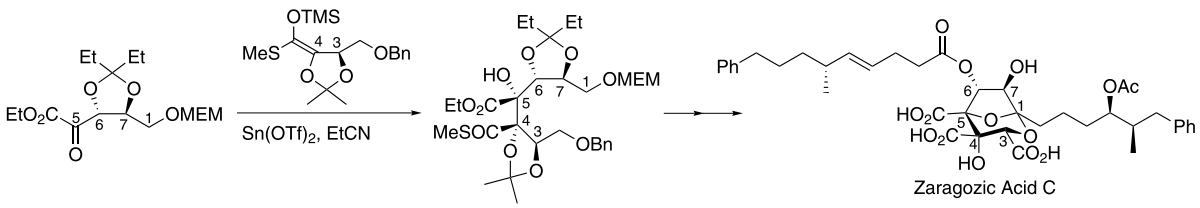
Contents

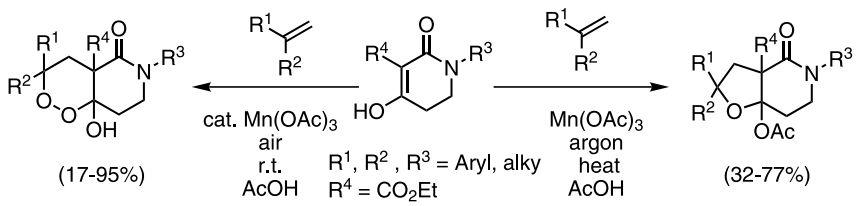
REPORT

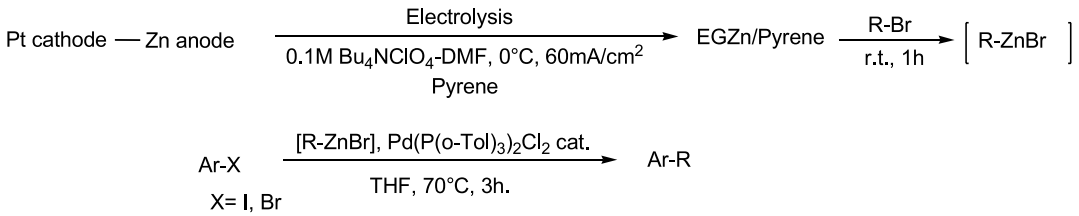


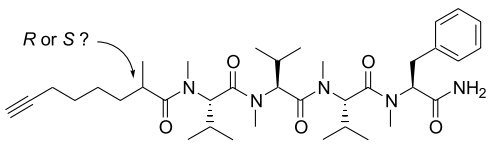
This is the first review on six dithienothiophene isomers, which covers their syntheses and electronic and optical properties.

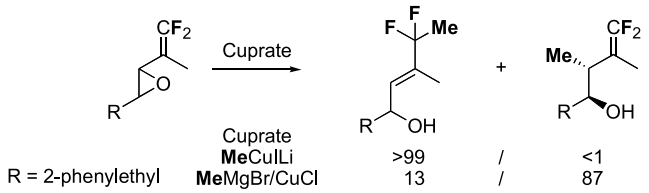
ARTICLES

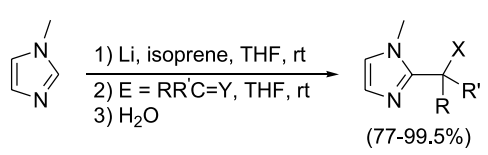


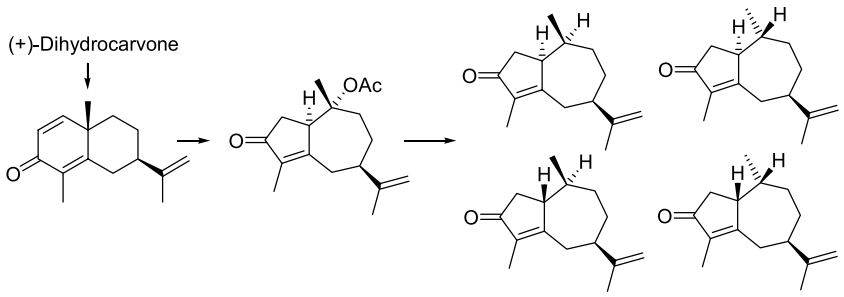


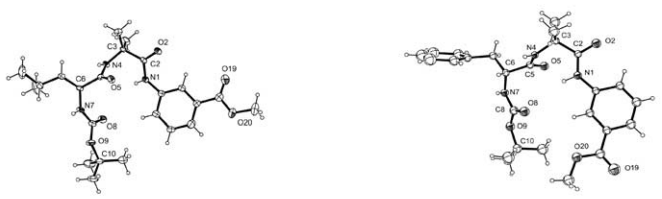






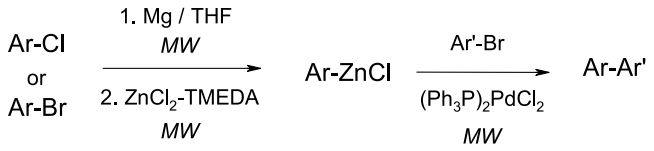


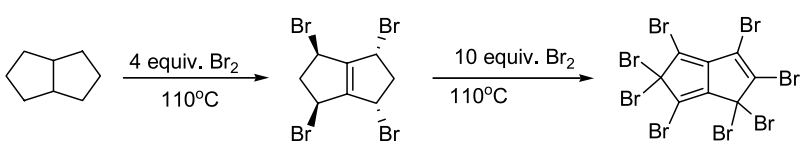


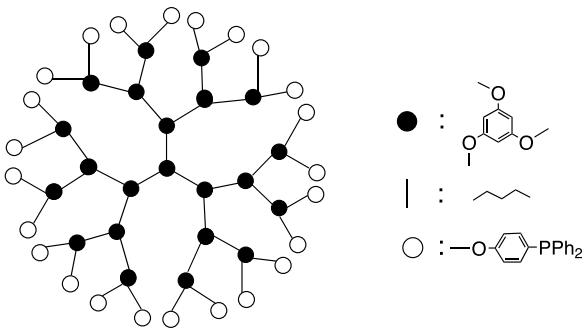


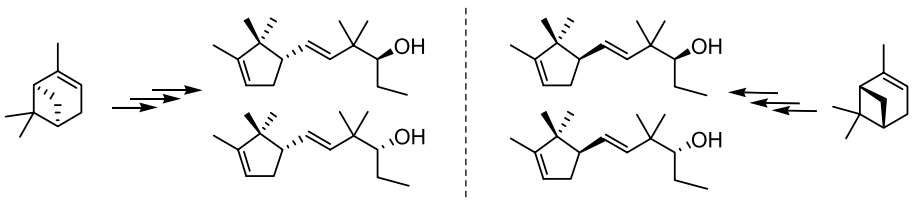
I II

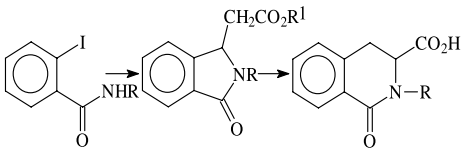
Peptides Boc-Leu-Aib-*m*-ABA-OMe (**I**) (Aib, α-aminoisobutyric acid; *m*-ABA, *meta*-aminobenzoic acid) and Boc-Phe-Aib-*m*-ABA-OMe (**II**) adopt a type-II β-turn conformation, solely stabilized by co-operative steric interactions amongst the amino acid residues.

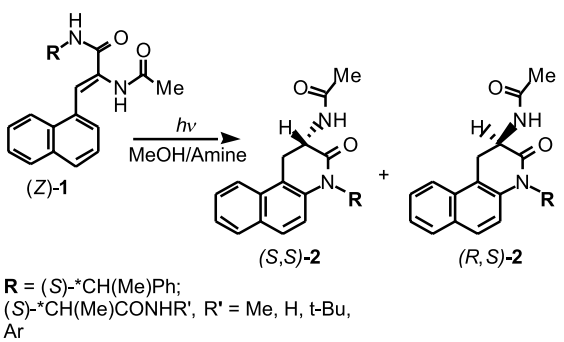


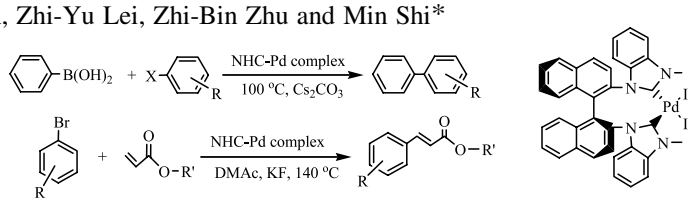






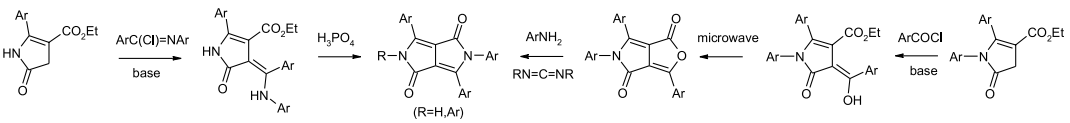


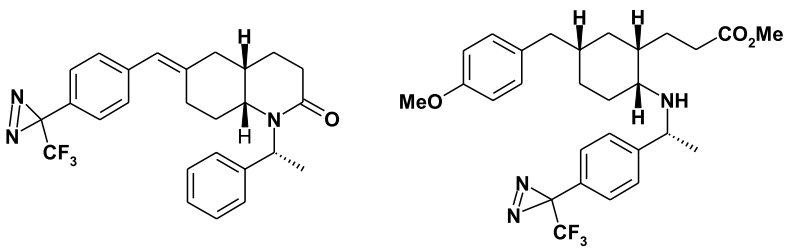




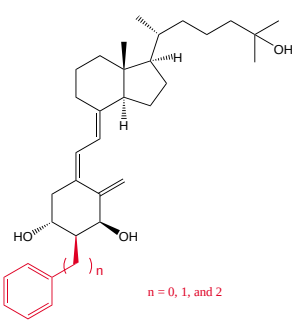
R= Me, OMe, Cl, C(O)Me , R'= Me or Bu and X= Cl, Br, I. yield: 44-96%.

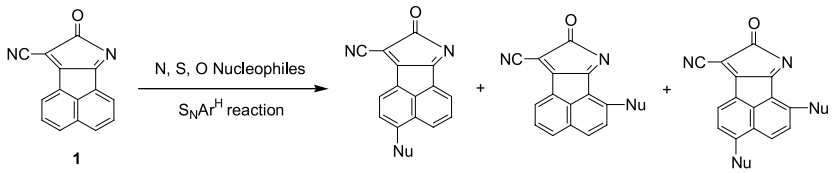
A novel Pd(II)–NHC complex, which has a 'normal' cis-chelating, bidentate structure is fairly effective in Suzuki and Heck-type cross-coupling reaction to give the products in good to excellent yields in most cases.

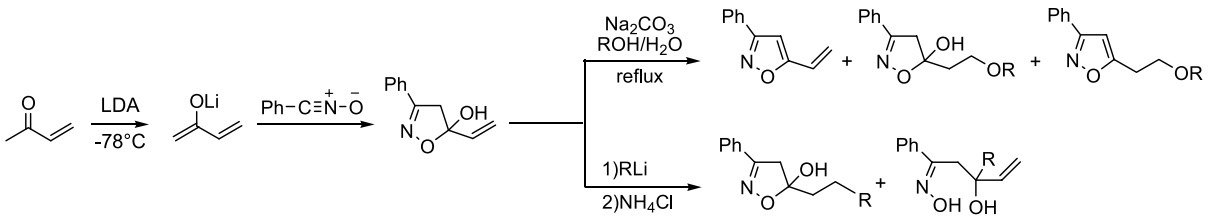


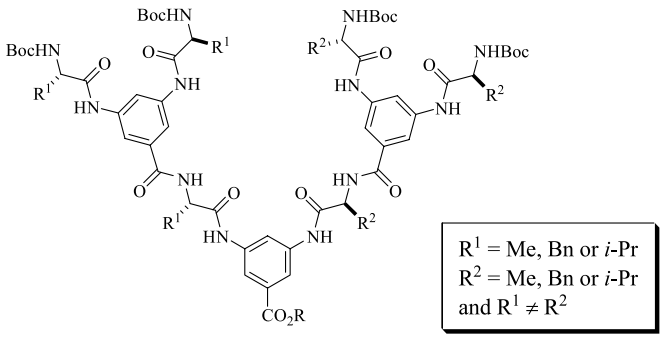


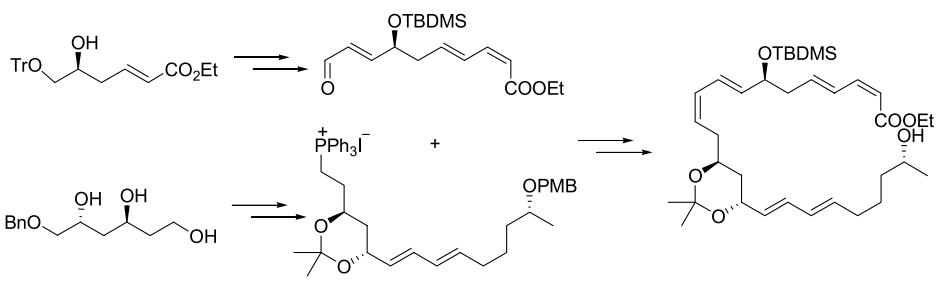
Concise synthesis of the novel 2α-phenyl-, 2α-benzyl-, and 2α-phenethyl-1α,25-dihydroxyvitamin D_3 derivatives and their biological evaluations are reported.











OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

A total synthesis of the squalene synthase inhibitor zaragozic acid C was achieved. The key steps include simultaneous creation of the contiguous quaternary stereocenters by a $Sn(OTf)_2$-promoted aldol coupling between an α-keto ester and a silyl ketene thioacetal derived from L- and D-tartaric acids, respectively, and construction of the bicyclic core structure by internal ketalization under kinetically controlled conditions. *Tetrahedron* **2005**, *61*, 11078–11106.

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

ELSEVIER

ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 11055–11077

Tetrahedron report number 741

Dithienothiophenes

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Received 25 July 2005

Available online 15 September 2005

Contents

Keywords: Thiophene; Dithienothiophene.

Abbreviations: CA, chloranil; CV, cyclic voltammetry; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMeDTT, dimethyldithienothiophene; DMF, *N*,*N*-dimethylformamide; ESR, electron spin resonance; LDA, lithium diisopropylamide; LED, light-emitting devices; LR, Lawesson's reagent; *m*CPBA, 3-chloroperoxybenzoic acid; NBS, *N*-bromosuccinimide; NMP, *N*-methylpyrrolidine; pDTDP, poly(dithienothiophene–dithienopyrrole); pDTT, polydithienothiophene; PPA, polyphosphoric acid; pT, polythiophene; pTT, polythienothiophene; TCNEO, tetracyanoethylene oxide; TCNQ, 7,7,8,8-tetracyano-*p*-quinodimethane; TFA, trifluoroacetic acid; TFT, thin-film transistor; TMS, trimethylsilyl; TTF, tetrathiafulvalene.

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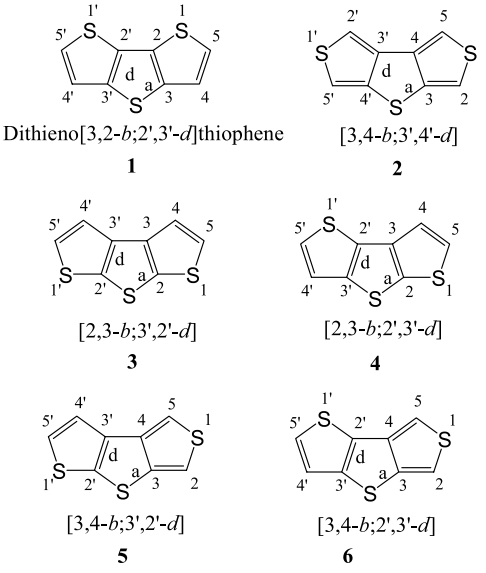
doi:10.1016/j.tet.2005.08.030

1. Introduction

Dithienothiophenes (DTT) possess three fused thiophene rings, the orientations of which vary depending on the locations of the sulfur atoms of the peripheral thiophenes. Six isomers, dithieno[3,2-*b*;2′,3′-*d*]thiophene **1**, dithieno[3,4-*b*;3′,4′-*d*]thiophene **2**, dithieno[2,3-*b*;3′,2′-*d*]thiophene **3**, dithieno[2,3-*b*;2′,3′-*d*]thiophene **4**, dithieno[3,4-*b*;3′,2′-*d*]thiophene **5**, and dithieno[3,4-*b*;2′,3′-*d*]thiophene **6** can be depicted and all have appeared in the literature.

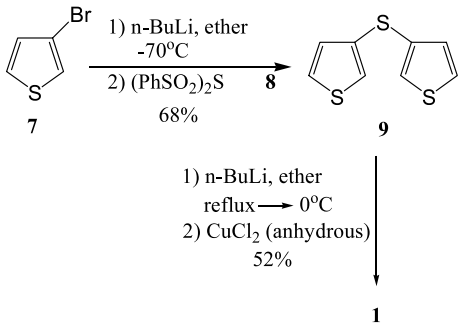
Due to their interesting electrochemical and optical properties, dithienothiophenes have been receiving increasing attention. As these compounds are rich in sulfur, with three S atoms, they are electron rich species, which makes them good electron donors and important building blocks of a wide variety of materials for electronic and optical applications such as electroluminescence, two-photon absorption, excited fluorescence, photochromism, nonlinear optical chromophores, transistors with high mobilities of on/off ratios, conducting polymers and charge-transfer complexes. Easy oxidation of the thiophene sulfur of the middle ring gives the molecules property of fluorescence, which makes them good candidates for labelling, particularly important for biological systems.



2. Dithieno[3,2-*b*; 2′,3′-*d*]thiophene 1

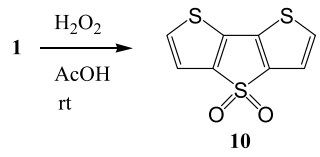
2.1. Methods for synthesizing the ring system

Although the first synthesis of **1** was claimed earlier, no spectroscopic data were reported.[1] In 1971, Jong and Janssen published its first synthesis with spectroscopic data.[2] The crystal structures of **1** and its charge-transfer complex with TCNQ were reported in 1983.[3] Jong and Janssen's synthesis started with lithiation of 3-bromothiophene **7** with *n*-BuLi at −70 °C, which was followed by addition of bis(phenylsulfonyl)sulfide **8** to afford 3,3′-dithienyl sulfide **9**. This was then dilithiated with *n*-BuLi and subjected to oxidative ring closure using $CuCl_2$ to afford **1**, (Scheme 1).



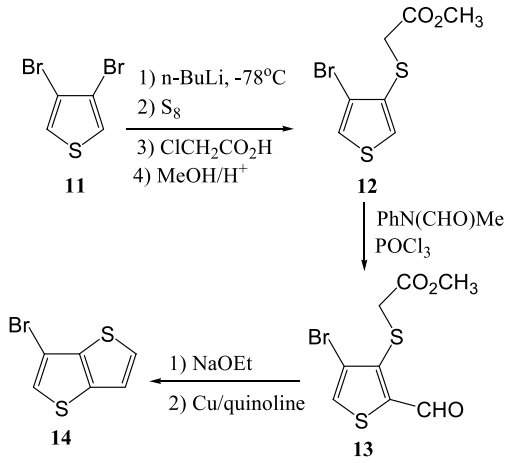
Scheme 1. First synthesis of dithienothiophene **1**.

Conversion of the dithienothiophene **1** into the corresponding dioxide **10** was performed by oxidation of the sulfur of the central thiophene to the sulfone with hydrogen peroxide, which yielded **10** in good yield (Scheme 2).



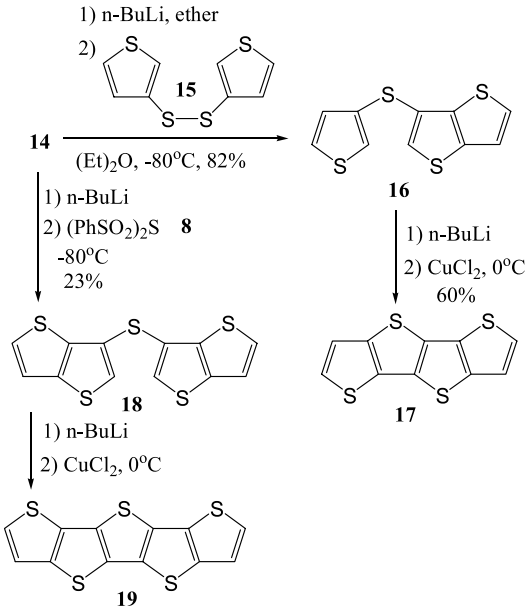
Scheme 2. Oxidation of **1**.

The second method of synthesis appeared in 1989 with the preparation of two higher homologues **17** and **19**, which contain four and five linearly condensed thiophenes.[4,5] The key intermediate bromothienothiophene **14** was synthesized starting from 3,4-dibromothiophene **11**, which was converted into **12** in a one-pot four-step reaction: (i) lithiation with *n*-BuLi; (ii) addition of sulfur; (iii) reaction with α-chloroacetic acid and (iv) esterification with methanol (Scheme 3). It was then formylated using methylphenylformamide/phosphorus oxychloride, which gave 2-formylthiophene **13**. Treatment of **13** with sodium ethoxide formed bromothienothiophenecarboxylic acid, and the carboxylic acid was removed by using Cu to afford the key intermediate bromothienothiophene **14**.

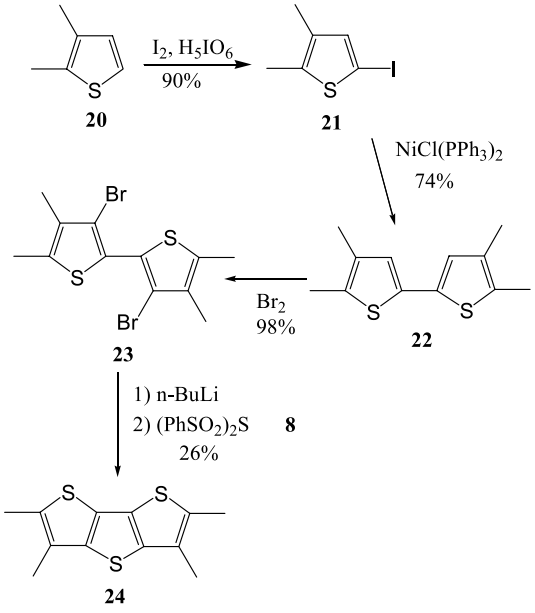


Scheme 3. Synthesis of higher homologues of **1**.

The thienothiophene **14** was initially treated with *n*-BuLi and then with the dithienyl disulfide **15** to obtain **16**, which was converted into the tetrafused thiophene **17** by oxidative ring closure, using *n*-BuLi and then $CuCl_2$. The X-ray crystal structure of **17** has also been reported (Scheme 4).[6] The fused pentathiophene **19** was obtained in a similar fashion using bis(phenylsulfonyl)sulfide **8** in place of the dithienyl disulfide **15** to provide a sulfur bridge between two thienothiophenes and, after an oxidative coupling of **18**, the fused pentathiophene **19** was obtained in 15–20% yield.



Scheme 4. Synthesis of higher homologues of **1**.

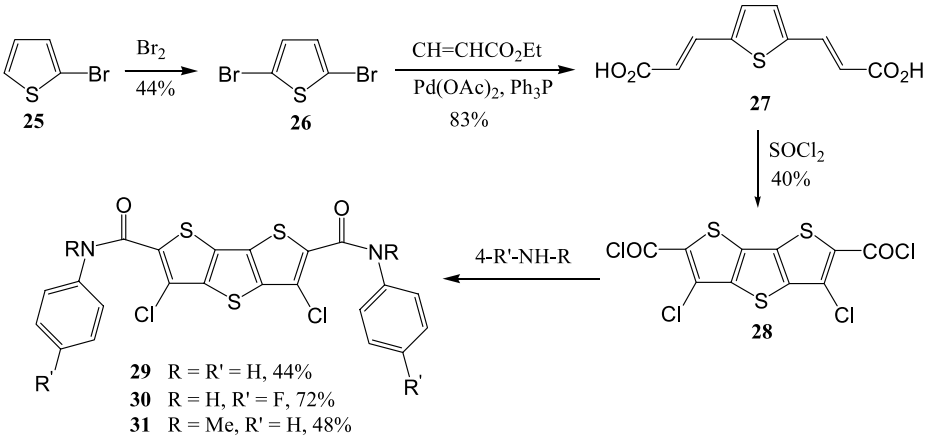


Scheme 5. Synthesis of tetramethyl derivative of **1**.

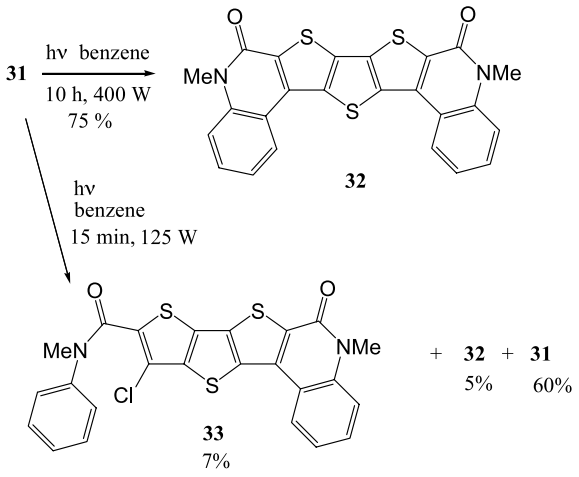
The third synthesis of the dithienothiophene ring was reported in 1995, for a tetramethyl derivative of **1**.[7] The synthesis was completed in four steps starting from 2,3-dimethylthiophene **20** (Scheme 5). Iodination of **20** afforded monoiodinated dimethylthiophene **21**, which was dimerized using nickel catalysis and the product **22** was dibrominated to obtain **23**. It was then dilithiated with *n*-BuLi, and the formation of the central thiophene ring was achieved using bis(phenylsulfonyl)sulfide **8** as a sulfur source. The final reaction gave the tetramethyl-DTT **24** in 26% yield.

Dicarbonyl chloride and dicarboxanilide derivatives of DTT were reported in 1995 with the construction of the dithienothiophene ring following a different method.[8,9] The synthesis started with the bromination of 2-bromothiophene **25** to obtain 2,5-dibromothiophene **26**, which was reacted with ethyl acrylate in the presence of a catalytic amount of Pd(II) acetate to afford the thiophene **27**, having two ethenylcarboxylic acid groups at the 2- and 5-positions (Scheme 6). Treatment of **27** with thionyl chloride let to dual ring closure and formation of the functionalized DTT **28**, which has two carbonyl chlorides and two chloro groups. The corresponding anilines were added to **28** to obtain the desired dianilides **29–31**. A benzene solution of **31** was subjected to light of different strength for various times. When **31** was irradiated with a 400 W high-pressure mercury arc lamp for 10 h, DTT **32** having two peripheral quinolones was formed (Scheme 7). On the other hand, when **31** was irradiated with a 125 W high-pressure mercury arc lamp fitted with a pyrex filter for 15 min, a mixture of starting material, **32** and mono-quinoline **33** was obtained in 60, 5 and 7% yields, respectively.

In 1997, it was reported that a reaction of thieno-anellated 1, 2-dithiins **40–42** led to the synthesis of the dithienothiophenes **24**, **1** and **43** (Scheme 8).[10] Because the strategy was particularly designed to synthesize the targeted dithiins **40–42** and then investigate their various reactions, this method to obtain the dithienothiophene is rather longer than the previous methods. The thiophenes **20**, **34** and **35** were lithiated and subsequent oxidative coupling using $CuCl_2$ gave the 2,2′-dithienyls **22**, **36** and **37**, which were brominated to obtain the 3,3′-dibromo-2,2′dithienyls **23**, **38** and **39**. The 1,2-dithiins **40–42** were synthesized in a four-step one-pot reaction: (i) lithiation with *n*-BuLi; (ii)



Scheme 6. Synthesis of dicarbonyl derivatives of **1**.



Scheme 7. Irradiation of **31**.

addition of elemental sulfur; (iii) hydrolysis with NaOH and finally (iv) oxidation using $K_3[Fe(CN)_6]$. Treatment of **40**–**42** with copper bronze at elevated temperature yielded the dithienothiophenes **24**, **1** and **43**.

In 2001, a similar synthesis to the first synthesis of DTT but using thionyl chloride in place of bis(phenylsulfonyl)sulfide **8** as a sulfur source was reported.[11,12]

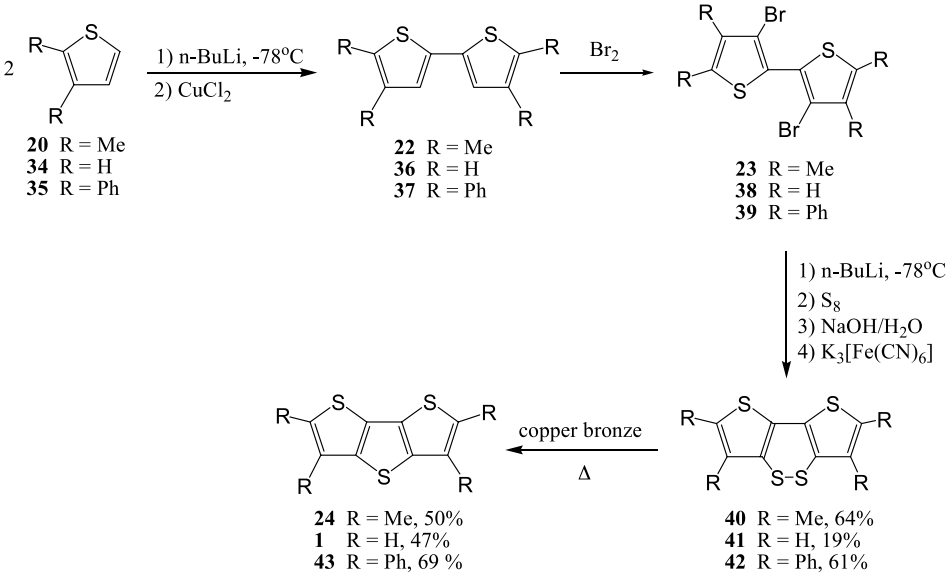
In 2002, a new method for the synthesis of the ring system was reported for the preparation of photochromic derivatives containing two dithienothiophenes having a perfluorocyclopentene bridge **49**.[13] The synthesis, which started with 5,5′-dimethyl-2,2′-bithiophene **44**, was completed in three steps to obtain the 2,6-dimethyl derivative **47** of DTT (Scheme 9). The dimethylbithiophene **44** was selectively dibrominated at the 3- and 3′-positions to yield **45**, which was converted into the 3′-bromo-3-thio derivative **46** by first lithiation with *n*-BuLi and then addition of elemental sulfur. Cyclization of **46** was achieved in the presence of Cu_2O in DMF to give the 2,6-dimethyl-DTT **47**. The target compound **49**, which possesses two 2,6-dimethyl-DTTs linked with hexafluorocyclopentene, was prepared in two additional steps. The dimethyl-DTT **47** was brominated with NBS to give **48**, which was reported to be a nonregioselective reaction and the product was isolated in low yield by column chromatography from a mixture of the products. Two moles of the 3-bromo-DTT **48** were then lithiated and reacted with one mole of octafluorocyclopentene to obtain the target molecule **49**.

Photocyclization of **49** was performed at $\lambda=313$ nm and the reverse reaction was carried out at $\lambda=578$ nm in MeCN. It was reported that the long-wavelength absorption bands were observed for **49** and **50** at 290 and 612 nm, respectively.

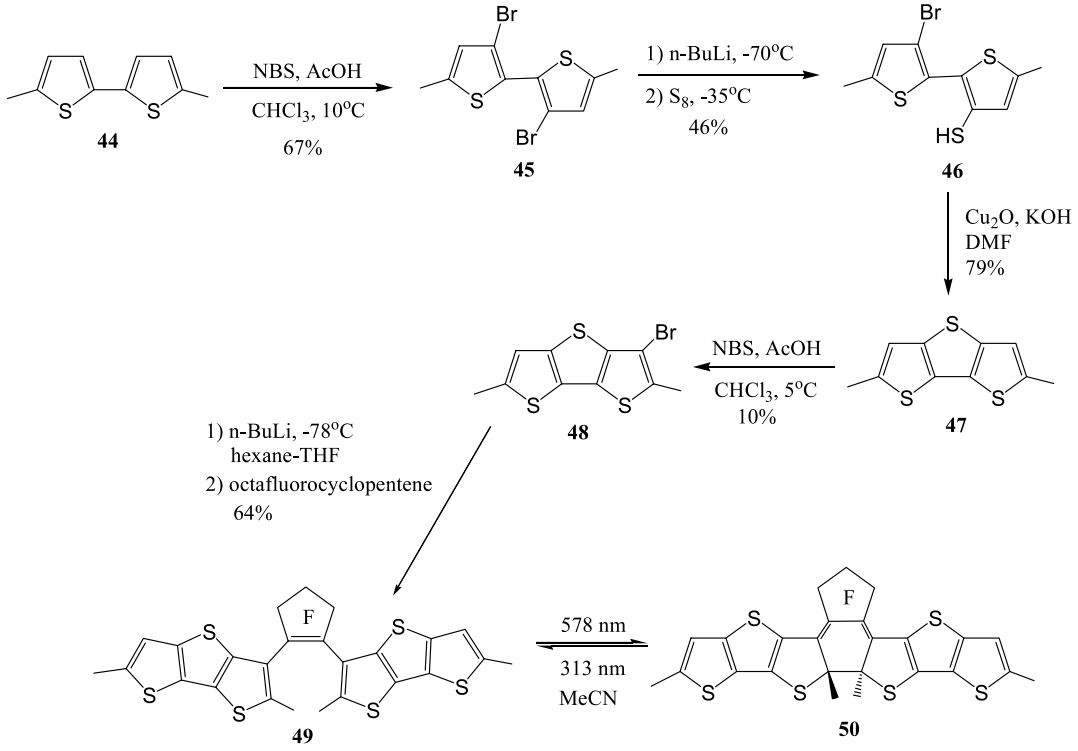
In 2002, two improved syntheses of DTT **1** appeared,[14,15] one of which started with the diformylation of tetrabromothiophene **51** by first dilithiation and then reacting with 1-formylpiperidine to obtain 3,4-dibromo-2,5-diformylthiophene **52** (Scheme 10). The dialdehyde **52** was converted into the diester **53** with ethyl mercaptoacetate, which gave the corresponding dicarboxylic acid derivative **54** upon reacting with LiOH. The DTT **1** was then obtained after decarboxylation of **54** using copper in quinoline at 230 °C. The overall yield was reported to be 47%.

In the second improved synthesis, 2,3-dibromothiophene **55** was used as a starting material (Scheme 11).[15] Lithiation of **55** was followed by usual oxidative coupling with $CuCl_2$ to obtain 3,3′-dibromo-2,2′-bithiophene **56**, which was converted into DTT **1** in two steps: (i) lithiation and (ii) addition of bis(phenylsulfonyl)sulfide **8** as a sulfur source.

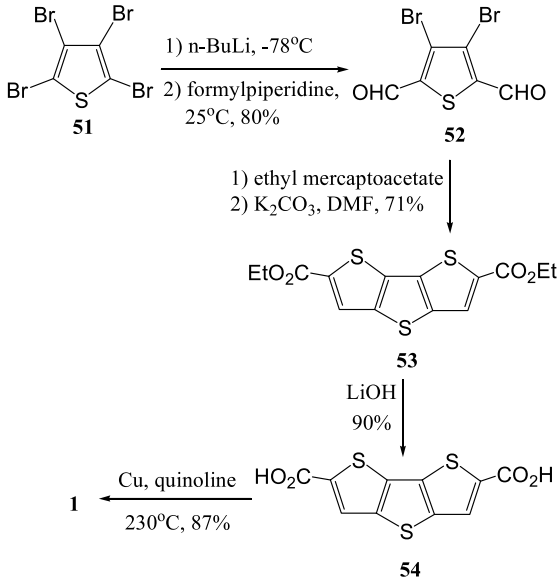
In 2003, a method to synthesize DTT appeared with slight differences from the previously described methods.[16] Bromination of bithiophene **57** with NBS gave 3,3′,5′,5-tetrabromo-2,2′-bithiophene **58**, and the bromines at the 3-



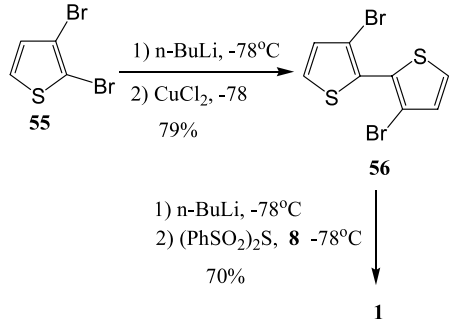
Scheme 8. Synthesis of **1** and its derivatives.



Scheme 9. Synthesis of photochromic derivative of **1**.



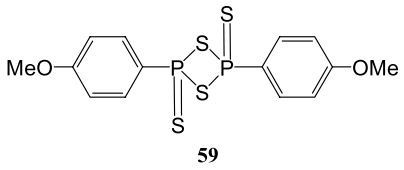
Scheme 10. Improved synthesis of **1**.



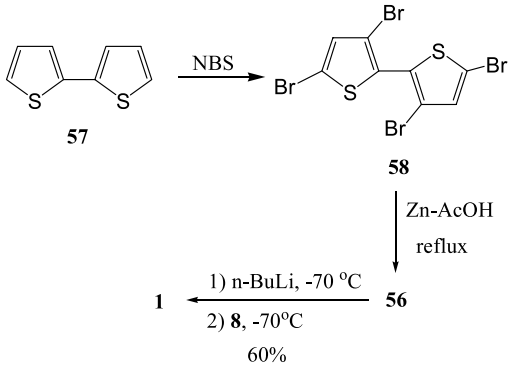
Scheme 11. Improved synthesis of **1**.

and 3′-positions were removed using zinc in refluxing acetic acid to give **56** (Scheme 12). The next step, lithiation and addition of **8** at −70 °C, gave the DTT.

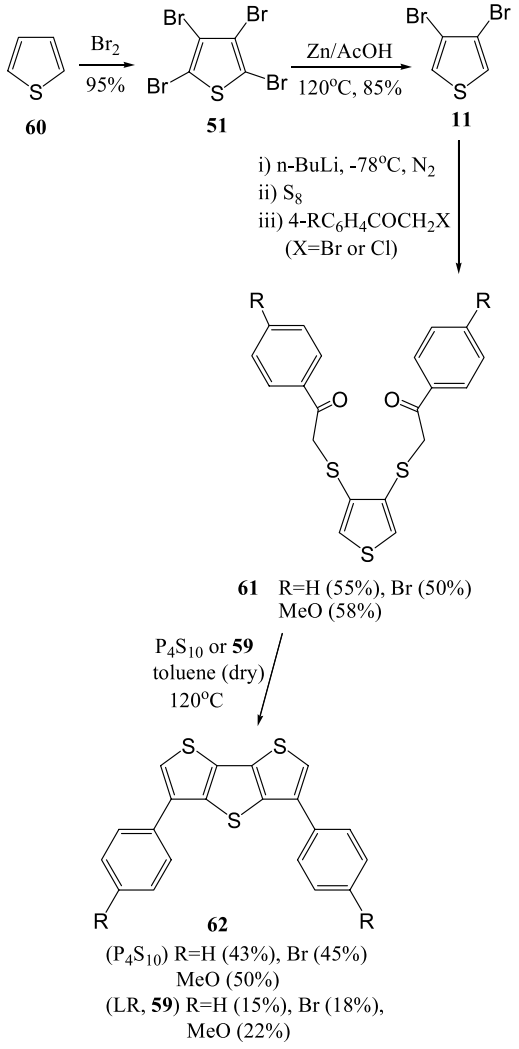
Recently, a new method for the synthesis of DTT functionalized at the 3- and 5-positions was reported.[17] This interesting method involved the use of P_4S_{10} or Lawesson's reagent (LR) **59** to form the DTT via a one-pot, two-ring-closure reaction of α-dithioketones at the 3- and 4-positions of the thiophene ring (Scheme 13).



The synthesis required four steps starting with the tetrabromination of thiophene **60** with Br_2 to give



Scheme 12. Synthesis of **1**, from bithiophene **57**.



Scheme 13. Synthesis of derivatives of **1**, using P_4S_{10} or LR.

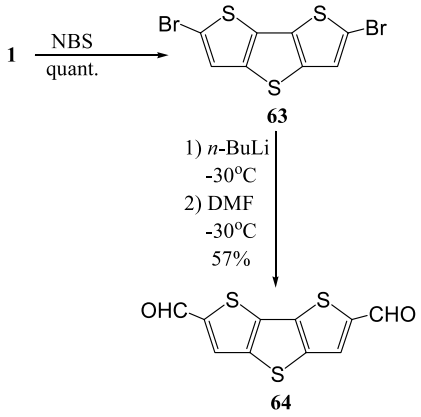
tetrabromothiophene **51**. Selective removal of the bromines at the 2- and 5-positions was carried out using Zn to yield 3,4-dibromothiophene **11**, to which α-thioketones were introduced at the 3- and 4-positions via a one-pot, three-step reaction: (i) lithiation with *n*-BuLi at −78 °C; (ii) addition of elemental sulfur and (iii) introduction of α-thioketones by adding α-bromoketones to the mixture. The crucial dual ring closure was achieved by treatment of the diketones **61** with P_4S_{10} in boiling anhydrous toluene, which was completed in 3 h, to give **62**. As indicated, in Scheme 13, when LR was used, lower yields were obtained.

The same molecule **62** (R=H) was also synthesized by a separate group,[18] following the slightly modified method[11,12] of the first[2] synthesis of DTT **1**.

2.2. Reactions and derivatization of the ring system

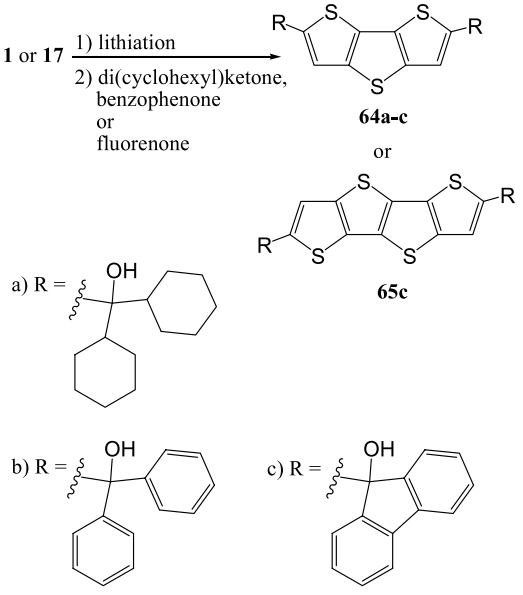
The DTTs are multi sulfur compounds, which makes them electron rich and they tend to give electrophilic reactions.[19] Reactions of the central thiophene sulfur with peroxides easily produce the sulfone **10**, which gives the compound the property of fluorescence (Scheme 2).[2,18,20–25] Various functional groups were generally provided, and these molecules could even be further functionalized, by initial lithiation or bromination of the α-position.

Double formylation of **1** was carried out for conformational analysis by means of ESR spectroscopy (Scheme 14).[26] The dibromo-DTT **63** was obtained in quantitative yield by bromination of **1** with *N*-bromosuccinimide (NBS), which was followed by treatment of **63** with *n*-butyllithium and then addition of dimethylformamide to obtain the dicarbaldehyde-DTT **64**.

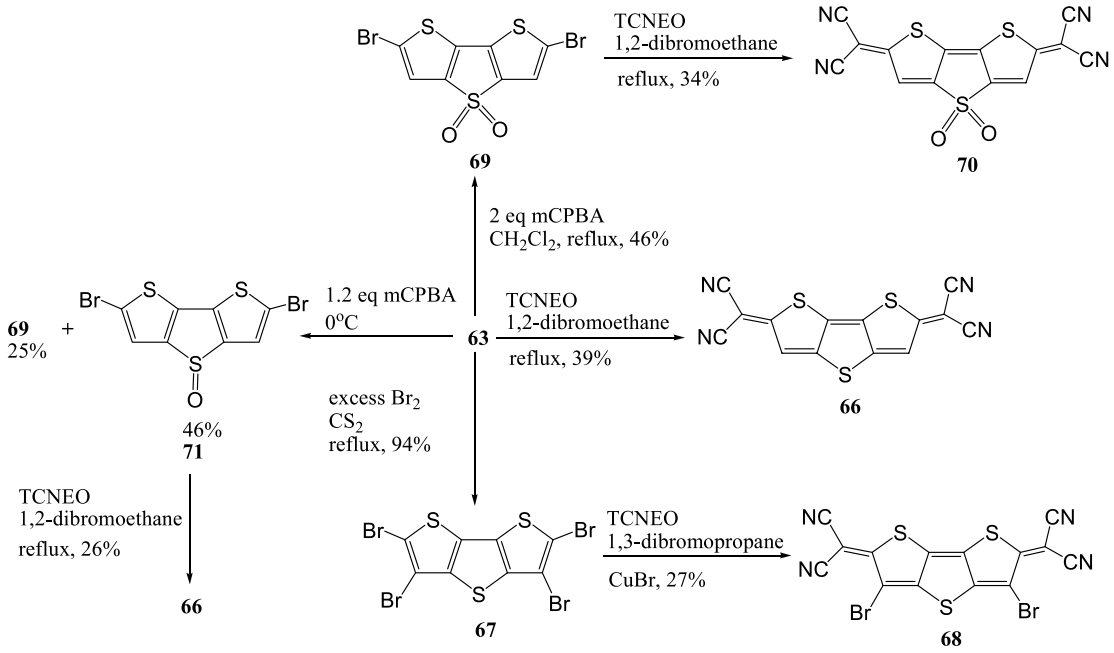


Scheme 14. Synthesis of diformyl-DTT.

To investigate the host–guest compositions and the conformation of the host molecules in crystalline inclusion compounds, a series of analogues of **1** and **17** were prepared by lithiation and then reacting with di(cyclohexyl)ketone, benzophenone and fluorenone to obtain **64a–c** and **65c** (Scheme 15).[27] A charge-transfer complex of **64c** with the electron acceptor, dichlorodicyanobenzoquinone (DDQ), was prepared and the X-ray crystal structure of the complex was reported.[28]

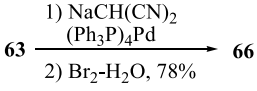


Scheme 15. Synthesis of analogues of **1** and **17**.

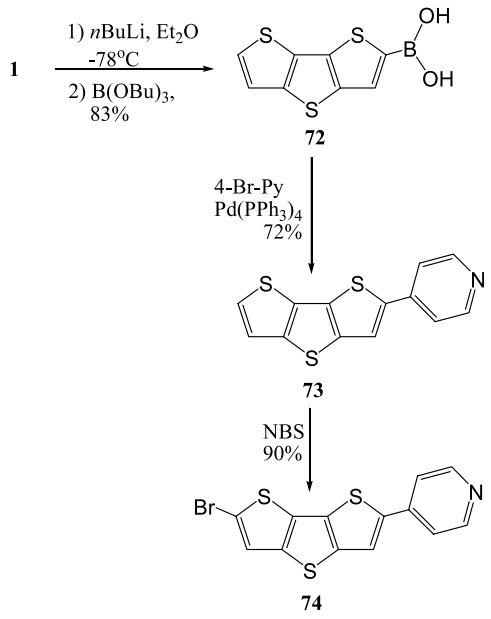


Scheme 16. Synthesis of analogues of DTT, bearing dicyanomethylene groups.

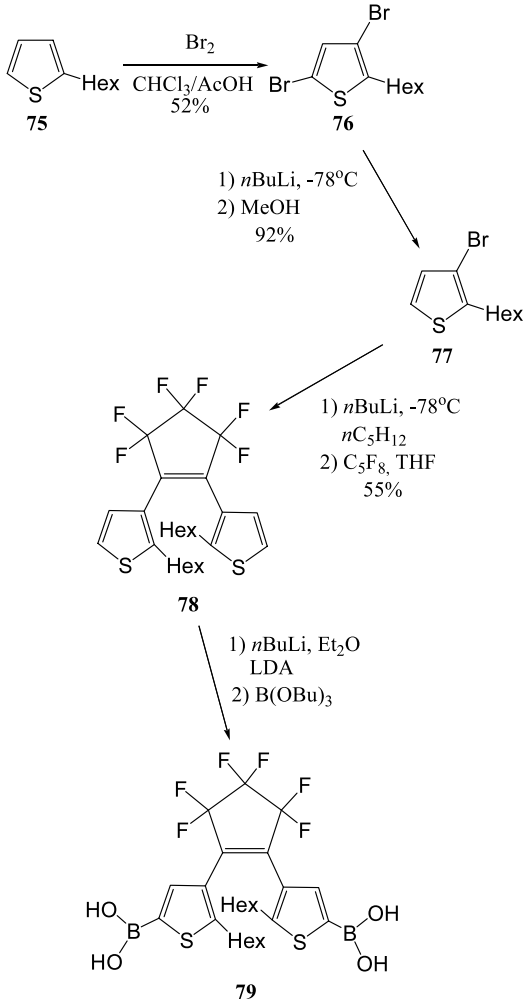
In 1989, electron-acceptor derivatives of **1** bearing bis(dicyanomethylene) were synthesized[29] by applying the Gronowitz reaction,[30] which is conversion of a 2,5-dihalothiophene into a 2,5-bis(dicyanomethylene)-2,5-dihydrothiophene, using tetracyanoethylene oxide (TCNEO) (Scheme 16). When TCNEO was applied to the 2,5-dibromo-DTT **63**, the dicyanomethylene derivative **66**



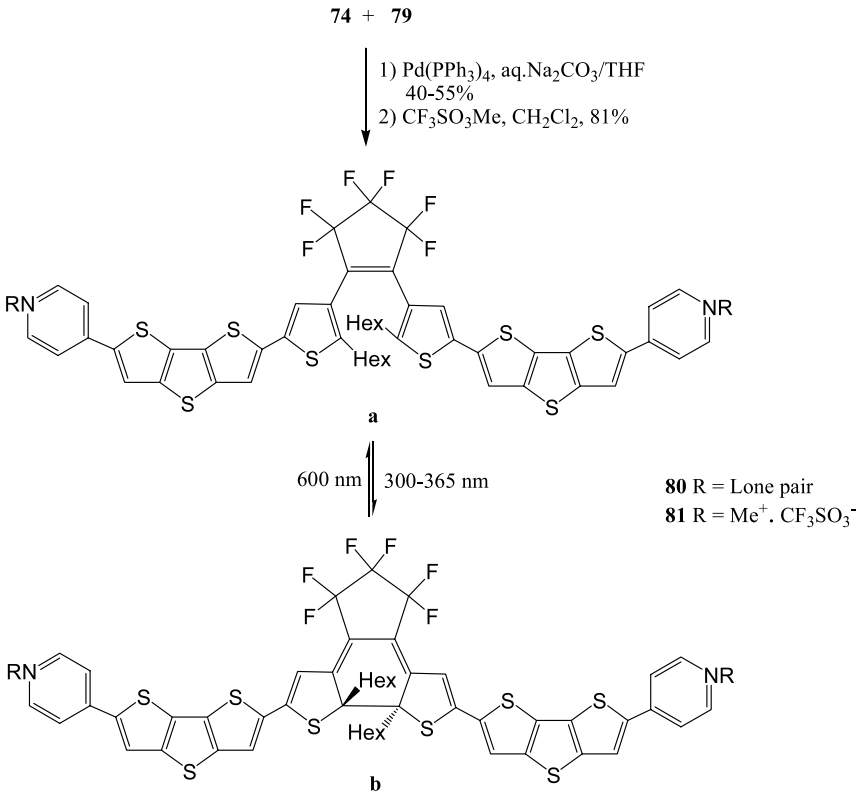
Scheme 17. Short synthesis of **66**.



Scheme 18. Synthesis of DTT, having pyridine unit **74**.



Scheme 19. Synthesis of the second intermediate **79**.

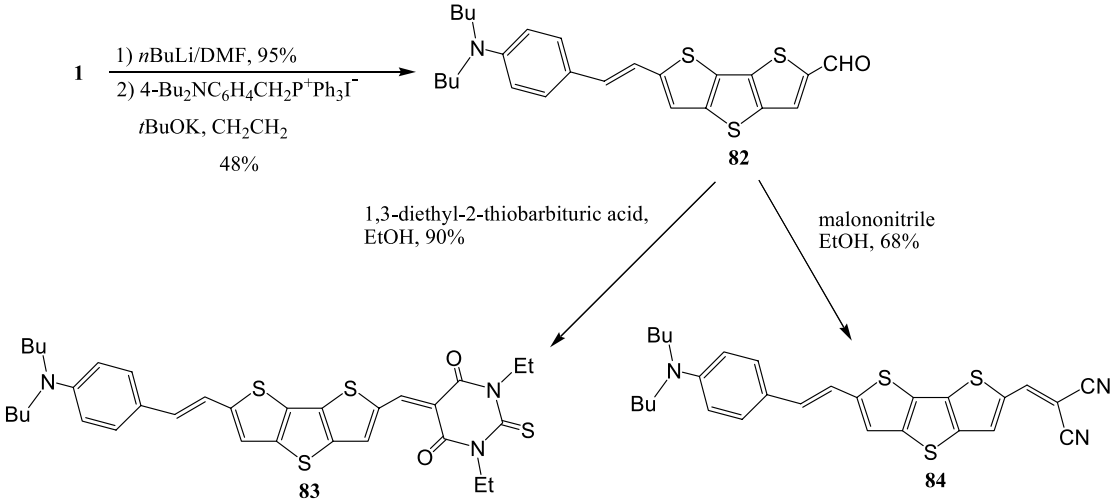


Scheme 20. Coupling of the intermediates **74** and **79**.

was obtained. The tetrabromo derivative **67**, which was synthesized by treatment of **63** with a large excess of bromine in refluxing carbon disulfide, was reacted with TCNEO in the presence of copper(I) bromide to obtain the dibromo-bis(dicyanomethylene)-DTT **68**.

To obtain the dioxide derivative, **63** was reacted with *m*-chloroperbenzoic acid (*m*CPBA) in refluxing dichloromethane, which gave the dibromo-DTT dioxide **69**. Treatment of **69** with TCNEO yielded the bis(dicyanomethylene)-DTT dioxide **70**. On the other hand, when **63** was oxidized with *m*CPBA at 0 °C, the monoxide **71** was obtained as the major product, along with **69**. Gronowitz reaction of **71** gave **66** in 26% yield. Furthermore, **66** was obtained in high yield (78%) when **63** was reacted with sodium dicyanomethanide in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium(0), followed by oxidation with bromine in water (Scheme 17).

Two dithienothiophene derivatives were synthesized as photoswitching materials in 1995.[31] The synthesis involved the preparation of two separate units **74** (Scheme 18) and **79**



Scheme 21. Introduction of donor and acceptor groups to **1**.

(Scheme 19), which were then coupled to obtain the desired target molecules **80** and **81** (Scheme 20). Dithienothiophene **1** was converted into its boronic acid derivative **72** by lithiation with *n*-BuLi and then reacting with tributyl borate (Scheme 18). Coupling of **72** with 4-bromopyridine in the presence of $Pd(PPh_3)_4$ yielded the pyridine-substituted dithienothiophene **73**, which was brominated with NBS to obtain the intermediate **74**.

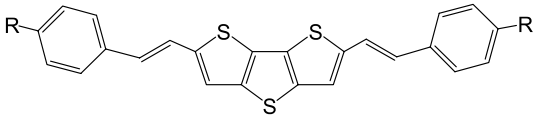
The second intermediate **79** was prepared starting with the bromination of 2-hexylthiophene **75** with bromine, which gave 3,5-dibromo-2-hexylthiophene **76** (Scheme 19). The bromine at C-5 of **76** was removed with *n*-BuLi and MeOH, and then two moles of 3-bromo-2-hexylthiophene **77** were lithiated and reacted with one mole of octafluorocyclopentene to obtain **78**. The intermediate **79** was then synthesized by lithiation of **78** and treatment with tributyl borate. Coupling of the intermediates **74** and **79**, using palladium, afforded the photoswitchable material **80**, the pyridyl groups of which were methylated with methyl trifluoromethanesulfonate to obtain its methyl pyridinium salt **81** (Scheme 20).

Quantitative ring closure of **80a** was observed to give **80b** when the compound was simply exposed to daylight. On the other hand, this did not happen with compound **81a**. It required irradiation at wavelengths of <400 nm to give 92% conversion into **81b**, and back conversion occurred in 98% yield on irradiation at $\lambda > 600$ nm.

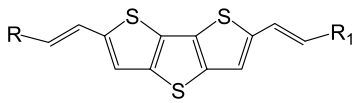
By adding donor (D) and acceptor (A) groups to the 2- and 6-positions of DTTs, various chromophores have been prepared. In 1996, nonlinear optical chromophores containing DTTs, with donor and acceptor groups, were synthesized to investigate their solvatochromic behaviour.[32,33] Recently, vibrational and quantum-chemical studies of these compounds were also reported.[34] The synthesis was carried out using the conventional reaction sequences (Scheme 21).

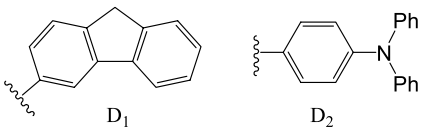
Double formylation of DTT **1** with *n*-BuLi/DMF was followed by the addition of a 4-*N*,*N*-dibutylaminobenzylidene group by means of a Wittig reaction to obtain the compound **82**, which had the D-DTT-A sequence. Then, the remaining aldehyde group was reacted with the acceptors, malononitrile and 1,3-diethyl-2-thiobarbituric acid, to obtain two new materials **83** and **84**, having the same D-DTT-A sequences. Their two-photon absorption and electrochemical properties were also reported.[35]

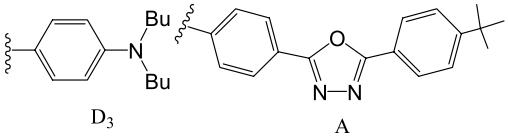
Quadrupolar fluorophores **85**, **86** and **87**, having electron-releasing or electron-accepting groups, with high two-photon excited fluorescence were prepared, following a similar synthetic strategy to that described above.[36,37,41]



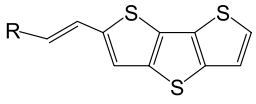
85 R = NBu_2 (D)
86 R = CF_3 (A)
87 R = NO_2 (A)



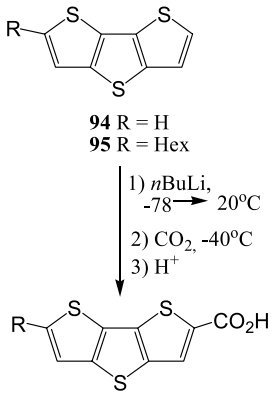




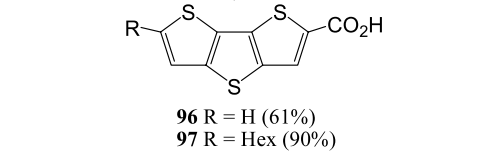
88 R = R_1 = D_1
89 R = D_1, R_1 = A
90 R = R_1 = D_2
91 R = D_2, R_1 = A
92 R = D_3, R_1 = D_3



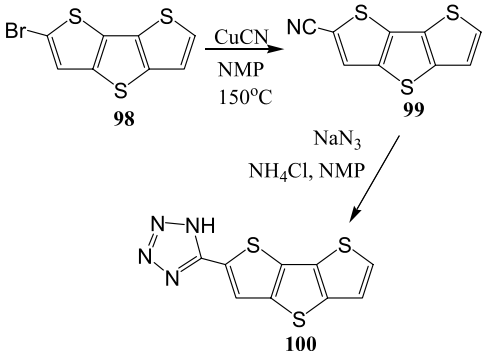
93 R = D_3



94 R = H
95 R = Hex



96 R = H (61%)
97 R = Hex (90%)



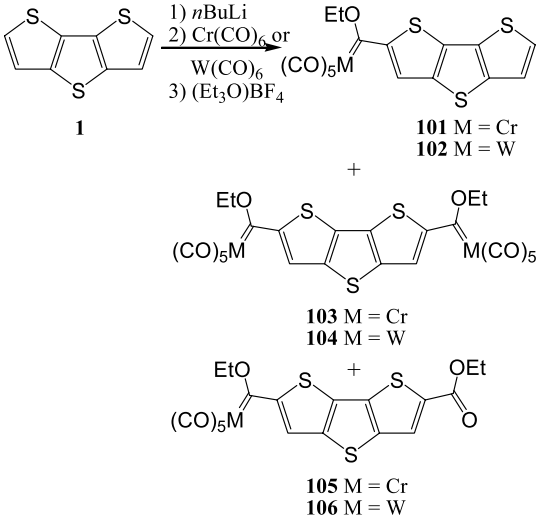
98 **99** **100**

Scheme 22. Synthesis of DTT derivatives having electroluminescent properties.

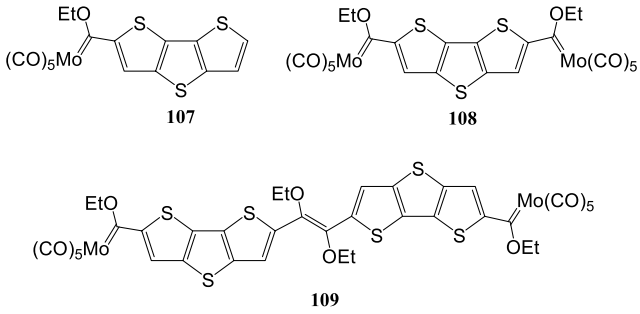
A new group of chromophores containing donor and acceptor side groups **88–93** were prepared, following the well-established formylation of **1** and employing the Wittig reaction sequence, and their two-photon-absorbing[38,39] photo/electroluminescent,[40] and optical/electrochemical[35,41] properties were investigated.

The synthesis and electroluminescent properties of DTT derivatives having carboxylic acid and tetrazole groups were reported (Scheme 22).[42,43] It was claimed that they show strong blue or blue-green photoluminescence in solution. The DTT derivatives **94** and **95**, the hexyl group of which was introduced by Friedel–Craft acylation with hexanoyl chloride and then reduction with lithium aluminium hydride in the presence of anhydrous $AlCl_3$, were converted into the carboxylic acid derivatives **96** and **97**, respectively, in three steps: (i) lithiation with *n*-BuLi; (ii) addition of CO_2 at −40 °C and (iii) acidification with HCl. Introduction of a tetrazole group was achieved by starting from DTT **1**, which was monobrominated to obtain 2-bromo-DTT **98**. This was then reacted with copper(I) cyanide in hot *N*-methylpyrrolidine (NMP) to give the corresponding nitrile **99**. The final product, tetrazole-DTT **100**, was synthesized by the reaction of **99** with a mixture of sodium azide and ammonium chloride in NMP.

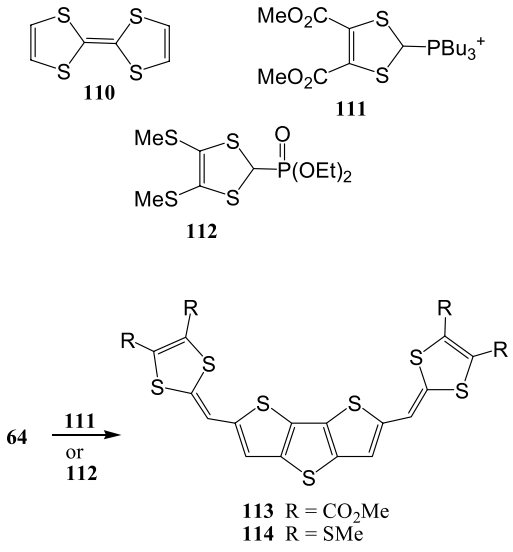
Chromium, tungsten and molybdenum biscarbene complexes of **1** were reported and their X-ray structures were disclosed (Scheme 23).[11,12] The dilithiated DTT **1** was treated with chromium or tungsten hexacarbonyl and subsequently quenched with alkylating agent $(Et_3O)BF_4$ to yield three products, monocarbene complexes **101** and **102**, biscarbene complexes **103** and **104** and oxidized products **105** and **106**.[11] When the same reactions were employed using molybdenum in place of chromium and tungsten, similar products **107**, **108** and a dimerized product, dinuclear biscarbene **109**, were obtained.



Scheme 23. Preperation of chromium and tungsten complexes of **1**.

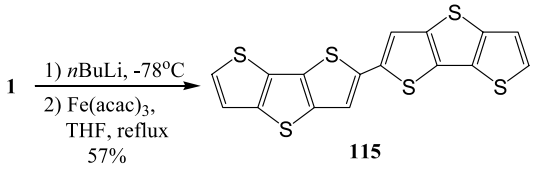


DTT **1** was also used as an extension unit in the synthesis of analogues of tetrathiafulvalene (TTF) **110**.[44] The synthesis was performed by applying Wittig or Wittig–Horner olefination reactions to the dialdehyde-DTT **64**, phosphorane **111** and phosphonate **112** (Scheme 24). The dialdehyde-DTT was reacted with both **111** and **112** to obtain the DTT derivatives **113** and **114**, respectively. Their cyclic voltammetry (CV) measurements exhibited two reversible one-electron transfer processes.



Scheme 24. TTF derivatives of **1**.

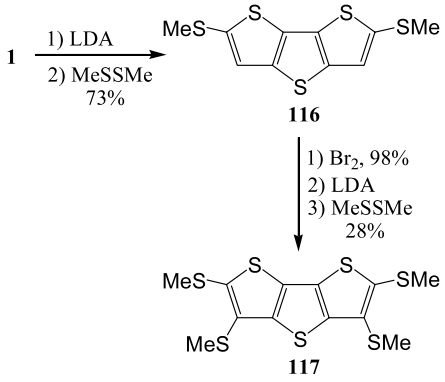
Dimerization of DTT was achieved using ferric acetylacetonate as the coupling reagent to produce new organic conductors for thin-film transistors (TFT) (Scheme 25).[45,46] Treatment of **1** with *n*-BuLi and then addition to a refluxing solution of ferric acetylacetonate gave the DTT–DTT dimer **115**, which was reported to have an unusual π-stacked structure, a very high on/off ratio and a wide HUMO–LUMO gap.



Scheme 25. Dimerization of **1**.

The di- and tetramethylthio-substituted DTT derivatives **116** and **117**, respectively, were synthesized by double

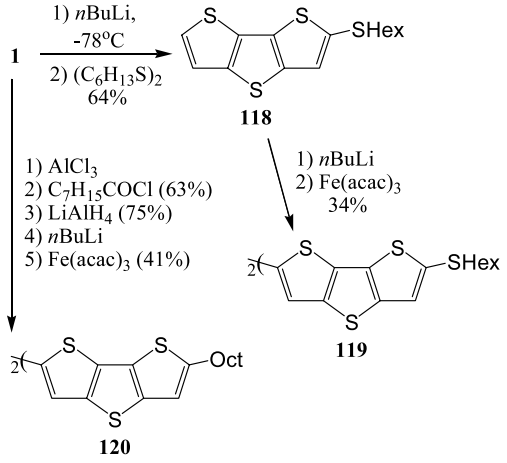
lithiation of DTT **1** and then reacting with dimethyl disulfide to obtain the bis(methylthio) derivative **116** (Scheme 26).[47] The tetramethylthio derivative **117** was then synthesized in three steps: (i) bromination of **116**; (ii) double lithiation with LDA, and (iii) treatment of the lithiated compound with dimethyl disulfide to yield the tetramethylthio derivative **117**.



Scheme 26. Synthesis of di- and tetramethyl derivatives of **1**.

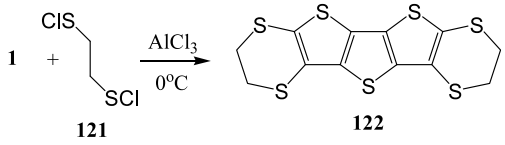
The electrochemical behaviour of the di- and tetramethylthio and dibromodimethylthio derivatives has been reported. All of these electron donors showed two reversible half waves of lower oxidation potentials. Their charge-transfer complexes with tetracyanoquinodimethane (TCNQ) and chloranil (CA) were prepared.

α,α′-Disubstituted bis(dithienothiophene) derivatives **119** and **120**, having long alkyl chains, were synthesized for organic thin-film transistors (Scheme 27).[48] Monolithiation of **1** and then treatment with dihexyl disulfide produced thiohexyl-DTT **118**, which was dimerized following the coupling procedure involving ferric acetylacetonate as the coupling reagent[45,46] to obtain dithiohexyl-bis-DTT **119**. Following the same protocol, dioctyl-bis-DTT **120** was synthesized, using the prior addition of octanoyl chloride DTT and reduction of the carbonyl group to the alkyl chain with $LiAlH_4$. It was reported that these materials exhibited high on/off ratios.



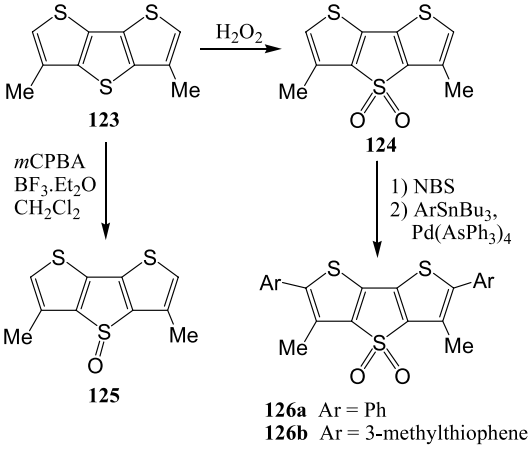
Scheme 27. Synthesis of substituted dimers of **1**.

On the way to making new electron donors, two dithiin groups were attached to the periphery of **1**.[49] The reaction of 1,2-ethanedisulfenyl dichloride **121**, which could be prepared by chlorinating ethanedithiol with sulfuryl chloride,[50,51] with **1** in the presence of $AlCl_3$ at 0 °C gave the dithiino-DTT **122** (Scheme 28).



Scheme 28. Synthesis of dithiin derivative of **1**.

The 4,4′-dioxide analogues of DTT **124**, with various substituents, have been synthesized in order to prepare light-emitting devices (LEDs) and fluorescent markers.[18,20,21,24] For the synthesis of LEDs, a well-established method was followed to obtain the 3,5-dimethyl-DTT **123**,[2] the oxidation of which with hydrogen peroxide and *m*CPBA gave the 4,4-dioxide **124** and 4-monooxide **125**, respectively (Scheme 29).[21] Bromination of **124** was followed by coupling with a phenyl- or thienyl-stannane in the presence of a palladium(0) catalyst, which gave the corresponding diphenyl-DTT dioxide **126a** and dithienyl-DTT dioxide **126b**, respectively.

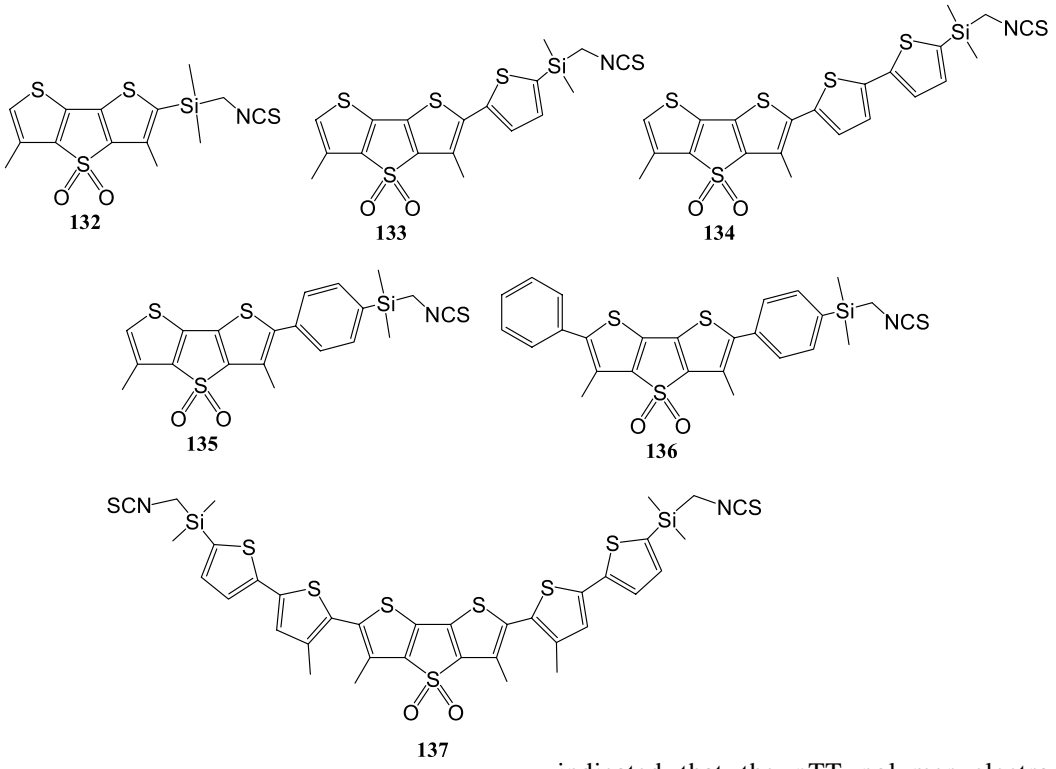


Scheme 29. Synthesis of substituted dioxide analogues of **1**.

A series of fluorescent markers as labelling agents for biological systems containing S,S-dioxide and isothiocyanates was synthesized.[18,24] Through their isothiocyanate groups, they form a stable linkage with bovine serum albumin and monoclonal antibodies. In the multistep synthesis, the intermediate compound, 3,5-diphenyl-DTT **62**, which was also synthesized through a different method by a separate group,[17] was prepared by following a conventional method.[11,12] Oxidation of **62** to the corresponding S,S-dioxide was performed with *m*CPBA, and then bromination with NBS was followed by Stille coupling with thienylstannane **127** in the presence of palladium to obtain **128** (Scheme 30). In the next step, **128** was brominated once more with NBS and then the second coupling with **129** afforded **130**. Treatment of the chloromethylsilyl side chain of **130** with sodium

thiocyanate produced the target labelling agent **131**, having a very reactive thiocyanate group.

Following the same methodology, various labelling agents **132–137** with efficient light-emitting properties were also synthesized.

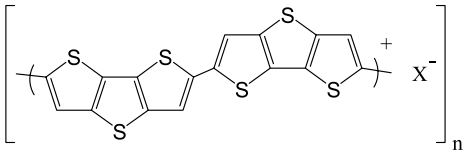


132 **133** **134** **135** **136** **137**

2.3. Poly-DTT (pDTT) 1, copolymers and properties

The thiophene-like nature of **1** enabled it to be polymerized electrochemically. Its first polymerization was conducted in 1985, which produced a cathode-active material **138**, doped with ClO_4^- and PF_6.[52,53]

It was reported that doped pDTT **1** presented some important features, which make it relevant for application in battery technology. On the other hand, it had a disadvantage of a fast self discharge. This was claimed not to be due to polymer degradation, as the pDTT electrodes could be recharged to recover their original voltage and cycling capabilities.[54] Therefore, rather than a degradation, the voltage decay due to a spontaneous undoping process of the polymer in solution was held responsible.



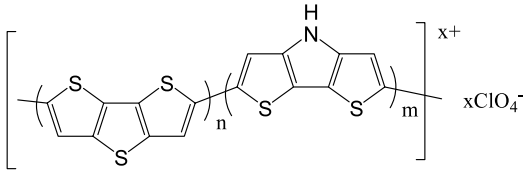
138 X = ClO_4^-, PF_6^-, $CF_3SO_3^-$,[55] Br^-[56]

Studies indicated that **1** had a lower irreversible oxidation potential compared to that of thiophene and pDTT, which showed a comparable oxidation potential with polythiophene.[55]

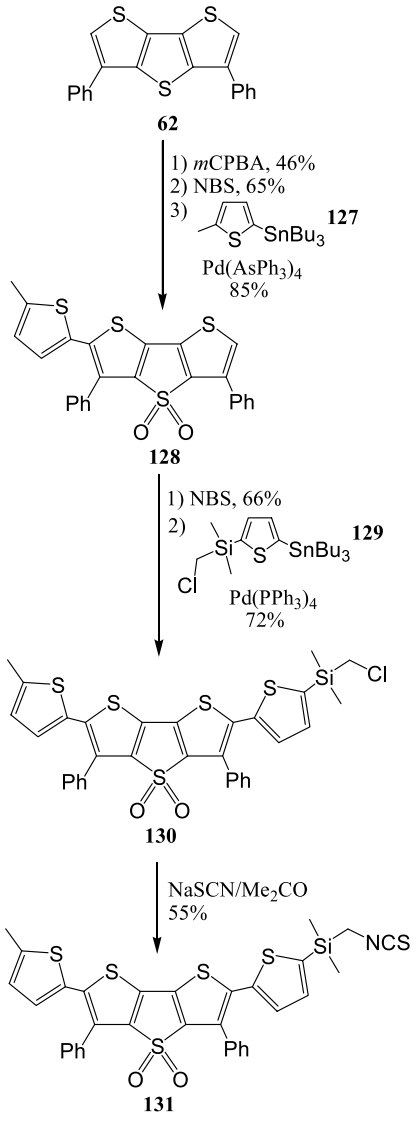
Further electrical and structural studies, including comparative studies with polythiophene (pT) and polythienothiophene (pTT), were also performed.[56–68] These studies indicated that the pTT polymer electrodes are not competitive in relation to their use as cathode active materials. It lacked fast kinetics of the doping–undoping process and high specific capacity. The pT and pTT showed similar properties, including the general problem of p-doped-based thiophene polymers, which is self discharge.

Studies on the electrochromic properties of pDTT revealed that it showed reversible electrochromic behaviour with a high contrast in colour between the red neutral state (absorption coefficient at 480 nm $\approx 3.5\times10^4\ cm^{-1}$) and the blue-black oxidized state.[69,70] It had a switching time of <1 s. It was reported to be a promising electrochromic material having a satisfactory stability to repeated switching and an optical memory up to 11,000 tested cycles.

A copolymer of **1** with dithienopyrrole, which formed the poly(dithienothiophene–dithienopyrrole)copolymer (pDTDP) **139**, was prepared by cyclic voltammetry and it was reported that a very stable junction with good rectifying characteristics was obtained.[71] Further studies indicated that pDTDP had good electrochromic characteristics.[72]



139



Scheme 30. Synthesis of derivative of **1** as a labelling agent.

Two new conjugate polymers incorporating **1** were synthesized by the Knoevenagel reaction (Scheme 31).[73]

Condensation of the 1,6-dialdehyde DTT **64** with the dinitriles **140** and **142** in the presence of *t*-BuOK produced the corresponding copolymers **141** and **143**, respectively (Scheme 31). The onset of their absorption was found to be in the near infrared, and the redox processes showed that both materials were p- and n-dopable. The polymer **141** was reported neither to be photovoltaic nor photoconductive.

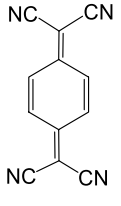
Photochemical polymerization[74,75] and photo-induced electron-transfer reactions of **1**, using laser flash photolysis,[76,77] were conducted in the presence of electron acceptors such as dinitrobenzene and CCl_4.

Nonlinear optical studies of **1**, to determine the relaxation kinetics and the size of the third-order nonlinear susceptibility, were also performed.[78,79]

The DTT and DTT-S,S-dioxide copolymers with thiophene were synthesized for photovoltaic applications and their blends with buckminsterfullerene C_{60} or TiO_2 were prepared.[22,23] Their synthesis involved coupling of the thienyltributylstannane **144** with both **63** and **69** to produce the monomers **145** and **147**, respectively, the polymerization of which, using $FeCl_3$, yielded the corresponding soluble polymers **146** and **148**, respectively (Scheme 32). It was reported that, while a C_{60} blend of **146** exhibited photo-induced electron transfer, **148** had a good interaction with TiO_2 nanoparticles and showed a photoluminescence quenching in copolymer/inorganic composites.

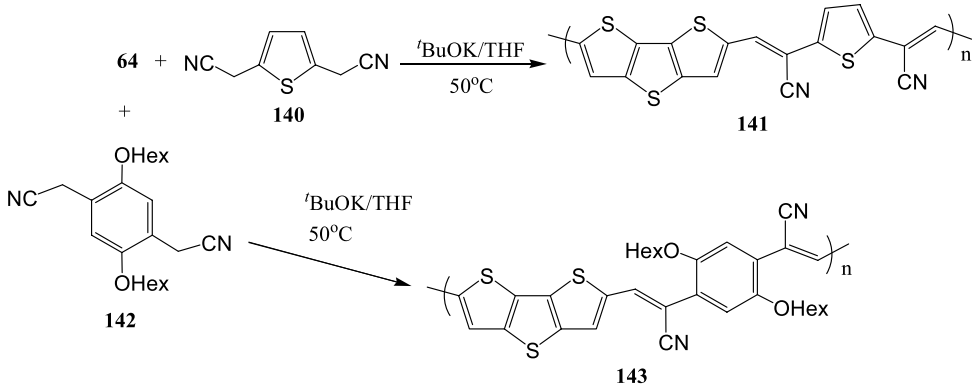
2.4. Miscellaneous

An X-ray single-crystal analysis of **1** was disclosed in 1983 and the crystals were monoclinic (space group $P2_1/n$).[80] In the same year, the charge-transfer complex of **1** with the electron acceptor 7,7,8,8-tetracyano-*p*-quinodimethane (TCNQ) **149**, was prepared and its X-ray diffraction analysis was reported.[81]

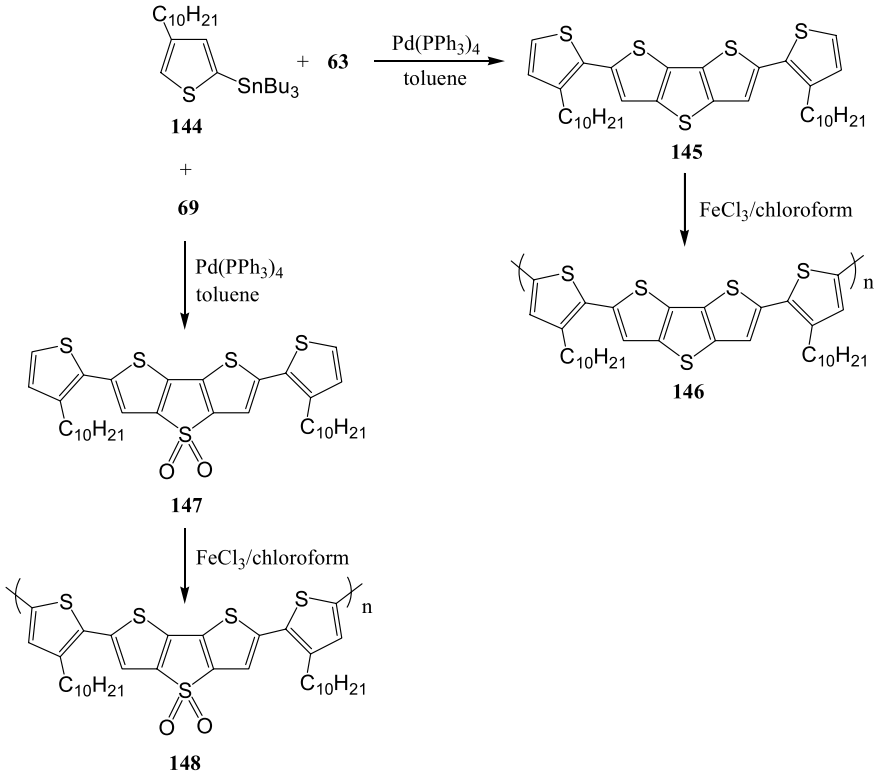


149

In a separate study, the conductivity of the charge-transfer



Scheme 31. Synthesis of conjugated polymers incorporating **1**.



Scheme 32. Synthesis of **1** and **1**-S,S-dioxide copolymers with thiophene.

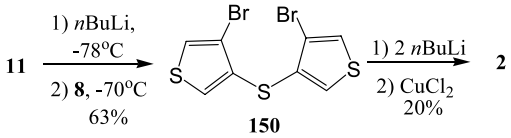
salt DTT–TCNQ was reported to be poor, which was related to its mixed-stack structure.[82]

Theoretical[83–90] and vibrational[91] spectral studies of **1** were presented by various groups.

3. Dithieno[3,4-*b*;3′,4′-*d*]thiophene 2

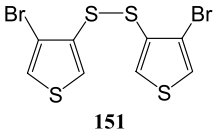
3.1. Methods to synthesize the ring system

The first synthesis of **2** appeared in 1971, along with the syntheses of its isomers **1**, **3** and **5** with a similar reaction sequence to the synthesis of **1**.[2] It utilized lithiation of 3,4-dibromothiophene **11** with *n*-BuLi and reaction with bis(phenylsulfonyl)sulfide **8** to obtain **150**, which was followed by dilithiation and then oxidative ring closure using $CuCl_2$ to afford the desired product **2** (Scheme 33).

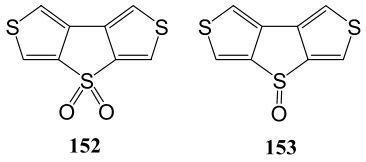


Scheme 33. First synthesis of **2**.

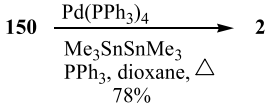
It was claimed that, alternatively, **150** could be obtained in high yield (83%) if the disulfide **151** was used in place of **8**.



Oxidation of **2** with hydrogen peroxide in acetic acid gave the corresponding sulfone **152**, along with the sulfoxide **153**.



The formation of dithieno[3,4-*b*;3′,4′-*d*]thiophene **2** following a different route appeared in 1997.[92,93] The reaction was performed by cyclization of **150** via palladium coupling using tetrakis(triphenylphosphinyl)palladium(0) and hexamethylditin, which afforded **2** in 78% yield (Scheme 34).

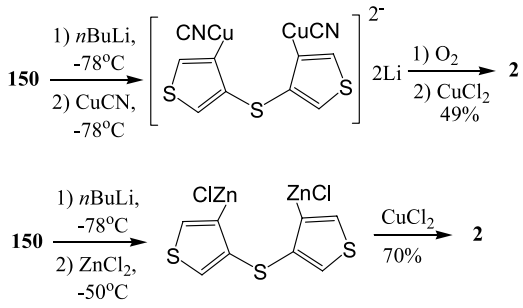


Scheme 34. Synthesis of **2**.

The same workers further developed the method and, using different reagents such as ate-type complexes and organozinc species, cyclization of **150** produced **2** (Scheme 35).[93]

3.2. Reaction and derivatization of the ring system

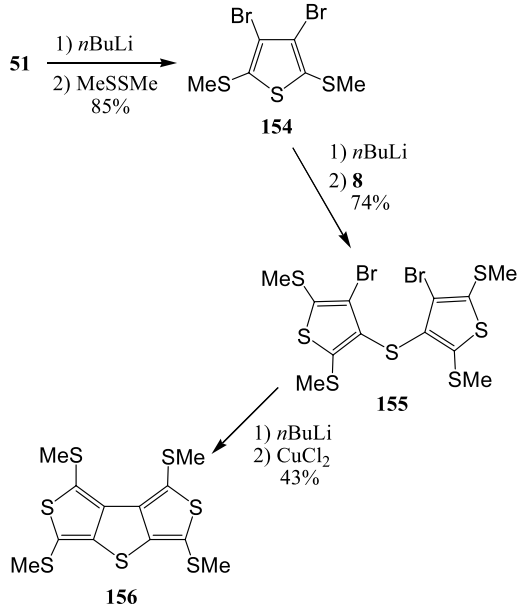
In order to prepare new donor molecules, a new DTT **2** analogue **156** having tetramethylthio groups was synthesized.[47] Its cyclovoltammetric behaviour, which demonstrated two reversible half waves at 0.82 and 1.14 V, cation



Scheme 35. Synthesis of **2**.

radical salts with PF_6 and AsF_6 and charge-transfer complex with chloranil were reported.

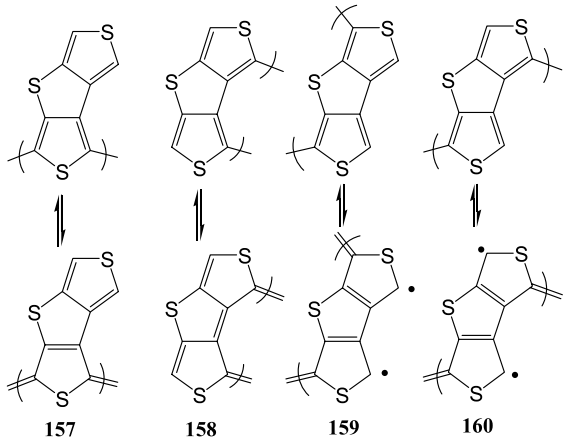
The synthesis started from tetrabromothiophene **51**, which was dilithiated using *n*-BuLi and then treated with dimethylsulfide to give 3,4-dibromo-2,5-dimethylthiophene **154** (Scheme 36). Following Jong and Janssen's well-established method,[2] **154** was then monolithiated and reacted with **8** to obtain the intermediate **155**, the oxidative coupling of which, applying the *n*-BuLi/$CuCl_2$ protocol, gave tetramethylthio-DTT **156**.



Scheme 36. Synthesis of tetramethylthio-**2**.

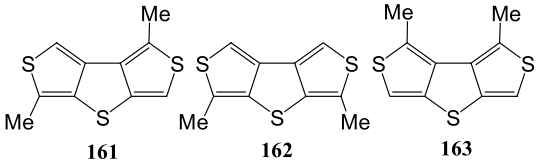
3.3. Poly-DTT 2, copolymers and properties

The first electropolymerization of **2** appeared in the literature in 1988, the oxidation potential of which remained constant at 1.04 V during the polymerization versus a standard calomel electrode.[94] Doping indicated that the polymer had one ClO_4^- ion for every three monomer units. Its electrical conductivity measured by the standard four-point technique gave a specific conductivity of 1.0 S cm^{-1}. An electrochromic study indicated that the polymer had a strong electrochromic effect. While its reduced (insulating) form was opaque, the oxidized (conductivity) state was colourless and semitransparent. Undoped (reduced) poly-DTT showed a low energy of the first π–π* electron transition with a maximum at 2.1 eV (590 nm) and a band gap of 1.1 eV, which are indications of the large π-electron delocalization.[95] As the molecule had four electroactive α positions, various possible polymerization situations **157–160** could be proposed (Scheme 37), among which **157** was found to be the more likely.[95–98]

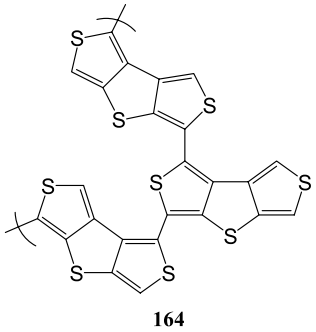


Scheme 37. Possible polymerization situations of **157–160**.

A mixture of dimethyl-substituted DTTs (DMeDTT) **161–163** in a ratio of 100:28:1, respectively, was synthesized,[99] following the conventional method.[2]

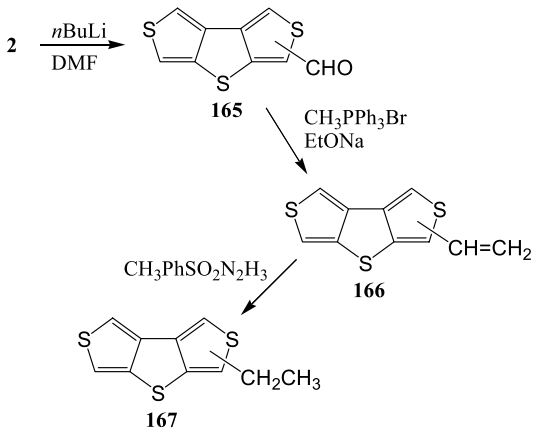


Electropolymerization of the mixture, unfortunately, gave only short oligomers, and, when DMeDTT was added to **2**, polymerization resulted in endcapping of the DTT oligomers and blocked formation of the conjugated polymer. Conclusions were reached that the structure of the poly-DTT was given by **164** and only two of the active α positions could be used among the four α positions during polymerization.



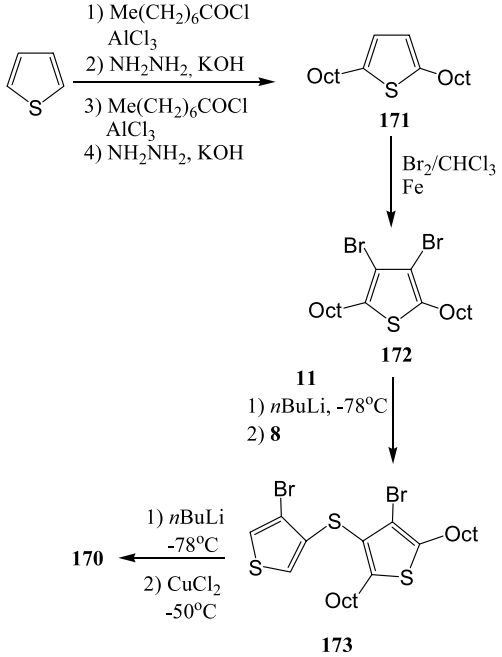
The DTT **2** was functionalized with either an ethylene or an ethyl group and polymerized to obtain new poly-DTTs.[100] The monomers **166** and **167** were synthesized starting with the formylation of **2** using *n*-BuLi and DMF to obtain **165**, which was converted into the monomer **166** through a

Wittig reaction (Scheme 38). Reduction of the ethylene chain of **166** using tosylhydrazine produced the second monomer **167**. Polymerization of **166** produced a grey film, which did not change colour during reduction. On the other hand, polymerization of **167** gave a blue-violet film, contrary to **166**, and its oxidation potential remained constant at 1.04 V (vs SCE). During reduction, the colour of the polymer shifted to grey, and it was found to be very sensitive to oxygen.

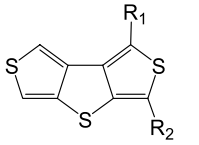


Scheme 38. Synthesis of the monomers **166** and **167**.

New DTT **2** analogues **168–170** having methyl and octyl groups at the 2- and 5-positions were synthesized and polymerized.[101,102] Additionally, the DTT 2-methyl derivative **169** was also synthesized by lithiation of **2** with *n*-BuLi at −78 °C and then treating with MeI.



Scheme 39. Synthesis of analogues of **2**.



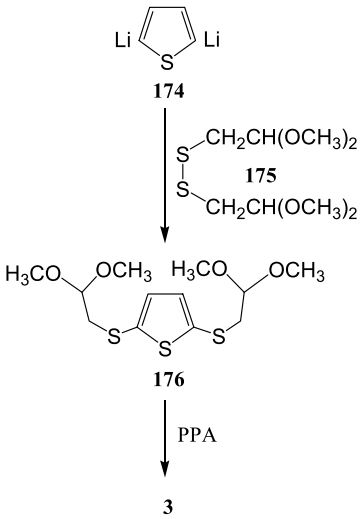
168 $R_1 = R_2 = Me$
169 $R_1 = H$, $R_2 = Me$
170 $R_1 = R_2 = Oct$

Contrary to the previous synthesis of dimethyl-DTT,[99] following the same conventional reaction path,[2] a mixture of 2,2′-, 2,5′- and 5,5′-dimethyl-DTT was claimed to be obtained. On the other hand, the 2,5-dioctyl derivative of DTT was synthesized as the only product starting from thiophene. Successive Friedel–Craft acylation and Wolf–Kishner reduction reactions gave 2,5-dioctylthiophene **171** (Scheme 39). Bromination of **171** gave 3,4-dibromo-2,5-dioctylthiophene **172**, a mixture of which with 3,4-dibromothiophene **11** was then lithiated and reacted with bis(phenylsulfonyl)sulfide **8** to yield **173**. Lithiation and oxidative coupling of **173** with $CuCl_2$ at −50 °C gave **170** as the only product. The mono- and dimethyl-DTT **168** and **169** were reported to be electrochromic and the dioctyl-DTT **170** underwent oxidation around 0.9 V, but dissolved from the electrode surface. Chemical polymerization of **170** was also performed with $FeCl_3$ in $CHCl_3$ to obtain the corresponding polymer, a thin-film of which, doped by exposure to iodine, had a conductivity of 5.1 S cm^{-1}.

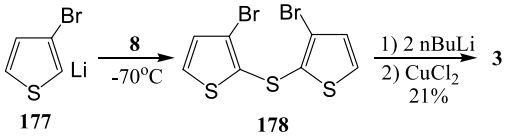
Electrochemical,[66,103–116] and photochemical[74–76,117] polymerization of **2** and their properties were also conducted by various research groups.

3.4. Miscellaneous

The X-ray single-crystal analysis of **2** was reported in 1988, the structure of which was monoclinic, $P2_1/n$.[118] A charge-transfer complex of theis donor was prepared with the acceptor TCNQ and its single-crystal analysis was also reported.[119] The conductivity of the single crystal was measured as $\sigma_{239\ K} = 2\times10^{-10}\ \Omega^{-1}\ cm^{-1}$.



Scheme 40. First synthesis of **3**.



Scheme 41. Second synthesis of **3**.

Theoretical calculations, including geometries and electronic spectra of the sulfone of **2**, were reported by various research groups.[84–87]

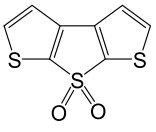
4. Dithieno[2,3-*b*;3′,2′-*d*]thiophene 3

4.1. Methods to synthesize the ring system

The synthesis of **3** first appeared in 1958, although no spectroscopic data were given.[120] The reaction of the dilithiated thiophene **174** with the disulfide **175** gave the disubstituted thiophene **176**, which underwent cyclization with polyphosphoric acid (PPA) in boiling chlorobenzene to obtain the DTT **3** (Scheme 40).

The second synthesis, with spectroscopic data, was reported in 1971.[2] This synthesis was similar to those of the analogues **1** and **2**, which were carried out by the same group.[2] 3-Bromo-2-lithiothiophene **177** was treated with **8** to produce the intermediate **178**, the subsequent oxidative coupling of which, with $CuCl_2$, yielded the DTT **3** (Scheme 41).

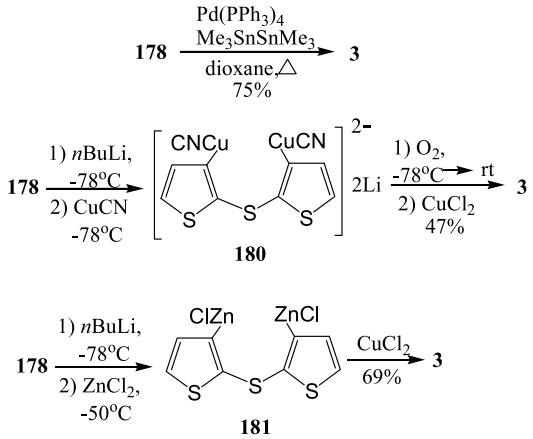
Oxidation of **3** with either H_2O_2 or *m*-chloroperbenzoic acid gave the corresponding 7,7-dioxide **179**, which showed a longer wavelength band in its UV spectrum.



179

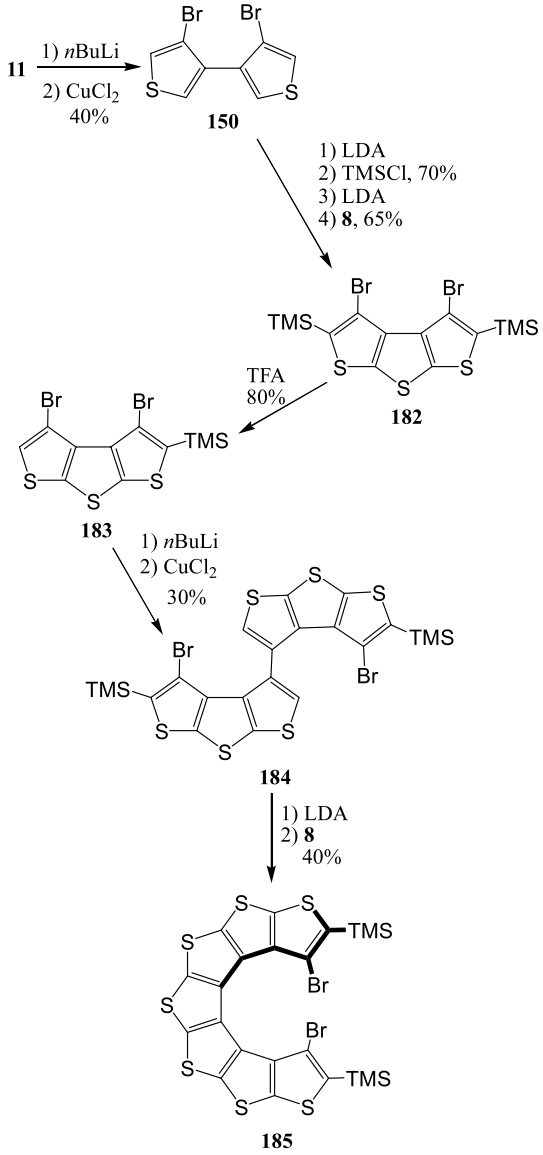
Alternative methods for coupling **178** to **3** employ palladium catalysis or ate-type copper complexes and organozinc species followed by $CuCl_2$-induced cyclizations (Scheme 42).[92,93] Palladium-catalyzed cyclization was performed on **178** using $Pd(PPh_3)_4$ and hexamethylditin, which produced **3** in 75% yield.

In the second method, **178** was initially dilithiated with *n*-BuLi and then reacted with CuCN to form the intermediate **180**, the oxidation of which with molecular oxygen from −78 °C to room temperature yielded **3**. Finally, the organozinc species **181** produced by treating **178** with *n*-BuLi and then $ZnCl_2$ at −50 °C was subsequently subjected to oxidative coupling using $CuCl_2$ to obtain **3**, (Scheme 42).

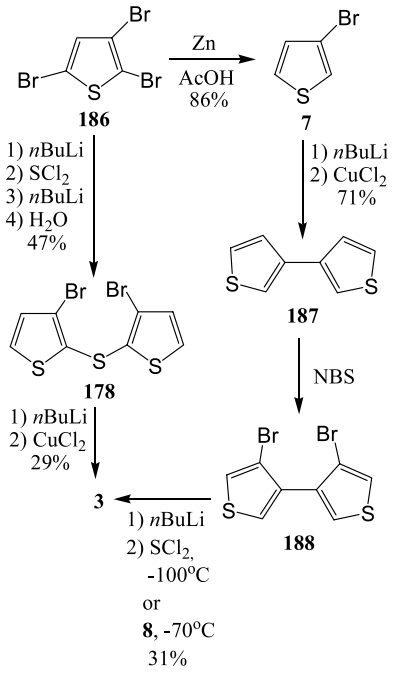


Scheme 42. Synthesis of **3** through coupling.

A heptathiophene analogue of DTT **3**, in which the thiophene rings are conjugated and annelated into a helix, has been reported.[121] 3,4-Dibromothiophene **11** was monolithiated with *n*-BuLi and coupled using $CuCl_2$ to produce 4,4′-dibromo-3,3′-bithienyl **150** (Scheme 43). TMS protection of the most acidic positions was followed by the introduction of sulfur with **8** to obtain the DTT **3** analogue **182**. One of the TMS groups was removed using



Scheme 43. Synthesis of a chiral heptathiophene analogue of **3**.

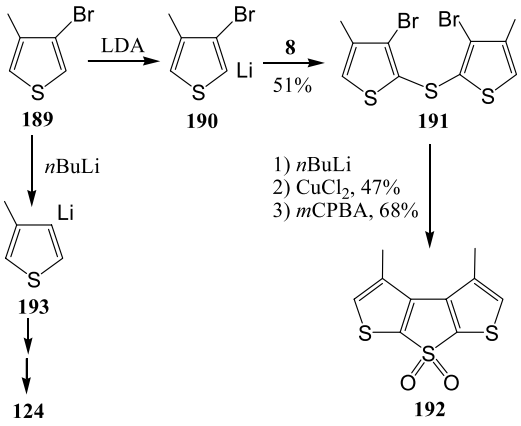


Scheme 44. Synthesis of **3** through two similar routes.

trifluoroacetic acid (TFA) to yield **183**. Treatment of **183** with *n*-BuLi and then oxidative coupling using $CuCl_2$ gave **184**, which was subsequently annelated to obtain the target compound **185**. The axial chirality was introduced in the final step.

The synthesis of DTT **3**, following two similar routes, was reported.[122] 2,3,5-Tribromothiophene **186** was employed as a starting material for both routes (Scheme 44). Treatment of **186** with zinc in acetic acid smoothly gave 3-bromothiophene **7**, which was lithiated and coupled with $CuCl_2$ to produce 3,3′-bithiophene **187**. Bromination of **187** with NBS gave **188**. Formation of the third thiophene ring on **188** was performed by lithiation and treatment with SCl_2, which yielded **3**. The second route, relatively shorter, was carried out by lithiation of tribromothiophene **186** and then treatment with SCl_2, followed by one more lithiation and reaction with H_2O to produce **178**. This was lithiated with *n*-BuLi and then coupled using $CuCl_2$ to give the target compound **3**.

The 3,4-dimethyl-7,7-dioxide derivative of **3** was synthesized to investigate its optical properties.[123] Although the synthesis was similar to the conventional synthesis of DTT, it was outlined that the use of the different lithiating agents such as *n*-BuLi or LDA resulted in different DTT isomers **2** or **3**, respectively (Scheme 45).[2,21] Lithiation of 3-bromo-4-methylthiophene **189** with LDA led to lithiation of α position to give **190**. Following the well-established method, **190** was reacted with **8** to produce **191**, which was converted into the dioxide **192** in three steps: (i) lithium–halogen exchange; (ii) coupling with $CuCl_2$ and (iii) oxidation with *m*CPBA. On the other hand, lithiation of **189** with *n*-BuLi yielded β-lithiation by replacement of bromine to form **193**, which led to the synthesis of **124**, following the same method describe above. The photoluminescence properties of sulfone **192** were reported to



Scheme 45. Synthesis of S,S-dioxide analogue of **3**.

make it less useful than the sulfone **124** for the preparation of molecular materials for electroluminescent devices.

The synthesis of further analogues of the mono- and diphenyl DTT-S,S-dioxides, **195** and **199**, respectively, was attempted (Scheme 46).[123] Treatment of **192** with NBS gave the corresponding monobromo derivative **194**. Unfortunately, all attempts for further bromination were unsuccessful. Moreover, the Stille coupling of **194** with phenyltributylstannane in the presence of palladium did not yield **195**. On the other hand, bromination of **196** with NBS smoothly gave the dibromo-DTT **197**, which was coupled with the phenylstannane to produce the 4,5-dimethyl-2,6-diphenyl-DTT **198**. Unfortunately, all attempts to oxidize the central S atom were unsuccessful.

Bis(benzothieno)thiophene **201**, an analogue of **3**, was synthesized as a byproduct in two ways starting from dibenzothienyl **200** (Scheme 47).[10] Treatment of **200** with either ethoxycarbonylsulfenyl chloride in the presence of $TiCl_4$ or with *n*-BuLi and then elemental sulfur resulted in the formation of **201**.

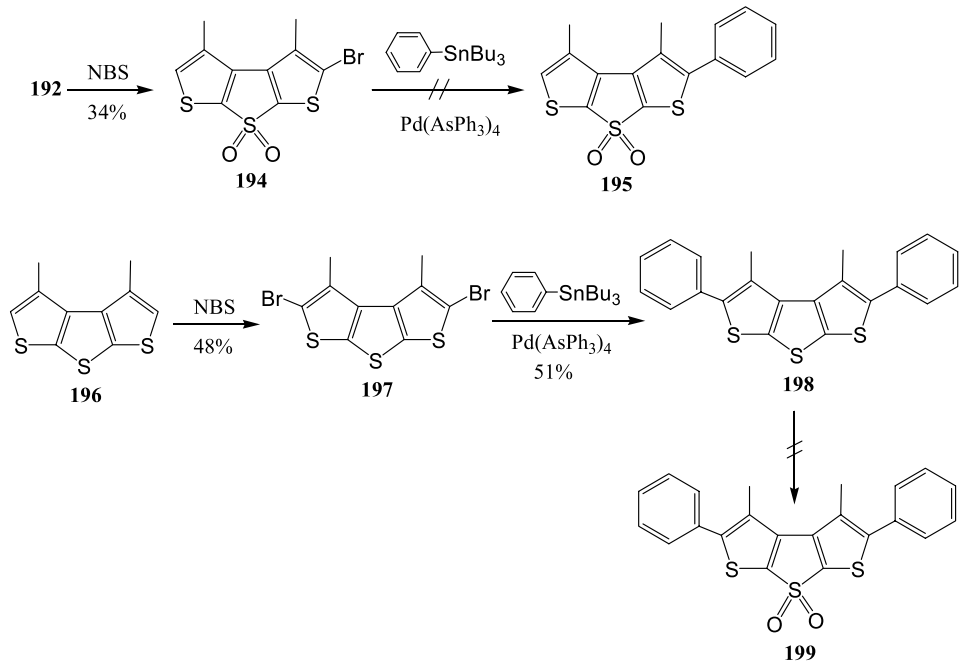
4.2. Miscellaneous

The theoretical and experimental proton chemical shifts of **3**, along with some condensed thiophenes,[124] and theoretical calculations, including electrophilic aromatic substitution,[19] geometries and electronic spectra, of its sulfone were reported by various research groups.[84–87]

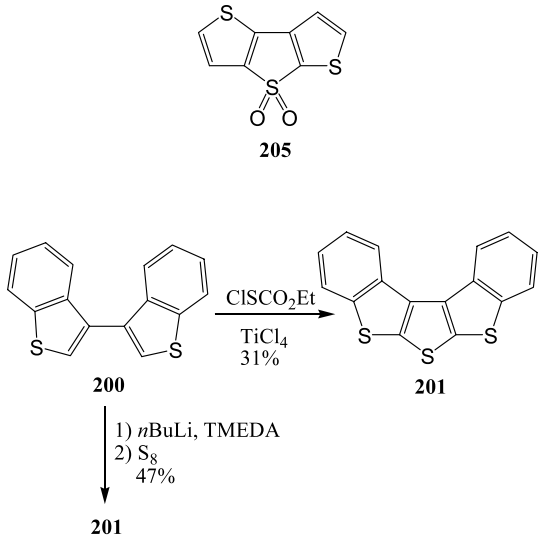
5. Dithieno[2,3-*b*;2′,3′-*d*]thiophene 4

5.1. Methods to synthesize the ring system

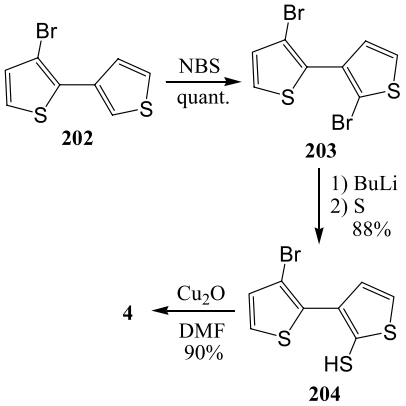
The only synthesis of **4** appeared in 1971 (Scheme 48).[125] It was prepared starting from 3-bromo-2-(thiophen-3-yl)thiophene **202**, which was brominated with NBS to obtain **203**. Monolithiation of **203** with *n*-BuLi was followed by the addition of elemental sulfur to yield the thiol **204**. This thermally unstable thiol was then directly treated with copper(I) oxide to form the third ring, which gave the target compound **4**. Oxidation of **4** with *m*CPBA provided the S,S-dioxide **205**.



Scheme 46. Synthesis of analogues of **3**.



Scheme 47. Synthesis of benzothiophene analogue of **3**.



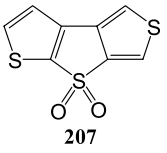
Scheme 48. Synthesis of **4**.

Theoretical calculations, including electrophilic aromatic substitution,[19] geometries and electronic spectra, of its sulfone were reported by various research groups.[84–87]

6. Dithieno[3,4-*b*;3′,2′-*d*]thiophene 5

6.1. Methods to synthesize the ring system

A similar synthesis of **5** to that of **3** was reported by the same group (Schemes 41 and 45), begining with the same starting material, 3-bromo-2-lithiothiophene **177**,[2] which was reacted with the disulfide **151** to afford the dibromodithienyl sulfide **206** (Scheme 49). Dilithiation with *n*-BuLi and then oxidative ring closure using $CuCl_2$ gave the target compound, dithienothiophene **5**, which was oxidized with *m*CPBA to obtain **207**.

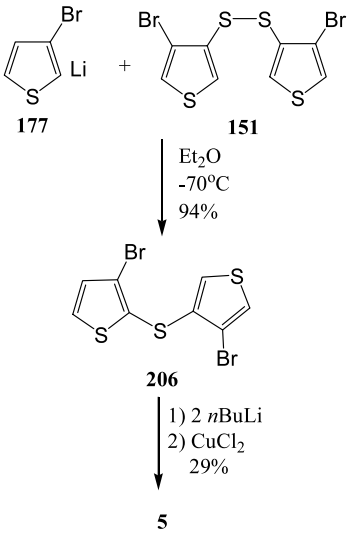


Theoretical,[85–87] and spectro- and electrochemical properties of the dithienothiophene **5** were investigated by various research groups.[66,116,126,127]

7. Dithieno[3,4-*b*;2′,3′-*d*]thiophene 6

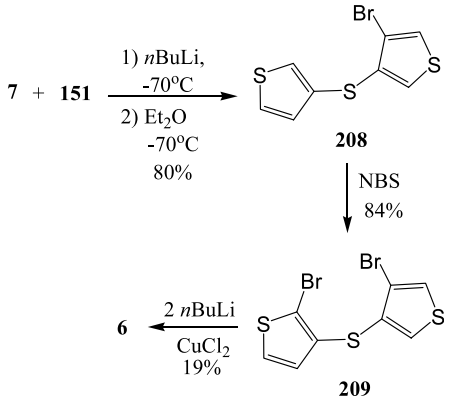
7.1. Methods to synthesize the ring system

The only method to synthesize **6** appeared in the literature in 1971,[125] using almost the same methodology as for the synthesis of **5** with a slight difference. Lithiation of 3-bromothiophene **7** with *n*-BuLi at −70 °C was followed by the addition of the disulfide **151**, which gave the

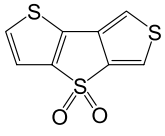


Scheme 49. Synthesis of **5**.

bromodithienyl sulfide **208**. Bromination of **208** with NBS yielded the dibromodithienyl sulfide **209**, which was then dilithiated with *n*-BuLi, and oxidative ring closure resulted in the formation of the target compound **6** (Scheme 50). Oxidation of **6** with *m*CPBA gave the corresponding S,S-dioxide **210**.



Scheme 50. Synthesis of **6**.



Theoretical,[85–87] and spectro- and electrochemical properties of the dithienothiophene **6** and polydithienothiophene were investigated by various research groups.[66,116,126–129]

Acknowledgements

We thank Istanbul Technical University and TUBITAK for supporting this work (TBAG 2378-103T122) and we thank Professor John D. Wallis (Nottingham Trent University) for his useful comments on the draft of the manuscript.

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Biographical sketch

Turan Ozturk was born in Kizilcaoren, a small village in Divrigi area in east central Anatolia, Turkey. He received his BSc and MSc degrees from Middle East Technical and Istanbul Technical Universities, respectively. He completed his PhD study at the University of East Anglia as a Turkish Government scholarship holder under the supervision of Professor A. McKillop on the synthesis of amphimedine alkaloid in 1990. He was then moved to the University of Kent at Canterbury to join Dr. John D. Wallis' group as a postdoctoral fellow (1991–1994), financed by SERC Molecular Electronics Committee and 21st Century Materials Initiative, and visiting research fellow (1995), where he worked on the synthesis of new bis(ethylenedithio)tetrathiafulvalene (BEDT-TTF) type organic superconductors and developed a new method for the synthesis of fused 1,4-dithiin and thiophene rings from 1,8-diketones using Lawesson's reagent and P_4S_{10}. In 1996, he took up a position as an Associate Professor at TUBITAK Marmara Research Centre, Gebze and then joined Istanbul Technical University as a full Professor in 2003. He has previously been British Council Research Fellow (1997), NATO Research Fellow (1997–1999) and Honorary Lecturer (1999) at the University of Kent at Canterbury as well as Senior Research Fellow at University of Waterloo, Canada (2000) and Lecturer at Middle East Technical University, Turkey (2003). His research interests concentrate on the development of new organic materials having electronic and optical properties, containing tetrathiafulvalene (TTF), dithienothiophene (DTT), dithienopyrrole (DTP), ethylenedioxythiophene (EDOT), ethylenedioxypyrrole (EDOP), ethenedithiothiophene (EDTT) and ethenedithiopyrrole (EDTP), as well as development of new organic reactions particularly the new reactions of Lawesson's reagent and P_4S_{10}.

Erdal Ertas was born in Erzincan, Turkey. He graduated from the University of Trakya in 1997 and completed his MSc and PhD studies in the University of Marmara under the direction of Professor Turan Ozturk in 2002 and 2005, respectively. His research focused on the development of new methodologies on the synthesis of new bis(ethylenedithio)tetrathiafulvalene (BEDT-TTF) and dithienothiophene (DTT) derivatives. He has been working at TUBITAK Marmara Research Centre as a researcher since 1997. His current research interests include the synthesis of new potential organic superconductors and conductors based on tetrathiafulvalene (TTF) and dithienothiophene (DTT) as well as development of new analysis and formulation methods for food chemistry such as toxics, additives and aroma formulation.

Olcay Mert was born in Saray, Tekirdag, Turkey. He graduated from Kocaeli University in 2002. He is currently a PhD student in Polymer Science and Technology Program under the direction of Professor Turan Ozturk and Professor Ayhan S. Demir at Middle East Technical University. His PhD research involves the synthesis of dithienothiophene (DTT) and ethenedithiothiophene (EDTT) type compounds and their electrochemical polymerizations. His other research area includes controlled release of anticancer drugs in biodegradable polymers.

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Tetrahedron 61 (2005) 11078–11106
Tetrahedron

Total synthesis of zaragozic acid C by an aldol-based strategy

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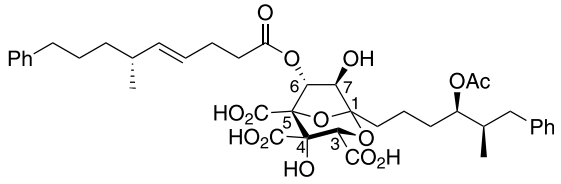
Received 10 August 2005; revised 9 September 2005; accepted 12 September 2005

Available online 7 October 2005

Abstract—A total synthesis of zaragozic acid C by a convergent strategy is described in which the key features include (1) the simultaneous creation of the C4 and C5 quaternary stereogenic centers by a $Sn(OTf)_2$-promoted aldol coupling reaction between an α-keto ester and a silyl ketene thioacetal derived from L- and D-tartaric acids, respectively, (2) the direct introduction of lithium acetylide as the C1 side chain equivalent onto the fully functionalized aldehyde, and (3) construction of the bicyclic core structure by acid-catalyzed internal ketalization under kinetically controlled conditions.

1. Introduction

The zaragozic acids and squalestatins, fungal metabolites isolated and characterized independently by researchers at Merck,[1] Glaxo,[2] and Tokyo Noko University/Mitsubishi Kasei Corporation[3] in 1992, have been shown to be picomolar competitive inhibitors of the enzyme squalene synthase. Consequently, they are considered to be promising lead compounds for the development of new serum cholesterol-lowering drugs.[4] Some members of this family have also been found to display farnesyl-protein transferase inhibitory activity,[1e,5] which has implications in the development of antitumor agents. Structurally, these molecules share a 4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]-octane-3,4,5-tricarboxylic acid core with an array of six stereogenic centers including contiguous quaternary ones, and represent considerable variations in the C1 alkyl and C6 acyl side chains. The gross structural similarity between presqualene pyrophosphate (PSPP) and zaragozic acids, that is, a highly acidic central core with two long lipophilic side chains, has led to the speculation that zaragozic acids inhibit squalene synthase by effectively mimicking the binding of PSPP to the enzyme.[1c,3] Due to the biological activity of these compounds and their novel structural aspects, zaragozic acids (squalestatins) have elicited considerable attention from numerous synthetic chemists.[6,7] Of a variety of approaches to preparing the densely oxygenated 2,8-dioxabicyclo[3.2.1]octane ring system by innovative strategies and tactics, the two research groups of Carreira[8] and Nicolaou[9] accomplished the first total syntheses of zaragozic acid C (**1**) and zaragozic acid A, respectively, in 1994. Since then the Evans[10] and Armstrong[11] groups reported the total syntheses of **1**, while the efforts of the Heathcock,[12] and Tomooka and Nakai[13] groups culminated in the total syntheses of zaragozic acid A. In addition to the six total syntheses, a total synthesis of 6,7-dideoxysqualestatin H5, a less oxygenated congener of the zaragozic acids, has also been reported by Martin and co-workers.[14] All of these approaches involve internal ketalization to construct the core structure; only Heathcock adopted a stepwise approach, wherein the full C1 alkyl side chain was installed after the ketalization event. Our own efforts in this area have led to two total syntheses of zaragozic acid C (**1**) through entirely distinct routes based on an aldol approach[15] and a carbonyl ylide cycloaddition approach,[16] respectively. In this article, we describe the details of the total synthesis of **1** by the aldol-based strategy.



Zaragozic Acid C (**1**)

2. Results and discussion

2.1. Synthetic plan

The main problem in zaragozic acid synthesis is the construction of the highly oxygenated bicyclic core bearing an array of six stereogenic centers, including contiguous

Keywords: Zaragozic acids; Aldol reaction; α-Keto ester; Silyl ketene thioacetal; Internal ketalization.
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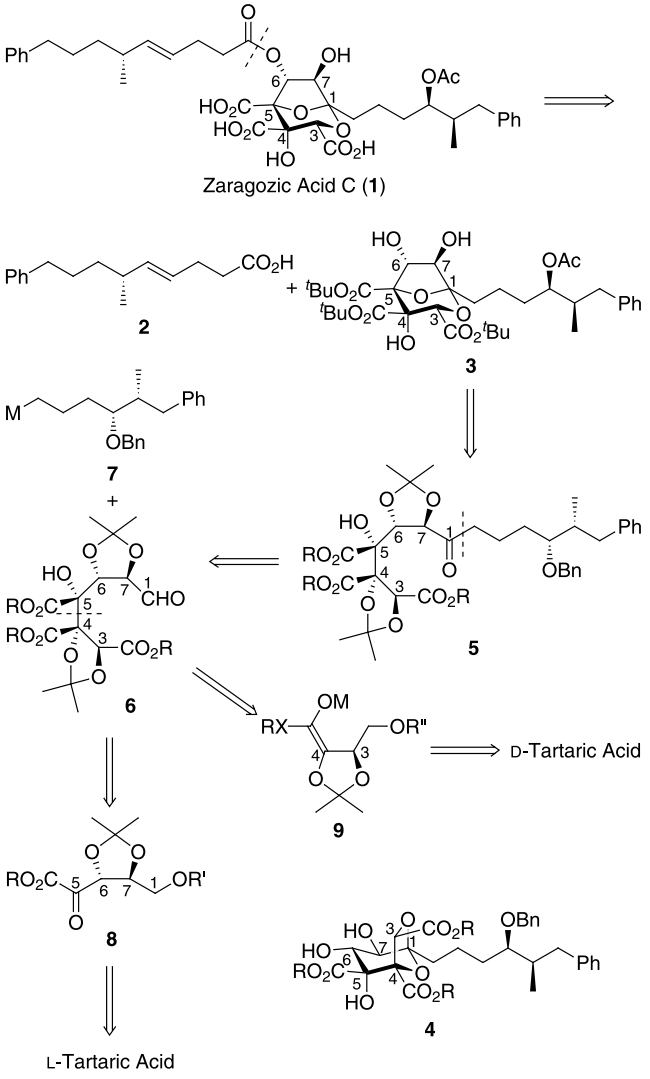
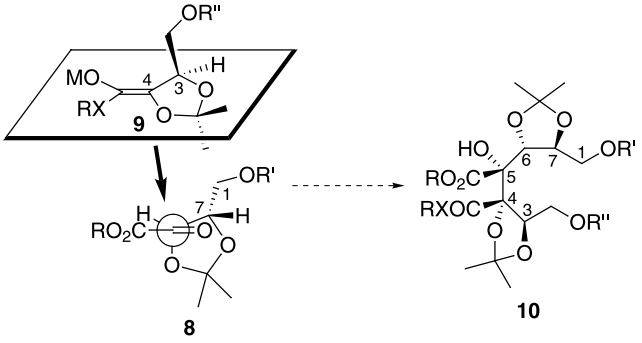
doi:10.1016/j.tet.2005.09.030

quaternary ones. Our retrosynthetic analysis of zaragozic acid C (**1**) originated from the identification of L- and D-tartaric acids in the core structure (Scheme 1).[17] While some concern arose over the formation of the isomeric bicycloketal **4**, we expected that the natural 2,8-dioxabicyclo[3.2.1]octane core structure **3** would be thermodynamically more stable than **4**. We envisioned that the addition of the metalated C1 alkyl side chain equivalent **7** to aldehyde **6**, followed by oxidation, would provide the ketalization precursor **5**. The aldol moiety in **6** allowed the indicated disconnection, defining the tartrate-derived α-keto ester **8** and enolate **9** as potential intermediates. This approach has the advantage of minimizing the use of protecting groups and oxidation state manipulation.



Scheme 1. Retrosynthetic analysis of zaragozic acid C (**1**).

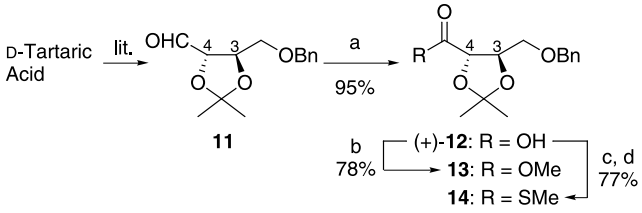
With regard to the aldol reactions associated with our scenario, Seebach and co-workers reported that the acetonide derivative of dimethyl L-tartrate could be deprotonated without β-elimination by LDA at −78 °C to provide the corresponding lithium enolate, the reaction of which with acetone took place preferentially from the less hindered face to give a 4:1 mixture of adducts in 60% yield.[18] Provided that the nucleophilic addition of enolate **9** to α-keto ester **8** occurs in accord with the Felkin-Anh model, the formation of the desired stereoisomer **10** with the correct stereochemistry would be expected (Eq. 1).[19]



(1)

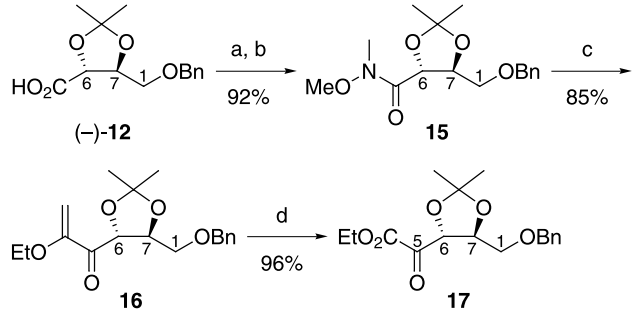
2.2. Preparation of substrates for the aldol coupling

At the outset of our studies, a number of enolate precursors and α-keto esters were prepared to investigate the key aldol reaction. The enolate precursors **13** and **14** were readily available via short synthetic routes depicted in Scheme 2. The known D-tartaric acid-derived aldehyde **11**[20] was subjected to a Pinnick oxidation[21] to give carboxylic acid (+)-**12** in 95% yield. Treatment of (+)-**12** with CH_2N_2 in Et_2O afforded methyl ester **13** in 78% yield, whereas the corresponding thioester **14** could be obtained through the intermediacy of the acid chloride in 77% yield in two steps.



Scheme 2. Reagents and conditions: (a) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH–H_2O, 18 h; (b) CH_2N_2, Et_2O, 0 °C, 30 min, then rt, 30 min; (c) $(COCl)_2$, cat. DMF, CH_2Cl_2, 1.5 h; (d) 20% aqueous MeSNa, Bu_4NI, CH_2Cl_2, 0 °C, 10 min.

On the other hand, α-keto ester **17** could be prepared from the L-tartaric acid-derived carboxylic acid (−)-**12** in four steps via the α-keto vinyl ether intermediate **16** (Scheme 3).[22] The reaction of (−)-**12** with $(COCl)_2$,

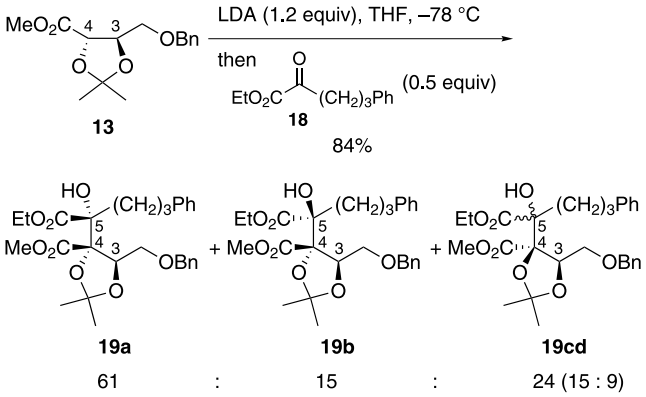


Scheme 3. Reagents and conditions: (a) $(COCl)_2$, cat. DMF, CH_2Cl_2, 30 min; (b) MeONHMe·HCl, pyridine, CH_2Cl_2, 0 °C, 1 h; (c) ethyl vinyl ether (EVE), ^{t}BuLi, THF, −78 °C, 3 h; (d) O_3, CH_2Cl_2, −78 °C, 10 min, then Me_2S, −78 °C to rt, 1 h.

followed by condensation with *N*,*O*-dimethylhydroxylamine hydrochloride, afforded the Weinreb amide **15** in 92% yield, which upon treatment with lithiated ethyl vinyl ether gave the α-keto vinyl ether **16** in 85% yield. Ozonolysis of **16** furnished the desired α-keto ester **17** in 96% yield. The synthetic schemes described above proved to be effective for a variety of thioesters and α-keto esters. Since the tartrate-derived α-keto esters were prone to hydration, they were azeotropically dried with benzene prior to use.

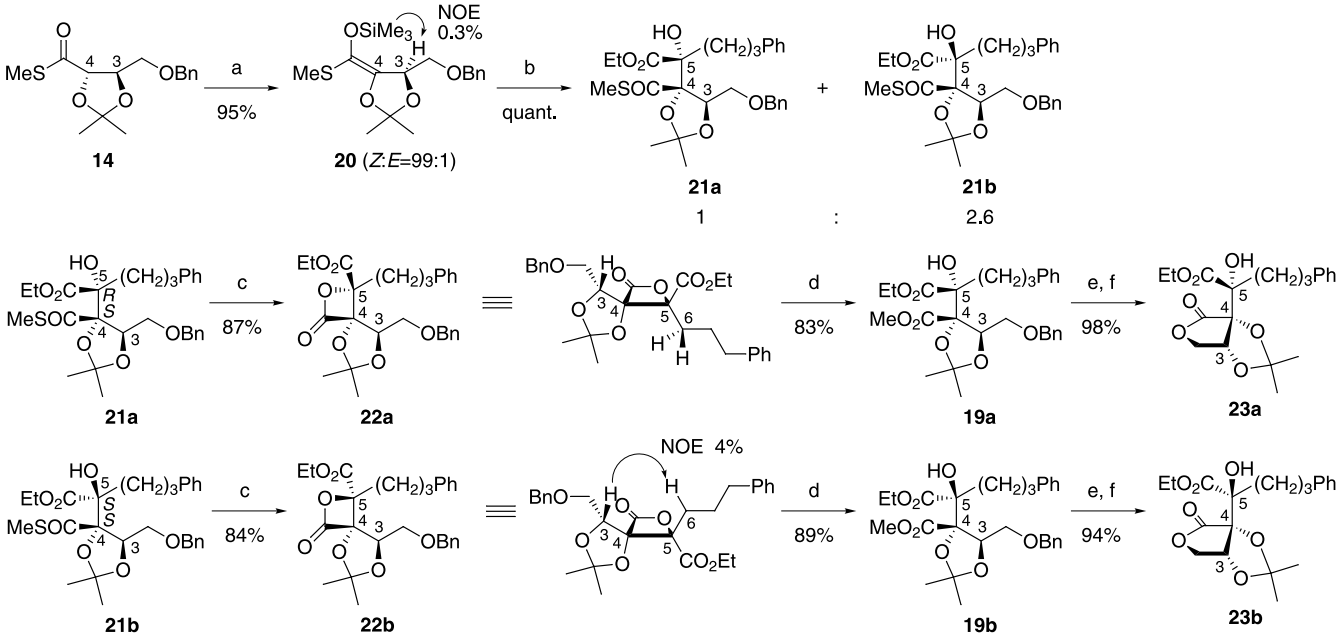
2.3. Aldol reaction

With the enolate precursors and α-keto esters in hand, we then proceeded to investigate the key aldol coupling reaction. Since the simultaneous creation of the consecutive quaternary stereogenic centers by an aldol reaction of α-keto esters is unprecedented in the literature,[23,24] we felt it was prudent to test the viability of the reaction using a simple α-keto ester. The known compound **18**[25] was then chosen as a model substrate for the reaction. We initially explored the reaction of the lithium enolate derived from ester **13** with α-keto ester **18** (Eq. 2). Treatment of ester **13** with LDA at −78 °C followed by the addition of α-keto ester **18** led to an inseparable mixture of four aldol adducts **19** in 84% combined yield, the ratio of which was determined to be 61:15:15:9 by 270 MHz ^{1}H NMR. The stereochemical assignment of the two isomers **19a** and **19b** will be presented later (vide infra). A similar result (84% yield, dr=60:17:16:7) was obtained when HMPA was used as a co-solvent. However, under these conditions the reaction with **17** did not proceed beyond a 50% conversion. As a result, we were prompted to investigate the Lewis acid-promoted aldol reaction.



(2)

The enolate precursors **13** and **14** could be converted to the corresponding silyl ketene acetals by treatment with LiHMDS at −78 °C followed by the addition of TMSCl (Scheme 4). Although the hydrolysis-prone silyl ketene acetal derived from ester **13** could not be obtained in synthetically useful levels of purity in our hands, silyl ketene thioacetal **20** (*Z*/*E*=99:1), derived from thioester **14** in 95% yield, was more stable than the corresponding ester derivative,[26] and could be purified on Florisil. The stereochemistry of the major isomer was verified by ^{1}H NOE correlation (0.3%) between Si(C*H*$_3$)$_3$ and the methine proton in **20**. At the inception of this project, several literature reports appeared documenting the effectiveness of $TiCl_4$ and $Sn(OTf)_2$ as promoters in the Mukaiyama aldol addition to α-keto esters.[23b–g] While $TiCl_4$ had no effect on the reaction of α-keto ester **18** with silyl ketene thioacetal **20**, the use of $Sn(OTf)_2$ in EtCN, a combination developed for aldol reactions of pyruvates by Kobayashi and co-workers,[23e,g,27] resulted in a quantitative reaction, whereby a 1:2.6 mixture of two adducts **21a** and **21b** with

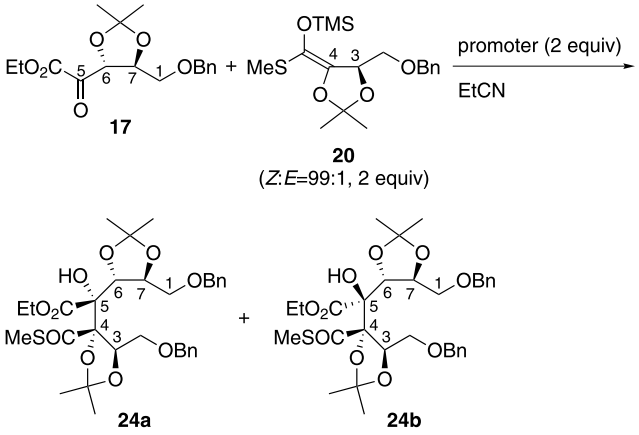


Scheme 4. Reagents and conditions: (a) LiHMDS, THF, −78 °C, 30 min, then TMSCl, −78 °C, 1 h, and rt, 15 min; (b) α-keto ester **18**, $Sn(OTf)_2$, EtCN, −78 °C, 30 min; (c) $Hg(OCOCF_3)_2$, MeCN; (d) K_2CO_3, MeOH; (e) H_2, 10% Pd/C, EtOH, 2 h; (f) DMAP, CH_2Cl_2, 1 h.

the correct stereochemistry at C4 out of the four possible diastereomers was obtained. The absolute stereochemical relationship of each of the easily separable diastereomers was determined based on the C3 stereocenter, the configuration of which was secure. The treatment of each diastereomer with $Hg(OCOCF_3)_2$ in MeCN resulted in the formation of β-lactone,[28] thus affording **22a** and **22b**, respectively, in high yields. The ^{1}H NOE (4%) between C3–H and C6–H confirmed the relative stereochemical relationship between the quaternary stereocenters in **22b**, whereas the absence of an NOE between C3–H and C6–H in **22a** indicated an opposite relationship to that in **22b**. Methanolysis of β-lactones **22a** and **22b** afforded methyl esters **19a** and **19b**, respectively. Debenzylation of **19a** and **19b** followed by treatment with DMAP effected the γ-lactone formation, insuring the relative stereochemical relationship between C3 and C4. This sequence of experiments established the stereochemistry of **21a/19a** and **21b/19b** as 4*S*,5*R* and 4*S*,5*S*, respectively. Despite the lack of carbonyl diastereofacial selectivity, it appeared attractive for the present coupling that the $Sn(OTf)_2$-promoted reaction occurred exclusively from the less hindered *si*-face of silyl ketene thioacetal **20** due to the steric demands of the benzyloxymethyl group, thus creating the proper configuration at C4. Following these results, this reaction was applied to the more functionalized substrate **17**.

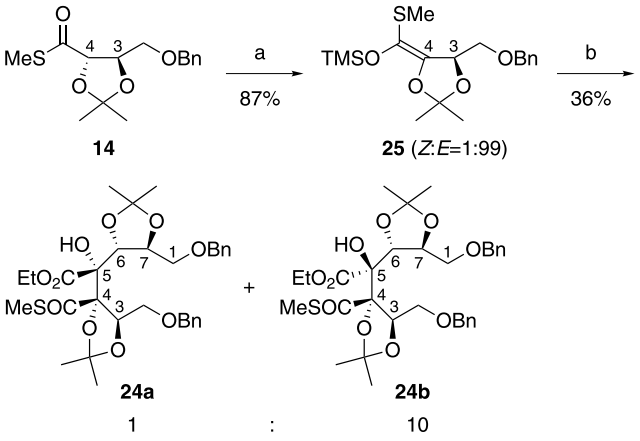
Under the foregoing conditions, the aldol reaction between α-keto ester **17** and silyl ketene thioacetal **20** (*Z*/*E*=99:1) proceeded to completion within 1.5 h to give a 1:2.2 mixture of aldol adducts **24a** and **24b** in 90% combined yield (Table 1, entry 1). In an effort to reverse the stereochemical outcome of the aldol reaction to give the desired stereoisomer, alternate conditions were investigated. A survey of reaction solvents (EtCN, CH_2Cl_2, toluene, THF, Et_2O) revealed that EtCN was the only solvent that permitted the present coupling to proceed. Of the Lewis acids screened, $Sc(OTf)_3$, TiF_4, and $(^iPrO)_2TiCl_2$ also promoted the formation of aldol adducts (entries 2–4). Although the diastereoselectivity could be improved by employing $(^iPrO)_2TiCl_2$ as a promoter, a much reduced yield (55%) was obtained, even when 5 equiv of **20** were used (entry 5). Kobayashi and co-workers demonstrated that the *syn*:*anti* stereoselectivity is controlled by the geometry of silyl ketene thioacetals in $Sn(OTf)_2$-promoted aldol additions to pyruvate esters.[23e,g,27] After considerable experimentation, it was found that the dropwise addition of KHMDS to the thioester **14** over a period of 2 h at −78 °C (inverse addition) followed by treatment with TMSCl furnished silyl ketene thioacetal **25** in 87% yield with virtually complete *E*-selectivity (*Z*/*E*=1:99, Scheme 5). Since the preferential formation of (*Z*)-silyl ketene thioacetal (*Z*/*E*=72:28) was observed with KHMDS at −78 °C by the internal quench method,[29] this outcome would be a consequence of thermodynamic control. Disappointingly, however, (*E*)-silyl ketene thioacetal **25** was found to be a less reactive nucleophile compared to the corresponding (*Z*)-isomer **20**, and the $Sn(OTf)_2$-promoted aldol reaction of **25** (*Z*/*E*=1:99) with α-keto ester **17** proceeded slowly at −55 °C to afford adducts in 36% yield with 1:10 stereoselectivity favoring the undesired diastereomer **24b**. These results definitely revealed the advantages of the (*Z*)-silyl ketene thioacetal over its (*E*) counterpart in terms of both yield and ratio of the desired product.

Table 1. Lewis acid-promoted aldol reaction of α-keto ester **17** with (*Z*)-silyl ketene thioacetal **20**



Entry	Lewis acid	Temperature (°C)	Time (h)	Yield (%)	**24a**:**24b**[a]
1	$Sn(OTf)_2$	−70	1.5	90	1:2.2
2	$Sc(OTf)_3$	−45	0.5	31	1:5.3
3	TiF_4	−60	2	70	1:5
4	$(^iPrO)_2TiCl_2$	rt	12	30	1:1.5
5[b]	$(^iPrO)_2TiCl_2$	rt	12	55	1:1.5

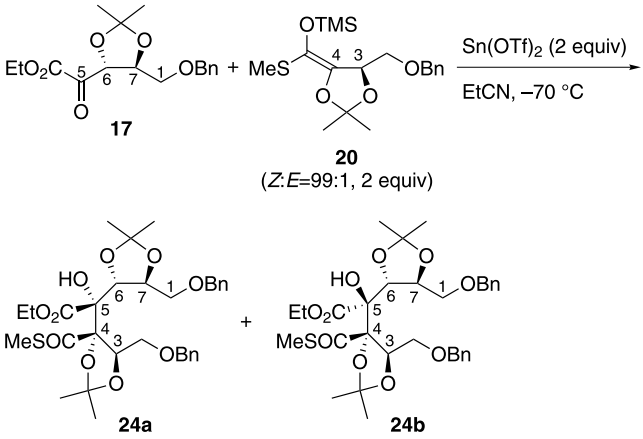
[a] The ratio was determined by 270 MHz ^{1}H NMR analysis of the crude mixture.
[b] The reaction was performed using 5 equiv of silyl ketene thioacetal **20**.



Scheme 5. Reagents and conditions: (a) KHMDS (inverse addition), THF, −78 °C, 2.5 h, then TMSCl, −78 °C, 30 min, and rt, 15 min; (b) α-keto ester **17**, $Sn(OTf)_2$, EtCN, −55 °C, 1 h.

These results suggest that $Sn(OTf)_2$ was the optimal Lewis acid and (*Z*)-silyl ketene thioacetal **20** was identified as a suitable coupling partner for this reaction. During the course of these studies, we found that when $Sn(OTf)_2$ was used as a promoter, the product ratio (**24a**:**24b**) changed as the reaction proceeded (Table 2). Although undesired isomer **24b** was exclusively formed during the initial 5-min period of the reaction (entry 1), a 1:2.2 mixture of adducts was obtained on completion of the reaction. Since the isomerization of **24b** to **24a** did not occur under these conditions, these observations suggest that multiple reaction pathways are involved in this coupling.

Table 2. $Sn(OTf)_2$-promoted aldol coupling between α-keto ester **17** and silyl ketene thioacetal **20**



Entry	Time (min)	Yield (%)	**24a**:**24b**[a]
1	5	28	0:1
2	15	75	1:3.2
3	90	90	1:2.2

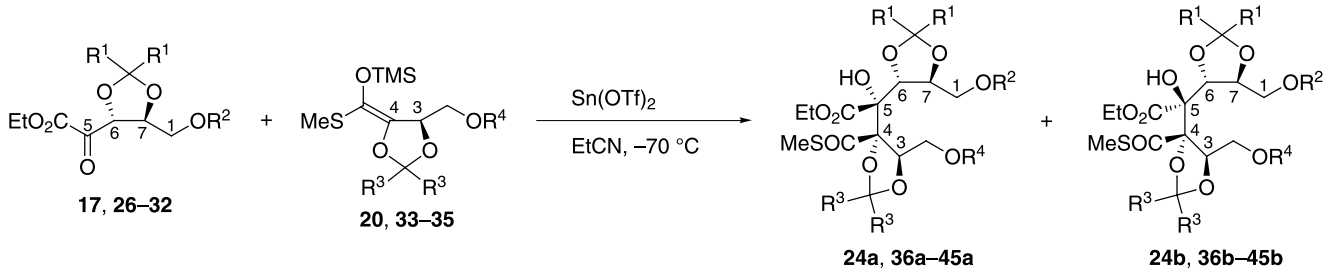
[a] The ratio was determined by 270 MHz ^{1}H NMR analysis of the crude mixture.

We next anticipated that the carbonyl π-facial selectivity might be reversed by the judicious choice of protecting groups imparted to each reaction partner. A number of thioesters and α-keto esters were prepared by routes analogous to that illustrated for **14** (Scheme 2) and **17** (Scheme 3), and evaluated as substrates for the $Sn(OTf)_2$-promoted aldol reaction. The results of the aldol reactions are shown in Table 3.

While the acetal moiety in the α-keto esters had a little influence on the carbonyl facial selectivity, the ratio of the desired product to the undesired C5 epimer increased slightly when the pentylidene acetal **27** was used (entries 3 vs 1, 2, and 4). With regard to acetal protection in silyl ketene thioacetals, an exceptionally high order of selectivity for the undesired C5 epimer was obtained in the case of methylene acetal **33**, with little variation being observed between isopropylidene and pentylidene acetals **20** and **34** (entries 5 vs 3 and 6). Switching protection of the primary alcohol in **20** or **27** from a benzyl ether to a *tert*-butyldiphenylsilyl ether led to the predominant formation of the undesired isomers **41b** and **42b** (entries 3 vs 7 and 8), suggesting that the chelating ability of the oxygen atoms might be responsible for the desired π-facial selectivity. Of the substituted methyl ethers surveyed for R^2 (entries 9–11), MEM ether proved to be the protecting group of choice for the primary alcohol at C1, providing a mixture of aldol adducts **45a** and **45b** in a ratio of 1.6:1 (entry 11).

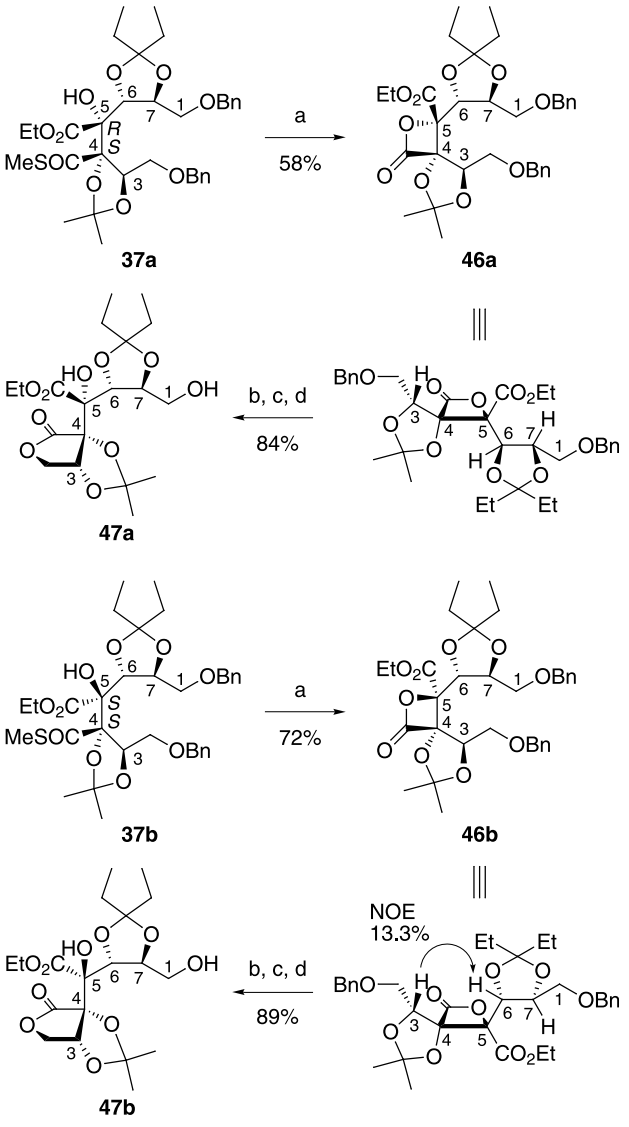
The stereochemical outcome of each reaction was inferred on the basis of the chemical transformations and NOE data analogous to that illustrated in Scheme 4. For example, isomers **37a** and **37b** were converted to β-lactones **46a** and **46b**, respectively, and the NOE experiments indicated unequivocally relative stereochemical relationships between the quaternary stereocenters for both isomers (Scheme 6). The fact that the methanolysis of β-lactones **46a** and **46b** followed by debenzylation and treatment with DMAP gave γ-lactones **47a** and **47b**, respectively, confirmed a 4*S* configuration. As the work progressed and we acquired a library of spectral data, we also noticed that these isomers were readily distinguishable by the ^{1}H NMR signals for the *S*-methyl protons, which were always 0.04–0.1 ppm downfield in the desired product relative to its C5 epimer. It is also noteworthy that the cyclization of undesired isomer **37b** proceeded to completion within 10 h, while extended reaction times (200 h) were required

Table 3. $Sn(OTf)_2$-promoted aldol coupling between an α-keto ester and a silyl ketene thioacetal



Entry	α-Keto ester			Silyl ketene thioacetal			Aldol adducts		
		R^1	R^2		R^3	R^4		Yield (%)	Desired: undesired[a]
1	**17**	Me	Bn	**20**	Me	Bn	**24**	90	1:2.2
2	**26**	H	Bn	**20**	Me	Bn	**36**	49	1:2.6
3	**27**	Et	Bn	**20**	Me	Bn	**37**	79	1:1.1
4	**28**	^{n}Pr	Bn	**20**	Me	Bn	**38**	82	1:1.6
5	**27**	Et	Bn	**33**	H	Bn	**39**	67	1:>20
6	**27**	Et	Bn	**34**	Et	Bn	**40**	67	1:1.9
7	**27**	Et	Bn	**35**	Me	TBDPS	**41**	65	1:>20
8	**29**	Et	TBDPS	**20**	Me	Bn	**42**	45	1:5
9	**30**	Et	MOM	**20**	Me	Bn	**43**	79	1.1:1
10	**31**	Et	BOM	**20**	Me	Bn	**44**	90	1:1.6
11	**32**	Et	MEM	**20**	Me	Bn	**45**	83	1.6:1

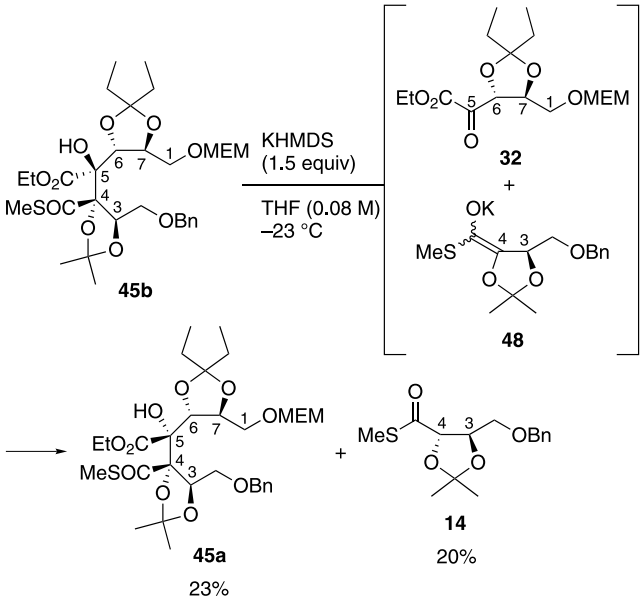
[a] The ratio was determined by 270 MHz ^{1}H NMR analysis of the crude mixture.



Scheme 6. Reagents and conditions: (a) $Hg(OCOCF_3)_2$, MeCN, 200 h (for **37a**) or 10 h (for **37b**); (b) K_2CO_3, MeOH, 1.5 h; (c) H_2, 10% Pd/C, MeOH, 1 h; (d) DMAP, MeCN, 1.5 h.

for the complete conversion of **37a** to **46a** under the same reaction conditions.

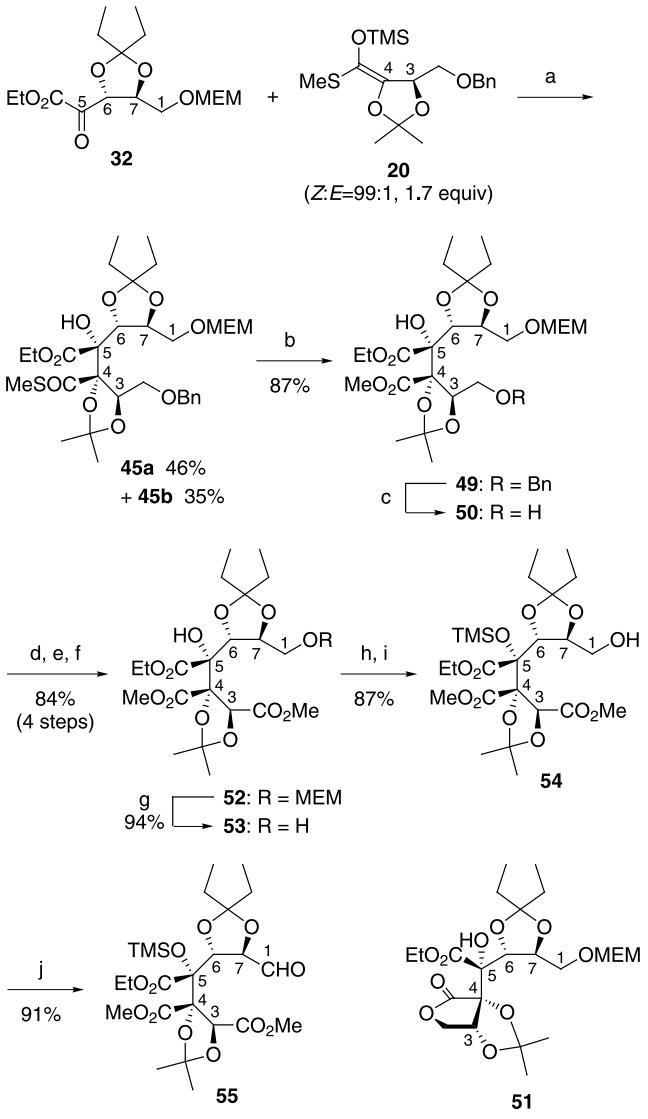
Ironically, the undesired diastereomers **39b** and **41b** were exclusively formed by the proper choice of the protecting groups for each reaction partner; however, it was quite difficult to obtain the desired isomer predominantly by this aldol coupling.[30] Our attention was then directed to recycling the undesired isomer back to the starting α-keto ester and thioester. After considerable experimentation, we found that the treatment of **45b** with KHMDS in THF at temperatures above −23 °C effected a retro-aldol reaction. Surprisingly, when the reaction was performed at substrate concentrations of more than 0.08 M, the undesired isomer **45b** was completely consumed within 2 h and the desired isomer **45a** was formed in 23% yield, along with 20% of thioester **14** (Eq. 3). It is clear that the observed isomerization of **45b** to **45a** is the result of an aldol reaction between α-keto ester **32** and potassium enolate **48**, produced by the retro-aldol reaction of **45b**, and that the desired isomer **45a** is thermodynamically more stable than **45b**.[32] The low yield can be attributed to the lability of **32** to base. Despite the low yields of the products, this equilibration/recycling process permitted the undesired isomer **45b** to be productively utilized and therefore enhanced the overall synthetic efficiency.



(3)

2.4. Synthesis of internal ketalization precursor

Having accomplished the simultaneous creation of the consecutive quaternary stereogenic centers by a $Sn(OTf)_2$-promoted aldol coupling between an α-keto ester and a silyl ketene thioacetal, we then proceeded to the elaboration of the internal ketalization precursor. The aldol coupling of α-keto ester **32**[33] with 1.7 equiv of silyl ketene thioacetal **20** on a multigram scale proceeded in 81% yield, albeit with a slightly diminished selectivity (**45a**:**45b** = 1.3:1, Scheme 7). After separation of the C5 epimer **45b**, thioester **45a** was converted to methyl ester **49** in 87% yield by treatment with $Hg(OCOCF_3)_2$ in refluxing MeOH.[28] Although the hydrogenolysis of **49** over 10% Pd/C in MeOH gave the corresponding alcohol **50**, we found these conditions to be capricious due to the formation of γ-lactone **51** as a byproduct. This side reaction could be minimized by the use of 20% $Pd(OH)_2$/C in AcOEt. The lactonization-prone alcohol **50** was then converted into a carboxylic acid by two successive oxidations (Dess-Martin periodinane;[35] $NaClO_2$), which was subjected to CH_2N_2 to provide triester **52** in 84% overall yield without intervening purification. It should be noted that the application of the standard Swern protocol[36] in place of the Dess-Martin procedure resulted in the significant epimerization at C3. The selective removal of the MEM ether was effected with TMSCl/NaI in MeCN at −23 °C,[37] affording diol **53** in 94% yield. At this juncture, the C5 tertiary alcohol was protected as its TMS ether via a two-step bissilylation–monodesilylation sequence[9b,d] to give alcohol **54** in 87% yield, which, upon treatment with Dess-Martin periodinane, furnished aldehyde **55** in 91% yield.

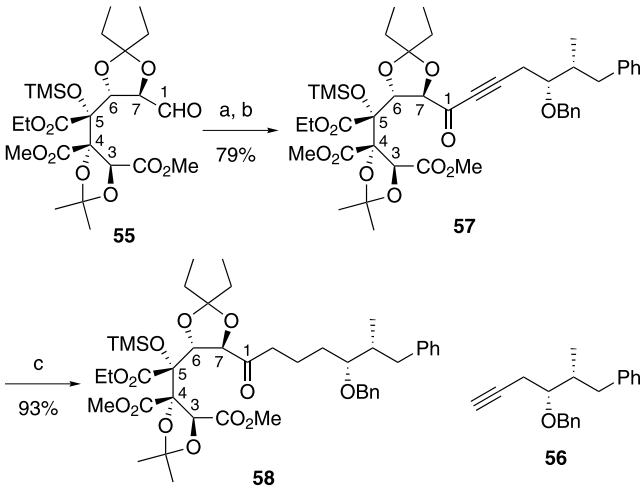


Scheme 7. Reagents and conditions: (a) $Sn(OTf)_2$, EtCN, −70 °C, 1.5 h; (b) $Hg(OCOCF_3)_2$, MeOH, reflux, 10 h; (c) H_2, 20% $Pd(OH)_2$/C, AcOEt, 10 h; (d) Dess–Martin periodinane, CH_2Cl_2, 8 h; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH–H_2O (10/3), 2.5 h; (f) CH_2N_2, Et_2O, 0 °C, 10 min; (g) TMSCl, NaI, MeCN, −23 °C, 2 h; (h) MeN(TMS)$COCF_3$, 90 °C, 3 h; (i) 10% aqueous HCl, Et_2O, 1.5 h; (j) Dess–Martin periodinane, CH_2Cl_2, 3.5 h.

To install the C1 alkyl side chain, initial attempts to employ Grignard reagent **7** (M=MgBr) resulted in a low yield. We then elected to use alkyne **56**[38] as a C1 alkyl side chain equivalent (Scheme 8). As anticipated, the installation of the C1 alkyl side chain was uneventfully achieved by the addition of the lithium acetylide, generated from alkyne **56**, to aldehyde **55**, providing a diastereomeric mixture of coupling products, which, upon treatment with Dess-Martin periodinane, furnished ynone **57** in 79% yield in two steps. Finally, catalytic hydrogenation of the triple bond gave the internal ketalization precursor **58** in 93% yield.

2.5. Internal ketalization

With a viable route to ketone **58** secured, the stage was now set for the crucial internal ketalization. Exposure of **58** to 90% aqueous TFA resulted in the removal of protecting

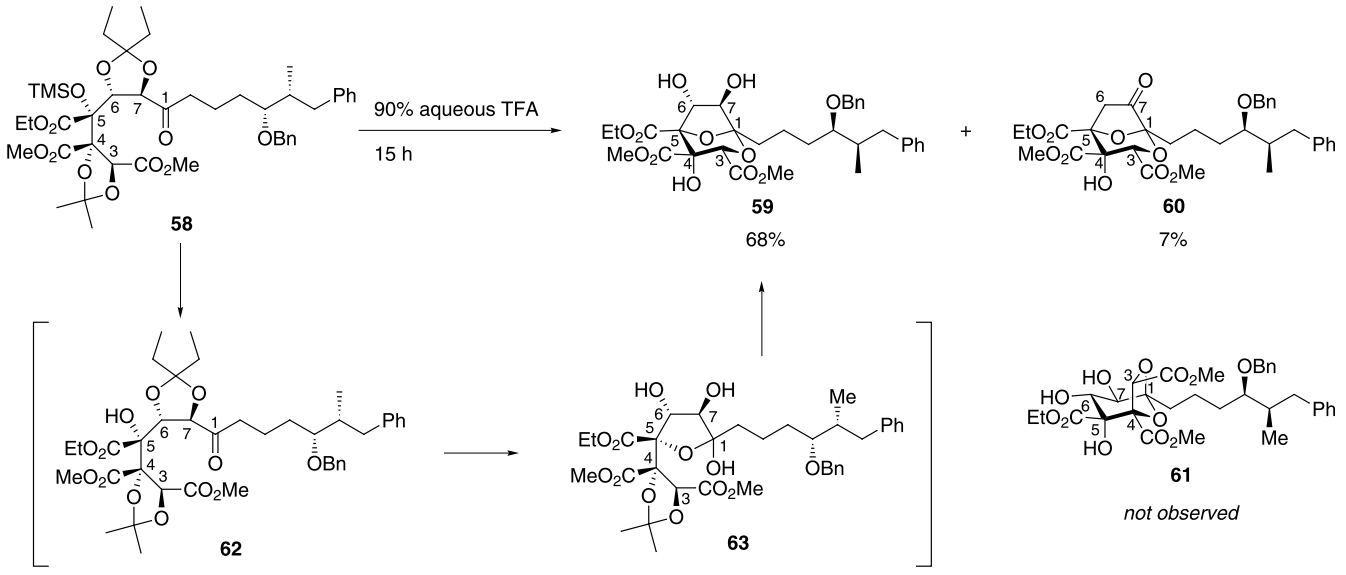


Scheme 8. Reagents and conditions: (a) alkyne **56**, BuLi, THF, −78 °C, 45 min, then aldehyde **55**, 30 min; (b) Dess–Martin periodinane, CH_2Cl_2, 11 h; (c) H_2, 10% Pd/C, AcOEt, 10 min.

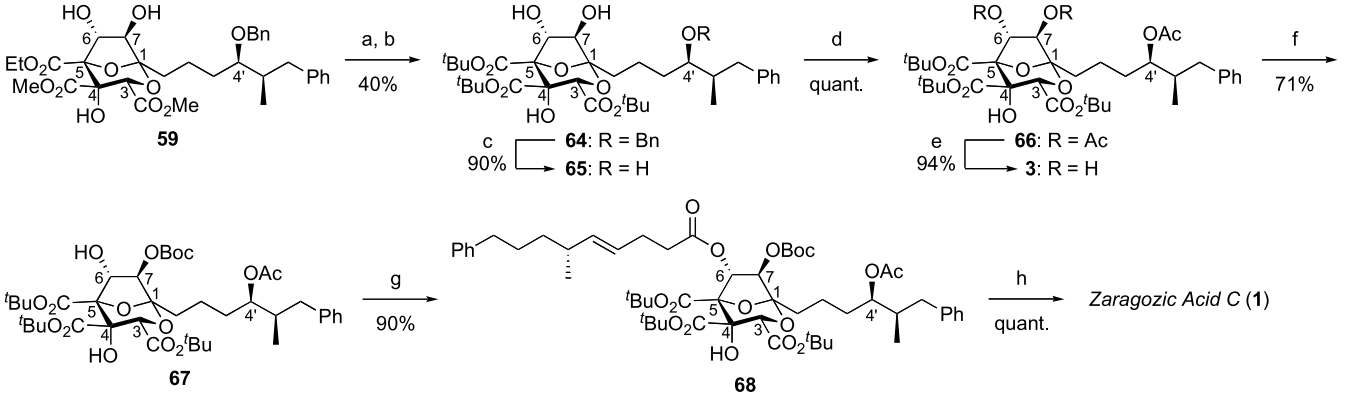
groups and concomitant ketalization, affording bicycloketal **59** in 68% yield (Scheme 9). While the formation of the 6,8-dioxabicyclo[3.2.1]octane isomer **61** was not observed, a minor byproduct **60** arising from dehydration of the C6 hydroxyl group was isolated.[39] When the reaction was quenched after a 10-min period, alcohol **62** and hemiketal **63** were obtained as intermediates in 53 and 29% yields, respectively. Monitoring the internal ketalization by TLC analysis showed that desilylation occurred immediately, forming hydroxyketone **62**, from which the pentylidene ketal was subsequently removed to give the five-membered hemiketal **63** through closure of the C5 hydroxyl group onto the C1 carbonyl. The steric congestion around the acetonide required 15 h for its hydrolytic removal to reach completion, and then the desired bicycloketal **59** was formed as a single stereoisomer. These observations suggest that the selectivity in the internal ketalization process is mainly due to the differential rates of hydrolysis of the protecting groups. Independent of our study, a similar conclusion was reached by Armstrong and co-workers in their total synthesis of zaragozic acid C.[11] The ratio of TFA/H_2O in this reaction is not arbitrary: extended reaction times (48 h) were required for complete conversion with 80% aqueous TFA, lowering the product yield due to the formation of a debenzylated byproduct.

2.6. Completion of the total synthesis

To avoid concomitant hydrolytic cleavage of the C6 acyl side chain at the end of the synthesis, the triesters present in **59** should be hydrolyzed and converted to the corresponding tri(*tert*-butyl) ester at this stage. Although the C4 methyl ester proved to be extremely resistant to hydrolysis, the reaction of **59** with 1 N aqueous KOH in dioxane at 100 °C furnished the triacid which, upon treatment with *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea,[40] gave tri(*tert*-butyl ester) **64** in 40% yield in two steps (Scheme 10). Hydrogenolysis of the C4′ benzyl ether provided tetraol **65** in 90% yield, which was acetylated to give triacetate **66** in quantitative yield. The route to **66** constitutes a formal synthesis of zaragozic acid C (**1**) since it intersects the same intermediate employed by Carreira and Du Bois.[8] However, the specific



Scheme 9. Internal ketalization.



Scheme 10. Reagents and conditions: (a) 1 N aqueous KOH, dioxane, 100 °C, 24 h; (b) ^{i}PrN=C(O^{t}Bu)NH^{i}Pr, CH_2Cl_2, 24 h; (c) H_2, 10% Pd/C, MeOH, 17 h; (d) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 30 min; (e) 0.2% K_2CO_3 in MeOH, 1 h; (f) $(Boc)_2O$, 4-pyrrolidinopyridine, Et_3N, CH_2Cl_2, 0 °C, 12 h; (g) carboxylic acid **2**, DCC, DMAP, CH_2Cl_2, 48 h; (h) TFA, CH_2Cl_2, 16 h.

rotation of compound **66** [$[\alpha]_D^{21}$ +17.6 (*c* 0.91, CH_2Cl_2)] was not in agreement with the reported value [$[\alpha]_D$ +69.9 (*c* 0.29, CH_2Cl_2)].[8b] Following the procedure developed by Carreira,[8b] selective removal of the C6 and C7 acetyl groups by treatment with 0.2% K_2CO_3 in MeOH, selective protection of the C7 hydroxyl group by $(Boc)_2O$, esterification with acid **2**,[1f] and global deprotection with TFA gave zaragozic acid C (**1**) in 60% overall yield. The synthetic material **1**, $[\alpha]_D^{23}$ +9.4 (*c* 0.30, EtOH) [lit.,[1b] $[\alpha]_D^{20}$ +9.6 (*c* 0.29, EtOH)], was obtained as a white film and relevant spectroscopic data were identical with those reported for natural zaragozic acid C (IR, ^{1}H NMR, ^{13}C NMR, HRMS).

3. Conclusion

The total synthesis of zaragozic acid C was completed in 30 steps for the longest linear sequence from diethyl L-tartrate and 1.4% overall yield. Although our synthesis incurs a stereochemical problem at C5 in the key fragment assembly aldol process, we found that the contiguous quaternary stereocenters at C4 and C5 could be formed simultaneously in a single operation by a $Sn(OTf)_2$-promoted aldol reaction between an α-keto ester and a silyl ketene thioacetal. We also demonstrate that the selectivity in the internal ketalization process was mainly due to the differential rates of hydrolysis of the protecting groups.

4. Experimental

4.1. General

Melting points were determined on a Büchi 535 digital melting point apparatus and were uncorrected. Optical rotations were recorded on JASCO DIP-370 or P-1030 digital polarimeters. Infrared (IR) spectra were recorded on a JASCO FT/IR-5300 spectrophotometer and absorbance bands are reported in wavenumber (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on JEOL EX-270 (270 MHz), JEOL EX-400 (400 MHz) or Bruker ARX500 (500 MHz) spectrometers with tetramethylsilane (δ_H 0.00) as an internal standard. Coupling

constants (J) are reported in hertz (Hz). Abbreviations of multiplicity are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Data are presented as follows: chemical shift, multiplicity, coupling constants, integration, and assignment. Zaragozic acid numbering is used for proton assignments of all intermediates. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on JEOL EX-270 (67.8 MHz), JEOL EX-400 (100.6 MHz) or Bruker ARX500 (125.8 MHz) spectrometers with $CDCl_3$ (δ_C 77.0) as an internal standard. Fast atom bombardment (FAB) mass spectra were recorded on a JEOL JMS-HX110 spectrometer.

Column chromatography was carried out on Merck Kieselgel 60 (63–200 μm or 40–63 μm), Fuji Davison silica gel BW-200 (40–50 μm) or Wakogel C-200 (75–150 μm). Analytical thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates. Visualization was accomplished with ultraviolet light and anisaldehyde or phosphomolybdic acid stain, followed by heating.

Reagents and solvents were purified by standard means or used as received unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium metal/benzophenone ketyl prior to use. Dichloromethane (CH_2Cl_2), propionitrile (EtCN), acetonitrile (MeCN), and diisopropylamine ($^iPr_2NH$) were distilled from calcium hydride prior to use. Dimethyl sulfoxide (DMSO) was distilled under reduced pressure from calcium hydride.

All reactions were conducted under an argon atmosphere. Ethyl 2-oxo-5-phenylpentanoate,[25] diisopropoxytitanium(IV) dichloride [$(^iPrO)_2TiCl_2$],[41] Dess-Martin periodinane[42] (4*R*,5*R*)-4-benzyloxy-5-methyl-6-phenyl-1-hexyne (**56**),[38] *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea[40] and (4*E*,6*R*)-6-methyl-9-phenyl-4-nonenoic acid (**2**)[1f] were prepared according to literature procedures.

4.2. Preparation of substrates for the aldol coupling

4.2.1. (2*S*,3*R*)-4-benzyloxy-2,3-(dimethylmethylenedioxy)butyric acid [(+)-12]. A solution of NaH_2PO_4 (5.8 g, 48.0 mmol) in water (80 mL) was added to a solution of (2*S*,3*R*)-4-benzyloxy-2,3-(dimethylmethylenedioxy)-butanal (**11**)[20] (12.0 g, 48.0 mmol) and 2-methyl-2-butene (21 mL, 199 mmol) in *tert*-butyl alcohol (250 mL). $NaClO_2$ (14.8 g, 164 mmol) was added portionwise to the mixture. After stirring at room temperature for 18 h, the mixture was evaporated in vacuo. The residue was dissolved in saturated aqueous $NaHCO_3$ (50 mL) and water (100 mL) and the whole was washed with *n*-hexane (3×30 mL). The aqueous layer was acidified with 10% aqueous HCl (40 mL), saturated with NaCl, and then extracted with AcOEt (3× 100 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel 100 g, AcOEt) afforded carboxylic acid (+)-**12** (12.1 g, 95%) as a pale yellow oil: $[\alpha]_D^{24}$ +13.7 (*c* 1.19, $CHCl_3$); IR (film) 3700–2300, 2990, 1734, 1454, 1383, 1215, 1101, 852, 752, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 3H, acetonide CH_3), 1.42 (s, 3H, acetonide CH_3), 3.63 (dd, J=5.2, 10.7 Hz, 1H, C*H*OBn), 3.71 (dd, J=3.2, 10.7 Hz, 1H, C*H*OBn), 4.29 (ddd, J=3.2, 5.2, 7.7 Hz, 1H, C3–*H*), 4.36 (d, J=7.7 Hz, 1H, C4–*H*), 4.54 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.57 (d, J=12.0 Hz, 1H, OC*H*Ph), 7.17–7.30 (m, 5H, Ar*H*), 9.51 (br s, 1H, CO_2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 25.6 (CH_3), 26.8 (CH_3), 69.6 (CH_2), 73.7 (CH_2), 75.3 (CH), 78.2 (CH), 111.9 (C), 127.7 (CH), 127.8 (CH), 128.4 (CH), 137.6 (C), 174.9 (C=O); FAB-HRMS *m*/*z* calcd for $C_{14}H_{19}O_5$ $(M+H)^+$ 267.1233, found 267.1240.

4.2.2. Methyl (2*S*,3*R*)-4-benzyloxy-2,3-(dimethylmethylenedioxy)butyrate (13). A solution of diazomethane in Et_2O was added to a solution of carboxylic acid (+)-**12** (4.32 g, 16.2 mmol) in Et_2O (30 mL) at 0 °C until a yellow color persisted. After stirring at 0 °C for 30 min and then room temperature for 30 min, the reaction was quenched with AcOH. The resulting mixture was washed successively with water (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel 100 g, 6:1 *n*-hexane/AcOEt) afforded methyl ester **13** (3.55 g, 78%) as a pale yellow oil: $[\alpha]_D^{21}$ +19.0 (*c* 1.30, $CHCl_3$); IR (film) 2992, 2938, 1761, 1454, 1381, 1208, 1107, 1024, 853, 740, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 3H, acetonide CH_3), 1.49 (s, 3H, acetonide CH_3), 3.68 (dd, J=5.3, 10.7 Hz, 1H, C*H*OBn), 3.75 (dd, J=3.2, 10.7 Hz, 1H, C*H*OBn), 3.76 (s, 3H, CO_2CH_3), 4.35 (ddd, J=3.2, 5.3, 7.6 Hz, 1H, C3–*H*), 4.40 (d, J=7.6 Hz, 1H, C4–*H*), 4.61 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.63 (d, J=12.0 Hz, 1H, OC*H*Ph), 7.25–7.37 (m, 5H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 25.7 (CH_3), 26.9 (CH_3), 52.3 (CH_3), 69.8 (CH_2), 73.6 (CH_2), 75.7 (CH), 78.4 (CH), 111.6 (C), 127.6 (CH), 127.7 (CH), 128.4 (CH), 137.9 (C), 171.0 (C=O); FAB-HRMS *m*/*z* calcd for $C_{15}H_{21}O_5$ $(M+H)^+$ 281.1389, found 281.1411.

4.2.3. *S*-methyl (2*S*,3*R*)-4-benzyloxy-2,3-(dimethylmethylenedioxy)butanethioate (14). Oxalyl chloride (1.8 mL, 20.6 mmol) and DMF (0.1 mL, 1.3 mmol) were added to a solution of carboxylic acid (+)-**12** (4.75 g, 17.8 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at room temperature for 1.5 h and evaporated in vacuo. The residual oil was dissolved in CH_2Cl_2 (50 mL), and *n*-Bu_4NI (76 mg, 0.2 mmol) and a 20% aqueous solution of MeSNa (7.5 mL, 21.4 mmol) were added at 0 °C. After stirring vigorously at 0 °C for 10 min, the mixture was partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The organic extract was washed successively with water (30 mL) and brine (30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel 100 g, 20:1 *n*-hexane/AcOEt) afforded thioester **14** (4.04 g, 77%) as a pale yellow oil: $[\alpha]_D^{25}$ −8.95 (*c* 1.2, $CHCl_3$); IR (film) 2990, 2930, 1676 (C=O), 1454, 1381, 1215, 1090, 852, 739, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 6H, 2×acetonide CH_3), 2.28 (s, 3H, SCH_3), 3.66 (dd, J=5.7, 10.8 Hz, 1H, C*H*OBn), 3.81 (dd, J=2.5, 10.8 Hz, 1H, C*H*OBn), 4.24 (ddd, J=2.5, 5.7, 8.0 Hz, 1H, C3–*H*), 4.35 (d, J=8.0 Hz, 1H, C4–*H*), 4.62 (s, 2H, OCH_2Ph), 7.25–7.38 (m, 5H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 10.8 (CH_3), 26.0 (CH_3), 27.1 (CH_3), 69.7 (CH_2), 73.6 (CH_2), 78.8 (CH), 81.6 (CH), 112.1 (C), 127.7 (CH), 128.4 (CH), 137.8 (CH), 201.4 (C=O); FAB-HRMS *m*/*z* calcd for $C_{15}H_{21}O_4S$ $(M+H)^+$

297.1161, found 297.1152. Anal. Calcd for $C_{15}H_{21}O_4S$: C, 60.79; H, 6.80; S, 10.82. Found: C, 60.63; H, 6.78; S, 11.07.

4.2.4. (2*R*,3*S*)-4-benzyloxy-2,3-(dimethylmethylenedioxy)-*N*-methoxy-*N*-methylbutanamide (15). Oxalyl chloride (6 mL, 69 mmol) and DMF (0.3 mL, 3.9 mmol) were added to a solution of carboxylic acid (−)-**12** (15.20 g, 57.1 mmol) in CH_2Cl_2 (170 mL). The mixture was stirred at room temperature for 30 min and evaporated in vacuo. The residual oil was dissolved in CH_2Cl_2 (170 mL), and *N*,*O*-dimethylhydroxylamine hydrochloride (6.1 g, 62.5 mmol) and pyridine (12 mL, 148 mmol) were added at 0 °C. After stirring at 0 °C for 1 h, the reaction was quenched with 1 N aqueous HCl (100 mL), and the layers were separated. The organic layer was washed successively with 1 N aqueous HCl (2×100 mL), saturated aqueous $NaHCO_3$ (80 mL) and brine (80 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel 150 g, 3:1→2:1 *n*-hexane/AcOEt) afforded amide **15** (16.28 g, 92%) as a colorless oil: $[\alpha]_D^{25}$ +3.97 (*c* 2.03, $CHCl_3$); IR (film) 2988, 2938, 1780, 1669, 1454, 1381, 1256, 1165, 1092, 997, 910, 855 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 3H, acetonide CH_3), 1.49 (s, 3H, acetonide CH_3), 3.20 (s, 3H, NCH_3), 3.63–3.71 (m, 2H, C1–H_2), 3.76 (s, 3H, OCH_3), 4.59 (m, 1H, C7–*H*), 4.60 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.61 (d, *J*=12.0 Hz, 1H, OC*H*Ph), 4.71 (br s, 1H, C6–*H*), 7.25–7.33 (m, 5H, Ar*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 26.1 (CH_3), 26.7 (CH_3), 32.3 (CH_3), 61.5 (CH_3), 69.8 (CH_2), 73.4 (CH_2), 74.1 (CH), 77.7 (CH), 111.2 (C), 127.6 (CH), 127.8 (CH), 138.0 (CH), 170.3 (C=O); FAB-HRMS *m*/*z* calcd for $C_{16}H_{23}NO_5$ $(M)^+$ 309.1576, found 309.1575.

4.2.5. (4*R*,5*S*)-6-benzyloxy-4,5-(dimethylmethylenedioxy)-2-ethoxy-1-hexen-3-one (16). *tert*-Butyllithium in pentane (2.13 M, 1.95 mL, 4.15 mmol) was added to a stirred solution of ethyl vinyl ether (0.4 mL, 4.18 mmol) in THF (4 mL) at −78 °C. After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C and a solution of amide **15** (437 mg, 1.41 mmol) in THF (1 mL) was added. After stirring at −78 °C for 3 h, the reaction mixture was poured into a well-stirred mixture of saturated aqueous NH_4Cl (20 mL) and Et_2O (10 mL) at 0 °C. The layers were separated, and the organic layer was washed with brine (8 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel 10 g, 10:1→7:1 *n*-hexane/AcOEt) afforded enone **16** (386 mg, 85%) as a colorless oil: $[\alpha]_D^{25}$ −49.9 (*c* 2.03, $CHCl_3$); IR (film) 2986, 2936, 1723, 1610, 1454, 1379, 1285, 1215, 1117, 1092, 976, 853 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.43 (s, 3H, acetonide CH_3), 1.51 (s, 3H, acetonide CH_3), 3.66 (dd, *J*=6.0, 10.5 Hz, 1H, C1–*H*), 3.75 (dd, *J*=3.1, 10.5 Hz, 1H, C1–*H*), 3.76 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 4.40 (ddd, *J*=3.1, 6.0, 6.5 Hz, 1H, C7–*H*), 4.53 (d, *J*=2.7 Hz, 1H, C*H*=C), 4.60 (d, *J*=12.3 Hz, 1H, OC*H*Ph), 4.64 (d, *J*=12.3 Hz, 1H, OC*H*Ph), 4.92 (d, *J*=6.5 Hz, 1H, C6–*H*), 5.31 (d, *J*=2.7 Hz, 1H, C*H*=C), 7.26–7.34 (m, 5H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.3 (CH_3), 26.7 (CH_3), 27.7 (CH_3), 64.1 (CH_3), 70.8 (CH_2), 73.8 (CH_2), 78.2 (CH), 79.1 (CH), 93.7 (CH), 112.1 (C), 127.9 (CH), 128.6 (CH), 138.2 (CH), 156.6 (CH_2), 194.2 (C=O); FAB-LRMS *m*/*z* 309 $(M-CH_2+H)^+$, 277 $(M-OEt+H)^+$.

4.2.6. Ethyl (3*R*,4*S*)-5-benzyloxy-3,4-(dimethylmethylenedioxy)-2-oxopentanoate (17). A stream of ozone in oxygen was bubbled through a stirred solution of enone **16** (386 mg, 1.21 mmol) in CH_2Cl_2 (7 mL) at −78 °C until the solution turned pale blue. After stirring at −78 °C for 10 min, excess ozone was removed by bubbling a stream of nitrogen, and Me_2S (1 mL) was added. After stirring at room temperature for 1 h, the volatile elements were removed in vacuo. The residue (548 mg) was purified by column chromatography (silica gel 10 g, 4:1→5:2 *n*-hexane/AcOEt) to give α-keto ester **17** (371 mg, 96%) as a colorless oil: $[\alpha]_D^{22}$ −5.39 (*c* 1.6, $CHCl_3$); IR (film) 3449, 2990, 1730, 1454, 1373, 1254, 1217, 1094, 1042, 853, 741, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.40 (s, 3H, acetonide CH_3), 1.50 (s, 3H, acetonide CH_3), 3.71 (dd, *J*=5.3, 10.5 Hz, 1H, C*H*OBn), 3.75 (dd, *J*=4.2, 10.5 Hz, 1H, C*H*OBn), 4.23–4.36 (m, 2H, $CO_2CH_2CH_3$), 4.43 (ddd, *J*=4.2, 5.3, 7.0 Hz, 1H, C7–*H*), 4.61 (s, 2H, OCH_2Ph), 4.85 (d, *J*=7.0 Hz, 1H, C6–*H*), 7.25–7.38 (m, 5H, Ar*H*); FAB-HRMS *m*/*z* calcd for $C_{17}H_{23}O_6$ $(M+H)^+$ 323.1495, found 323.1508.

Since the tartrate-derived α-keto esters were prone to hydration, they were azeotropically dried with benzene prior to use.

4.3. Aldol reaction

4.3.1. Reaction of α-keto ester 18 with lithium enolate generated from ester 13. Butyllithium in *n*-hexane (1.60 M, 0.35 mL, 0.56 mmol) was added to a solution of $^iPr_2NH$ (0.08 mL, 0.61 mmol) in THF (1.5 mL) at −5 °C. After stirring at −5 °C for 20 min, the solution was cooled to −78 °C, and a solution of ester **13** (129 mg, 0.46 mmol) in THF (0.6 mL) was added dropwise over 10 min. After stirring at −78 °C for 1 h, a solution of α-keto ester **18** (51 mg, 0.23 mmol) in THF (0.3 mL) was added to the mixture at −78 °C. After stirring at −78 °C for 10 min, the mixture was quenched with saturated aqueous NH_4Cl (3 mL), and the whole was extracted with AcOEt (15 mL). The organic extract was washed with brine (2×5 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (168 mg), which was purified by flash column chromatography (silica gel 5 g, 10:1→3:1 *n*-hexane/AcOEt) to give an inseparable mixture of aldol adducts **19** (96 mg, 84%) as a colorless oil. The ratio of the adducts was determined to be 61:15:15:9 by 270 MHz ^1H NMR: ^1H NMR (270 MHz, $CDCl_3$) δ 1.10–1.60 (m, 10H, $CO_2CH_2CH_3$, 2×acetonide CH_3, one of CH_2), 1.70–1.95 (m, 2H, CH_2), 1.95–2.15 (m, 1H, one of CH_2), 2.46–2.71 (m, 2H, PhCH_2), 3.35–3.53 (m, 1H, BnOC*H*), 3.65 (s, 1.83H, OCH_3), 3.67 (s, 0.45H, OCH_3), 3.74 (s, 0.27H, OCH_3), 3.75 (s, 0.45H, OCH_3), 3.82–4.32 (m, 4H, BnOC*H*, $CO_2CH_2CH_3$, O*H*), 4.40–4.75 (m, 3H, C3–*H*, PhCH_2O), 7.25–7.38 (m, 10H, Ar*H*).

4.3.2. (*R*,*Z*)-4-(benzyloxy)methyl-5-[methylthio(trimethylsilyloxy)methylene]-2,2-dimethyl-1,3-dioxolane (20). Butyllithium in *n*-hexane (1.61 M, 12.7 mL, 20.4 mmol) was added to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (4.5 mL, 21.3 mmol) in THF (80 mL) at −5 °C. After stirring at −5 °C for 30 min, the solution was cooled to −78 °C, and a solution of thioester **14**

(5.51 g, 18.6 mmol) in THF (15 mL) was added. After stirring at −78 °C for 30 min, TMSCl (2.7 mL, 21.3 mmol) was added, and the resulting mixture was stirred at −78 °C for 1 h. The mixture was allowed to warm to room temperature. After stirring at room temperature for 15 min, the volatile elements were removed in vacuo. The residue was suspended in *n*-hexane and passed through a short plug of Florisil (eluting with AcOEt) to give silyl ketene thioacetal **20** (6.71 g, 95%, *Z*/*E*=99:1) as a yellow oil: $[\alpha]_D^{26}$ +148.7 (*c* 1.16, benzene); IR (film) 2990, 2957, 2865, 1740, 1680, 1454, 1373, 1254, 1213, 1138, 1028, 883, 849, 737 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.23 (s, 9H, $Si(CH_3)_3$), 1.33 (s, 3H, acetonide CH_3), 1.53 (s, 3H, acetonide CH_3), 2.12 (s, 3H, SCH_3), 3.74 (dd, *J*=6.2, 10.6 Hz, 1H, C*H*OBn), 4.04 (dd, *J*=1.9, 10.6 Hz, 1H, C*H*OBn), 4.52 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.58 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 5.11 (dd, *J*=1.9, 6.2 Hz, 1H, C3–*H*), 7.08–7.24 (m, 3H, Ar*H*), 7.36 (m, 2H, Ar*H*); ^{13}C NMR (67.8 MHz, C_6D_6) δ 1.0 (CH_3), 16.6 (CH_3), 26.2 (CH_3), 27.1 (CH_3), 71.3 (CH_2), 73.9 (CH_2), 79.0 (CH), 112.1 (C), 123.9 (C), 128.2 (CH), 129.0 (CH), 139.6 (C), 144.7 (C); FAB-LRMS *m*/*z* 369 $(M+H)^+$, 277 $(M-Bn+H)^+$.

4.3.3. Ethyl (3*S*,4*R*)-5-benzyloxy-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methylthio)carbonyl-2-(3-phenylpropyl)pentanoate (21). $Sn(OTf)_2$ (566 mg, 1.36 mmol) was added to a stirred solution of α-keto ester **18** (149 mg, 0.68 mmol) and silyl ketene thioacetal **20** (500 mg, 1.36 mmol) in EtCN (14 mL) at −78 °C. After stirring at −78 °C for 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was diluted with AcOEt (10 mL) and *n*-hexane (1 mL), and filtered through a Celite pad. The filtrate was extracted with AcOEt (10 mL), and the organic extract was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (850 mg), which was purified by flash column chromatography (silica gel 20 g, 20:1→15:1 *n*-hexane/AcOEt) to give aldol adducts **21a** (98 mg, 28%) and **21b** (252 mg, 72%) as pale yellow oils. *Data for (2R,3S,4R)-isomer (***21a***).* $[\alpha]_D^{24}$ −33.5 (*c* 1.81, $CHCl_3$); IR (film) 3499, 2980, 2930, 2866, 1734, 1682, 1454, 1381, 1256, 1113, 1022, 750, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.25 (m, 1H, one of $(CH_2)_2$), 1.50 (s, 3H, acetonide CH_3), 1.68 (m, 1H, one of $(CH_2)_2$), 1.73 (s, 3H, acetonide CH_3), 1.81 (m, 1H, one of $(CH_2)_2$), 2.12 (m, 1H, one of $(CH_2)_2$), 2.15 (s, 3H, $COSCH_3$), 2.56 (dt, *J*=10.3, 3.2 Hz, 2H, CH_2Ph), 3.33 (dd, *J*=8.0, 10.9 Hz, 1H, C*H*OBn), 3.67 (s, 1H, O*H*), 3.86 (dd, *J*=1.7, 10.9 Hz, 1H, C*H*OBn), 4.00 (dq, *J*=10.8, 7.2 Hz, 1H, CO_2CHCH_3), 4.22 (dq, *J*=10.8, 7.2 Hz, 1H, CO_2CHCH_3), 4.46 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.65 (d, *J*=12.2 Hz, 1H, OC*H*Ph), 4.66 (dd, *J*=1.7, 8.0 Hz, 1H, C3–*H*), 7.11 (m, 2H, Ar*H*), 7.16 (m, 1H, Ar*H*), 7.22–7.31 (m, 3H, Ar*H*), 7.31–7.38 (m, 4H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 11.9 (CH_3), 13.9 (CH_3), 25.2 (CH_2), 26.4 (CH_3), 27.0 (CH_3), 32.5 (CH_2), 35.8 (CH_2), 62.4 (CH_2), 70.2 (CH_2), 73.4 (CH_2), 79.0 (CH), 79.2 (C), 92.4 (C), 111.9 (C), 125.8 (CH), 127.6 (CH), 127.8 (CH), 138.0 (C), 141.8 (C), 172.4 (C=O), 203.0 (C=O); FAB-HRMS calcd for $C_{28}H_{37}O_7S$ $(M+H)^+$ 517.2260, found 517.2252. *Data for (2S,3S,4R)-isomer (***21b***).* $[\alpha]_D^{23}$ −23.2 (*c* 1.63, $CHCl_3$); IR (film) 3518, 2980, 2932, 2866, 1738, 1678, 1454, 1381, 1254, 1219, 1182, 1089, 1022, 853, 739, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.25 (m, 1H, one of $(CH_2)_2$), 1.40 (s, 3H, acetonide CH_3), 1.74 (s, 3H, acetonide CH_3), 1.78–1.95 (m, 3H, three of $(CH_2)_2$), 2.14 (s, 3H, $COSCH_3$), 2.54 (ddd, *J*=2.1, 6.7, 13.7 Hz, 1H, C*H*Ph), 2.63 (ddd, *J*=3.0, 5.9, 13.7 Hz, 1H, C*H*Ph), 3.39 (dd, *J*=8.0, 11.1 Hz, 1H, C*H*OBn), 3.54 (s, 1H, O*H*), 3.94 (dd, *J*=1.8, 11.1 Hz, 1H, C*H*OBn), 4.14 (dq, *J*=10.9, 7.1 Hz, 1H, CO_2CHCH_3), 4.21 (dq, *J*=10.9, 7.1 Hz, 1H, CO_2CHCH_3), 4.50 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.61 (d, *J*=12.1 Hz, 1H, OC*H*Ph), 4.67 (dd, *J*=1.8, 8.0 Hz, 1H, C3–*H*), 7.12 (m, 2H, Ar*H*), 7.16 (m, 1H, Ar*H*), 7.22–7.30 (m, 3H, Ar*H*), 7.30–7.37 (m, 4H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 11.8 (CH_3), 14.0 (CH_3), 25.2 (CH_2), 26.4 (CH_3), 27.3 (CH_3), 32.7 (CH_2), 35.8 (CH_2), 62.3 (CH_2), 70.2 (CH_2), 73.4 (CH_2), 79.4 (CH), 80.9 (C), 91.3 (C), 112.1 (C), 125.8 (CH), 127.6 (CH), 127.7 (CH), 128.3 (CH), 138.0 (C), 141.8 (C), 172.4 (C=O), 203.8 (C=O); FAB-HRMS calcd for $C_{28}H_{37}O_7S$ $(M+H)^+$ 517.2260, found 517.2267.

4.3.4. Ethyl (3*R*,4*S*,8*R*)-8-(benzyloxymethyl)-6,6-dimethyl-1-oxo-3-(3-phenylpropyl)-2,5,7-trioxaspiro[3.4]octane-3-carboxylate (22a). $Hg(OCOCF_3)_2$ (139 mg, 0.325 mmol) was added to a stirred solution of thioester **21a** (80 mg, 0.155 mmol) in MeCN (16 mL). After stirring for 48 h, the reaction mixture was evaporated in vacuo. The residue was suspended in Et_2O (5 mL) and passed through a short plug of silica gel (eluting with Et_2O) to remove insoluble Hg salt. Purification of the crude product (87 mg) by column chromatography (silica gel 10 g, 8:1 *n*-hexane/AcOEt) afforded β-lactone **22a** (63 mg, 87%) as a colorless oil: $[\alpha]_D^{26}$ +50.3 (*c* 2.01, $CHCl_3$); IR (film) 2931, 1844, 1734, 1509, 1456, 1375, 1094 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, *J*=7.3 Hz, 3H, $CO_2CH_2CH_3$), 1.39 (s, 3H, acetonide CH_3), 1.54 (s, 3H, acetonide CH_3), 1.56 (m, 1H, C7–*H*), 1.87 (m, 1H, C7–*H*), 2.05 (ddd, *J*=4.8, 11.5, 14.7 Hz, 1H, C6–*H*), 2.14 (ddd, *J*=5.0, 11.5, 14.7 Hz, 1H, C6–*H*), 2.65 (ddd, *J*=6.6, 8.8, 13.6 Hz, 1H, C*H*Ph), 2.67 (ddd, *J*=6.6, 8.8, 13.6 Hz, 1H, C*H*Ph), 3.56 (dd, *J*=7.3, 9.1 Hz, 1H, C*H*OBn), 3.75 (dd, *J*=6.3, 9.1 Hz, 1H, C*H*OBn), 3.97 (dq, *J*=10.9, 7.3 Hz, 1H, CO_2CHCH_3), 4.21 (dq, *J*=10.9, 7.3 Hz, 1H, CO_2CHCH_3), 4.44 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.50 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.60 (dd, *J*=6.3, 7.3 Hz, 1H, C3–*H*), 7.13–7.23 (m, 3H, Ar*H*), 7.23–-7.40 (m, 7H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.0 (CH_3), 24.9 (CH_2), 25.2 (CH_3), 26.5 (CH_3), 32.9 (CH_2), 35.5 (CH_2), 61.2 (CH_2), 68.7 (CH_2), 73.8 (CH_2), 76.7 (CH), 86.6 (C), 94.6 (C), 112.9 (C), 126.0 (CH), 127.8 (CH), 128.1 (CH), 128.31 (CH), 128.34 (CH), 128.4 (CH), 137.1 (C), 141.3 (C), 168.16 (C=O), 168.23 (C=O); FAB-HRMS *m*/*z* calcd for $C_{27}H_{33}O_7$ $(M+H)^+$ 469.2226, found 469.2243.

4.3.5. Ethyl (2*R*,3*S*,4*R*)-5-benzyloxy-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-methoxycarbonyl-2-(3-phenylpropyl)pentanoate (19a). Potassium carbonate (20 mg, 0.145 mmol) was added to a solution of β-lactone **22a** (52 mg, 0.111 mmol) in MeOH (1 mL). After stirring for 30 min, the mixture was evaporated in vacuo. The residue (75 mg) was purified by column chromatography (silica gel 10 g, 4:1 *n*-hexane/AcOEt) to give methyl ester **19a** (46 mg, 83%) as a colorless oil: $[\alpha]_D^{26}$ −14.8 (*c* 1.07, $CHCl_3$); IR (film) 3501, 3027, 2988, 1732, 1497, 1454,

1373, 1250, 1181, 1105 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 (t, $J=7.1$ Hz, 3H, $CO_2CH_2CH_3$), 1.25 (m, 1H, C7–*H*), 1.44 (s, 3H, acetonide CH_3), 1.56 (s, 3H, acetonide CH_3), 1.80 (ddd, $J=4.2$, 12.1, 13.9 Hz, 1H, C6–*H*), 1.82 (m, 1H, C7–*H*), 2.06 (ddd, $J=4.2$, 12.1, 13.9 Hz, 1H, C6–*H*), 2.58 (ddd, $J=6.5$, 8.4, 14.3 Hz, 1H, C*H*Ph), 2.59 (ddd, $J=6.5$, 8.4, 14.3 Hz, 1H, C*H*Ph), 3.39 (dd, $J=7.2$, 11.0 Hz, 1H, C*H*OBn), 3.61 (s, 1H, O*H*), 3.64 (s, 3H, CO_2CH_3), 3.85 (dd, $J=1.8$, 11.0 Hz, 1H, C*H*OBn), 4.06 (dq, $J=10.8$, 7.1 Hz, 1H, CO_2CHCH_3), 4.20 (dq, $J=10.8$, 7.1 Hz, 1H, CO_2CHCH_3), 4.48 (d, $J=12.1$ Hz, 1H, OC*H*Ph), 4.62 (dd, $J=1.8$, 7.2 Hz, 1H, C3–*H*), 4.63 (d, $J=12.1$ Hz, 1H, OC*H*Ph), 7.11 (d, $J=7.3$ Hz, 2H, Ar*H*), 7.15 (t, $J=7.3$ Hz, 1H, Ar*H*), 7.23–7.32 (m, 3H, Ar*H*), 7.34 (m, 4H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.2 (CH_3), 25.4 (CH_3), 26.8 (CH_3), 27.3 (CH_3), 33.1 (CH_2), 36.0 (CH_2), 52.3 (CH_2), 62.7 (CH_2), 70.4 (CH_2), 73.7 (CH_2), 79.2 (C), 79.6 (C), 89.2 (C), 111.3 (C), 126.1 (CH), 127.9 (CH), 128.1 (CH), 128.56 (CH), 128.59 (CH), 138.2 (CH), 142.0 (C), 171.1 (C=O), 172.8 (C=O); FAB-HRMS *m/z* calcd for $C_{28}H_{37}O_8$ $(M+H)^+$ 501.2488, found 501.2497.

4.3.6. Ethyl [2*R*,2(3a*S*,6a*R*)]-2-hydroxy-5-phenyl-2-(tetrahydro-2,2-dimethyl-4-oxofuro[3,4-*d*][1,3]dioxol-3a-yl)pentanoate (23a). Palladium on carbon (10%, 7 mg) was added to a solution of benzyl ether **19a** (44 mg, 0.088 mmol) in EtOH (1 mL), and the mixture was vigorously stirred under 1 atm of hydrogen for 2 h. The catalyst was filtered through a Celite pad, and the filtrate was evaporated in vacuo. The crude product (33 mg) thus obtained was used without further purification.

DMAP (43 mg, 0.352 mmol) was added to a solution of the crude γ-hydroxyester (33 mg) in CH_2Cl_2 (1 mL). After stirring for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (6 mL), and the whole was extracted with AcOEt (10 mL). The organic extract was washed with brine (6 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (33 mg), which was purified by column chromatography (silica gel 10 g, 5:1 *n*-hexane/AcOEt) to give γ-lactone **23a** (33 mg, 98%) as a colorless oil: $[\alpha]_D^{24}$ −55.9 (*c* 1.02, $CHCl_3$); IR (film) 3486, 2990, 2940, 2866, 1790, 1728, 1456, 1377, 1263, 1117, 1019, 972, 914 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (m, 1H, C7–*H*), 1.32 (t, $J=7.1$ Hz, 3H, $CO_2CH_2CH_3$), 1.38 (s, 3H, acetonide CH_3), 1.44 (s, 3H, acetonide CH_3), 1.82 (m, 1H, C7–*H*), 2.12 (ddd, $J=4.6$, 12.3, 13.8 Hz, 1H, C6–*H*), 2.20 (ddd, $J=4.6$, 12.3, 13.8 Hz, 1H, C6–*H*), 2.60 (ddd, $J=6.0$, 9.5, 14.0 Hz, 1H, C*H*Ph), 2.66 (ddd, $J=6.0$, 9.5, 14.0 Hz, 1H, C*H*Ph), 3.76 (s, 1H, O*H*), 4.23 (dq, $J=10.8$, 7.1 Hz, 1H, CO_2CHCH_3), 4.32 (d, $J=1.7$ Hz, 2H, lactone CH_2), 4.36 (dq, $J=10.8$, 7.1 Hz, 1H, CO_2CHCH_3), 4.56 (t, $J=1.7$ Hz, 1H, C3–*H*), 7.13–7.19 (m, 3H, Ar*H*), 7.26–7.28 (m, 2H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.3 (CH_3), 25.3 (CH_3), 26.9 (CH_3), 27.4 (CH_2), 32.1 (CH_2), 36.0 (CH_2), 63.3 (CH_2), 71.0 (CH_2), 78.0 (CH), 79.1 (C), 86.4 (C), 114.3 (C), 126.1 (CH), 128.5 (CH), 128.6 (CH), 142.1 (C), 173.3 (C=O), 174.2 (C=O); FAB-HRMS calcd for $C_{20}H_{27}O_7$ $(M+H)^+$ 379.1757, found 379.1753.

4.3.7. Ethyl (3*S*,4*S*,8*R*)-8-(benzyloxymethyl)-6,6-dimethyl-1-oxo-3-(3-phenylpropyl)-2,5,7-trioxaspiro[3.4]octane-3-carboxylate (22b). $Hg(OCOCF_3)_2$ (209 mg, 0.489 mmol) was added to a stirred solution of thioester **21b** (120 mg, 0.233 mmol) in MeCN (23 mL). After stirring for 4 h, the reaction mixture was evaporated in vacuo. The residue was suspended in Et_2O (5 mL) and passed through a short plug of silica gel (eluting with Et_2O) to remove insoluble Hg salt. Purification of the crude product (130 mg) by column chromatography (silica gel 10 g, 8:1 *n*-hexane/AcOEt) afforded β-lactone **22b** (92 mg, 84%) as a colorless oil: $[\alpha]_D^{26}$ −18.1 (*c* 2.06, benzene); IR (film) 2935, 1842, 1757, 1454, 1381, 1271, 1094 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, $J=7.2$ Hz, 3H, $CO_2CH_2CH_3$), 1.31 (s, 3H, acetonide CH_3), 1.49 (s, 3H, acetonide CH_3), 1.53 (m, 1H, C7–*H*), 1.74 (m, 1H, C7–*H*), 2.04 (ddd, $J=6.8$, 8.7, 13.9 Hz, 1H, C6–*H*), 2.15 (ddd, $J=6.4$, 8.9, 13.9 Hz, 1H, C6–*H*), 2.46 (ddd, $J=4.9$, 11.3, 13.7 Hz, 1H, C*H*Ph), 2.47 (ddd, $J=4.9$, 11.3, 13.7 Hz, 1H, C*H*Ph), 3.66 (dd, $J=8.7$, 9.1 Hz, 1H, C*H*OBn), 3.85 (dd, $J=5.1$, 8.7 Hz, 1H, C*H*OBn), 4.24 (dq, $J=10.9$, 7.2 Hz, 1H, CO_2CHCH_3), 4.32 (dq, $J=10.9$, 7.2 Hz, 1H, CO_2CHCH_3), 4.40 (d, $J=11.1$ Hz, 1H, OC*H*Ph), 4.50 (d, $J=11.1$ Hz, 1H, OC*H*Ph), 4.62 (dd, $J=5.1$, 9.1 Hz, 1H, C3–*H*), 7.07 (d, $J=7.2$ Hz, 2H, Ar*H*), 7.16 (t, $J=7.3$ Hz, 1H, Ar*H*), 7.20–7.38 (m, 7H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.1 (CH_3), 25.2 (CH_2), 25.4 (CH_3), 26.8 (CH_3), 31.1 (CH_2), 35.3 (CH_2), 62.1 (CH_2), 68.6 (CH_2), 73.8 (CH_2), 75.7 (CH), 87.7 (C), 95.5 (C), 113.1 (C), 125.9 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 137.1 (C), 141.3 (C), 167.9 (C=O), 168.1 (C=O); FAB-HRMS *m/z* calcd for $C_{27}H_{33}O_7$ $(M+H)^+$ 469.2226, found 469.2257.

4.3.8. Ethyl (2*S*,3*S*,4*R*)-5-benzyloxy-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-methoxycarbonyl-2-(3-phenylpropyl)pentanoate (19b). Potassium carbonate (24 mg, 0.175 mmol) was added to a solution of β-lactone **22b** (63 mg, 0.134 mmol) in MeOH (1.3 mL). After stirring for 1 h, the mixture was evaporated in vacuo. The residue (68 mg) was purified by column chromatography (silica gel 10 g, 4:1 *n*-hexane/AcOEt) to give methyl ester **19b** (60 mg, 89%) as a colorless oil: $[\alpha]_D^{26}$ +13.5 (*c* 2.03, $CHCl_3$); IR (film) 3513, 3029, 2986, 1732, 1497, 1454, 1373, 1240, 1101, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (m, 1H, C7–*H*), 1.29 (t, $J=7.2$ Hz, 3H, $CO_2CH_2CH_3$), 1.35 (s, 3H, acetonide CH_3), 1.57 (s, 3H, acetonide CH_3), 1.82 (m, 1H, C7–*H*), 1.86 (ddd, $J=2.8$, 8.2, 12.0 Hz, 1H, C6–*H*), 2.02 (ddd, $J=3.4$, 8.9, 12.0 Hz, 1H, C6–*H*), 2.53 (ddd, $J=6.3$, 8.4, 13.6 Hz, 1H, C*H*Ph), 2.61 (ddd, $J=4.9$, 8.7, 13.6 Hz, 1H, C*H*Ph), 3.47 (dd, $J=7.2$, 11.1 Hz, 1H, C*H*OBn), 3.66 (s, 3H, CO_2CH_3), 3.68 (s, 1H, O*H*), 3.93 (dd, $J=1.8$, 11.1 Hz, 1H, C*H*OBn), 4.17 (dq, $J=10.8$, 7.2 Hz, 1H, CO_2CHCH_3), 4.28 (dq, $J=10.8$, 7.2 Hz, 1H, CO_2CHCH_3), 4.52 (d, $J=12.2$ Hz, 1H, OC*H*Ph), 4.63 (d, $J=12.2$ Hz, 1H, OC*H*Ph), 4.66 (dd, $J=1.8$, 7.2 Hz, 1H, C3–*H*), 7.07 (d, $J=7.2$ Hz, 2H, Ar*H*), 7.16 (t, $J=7.4$ Hz, 1H, Ar*H*), 7.23–7.35 (m, 7H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.3 (CH_3), 25.4 (CH_3), 26.7 (CH_3), 27.2 (CH_3), 33.3 (CH_2), 36.0 (CH_2), 52.4 (CH_2), 62.7 (CH_2), 70.3 (CH_2), 73.8 (CH_2), 79.3 (C), 81.2 (C), 88.3 (C), 111.6 (C), 126.1 (CH), 127.9 (CH), 128.0 (CH), 128.57 (CH), 128.60 (CH), 138.2 (CH), 142.1 (C), 171.1 (C=O), 172.9 (C=O); FAB-HRMS *m/z* calcd for $C_{28}H_{37}O_8$ $(M+H)^+$ 501.2488, found 501.2501.

4.3.9. Ethyl [2*S*,2(3a*S*,6a*R*)]-2-hydroxy-5-phenyl-2-(tetrahydro-2,2-dimethyl-4-oxofuro[3,4-*d*][1,3]dioxol-3a-yl)pentanoate (23b). Palladium on carbon (10%, 7 mg) was added to a solution of benzyl ether **19b** (41 mg, 0.082 mmol) in EtOH (1 mL), and the mixture was vigorously stirred under 1 atm of hydrogen for 2 h. The catalyst was filtered through a Celite pad, and the filtrate was evaporated in vacuo. The crude product (32 mg) thus obtained was used without further purification.

DMAP (40 mg, 0.328 mmol) was added to a solution of the crude γ-hydroxyester (32 mg) in CH_2Cl_2 (1 mL). After stirring for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (6 mL), and the whole was extracted with AcOEt (10 mL). The organic extract was washed with brine (6 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (30 mg), which was purified by column chromatography (silica gel 5 g, 5:1 *n*-hexane/AcOEt) to give γ-lactone **23b** (29 mg, 94%) as a colorless oil: $[\alpha]_D^{26}$ −24.0 (*c* 1.46, $CHCl_3$); IR (film) 3472, 2990, 2938, 1786, 1726, 1497, 1456, 1377, 1256, 1218, 1179, 1101, 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (m, 1H, C7–*H*), 1.32 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.44 (s, 6H, 2×acetonide CH_3), 1.74 (ddd, *J*=4.4, 12.3, 16.0 Hz, 1H, C6–*H*), 1.82 (m, 1H, C7–*H*), 2.24 (ddd, *J*=4.4, 12.3, 16.0 Hz, 1H, C6–*H*), 2.63 (ddd, *J*=6.1, 8.6, 13.7 Hz, 1H, C*H*Ph), 2.65 (ddd, *J*=6.1, 8.6, 13.7 Hz, 1H, C*H*Ph), 3.72 (s, 1H, O*H*), 4.26 (dd, *J*=3.8, 10.5 Hz, 1H, one of lactone CH_2), 4.31 (dd, *J*=3.8, 10.5 Hz, 1H, one of lactone CH_2), 4.34 (dq, *J*=10.9, 7.2 Hz, 1H, CO_2CHCH_3), 4.35 (dq, *J*=10.9, 7.2 Hz, 1H, CO_2CHCH_3), 4.82 (t, *J*=3.8 Hz, 1H, C3–*H*), 7.14–7.19 (m, 3H, Ar*H*), 7.27 (m, 2H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 15.1 (CH_3), 25.6 (CH_3), 27.8 (CH_3), 28.3 (CH_2), 33.9 (CH_2), 36.8 (CH_2), 64.4 (CH_2), 72.2 (CH_2), 78.4 (CH), 79.5 (C), 88.2 (C), 115.5 (C), 127.1 (CH), 129.4 (CH), 129.5 (CH), 142.7 (C), 174.1 (C=O), 175.8 (C=O); FAB-HRMS *m*/*z* calcd for $C_{20}H_{27}O_7$ $(M+H)^+$ 379.1757, found 379.1763.

4.3.10. Typical procedure for the aldol reaction of α-keto esters with silyl ketene thioacetals: ethyl [2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[3-benzyloxy-1,2-(dimethylmethylenedioxy)propyl]-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methylthio)carbonylpentanoate (24). $Sn(OTf)_2$ (42 mg, 0.10 mmol) was added to a stirred solution of α-keto ester **17** (16.5 mg, 0.051 mmol) and silyl ketene thioacetal **20** (37 mg, 0.10 mmol) in EtCN (1 mL) at −70 °C. After stirring at −70 °C for 1.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL). The mixture was diluted with 1:1 AcOEt/*n*-hexane (10 mL) and filtered through a Celite pad. The layers were separated, and the organic layer was washed successively with saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (45 mg), whose ^1H NMR revealed a **24a**/**24b** ratio of 1:2.2. Purification by column chromatography (silica gel 5 g, 7:1→4:1 *n*-hexane/AcOEt) afforded aldol adducts **24b** (19.5 mg, 62%) and **24a** (8.9 mg, 28%) as colorless oils. *Data for [2R,2(1R,2S),3S,4R]-isomer (***24a***).* $[\alpha]_D^{24}$ −12.1 (*c* 0.36, $CHCl_3$); IR (film) 3468, 2928, 1734, 1671, 1456, 1373, 1259, 1219, 1086, 866, 737, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.23 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.36 (s, 6H, 2×acetonide CH_3), 1.62 (s, 3H, acetonide CH_3), 1.82 (s, 3H, acetonide CH_3), 2.17 (s, 3H, $COSCH_3$), 3.25 (dd, *J*=7.8, 10.4 Hz, 1H, C*H*OBn), 3.56 (dd, *J*=6.4, 10.4 Hz, 1H, C1–*H*), 3.72 (dd, *J*=3.4, 10.4 Hz, 1H, C1–*H*), 3.83 (dd, *J*=1.7, 10.4 Hz, 1H, C*H*OBn), 3.98 (s, 1H, O*H*), 3.99 (ddd, *J*=3.4, 6.4, 8.0 Hz, 1H, C7–*H*), 4.12 (dq, *J*=10.7, 7.2 Hz, 1H, CO_2CHCH_3), 4.23 (dq, *J*=10.7, 7.2 Hz, 1H, CO_2CHCH_3), 4.41 (d, *J*=8.0 Hz, 1H, C6–*H*), 4.48 (d, *J*=12.4 Hz, 1H, OC*H*Ph), 4.57 (s, 2H, OCH_2Ph), 4.65 (d, *J*=12.4 Hz, 1H, OC*H*Ph), 5.32 (dd, *J*=1.7, 7.8 Hz, 1H, C3–*H*), 7.21–7.39 (m, 10H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 12.1 (CH_3), 14.1 (CH_3), 26.2 (CH_3), 27.1 (CH_3), 27.3 (CH_3), 27.5 (CH_3), 63.3 (CH_2), 70.7 (CH_2), 72.1 (CH_2), 73.5 (CH_2), 73.6 (CH_2), 76.7 (CH), 77.5 (CH), 78.1 (CH), 79.1 (C), 93.9 (C), 110.9 (C), 112.2 (C), 127.8 (CH), 127.85 (CH), 127.91 (CH), 127.93 (CH), 128.5 (CH), 128.6 (CH), 138.1 (C), 138.5 (C), 170.2 (C=O), 204.3 (C=O); FAB-HRMS *m*/*z* calcd for $C_{32}H_{43}O_{10}S$ $(M+H)^+$ 619.2577, found 619.2588. *Data for [2S,2(1R,2S),3S,4R]-isomer (***24b***).* $[\alpha]_D^{25}$ −30.9 (*c* 0.74, $CHCl_3$); IR (film) 3510, 2930, 1736, 1670, 1381, 1260, 1219, 1148, 1088, 860, 737, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.09 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.42 (s, 3H, acetonide CH_3), 1.49 (s, 3H, acetonide CH_3), 1.68 (s, 3H, acetonide CH_3), 1.82 (s, 3H, acetonide CH_3), 2.08 (s, 3H, $COSCH_3$), 3.34 (d, *J*=4.5 Hz, 2H, C1–H_2), 3.35 (dd, *J*=7.7, 10.8 Hz, 1H, C*H*OBn), 3.69 (d, *J*=0.8 Hz, 1H, O*H*), 3.75 (dq, *J*=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 3.86 (dd, *J*=2.2, 10.8 Hz, 1H, C*H*OBn), 3.90 (dq, *J*=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.23 (dt, *J*=7.5, 4.5 Hz, 1H, C7–*H*), 4.49 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 4.51 (dd, *J*=0.8, 7.5 Hz, 1H, C6–*H*), 4.52 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 4.61 (d, *J*=12.5 Hz, 2H, 2×OC*H*Ph), 5.37 (dd, *J*=2.2, 7.7 Hz, 1H, C3–*H*), 7.20–7.38 (m, 10H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 12.0 (CH_3), 13.9 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 27.79 (CH_3), 27.83 (CH_3), 62.5 (CH_2), 70.4 (CH_2), 71.0 (CH_2), 73.3 (CH_2), 73.6 (CH_2), 76.7 (CH), 77.5 (CH), 79.2 (CH), 80.1 (C), 91.0 (C), 111.2 (C), 113.6 (C), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 128.6 (CH), 138.2 (C), 138.4 (C), 171.2 (C=O), 205.6 (C=O); FAB-HRMS *m*/*z* calcd for $C_{32}H_{43}O_{10}S$ $(M+H)^+$ 619.2577, found 619.2571.

4.3.11. (*R*,*E*)-4-(benzyloxy)methyl-5-[methylthio(trimethylsilyloxy)methylene]-2,2-dimethyl-1,3-dioxolane (25). KHMDS in toluene (0.5 M, 5.0 mL, 2.5 mmol) was added to a stirred solution of thioester **14** (697 mg, 2.35 mmol) in THF (10 mL) at −78 °C over a 2-h period. After stirring at −78 °C for 30 min, TMSCl (0.33 mL, 21.3 mmol) was added, and the resulting mixture was stirred at −78 °C for 30 min. The mixture was allowed to warm to room temperature. After stirring at room temperature for 15 min, the mixture was evaporated in vacuo. The residue was suspended in *n*-hexane and passed through a short plug of Florisil (eluting with AcOEt) to give silyl ketene thioacetal **25** (751 mg, 87%, *Z*/*E*=1:99) as a yellow oil: ^1H NMR (500 MHz, C_6D_6) δ 0.36 (s, 9H, $Si(CH_3)_3$), 1.33 (s, 3H, acetonide CH_3), 1.51 (s, 3H, acetonide CH_3), 1.98 (s, 3H, SCH_3), 3.84 (dd, *J*=5.6, 10.6 Hz, 1H, C*H*OBn), 3.94 (dd, *J*=2.0, 10.6 Hz, 1H, C*H*OBn), 4.51 (s, 2H, OCH_2Ph), 5.13 (dd, *J*=2.0, 5.6 Hz, 1H, C3–*H*), 7.07–7.37 (m, 5H, Ar*H*); ^{13}C NMR (67.8 MHz, C_6D_6) δ 1.1 (CH_3), 16.3 (CH_3), 27.2 (CH_3), 27.5 (CH_3), 72.8 (CH_2), 73.9 (CH_2), 78.8 (CH),

112.8 (C), 121.8 (C), 128.2 (CH), 128.9 (CH), 139.5 (C), 141.5 (C).

4.3.12. $Sn(OTf)_2$-promoted aldol reaction between α-keto ester 17 and (*E*)-silyl ketene thioacetal 25. The aldol reaction was performed according to the typical procedure (2 mL EtCN, −55 °C, 1 h) employing α-keto ester **17** (30 mg, 0.093 mmol), (*E*)-silyl ketene thioacetal **25** (69 mg, 0.187 mmol), and $Sn(OTf)_2$ (78 mg, 0.187 mmol). A diastereomeric mixture of aldol adducts **24** (21 mg, 36%, **24a**:**24b**=1:10) was obtained as a colorless oil after flash column chromatography (silica gel 5 g, 8:1 *n*-hexane/AcOEt).

4.3.13. Ethyl [2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[3-benzyloxy-1,2-(methylenedioxy)propyl]-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methylthio)carbonylpentanoate (36). The aldol reaction was performed according to the typical procedure (1.2 mL EtCN, −70 °C, 1.5 h) employing α-keto ester **26** (19 mg, 0.063 mmol), silyl ketene thioacetal **20** (50 mg, 0.136 mmol), and $Sn(OTf)_2$ (53 mg, 0.127 mmol). The diastereomeric ratio of the products was determined to be 1:2.6 by ^{1}H NMR of the crude product (43 mg), from which an inseparable mixture of aldol adducts **36** (18 mg, 49%, **36a**:**36b**=1:2.6) was obtained as a colorless oil after flash column chromatography (silica gel 8 g, 5:1→3:1 *n*-hexane/AcOEt): $[\alpha]_D^{26}$ −40.0 (*c* 0.81, $CHCl_3$); IR (film) 3504, 2869, 1734, 1671, 1456, 1383, 1261, 1221, 1094, 737, 698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) for **36b** δ 1.12 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.66 (s, 3H, acetonide CH_3), 1.81 (s, 3H, acetonide CH_3), 2.09 (s, 3H, $COSCH_3$), 3.38 (dd, *J*=7.6, 10.8 Hz, 1H, C*H*OBn), 3.41 (dd, *J*=6.0, 10.6 Hz, 1H, C1–*H*), 3.49 (dd, *J*=3.1, 10.6 Hz, 1H, C1–*H*), 3.72 (d, *J*=0.8 Hz, 1H, O*H*), 3.85 (dq, *J*=10.8, 7.1 Hz, 1H, CO_2CHCH_3), 3.89 (dd, *J*=2.2, 10.8 Hz, 1H, C*H*OBn), 4.03 (dq, *J*=10.8, 7.1 Hz, 1H, CO_2CHCH_3), 4.15 (dt, *J*=3.1, 6.0 Hz, 1H, C7–*H*), 4.52 (d, *J*=12.3 Hz, 1H, OC*H*Ph), 4.53 (d, *J*=12.3 Hz, 1H, OC*H*Ph), 4.55 (m, 1H, C6–*H*), 4.59 (d, *J*=12.3 Hz, 2H, 2×OC*H*Ph), 5.10 (s, 2H, OCH_2O), 5.40 (dd, *J*=2.2, 7.6 Hz, 1H, C3–*H*), 7.22–7.38 (m, 10H, Ar*H*). The minor isomer (**36a**) had additional signals at 1.22 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.17 (s, 3H, $COSCH_3$), and 5.40 (dd, *J*=1.6, 7.7 Hz, 1H, C3–*H*); FAB-LRMS *m*/*z* 591 $(M+H)^+$.

4.3.14. Ethyl [2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[3-benzyloxy-1,2-(diethylmethylenedioxy)propyl]-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methylthio)carbonylpentanoate (37). The aldol reaction was performed according to the typical procedure (4 mL EtCN, −70 °C, 1.5 h) employing α-keto ester **27** (111 mg, 0.32 mmol), silyl ketene thioacetal **20** (204 mg, 0.055 mmol), and $Sn(OTf)_2$ (269 mg, 0.65 mmol). The diastereomeric ratio of the products was determined to be 1:1.1 by ^{1}H NMR of the crude product (263 mg), from which aldol adducts **37a** (79 mg, 39%) and **37b** (82 mg, 40%) were obtained as colorless oils after flash column chromatography (silica gel 13 g, 8:1→6:1 *n*-hexane/AcOEt). *Data for [2R,2(1R,2S),3S,4R]-isomer (***37a***).* $[\alpha]_D^{22}$ −13.3 (*c* 0.45, $CHCl_3$); IR (film) 3461, 2930, 1725, 1673, 1455, 1377, 1257, 1221, 1174, 1097, 736, 698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86 (t, *J*=7.6 Hz, 3H, pentylidene CH_3), 0.91 (t, *J*=7.6 Hz, 3H, pentylidene CH_3), 1.22 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.39–1.74 (m, 4H, 2×pentylidene CH_2), 1.63 (s, 3H, acetonide CH_3), 1.82 (s, 3H, acetonide CH_3), 2.17 (s, 3H, $COSCH_3$), 3.28 (dd, *J*=7.8, 10.5 Hz, 1H, C*H*OBn), 3.57 (dd, *J*=6.1, 10.4 Hz, 1H, C1–*H*), 3.73 (dd, *J*=3.5, 10.4 Hz, 1H, C1–*H*), 3.86 (dd, *J*=1.8, 10.5 Hz, 1H, C*H*OBn), 4.00 (ddd, *J*=3.5, 6.1, 8.5 Hz, 1H, C7–*H*), 4.03 (s, 1H, O*H*), 4.13 (dq, *J*=10.7, 7.2 Hz, 1H, CO_2CHCH_3), 4.19 (dq, *J*=10.7, 7.2 Hz, 1H, CO_2CHCH_3), 4.37 (d, *J*=8.5 Hz, 1H, C6–*H*), 4.48 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 4.57 (s, 2H, OCH_2Ph), 4.66 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 5.35 (dd, *J*=1.8, 7.8 Hz, 1H, C3–*H*), 7.22–7.38 (m, 10H, Ar*H*); FAB-HRMS *m*/*z* calcd for $C_{34}H_{47}O_{10}S$ $(M+H)^+$ 647.2890, found 647.2911. *Data for [2S,2(1R,2S),3S,4R]-isomer (***37b***).* $[\alpha]_D^{24}$ −27.7 (*c* 0.51, $CHCl_3$); IR (film) 3515, 2928, 1736, 1671, 1456, 1383, 1261, 1147, 1090, 737, 698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.3 Hz, 3H, pentylidene CH_3), 0.94 (t, *J*=7.5 Hz, 3H, pentylidene CH_3), 1.09 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.47–1.85 (m, 4H, 2×pentylidene CH_2), 1.69 (s, 3H, acetonide CH_3), 1.82 (s, 3H, acetonide CH_3), 2.09 (s, 3H, $COSCH_3$), 3.337 (d, *J*=4.2 Hz, 2H, C1–H_2), 3.340 (dd, *J*=7.9, 10.6 Hz, 1H, C*H*OBn), 3.66 (s, 1H, O*H*), 3.73 (dq, *J*=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 3.87 (dd, *J*=2.0, 10.6 Hz, 1H, C*H*OBn), 3.88 (dq, *J*=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.24 (dt, *J*=8.2, 4.2 Hz, 1H, C7–*H*), 4.44 (d, *J*=8.2 Hz, 1H, C6–*H*), 4.48 (d, *J*=12.4 Hz, 1H, OC*H*Ph), 4.50 (d, *J*=12.4 Hz, 1H, OC*H*Ph), 4.61 (d, *J*=12.4 Hz, 1H, OC*H*Ph), 4.62 (d, *J*=12.4 Hz, 1H, OC*H*Ph), 5.39 (dd, *J*=2.0, 7.9 Hz, 1H, C3–*H*), 7.21–7.37 (m, 10H, Ar*H*); FAB-HRMS *m*/*z* calcd for $C_{34}H_{47}O_{10}S$ $(M+H)^+$ 647.2890, found 647.2881.

4.3.15. Ethyl [2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[3-benzyloxy-1,2-(dipropylmethylenedioxy)propyl]-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methylthio)carbonylpentanoate (38). The aldol reaction was performed according to the typical procedure (1.2 mL EtCN, −70 °C, 1.5 h) employing α-keto ester **28** (21.0 mg, 0.055 mmol), silyl ketene thioacetal **20** (52.1 mg, 0.14 mmol), and $Sn(OTf)_2$ (39.0 mg, 0.094 mmol). The diastereomeric ratio of the products was determined to be 1:1.6 by ^{1}H NMR of the crude product (62 mg), from which aldol adducts **38a** (12.8 mg, 34%) and **38b** (17.8 mg, 48%) were obtained as colorless oils after flash column chromatography (silica gel 8 g, 10:1→8:1→5:1 *n*-hexane/AcOEt). *Data for [2R,2(1R,2S),3S,4R]-isomer (***38a***).* $[\alpha]_D^{25}$ −13.6 (*c* 0.52, $CHCl_3$); IR (film) 3464, 2961, 1734, 1676, 1456, 1375, 1260, 1219, 1103, 735, 698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.82 (t, *J*=7.3 Hz, 3H, heptylidene CH_3), 0.92 (t, *J*=7.3 Hz, 3H, heptylidene CH_3), 1.22 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.20–1.72 (m, 8H, 4×heptylidene CH_2), 1.62 (s, 3H, acetonide CH_3), 1.82 (s, 3H, acetonide CH_3), 2.17 (s, 3H, $COSCH_3$), 3.27 (dd, *J*=7.8, 10.4 Hz, 1H, C*H*OBn), 3.55 (dd, *J*=6.0, 10.3 Hz, 1H, C1–*H*), 3.72 (dd, *J*=3.7, 10.3 Hz, 1H, C1–*H*), 3.85 (dd, *J*=1.5, 10.4 Hz, 1H, C*H*OBn), 3.97 (m, 1H, C7–*H*), 4.03 (s, 1H, O*H*), 4.14 (dq, *J*=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.19 (dq, *J*=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.38 (d, *J*=8.3 Hz, 1H, C6–*H*), 4.48 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 4.56 (s, 2H, OCH_2Ph), 4.66 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 5.33 (dd, *J*=1.5, 7.8 Hz, 1H, C3–*H*), 7.20–7.40 (m, 10H, Ar*H*); FAB-LRMS *m*/*z* 675 $(M+H)^+$, 631 $(M-C_3H_7)^+$. *Data for [2S,2(1R,2S),3S,4R]-isomer (***38b***).* $[\alpha]_D^{26}$ −25.3 (*c* 0.76,

$CHCl_3$); IR (film) 3510, 2961, 1736, 1669, 1456, 1383, 1261, 1148, 1090, 736, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.85 (t, $J=7.3$ Hz, 3H, heptylidene CH_3), 0.92 (t, $J=7.3$ Hz, 3H, heptylidene CH_3), 1.09 (t, $J=7.1$ Hz, 3H, $CO_2CH_2CH_3$), 1.18–1.80 (m, 8H, 4×heptylidene CH_2), 1.68 (s, 3H, acetonide CH_3), 1.82 (s, 3H, acetonide CH_3), 2.09 (s, 3H, $COSCH_3$), 3.33 (d, $J=4.5$ Hz, 2H, C1–H_2), 3.34 (dd, $J=7.9$, 10.7 Hz, 1H, CHOBn), 3.67 (d, $J=0.8$ Hz, 1H, OH), 3.74 (dq, $J=10.7$, 7.1 Hz, 1H, CO_2CHCH_3), 3.86 (dd, $J=2.1$, 10.7 Hz, 1H, CHOBn), 3.88 (dq, $J=10.7$, 7.1 Hz, 1H, CO_2CHCH_3), 4.23 (dt, $J=7.9$, 4.5 Hz, 1H, C7–H), 4.43 (dd, $J=0.8$, 7.9 Hz, 1H, C6–H), 4.48 (d, $J=12.5$ Hz, 1H, OCHPh), 4.53 (d, $J=12.5$ Hz, 1H, OCHPh), 4.59 (d, $J=12.5$ Hz, 1H, OCHPh), 4.61 (d, $J=12.5$ Hz, 1H, OCHPh), 5.37 (dd, $J=2.1$, 7.9 Hz, 1H, C3–H), 7.20–7.40 (m, 10H, ArH); FAB-LRMS *m/z* 675 $(M+H)^+$, 631 $(M-C_3H_7)^+$.

4.3.16. Ethyl [2*S*,2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[3-benzyloxy-1,2-(diethylmethylenedioxy)propyl]-2-hydroxy-3,4-(methylenedioxy)-3-(methylthio)carbonylpentanoate (39b). The aldol reaction was performed according to the typical procedure (1.5 mL EtCN, −70 °C, 1.5 h) employing α-keto ester **27** (27.3 mg, 0.078 mmol), silyl ketene thioacetal **33** (53.2 mg, 0.156 mmol), and $Sn(OTf)_2$ (65.0 mg, 0.156 mmol). The diastereomeric ratio of the products was determined to be 1:>20 by ^1H NMR of the crude product (83.2 mg), from which aldol adduct **39b** (32.3 mg, 67%) was obtained as a colorless oil after flash column chromatography (silica gel 5 g, 8:1→5:1 *n*-hexane/AcOEt): $[\alpha]_D^{24}$ −3.0 (*c* 0.92, $CHCl_3$); IR (film) 3493, 2975, 1738, 1672, 1454, 1368, 1260, 1150, 1094, 980, 752, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, $J=7.5$ Hz, 3H, pentylidene CH_3), 0.94 (t, $J=7.5$ Hz, 3H, pentylidene CH_3), 1.09 (t, $J=7.2$ Hz, 3H, $CO_2CH_2CH_3$), 1.60–1.83 (m, 4H, 2×pentylidene CH_2), 2.11 (s, 3H, $COSCH_3$), 3.31 (d, $J=4.2$ Hz, 2H, C1–H_2), 3.36 (dd, $J=7.8$, 10.7 Hz, 1H, CHOBn), 3.62 (s, 1H, OH), 3.74 (dq, $J=10.6$, 7.2 Hz, 1H, CO_2CHCH_3), 3.78 (dd, $J=2.2$, 10.7 Hz, 1H, CHOBn), 4.01 (dq, $J=10.6$, 7.2 Hz, 1H, CO_2CHCH_3), 4.21 (dt, $J=8.0$, 4.2 Hz, 1H, C7–H), 4.44 (d, $J=8.0$ Hz, 1H, C6–H), 4.47 (d, $J=12.3$ Hz, 1H, OCHPh), 4.52 (d, $J=12.3$ Hz, 1H, OCHPh), 4.57 (d, $J=12.3$ Hz, 2H, 2×OCHPh), 5.16 (dd, $J=2.2$, 7.8 Hz, 1H, C3–H), 5.36 (s, 1H, OCHO), 5.50 (s, 1H, OCHO), 7.22–7.37 (m, 10H, ArH); FAB-LRMS *m/z* 619 $(M+H)^+$, 589 $(M-Et)^+$.

4.3.17. Ethyl [2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[3-benzyloxy-1,2-(diethylmethylenedioxy)propyl]-3,4-(diethylmethylenedioxy)-2-hydroxy-3-(methylthio)carbonylpentanoate (40). The aldol reaction was performed according to the typical procedure (3 mL EtCN, −70 °C, 1.5 h) employing α-keto ester **27** (62.2 mg, 0.178 mmol), silyl ketene thioacetal **34** (137.3 mg, 0.346 mmol), and $Sn(OTf)_2$ (151.6 mg, 0.364 mmol). The diastereomeric ratio of the products was determined to be 1:1.9 by ^1H NMR of the crude product (161.6 mg), from which aldol adducts **40a** (31.3 mg, 26%) and **40b** (49.2 mg, 41%) were obtained as colorless oils after flash column chromatography (silica gel 10 g, 15:1→10:1→8:1 *n*-hexane/AcOEt). *Data for [2R,2(1R,2S),3S,4R]-isomer (**40a**).* $[\alpha]_D^{29}$ −5.4 (*c* 1.0, $CHCl_3$); IR (film) 3464, 2975, 1723, 1672, 1456, 1366, 1256, 936, 737, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, $J=7.5$ Hz, 3H, pentylidene CH_3), 0.90 (t, $J=7.4$ Hz, 3H, pentylidene CH_3), 0.94 (t, $J=7.5$ Hz, 3H, pentylidene CH_3), 1.05 (t, $J=7.5$ Hz, 3H, pentylidene CH_3), 1.25 (t, $J=7.2$ Hz, 3H, $CO_2CH_2CH_3$), 1.47–1.75 (m, 4H, 2×pentylidene CH_2), 1.86–1.98 (m, 2H, pentylidene CH_2), 2.05–2.20 (m, 2H, pentylidene CH_2), 2.14 (s, 3H, $COSCH_3$), 3.29 (dd, $J=7.2$, 10.6 Hz, 1H, CHOBn), 3.57 (dd, $J=6.0$, 10.4 Hz, 1H, C1–H), 3.76 (dd, $J=3.1$, 10.4 Hz, 1H, C1–H), 3.86 (dd, $J=1.7$, 10.6 Hz, 1H, CHOBn), 3.93 (s, 1H, OH), 4.01 (ddd, $J=3.1$, 6.0, 8.2 Hz, 1H, C7–H), 4.17 (dq, $J=10.7$, 7.2 Hz, 1H, CO_2CHCH_3), 4.23 (dq, $J=10.7$, 7.2 Hz, 1H, CO_2CHCH_3), 4.39 (d, $J=8.2$ Hz, 1H, C6–H), 4.49 (d, $J=12.5$ Hz, 1H, OCHPh), 4.57 (s, 2H, OCH_2Ph), 4.61 (d, $J=12.5$ Hz, 1H, OCHPh), 5.30 (dd, $J=1.7$, 7.2 Hz, 1H, C3–H), 7.22–7.37 (m, 10H, ArH); FAB-HRMS *m/z* calcd for $C_{36}H_{51}O_{10}S$ $(M+H)^+$ 675.3203, found 675.3234. *Data for [2S,2(1R,2S),3S,4R]-isomer (**40b**).* $[\alpha]_D^{27}$ −27.0 (*c* 0.68, $CHCl_3$); IR (film) 3512, 2940, 1738, 1667, 1368, 1090, 930, 737, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, $J=7.4$ Hz, 3H, pentylidene CH_3), 0.925 (t, $J=7.5$ Hz, 3H, pentylidene CH_3), 0.928 (t, $J=7.5$ Hz, 3H, pentylidene CH_3), 1.04 (t, $J=7.5$ Hz, 3H, pentylidene CH_3), 1.10 (t, $J=7.1$ Hz, 3H, $CO_2CH_2CH_3$), 1.55–1.82 (m, 4H, 2×pentylidene CH_2), 1.92–2.18 (m, 4H, 2×pentylidene CH_2), 2.07 (s, 3H, $COSCH_3$), 3.33 (dd, $J=6.0$, 11.2 Hz, 1H, C1–H), 3.37 (dd, $J=7.2$, 11.2 Hz, 1H, CHOBn), 3.40 (dd, $J=2.4$, 11.2 Hz, 1H, C1–H), 3.69 (dq, $J=10.7$, 7.1 Hz, 1H, CO_2CHCH_3), 3.74 (s, 1H, OH), 3.88 (dq, $J=10.7$, 7.1 Hz, 1H, CO_2CHCH_3), 3.89 (dd, $J=2.3$, 11.2 Hz, 1H, CHOBn), 4.22 (ddd, $J=2.4$, 6.0, 7.8 Hz, 1H, C7–H), 4.49 (d, $J=7.8$ Hz, 1H, C6–H), 4.51 (d, $J=12.5$ Hz, 1H, OCHPh), 4.59 (d, $J=12.5$ Hz, 1H, OCHPh), 4.60 (d, $J=12.5$ Hz, 1H, OCHPh), 4.60 (d, $J=12.5$ Hz, 1H, OCHPh), 5.39 (dd, $J=2.3$, 7.2 Hz, 1H, C3–H), 7.20–7.40 (m, 10H, ArH); FAB-HRMS *m/z* calcd for $C_{36}H_{51}O_{10}S$ $(M+H)^+$ 675.3203, found 675.3214.

4.3.18. Ethyl [2*S*,2(1*R*,2*S*),3*S*,4*R*]-2-[3-benzyloxy-1,2-(diethylmethylenedioxy)propyl]-5-(*tert*-butyldiphenylsilyl)oxy-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methylthio)carbonylpentanoate (41b). The aldol reaction was performed according to the typical procedure (5 mL EtCN, −70 °C, 1.5 h) employing α-keto ester **27** (69.6 mg, 0.199 mmol), silyl ketene thioacetal **35** (209.1 mg, 0.405 mmol), and $Sn(OTf)_2$ (170.6 mg, 0.409 mmol). The diastereomeric ratio of the products was determined to be 1:>20 by ^1H NMR of the crude product (284.2 mg), from which aldol adduct **41b** (102.0 mg, 65%) was obtained as a colorless oil after flash column chromatography (silica gel 15 g, 15:1 *n*-hexane/AcOEt): $[\alpha]_D^{23}$ −10.6 (*c* 0.39, $CHCl_3$); IR (film) 3515, 2932, 2884, 2859, 1738, 1667, 1462, 1427, 1375, 1262, 1221, 1111, 1026, 912, 887 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, $J=7.4$ Hz, 3H, pentylidene CH_3), 0.92 (t, $J=7.4$ Hz, 3H, pentylidene CH_3), 1.03 (s, 9H, $SiC(CH_3)_3$), 1.07 (t, $J=7.1$ Hz, 3H, $CO_2CH_2CH_3$), 1.50–1.79 (m, 4H, 2×pentylidene CH_2), 1.69 (s, 3H, acetonide CH_3), 1.79 (s, 3H, acetonide CH_3), 2.01 (s, 3H, $COSCH_3$), 3.33 (d, $J=4.1$ Hz, 2H, C1–H_2), 3.54 (dd, $J=7.2$, 11.2 Hz, 1H, CHOTBDPS), 3.69 (s, 1H, OH), 3.71 (dq, $J=10.7$, 7.1 Hz, 1H, CO_2CHCH_3), 3.85 (dq, $J=10.7$, 7.1 Hz, 1H, CO_2CHCH_3), 4.01 (dd, $J=2.7$, 11.2 Hz, 1H, CHOTBDPS), 4.26 (dt, $J=8.0$, 4.1 Hz, 1H, C7–H), 4.41 (d, $J=8.0$ Hz, 1H,

C6–*H*), 4.47 (d, J=12.5 Hz, 1H, OC*H*Ph), 4.62 (d, J=12.5 Hz, 1H, OC*H*Ph), 5.31 (dd, J=2.7, 7.2 Hz, 1H, C3–*H*), 7.23–7.45 (m, 9H, Ar*H*), 7.66–7.73 (m, 6H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 5.4 (CH_3), 6.5 (CH_3), 9.5 (CH_3), 11.4 (CH_3), 17.0 (CH_3), 23.8 (CH_3), 24.5 (CH_3), 25.3 (CH_3), 26.9 (CH_3), 27.9 (CH_2), 59.9 (CH_2), 62.1 (CH_2), 68.5 (CH_2), 71.0 (CH_2), 73.9 (CH_2), 76.9 (CH), 79.5 (C), 88.5 (C), 110.8 (C), 112.7 (C), 125.2 (CH), 125.3 (CH), 125.4 (CH), 125.6 (CH), 126.1 (CH), 127.2 (CH), 128.5 (CH), 133.5 (C), 133.6 (C), 168.9 (C=O), 203.5 (C=O); FAB-HRMS *m/z* calcd for $C_{43}H_{59}O_{10}SSi$ $(M+H)^+$ 795.3598, found 795.3590.

4.3.19. Ethyl [2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[3-(*tert*-butyldiphenylsilyl)oxy-1,2-(diethylmethylenedioxy)propyl]-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methylthio)carbonylpentanoate (42). The aldol reaction was performed according to the typical procedure (1.2 mL EtCN, −70 °C, 1.5 h) employing α-keto ester **29** (28 mg, 0.056 mmol), silyl ketene thioacetal **20** (43 mg, 0.117 mmol), and $Sn(OTf)_2$ (47 mg, 0.113 mmol). The diastereomeric ratio of the products was determined to be 1:5 by ^{1}H NMR of the crude product (57 mg), from which an inseparable mixture of aldol adducts **42** (20 mg, 45%, **42a**:**42b**=1:5) was obtained as a colorless oil after flash column chromatography (silica gel 8 g, 7:1 *n*-hexane/AcOEt): $[\alpha]_D^{23}$ −25.8 (*c* 0.97, $CHCl_3$); IR (film) 3511, 2934, 1736, 1667, 1462, 1429, 1381, 1262, 1219, 1088, 741, 702 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) for **42b** δ 0.91 (t, J=7.5 Hz, 3H, pentylidene CH_3), 0.95 (t, J=7.5 Hz, 3H, pentylidene CH_3), 1.01 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.07 (s, 9H, $SiC(CH_3)_3$), 1.60–1.86 (m, 4H, 2×pentylidene CH_2), 1.72 (s, 3H, acetonide CH_3), 1.83 (s, 3H, acetonide CH_3), 2.09 (s, 3H, COSCH_3), 3.32 (dd, J=4.3, 11.7 Hz, 1H, C1–*H*), 3.36 (dd, J=7.9, 10.6 Hz, 1H, C*H*OBn), 3.56 (dq, J=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 3.66 (d, J=0.8 Hz, 1H, O*H*), 3.76 (dd, J=1.6, 11.7 Hz, 1H, C1–*H*), 3.87 (dd, J=2.1, 10.6 Hz, 1H, C*H*OBn), 3.92 (dq, J=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.14 (ddd, J=1.6, 4.3, 7.8 Hz, 1H, C7–*H*), 4.51 (d, J=12.4 Hz, 1H, OC*H*Ph), 4.62 (d, J=12.4 Hz, 1H, OC*H*Ph), 4.75 (dd, J=0.8, 7.8 Hz, 1H, C6–*H*), 5.47 (dd, J=2.1, 7.9 Hz, 1H, C3–*H*), 7.21–7.46 (m, 11H, Ar*H*), 7.64–7.75 (m, 4H, Ar*H*). The minor isomer (**42a**) had additional signals at 1.05 (s, 9H, $SiC(CH_3)_3$), 2.16 (s, 3H, COSCH_3), and 5.34 (dd, J=1.6, 7.7 Hz, 1H, C3–*H*); FAB-LRMS *m/z* 795 $(M+H)^+$, 765 $(M-Et)^+$.

4.3.20. Ethyl [2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[1,2-(diethylmethylenedioxy)-3-(methoxymethoxy)]propyl-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methylthio)carbonylpentanoate (43). The aldol reaction was performed according to the typical procedure (1.2 mL EtCN, −70 °C, 1.5 h) employing α-keto ester **30** (18 mg, 0.059 mmol), silyl ketene thioacetal **20** (52 mg, 0.141 mmol), and $Sn(OTf)_2$ (54 mg, 0.13 mmol). The diastereomeric ratio of the products was determined to be 1.1:1 by ^{1}H NMR of the crude product (55 mg), from which aldol adducts **43a** (14.7 mg, 41%) and **43b** (13.5 mg, 38%) were obtained as colorless oils after flash column chromatography (silica gel 8 g, 10:1→6:1→4:1 *n*-hexane/AcOEt). *Data for [2R,2(1R,2S),3S,4R]-isomer (**43a**).* $[\alpha]_D^{27}$ −12.3 (*c* 0.66, $CHCl_3$); IR (film) 3462, 2930, 1732, 1672, 1458, 1383, 1256, 1219, 1098, 1042, 735, 698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, J=7.5 Hz, 3H, pentylidene CH_3), 0.92 (t, J=7.5 Hz, 3H, pentylidene CH_3), 1.22 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.43–1.70 (m, 4H, 2×pentylidene CH_2), 1.65 (s, 3H, acetonide CH_3), 1.83 (s, 3H, acetonide CH_3), 2.17 (s, 3H, COSCH_3), 3.29 (dd, J=7.8, 10.4 Hz, 1H, C*H*OBn), 3.35 (s, 3H, OCH_3), 3.65 (dd, J=6.6, 10.8 Hz, 1H, C1–*H*), 3.83 (dd, J=3.0, 10.8 Hz, 1H, C1–*H*), 3.83 (dd, J=1.7, 10.4 Hz, 1H, C*H*OBn), 3.95 (s, 1H, O*H*), 3.99 (ddd, J=3.0, 6.6, 8.3 Hz, 1H, C7–*H*), 4.13 (dq, J=10.8, 7.1 Hz, 1H, CO_2CHCH_3), 4.19 (dq, J=10.8, 7.1 Hz, 1H, CO_2CHCH_3), 4.39 (d, J=8.3 Hz, 1H, C6–*H*), 4.48 (d, J=12.5 Hz, 1H, OC*H*Ph), 4.64 (s, 2H, OCH_2O), 4.67 (d, J=12.5 Hz, 1H, OC*H*Ph), 5.33 (dd, J=1.7, 7.8 Hz, 1H, C3–*H*), 7.20–7.45 (m, 5H, Ar*H*); FAB-LRMS *m/z* 601 $(M+H)^+$, 543 $(M-C_4H_9)^+$. *Data for [2S,2(1R,2S),3S,4R]-isomer (**43b**).* $[\alpha]_D^{27}$ −33.3 (*c* 0.67, $CHCl_3$); IR (film) 3525, 2932, 1736, 1671, 1458, 1383, 1261, 1149, 1096, 1043 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, J=7.4 Hz, 3H, pentylidene CH_3), 0.94 (t, J=7.4 Hz, 3H, pentylidene CH_3), 1.24 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.55–1.86 (m, 4H, 2×pentylidene CH_2), 1.71 (s, 3H, acetonide CH_3), 1.83 (s, 3H, acetonide CH_3), 2.11 (s, 3H, COSCH_3), 3.34 (s, 3H, OCH_3), 3.35 (dd, J=7.8, 10.8 Hz, 1H, C*H*OBn), 3.40 (dd, J=6.4, 11.2 Hz, 1H, C1–*H*), 3.50 (dd, J=2.2, 11.2 Hz, 1H, C1–*H*), 3.69 (d, J=0.7 Hz, 1H, O*H*), 3.88 (dd, J=2.2, 10.8 Hz, 1H, C*H*OBn), 4.10 (dq, J=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.19 (dq, J=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.22 (ddd, J=2.2, 6.4, 7.7 Hz, 1H, C7–*H*), 4.46 (dd, J=0.7, 7.7 Hz, 1H, C6–*H*), 4.51 (d, J=12.5 Hz, 1H, OC*H*Ph), 4.61 (s, 2H, OCH_2O), 4.62 (d, J=12.5 Hz, 1H, OC*H*Ph), 5.41 (dd, J=2.2, 7.8 Hz, 1H, C3–*H*), 7.20–7.40 (m, 5H, Ar*H*); FAB-LRMS *m/z* 601 $(M+H)^+$.

4.3.21. Ethyl [2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[3-benzyloxymethoxy-1,2-(diethylmethylenedioxy)propyl]-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methylthio) carbonylpentanoate (44). The aldol reaction was performed according to the typical procedure (1.2 mL EtCN, −70 °C, 1.5 h) employing α-keto ester **31** (19.6 mg, 0.052 mmol), silyl ketene thioacetal **20** (51.0 mg, 0.138 mmol), and $Sn(OTf)_2$ (60 mg, 0.144 mmol). The diastereomeric ratio of the products was determined to be 1:1.6 by ^{1}H NMR of the crude product, from which aldol adducts **44a** (12.4 mg, 36%) and **44b** (18.9 mg, 54%) were obtained as colorless oils after flash column chromatography (silica gel 8 g, 6:1 *n*-hexane/AcOEt). *Data for [2R,2(1R,2S),3S,4R]-isomer (**44a**).* $[\alpha]_D^{27}$ −11.6 (*c* 0.55, $CHCl_3$); IR (film) 3462, 2936, 1734, 1671, 1456, 1380, 1256, 1171, 1096, 1042, 737, 698 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, J=7.5 Hz, 3H, pentylidene CH_3), 0.92 (t, J=7.5 Hz, 3H, pentylidene CH_3), 1.21 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.45–1.73 (m, 4H, 2×pentylidene CH_2), 1.65 (s, 3H, acetonide CH_3), 1.82 (s, 3H, acetonide CH_3), 2.17 (s, 3H, COSCH_3), 3.28 (dd, J=7.8, 10.4 Hz, 1H, C*H*OBn), 3.72 (dd, J=6.5, 10.8 Hz, 1H, C1–*H*), 3.86 (dd, J=1.7, 10.4 Hz, 1H, C*H*OBn), 3.90 (dd, J=3.0, 10.8 Hz, 1H, C1–*H*), 3.92 (s, 1H, O*H*), 4.01 (ddd, J=3.0, 6.5, 8.3 Hz, 1H, C7–*H*), 4.13 (dq, J=10.8, 7.1 Hz, 1H, CO_2CHCH_3), 4.16 (dq, J=10.8, 7.1 Hz, 1H, CO_2CHCH_3), 4.43 (d, J=8.3 Hz, 1H, C6–*H*), 4.48 (d, J=12.6 Hz, 1H, OC*H*Ph), 4.61 (s, 2H, OCH_2O), 4.68 (d, J=12.6 Hz, 1H, OC*H*Ph), 4.78 (s, 2H, OCH_2Ph), 5.34 (dd, J=1.7, 7.8 Hz, 1H, C3–*H*), 7.22–7.39 (m, 10H, Ar*H*); FAB-LRMS *m/z* 677

$(M+H)^+$, 647 $(M-Et)^+$. *Data for [2S,2(1R,2S),3S,4R]-isomer (**44b**).* $[\alpha]_D^{27}$ −27.2 (*c* 0.86, $CHCl_3$); IR (film) 3506, 2937, 1736, 1671, 1456, 1383, 1261, 1148, 1090, 1044, 735, 698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.3 Hz, 3H, pentylidene CH_3), 0.95 (t, *J*=7.3 Hz, 3H, pentylidene CH_3), 1.14 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.55–1.87 (m, 4H, 2×pentylidene CH_2), 1.72 (s, 3H, acetonide CH_3), 1.84 (s, 3H, acetonide CH_3), 2.11 (s, 3H, COSCH_3), 3.35 (dd, *J*=8.1, 10.6 Hz, 1H, C*H*OBn), 3.44 (dd, *J*=6.6, 11.2 Hz, 1H, C1–*H*), 3.58 (dd, *J*=2.2, 11.2 Hz, 1H, C1–*H*), 3.68 (s, 1H, O*H*), 3.88 (dd, *J*=2.2, 10.6 Hz, 1H, C*H*OBn), 3.97 (dq, *J*=10.6, 7.2 Hz, 1H, CO_2CHCH_3), 4.11 (dq, *J*=10.6, 7.2 Hz, 1H, CO_2CHCH_3), 4.26 (m, 1H, C7–*H*), 4.48 (d, *J*=8.1 Hz, 1H, C6–*H*), 4.51 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 4.59 (s, 2H, OCH_2Ph), 4.63 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 4.74 (d, *J*=6.8 Hz, 1H, OC*H*O), 4.77 (d, *J*=6.8 Hz, 1H, OC*H*O), 5.41 (dd, *J*=2.2, 8.1 Hz, 1H, C3–*H*), 7.20–7.40 (m, 10H, Ar*H*); FAB-LRMS *m/z* 677 $(M+H)^+$, 647 $(M-Et)^+$.

4.3.22. Ethyl [2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[1,2-(diethylmethylenedioxy)-3-[(2-methoxyethoxy)methoxy]propyl]-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methylthio)carbonylpentanoate (45). The aldol reaction was performed according to the typical procedure (1.2 mL EtCN, −70 °C, 1.5 h) employing α-keto ester **32** (24 mg, 0.069 mmol), silyl ketene thioacetal **20** (52 mg, 0.141 mmol), and $Sn(OTf)_2$ (49 mg, 0.118 mmol). The diastereomeric ratio of the products was determined to be 1.6:1 by ^1H NMR of the crude product (58 mg), from which aldol adducts **45a** (22.6 mg, 51%) and **45b** (14.2 mg, 32%) were obtained as colorless oils after flash column chromatography (silica gel 8 g, 4:1→7:2 *n*-hexane/AcOEt). *Data for [2R,2(1R,2S),3S,4R]-isomer (**45a**).* $[\alpha]_D^{25}$ −13.1 (*c* 1.0, $CHCl_3$); IR (film) 3459, 2938, 1732, 1672, 1462, 1377, 1254, 1175, 1046, 858, 793, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.5 Hz, 3H, pentylidene CH_3), 0.91 (t, *J*=7.5 Hz, 3H, pentylidene CH_3), 1.22 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.55–1.70 (m, 4H, 2×pentylidene CH_2), 1.65 (s, 3H, acetonide CH_3), 1.83 (s, 3H, acetonide CH_3), 2.17 (s, 3H, COSCH_3), 3.29 (dd, *J*=7.8, 10.4 Hz, 1H, C*H*OBn), 3.37 (s, 3H, OCH_3), 3.52–3.57 (m, 2H, OCH_2), 3.67 (dd, *J*=6.4, 10.7 Hz, 1H, C1–*H*), 3.67–3.72 (m, 2H, OCH_2), 3.87 (dd, *J*=1.4, 10.4 Hz, 1H, C*H*OBn), 3.88 (dd, *J*=2.8, 10.7 Hz, 1H, C1–*H*), 3.98 (ddd, *J*=2.8, 6.4, 8.4 Hz, 1H, C7–*H*), 3.99 (s, 1H, O*H*), 4.13 (dq, *J*=10.7, 7.2 Hz, 1H, CO_2CHCH_3), 4.19 (dq, *J*=10.7, 7.2 Hz, 1H, CO_2CHCH_3), 4.39 (d, *J*=8.4 Hz, 1H, C6–*H*), 4.48 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 4.67 (d, *J*=12.5 Hz, 1H, OC*H*Ph), 4.72 (s, 2H, OCH_2O), 5.33 (dd, *J*=1.4, 7.8 Hz, 1H, C3–*H*), 7.27 (m, 1H, Ar*H*), 7.29–7.37 (m, 4H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 8.1 (CH_3), 8.3 (CH_3), 11.8 (CH_3), 13.7 (CH_3), 26.2 (CH_3), 27.2 (CH_3), 29.1 (CH_2), 29.8 (CH_2), 58.9 (CH_3), 63.1 (CH_2), 66.7 (CH_2), 69.3 (CH_2), 70.3 (CH_2), 71.2 (CH_2), 73.1 (CH_2), 76.4 (CH), 77.9 (CH), 78.9 (CH), 79.1 (C), 93.6 (C), 95.4 (CH_2), 111.8 (C), 114.8 (C), 127.5 (CH), 127.6 (CH), 128.2 (CH), 138.3 (C), 170.6 (C=O), 193.7 (C=O); FAB-HRMS *m/z* calcd for $C_{31}H_{49}O_{12}S$ $(M+H)^+$ 645.2945, found 645.2916. Anal. Calcd for $C_{31}H_{48}O_{12}S$: C, 57.75; H, 7.50; S, 4.97. Found: C, 57.47; H, 7.43; S, 4.84. *Data for [2S,2(1R,2S),3S,4R]-isomer (**45b**).* $[\alpha]_D^{25}$ −33.5 (*c* 1.5, $CHCl_3$); IR (film) 3459, 2938, 1732, 1672, 1462, 1377, 1254, 1175, 1046, 858, 793, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.4 Hz, 3H, pentylidene CH_3), 0.94 (t, *J*=7.5 Hz, 3H, pentylidene CH_3), 1.24 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.58–1.87 (m, 4H, 2×pentylidene CH_2), 1.71 (s, 3H, acetonide CH_3), 1.83 (s, 3H, acetonide CH_3), 2.11 (s, 3H, COSCH_3), 3.35 (dd, *J*=7.8, 10.5 Hz, 1H, C*H*OBn), 3.42 (dd, *J*=6.6, 11.2 Hz, 1H, C1–*H*), 3.38 (s, 3H, OCH_3), 3.52 (dd, *J*=2.0, 11.2 Hz, 1H, C1–*H*), 3.52–3.57 (m, 2H, OCH_2), 3.63–3.72 (m, 2H, OCH_2), 3.69 (s, 1H, O*H*), 3.88 (dd, *J*=2.0, 10.5 Hz, 1H, C*H*OBn), 4.09 (dq, *J*=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.19 (dq, *J*=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.22 (m, 1H, C7–*H*), 4.45 (d, *J*=7.9 Hz, 1H, C6–*H*), 4.51 (d, *J*=12.4 Hz, 1H, OC*H*Ph), 4.61 (d, *J*=12.4 Hz, 1H, OC*H*Ph), 4.69 (d, *J*=6.8 Hz, 1H, OC*H*O), 4.71 (d, *J*=6.8 Hz, 1H, OC*H*O), 5.40 (dd, *J*=2.0, 7.8 Hz, 1H, C3–*H*), 7.25 (m, 1H, Ar*H*), 7.29–7.38 (m, 4H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 7.5 (CH_3), 8.5 (CH_3), 11.8 (CH_3), 13.7 (CH_3), 26.0 (CH_3), 27.4 (CH_3), 29.3 (CH_2), 30.0 (CH_2), 58.9 (CH_3), 62.5 (CH_2), 66.8 (CH_2), 68.1 (CH_2), 70.2 (CH_2), 71.6 (CH_2), 73.1 (CH_2), 76.0 (CH), 76.8 (CH), 79.0 (C), 79.9 (CH), 90.7 (C), 95.5 (CH_2), 113.2 (C), 114.9 (C), 127.4 (CH), 127.5 (CH), 128.2 (CH), 138.1 (C), 170.9 (C=O), 205.5 (C=O); FAB-HRMS *m/z* calcd for $C_{31}H_{49}O_{12}S$ $(M+H)^+$ 645.2945, found 645.2950.

4.3.23. Ethyl [3*R*,3(1*R*,2*S*),4*S*,8*R*]-3-[3-benzyloxy-1,2-(diethylmethylenedioxy)propyl]-8-(benzyloxymethyl)-6,6-dimethyl-1-oxo-2,5,7-trioxaspiro[3.4]octane-3-carboxylate (46a). $Hg(OCOCF_3)_2$ (133 mg, 0.31 mmol) was added to a stirred solution of thioester **37a** (98 mg, 0.15 mmol) in MeCN (16 mL). After stirring for 200 h, the reaction mixture was evaporated in vacuo. The residue was suspended in Et_2O and passed through a short plug of silica gel (eluting with Et_2O) to remove insoluble Hg salt. Purification of the residue (97 mg) by column chromatography (silica gel 5 g, 11:1 *n*-hexane/AcOEt) afforded β-lactone **46a** (52 mg, 58%) as a colorless oil: $[\alpha]_D^{29}$ +18.6 (*c* 1.15, $CHCl_3$); IR (film) 2978, 1848, 1730, 1456, 1379, 1219, 1103, 1094 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.85 (t, *J*=7.5 Hz, 3H, pentylidene CH_3), 0.89 (t, *J*=7.5 Hz, 3H, pentylidene CH_3), 1.17 (t, *J*=7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.35 (s, 3H, acetonide CH_3), 1.41 (s, 3H, acetonide CH_3), 1.59–1.72 (m, 4H, 2×pentylidene CH_2), 3.50 (dd, *J*=7.9, 8.2 Hz, 1H, C*H*OBn), 3.64 (dd, *J*=5.5, 10.6 Hz, 1H, C1–*H*), 3.76 (dd, *J*=6.0, 8.2 Hz, 1H, C*H*OBn), 3.78 (dd, *J*=5.5, 10.6 Hz, 1H, C1–*H*), 3.96 (dq, *J*=10.6, 7.0 Hz, 1H, CO_2CHCH_3), 4.27 (dq, *J*=10.6, 7.0 Hz, 1H, CO_2CHCH_3), 4.37 (m, 1H, C7–*H*), 4.39 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 4.51 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 4.60 (s, 2H, OCH_2Ph), 4.63 (d, *J*=6.5 Hz, 1H, C6–*H*), 4.81 (dd, *J*=6.0, 7.9 Hz, 1H, C3–*H*), 7.25–7.37 (m, 10H, Ar*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 8.0 (CH_3), 8.1 (CH_3), 8.2 (CH_3), 13.9 (CH_3), 24.9 (CH_3), 26.4 (CH_2), 26.5 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 62.1 (CH_2), 68.1 (CH_2), 70.1 (CH_2), 73.4 (CH), 73.8 (CH), 76.4 (CH), 85.6 (C), 94.2 (C), 113.3 (C), 114.6 (C), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 128.9 (CH), 136.9 (C), 138.1 (C), 166.1 (C=O), 167.5 (C=O); FAB-HRMS *m/z* calcd for $C_{33}H_{43}O_{10}$ $(M+H)^+$ 599.2856, found 599.2826.

4.3.24. Ethyl [2*R*,2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[3-benzyloxy-1,2-(diethylmethylenedioxy)propyl]-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methoxycarbonyl)pentanoate. Potassium carbonate (15.6 mg, 0.113 mmol) was

added to a solution of β-lactone **46a** (51.6 mg, 0.086 mmol) in MeOH (1.5 mL). After stirring for 1.5 h, the mixture was partitioned between AcOEt (10 mL) and brine (7 mL). The organic extract was washed successively with saturated aqueous NH_4Cl (7 mL) and brine (7 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (57.3 mg), which was purified by column chromatography (silica gel 8 g, 7:2 *n*-hexane/AcOEt) to give methyl ester (46.5 mg, 86%) as a colorless oil: $[\alpha]_D^{28}$ −5.20 (*c* 1.0, $CHCl_3$); IR (film) 3464, 2976, 2940, 1732, 1497, 1454, 1372, 1258, 1090, 936 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, J=7.4 Hz, 3H, pentylidene C*H*$_3$), 0.90 (t, J=7.5 Hz, 3H, pentylidene C*H*$_3$), 1.24 (t, J=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.53 (q, J=7.4 Hz, 2H, pentylidene C*H*$_2$), 1.55 (s, 3H, acetonide C*H*$_3$), 1.62 (q, J=7.5 Hz, 2H, pentylidene C*H*$_2$), 1.64 (s, 3H, acetonide C*H*$_3$), 3.40 (dd, J=6.3, 10.6 Hz, 1H, C*H*OBn), 3.60 (dd, J=5.8, 10.3 Hz, 1H, C1–*H*), 3.61 (s, 3H, CO_2CH_3), 3.70 (dd, J=3.9, 10.3 Hz, 1H, C1–*H*), 3.90 (dd, J=1.3, 10.6 Hz, 1H, C*H*OBn), 4.00 (ddd, J=3.9, 5.8, 8.6 Hz, 1H, C7–*H*), 4.14 (dq, J=10.8, 7.2 Hz, 1H, CO_2CHCH_3), 4.20 (s, 1H, O*H*), 4.24 (dq, J=10.8, 7.2 Hz, 1H, CO_2CHCH_3), 4.41 (d, J=8.6 Hz, 1H, C6–*H*), 4.51 (d, J=12.4 Hz, 1H, OC*H*Ph), 4.57 (s, 2H, OC*H*$_2$Ph), 4.62 (d, J=12.4 Hz, 1H, OC*H*Ph), 5.34 (dd, J=1.3, 6.3 Hz, 1H, C3–*H*), 7.26–7.33 (m, 10H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 8.1 (CH_3), 8.2 (CH_3), 13.8 (CH_3), 26.7 (CH_3), 27.2 (CH_3), 29.3 (CH_2), 29.9 (CH_2), 52.2 (CH_3), 62.8 (CH_2), 70.1 (CH_2), 71.5 (CH_2), 73.3 (CH_2), 73.4 (CH_2), 77.6 (CH), 78.8 (CH), 79.2 (C), 89.6 (C), 111.2 (C), 114.4 (C), 127.5 (CH), 127.6 (CH), 127.7 (CH), 128.2 (CH), 128.3 (CH), 137.7 (C), 138.3 (C), 170.5 (C=O), 171.3 (C=O); FAB-HRMS *m*/*z* calcd for $C_{34}H_{47}O_{11}$ $(M+H)^+$ 631.3118, found 631.3139.

4.3.25. Ethyl [2*R*,2(3a*S*,6a*R*),3*R*,4*S*]-3,4-(diethylmethylenedioxy)-2,5-dihydroxy-2-(tetrahydro-2,2-dimethyl-4-oxofuro[3,4-*d*][1,3]dioxol-3a-yl)pentanoate (47a). Palladium on carbon (10%, 10.8 mg) was added to a solution of benzyl ether (46.2 mg, 0.073 mmol) in MeOH (2 mL), and the mixture was vigorously stirred under 1 atm of hydrogen for 1 h. The catalyst was filtered through a Celite pad, and the filtrate was evaporated in vacuo. The crude product (32.9 mg) thus obtained was used without further purification.

DMAP (38.6 mg, 0.316 mmol) was added to a solution of the crude γ-hydroxyester (32.9 mg) in MeCN (1.5 mL). After stirring for 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl (6 mL), and the whole was extracted with AcOEt (15 mL). The organic extract was washed with brine (6 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (36.5 mg), which was purified by column chromatography (silica gel 5 g, 2:1 *n*-hexane/AcOEt) to give γ-lactone **47a** (30.0 mg, 98%) as a colorless oil: $[\alpha]_D^{28}$ −77.5 (*c* 1.01, $CHCl_3$); IR (film) 3480, 2978, 2942, 1790, 1730, 1464, 1377, 1256, 1171, 1090, 976 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, J=7.5 Hz, 3H, pentylidene C*H*$_3$), 0.89 (t, J=7.4 Hz, 3H, pentylidene C*H*$_3$), 1.35 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.46 (s, 3H, acetonide C*H*$_3$), 1.50 (s, 3H, acetonide C*H*$_3$), 1.58 (q, J=7.4 Hz, 2H, pentylidene C*H*$_2$), 1.64 (q, J=7.5 Hz, 2H, pentylidene C*H*$_2$), 2.23 (br s, 1H, O*H*), 3.92 (dd, J=4.7, 9.5 Hz, 1H, one of lactone C*H*$_2$), 4.00 (dd, J=9.5, 10.4 Hz, 1H, one of lactone C*H*$_2$), 4.23 (dq, J=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.35 (dq, J=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.36 (dd, J=3.7, 11.2 Hz, 1H, C1–*H*), 4.38 (dd, J=7.9, 11.2 Hz, 1H, C1–*H*), 4.39 (s, 1H, O*H*), 4.48 (ddd, J=3.7, 4.4, 7.9 Hz, 1H, C7–*H*), 4.61 (dd, J=4.7, 10.4 Hz, 1H, C3–*H*), 5.05 (d, J=4.4 Hz, 1H, C6–*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 8.1 (CH_3), 8.2 (CH_3), 14.2 (CH_3), 27.1 (CH_3), 27.2 (CH_3), 30.0 (CH_2), 30.2 (CH_2), 63.15 (CH_2), 63.21 (CH_2), 73.1 (CH_2), 76.8 (CH), 77.8 (CH), 79.0 (CH), 79.1 (C), 85.1 (C), 113.4 (C), 114.2 (C), 171.5 (C=O), 176.1 (C=O); FAB-HRMS *m*/*z* calcd for $C_{19}H_{31}O_{10}$ $(M+H)^+$ 419.1917, found 419.1890.

4.3.26. Ethyl [3*S*,3(1*R*,2*S*),4*S*,8*R*]-3-[3-benzyloxy-1,2-(diethylmethylenedioxy)propyl]-8-(benzyloxymethyl)-6,6-dimethyl-1-oxo-2,5,7-trioxaspiro[3.4]octane-3-carboxylate (46b). $Hg(OCOCF_3)_2$ (155 mg, 0.36 mmol) was added to a stirred solution of thioester **37b** (112 mg, 0.17 mmol) in MeCN (18 mL). After stirring for 10 h, the reaction mixture was evaporated in vacuo. The residue was suspended in Et_2O and passed through a short plug of silica gel (eluting with Et_2O) to remove insoluble Hg salt. Purification of the residue by column chromatography (silica gel 5 g, 8:1 *n*-hexane/AcOEt) afforded β-lactone **46b** (74.5 mg, 72%) as a colorless oil: $[\alpha]_D^{29}$ +6.52 (*c* 1.09, $CHCl_3$); IR (film) 2980, 2939, 2882, 1852, 1762, 1738, 1497, 1454, 1375, 1273, 1204, 1171, 1098, 1026, 937 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.76 (t, J=7.5 Hz, 3H, pentylidene C*H*$_3$), 0.86 (t, J=7.4 Hz, 3H, pentylidene C*H*$_3$), 1.21 (t, J=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.38 (s, 3H, acetonide C*H*$_3$), 1.42–1.67 (m, 4H, 2× pentylidene C*H*$_2$), 1.53 (s, 3H, acetonide C*H*$_3$), 3.46 (dd, J=6.6, 11.0 Hz, 1H, C1–*H*), 3.58 (dd, J=3.2, 11.0 Hz, 1H, C1–*H*), 3.72 (dd, J=8.7, 9.7 Hz, 1H, C*H*OBn), 3.87 (dd, J=2.0, 9.7 Hz, 1H, C*H*OBn), 4.09 (ddd, J=3.2, 6.6, 8.1 Hz, 1H, C7–*H*), 4.10 (q, J=7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.49 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.52 (d, J=12.5 Hz, 1H, OC*H*Ph), 4.56 (d, J=12.5 Hz, 1H, OC*H*Ph), 4.61 (d, J=8.1 Hz, 1H, C6–*H*), 4.68 (d, J=12.0 Hz, 1H, OC*H*Ph), 4.94 (dd, J=2.0, 8.7 Hz, 1H, C3–*H*), 7.26–7.38 (m, 10H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 7.8 (CH_3), 7.9 (CH_3), 13.9 (CH_3), 25.8 (CH_3), 27.2 (CH_3), 29.6 (CH_2), 29.9 (CH_2), 62.5 (CH_2), 69.2 (CH_2), 70.6 (CH_2), 73.6 (CH_2), 73.7 (CH_2), 75.2 (CH), 76.2 (CH), 79.0 (CH), 85.7 (CH), 96.4 (C), 113.7 (C), 114.5 (C), 127.65 (C), 127.70 (CH), 127.74 (CH), 128.0 (CH), 128.35 (CH), 128.37 (CH), 137.70 (C), 137.73 (C), 165.3 (C=O), 166.6 (C=O); FAB-HRMS *m*/*z* calcd for $C_{33}H_{43}O_{10}$ $(M+H)^+$ 599.2856, found 599.2830.

4.3.27. Ethyl [2*S*,2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[3-benzyloxy-1,2-[1,2-(diethylmethylenedioxy)propyl]-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methoxycarbonyl)pentanoate. Potassium carbonate (22.0 mg, 0.159 mmol) was added to a solution of β-lactone **46b** (74.5 mg, 0.124 mmol) in MeOH (1.5 mL). After stirring for 1.5 h, the mixture was partitioned between AcOEt (10 mL) and brine (7 mL). The organic extract was washed successively with saturated aqueous NH_4Cl (7 mL) and brine (7 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (85.3 mg), which was purified by column chromatography (silica gel 8 g, 5:1 *n*-hexane/AcOEt) to give methyl ester (78.3 mg, quant.) as a colorless oil: $[\alpha]_D^{30}$ +6.76 (*c* 1.0,

$CHCl_3$); IR (film) 3513, 2978, 2942, 1738, 1496, 1454, 1372, 1262, 1221, 1093, 932 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, $J=7.4$ Hz, 3H, pentylidene CH_3), 0.94 (t, $J=7.5$ Hz, 3H, pentylidene CH_3), 1.09 (t, $J=7.1$ Hz, 3H, $CO_2CH_2CH_3$), 1.61 (s, 3H, acetonide CH_3), 1.66 (s, 3H, acetonide CH_3), 1.73 (m, 2H, pentylidene CH_2), 1.77 (m, 2H, pentylidene CH_2), 3.26 (dd, $J=2.5$, 10.7 Hz, 1H, C1–*H*), 3.35 (dd, $J=6.4$, 10.7 Hz, 1H, C1–*H*), 3.42 (dd, $J=6.8$, 11.0 Hz, 1H, C*H*OBn), 3.56 (s, 3H, CO_2CH_3), 3.63 (s, 1H, O*H*), 3.74 (dq, $J=10.7$, 7.1 Hz, 1H, CO_2CHCH_3), 3.84 (dd, $J=2.3$, 11.0 Hz, 1H, C*H*OBn), 3.93 (dq, $J=10.7$, 7.1 Hz, 1H, CO_2CHCH_3), 4.29 (ddd, $J=2.5$, 6.4, 8.1 Hz, 1H, C7–*H*), 4.40 (d, $J=8.1$ Hz, 1H, C6–*H*), 4.47 (d, $J=12.6$ Hz, 1H, OC*H*Ph), 4.55 (d, $J=12.2$ Hz, 1H, OC*H*Ph), 4.59 (d, $J=12.2$ Hz, 1H, OC*H*Ph), 4.62 (d, $J=12.6$ Hz, 1H, OC*H*Ph), 5.30 (dd, $J=2.3$, 6.8 Hz, 1H, C3–*H*), 7.22–7.36 (m, 10H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 8.7 (CH_3), 9.7 (CH_3), 14.9 (CH_3), 27.6 (CH_3), 28.4 (CH_3), 30.5 (CH_2), 31.4 (CH_2), 53.1 (CH_3), 63.3 (CH_2), 71.0 (CH_2), 71.9 (CH_2), 74.4 (CH_2), 74.5 (CH_2), 77.0 (CH), 78.4 (CH), 78.7 (CH), 79.8 (CH), 80.8 (C), 87.7 (C), 113.9 (C), 115.8 (C), 128.6 (CH), 128.75 (CH), 128.79 (CH), 129.0 (CH), 129.1 (CH), 129.2 (CH), 129.4 (CH), 129.5 (CH), 139.1 (C), 139.2 (C), 173.1 (C=O), 173.8 (C=O); FAB-HRMS *m/z* calcd for $C_{34}H_{47}O_{11}$ $(M+H)^+$ 631.3118, found 631.3152.

4.3.28. Ethyl [2*S*,2(3a*S*,6a*R*),3*R*,4*S*]-3,4-(diethylmethylenedioxy)-2,5-dihydroxy-2-(tetrahydro-2,2-dimethyl-4-oxofuro[3,4-*d*][1,3]dioxol-3a-yl)pentanoate (47b). Palladium on carbon (10%, 11.7 mg) was added to a solution of benzyl ether (78.3 mg, 0.124 mmol) in MeOH (2 mL), and the mixture was vigorously stirred under 1 atm of hydrogen for 1 h. The catalyst was filtered through a Celite pad, and the filtrate was evaporated in vacuo. The crude product (64.3 mg) thus obtained was used without further purification.

DMAP (76.4 mg, 0.625 mmol) was added to a solution of the crude γ-hydroxyester (64.3 mg) in MeCN (1 mL). After stirring for 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl (6 mL), and the whole was extracted with AcOEt (10 mL). The organic extract was washed with brine (6 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (68 mg), which was purified by column chromatography (silica gel 5 g, 2:1 *n*-hexane/AcOEt) to give γ-lactone **47b** (46.2 mg, 89%) as a colorless oil: $[\alpha]_D^{28}$ −49.9 (*c* 1.5, $CHCl_3$); IR (film) 3459, 2978, 2942, 2883, 1782, 1730, 1462, 1377, 1206, 1022, 928, 907 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, $J=7.5$ Hz, 3H, pentylidene CH_3), 0.91 (t, $J=7.5$ Hz, 3H, pentylidene CH_3), 1.40 (t, $J=7.1$ Hz, 3H, $CO_2CH_2CH_3$), 1.43 (s, 3H, acetonide CH_3), 1.48 (s, 3H, acetonide CH_3), 1.67 (q, $J=7.5$ Hz, 2H, pentylidene CH_2), 1.71 (q, $J=7.5$ Hz, 2H, pentylidene CH_2), 1.97 (br s, 1H, O*H*), 3.38 (dd, $J=3.3$, 12.2 Hz, 1H, one of lactone CH_2), 3.72 (dd, $J=1.6$, 12.2 Hz, 1H, one of lactone CH_2), 4.11 (m, 2H, C1–H_2), 4.32 (dq, $J=10.7$, 7.1 Hz, 1H, CO_2CHCH_3), 4.35 (dq, $J=10.7$, 7.1 Hz, 1H, CO_2CHCH_3), 4.37 (s, 1H, O*H*), 4.40 (ddd, $J=3.6$, 3.9, 8.1 Hz, 1H, C7–*H*), 4.49 (d, $J=8.1$ Hz, 1H, C6–*H*), 5.51 (dd, $J=1.6$, 3.3 Hz, 1H, C3–*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 7.8 (CH_3), 8.2 (CH_3), 13.9 (CH_3), 26.5 (CH_3), 27.4 (CH_3), 29.6 (CH_2), 29.9 (CH_2), 61.9 (CH_2), 63.6 (CH_2), 71.5 (CH_2), 76.1 (CH), 76.5 (CH), 77.1 (CH), 78.5 (C), 85.9 (C), 114.0 (C), 114.3 (C), 170.8 (C=O), 175.5 (C=O); FAB-HRMS *m/z* calcd for $C_{19}H_{31}O_{10}$ $(M+H)^+$ 419.1917, found 419.1925.

4.3.29. Isomerization of 45b to 45a. KHMDS in toluene (0.5 M, 1.54 mL, 0.77 mmol) was added to a solution of undesired isomer **45b** (332 mg, 0.51 mmol) in THF (5 mL) at −78 °C under an argon atmosphere, and the resulting mixture was stirred at −23 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the whole was extracted with AcOEt (20 mL). The organic extract was washed with brine (2×5 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (308 mg), which was purified by flash column chromatography (silica gel 10 g, 15:1→3:1 *n*-hexane/AcOEt) to give desired isomer **45a** (77 mg, 23%) as a colorless oil, along with thioester **14** (30 mg, 20%) as a pale yellow oil.

4.3.30. Aldol reaction of α-keto ester 32 with potassium enolate 48 generated from thioester 14. A solution of thioester **14** (34 mg, 0.115 mmol) in THF (0.2 mL) was added to a 0.6 M solution of KHMDS in toluene (0.23 mL, 0.137 mmol) at −78 °C. After stirring at −78 °C for 30 min, a solution of α-keto ester **32** (20 mg, 0.057 mmol) in THF (0.2 mL) was added. After stirring at −23 °C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the whole was extracted with AcOEt (15 mL). The organic extract was washed with brine (8 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (62 mg), whose ^1H NMR revealed a **45a/45b** ratio of 2:1. Purification by column chromatography (silica gel 8 g, 4:1→7:2 *n*-hexane/AcOEt) afforded aldol adducts **45a** (8.9 mg, 23%) and **45b** (4.4 mg, 12%) as colorless oils.

4.4. Synthesis of internal ketalization precursor

4.4.1. Diethyl (4*R*,5*R*)-2,2-diethyl-1,3-dioxolane-4,5-dicarboxylate. *p*-Toluenesulfonic acid (202 mg, 1.6 mmol) was added to a stirred solution of diethyl L-(+)-tartrate (26.2 g, 0.127 mol) and 3,3-dimethoxypentane (25.1 g, 0.190 mol) in benzene (200 mL). The flask was fitted with a Soxhlet extractor and reflux condenser, and a thimble containing freshly activated 4 Å molecular sieves (11 g) was placed in the Soxhlet extractor. The whole was refluxed for 3 h, during which time the thimble was recharged with fresh sieves every 1 h. The reaction mixture was cooled to room temperature, and anhydrous K_2CO_3 (400 mg) was added. After stirring at room temperature for 10 min, the mixture was filtered, and the filtrate was evaporated in vacuo. The residue was partitioned between AcOEt (150 mL) and water (50 mL). The organic extract was washed successively with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by distillation under reduced pressure afforded the title compound (19.59 g, 96%) as a pale yellow oil: bp 124–125 °C (0.1 mmHg); $[\alpha]_D^{22}$ −20.2 (*c* 1.3, $CHCl_3$); IR (film) 2980, 2943, 1757, 1466, 1200, 1113 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.95 (t, $J=7.5$ Hz, 6H, 2×pentylidene CH_3), 1.32 (t, $J=7.1$ Hz, 6H, 2×$CO_2CH_2CH_3$), 1.74 (q, $J=7.5$ Hz, 4H, 2×pentylidene CH_2), 4.28 (q, $J=7.1$ Hz,

4H, 2×$CO_2CH_2CH_3$), 4.71 (s, 2H, 2×C*H*CO_2Et); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.8 (CH_3), 14.1 (CH_2), 29.6 (CH_2), 61.8 (CH_2), 77.4 (CH), 117.8 (C), 169.5 (C=O); FAB-HRMS *m/z* calcd for $C_{13}H_{23}O_6$ $(M+H)^+$ 275.1495, found 275.1506. Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.72; H, 8.01.

4.4.2. (2*S*,3*S*)-2,3-(diethylmethylenedioxy)butane-1,4-diol. A solution of the diester (30.2 g, 0.11 mol) in THF (50 mL) was added dropwise over a 50-min period to a stirred suspension of $LiAlH_4$ (8.3 g, 0.22 mol) in THF (200 mL) at 0 °C. After stirring at 0 °C for 40 min, the reaction was quenched by dropwise addition of water (8 mL) followed by 15% aqueous NaOH (8 mL) and water (24 mL). The mixture was stirred vigorously for 10 min, and then anhydrous $MgSO_4$ was added. After stirring at room temperature for additional 1 h, the suspension was filtered through a Celite pad, and the filtrate was evaporated in vacuo. Purification of the residue by column chromatography (silica gel 60 g, 2:1→1:2 *n*-hexane/AcOEt) afforded the title compound (19.0 g, 91%) as a white solid: mp 39.5–41.5 °C; $[\alpha]_D^{22}$ +5.05 (*c* 5.00, $CHCl_3$); IR (film) 3410 (br), 2934, 1464, 1201, 1172, 1053 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.92 (t, *J*=7.5 Hz, 6H, 2×pentylidene C*H*$_3$), 1.67 (q, *J*=7.5 Hz, 4H, 2×pentylidene C*H*$_2$), 2.44 (br s, 2H, O*H*), 3.67–3.85 (m, 4H, 2×C*H*$_2$OH), 3.97 (m, 2H, 2×OC*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 8.0 (CH_3), 30.4 (CH_2), 61.2 (CH_2), 78.4 (CH), 113.0 (C); FAB-HRMS *m/z* calcd for $C_9H_{19}O_4$ $(M+H)^+$ 191.1285, found 191.1290.

4.4.3. (2*S*,3*S*)-2,3-Diethylmethylenedioxy-4-[(2-methoxyethoxy)methoxy]-1-butanol. A solution of the diol (2.00 g, 10.5 mmol) in THF (6 mL) was added dropwise to a suspension of NaH (60% in oil, 430 mg, 10.8 mmol) in THF (40 mL). After stirring at room temperature for 1 h, the mixture was cooled to 0 °C, and MEMCl (1.82 mL, 10.5 mmol) was added. After stirring at 0 °C for 1.5 h, the mixture was poured into brine (100 mL), and the whole was extracted with AcOEt (2×50 mL). The combined organic extracts were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel 50 g, 1:1 *n*-hexane/AcOEt) afforded the title compound (2.72 g, 93%) as a colorless oil: $[\alpha]_D^{25}$ −7.16 (*c* 1.0, EtOH); IR (film) 3472 (br), 2973, 2938, 2882, 1464, 1202, 1175, 1092, 1046, 982, 934, 849 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, *J*=7.5 Hz, 3H, pentylidene C*H*$_3$), 0.92 (t, *J*=7.5 Hz, 3H, pentylidene C*H*$_3$), 1.60–1.73 (m, 4H, 2×pentylidene C*H*$_2$), 2.25 (br s, 1H, O*H*), 3.39 (s, 3H, OC*H*$_3$), 3.53–3.60 (m, 2H, OC*H*$_2$), 3.65–3.83 (m, 6H, 3×OC*H*$_2$), 3.91 (dt, *J*=8.5, 4.2 Hz, 1H, OC*H*), 4.03 (dt, *J*=8.5, 5.2 Hz, 1H, OC*H*), 4.75 (s, 2H, OC*H*$_2$O); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 8.0 (CH_3), 30.36 (CH_2), 30.41 (CH_2), 59.0 (CH_3), 62.6 (CH_2), 67.0 (CH_2), 68.1 (CH_2), 71.7 (CH_2), 76.8 (CH), 79.6 (CH), 97.5 (CH_2), 113.2 (C); FAB-HRMS *m/z* calcd for $C_{13}H_{27}O_6$ $(M+H)^+$ 279.1808, found 279.1795.

4.4.4. (2*R*,3*S*)-2,3-(diethylmethylenedioxy)-4-[(2-methoxyethoxy)methoxy]butyric acid. A solution of DMSO (1.1 mL, 15.5 mmol) in CH_2Cl_2 (3 mL) was added to a stirred solution of oxalyl chloride (1.1 mL, 12.6 mmol) in CH_2Cl_2 (40 mL) at −78 °C. After 15 min, a solution of the alcohol (2.00 g, 10.5 mmol) in CH_2Cl_2 (7 mL) was added, and the mixture was stirred for 15 min. Et_3N (15 mL, 110 mmol) was added, and the resulting mixture was stirred at −40 °C for 15 min. The reaction mixture was poured into pH 7 phosphate buffer (100 mL), and the whole was extracted with Et_2O (50 mL). The aqueous layer was saturated with NaCl and extracted with Et_2O (3×30 mL). The combined organic extracts were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (2.77 g), which was used without further purification for the next reaction.

A solution of NaH_2PO_4 (1.30 g, 10.8 mmol) in water (12 mL) was added to a solution of the crude aldehyde (2.77 g) and 2-methyl-2-butene (7 mL, 66 mmol) in *tert*-butyl alcohol (50 mL). $NaClO_2$ (4.70 g, 40.5 mmol) was added portionwise to the mixture. After stirring at room temperature for 8 h, the mixture was evaporated in vacuo. The residue was dissolved in 10% aqueous NaOH (5 mL) and water (30 mL), and the whole was washed with 1:1 *n*-hexane/Et_2O (3×20 mL). The aqueous layer was acidified with 10% aqueous HCl (8 mL), saturated with NaCl, and extracted with AcOEt (3×50 mL). The combined organic extracts were washed with brine (3×50 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel 25 g, 10:1 $CHCl_3$/MeOH) afforded the title compound (2.26 g, 79%) as a colorless oil: $[\alpha]_D^{23}$ −8.26 (*c* 2.0, $CHCl_3$); IR (film) 3700–3300 (br), 2940, 1736, 1462, 1175, 1107, 1044, 982, 928, 849 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, *J*=7.4 Hz, 3H, pentylidene C*H*$_3$), 0.95 (t, *J*=7.4 Hz, 3H, pentylidene C*H*$_3$), 1.71 (q, *J*=7.4 Hz, 4H, 2×pentylidene C*H*$_2$), 3.40 (s, 3H, OC*H*$_3$), 3.56–3.61 (m, 2H, OC*H*$_2$), 3.70–3.75 (m, 2H, OC*H*$_2$), 3.77 (dd, *J*=5.3, 11.1 Hz, 1H, C1–*H*), 3.93 (dd, *J*=2.9, 11.1 Hz, 1H, C1–*H*), 4.31 (ddd, *J*=2.9, 5.3, 8.4 Hz, 1H, C7–*H*), 4.40 (d, *J*=8.4 Hz, 1H, C6–*H*), 4.78 (d, *J*=6.8 Hz, 1H, OC*H*O), 4.80 (d, *J*=6.8 Hz, 1H, OC*H*O), 8.5 (br s, 1H, COO*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 7.5 (CH_3), 8.2 (CH_3), 29.7 (CH_2), 29.8 (CH_2), 58.9 (CH_3), 66.9 (CH_2), 67.1 (CH_2), 71.7 (CH_2), 75.5 (CH), 78.4 (CH), 95.8 (CH_2), 115.9 (C), 173.7 (C=O); FAB-HRMS *m/z* calcd for $C_{13}H_{25}O_7$ $(M+H)^+$ 293.1600, found 293.1619.

4.4.5. (2*R*,3*S*)-2,3-(diethylmethylenedioxy)-*N*-methoxy-4-[(2-methoxyethoxy)methoxy]-*N*-methylbutanamide. To a solution of the carboxylic acid (199 mg, 0.682 mmol) in DMF (5 mL) at 0 °C was added *N*,*O*-dimethylhydroxylamine hydrochloride (110 mg, 1.13 mmol), followed by addition of diethyl cyanophosphonate (DEPC, 0.12 mL, 0.791 mmol) and Et_3N (0.26 mL, 1.87 mmol). After stirring at room temperature for 1.5 h, the reaction was quenched with 1 N aqueous HCl (5 mL), and the whole was extracted with AcOEt (2×15 mL). The combined organic extracts were washed successively with brine (8 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (8 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (267 mg), which was purified by column chromatography (silica gel 10 g, 3:2 *n*-hexane/AcOEt) to give the title compound (203 mg, 89%) as a colorless oil: $[\alpha]_D^{24}$ −17.1 (*c* 2.0, benzene); IR (film) 2940, 1672, 1464, 1175, 1098, 1046, 993, 932, 846 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.926 (t, *J*=7.5 Hz, 3H,

pentylidene CH_3), 0.931 (t, J=7.5 Hz, 3H, pentylidene CH_3), 1.65–1.79 (m, 4H, 2×pentylidene CH_2), 3.24 (s, 3H, NCH_3), 3.39 (s, 3H, OCH_3), 3.53–3.59 (m, 2H, OCH_2), 3.65–3.74 (m, 3H, OCH_2, C1–*H*), 3.75 (s, 3H, NOCH_3), 3.82 (dd, J=3.2, 10.8 Hz, 1H, C1–*H*), 4.48–4.68 (m, 2H, C6–*H*, C7–*H*), 4.76 (d, J=6.8 Hz, 1H, OC*H*O), 4.78 (d, J=6.8 Hz, 1H, OC*H*O); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 7.6 (CH_3), 8.2 (CH_3), 29.5 (CH_2), 29.9 (CH_2), 32.2 (CH_3), 58.8 (CH_3), 61.6 (CH_3), 66.8 (CH_2), 67.2 (CH_2), 71.6 (CH_2), 74.1 (CH), 77.5 (CH), 95.7 (CH_2), 114.9 (C), 169.9 (C=O); FAB-HRMS *m*/*z* calcd for $C_{15}H_{30}NO_7$ $(M+H)^+$ 336.2022, found 336.2016.

4.4.6. (4*R*,5*S*)-4,5-(diethylmethylenedioxy)-2-ethoxy-6-[(2-methoxyethoxy)methoxy]-1-hexen-3-one. *tert*-Butyllithium in pentane (2.13 M, 6.0 mL, 12.8 mmol) was added to a stirred solution of ethyl vinyl ether (1.4 mL, 14.7 mmol) in THF (18 mL) at −78 °C. After stirring at 0 °C for 30 min, the mixture was added to a stirred solution of the amide (1.38 g, 4.12 mmol) in THF (30 mL) at −78 °C via cannula over a 20-min period. After stirring at −78 °C for 30 min, the reaction was quenched with saturated aqueous NH_4Cl (50 mL), and the whole was partitioned between AcOEt (100 mL) and water (30 mL). The organic extract was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel 15 g, 4:1 *n*-hexane/AcOEt) afforded the title compound (1.29 g, 90%) as a colorless oil: $[\alpha]_D^{23}$ −35.1 (*c* 1.0, $CHCl_3$); IR (film) 2976, 2940, 1732, 1611, 1462, 1366, 1287, 1175, 1098, 1046, 978, 851 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93 (t, J=7.4 Hz, 6H, 2×pentylidene CH_3), 1.40 (t, J=7.0 Hz, 3H, OCH$_2$CH_3), 1.66 (q, J=7.4 Hz, 2H, pentylidene CH_2), 1.73 (q, J=7.4 Hz, 2H, pentylidene CH_2), 3.39 (s, 3H, OCH_3), 3.52–3.60 (m, 2H, OCH_2), 3.68–3.77 (m, 3H, OCH_2, C1–*H*), 3.85 (q, J=7.0 Hz, 2H, OCH_2CH$_3$), 3.92 (dd, J=3.0, 10.9 Hz, 1H, C1–*H*), 4.35 (ddd, J=3.0, 6.4, 7.3 Hz, 1H, C7–*H*), 4.60 (d, J=2.8 Hz, 1H, C=C*H*), 4.77 (d, J=6.8 Hz, 1H, OC*H*O), 4.79 (d, J=6.8 Hz, 1H, OC*H*O), 4.84 (d, J=7.3 Hz, 1H, C6–*H*), 5.35 (d, J=2.8 Hz, 1H, C=C*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.7 (CH_3), 8.3 (CH_3), 14.2 (CH_3), 29.6 (CH_2), 30.1 (CH_2), 59.0 (CH_3), 63.9 (CH_2), 66.9 (CH_2), 68.1 (CH_2), 71.7 (CH_2), 77.7 (CH), 78.7 (CH), 93.8 (CH_2), 95.8 (CH_2), 115.5 (C), 156.5 (CH_2), 193.7 (C=O); FAB-HRMS *m*/*z* calcd for $C_{17}H_{31}O_7$ $(M+H)^+$ 347.2070, found 347.2044.

4.4.7. Ethyl (3*R*,4*S*)-3,4-(diethylmethylenedioxy)-5-[(2-methoxyethoxy)methoxy]-2-oxopentanoate (32). A stream of ozone in oxygen was bubbled through a stirred solution of the enone (1.27 g, 3.67 mmol) in CH_2Cl_2 (15 mL) at −78 °C until the solution turned pale blue. After stirring at −78 °C for 10 min, excess ozone was removed by bubbling a stream of nitrogen, and Me_2S (3 mL) was added. After stirring at room temperature for 1 h, the volatile elements were removed in vacuo. The residue was purified by column chromatography (silica gel 20 g, 4:1 *n*-hexane/AcOEt) to give α-keto ester **32** (1.10 g, 86%) as a colorless oil: $[\alpha]_D^{24}$ +7.71 (*c* 2.0, $CHCl_3$); IR (film) 2976, 2940, 1732, 1611, 1462, 1366, 1287, 1175, 1098, 1046, 978, 851 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J=7.5 Hz, 3H, pentylidene CH_3), 0.92 (t, J=7.5 Hz, 3H, pentylidene CH_3), 1.38 (t, J=7.2 Hz, 3H, CO$_2$CH$_2$CH_3), 1.57–1.76 (m, 4H, 2×pentylidene CH_2), 3.40 (s, 3H, OCH_3), 3.52–3.60 (m, 2H, OCH_2), 3.67–3.76 (m, 2H, OCH_2), 3.78 (dd, J=5.4, 10.8 Hz, 1H, C1–*H*), 3.88 (dd, J=5.4, 10.8 Hz, 1H, C1–*H*), 4.36 (q, J=7.2 Hz, 2H, CO$_2$CH_2-CH$_3$), 4.42 (m, 1H, C7–*H*), 4.73–4.81 (m, 3H, C6–*H*, OCH_2O); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 7.5 (CH_3), 8.2 (CH_3), 13.9 (CH_3), 29.3 (CH_2), 29.8 (CH_2), 58.9 (CH_3), 62.5 (CH_2), 66.9 (CH_2), 67.2 (CH_2), 71.6 (CH_2), 77.3 (CH), 80.0 (CH), 95.7 (CH_2), 116.0 (C), 162.0 (C), 193.0 (C=O); FAB-HRMS *m*/*z* calcd for $C_{16}H_{29}O_8$ $(M+H)^+$ 349.1863, found 349.1850.

4.4.8. Ethyl [2*R*,2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-{1,2-(diethylmethylenedioxy)-3-[(2-methoxyethoxy)methoxy]propyl}-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methylthio)carbonylpentanoate (45a). A solution of α-keto ester **32** (3.62 g, 10.4 mmol) and silyl ketene thioacetal **20** (6.71 g, 17.7 mmol) in EtCN (15 mL) was added to a solution of $Sn(OTf)_2$ (7.08 g, 17.0 mmol) in EtCN (60 mL) at −70 °C. After stirring at −70 °C for 1.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL). The mixture was diluted with AcOEt (300 mL) and *n*-hexane (30 mL), and filtered through a Celite pad. The layers were separated and the organic layer was washed successively with saturated aqueous $NaHCO_3$ (100 mL) and brine (2×100 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (9.98 g), which was purified by flash column chromatography (silica gel 360 g, 4:1→7:2 *n*-hexane/AcOEt) to give aldol adducts **45a** (3.09 g, 46%) and **45b** (2.37 g, 35%) as colorless oils.

4.4.9. Ethyl [2*R*,2(1*R*,2*S*),3*S*,4*R*]-5-benzyloxy-2-[1,2-(diethylmethylenedioxy)-3-[(2-methoxyethoxy)methoxy]propyl]-3,4-(dimethylmethylenedioxy)-2-hydroxy-3-(methoxycarbonyl)pentanoate (49). $Hg(OCOCF_3)_2$ (4.06 g, 9.52 mmol) was added to a stirred solution of thioester **45a** (3.06 g, 4.75 mmol) in MeOH (120 mL). The mixture was refluxed for 10 h and evaporated in vacuo. The residue was suspended in Et_2O (30 mL) and passed through a short plug of silica gel (eluting with Et_2O) to remove insoluble Hg salt. Purification by column chromatography (silica gel 150 g, 2:1→3:2 *n*-hexane/AcOEt) afforded methyl ester **49** (2.59 g, 87%) as a colorless oil: $[\alpha]_D^{23}$ +5.58 (*c* 3.4, benzene); IR (film) 3461 (br), 2942, 1730, 1456, 1372, 1252, 1175, 1096, 935, 864, 739, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J=7.5 Hz, 3H, pentylidene CH_3), 0.90 (t, J=7.5 Hz, 3H, pentylidene CH_3), 1.24 (t, J=7.3 Hz, 3H, CO$_2$CH$_2$CH_3), 1.57 (s, 3H, acetonide CH_3), 1.65 (s, 3H, acetonide CH_3), 1.48–1.65 (m, 4H, 2×pentylidene CH_2), 3.37 (s, 3H, OCH_3), 3.40 (dd, J=6.3, 10.6 Hz, 1H, C*H*OBn), 3.54 (m, 2H, OCH_2), 3.62 (s, 3H, CO$_2$CH_3), 3.68 (m, 2H, OCH_2), 3.69 (dd, J=6.2, 10.6 Hz, 1H, C1–*H*), 3.86 (dd, J=3.1, 10.6 Hz, 1H, C1–*H*), 3.89 (dd, J=1.9, 10.6 Hz, 1H, C*H*OBn), 3.99 (ddd, J=3.1, 6.2, 8.4 Hz, 1H, C7–*H*), 4.12 (br s, 1H, O*H*), 4.15 (dq, J=10.9, 7.3 Hz, 1H, CO$_2$C*H*CH$_3$), 4.23 (dq, J=10.9, 7.3 Hz, 1H, CO$_2$C*H*CH$_3$), 4.42 (d, J=8.4 Hz, 1H, C6–*H*), 4.51 (d, J=12.3 Hz, 1H, OC*H*Ph), 4.63 (d, J=12.3 Hz, 1H, OC*H*Ph), 4.73 (s, 2H, OCH_2O), 5.32 (dd, J=1.9, 6.3 Hz, 1H, C3–*H*), 7.25–7.35 (m, 5H, Ar*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 8.1 (CH_3), 8.2 (CH_3), 13.8 (CH_3), 26.7 (CH_3), 27.2 (CH_3), 29.3 (CH_2), 29.9 (CH_2), 52.2 (CH_3), 58.9 (CH_3),

63.0 (CH_3), 66.8 (CH_2), 69.2 (CH_2), 70.0 (CH_2), 71.7 (CH_2), 73.3 (CH_2), 77.0 (CH), 77.7 (CH), 78.8 (CH), 79.2 (C), 89.7 (C), 95.5 (CH_2), 111.3 (C), 114.5 (C), 127.5 (CH), 127.6 (CH), 128.2 (CH), 138.3 (C), 170.6 (C=O), 171.3 (C=O); FAB-HRMS *m/z* calcd for $C_{31}H_{49}O_{13}$ $(M+H)^+$ 629.3173, found 629.3203. Anal. Calcd for $C_{31}H_{48}O_{13}$: C, 59.22; H, 7.70. Found: C, 59.04; H, 7.65.

4.4.10. 3-Ethyl 1,2-dimethyl (1*S*,2*S*,3*R*,4*R*,5*S*)-4,5-(diethylmethylenedioxy)-1,2-(dimethylmethylenedioxy)-3-hydroxy-6-[(2-methoxyethoxy)methoxy]hexane-1,2,3-tricarboxylate (52). Palladium hydroxide on carbon (20%, 240 mg) was added to a solution of benzyl ether **49** (2.39 g, 3.81 mmol) in AcOEt (20 mL), and the mixture was vigorously stirred under 1 atm of hydrogen for 10 h. The catalyst was filtered through a Celite pad, and the filtrate was evaporated in vacuo to furnish the crude product (2.47 g) as a colorless oil.

Dess-Martin periodinane (4.36 g, 10.3 mmol) was added to a solution of the crude alcohol **50** (2.47 g) in CH_2Cl_2 (30 mL). After stirring at room temperature for 8 h, the mixture was diluted with Et_2O (40 mL) and poured into an ice-cooled saturated aqueous $NaHCO_3$ (100 mL) containing $Na_2S_2O_3\cdot 5H_2O$ (15 g). The layers were separated, and the organic layer was washed successively with saturated aqueous $NaHCO_3$ (2×50 mL), water (40 mL) and brine (50 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo gave the crude product (2.14 g), which was used without further purification.

A solution of NaH_2PO_4 (915 mg, 7.62 mmol) in water (10 mL) was added to a solution of the crude aldehyde (2.14 g) and 2-methyl-2-butene (10 mL, 95 mmol) in *tert*-butyl alcohol (50 mL), followed by addition of a solution of $NaClO_2$ (1.10 g, 9.52 mmol) in water (5 mL). After stirring at room temperature for 2.5 h, the mixture was evaporated in vacuo, and the residue was partitioned between AcOEt (120 mL) and 1 N HCl (60 mL). The aqueous layer was saturated with NaCl and extracted with AcOEt (2×40 mL). The combined organic extracts were washed with brine (40 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (2.31 g), which was used without further purification.

A solution of diazomethane in Et_2O was added to a solution of the crude carboxylic acid (2.31 g) in Et_2O (20 mL) at 0 °C until a yellow color persisted. The mixture was evaporated in vacuo to furnish the crude product (2.28 g), which was purified by column chromatography (silica gel 50 g, 2:1→1:1 *n*-hexane/AcOEt) to give methyl ester **52** (1.81 g, 84% for four steps) as a colorless oil: $[\alpha]_D^{26}$ −9.39 (*c* 2.1, benzene); IR (film) 3463 (br), 2978, 2944, 2884, 1738, 1462, 1441, 1383, 1254, 1209, 1177, 1117, 982, 937, 756 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.4 Hz, 3H, pentylidene CH_3), 0.90 (t, *J*=7.4 Hz, 3H, pentylidene CH_3), 1.34 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.58 (s, 3H, acetonide CH_3), 1.68 (s, 3H, acetonide CH_3), 1.45–1.71 (m, 4H, 2×pentylidene CH_2), 3.38 (s, 3H, OCH_3), 3.52–3.59 (m, 2H, OCH_2), 3.69 (dd, *J*=6.1, 10.8 Hz, 1H, C1–*H*), 3.65–3.74 (m, 2H, OCH_2), 3.75 (s, 3H, CO_2CH_3), 3.76 (s, 3H, CO_2CH_3), 3.89 (dd, *J*=3.0, 10.8 Hz, 1H, C1–*H*), 4.09 (s, 1H, O*H*), 4.12 (ddd, *J*=3.0, 6.1, 8.5 Hz, 1H, C7–*H*), 4.28 (dq, *J*=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.35 (dq, *J*=10.7, 7.1 Hz, 1H, CO_2CHCH_3), 4.38 (d, *J*=8.5 Hz, 1H, C6–*H*), 4.75 (s, 2H, OCH_2O), 5.73 (s, 1H, C3–*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 8.0 (CH_3), 8.1 (CH_3), 13.6 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 29.5 (CH_2), 30.0 (CH_2), 52.4 (CH_3), 52.6 (CH_3), 58.9 (CH_3), 63.0 (CH_3), 66.8 (CH_2), 69.0 (CH_2), 71.7 (CH_2), 76.5 (CH), 77.6 (CH), 79.1 (C), 79.3 (CH), 91.2 (C), 95.5 (CH_2), 114.2 (C), 114.4 (C), 169.4 (C=O), 170.5 (C=O), 170.8 (C=O); FAB-HRMS *m/z* calcd for $C_{25}H_{43}O_{14}$ $(M+H)^+$ 567.2653, found 567.2664. Anal. Calcd for $C_{25}H_{42}O_{14}$: C, 53.00; H, 7.47. Found: C, 53.24; H, 7.48.

*Data for ethyl [2R,2(3aS,6aR),3R,4S]-3,4-(diethylmethylenedioxy)-2-hydroxy-5-[(2-methoxyethoxy)methoxy]-2-(tetrahydro-2,2-dimethyl-4-oxofuro[3,4-d][1,3]dioxol-3a-yl)pentanoate (***51***).* $[\alpha]_D^{25}$ −59.2 (*c* 2.2, $CHCl_3$); IR (film) 3478 (br), 2976, 2942, 2883, 1790, 1761, 1730, 1462, 1375, 1248, 1173, 1096, 1046 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, *J*=7.4 Hz, 3H, pentylidene CH_3), 0.87 (t, *J*=7.4 Hz, 3H, pentylidene CH_3), 1.33 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.46 (s, 3H, acetonide CH_3), 1.50 (s, 3H, acetonide CH_3), 1.54–1.66 (m, 4H, 2×pentylidene CH_2), 3.39 (s, 3H, OCH_3), 3.57 (t, *J*=4.5 Hz, 2H, OCH_2), 3.75 (dd, *J*=4.9, 10.3 Hz, 1H, one of lactone CH_2), 3.76 (t, *J*=4.5 Hz, 2H, OCH_2), 4.05 (dd, *J*=2.1, 10.5 Hz, 1H, C1–*H*), 4.22 (dq, *J*=10.9, 7.2 Hz, 1H, CO_2CHCH_3), 4.31 (s, 1H, O*H*), 4.32 (dd, *J*=8.3, 10.5 Hz, 1H, C1–*H*), 4.33 (dq, *J*=10.9, 7.2 Hz, 1H, CO_2CHCH_3), 4.38 (dd, *J*=10.3, 10.5 Hz, 1H, one of lactone CH_2), 4.60 (ddd, *J*=2.1, 4.7, 8.3 Hz, 1H, C7–*H*), 4.65 (dd, *J*=4.9, 10.5 Hz, 1H, C3–*H*), 4.79 (d, *J*=8.9 Hz, 1H, OC*H*O), 4.81 (d, *J*=8.9 Hz, 1H, OC*H*O), 5.15 (d, *J*=4.7 Hz, 1H, C6–*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 8.08 (CH_3), 8.13 (CH_3), 14.2 (CH_3), 27.0 (CH_3), 27.3 (CH_3), 30.0 (CH_3), 30.3 (CH_2), 59.2 (CH_2), 63.0 (CH_2), 66.9 (CH_2), 68.8 (CH_2), 72.0 (CH_2), 73.5 (CH_2), 75.9 (CH_2), 77.5 (CH), 78.8 (CH), 79.3 (CH), 85.0 (C), 96.0 (C), 113.8 (C), 114.0 (C), 171.5 (C=O), 176.2 (C=O); FAB-HRMS *m/z* calcd for $C_{23}H_{39}O_{12}$ $(M+H)^+$ 507.2442, found 507.2453.

4.4.11. 3-Ethyl 1,2-dimethyl (1*S*,2*S*,3*R*,4*R*,5*S*)-4,5-(diethylmethylenedioxy)-1,2-(dimethylmethylenedioxy)-3,6-dihydroxyhexane-1,2,3-tricarboxylate (53). To a solution of MEM ether **52** (1.23 g, 2.18 mmol) in MeCN (25 mL) was added sodium iodide (3.27 g, 21.8 mmol) followed by addition of chlorotrimethylsilane (2.35 g, 21.7 mmol) at −23 °C. After stirring at −23 °C for 2 h, the mixture was poured into brine (30 mL), and the whole was partitioned between AcOEt (30 mL) and water (10 mL). The organic layer was washed successively with saturated aqueous $Na_2S_2O_3$ (3×20 mL) and brine (15 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (1.16 g), which was purified by column chromatography (silica gel 30 g, 1:1 *n*-hexane/AcOEt) to give diol **53** (978 mg, 94%) as a colorless oil: $[\alpha]_D^{24}$ +4.19 (*c* 3.1, $CHCl_3$); IR (film) 3468 (br), 2978, 2946, 2884, 1748, 1462, 1441, 1381, 1256, 1221, 1177, 1092, 935 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.4 Hz, 3H, pentylidene CH_3), 0.90 (t, *J*=7.4 Hz, 3H, pentylidene CH_3), 1.34 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.58 (s, 3H, acetonide CH_3), 1.67 (s, 3H, acetonide CH_3), 1.50–1.70 (m, 4H, 2×pentylidene CH_2), 2.07 (t, *J*=6.1 Hz, 1H, C1-O*H*), 3.76 (s, 6H, 2×CO_2CH_3), 3.77 (ddd, *J*=5.0,

6.1, 11.7 Hz, 1H, C1–*H*), 3.88 (ddd, J=3.7, 6.1, 11.7 Hz, 1H, C1–*H*), 4.02 (s, 1H, C5–O*H*), 4.07 (ddd, J=3.7, 5.0, 8.4 Hz, 1H, C7–*H*), 4.30 (dq, J=10.7, 7.2 Hz, 1H, $CO_2C\mathit{H}CH_3$), 4.35 (dq, J=10.7, 7.2 Hz, 1H, $CO_2C\mathit{H}CH_3$), 4.44 (d, J=8.4 Hz, 1H, C6–*H*), 5.67 (s, 1H, C3–*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 8.0 (CH_3), 8.1 (CH_3), 13.6 (CH_3), 26.7 (CH_3), 26.9 (CH_3), 29.6 (CH_2), 30.0 (CH_2), 52.4 (CH_3), 52.7 (CH_3), 58.9 (CH_3), 63.2 (CH_2), 63.7 (CH_2), 76.4 (CH), 78.5 (CH), 79.1 (C), 79.2 (CH), 91.1 (C), 114.1 (C), 114.3 (C), 169.3 (C=O), 170.6 (C=O), 170.9 (C=O); FAB-HRMS m/z calcd for $C_{21}H_{35}O_{12}$ $(M+H)^+$ 479.2129, found 479.2144.

4.4.12. 3-Ethyl 1,2-dimethyl (1*S*,2*S*,3*R*,4*R*,5*S*)-4,5-(diethylmethylenedioxy)-1,2-(dimethylmethylenedioxy)-6-hydroxy-3-(trimethylsilyloxy)hexane-1,2,3-tricarboxylate (54). A mixture of diol **53** (978 mg, 2.04 mmol) and *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (3.0 mL, 16.2 mmol) was heated at 90 °C for 3 h. After cooling to room temperature, the mixture was evaporated in vacuo to provide a crude product (1.42 g), which was used without further purification.

To a solution of the crude bis(trimethylsilyl) ether in Et_2O (15 mL) was added 10% aqueous HCl (2 mL), and the biphasic mixture was stirred vigorously at room temperature for 1.5 h. The reaction was quenched by addition of solid $NaHCO_3$ at 0 °C, and the layers were separated. The organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (1.16 g), which was purified by column chromatography (silica gel 30 g, 4:1 *n*-hexane/AcOEt) to give alcohol **54** (975 mg, 87%) as a white solid: mp 105–106 °C (colorless prisms from *n*-hexane); $[\alpha]_D^{24}$ −12.6 (*c* 1.1, $CHCl_3$); IR (nujol) 3526 (br), 2978, 1738, 1437, 1375, 1252, 846, 758 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.15 (s, 9H, $Si(CH_3)_3$), 0.85 (t, J=7.5 Hz, 3H, pentylidene CH_3), 0.89 (t, J=7.5 Hz, 3H, pentylidene CH_3), 1.30 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.54 (s, 3H, acetonide CH_3), 1.64 (s, 3H, acetonide CH_3), 1.44–1.67 (m, 4H, 2× pentylidene CH_2), 2.01 (t, J=6.5 Hz, 1H, O*H*), 3.70 (ddd, J=4.8, 6.5, 11.8 Hz, 1H, C1–*H*), 3.73 (s, 3H, CO_2CH_3), 3.76 (s, 3H, CO_2CH_3), 3.90 (ddd, J=2.8, 6.5, 11.8 Hz, 1H, C1–*H*), 4.22 (ddd, J=2.8, 4.8, 8.5 Hz, 1H, C7–*H*), 4.17 (dq, J=10.7, 7.1 Hz, 1H, $CO_2C\mathit{H}CH_3$), 4.29 (dq, J=10.7, 7.1 Hz, 1H, $CO_2C\mathit{H}CH_3$), 4.42 (d, J=8.5 Hz, 1H, C6–*H*), 5.49 (s, 1H, C3–*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 2.7 (CH_3), 8.0 (CH_3), 8.1 (CH_3), 13.8 (CH_3), 26.7 (CH_3), 27.2 (CH_3), 29.7 (CH_2), 30.2 (CH_2), 52.3 (CH_3), 52.4 (CH_3), 61.9 (CH_3), 63.8 (CH_2), 76.2 (CH), 78.4 (CH), 79.6 (CH), 89.3 (C), 91.3 (C), 113.7 (C), 169.4 (C=O), 169.7 (C=O), 169.9 (C=O); FAB-HRMS m/z calcd for $C_{24}H_{43}O_{12}Si$ $(M+H)^+$ 551.2524, found 551.2549. Anal. Calcd for $C_{24}H_{42}O_{12}Si$: C, 52.35; H, 7.69. Found: C, 52.30; H, 7.53.

4.4.13. 3-Ethyl 1,2-dimethyl (1*S*,2*S*,3*R*,4*R*,5*R*)-4,5-(diethylmethylenedioxy)-1,2-(dimethylmethylenedioxy)-5-formyl-3-(trimethylsilyloxy)pentane-1,2,3-tricarboxylate (55). A solution of alcohol **54** (425 mg, 0.771 mmol) in CH_2Cl_2 (1.5 mL) was added to a suspension of Dess-Martin periodinane (890 mg, 2.10 mmol) in CH_2Cl_2 (4 mL). After stirring at room temperature for 3.5 h, the mixture was diluted with Et_2O (10 mL) and poured into an ice-cooled saturated aqueous $NaHCO_3$ (60 mL) containing $Na_2S_2O_3\cdot 5H_2O$ (10 g). The layers were separated, and the organic layer was washed successively with saturated aqueous $NaHCO_3$ (2×20 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (436 mg), which was purified by column chromatography (silica gel 8 g, 4:1 *n*-hexane/AcOEt) to give aldehyde **55** (387 mg, 91%) as a white solid: mp 104.5–105.5 °C (colorless prisms from *n*-hexane); $[\alpha]_D^{25}$ −12.5 (*c* 2.0, $CHCl_3$); IR (nujol) 2978, 2953, 1740, 1462, 1439, 1375, 1252, 1175, 1132, 849, 758 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.14 (s, 9H, $Si(CH_3)_3$), 0.89 (t, J=7.6 Hz, 3H, pentylidene CH_3), 0.90 (t, J=7.4 Hz, 3H, pentylidene CH_3), 1.32 (t, J=7.3 Hz, 3H, $CO_2CH_2CH_3$), 1.51 (s, 3H, acetonide CH_3), 1.63 (s, 3H, acetonide CH_3), 1.48–1.72 (m, 4H, 2×pentylidene CH_2), 3.74 (s, 3H, CO_2CH_3), 3.76 (s, 3H, CO_2CH_3), 4.21 (dq, J=10.9, 7.3 Hz, 1H, $CO_2C\mathit{H}CH_3$), 4.30 (dq, J=10.9, 7.3 Hz, 1H, $CO_2C\mathit{H}CH_3$), 4.63 (dd, J=1.0, 6.9 Hz, 1H, C7–*H*), 4.76 (d, J=6.9 Hz, 1H, C6–*H*), 5.49 (s, 1H, C3–*H*), 9.72 (d, J=1.0 Hz, 1H, C*H*O); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 2.6 (CH_3), 8.0 (CH_3), 8.2 (CH_3), 13.8 (CH_3), 26.7 (CH_3), 27.0 (CH_3), 28.5 (CH_2), 29.0 (CH_2), 52.4 (CH_3), 62.1 (CH_3), 77.7 (CH), 79.4 (CH), 80.9 (CH), 82.8 (C), 90.8 (C), 113.5 (C), 116.2 (C), 169.0 (C=O), 169.2 (C=O), 169.8 (C=O), 198.6 (C=O); FAB-HRMS m/z calcd for $C_{24}H_{41}O_{12}Si$ $(M+H)^+$ 549.2368, found 549.2350. Anal. Calcd for $C_{24}H_{40}O_{12}Si$: C, 52.54; H, 7.35. Found: C, 52.44; H, 7.28.

4.4.14. 3-Ethyl 1,2-dimethyl (1*S*,2*S*,3*R*,4*R*,5*R*,10*R*,11*R*)-10-benzyloxy-4,5-(diethylmethylenedioxy)-1,2-(dimethylmethylenedioxy)-11-methyl-6-oxo-12-phenyl-3-(trimethylsilyloxy)-7-dodecyne-1,2,3-tricarboxylate (57). Butyllithium in *n*-hexane (1.54 M, 0.91 mL, 1.40 mmol) was added to a solution of alkyne **56** (440 mg, 1.58 mmol) in THF (5 mL) at −78 °C. After stirring at −78 °C for 45 min, a solution of aldehyde **55** (387 mg, 0.705 mmol) in THF (2 mL) was added. After stirring at −78 °C for 30 min, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the whole was extracted with AcOEt (2× 15 mL). The combined organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (888 mg), which was purified by column chromatography (silica gel 8 g, 20:1→6:1 *n*-hexane/AcOEt) to give a diastereomeric mixture of coupling products (565 mg, 97%) as a colorless viscous oil, along with recovered alkyne **56** (261 mg) as a colorless oil.

A solution of the coupling product (565 mg) in CH_2Cl_2 (2 mL) was added to a suspension of Dess-Martin periodinane (727 mg, 1.71 mmol) in CH_2Cl_2 (5 mL). After stirring at room temperature for 11 h, the mixture was diluted with Et_2O (20 mL) and poured into an ice-cooled saturated aqueous $NaHCO_3$ (20 mL) containing $Na_2S_2O_3\cdot 5H_2O$ (1 g). The layers were separated, and the organic layer was washed successively with saturated aqueous $NaHCO_3$ (2×5 mL) and brine (5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel 23 g, 8:1 *n*-hexane/AcOEt) afforded ynone **57** (461 mg, 82%) as a colorless oil: $[\alpha]_D^{25}$ −8.31 (*c* 1.2, $CHCl_3$); IR (film) 2976, 2211, 1748, 1682, 1456, 1373, 1250, 1098, 849, 700 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 9H, Si(CH_3)$_3$), 0.87 (t, J=7.5 Hz, 3H, pentylidene CH_3), 0.91 (t, J=7.4 Hz, 3H, pentylidene CH_3), 0.96 (d, J=6.8 Hz, 3H, C5′–CH_3), 1.33 (t, J=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.56 (s, 3H, acetonide CH_3), 1.67 (s, 3H, acetonide CH_3), 1.45–1.77 (m, 4H, 2× pentylidene CH_2), 2.19 (m, 1H, C5′–*H*), 2.51 (dd, J=8.8, 13.5 Hz, 1H, C6′–*H*), 2.66 (dd, J=6.6, 17.4 Hz, 1H, C3′–*H*), 2.79 (dd, J=6.2, 17.4 Hz, 1H, C3′–*H*), 2.84 (dd, J=6.2, 13.5 Hz, 1H, C6′–*H*), 3.63 (m, 1H, C4′–*H*), 3.75 (s, 3H, CO_2CH_3), 3.77 (s, 3H, CO_2CH_3), 4.22 (dq, J=10.8, 7.2 Hz, 1H, CO_2CHCH_3), 4.31 (dq, J=10.8, 7.2 Hz, 1H, CO_2CHCH_3), 4.54 (d, J=11.6 Hz, 1H, OC*H*Ph), 4.65 (d, J=5.7 Hz, 1H, C6–*H*), 4.73 (d, J=11.6 Hz, 1H, OC*H*Ph), 5.09 (d, J=5.7 Hz, 1H, C7–*H*), 5.67 (s, 1H, C3–*H*), 7.15 (m, 2H, Ar*H*), 7.20 (m, 1H, Ar*H*), 7.26–7.35 (m, 3H, Ar*H*), 7.37–7.42 (m, 4H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 2.5 (CH_3), 8.0 (CH_3), 8.5 (CH_3), 13.6 (CH_3), 13.8 (CH_3), 22.6 (CH_2), 26.7 (CH_3), 26.9 (CH_3), 28.1 (CH_2), 28.7 (CH_2), 38.7 (CH), 39.6 (CH_2), 52.3 (CH_3), 62.0 (CH_3), 72.3 (CH_2), 77.5 (CH), 79.4 (CH), 81.4 (C), 81.8 (CH), 82.8 (C), 90.9 (C), 95.1 (C), 113.7 (C), 116.4 (C), 125.9 (CH), 127.6 (CH), 127.7 (CH), 128.3 (CH), 128.4 (CH), 129.1 (CH), 138.3 (C), 140.6 (C), 169.3 (C=O), 169.5 (C=O), 170.0 (C=O), 184.8 (C=O); FAB-HRMS *m/z* calcd for $C_{44}H_{61}O_{13}Si$ $(M+H)^+$ 825.3882, found 825.3849.

4.4.15. 3-Ethyl 1,2-dimethyl (1*S*,2*S*,3*R*,4*R*,5*R*,10*R*,11*R*)-10-benzyloxy-4,5-(diethylmethylenedioxy)-1,2-(dimethylmethylenedioxy)-11-methyl-6-oxo-12-phenyl-3-(trimethylsilyloxy)dodecane-1,2,3-tricarboxylate (58). Palladium on carbon (10%, 240 mg) was added to a solution of alkyne **57** (461 mg, 0.559 mmol) in AcOEt (15 mL), and the mixture was vigorously stirred under 1 atm of hydrogen for 10 min. The catalyst was filtered through a Celite pad, and the filtrate was evaporated in vacuo. Purification of the residue by column chromatography (silica gel 20 g, 7:1 *n*-hexane/AcOEt) afforded ketone **58** (432 mg, 93%) as a colorless oil: $[\alpha]_D^{27}$ −2.97 (*c* 3.2, EtOH); IR (film) 2951, 1740, 1456, 1375, 1252, 1209, 1111, 910, 847, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 9H, Si(CH_3)$_3$), 0.81 (t, J=7.5 Hz, 3H, pentylidene CH_3), 0.87 (d, J=6.8 Hz, 3H, C5′-CH_3), 0.89 (t, J=7.5 Hz, 3H, pentylidene CH_3), 1.31 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.54 (s, 3H, acetonide CH_3), 1.63 (s, 3H, acetonide CH_3), 1.37–1.81 (m, 8H, 2× pentylidene CH_2, C2′–H_2, C3′–H_2), 2.05 (m, 1H, C5′–*H*), 2.34 (dd, J=9.8, 13.3 Hz, 1H, C6′–*H*), 2.62 (m, 1H, C1′–*H*), 2.77 (m, 1H, C1′–*H*), 2.90 (dd, J=4.9, 13.3 Hz, 1H, C6′–*H*), 3.32 (m, 1H, C4′–*H*), 3.72 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 4.19 (dq, J=10.8, 7.1 Hz, 1H, CO_2CHCH_3), 4.28 (dq, J=10.8, 7.1 Hz, 1H, CO_2CHCH_3), 4.56 (s, 2H, OCH_2Ph), 4.58 (d, J=5.7 Hz, 1H, C6–*H*), 5.03 (d, J=5.7 Hz, 1H, C7–*H*), 5.61 (s, 1H, C3–*H*), 7.11 (m, 2H, Ar*H*), 7.17 (m, 1H, Ar*H*), 7.22–7.30 (m, 3H, Ar*H*), 7.31–7.41 (m, 4H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 2.4 (CH_3), 8.1 (CH_3), 8.5 (CH_3), 13.8 (CH_3), 14.4 (CH_3), 19.9 (CH_2), 26.7 (CH_3), 26.8 (CH_3), 27.8 (CH_2), 28.6 (CH_2), 30.1 (CH_2), 37.9 (CH), 38.7 (CH_2), 40.3 (CH_2), 52.3 (CH_3), 61.9 (CH_3), 71.7 (CH_2), 77.2 (CH), 79.4 (CH), 80.6 (CH), 82.4 (CH), 82.9 (CH), 90.9 (C), 113.7 (C), 115.7 (C), 125.7 (CH), 127.4 (CH), 127.6 (CH), 128.2 (CH), 128.3 (CH), 129.1 (CH), 139.1 (C), 141.6 (C), 169.4 (C=O), 169.5 (C=O), 170.0 (C=O), 207.6 (C=O); FAB-HRMS *m/z* calcd for $C_{44}H_{65}O_{13}Si$ $(M+H)^+$ 829.4195, found 829.4153. Anal. Calcd for $C_{44}H_{64}O_{13}Si$: C, 63.74; H, 7.78. Found: C, 63.59; H, 7.79.

4.5. Internal ketalization

4.5.1. 5-Ethyl 3,4-dimethyl [1*S*,1(4*R*,5*R*),3*S*,4*S*,5*R*,6*R*,7*R*]-1-(4-benzyloxy-5-methyl-6-phenylhexyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (59). A solution of ketone **58** (95 mg, 0.115 mmol) in 90% aqueous trifluoroacetic acid (10 mL) was stirred at room temperature for 15 h. The reaction mixture was evaporated in vacuo, and the crude product was concentrated from toluene (2×20 mL) to remove residual trifluoroacetic acid. Purification of the residue by column chromatography (silica gel 10 g, 1:1→1:2 *n*-hexane/AcOEt) afforded bicyclic compound **59** (49.5 mg, 68%) as a colorless oil, along with ketone **60** (4.9 mg, 7%) as a colorless oil: $[\alpha]_D^{24}$ +3.30 (*c* 3.0, acetone); IR (film) 3493, 2975, 2870, 1748, 1495, 1441, 1373, 1279, 1117, 958, 833, 747 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, J=6.9 Hz, 3H, C5′-CH_3), 1.27 (t, J=7.1 Hz, 3H, CO_2CH_2-CH_3), 1.52–1.75 (m, 4H, C2′–H_2, C3′–H_2), 1.90–2.00 (m, 2H, C1′–H_2), 2.07 (m, 1H, C5′–*H*), 2.31 (dd, J=10.0, 13.2 Hz, 1H, C6′–*H*), 2.90 (dd, J=4.4, 13.2 Hz, 1H, C6′–*H*), 3.15 (br s, 1H, O*H*), 3.26–3.40 (m, 2H, O*H*, C4′–*H*), 3.72 (s, 3H, CO_2CH_3), 3.83 (s, 1H, C4–O*H*), 3.89 (s, 3H, CO_2CH_3), 4.13 (m, 1H, C7–*H*), 4.25 (q, J=7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.55 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.58 (d, J=11.7 Hz, 1H, OC*H*Ph), 5.06 (m, 1H, C6–*H*), 5.18 (s, 1H, C3–*H*), 7.11 (m, 2H, Ar*H*), 7.17 (m, 1H, Ar*H*), 7.22–7.31 (m, 3H, Ar*H*), 7.31–7.41 (m, 4H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.0 (CH_3), 14.7 (CH_3), 19.6 (CH_2), 29.7 (CH_2), 35.2 (CH_2), 37.7 (CH), 38.3 (CH_2), 52.6 (CH_3), 53.5 (CH_3), 62.5 (CH_2), 71.6 (CH_2), 74.8 (C), 75.5 (CH), 78.4 (CH), 82.2 (CH), 82.5 (CH), 91.1 (C), 106.4 (C), 125.7 (CH), 127.6 (CH), 127.9 (CH), 128.2 (CH), 128.4 (CH), 129.1 (CH), 138.9 (C), 141.6 (C), 166.4 (C=O), 167.2 (C=O), 169.9 (C=O); FAB-HRMS *m/z* calcd for $C_{33}H_{43}O_{12}$ $(M+H)^+$ 631.2754, found 631.2758.

*Data for 5-ethyl 3,4-dimethyl [1S,1(4R,5R),3S,4S,5R]-1-(4-benzyloxy-5-methyl-6-phenylhexyl)-4-hydroxy-7-oxo-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (**60**).* IR ($CHCl_3$) 3543, 1772, 1741, 1263, 1228, 1150 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, J=6.9 Hz, 3H, C5′-CH_3), 1.30 (t, J=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.40–1.69 (m, 4H, C2′–H_2, C3′–H_2), 1.93 (m, 1H, C1′–*H*), 1.97–2.07 (m, 2H, C1′–*H*, C5′–*H*), 2.34 (dd, J=9.7, 13.3 Hz, 1H, C6′–*H*), 2.68 (d, J=18.8 Hz, 1H, C6–*H*), 2.88 (dd, J=4.4, 13.3 Hz, 1H, C6′–*H*), 3.31 (m, 1H, C4′–*H*), 3.55 (d, J=18.8 Hz, 1H, C6–*H*), 3.75 (s, 3H, CO_2CH_3), 3.90 (s, 1H, C4O*H*), 3.91 (s, 3H, CO_2CH_3), 4.28 (dq, J=10.7, 7.2 Hz, 1H, CO_2CHCH_3), 4.30 (dq, J=10.7, 7.2 Hz, 1H, CO_2CHCH_3), 4.54 (s, 2H, OCH_2Ph), 4.88 (s, 1H, C3–*H*), 7.10–7.40 (m, 10H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 13.9 (CH_3), 14.5 (CH_3), 18.9 (CH_2), 30.3 (CH_2), 31.3 (CH_2), 37.8 (CH), 38.7 (CH_2), 41.7 (CH_3), 52.9 (CH_3), 53.7 (CH_3), 62.8 (CH_2), 71.6 (CH_2), 74.9 (C), 75.8 (CH), 82.2 (CH), 83.8 (C), 101.9 (C), 125.7 (CH), 127.4 (CH), 127.7 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 129.1 (CH), 139.2 (C), 141.6 (C), 166.3 (C=O), 166.8 (C=O), 169.4 (C=O), 205.4 (C=O); FAB-HRMS *m/z* calcd for $C_{33}H_{41}O_{11}$ $(M+H)^+$ 613.2649, found 613.2653.

4.5.2. Isolation of the cyclization intermediates 62 and 63. Aqueous trifluoroacetic acid (90%, 5 mL) was added to ketone **58** (113 mg, 0.136 mmol) at 0 °C. After stirring at room temperature for 10 min, the reaction mixture was diluted with toluene (10 mL) and evaporated in vacuo. The residue was azeotropically dried with toluene (2×10 mL) and purified by flash column chromatography (silica gel 7.5 g, 4:1→2:1→1:1→1:2 *n*-hexane/AcOEt) to give hydroxyketone **62** (55 mg, 53%) and hemiketal **63** (28 mg, 29%) as white foams.

*Data for 3-ethyl 1,2-dimethyl (1S,2S,3R,4R,5R,10R,11R)-10-benzyloxy-4,5-(diethylmethylenedioxy)-1,2-(dimethylmethylenedioxy)-3-hydroxy-11-methyl-6-oxo-12-phenyldodecane-1,2,3-tricarboxylate (**62**).* $[\alpha]_D^{26}$ −5.27 (*c* 1.1, $CHCl_3$); IR (film) 3472, 2942, 1732, 1454, 1375, 1254, 1096, 932, 741 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.85 (d, J=6.6 Hz, 3H, C5′-CH_3), 0.88 (t, J=7.3 Hz, 6H, 2× pentylidene CH_3), 1.33 (t, J=7.3 Hz, 3H, $CO_2CH_2CH_3$), 1.53 (s, 3H, acetonide CH_3), 1.65 (s, 3H, acetonide CH_3), 1.50–1.80 (m, 8H, 2×pentylidene CH_2, C2′–H_2, C3′–H_2), 2.04 (m, 1H, C5′–*H*), 2.33 (dd, J=9.9, 13.2 Hz, 1H, C6′–*H*), 2.68 (t, J=6.6 Hz, 2H, C1′–H_2), 2.89 (dd, J=5.3, 13.2 Hz, 1H, C6′–*H*), 3.30 (m, 1H, C4′–*H*), 3.736 (s, 3H, CO_2CH_3), 3.743 (s, 3H, CO_2CH_3), 4.13 (s, 1H, O*H*), 4.26–4.37 (m, 2H, $CO_2CH_2CH_3$), 4.49 (d, J=6.6 Hz, 1H, C6–*H*), 4.55 (s, 2H, OCH_2Ph), 4.83 (d, J=6.6 Hz, 1H, C7–*H*), 5.58 (s, 1H, C3–*H*), 7.11 (m, 2H, Ar*H*), 7.18 (m, 1H, Ar*H*), 7.22–7.33 (m, 3H, Ar*H*), 7.34–7.40 (m, 4H, Ar*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 7.9 (CH_3), 8.4 (CH_3), 13.7 (CH_3), 14.4 (CH_3), 19.7 (CH_2), 26.6 (CH_3), 26.8 (CH_3), 29.09 (CH_2), 29.15 (CH_2), 29.9 (CH_2), 37.8 (CH), 38.7 (CH_2), 39.7 (CH_2), 52.4 (CH_3), 52.6 (CH_3), 62.9 (CH_2), 71.6 (CH_2), 76.7 (CH), 79.0 (CH), 79.2 (C), 81.0 (CH), 82.3 (CH), 90.7 (C), 114.0 (C), 116.0 (C), 125.6 (CH), 127.4 (CH), 127.6 (CH), 128.2 (CH), 128.3 (CH), 129.1 (CH), 139.1 (C), 141.5 (C), 169.1 (C=O), 170.0 (C=O), 170.1 (C=O), 208.5 (C=O); FAB-HRMS *m/z* calcd for $C_{41}H_{57}O_{13}$ $(M+H)^+$ 757.3799, found 757.3790.

*Data for dimethyl {4S,4[2R,3R,4R,5(4R,5R)],5S}-4-[5-(4-benzyloxy-5-methyl-6-phenylhexyl)-2-ethoxycarbonyl-3,4,5-trihydroxytetrahydrofuran-2-yl]-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (**63**).* $[\alpha]_D^{24}$ +16.5 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3543, 3028, 2955, 1738, 1439, 1373, 1260, 1109, 1055 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, J=6.9 Hz, 3H, C5′-CH_3), 1.26 (t, J=7.1 Hz, 3H, CO_2CH_2-CH_3), 1.45 (s, 3H, acetonide CH_3), 1.51–1.76 (m, 4H, C2′–H_2, C3′–H_2), 1.66 (s, 3H, acetonide CH_3), 1.88–2.03 (m, 2H, C1′–H_2), 2.10 (m, 1H, C5′–*H*), 2.30 (dd, J=9.9, 13.2 Hz, 1H, C6′–*H*), 2.52 (d, J=8.2 Hz, 1H, C7–O*H*), 2.92 (dd, J=4.5, 13.2 Hz, 1H, C6′–*H*), 3.38 (m, 1H, C4′–*H*), 3.68 (d, J=2.6 Hz, 1H, C6–O*H*), 3.77 (s, 3H, CO_2CH_3), 3.83 (s, 3H, CO_2CH_3), 4.09 (s, 1H, C1–O*H*), 4.11–4.19 (m, 2H, C7–*H*, CO_2CHCH_3), 4.25 (dq, J=10.9, 7.1 Hz, 1H, CO_2CHCH_3), 4.52 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.62 (d, J=11.7 Hz, 1H, OC*H*Ph), 4.73 (dd, J=2.6, 8.7 Hz, 1H, C6–*H*), 5.37 (s, 1H, C3–*H*), 7.12 (m, 2H, Ar*H*), 7.19 (m, 1H, Ar*H*), 7.22–7.40 (m, 7H, Ar*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.0 (CH_3), 14.7 (CH_3), 19.8 (CH_2), 26.5 (CH_3), 26.9 (CH_3), 30.0 (CH_2), 37.8 (CH), 38.1 (CH_2), 38.3 (CH_2), 52.8 (CH_3), 53.2 (CH_3), 61.9 (CH_2), 71.7 (CH_2), 77.1 (CH), 78.2 (CH), 79.0 (CH), 82.9 (CH), 87.7 (C), 89.0 (C), 102.2 (C), 114.1 (C), 125.7 (CH), 127.6 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 129.0 (CH), 138.7 (C), 141.5 (C), 169.3 (C=O), 169.5 (C=O), 173.7 (C=O); FAB-HRMS *m/z* calcd for $C_{36}H_{49}O_{13}$ $(M+H)^+$ 689.3173, found 689.3198.

4.6. Completion of the total synthesis

4.6.1. Tri(*tert*-butyl) [1*S*,1(4*R*,5*R*),3*S*,4*S*,5*R*,6*R*,7*R*]-1-(4-benzyloxy-5-methyl-6-phenylhexyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (64). A 1 N aqueous KOH (1.5 mL, 1.5 mmol) was added to a solution of triester **59** (49 mg, 0.078 mmol) in 1,4-dioxane (3 mL), and the whole was heated at 100 °C for 24 h. After cooling, 1 N aqueous HCl (2 mL) was added, and the mixture was evaporated in vacuo. The crude mixture thus obtained was suspended in CH_2Cl_2 (5 mL), and *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea (505 mg, 2.53 mmol) was added. After stirring at room temperature for 24 h, the mixture was filtered through a Celite pad, and the filtrate was evaporated in vacuo. Purification of the residue by column chromatography (silica gel 8 g, 3:2→1:1 *n*-hexane/AcOEt) afforded tri(*tert*-butyl) ester **64** (23 mg, 40%) as a colorless oil: $[\alpha]_D^{23}$ −2.90 (*c* 1.5, EtOH); IR (film) 3486 (br), 2932, 1732, 1456, 1370, 1157, 843, 739, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, J=6.8 Hz, 3H, C5′-CH_3), 1.44 (s, 9H, $CO_2C(CH_3)_3$), 1.48 (s, 9H, $CO_2C(CH_3)_3$), 1.52–1.73 (m, 4H, C2′–H_2, C3′–H_2), 1.59 (s, 9H, $CO_2C(CH_3)_3$), 1.86–1.99 (m, 2H, C1′–H_2), 2.05 (m, 1H, C5′–*H*), 2.35 (dd, J=9.7, 13.3 Hz, 1H, C6′–*H*), 2.50 (br s, 2H, 2×O*H*), 2.88 (dd, J=4.8, 13.3 Hz, 1H, C6′–*H*), 3.32 (m, 1H, C4′–*H*), 3.90 (s, 1H, C4–O*H*), 4.07 (br s, 1H, C7–*H*), 4.55 (d, J=11.8 Hz, 1H, OC*H*Ph), 4.56 (d, J=11.8 Hz, 1H, OC*H*Ph), 4.92 (s, 1H, C3–*H*), 5.02 (br s, 1H, C6–*H*), 7.11 (d, J=7.3 Hz, 2H, Ar*H*), 7.17 (t, J=7.3 Hz, 1H, Ar*H*), 7.23–7.31 (m, 3H, Ar*H*), 7.32–7.41 (m, 4H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.5 (CH_3), 19.6 (CH_2), 28.0 (CH_3), 28.1 (CH_3), 28.2 (CH_3), 29.9 (CH_2), 35.4 (CH_2), 37.7 (CH), 38.7 (CH_2), 71.6 (CH_2), 74.3 (C), 75.1 (CH), 78.8 (CH), 82.1 (CH), 82.4 (CH), 83.1 (C), 84.2 (C), 85.0 (C), 91.2 (C), 105.2 (C), 125.6 (CH), 127.5 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 129.1 (CH), 139.1 (C), 141.7 (C), 165.9 (C=O), 166.5 (C=O), 168.5 (C=O); FAB-HRMS *m/z* calcd for $C_{41}H_{59}O_{12}$ $(M+H)^+$ 743.4007, found 743.3984.

4.6.2. Tri(*tert*-butyl) [1*S*,1(4*R*,5*R*),3*S*,4*S*,5*R*,6*R*,7*R*]-4,6,7-trihydroxy-1-(4-hydroxy-5-methyl-6-phenylhexyl)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (65). Palladium on carbon (10%, 28.6 mg) was added to a solution of benzyl ether **64** (57.7 mg, 0.077 mmol) in MeOH (2 mL), and the mixture was vigorously stirred under 1 atm of hydrogen for 17 h. The catalyst was filtered through a Celite pad, and the filtrate was evaporated in vacuo. Purification of the residue (55.1 mg) by column chromatography (silica gel 8 g, 1:1→1:2 *n*-hexane/AcOEt) afforded tetraol **65** (46 mg, 90%) as a white foam: $[\alpha]_D^{23}$ +4.69 (*c* 1.3, EtOH); IR (film) 3481 (br), 2980, 2932, 1732, 1370, 1262, 1155, 739, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, J=6.8 Hz, 3H, C5′-CH_3), 1.44 (s, 9H, $CO_2C(CH_3)_3$), 1.48 (s, 9H, $CO_2C(CH_3)_3$), 1.50–1.85 (m, 4H, C2′–H_2, C3′–H_2), 1.59 (s, 9H, $CO_2C(CH_3)_3$), 1.86–2.03 (m, 3H, C1′–H_2, C5′–*H*), 2.41 (dd, J=9.0, 13.3 Hz, 1H, C6′–*H*), 2.80 (dd, J=5.9, 13.3 Hz, 1H, C6′–*H*), 3.10 (br s, 1H, O*H*), 3.50–3.60 (m, 2H, C4′–*H*, O*H*), 3.99 (s, 1H,

C4–O*H*), 4.14 (br s, 1H, C7–*H*), 4.97 (s, 1H, C3–*H*), 5.01 (br s, 1H, C6–*H*), 7.13–7.20 (m, 3H, Ar*H*), 7.23–7.29 (m, 2H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 11.4 (CH_3), 19.7 (CH_2), 28.0 (CH_3), 28.1 (CH_3), 28.2 (CH_3), 33.9 (CH_2), 35.1 (CH_2), 39.8 (CH_2), 40.6 (CH), 74.2 (CH), 74.3 (C), 75.1 (CH), 78.8 (CH), 82.5 (CH), 83.4 (C), 84.2 (C), 85.0 (C), 91.3 (C), 105.3 (C), 125.7 (CH), 128.2 (CH), 129.2 (CH), 141.2 (C), 166.2 (C=O), 166.4 (C=O), 168.7 (C=O); FAB-HRMS *m/z* calcd for $C_{34}H_{53}O_{12}$ $(M+H)^+$ 653.3537, found 653.3527.

4.6.3. Tri(*tert*-butyl) [1*S*,1(4*R*,5*R*),3*S*,4*S*,5*R*,6*R*,7*R*]-6,7-diacetoxy-1-(4-acetoxy-5-methyl-6-phenylhexyl)-4-hydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (66). To a solution of tetraol **65** (45.7 mg, 0.070 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added 4-*N*,*N*-dimethylaminopyridine (86 mg, 0.705 mmol) followed by addition of acetic anhydride (0.035 mL, 0.37 mmol). After stirring at 0 °C for 30 min, the reaction was quenched with 1 N aqueous KH_2PO_4 (5 mL) and the mixture was extracted with 10:1 Et_2O/*n*-hexane (11 mL). The organic extract was washed with brine (2×4 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (59.8 mg), which was purified by column chromatography (silica gel 5 g, 7:3 *n*-hexane/AcOEt) to give triacetate **66** (54 mg, quant.) as a white foam: $[\alpha]_D^{21}$ +17.6 (*c* 0.91, CH_2Cl_2) [lit.[8b] $[\alpha]_D$ +69.9 (*c* 0.29, CH_2Cl_2)]; IR (film) 3453 (br), 2978, 2934, 1759, 1732, 1477, 1456, 1372, 1236, 1154, 1119, 1040, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, *J*=6.8 Hz, 3H, C5′-C*H*$_3$), 1.460 (s, 9H, $CO_2C(CH_3)_3$), 1.464 (s, 9H, $CO_2C(CH_3)_3$), 1.51–1.71 (m, 4H, C2′–*H*$_2$, C3′–*H*$_2$), 1.62 (s, 9H, $CO_2C(CH_3)_3$), 1.88–2.12 (m, 3H, C1′–*H*$_2$, C5′–*H*), 2.05 (s, 3H, COC*H*$_3$), 2.07 (s, 3H, COC*H*$_3$), 2.15 (s, 3H, COC*H*$_3$), 2.30 (dd, *J*=9.7, 13.4 Hz, 1H, C6′–*H*), 2.76 (dd, *J*=4.9, 13.4 Hz, 1H, C6′–*H*), 4.07 (s, 1H, C4–O*H*), 4.88 (m, 1H, C4′–*H*), 4.88 (s, 1H, C3–*H*), 5.09 (d, *J*=1.8 Hz, 1H, C7–*H*), 6.34 (d, *J*=1.8 Hz, 1H, C6–*H*), 7.13 (m, 2H, Ar*H*), 7.17 (m, 1H, Ar*H*), 7.23–7.31 (m, 2H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.3, 20.1, 20.5, 20.7, 21.1, 28.4, 28.5, 32.3, 36.5, 39.7, 40.6, 75.6, 76.9, 77.9, 81.6, 85.0, 85.4, 86.4, 91.2, 105.6, 127.0, 129.3, 130.2, 142.0, 165.6, 167.4, 168.8, 170.2, 171.1, 173.0; FAB-HRMS *m/z* calcd for $C_{40}H_{59}O_{15}$ $(M+H)^+$ 779.3853, found 779.3823.

4.6.4. Tri(*tert*-butyl) [1*S*,1(4*R*,5*R*),3*S*,4*S*,5*R*,6*R*,7*R*]-1-(4-acetoxy-5-methyl-6-phenylhexyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (3). A 0.2% solution of potassium carbonate in MeOH (1.5 mL) was added to triacetate **66** (50.7 mg, 0.065 mmol) at 0 °C. After stirring at room temperature for 1 h, the reaction was quenched with 0.3 N aqueous KH_2PO_4 (1 mL), and the whole was partitioned between AcOEt (10 mL) and brine (4 mL). The organic layer was washed with brine (4 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel 5 g, 3:2 *n*-hexane/AcOEt) afforded triol **3** (42.5 mg, 94%) as a white foam: $[\alpha]_D^{23}$ +7.58 (*c* 1.0, CH_2Cl_2); IR (film) 3482, 2980, 2932, 1733, 1456, 1393, 1372, 1258, 1156, 965, 845, 701 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 0.87 (d, *J*=6.9 Hz, 3H, C5′-C*H*$_3$), 1.45 (s, 9H, $CO_2C(CH_3)_3$), 1.46 (s, 9H, $CO_2C(CH_3)_3$), 1.52–1.65 (m, 2H, C2′–*H*$_2$), 1.60 (s, 9H, $CO_2C(CH_3)_3$), 1.66–1.75 (m, 2H, C3′–*H*$_2$), 1.79–1.93 (m, 2H, C1′–*H*$_2$), 2.05 (m, 1H, C5′–*H*), 2.06 (s, 3H, COC*H*$_3$), 2.36 (dd, *J*=9.1, 13.4 Hz, 1H, C6′–*H*), 2.74 (dd, *J*=5.6, 13.4 Hz, 1H, C6′–*H*), 4.00 (d, *J*=1.8 Hz, 1H, C7–*H*), 4.87 (m, 1H, C4′–*H*), 4.96 (d, *J*=1.8 Hz, 1H, C6–*H*), 4.97 (s, 1H, C3–*H*), 7.12–7.18 (m, 3H, Ar*H*), 7.21–7.27 (m, 2*H*, ArH); ^{13}C NMR (125.8 MHz, CD_3OD) δ 14.2, 20.1, 21.1, 28.4, 28.5, 28.7, 32.5, 36.6, 39.5, 40.6, 76.0, 76.8, 78.3, 79.9, 84.2, 84.3, 84.5, 93.2, 106.4, 126.9, 129.3, 130.2, 142.0, 167.4, 168.3, 169.8, 173.0; FAB-HRMS *m/z* calcd for $C_{36}H_{55}O_{13}$ $(M+H)^+$ 695.3643, found 695.3670.

4.6.5. Tri(*tert*-butyl) [1*S*,1(4*R*,5*R*),3*S*,4*S*,5*R*,6*R*,7*R*]-1-(4-acetoxy-5-methyl-6-phenylhexyl)-7-(*tert*-butoxycarbonyl)oxy-4,6-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (67). A 0.1 M solution of di-*tert*-butyl dicarbonate in CH_2Cl_2 (0.84 mL, 0.084 mmol) was added to a solution of triol **3** (14.5 mg, 0.0209 mmol), 4-pyrrolidinopyridine (4.9 mg, 0.033 mmol) and Et_3N (12 μL, 0.086 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. After stirring at 0 °C for 12 h, the mixture was diluted with 1:1 *n*-hexane/Et_2O (12 mL) and quenched with 1 M aqueous K_2HPO_4 (3 mL). The layers were separated, and the organic layer was washed with brine (3 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel 8 g, 3:1 *n*-hexane/AcOEt) afforded *tert*-butyl carbonate **67** (11.8 mg, 71%) as a colorless foam: $[\alpha]_D^{21}$ +23.8 (*c* 0.59, EtOH) [lit. $[\alpha]_D$ +43.3 (*c* 0.25, CH_2Cl_2),[8b] $[\alpha]_D^{27}$ +25.8 (*c* 0.47, CH_2Cl_2)[11b]]; IR (film) 3459 (br), 2980, 2933, 1733, 1456, 1395, 1371, 1278, 1257, 1159, 1121, 967, 845, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, *J*=6.9 Hz, 3H, C5′–C*H*$_3$), 1.45 (s, 9H, $CO_2C(CH_3)_3$), 1.49 (s, 9H, $CO_2C(CH_3)_3$), 1.50 (s, 9H, $CO_2C(CH_3)_3$), 1.58 (s, 9H, $CO_2C(CH_3)_3$), 1.54–1.73 (m, 4H, C2′–*H*$_2$, C3′–*H*$_2$), 1.87–2.12 (m, 3H, C1′–*H*$_2$, C5′–*H*), 2.06 (s, 3H, COC*H*$_3$), 2.31 (dd, *J*=9.6, 13.4 Hz, 1H, C6′–*H*), 2.75 (dd, *J*=4.9, 13.4 Hz, 1H, C6′–*H*), 2.85 (d, *J*=3.5 Hz, 1H, C6–O*H*), 3.94 (s, 1H, C4–O*H*), 4.64 (d, *J*=1.8 Hz, 1H, C7–*H*), 4.72 (s, 1H, C3–*H*), 4.88 (s, 1H, C4′–*H*), 5.11 (brs, 1H, C6–*H*), 7.13 (m, 2H, Ar*H*), 7.17 (m, 1H, Ar*H*), 7.23–7.29 (m, 2H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 13.8, 18.9, 21.2, 27.7, 27.79, 28.04, 28.1, 30.9, 35.5, 37.9, 39.4, 74.0, 75.3, 76.9, 77.0, 83.2, 83.8, 84.0, 85.0, 85.5, 90.7, 103.8, 125.8, 128.2, 129.1, 140.7, 153.7, 165.2, 165.8, 168.5, 170.9; FAB-HRMS *m/z* calcd for $C_{41}H_{62}O_{15}Na$ $(M+Na)^+$ 817.3986, found 817.3989.

4.6.6. Tri(*tert*-butyl) [1*S*,1(4*R*,5*R*),3*S*,4*S*,5*R*,6*R*,6(4*E*,6*R*),7*R*]-1-(4-acetoxy-5-methyl-6-phenylhexyl)-7-(*tert*-butoxycarbonyloxy)-4-hydroxy-6-(6-methyl-9-phenyl-4-nonenoyl)oxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (68). DCC (31 mg, 0.150 mmol) was added to a solution of carboxylic acid **2** (37 mg, 0.150 mmol) in CH_2Cl_2 (1.5 mL), and the mixture was stirred at room temperature for 15 min. The solution of DCC–carboxylic acid **2** in CH_2Cl_2 (0.5 mL) was added to a solution of diol **67** (11.8 mg, 0.0149 mmol) and DMAP (14.5 mg, 0.119 mmol) in CH_2Cl_2 (2 mL). After stirring at room temperature for 48 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (6 mL), and the whole was extracted with 3:1 Et_2O/*n*-hexane (8 mL). The organic extract was washed successively with saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL), and dried over anhydrous Na_2SO_4. Filtration

and evaporation in vacuo followed by column chromatography (silica gel 8 g, 5:1 *n*-hexane/AcOEt) afforded ester **68** (13.7 mg, 90%) as a colorless oil: $[\alpha]_D^{23}$ +8.4 (*c* 0.38, CH_2Cl_2) [lit. $[\alpha]_D$ +8.5 (*c* 0.27, CH_2Cl_2),[8b] $[\alpha]_D^{23}$ +9.0 (*c* 0.27, CH_2Cl_2)[11b]]; IR (film) 3452 (br), 2978, 2932, 1748, 1456, 1395, 1372, 1281, 1256, 1159, 1119, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.83 (d, J=6.8 Hz, 3H, C5′–CH_3), 0.93 (d, J=6.7 Hz, 3H, C6″–CH_3), 1.29 (q, J=7.7 Hz, 2H, C7″–H_2), 1.44 (s, 9H, $CO_2C(CH_3)_3$), 1.45 (s, 9H, $CO_2C(CH_3)_3$), 1.47 (s, 9H, $CO_2C(CH_3)_3$), 1.61 (s, 9H, $CO_2C(CH_3)_3$), 1.50–1.72 (m, 6H, C2′–H_2, C3′–H_2, C8″–H_2), 1.89–2.13 (m, 4H, C1′–H_2, C5′–*H*, C6″–*H*), 2.04 (s, 3H, $COCH_3$), 2.24–2.43 (m, 5H, C6′–*H*, C2″–H_2, C3″–H_2), 2.57 (t, J=7.7 Hz, 2H, C9″–H_2), 2.76 (dd, J=4.7, 13.4 Hz, 1H, C6′–*H*), 4.06 (s, 1H, C4–O*H*), 4.86 (d, J=1.7 Hz, 1H, C7–*H*), 4.87 (m, 1H, C4′–*H*), 4.91 (s, 1H, C3–*H*), 5.28–5.40 (m, 2H, C4″–*H*, C5″–*H*), 6.40 (d, J=1.7 Hz, 1H, C6–*H*), 7.10–7.20 (m, 6H, Ar*H*), 7.23–7.30 (m, 4H, Ar*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 13.9, 18.9, 20.6, 21.2, 27.68, 27.71, 27.9, 28.0, 28.1, 29.2, 30.9, 34.1, 35.8, 36.1, 36.5, 36.6, 38.0, 39.4, 74.0, 75.3, 76.2, 77.0, 83.1, 83.3, 83.4, 83.9, 86.1, 89.8, 103.8, 125.6, 125.8, 126.1, 128.20, 128.23, 128.4, 129.1, 137.6, 140.8, 142.8, 152.4, 164.0, 165.6, 168.6, 170.7, 170.8; FAB-HRMS *m/z* calcd for $C_{57}H_{82}O_{16}Na$ $(M+Na)^+$ 1045.5500, found 1045.5450.

4.6.7. Zaragozic acid C (1). Trifluoroacetic acid (2.2 mL) was added to a solution of compound **68** (13.5 mg, 0.0132 mmol) in CH_2Cl_2 (6.5 mL). After stirring at room temperature for 16 h, the mixture was evaporated in vacuo, and the crude product was concentrated from toluene (10 mL) to remove residual trifluoroacetic acid. Trituration of the residue with petroleum ether provided zaragozic acid C (**1**) (10.1 mg, quant.) as a white film: $[\alpha]_D^{23}$ +9.4 (*c* 0.30, EtOH) [lit. $[\alpha]_D^{20}$ +9.6 (*c* 0.29, EtOH),[1b] $[\alpha]_D$ +9.0 (*c* 0.23, EtOH),[8b] $[\alpha]_D^{24}$ +9.6 (*c* 1.0, EtOH)[11b]]; IR (film) 3453 (br), 2928, 1732, 1495, 1454, 1375, 1250, 1148, 1026, 970, 745, 700 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.86 (d, J=6.8 Hz, 3H, C5′-CH_3), 0.93 (d, J=6.7 Hz, 3H, C6″-CH_3), 1.19–1.37 (m, 2H, C7″–H_2), 1.50–1.64 (m, 4H, C2′–H_2, C8″–H_2), 1.64–1.73 (m, 2H, C3′–H_2), 1.82–1.94 (m, 2H, C1′–H_2), 1.97–2.12 (m, 2H, C5′–*H*, C6″–*H*), 2.05 (s, 3H, $COCH_3$), 2.22–2.30 (m, 2H, C3″–H_2), 2.30–2.39 (m, 3H, C6′–*H*, C2″–H_2), 2.50–2.61 (m, 2H, C9″–H_2), 2.73 (dd, J=5.6, 13.3 Hz, 1H, C6′–*H*), 4.00 (d, J=1.6 Hz, 1H, C7–*H*), 4.90 (m, 1H, C4′–*H*), 5.22 (s, 1H, C3–*H*), 5.31 (dd, J=7.6, 15.3 Hz, 1H, C5″–*H*), 5.37 (dt, J=15.3, 6.2 Hz, 1H, C4″–*H*), 6.23 (br s, 1H, C6–*H*), 7.09–7.17 (m, 6H, Ar*H*), 7.19–7.27 (m, 4H, Ar*H*); ^{13}C NMR (125.8 MHz, CD_3OD) δ 14.3, 20.2, 21.1, 21.3, 28.8, 30.5, 32.5, 35.4, 36.3, 36.9, 37.6, 37.8, 39.7, 40.5, 75.7, 76.7, 78.2, 81.3, 82.3, 91.1, 107.2, 126.6, 126.9, 127.6, 129.26, 129.28, 129.4, 130.2, 138.8, 142.0, 143.9, 168.7, 170.3, 172.6, 173.1, 173.2; FAB-HRMS *m/z* calcd for $C_{40}H_{50}O_{14}Na$ $(M+Na)^+$ 777.3098, found 777.3049.

Acknowledgements

This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank Ms. H. Matsumoto, A. Maeda, K. Nakaoka, and S. Oka of the Center for Instrumental Analysis, Hokkaido University, for technical assistance in MS and elemental analysis.

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Manganese(III)-based oxidation of 2,4-piperidinediones in the presence of alkenes

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Received 5 August 2005; revised 10 September 2005; accepted 12 September 2005

Available online 26 September 2005

Abstract—The manganese(III)-catalyzed aerobic oxidation of 2,4-piperidinediones was performed in the presence of alkenes at room temperature, producing 1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-ones in excellent yields. On the other hand, the 6-acetoxy-3-aza-7-oxabicyclo[4.3.0]nonan-2-ones were obtained by the oxidation of the 2,4-piperidinedione-3-carboxylates with manganese(III) acetate in the presence of alkenes at elevated temperature under an argon atmosphere. A similar oxidation using decarboxylated 2,4-piperidinediones produced the 2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(5*H*)-ones and/or 2,3,6,7-tetrahydrofuro[2,3-*b*]pyridin-4(5*H*)-ones in good yields. The structure determination and the decomposition reaction of the azabicyclic peroxides in acetic acid or acetic anhydride, and the reaction pathway were also described.

1. Introduction

The 1,2-dioxane scaffold containing nitrogen heterocycles is important in nature as a metabolite and biologically active substance.[1] The structure sometimes appears as an intermediate during respiration, digestion, and detoxification in animals.[2] Some plants also produce 1,2-dioxane derivatives in order to protect themselves and their territory.[3] These cyclic peroxides are labile and have potent activities toward cells.[4] Therefore, the synthesis of the peroxide framework has attracted considerable attention from the viewpoint of the development of new antibiotics in spite of its instability.

In recent years, our research group has developed various manganese(III)-based oxidations.[5] The characteristics of the oxidation is that manganese(III) acetate can readily undergo a ligand exchange with 1,3-dicarbonyl compounds in acetic acid to generate the manganese(III)-enolate complex in situ, followed by the one-electron oxidation from electron-rich carbon–carbon double bonds to manganese(III) to give the corresponding carbon radicals.[6] When the reaction was carried out at ambient temperature in air, the carbon radicals take up the dissolved molecular oxygen in acetic acid to selectively produce cyclic peroxides.[7] In contrast, when the reaction was conducted at reflux temperature under an argon atmosphere, the carbon radicals were oxidized by the manganese(III) species followed by intramolecular cyclization to give dihydrofuran derivatives.[7] In a continuation of our studies,[5] we have investigated the manganese(III)-based oxidation using 2,4-piperidinedione derivatives in the hope of developing a new azadioxabicyclic framework such as an antimalarial analogue[8] and furopyridinones having antifungal and antibacterial activities.[9] Herein, we report the successful one-pot synthesis of 1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-ones and furo[3,2-*c*]pyridin-4(2*H*)-one derivatives using simple alkenes both at ambient temperature in air and at reflux temperature under an argon atmosphere.[10]

2. Results and discussion

2.1. Preparation of 2,4-piperidinedione derivatives

First of all, we prepared the 2,4-piperidinedione derivatives **2a**–**m** according to the literature.[11] The alkyl 2,4-piperidinedione-3-carboxylates **2a**–**g** were synthesized by the Michael addition of alkyl acrylates with primary amines followed by condensation with alkyl malonyl chlorides and subsequent Dieckmann condensation in the presence of sodium ethoxide.[11] The obtained piperidinediones **2a**–**g** were confirmed as the enol form, 4-hydroxy-5,6-dihydro-1*H*-

Keywords: Endoperoxides; Aerobic oxidation; Manganese(III) acetate; 2,4-Piperidinediones; Tetrahydrofuropyridinones.
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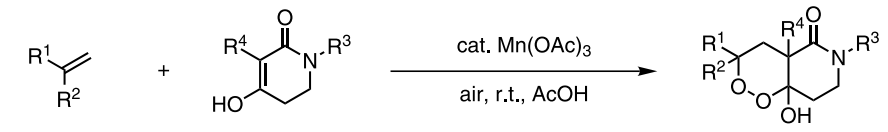
doi:10.1016/j.tet.2005.09.029

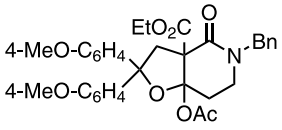


1a-l **2a-m** **3**

1a : $R^1 = R^2 =$ Ph
1b : $R^1 = R^2 =$ 4-Me-C_6H_4
1c : $R^1 = R^2 =$ 4-MeO-C_6H_4
1d : $R^1 = R^2 =$ 4-Cl-C_6H_4
1e : $R^1 = R^2 =$ 4-F-C_6H_4
1f : R^1 = Ph, R^2 = Me
1g : R^1 = 4-Me-C_6H_4, R^2 = Me
1h : R^1 = 4-Cl-C_6H_4, R^2 = Me
1i : $R^1 = R^2$ = Et
1j : $R^1 = R^2$ = Me
1k : R^1 = Ph, R^2 = H
1l : R^1 = Heptyl, R^2 = H

2a : R^3 = Bn, $R^4 = CO_2Et$
2b : R^3 = Me, $R^4 = CO_2Et$
2c : R^3 = Et, $R^4 = CO_2Et$
2d : R^3 = Pr, $R^4 = CO_2Et$
2e : R^3 = *i*-Pr, $R^4 = CO_2Et$
2f : R^3 = Ph, $R^4 = CO_2Et$
2g : R^3 = Bn, $R^4 = CO_2Pr$-*i*
2h : R^3 = Bn, R^4 = H
2i : R^3 = Me, R^4 = H
2j : R^3 = Et, R^4 = H
2k : R^3 = Pr, R^4 = H
2l : R^3 = *i*-Pr, R^4 = H
2m: R^3 = Ph, R^4 = H

3aa : $R^1 = R^2$ = Ph, R^3 = Bn, $R^4 = CO_2Et$
3ba : $R^1 = R^2$ = 4-Me-C_6H_4, R^3 = Bn, $R^4 = CO_2Et$
3ca : $R^1 = R^2$ = 4-MeO-C_6H_4, R^3 = Bn, $R^4 = CO_2Et$
3da : $R^1 = R^2$ = 4-Cl-C_6H_4, R^3 = Bn, $R^4 = CO_2Et$
3ea : $R^1 = R^2$ = 4-F-C_6H_4, R^3 = Bn, $R^4 = CO_2Et$
3fa : R^1 = Ph, R^2 = Me, R^3 = Bn, $R^4 = CO_2Et$
3ga : R^1 = 4-Me-C_6H_4, R^2 = Me, R^3 = Bn, $R^4 = CO_2Et$
3ha : R^1 = 4-Cl-C_6H_4, R^2 = Me, R^3 = Bn, $R^4 = CO_2Et$
3ia : $R^1 = R^2$ = Et, R^3 = Bn, $R^4 = CO_2Et$
3ja : $R^1 = R^2$ = Me, R^3 = Bn, $R^4 = CO_2Et$
3ka : R^1 = Ph, R^2 = H, R^3 = Bn, $R^4 = CO_2Et$
3la : R^1 = Heptyl, R^2 = H, R^3 = Bn, $R^4 = CO_2Et$
3ab : $R^1 = R^2$ = Ph, R^3 = Me, $R^4 = CO_2Et$
3ac : $R^1 = R^2$ = Ph, R^3 = Et, $R^4 = CO_2Et$
3ad : $R^1 = R^2$ = Ph, R^3 = Pr, $R^4 = CO_2Et$
3ae : $R^1 = R^2$ = Ph, R^3 = *i*-Pr, $R^4 = CO_2Et$
3af : $R^1 = R^2 = R^3$ = Ph, $R^4 = CO_2Et$
3ag : $R^1 = R^2$ = Ph, R^3 = Bn, $R^4 = CO_2Pr$-*i*
3ah : $R^1 = R^2$ = Ph, R^3 = Bn, R^4 = H
3bh : $R^1 = R^2$ = 4-Me-C_6H_4, R^3 = Bn, R^4 = H
3ch : $R^1 = R^2$ = 4-MeO-C_6H_4, R^3 = Bn, R^4 = H
3dh : $R^1 = R^2$ = 4-Cl-C_6H_4, R^3 = Bn, R^4 = H
3ai : $R^1 = R^2$ = Ph, R^3 = Me, R^4 = H
3aj : $R^1 = R^2$ = Ph, R^3 = Et, R^4 = H
3ak : $R^1 = R^2$ = Ph, R^3 = Pr, R^4 = H
3al : $R^1 = R^2$ = Ph, R^3 = *i*-Pr, R^4 = H
3am: $R^1 = R^2 = R^3$ = Ph, R^4 = H



4ca

Scheme 1.

pyridin-2-one-3-carboxylates, by a spectroscopic method. The decarboxylation of **2a**–**g** was carried out in a 10% aqueous sulfuric acid solution at reflux temperature to provide the corresponding 2,4-piperidinediones **2h**–**m**, which exist as the keto form.[11a] The used alkenes **1a**–**l** and synthesized piperidinediones **2a**–**m** are shown in Scheme 1.

2.2. Manganese(III)-catalyzed aerobic oxidation of a mixture of various alkenes 1a–l and 2,4-piperidinediones 2a–m at room temperature

With alkenes **1a**–**l** and 2,4-piperidinediones **2a**–**m** in hand, a mixture of 1,1-diphenylethene (**1a**) (0.5 mmol) and ethyl1-benzyl-2,4-piperidinedione-3-carboxylate (**2a**) (1 mmol) was initially allowed to react with manganese(III) acetate (0.5 mmol) in glacial acetic acid (20 mL) at room temperature in air, and the desired azabicyclic peroxide **3aa** was obtained in 43% yield together with a complex mixture of degraded material (Table 1, entry 1). The reaction was then carried out using a catalytic amount of manganese(III) acetate (0.15 mmol) until **1a** was completely consumed. After chromatographic separation, only one product **3aa** was isolated and the best yield (88%) was achieved (entry 2). In order to apply the catalytic reaction to other various alkenes, a similar reaction of alkenes **1b**–**l** with **2a** was investigated and the corresponding azabicyclic peroxides **3** resulted in excellent to good yields except for 1-nonene (**1l**) (entries 3–13). Even after stirring the reaction mixture for 21 h containing **1c**, the azabicyclic peroxide **3ca** was produced only in 30% yield along with **1c** being recovered (33%). The use of a slight excess amount of catalyst (1 equiv) then overcame the low yield (entry 4). However, a small amount of by-product **4ca** was also formed (see vide infra). The use of other piperidinedione-3-carboxylates **2b**–**g** also gave cyclic peroxides **3** (entries 14–19). In the case of **2c**–**e**, a small amount of decarboxylated cyclic peroxides **3aj**, **3ak**, and **3al** were also isolated (entries 15–17). The reaction of the decarboxylated 2,4-piperidinediones **2h**–**m** was next examined. Although it needed longer reaction times and slightly excess amounts of the catalyst to consume the alkenes **1** in comparison with the reaction using the 3-alkoxycarbonyl-substituted piperidinediones **2a**–**g**, the desired cyclic peroxides **3** were obtained in excellent to good yields (entries 20–28). Surprisingly, small amounts of 2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(5*H*)-ones **5** and/or 2,3,6,7-tetrahydrofuro[2,3-*b*]pyridin-4(5*H*)-ones **6** were also isolated as by-products (entries 21–27) (see vide infra).

2.3. Structure determination of azabicyclic peroxides 3

The obtained azabicyclic peroxides **3** were characterized by a spectroscopic method and elemental analysis as well as X-ray analysis. The ^{13}C NMR spectral peaks of the product **3aa** at δ 96.6 (C-1) and 85.1 ppm (C-4) were assigned to the

Table 1. Mn(III)-catalyzed aerobic oxidation of a mixture of various alkenes **1a–l** and 2,4-piperidinedioenes **2a–m**

Entry	Alkene **1**	Piperidinedione **2**	**1**:**2**:$Mn(OAc)_3$	Reaction time (h)	Product (yield, %)[a]		
1	**1a**	**2a**	1:2:1	8	**3aa** (43)		
2	**1a**	**2a**	1:2:0.3	9	**3aa** (88)		
3	**1b**	**2a**	1:2:0.3	9	**3ba** (85)		
4	**1c**	**2a**	1:2:1	15	**3ca** (81)	**4ca** (11)	
5	**1d**	**2a**	1:2:0.3	9	**3da** (74)		
6	**1e**	**2a**	1:2:0.5	10	**3ea** (71)		
7	**1f**	**2a**	1:2:0.3	9	**3fa** (93)[b]		
8	**1g**	**2a**	1:2:0.3	9	**3ga** (82)[b]		
9	**1h**	**2a**	1:2:0.3	10	**3ha** (95)[b]		
10	**1i**	**2a**	10:1:0.3	13.5	**3ia** (66)[c]		
11	**1j**	**2a**	Excess:2:0.3[d]	9	**3ja** (77)[c]		
12	**1k**	**2a**	1:2:0.3	9	**3ka** (75)[b]		
13	**1l**	**2a**	1:2:0.3	9	**3la** (17)[b]		
14	**1a**	**2b**	1:2:0.3	9	**3ab** (90)		
15	**1a**	**2c**	1:2:0.3	9	**3ac** (82)	**3aj** (6)	
16	**1a**	**2d**	1:2:0.3	9	**3ad** (88)	**3ak** (4)	
17	**1a**	**2e**	1:2:0.3	9	**3ae** (78)	**3al** (5)	
18	**1a**	**2f**	1:2:0.3	15	**3af** (50)		
19	**1a**	**2g**	1:2:0.3	12	**3ag** (93)		
20	**1a**	**2h**	1:2:0.3	18	**3ah** (99)		
21	**1b**	**2h**	1:2:1	16	**3bh** (87)	**5bh** (12)	
22	**1c**	**2h**	1:2:1	13.5	**3ch** (66)	**5ch** (16)	
23	**1d**	**2h**	1:2:1	16	**3dh** (77)	**5dh** (10)	**6dh** (8)
24	**1a**	**2i**	1:1.1:1	14	**3ai** (60)[e]	**5ai** (16)	
25	**1a**	**2j**	1:2:1	14	**3aj** (81)	**5aj** (5)	
26	**1a**	**2k**	1:2:1	9	**3ak** (72)	**5ak** (8)	
27	**1a**	**2l**	1:2:1	18	**3al** (77)	**5al** (11)	**6al** (12)
28	**1a**	**2m**	1:2:1	30	**3am** (70)		

The reaction of the alkene **1** (0.5 mmol) with 2,4-piperidinedione **2** was carried out in glacial acetic acid (20 mL) in the presence of manganese(III) acetate dihydrate in air at room temperature except for entries **10** and **11**.
[a] Isolated yield based on the amount of the alkene **1** used except for entries **10** and **11**.
[b] Total yield of stereoisomers.
[c] The yield based on the amount of piperidinedione **2a** used.
[d] 2-Methylpropene (**1j**) was bubbled through the reaction mixture.
[e] The alkene **1a** was recovered in 18% yield.

characteristic peak of the 1,2-dioxan-3-ol ring system[5,6b,12] together with an ester carbonyl, amide carbonyl (δ 168.9 and 166.6 ppm), and quaternary carbon (C-6) at the ring junction (δ 55.9 ppm).[5] The ^{1}H NMR spectrum of **3aa** indicated the presence of two sets of an AB quartet of benzyl protons and H-5 methylene protons at δ 4.78 (1H, d, J=15.03 Hz), 2.94 (1H, d, J=15.03 Hz), 3.80 (1H, d, J=14.72 Hz), and 3.43 ppm (1H, d, J=14.72 Hz), respectively. The methylene protons of H-9 and H-10 appeared as a broad doublet at 2.86 (2H, J=9.62 Hz, H-9), a triplet of doublets at 2.61 (1H, J=13.52, 9.62 Hz), and broad doublet at 1.85 (1H, J=13.52 Hz). All the peaks in the NMR spectrum were also correlated by H–H COSY and H–C COSY. In addition, the absorption band of the hydroxyl group appeared at 3400–3100 cm^{-1} together with two carbonyls at 1751 and 1639 cm^{-1} in the IR spectrum. Accordingly, the product **3aa** was determined to be ethyl 8-benzyl-1-hydroxy-4,4-diphenyl-8-aza-2,3-dioxa-bicyclo-[4.4.0]decan-7-one-6-carboxylate, and the combustion analysis also supported the structure. In order to clarify the stereochemistry, the single crystals were grown in chloroform–hexane and subjected to X-ray crystallographic measurements. As a result, the X-ray crystallographic data for **3aa** illustrate that the hydroxyl group at C-1 is in an axial-like orientation due to the anomer effect, and the relationship between the hydroxyl group and the ethoxycarbonyl group at C-6 is the cis configuration (Fig. 1).[5d,g,j,7b,c] Furthermore, it was found that one of the benzyl protons (δ 2.94 ppm) was shielded by the anisotropic effect of one of the phenyl groups substituted at C-4.

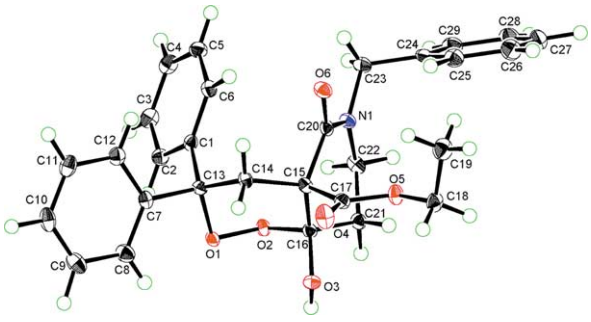


Figure 1. ORTEP drawing of **3aa**

2.4. Oxidation of a mixture of 1,1-disubstituted ethenes 1 and 2,4-piperidinediones 2 with manganese(III) acetate at elevated temperature

In the above aerobic oxidation using decarboxylated 2,4-piperidinediones **2h–l**, small amounts of tetrahydrofuro[3,2-*c*]pyridinones **5** and/or tetrahydrofuro[2,3-*b*]pyridinones **6** were produced besides the azabicyclic peroxides **3**. Since it seemed that these by-products would be formed by the direct oxidation of the piperidinediones **2h–l** with manganese(III) acetate in the presence of alkenes **1**, we then investigated the oxidation at elevated temperature from the viewpoint of the synthetic utility of the tetrahydrofuropyridinone skeleton.[9] We previously

Table 2. Oxidation of a mixture of alkenes **1a–d** and 2,4-piperidinedioenes **2a–f**,**h–m** with manganese(III) acetate at elevated temperature

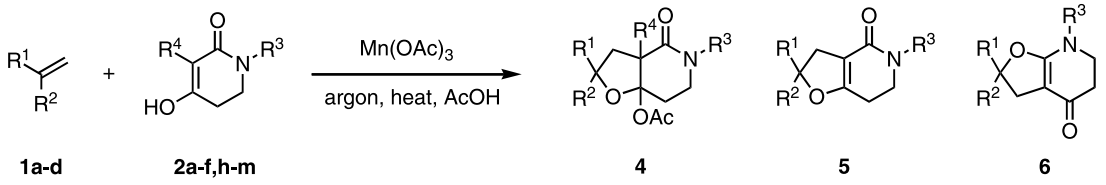
Entry	Alkene **1**	Piperidinedione **2**	**1**:**2**:$Mn(OAc)_3$	Temperature (°C)	Reaction time (min)	Product (yield, %)[a]	
1	**1a**	**2a**	2:1:4.5	50–60	54	**4aa** (62)	
2	**1b**	**2a**	2:1:4.5	50–60	131	**4ba** (74)	
3	**1d**	**2a**	2:1:4.5	50–60	270	**4da** (74)	
4	**1a**	**2b**	2:1:4.5	50–60	23	**4ab** (53)	
5	**1a**	**2c**	2:1:4.5	50–60	53	**4ac** (77)	
6	**1a**	**2d**	2:1:4.5	50–60	53	**4ad** (62)	
7	**1a**	**2e**	2:1:4.5	50–60	85	**4ae** (59)	
8	**1a**	**2f**	2:1:4.5	50–60	48	**4af** (58)	
9	**1a**	**2h**	1:2:3	Reflux	1	**5ah** (66)	**6ah** (16)[b]
10	**1a**	**2h**	1:2:3	Reflux	1	**5ah** (52)	**6ah** (32)
11	**1b**	**2h**	1:2:4	Reflux	1	**5bh** (84)	
12	**1c**	**2h**	1:2:4	Reflux	1	**5ch** (82)	
13	**1d**	**2h**	1:2:5	Reflux	1	**5dh** (59)	**6dh** (25)
14	**1a**	**2i**	1:2:6	Reflux	1	**5ai** (50)	
15	**1a**	**2j**	1:2:7	Reflux	0.5	**5aj** (53)	
16	**1a**	**2k**	1:2:3	Reflux	1	**5ak** (61)	**6ak** (39)
17	**1a**	**2l**	1:2:3	Reflux	1	**5al** (59)	**6al** (29)
18	**1a**	**2m**	1:2:4	Reflux	1	**5am** (55)	**6am** (39)

The oxidation of a mixture of the alkene **1** (0.5 mmol) and the 2,4-piperidinedione **2** was carried out using manganese(III) acetate dihydrate in boiling acetic acid (20 mL) under an argon atmosphere.

[a] Isolated yield based on the amount of the alkene **1** used (entries 9–18) or the piperidinedione **2** used (entries 1–8).

[b] The oxidation was conducted in air and the azabicyclic peroxide **3ah** (13%) was also isolated.

established and developed the selective dihydrofuran synthesis using the managanese(III) oxidation of 1,3-dicarbonyl derivatives in the presence of various alkenes.[7] The reaction normally proceeds at elevated temperature under an inert atmosphere. Therefore, we adopted the typical reaction conditions, that is, using a stoichiometric or more than stoichiometric amount of oxidant at reflux temperature under an argon atmosphere. However, the reaction of piperidinedione **2a** with alkene **1a** in boiling acetic acid afforded the desired oxofuropyridinecarboxylate **4aa** in a low yield (32%) (Scheme 2). After several attempts, the yield of **4aa** was improved to 62% using the reaction conditions at 50–60 °C and sufficient ultrasonic degassing for 30 min under reduced pressure before the reaction (Table 2, entry 1).[13] The use of other alkenes **1b**,**d** and 2,4-piperidinedione-3-carboxylates **2b–f** also led to the production of oxofuropyridinecarboxylates **4** in acceptable yields (entries 2–8). The reaction of the decarboxylated piperidinedines **2h–m** with alkenes **1a–d** was carried out at reflux temperature and the oxidant was consumed within almost 1 min providing the tetrahydrofuro[3,2-*c*]pyridinones **5** and/or tetrahydrofuro[2,3-*b*]pyridinones **6** (entries 9–18). The structures of these furopiridinones **4**,**5**,**6** were determined by a spectroscopic method and elemental analysis. Although the FAB mass spectra of the colorless liquids **4aa**, **4da**, **4ac**, and **4ad** did not show the corresponding molecular ion peaks (see Section 4), the structures were supported by the hydrolysis of the acetate **4aa** with a 10% aqueous solution of sulfuric acid, giving the corresponding ethyl 6-hydroxy-3-aza-7-oxabicyclo[4.3.0]nonan-2-one-1-carboxylate (74%), which was characterized by a



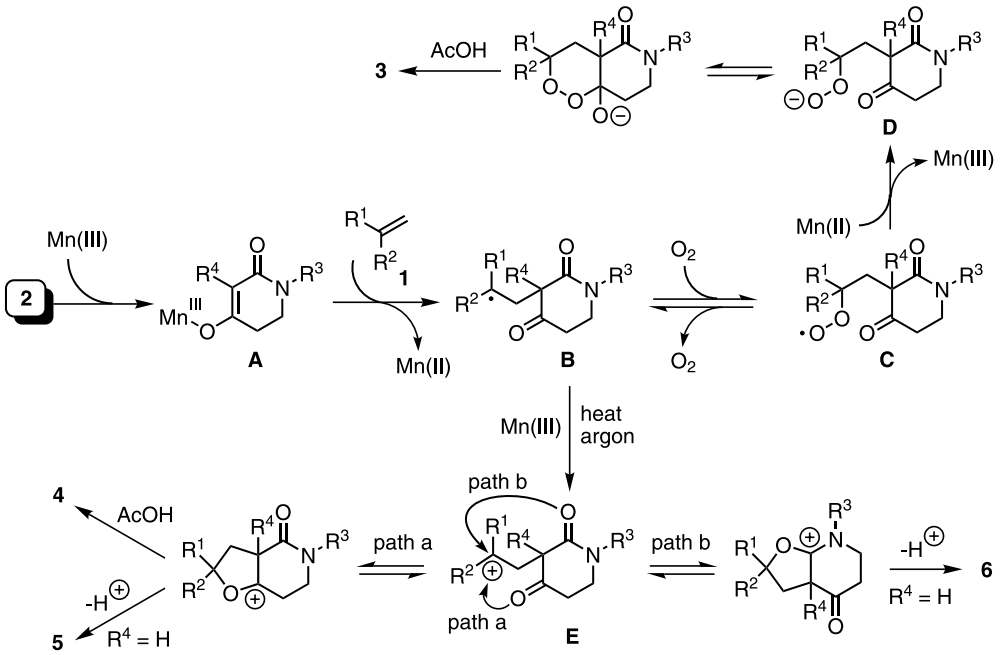
1a-d **2a-f,h-m** **4** **5** **6**

4aa : $R^1 = R^2 = Ph$, $R^3 = Bn$, $R^4 = CO_2Et$
4ba : $R^1 = R^2 = 4\text{-Me-}C_6H_4$, $R^3 = Bn$, $R^4 = CO_2Et$
4da : $R^1 = R^2 = 4\text{-Cl-}C_6H_4$, $R^3 = Bn$, $R^4 = CO_2Et$
4ab : $R^1 = R^2 = Ph$, $R^3 = Me$, $R^4 = CO_2Et$
4ac : $R^1 = R^2 = Ph$, $R^3 = Et$, $R^4 = CO_2Et$
4ad : $R^1 = R^2 = Ph$, $R^3 = Pr$, $R^4 = CO_2Et$
4ae : $R^1 = R^2 = Ph$, $R^3 = i\text{-Pr}$, $R^4 = CO_2Et$
4af : $R^1 = R^2 = R^3 = Ph$, $R^4 = CO_2Et$

5ah : $R^1 = R^2 = Ph$, $R^3 = Bn$
5bh : $R^1 = R^2 = 4\text{-Me-}C_6H_4$, $R^3 = Bn$
5ch : $R^1 = R^2 = 4\text{-MeO-}C_6H_4$, $R^3 = Bn$
5dh : $R^1 = R^2 = 4\text{-Cl-}C_6H_4$, $R^3 = Bn$
5ai : $R^1 = R^2 = Ph$, $R^3 = Me$
5aj : $R^1 = R^2 = Ph$, $R^3 = Et$
5ak : $R^1 = R^2 = Ph$, $R^3 = Pr$
5al : $R^1 = R^2 = Ph$, $R^3 = i\text{-Pr}$
5am: $R^1 = R^2 = R^3 = Ph$

6ah : $R^1 = R^2 = Ph$, $R^3 = Bn$
6dh : $R^1 = R^2 = 4\text{-Cl-}C_6H_4$, $R^3 = Bn$
6ak : $R^1 = R^2 = Ph$, $R^3 = Pr$
6al : $R^1 = R^2 = Ph$, $R^3 = i\text{-Pr}$
6dm: $R^1 = R^2 = R^3 = Ph$

Scheme 2.



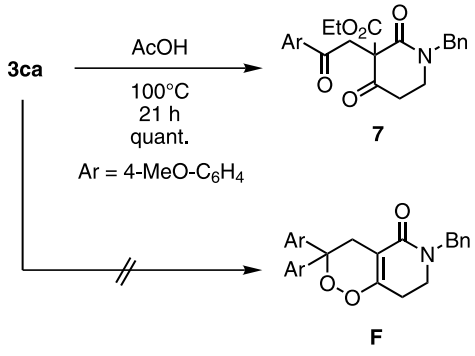
Scheme 3.

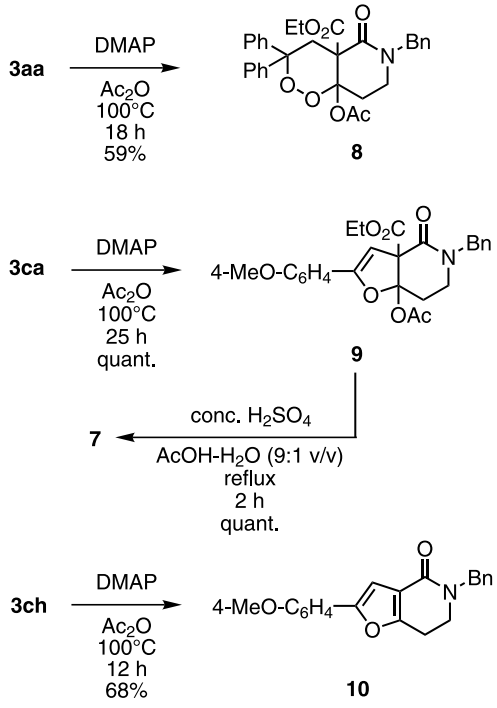
spectroscopic method and elemental analysis (see Section 4). In addition, the combustion analyses of other crystalline acetates **4ba**, **4ab**, **4ae**, and **4af** were in agreement with their structures.

2.5. Mechanism

The manganese(III)-catalyzed aerobic oxidation could be explained by a similar mechanism for the reaction using the 2,3-pyrrolidinediones,[5a,b] 2,4-pyrrolidinediones,[5c,d] and 4-piperidone-3-carboxylates.[5e] The manganese(III)-piperidinedione enolate complex **A** would be formed by the reaction of the 2,4-piperidinediones **2** with manganese(III) acetate during the first stage (Scheme 3). The enolate complex formation is the key to the catalytic reaction. The enolate complex easily oxidized the alkenes **1** to produce the corresponding carbon radicals **B**, which take up dissolved molecular oxygen in the solvent to form the peroxy radicals **C**. The peroxy radicals **C** could be reduced by the manganese(II) species followed by cyclization to finally produce the thermodynamically stable 1,6-*cis*-azabicyclic peroxides **3**.[5b,j,14] The manganese(III) species should be reproduced in the reaction system, and the catalytic cycle must be continued until the added alkenes **1** are completely consumed. The 2,4-piperidinedione-3-carboxylates **2a–g** exist in the solvent as the enol form so that the manganese(III)-enolate complex should be easily formed in situ using the hydroxyl and carboxylate moieties. However, the decarboxylated 2,4-piperidinediones **2h–m** are present as the keto form and the rate of the enolization would be slow in a protic solvent. Since the formation of the manganese(III)-2,4-piperidinedione enolate complex would be the rate-determining step,[6c,15] it could be understood that it took a longer reaction time using the 2,4-piperidinediones **2h–m** (Table 1, entries 20–28) than that using the 2,4-piperidinedione-3-carboxylates **2a–g** (Table 1, entries 1–19). Furthermore, the production of **3la** would be inhibited because the corresponding secondary alkyl radicals **B** produced from **1l** (R^1=heptyl, R^2 =H) were not stable compared to other tertiary and benzyl radicals formed from **1a–k** (Table 1, entry 13). In contrast, the formed carbon radicals **B** would be quickly oxidized by manganese(III) species in the reaction at elevated temperature due to the absence of dissolved molecular oxygen and the presence of a sufficient metal oxidant. As a result, the carbocations **E** would be produced and cyclize at the keto or amido carbonyl oxygen. When the cations **E** bear an ethoxycarbonyl substituent at R^4, the acetate group would be introduced after cyclization to give **4**, whereas the cations **E** having no substituent at R^4 would cyclize at the keto or amido carbonyl oxygen to provide **5** and/or **6** via deprotonation. Priority of producing **5** (path a) could be explained by the difference of the nucleophilicity between the keto and amido carbonyl oxygen in the cations **E**.[5k] During the catalytic endoperoxidation, a small amount of **5** and **6** was probably formed due to the reversibility of the endoperoxidation and use of an excess amount of catalyst, which caused the rapid oxidation of the tertiary carbon radicals **B** even at ambient temperature (Table 1, entries 21–27). The reaction pathways are depicted in Scheme 3.

2.6. Some reactions of the azabicyclic peroxides





Since the endoperoxide skeleton is sensitive to acid and base,[16] the exposure of the azabicyclic peroxides **3** to acid or base might be useful for transformation into other interesting functionalized azabicyclic compounds. Therefore, the azabicyclic compound **3ca** was treated only with acetic acid at 100 °C in order to convert it into 3,4,7,8-tetrahydro-[1,2]dioxino[4,3-*c*]pyridin-5(6*H*)-one **F** such as a root inhibitor analogue[3c–e] or antimalarial congener.[1e,3f,g,8] After 21 h, the expected decarboxylation and dehydration did not occur, but the acid-catalyzed decomposition of the peroxy bond occurred and the ring-opened product **7** was quantitatively obtained.[5a,b,d]

The reaction of the diphenyl-substituted **3aa** with DMAP in acetic anhydride afforded the acetoxylated azabicyclic peroxide **8** (59%), however, a similar reaction of **3ca** bearing bis(4-methoxyphenyl) substituents for 12 h gave 7a-acetoxy-3a,4,5,6,7,7a-hexahydro-4-oxofuro[3,2-*c*]pyridine-3a-carboxylate **9** (68%). Prolonged heating for 25 h of the reaction mixture led to the quantitative conversion into **9**. This would be due to the difference in the migratory aptitude of the phenyl and 4-methoxyphenyl group.[16c] The treatment of the decarboxylated **3ch** with DMAP in acetic anhydride provided 6,7-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-one **10** (68%). It is apparent that it is liable to undergo deacetoxylation of an intermediate such as the corresponding acetoxycarboxylate **9** as there is no substituent at the C-1 position of the hexahydrofuropyridine intermediate. Although the acid-catalyzed hydrolysis of **9** was examined in boiling acetic acid containing concentrated sulfuric acid for 2 h in order to clarify the formation of **10**, the attempt was failed and the ring-opened product **7** was quantitatively produced.

3. Conclusion

We developed the convenient synthesis of 1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one derivatives **3** using various alkenes **1** and 2,4-piperidinediones **2** in the presence of a catalytic amount of manganese(III) acetate in air. We also demonstrated the convenient route to the 6-acetoxy-3-aza-7-oxabicyclo[4.3.0]nonan-2-one-1-carboxylates **4**, tetrahydrofuro[3,2-*c*]- **5** and/or tetrahydrofuro[2,3-*b*]-pyridinones **6** using a similar reaction but at elevated temperature under an argon atmosphere. The azadioxabicyclo[4.4.0]decanone scaffold is attracitve from the viewpoint of biological activity. For example, naturally occurring artemisinin is a well-known strong antimalarial agent,[3a,f,g,8] and the activity of azaartemisinin as an analogue of 7-aza-2,3,5-trioxabicyclo[4.4.0]decan-8-one is stronger than that of natural artemisinin,[1e] while many biologically active tetrahydrofuropyridinones are known, such as antifungal and antibacterial heterocycles.[9] The screening of these heterocyclic compounds is currently underway in our department using yeast in order to confirm the alternative splicing of the mRNA.[17]

4. Experimental

The NMR spectra were recorded using a JNM EX300 FT NMR spectrometer at 300 MHz for ^{1}H and at 75 MHz for ^{13}C, with tetramethylsilane as the internal standard. The chemical shifts are reported in δ values (ppm). The IR spectra of neat samples were measured by the ATR method using a Shimadzu 8400 FT IR spectrophotometer and MIRacle A, and expressed in cm^{-1}. The EI MS spectra were recorded by a Shimadzu QP-5050A gas-chromatograph-mass spectrometer at the ionizing voltage of 70 eV. The high resolution mass spectra were measured at the Institute for Materials Chemistry and Engineering, Kyushu University, Fukuoka, Japan. The elemental analyses were performed at the Analytical Center of Kumamoto University, Kumamoto, Japan. Manganese(II) acetate tetrahydrate was purchased from Wako Pure Chemical Ind., Ltd. Manganese(III) acetate dihydrate, $Mn(OAc)_3 \cdot 2H_2O$, was prepared according to the method described in the literature.[5–7] The alkenes **2** were synthesized according to the literature,[7c] except for **1f**, **1i**, **1j**, **1k**, and **1l**, which were purchased from Tokyo Kasei Co. Ltd.

4.1. Preparation of piperidine-2,4-diones

The piperidine-2,4-dione derivatives **2a**–**m** were prepared according to the literature methods, and their physical data are given below.

4.1.1. Ethyl 1-benzylpiperidine-2,4-dione-3-carboxylate (2a).[11a] R_f=0.47 (diethyl ether); yellow oil; IR ν 1703 (C=O), 1649 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.1 (1H, s, O*H*), 7.34–7.29 (5H, m, arom. H), 4.65 (2H, s, Ph-CH_2), 4.40 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 3.32 (2H, t, J=6.8 Hz, H-6), 2.58 (2H, t, J=6.8 Hz, H-5), 1.42 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.0 (C-4), 172.0 (C=O), 162.4 (C=O), 137.7 (arom. C), 128.6, 128.0, 127.4 (3C, arom. *C*H), 98.2 (C-3), 61.8 (O*C*H$_2$CH$_3$), 49.4 (Ph-*C*H$_2$), 41.5 (C-6), 29.6 (C-5), 14.2 (OCH$_2$*C*H$_3$).

4.1.2. Ethyl 1-methylpiperidine-2,4-dione-3-carboxylate (2b).[18a] R_f=0.11 (diethyl ether); colorless microcrystals (from ethyl acetate/hexane); mp 59 °C; IR ν 1716 (C=O),

1639 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.0 (1H, s, O*H*), 4.36 (2H, q, J=7.0 Hz, OCH_2CH$_3$), 3.42 (2H, t, J=6.8 Hz, H-6), 3.01 (3H, s, N-CH_3), 2.69 (2H, t, J=6.8 Hz, H-5), 1.39 (3H, t, J=7.0 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.7 (C-4), 171.7 (C=O), 162.8 (C=O), 98.1 (C-3), 61.6 (O*C*H$_2$CH$_3$), 44.4 (C-6), 34.4 (N-*C*H$_3$), 29.2 (C-5), 14.0 (OCH$_2$*C*H$_3$).

4.1.3. Ethyl 1-ethylpiperidine-2,4-dione-3-carboxylate (2c).[18b] R_f=0.29 (diethyl ether); yellow oil; IR ν 1732 (C=O), 1661 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.0 (1H, s, O*H*), 4.37 (2H, q, J=7.0 Hz, OCH_2CH$_3$), 3.48 (2H, q, J=7.2 Hz, N-CH_2CH$_3$), 3.41 (2H, t, J=7.0 Hz, H-6), 2.66 (2H, t, J=7.0 Hz, H-5), 1.40 (3H, t, J=7.0 Hz, OCH$_2$CH_3), 1.14 (3H, t, J=7.2 Hz, N-CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.7 (C-4), 172.0 (C=O), 162.0 (C=O), 98.4 (C-3), 61.7 (O*C*H$_2$CH$_3$), 41.9, 41.4 (2C, C-6 and N-*C*H$_2$CH$_3$), 29.6 (C-5), 14.1 (OCH$_2$*C*H$_3$), 12.9 (N-CH$_2$*C*H$_3$).

4.1.4. Ethyl 1-propylpiperidine-2,4-dione-3-carboxylate (2d).[18c] R_f=0.42 (diethyl ether); yellow oil; IR ν 1732 (C=O), 1643 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.0 (1H, s, O*H*), 4.37 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 3.49–3.36 (4H, m, H-6 and N-CH_2CH$_2$CH$_3$), 2.66 (2H, t, J=6.8 Hz, H-5), 1.58 (2H, m, N-CH$_2$CH_2CH$_3$), 1.39 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 0.92 (3H, t, J=7.4 Hz, N-CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.7 (C-4), 172.0 (C=O), 162.2 (C=O), 98.4 (C-3), 61.7 (O*C*H$_2$CH$_3$), 48.4 (N-*C*H$_2$CH$_2$-CH$_3$), 42.6 (C-6), 29.7 (C-5), 21.2 (N-CH$_2$*C*H$_2$CH$_3$), 14.2 (OCH$_2$*C*H$_3$), 11.4 (N-CH$_2$*C*H$_3$).

4.1.5. Ethyl 1-isopropylpiperidine-2,4-dione-3-carboxylate (2e). R_f=0.28 (diethyl ether); yellow oil; IR ν 1732 (C=O), 1634 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.9 (1H, s, O*H*), 4.95 (1H, sep, J=6.8 Hz, N-C*H*<), 4.38 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 3.29 (2H, t, J=6.8 Hz, H-6), 2.60 (2H, t, J=6.8 Hz, H-5), 1.40 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 1.12 (6H, d, J=6.8 Hz, CH_3×2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.4 (C-4), 172.0 (C=O), 161.7 (C=O), 98.7 (C-3), 61.7 (O*C*H$_2$CH$_3$), 42.8 (N-*C*H<), 35.7 (C-6), 30.0 (C-5), 19.8 (2C, *C*H$_3$), 14.2 (OCH$_2$*C*H$_3$). FAB HRMS (acetone–NBA) calcd for $C_{11}H_{18}NO_4$ 228.1236 (M+1). Found 228.1237.

4.1.6. Ethyl 1-phenylpiperidine-2,4-dione-3-carboxylate (2f). R_f=0.58 (diethyl ether); yellow oil; IR ν 1732 (C=O), 1636 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.2 (1H, s, O*H*), 7.38–7.20 (5H, m, arom. H), 4.35 (2H, q, J=7.0 Hz, OCH_2CH$_3$), 3.84 (2H, t, J=6.1 Hz, H-6), 2.82 (2H, t, J=6.1 Hz, H-5), 1.36 (3H, t, J=7.0 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.7 (C-4), 171.9 (C=O), 162.3 (C=O), 142.5 (arom. C), 128.8, 126.1, 125.5 (3C, arom. *C*H), 98.5 (C-3), 61.9 (O*C*H$_2$CH$_3$), 45.6 (C-6), 30.1 (C-5), 14.1 (OCH$_2$*C*H$_3$). FAB HRMS (acetone–NBA) calcd for $C_{14}H_{16}NO_4$ 262.1079 (M+1). Found 262.1079.

4.1.7. Isopropyl 1-benzylpiperidine-2,4-dione-3-carboxylate (2g). R_f=0.57 (diethyl ether); colorless oil; IR ν 1717 (C=O), 1651 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.2 (1H, s, OH), 7.34–7.28 (5H, m, arom. H), 5.24 (1H, sep, J=6.2 Hz, O-C*H*<), 4.64 (2H, s, Ph-CH_2), 3.31 (2H, t, J=6.6 Hz, H-6), 2.55 (2H, t, J=6.6 Hz, H-5), 1.41 (6H, d, J=6.2 Hz, CH_3×2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.8 (C-4), 171.6 (C=O), 162.5 (C=O), 98.7 (C-3), 137.8 (arom. C), 128.6, 128.0, 127.4 (3C, arom. *C*H), 98.4 (C-3), 69.7 (O-*C*H<), 49.3 (Ph-*C*H$_2$), 41.4 (C-6), 29.7 (C-5), 21.8 (2C, *C*H$_3$). FAB HRMS (acetone–NBA) calcd for $C_{16}H_{20}NO_4$ 290.1392 (M+1). Found 290.1380.

4.1.8. 1-Benzylpiperidine-2,4-dione (2h).[11a] R_f=0.36 (diethyl ether/methanol 97:3 v/v); colorless microcrystals (from ethyl acetate); mp 50 °C; IR ν 1724 (C=O), 1649 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (5H, m, arom. H), 4.69 (2H, s, Ph-CH_2), 3.49 (2H, t, J=6.2 Hz, H-6), 3.42 (2H, s, H-3), 2.54 (2H, t, J=6.2 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5 (C=O), 166.4 (C=O), 136.5 (arom. C), 128.9, 128.1, 127.9 (3C, arom. *C*H), 50.0 (Ph-*C*H$_2$), 48.9 (C-3), 42.3 (C-6), 38.7 (C-5).

4.1.9. 1-Methylpiperidine-2,4-dione (2i).[18d] R_f=0.28 (diethyl ether/methanol 97:3 v/v); colorless oil; IR ν 1724 (C=O), 1647 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (2H, t, J=6.2 Hz, H-6), 3.33 (2H, s, H-3), 3.08 (3H, s, CH_3), 2.67 (2H, t, J=6.2 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3 (C=O), 166.1 (C=O), 48.2 (C-3), 44.8 (C-6), 38.1 (C-5), 34.3 (*C*H$_3$).

4.1.10. 1-Ethylpiperidine-2,4-dione (2j).[18b] R_f=0.19 (diethyl ether/methanol 97:3 v/v); colorless microcrystals (from ethyl acetate); mp 44 °C; IR ν 1726 (C=O), 1649 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62–3.51 (4H, m, H-6 and N-CH_2CH$_3$), 3.34 (2H, s, H-3), 2.64 (2H, t, J=6.1 Hz, H-5), 1.18 (3H, t, J=7.3 Hz, N-CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8 (C=O), 165.8 (C=O), 48.9 (C-3), 42.6, 41.8 (2C, C-6 and N-*C*H$_2$CH$_3$), 38.7 (C-5), 12.7 (N-CH$_2$*C*H$_3$).

4.1.11. 1-Propylpiperidine-2,4-dione (2k). R_f=0.21 (diethyl ether/methanol 97:3 v/v); colorless oil; IR ν 1726 (C=O), 1649 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (2H, t, J=6.1 Hz, H-6), 3.46 (2H, t, J=7.2 Hz, N-CH_2CH$_2$CH$_3$), 3.35 (2H, s, H-3), 2.62 (2H, t, J=6.1 Hz, H-5), 1.61 (2H, sex, J=7.3 Hz, N-CH$_2$CH_2CH$_3$), 0.94 (3H, t, J=7.5 Hz, N-CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7 (C=O), 165.7 (C=O), 48.7, 48.3 (2C, C-3 and N-*C*H$_2$CH$_2$CH$_3$), 42.9 (C-6), 38.3 (C-5), 20.5 (N-CH$_2$*C*H$_2$-CH$_3$), 11.0 (N-CH$_2$CH$_2$*C*H$_3$). FAB HRMS (acetone–NBA) calcd for $C_8H_{14}NO_2$ 156.1025 (M+1). Found 156.1039.

4.1.12. 1-Isopropylpiperidine-2,4-dione (2l). R_f=0.26 (diethyl ether/methanol 97:3 v/v); colorless microcrystals (from ethyl acetate); mp 45–48 °C; IR ν 1728 (C=O), 1647 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (1H, sep, J=6.8 Hz, N-C*H*<), 3.51 (2H, t, J=6.1 Hz, H-6), 3.36 (2H, s, H-3), 2.56 (2H, t, J=6.1 Hz, H-5), 1.17 (6H, d, J=6.8 Hz, CH_3×2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9 (C=O), 165.3 (C=O), 49.3 (C-3), 43.5 (N-*C*H<), 38.4 (C-6), 35.9 (C-5), 19.2 (2C, *C*H$_3$). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.52; H, 8.21; N, 8.57.

4.1.13. 1-Phenylpiperidine-2,4-dione (2m).[18e] R_f=0.44 (diethyl ether/methanol 97:3 v/v); colorless oil; IR ν 1726 (C=O), 1664 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.27 (5H, m, arom. H), 4.01 (2H, t, J=6.1 Hz, H-6), 3.55 (2H, s, H-3), 2.77 (2H, t, J=6.1 Hz, H-5); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 203.2 (C=O), 165.9 (C=O), 141.8 (arom. C), 129.3, 127.1, 125.3 (3C, arom. *C*H), 49.9 (C-3), 46.5 (C-6), 38.8 (C-5).

4.2. Manganese(III)-catalyzed aerobic oxidation of a mixture of various alkenes 1a–l and 2,4-piperidinediones 2a–m at room temperature

An alkene **1** (0.5 mmol), piperidinedione **2** (2 mmol), manganese(III) acetate dihydrate (0.15 mmol), and glacial acetic acid (20 mL) were placed in a 50 mL flask, and the mixture was stirred at 23 °C in air until the alkene **1** was completely consumed. The solvent was removed in vacuo and the residue was triturated with water followed by extraction with chloroform (10 mL×3). The combined extracts were dried over anhydrous magnesium sulfate, and concentrated to dryness. The residue was separated by TLC (wakogel B-10) while eluting with 1% methanol–chloroform. The products **3** were further purified by recrystallization from the appropriate solvents.

4.2.1. Ethyl 8-benzyl-1-hydroxy-4,4-diphenyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3aa). R_f=0.21 (chloroform/methanol 99:1 v/v); colorless microcrystals (from ethyl acetate); mp 209–210 °C; IR (KBr) ν 3400–3100 (OH), 1751, 1639 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.03 (15H, m, arom. H), 4.78 (1H, d, *J*=15.0 Hz, Ph-C*H*$_2$), 4.32–4.08 (3H, m, OC*H*$_2$CH$_3$ and O*H*), 3.80 (1H, d, *J*=14.7 Hz, H-5), 3.43 (1H, d, *J*=14.7 Hz, H-5), 2.94 (1H, d, *J*=15.0 Hz, Ph-C*H*$_2$), 2.86 (2H, br d, *J*=9.6 Hz, H-9), 2.62 (1H, dt, *J*=13.5, 9.6 Hz, H-10), 1.85 (1H, br d, *J*=13.5 Hz, H-10), 1.27 (3H, t, *J*=7.2 Hz, OCH$_2$*C*H$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9 (C=O), 166.6 (C=O), 143.1, 139.7, 136.5 (3C, arom. C), 128.4, 128.0, 127.6, 127.6, 127.5, 127.3, 127.2, 127.1, 125.5 (15C, arom. *C*H), 96.5 (C-1), 85.1 (C-4), 62.4 (O*C*H$_2$CH$_3$), 55.8 (C-6), 49.5 (Ph-*C*H$_2$), 41.4 (C-9), 33.7 (C-5), 29.3 (C-10), 13.9 (*C*H$_3$). Anal. Calcd for $C_{29}H_{29}NO_6$: C, 71.44; H, 6.00; N, 2.87. Found: C, 71.20; H, 5.85; N, 2.84.

X-ray crystallographic data of **3aa**. Empirical formula $C_{29}H_{29}NO_6$; formula weight 487.55; colorless plates; crystal dimensions 0.25×0.13×0.35 mm; triclinic; space group *P*1 (#2); *a*=9.0735(3), *b*=11.9814(4), *c*=12.1693(3) Å, α=69.1821(6)°, β=74.2866(9)°, γ=78.5339(7)°, *V*=1182.63(6) Å^3, *Z*=2; D_{calcd}=1.369 g/cm^3; F_{000}=516.00; μ (Mo Kα)=0.96 cm^{-1}; $2\theta_{max}$=55.0°; no. of reflections measured 10696; no. of reflections (All, 2θ<54.96°) 5327; no. of variables 325; reflection/parameter ratio 16.39; *R*=0.065; R_w=0.106; GOF 1.28. The X-ray crystallographic data have been deposited as supplementary publication numbers CCDC 272197. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

4.2.2. Ethyl 8-benzyl-1-hydroxy-4,4-bis(4-methylphenyl)-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3ba). R_f=0.44 (chloroform/methanol 97:3 v/v); colorless microcrystals (from ethyl acetate); mp 219–220 °C; IR ν 3450–3150 (OH), 1746, 1632 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.01 (13H, m, arom. H), 4.74 (1H, d, *J*=15.1 Hz, Ph-C*H*$_2$), 4.30–4.13 (3H, m, OC*H*$_2$CH$_3$ and O*H*), 3.73 (2H, d, *J*=14.9 Hz, H-5), 3.40 (2H, d, *J*=14.9 Hz, H-5), 3.00 (1H, d, *J*=15.1 Hz, Ph-C*H*$_2$), 2.84 (2H, m, H-9), 2.60 (1H, ddd, *J*=11.6, 13.4, 7.5 Hz, H-10), 2.28 (6H, d, *J*=16.9 Hz, Ph-C*H*$_3$×2), 1.84 (1H, dt, *J*=13.4, 2.8 Hz, H-10), 1.25 (3H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (C=O), 166.7 (C=O), 140.5, 137.7, 137.1, 136.6, 136.4 (5C, arom. C), 129.0, 128.4, 128.1, 127.6, 127.3, 125.6 (13C, arom. *C*H), 96.5 (C-1), 85.0 (C-4), 62.3 (O*C*H$_2$CH$_3$), 56.0 (C-6), 49.5 (Ph-*C*H$_2$), 41.5 (C-9), 33.8 (C-5), 29.4 (C-10), 21.0 (2C, Ph-*C*H$_3$), 13.9 (OCH$_2$*C*H$_3$). Anal. Calcd for $C_{31}H_{33}NO_6$: C, 72.21; H, 6.45; N, 2.72. Found: C, 72.44; H, 6.34; N, 2.81.

4.2.3. Ethyl 8-benzyl-1-hydroxy-4,4-bis(4-methoxyphenyl)-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3ca). R_f=0.40 (chloroform/methanol 97:3 v/v); colorless needles (from ethyl acetate); mp 114–115 °C; IR ν 3500–3100 (OH), 1742, 1634 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (2H, d, *J*=8.6 Hz, arom. H), 7.29–7.20 (5H, m, arom. H), 7.03 (2H, br d, *J*=6.4 Hz, arom. H), 6.86 (2H, d, *J*=8.6 Hz, arom. H), 6.76 (2H, d, *J*=8.8 Hz, arom. H), 4.79 (1H, d, *J*=15.1 Hz, Ph-C*H*$_2$), 4.56 (1H, br s, O*H*), 4.27–4.13 (2H, m, OC*H*$_2$CH$_3$), 3.74 (6H, d, *J*=16.9 Hz, OC*H*$_3$×2), 3.66 (2H, d, *J*=14.7 Hz, H-5), 3.43 (2H, d, *J*=14.7 Hz, H-5), 3.07 (1H, d, *J*=15.1 Hz, Ph-C*H*$_2$), 2.87–2.82 (2H, m, H-9), 2.66–2.55 (1H, m, H-10), 1.86–1.81 (2H, br d, *J*=13.6 Hz, H-10), 1.25 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (C=O), 166.8 (C=O), 159.1, 158.4, 136.5, 135.6, 132.0 (5C, arom. C), 128.8, 128.5, 127.6, 127.5, 127.3, 113.6, 112.8 (13C, arom. *C*H), 96.4 (C-1), 84.8 (C-4), 62.3 (O*C*H$_2$CH$_3$), 55.9 (C-6), 55.3, 55.2 (2C, O*C*H$_3$), 49.5 (Ph-*C*H$_2$), 41.6 (C-9), 33.8 (C-5), 29.5 (C-10), 13.9 (OCH$_2$*C*H$_3$). Anal. Calcd for $C_{31}H_{33}NO_8$: C, 67.99; H, 6.07; N, 2.56. Found: C, 67.70; H, 6.16; N, 2.51.

4.2.4. Ethyl 8-benzyl-4,4-bis(4-chlorophenyl)-1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3da). R_f=0.36 (chloroform/methanol 97:3 v/v); colorless microcrystals (from ethyl acetate); mp 181.5–182 °C; IR ν 3500–3200 (OH), 1746, 1634 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, d, *J*=8.4 Hz, arom. H), 7.32–7.22 (9H, m, arom. H), 7.06–7.03 (2H, m, arom. H), 4.77 (1H, d, *J*=15.1 Hz, Ph-C*H*$_2$), 4.51 (1H, br s, O*H*), 4.29–4.15 (2H, m, OC*H*$_2$CH$_3$), 3.70 (1H, d, *J*=14.9 Hz, H-5), 3.37 (1H, d, *J*=14.9 Hz, H-5), 3.08 (1H, d, *J*=15.1 Hz, Ph-C*H*$_2$), 2.88–2.78 (2H, m, H-9), 2.68–2.78 (2H, m, H-10), 1.86 (2H, br d, *J*=13.6 Hz, H-10), 1.27 (3H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6 (C=O), 166.4 (C=O), 141.2, 138.1, 136.2, 134.2, 133.2 (5C, arom. C), 128.9, 128.7, 128.5, 127.8, 127.6, 127.4, 127.1 (13C, arom. *C*H), 96.7 (C-1), 84.4 (C-4), 62.5 (O*C*H$_2$CH$_3$), 55.7 (C-6), 49.5 (Ph-*C*H$_2$), 41.5 (C-9), 33.5 (C-5), 29.4 (C-10), 13.9 (OCH$_2$*C*H$_3$). Anal. Calcd for $C_{29}H_{27}Cl_2NO_6$: C, 62.60; H, 4.89; N, 2.52. Found: C, 62.38; H, 4.99; N, 2.29.

4.2.5. Ethyl 8-benzyl-4,4-bis(4-fluorophenyl)-1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decane-7-one-6-carboxylate (3ea). R_f=0.30 (chloroform/methanol 97:3 v/v); colorless needles (from ethyl acetate); mp 194–196 °C; IR ν 3500–3200 (OH), 1747, 1634 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–6.89 (13H, m, arom. H), 4.81 (1H, d, *J*=

15.1 Hz, Ph-CH_2), 4.63 (1H, br s, OH), 4.24–4.17 (2H, m, OCH_2CH$_3$), 3.69 (2H, d, J=14.9 Hz, H-5), 3.40 (2H, d, J=14.9 Hz, H-5), 3.05 (1H, d, J=15.1 Hz, Ph-CH_2), 2.88–2.83 (2H, m, H-9), 2.67–2.59 (1H, m, H-10), 1.85 (2H, br d, J=13.8 Hz, H-10), 1.26 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.7 (C=O), 166.5 (C=O), 163.9, 163.5, 160.6, 160.2, 136.2, 136.1, 135.4 (5C, arom. C), 129.4, 129.2, 128.6, 128.4, 127.8, 127.6, 127.5, 127.3, 127.4, 115.4, 115.1, 114.5, 114.2 (13C, arom. CH), 96.5 (C-1), 84.5 (C-4), 62.4 (OCH$_2$CH$_3$), 55.7 (C-6), 49.5 (Ph-CH$_2$), 41.5 (C-9), 33.8 (C-5), 29.4 (C-10), 13.8 (OCH$_2$$CH_3$). Anal. Calcd for $C_{29}H_{27}F_2NO_6$: C, 66.53; H, 5.20; N, 2.68. Found: C, 66.78; H, 5.19; N, 2.64.

4.2.6. Ethyl 8-benzyl-1-hydroxy-4-methyl-4-phenyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3fa). R_f=0.29 (chloroform/methanol 97:3 v/v); colorless prisms (from ethyl acetate); mp 174.5–175.0 °C; IR ν 3500–3200 (OH), 1746, 1636 (C=O); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.43–7.25 (10H, m, arom. H), 5.16 (1H, d, J=14.5 Hz, Ph-CH_2), 4.21–4.13 (4H, m, OCH_2CH$_3$, Ph-CH_2, OH), 3.50 (1H, td, J=12.7, 4.8 Hz, H-9), 3.28 (1H, dd, J=12.7, 6.2 Hz, H-9), 3.10 (1H, d, J=14.3 Hz, H-5), 2.96 (1H, d, J=14.3 Hz, H-5), 2.75 (1H, td, J=13.4, 6.8 Hz, H-10), 2.00 (2H, dd, J=14.2, 3.9 Hz, H-10), 1.47 (3H, s, CH_3), 1.23 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.7 (C=O), 167.4 (C=O), 144.5, 136.3 (2C, arom. C), 128.6, 128.3, 128.2, 127.63, 127.58, 124.3 (10C, arom. CH), 97.1 (C-1), 80.8 (C-4), 62.4 (OCH$_2$CH$_3$), 56.3 (C-6), 50.8 (Ph-CH$_2$), 42.2 (C-9), 35.3 (C-5), 29.1 (C-10), 24.4 (CH$_3$), 13.9 (OCH$_2$$CH_3$). Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.78; H, 6.50; N, 3.36.

4.2.7. Stereoisomer of 3fa. R_f=0.21 (chloroform/methanol 97:3 v/v); colorless needles (from ethyl acetate); mp 201.5–202.0 °C; IR ν 3400–3200 (OH), 1717, 1638 (C=O); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.50–6.97 (10H, m, arom. H), 4.67 (1H, d, J=15.1 Hz, Ph-CH_2), 4.27–4.17 (3H, m, OCH_2CH$_3$, OH), 3.42 (1H, d, J=14.7 Hz, H-5), 2.97 (1H, d, J=14.7 Hz, H-5), 2.96 (1H, d, J=15.1 Hz, Ph-CH_2), 2.82–2.77 (2H, m, H-9), 2.58–2.55 (1H, m, H-10), 1.80 (1H, dt, J=13.2, 2.8 Hz, H-10), 1.46 (3H, s, CH_3), 1.28 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.0 (C=O), 166.3 (C=O), 141.2, 136.5 (2C, arom. C), 128.4, 127.5, 127.4, 127.2, 126.8, 126.2 (10C, arom. CH), 96.2 (C-1), 82.3 (C-4), 62.2 (OCH$_2$CH$_3$), 55.5 (C-6), 49.4 (Ph-CH$_2$), 41.4 (C-9), 34.3 (C-5), 29.2 (C-10), 30.7 (CH$_3$), 13.8 (OCH$_2$$CH_3$). Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.78; H, 6.60; N, 3.36.

4.2.8. Ethyl 8-benzyl-1-hydroxy-4-(4-methylphenyl)-4-methyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3ga). R_f=0.45 (chloroform/methanol 97:3 v/v); colorless microcrystals (from ethyl acetate); mp 162.5–163.0 °C; IR ν 3500–3100 (OH), 1717, 1645 (C=O); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.33–7.15 (9H, m, arom. H), 5.18 (1H, d, J=14.5 Hz, Ph-CH_2), 4.23–4.08 (4H, m, OCH_2CH$_3$, Ph-CH_2, OH), 3.52 (1H, td, J=12.7, 4.6 Hz, H-9), 3.32–3.26 (1H, dd, J=12.7, 6.8 Hz, H-9), 3.10 (1H, d, J=14.3 Hz, H-5), 2.96 (1H, d, J=14.3 Hz, H-5), 2.76 (1H, sex, J=6.8 Hz, H-10), 2.01 (1H, dd, J=14.3, 3.9 Hz, H-5), 2.34 (3H, s, Ph-CH_3), 1.47 (3H, s, CH_3), 1.26 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.7 (C=O), 167.4 (C=O), 141.3, 137.5, 136.4 (3C, arom. C), 129.0, 128.5, 128.1, 127.6, 124.3 (9C, arom. CH), 97.1 (C-1), 80.8 (C-4), 62.5 (OCH$_2$CH$_3$), 56.3 (C-6), 50.8 (Ph-CH$_2$), 42.2 (C-9), 35.2 (C-5), 29.0 (C-10), 24.3 (CH$_3$), 21.1 (Ph-CH$_3$), 13.9 (OCH$_2$$CH_3$). Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.22; H, 6.63; N, 3.11.

4.2.9. Stereoisomer of 3ga. R_f=0.33 (chloroform/methanol 97:3 v/v); colorless microcrystals (from ethyl acetate); mp 167.0–169.5 °C; IR ν 3500–3100 (OH), 1717, 1636 (C=O); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38–6.96 (9H, m, arom. H), 4.64 (1H, d, J=15.1 Hz, Ph-CH_2), 4.43 (1H, br s, OH), 4.21 (2H, m, OCH_2CH$_3$), 3.38 (1H, d, J=14.7 Hz, H-5), 3.04 (1H, d, J=15.1 Hz, Ph-CH_2), 2.94 (1H, d, J=14.7 Hz, H-5), 2.97 (2H, br d, J=8.8 Hz, H-9), 2.62–2.51 (1H, m, H-5), 2.34 (3H, s, Ph-CH_3), 1.80 (1H, br d, J=13.4 Hz, H-10), 1.43 (3H, s, CH_3), 1.27 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.1 (C=O), 166.5 (C=O), 138.3, 136.5, 136.3 (3C, arom. C), 128.5, 128.3, 128.1, 127.5, 127.2, 126.1, 124.3 (9C, arom. CH), 96.2 (C-1), 82.1 (C-4), 62.2 (OCH$_2$CH$_3$), 55.5 (C-6), 49.4 (Ph-CH$_2$), 41.5 (C-9), 34.3 (C-5), 29.3 (C-10), 30.7 (CH$_3$), 21.0 (Ph-CH$_3$), 13.9 (OCH$_2$$CH_3$). Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.38; H, 6.73; N, 3.22.

4.2.10. Ethyl 8-benzyl-4-(4-chlorophenyl)-1-hydroxy-4-methyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3ha). R_f=0.43 (chloroform/methanol 97:3 v/v); colorless microcrystals (from ethyl acetate); mp 165.5–166.0 °C; IR ν 3500–3100 (OH), 1738, 1618 (C=O); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35–7.18 (9H, m, arom. H), 5.15 (1H, d, J=14.5 Hz, Ph-CH_2), 4.47 (1H, br s, OH), 4.21–4.12 (3H, m, OCH_2CH$_3$, Ph-CH_2), 3.51 (1H, td, J=12.9, 3.9 Hz, H-9), 3.28 (1H, dd, J=12.1, 6.4 Hz, H-9), 3.06 (1H, d, J=14.1 Hz, H-5), 2.90 (1H, d, J=14.1 Hz, H-5), 2.74 (1H, td, J=13.6, 6.42 Hz, H-10), 2.01 (1H, br d, J=13.6 Hz, H-10), 1.43 (3H, s, CH_3), 1.24 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.6 (C=O), 167.2 (C=O), 142.9, 136.2, 133.6 (3C, arom. C), 128.6, 128.5, 128.1, 127.6, 125.8 (9C, arom. CH), 97.3 (C-1), 80.6 (C-4), 62.6 (OCH$_2$CH$_3$), 56.2 (C-6), 50.8 (Ph-CH$_2$), 42.2 (C-9), 35.3 (C-5), 29.1 (C-10), 24.4 (CH$_3$), 13.9 (OCH$_2$$CH_3$). Anal. Calcd for $C_{24}H_{26}ClNO_6$: C, 62.68; H, 5.70; N, 3.05. Found: C, 62.72; H, 5.43; N, 3.17.

4.2.11. Stereoisomer of 3ha. R_f=0.33 (chloroform/methanol 97:3 v/v); colorless needles (from ethyl acetate); mp 200.5–201.5 °C; IR ν 3500–3150 (OH), 1717, 1636 (C=O); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.44–6.98 (9H, m, arom. H), 4.67 (1H, d, J=15.1 Hz, Ph-CH_2), 4.29–4.19 (3H, m, OCH_2CH$_3$, OH), 3.37 (1H, d, J=14.9 Hz, H-5), 3.14 (1H, d, J=15.1 Hz, Ph-CH_2), 2.97 (1H, d, J=14.9 Hz, H-5), 2.85–2.78 (2H, m, H-9), 2.58 (1H, m, H-10), 1.81 (1H, br d, J=13.8 Hz, H-10), 1.43 (3H, s, CH$_3$), 1.28 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.8 (C=O), 166.3 (C=O), 139.9, 136.2, 132.7 (3C, arom. C), 128.4, 127.8, 127.6, 127.5, 127.3 (9C, arom. CH), 96.3 (C-1), 81.9 (C-4), 62.4 (OCH$_2$CH$_3$), 55.4 (C-6), 49.5 (Ph-CH$_2$), 41.5 (C-9), 34.1 (C-5), 29.2 (C-10), 30.7 (CH$_3$), 13.9 (OCH$_2$$CH_3$). Anal. Calcd for $C_{24}H_{26}ClNO_6$: C, 62.68; H, 5.70; N, 3.05. Found: C, 62.85; H, 5.45; N, 2.99.

4.2.12. Ethyl 8-benzyl-4,4-diethyl-1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3ia). R_f= 0.15 (chloroform/methanol 97:3 v/v); colorless microcrystals (from ethyl acetate); mp 114.8 °C; IR ν 3500–3100 (OH), 1744, 1616 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.27 (5H, m, arom. H), 4.94 (1H, d, J=14.5 Hz, Ph-CH_2), 4.33 (1H, d, J=14.5 Hz, Ph-CH_2), 4.27–4.19 (2H, m, OCH_2CH$_3$), 4.05 (1H, br s, OH), 3.42 (1H, td, J=12.7, 4.4 Hz, H-9), 3.23 (1H, dd, J=12.7, 6.2 Hz, H-9), 2.73 (1H, sex, J=6.8 Hz, H-10), 2.73 (1H, d, J=14.3 Hz, H-5), 2.52 (1H, d, J=14.3 Hz, H-5), 1.93 (1H, dd, J=14.3, 3.9 Hz, H-10), 1.60–1.50 (2H, m, CH_2CH$_3$), 1.45–1.30 (2H, m, CH_2CH$_3$), 1.26 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 0.90 (3H, t, J=7.3 Hz, CH$_2$CH_3), 0.78 (3H, t, J=7.3 Hz, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (C=O), 167.4 (C=O), 136.4 (arom. C), 128.6, 128.3, 127.6 (5C, arom. *C*H), 96.5 (C-1), 80.6 (C-4), 62.4 (O*C*H$_2$CH$_3$), 55.7 (C-6), 50.9 (Ph-*C*H$_2$), 42.2 (C-9), 32.5 (C-5), 28.9 (C-10), 28.7, 24.1 (2C, *C*H$_2$CH$_3$), 13.9 (OCH$_2$*C*H$_3$), 7.47, 6.99 (2C, CH$_2$*C*H$_3$). Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.33; H, 7.34; N, 3.54.

4.2.13. Ethyl 8-benzyl-1-hydroxy-4,4-dimethyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3ja). R_f=0.29 (chloroform/methanol 97:3 v/v); colorless microcrystals (from ethyl acetate); mp 128.0 °C; IR ν 3500–3100 (OH), 1751, 1628 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.28 (5H, m, arom. H), 5.16 (1H, d, J=14.7 Hz, Ph-CH_2), 4.22 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 4.12 (1H, d, J= 14.7 Hz, Ph-CH_2), 3.43 (1H, td, J=12.5, 4.6 Hz, H-9), 3.23 (1H, dd, J=12.5, 6.8 Hz, H-9), 2.77–2.59 (1H, m, H-10), 2.64 (2H, s, H-5), 1.95 (1H, dd, J=14.0, 4.6 Hz, H-10), 1.27 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 1.24 (3H, s, CH_3), 1.19 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9 (C=O), 167.4 (C=O), 136.4 (arom. C), 128.6, 128.2, 127.6 (5C, arom. *C*H), 96.4 (C-1), 78.0 (C-4), 62.4 (O*C*H$_2$CH$_3$), 55.9 (C-6), 50.7 (Ph-*C*H$_2$), 42.2 (C-9), 32.5 (C-5), 28.8 (C-10), 27.6, 23.0 (2C, *C*H$_3$), 13.9 (OCH$_2$*C*H$_3$). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.70; H, 6.85; N, 3.88.

4.2.14. Ethyl 8-benzyl-1-hydroxy-4-phenyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3ka). A mixture of two stereoisomers; R_f =0.34 (chloroform/methanol 97:3 v/v); colorless oil; IR ν 3500–3150 (OH), 1749, 1628 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.16 (20H, m, arom. H), 5.16 (1H, d, J=14.9 Hz, Ph-CH_2), 4.98 (1H, dd, J=9.2, 4.8 Hz, Ph-CH_2), 4.49–4.19 (5H, m, OCH_2CH$_3$×2, Ph-CH_2), 3.65–2.94 (m, Ph-CH_2, CH$_2$), 2.73–2.51 (m, CH$_2$), 2.16 (1H, dt, J=13.6, 4.4 Hz, CH$_2$), 1.96 (1H, dd, J=14.1, 4.8 Hz, CH$_2$), 1.37 (1H, t, J=7.2 Hz, OCH$_2$CH_3), 1.24 (2H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 168.7 (2C, C=O), 167.5, 166.6 (2C, C=O), 136.8, 136.6, 136.2 (4C, arom. C), 128.9, 128.7, 128.6, 128.5, 127.8, 127.7, 127.6, 127.5, 127.3, 126.5 (20C, arom. *C*H), 99.3, 97.2 (2C, C-1), 80.5, 80.3 (2C, C-4), 63.1, 62.4 (2C, O*C*H$_2$CH$_3$), 57.5, 55.5 (2C, C-6), 50.7, 50.2 (2C, Ph-*C*H$_2$), 43.0, 42.3 (2C, C-9), 36.2, 31.6 (2C, C-5), 28.7, 28.4 (2C, C-10), 13.9 (2C, OCH$_2$*C*H$_3$). FAB HRMS (acetone–NBA) calcd for $C_{23}H_{26}NO_6$ 412.1760 (M+1). Found 412.1718.

4.2.15. Ethyl 8-benzyl-4-heptyl-1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3la). A mixture of two stereoisomers; R_f =0.41 (diethyl ether/hexane 9:1 v/v); colorless oil; IR ν 3600–3100 (OH), 1744, 1628 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.22 (10H, m, arom. H), 5.10 (1H, d, J=14.9 Hz, Ph-CH_2), 4.58 (2H, dd, J=32.9, 14.7 Hz, Ph-CH_2), 4.36 (2H, qd, J=17.2, 2.2 Hz, OCH_2CH$_3$), 4.26–4.19 (7H, m, OCH_2CH$_3$, Ph-CH_2, H-4, OH), 4.01 (1H, m, H-4), 3.34–3.22 (4H, m, H-9), 2.76 (1.2H, d, J=13.94 Hz, H-10), 2.70–2.47 (2H, m, H-5), 2.40 (2H, d, J=14.0 Hz, H-5), 2.36 (2H, d, J=14.0 Hz, H-5), 2.17–2.03 (3H, m, H-10), 1.93 (1H, dd, J=14.0, 5.0 Hz, H-10), 1.55–1.14 (24H, m, CH_2), 1.36 (6H, t, J=7.2 Hz, OCH$_2$CH_3), 0.88 (6H, t, J=6.8 Hz, CH_3×2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 168.9, 167.9, 166.5 (4C, C=O), 136.6, 136.3 (2C, arom. C), 128.8, 128.6, 128.0, 127.8, 127.7, 127.5 (10C, arom. *C*H), 99.2, 97.0 (2C, C-1), 79.2, 78.9 (2C, C-4), 63.0, 62.4 (2C, O*C*H$_2$CH$_3$), 57.2, 55.4 (2C, C-6), 50.7, 50.4 (2C, Ph-*C*H$_2$), 43.0, 42.1 (2C, C-9), 31.9, 31.7 (2C, C-5), 28.5, 28.2 (2C, C-10), 33.1–22.6 (12C, *C*H$_2$), 14.1–13.9 (4C, *C*H$_3$×2, OCH$_2$*C*H$_3$×2). FAB HRMS (acetone–NBA) calcd for $C_{24}H_{36}NO_6$ 434.2543 (M+1). Found 434.2545.

4.2.16. Ethyl 1-hydroxy-4,4-diphenyl-8-methyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3ab). R_f=0.29 (chloroform/ethanol 98:2 v/v); colorless needles (from ethyl acetate); mp 186.0 °C; IR ν 3500–3100 (OH), 1734, 1626 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.14 (10H, m, arom. H), 4.18 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 3.73 (1H, d, J=14.7 Hz, H-5), 3.64 (1H, br s, OH), 3.37 (1H, d, J=14.7 Hz, H-5), 2.98–2.91 (2H, m, H-9), 2.83–2.76 (1H, m, H-10), 2.34 (3H, s, N-CH_3), 1.90 (1H, d, J=13.4 Hz, H-10), 1.24 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (C=O), 166.2 (C=O), 143.2, 139.7 (2C, arom. C), 128.4, 127.9, 127.4, 127.2, 126.8, 125.5 (10C, arom. *C*H), 96.7 (C-1), 85.1 (C-4), 62.3 (O*C*H$_2$CH$_3$), 55.6 (C-6), 44.6 (C-9), 34.7 (N-*C*H$_3$), 33.9 (C-5), 29.3 (C-10), 13.9 (OCH$_2$*C*H$_3$). Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.23; H, 6.08; N, 3.36.

4.2.17. Ethyl 8-ethyl-1-hydroxy-4,4-diphenyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3ac). R_f=0.35 (chloroform/methanol 98:2 v/v); colorless needles (from ethyl acetate); mp 229.5 °C; IR ν 3400–3100 (OH), 1744, 1632 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.11 (10H, m, arom. H), 4.35 (1H, s, OH), 4.18 (2H, q, J= 7.2 Hz, OCH_2CH$_3$), 3.78 (1H, d, J=14.9 Hz, H-5), 3.37 (1H, d, J=14.9 Hz, H-10), 3.00–2.89 (3H, m, N-CH_2, H-9), 2.79–2.68 (2H, m, H-9, H-10), 1.93 (1H, d, J=13.4 Hz, H-10), 1.22 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 0.66 (3H, t, J= 7.2 Hz, N-CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (C=O), 165.4 (C=O), 143.4, 140.0 (2C, arom. C), 128.3, 127.8, 127.5, 127.1, 126.9, 125.5 (10C, arom. *C*H), 96.7 (C-1), 85.0 (C-4), 62.2 (O*C*H$_2$CH$_3$), 55.7 (C-6), 42.1 (C-9), 41.8 (N-*C*H$_2$CH$_3$), 33.4 (C-5), 29.3 (C-10), 13.8 (OCH$_2$*C*H$_3$), 11.2 (N-CH$_2$*C*H$_3$). Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.73; H, 6.38; N, 3.27.

4.2.18. Ethyl 1-hydroxy-4,4-diphenyl-8-propyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3ad). R_f=0.33 (chloroform/methanol 99:1 v/v); colorless

microcrystals (from ethyl acetate); mp 191.0 °C; IR ν 3400–3000 (OH), 1747, 1622 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.12 (10H, m, arom. H), 4.32 (1H, br s, OH), 4.18 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 3.76 (1H, d, J=14.7 Hz, H-5), 3.37 (1H, d, J=14.7 Hz, H-5), 3.06–2.91 (3H, m, N-CH_2CH$_2$CH$_3$, H-9), 2.78–2.70 (1H, m, H-9), 2.40 (1H, m, H-10), 1.91 (1H, br d, J=13.6 Hz, H-10), 1.30–0.99 (2H, m, N-CH$_2$$CH_2CH_3$), 1.22 (3H, t, J=7.2 Hz, OCH$_2$$CH_3$), 0.73 (3H, t, J=7.3 Hz, N-CH$_2$CH$_2$$CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (C=O), 165.8 (C=O), 143.3, 139.8 (2C, arom. C), 128.3, 127.9, 127.5, 127.1, 126.9, 125.5 (10C, arom. *C*H), 96.6 (C-1), 85.0 (C-4), 62.2 (OCH_2CH$_3$), 55.7 (C-6), 48.7 (N-CH_2CH$_2$CH$_3$), 42.4 (C-9), 33.4 (C-5), 29.4 (C-10), 19.5 (N-CH$_2$$CH_2CH_3$), 13.8 (OCH$_2$$CH_3$), 11.1 (N-CH$_2CH_2$$CH_3$). Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.56; H, 6.65; N, 3.36.

4.2.19. Ethyl 1-hydroxy-4,4-diphenyl-8-isopropyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3ae). R_f=0.35 (chloroform/methanol 99:1 v/v); colorless needles (from ethyl acetate); mp 217.0 °C; IR ν 3400–3100 (OH), 1747, 1622 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.13 (10H, m, arom. H), 4.79 (1H, s, O*H*), 4.27–3.98 (3H, m, OCH_2CH$_3$, –C*H*<), 3.78 (1H, d, J=14.9 Hz, H-5), 3.39 (1H, d, J=14.9 Hz, H-5), 2.90–2.86 (1H, m, H-9), 2.79–2.59 (2H, m, H-9, H-10), 1.96 (1H, br d, J=12.5 Hz, H-10), 1.17 (3H, t, J=7.2 Hz, OCH$_2$$CH_3$), 0.92 (3H, d, J=6.8 Hz, –CH<(CH_3)$_2$), 0.43 (3H, d, J=6.8 Hz, –CH<(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (C=O), 165.5 (C=O), 143.6, 140.1 (2C, arom. C), 128.2, 127.7, 127.5, 127.1, 126.9, 125.4 (10C, arom. *C*H), 96.2 (C-1), 84.9 (C-4), 62.0 (OCH_2CH$_3$), 55.8 (C-6), 44.5 (–*C*H<), 35.8 (C-9), 33.4 (C-5), 29.3 (C-10), 18.3, 18.1 (2C, –CH<(*C*H$_3$)$_2$), 13.8 (OCH$_2$$CH_3$). Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.35; H, 6.65; N, 3.13.

4.2.20. Ethyl 1-hydroxy-4,4,8-triphenyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3af). R_f=0.38 (chloroform/methanol 99:1 v/v); colorless microcrystals (from chloroform); mp 238.0 °C; IR ν 3400–3200 (OH), 1724, 1634 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50–7.21 (13H, m, arom. H), 6.36 (2H, d, J=5.0 Hz, arom. H), 4.15 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 3.58 (1H, d, J=13.8 Hz, H-5), 3.39 (1H, br s, O*H*), 3.24 (3H, m, H-5, H-9), 2.80 (1H, br q, J=9.9 Hz, H-10), 1.99 (1H, d, J=9.9 Hz, H-10), 1.21 (3H, t, J=7.2 Hz, OCH$_2$$CH_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.3 (C=O), 166.0 (C=O), 144.2, 142.7, 140.8 (3C, arom. C), 128.5, 128.3, 127.7, 127.6, 127.0, 126.7, 126.2, 125.1 (15C, arom. *C*H), 96.4 (C-1), 83.8 (C-4), 61.4 (OCH_2CH$_3$), 55.7 (C-6), 46.4 (C-9), 33.0 (C-5), 30.0 (C-10), 13.7 (OCH$_2$$CH_3$). Anal. Calcd for $C_{28}H_{27}NO_6$: C, 71.02; H, 5.75; N, 2.96. Found: C, 70.69; H, 5.54; N, 2.98.

4.2.21. Isopropyl 8-benzyl-1-hydroxy-4,4-diphenyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (3ag). R_f=0.29 (chloroform/methanol 98:2 v/v); colorless microcrystals (from ethyl acetate); mp 221.0 °C; IR ν 3400–3200 (OH), 1734, 1638 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.02 (15H, m, arom. H), 5.10 (1H, sep, J=6.2 Hz, –C*H*<), 4.80 (1H, d, J=15.2 Hz, Ph-CH_2), 4.30 (1H, br s, O*H*), 3.77 (1H, d, J=14.7 Hz, H-5), 3.43 (1H, d, J=14.7 Hz, H-5), 2.87–2.75 (3H, m, Ph-CH_2, H-9), 2.64–2.53 (1H, m, H-10), 1.85 (1H, dt, J=13.6, 2.6 Hz, H-10), 1.26 (3H, d, J=6.2 Hz, –CH<(CH_3)$_2$), 1.23 (3H, d, J=6.2 Hz, –CH<(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (C=O), 166.6 (C=O), 143.1, 139.8, 136.7 (3C, arom. C), 128.4, 128.3, 128.1, 128.0, 127.8, 127.5, 127.3, 127.0, 126.4, 125.9, 125.5 (15C, arom. *C*H), 96.5 (C-1), 85.1 (C-4), 70.1 (–*C*H<), 55.8 (C-6), 49.4 (Ph-*C*H$_2$), 41.4 (C-9), 33.8 (C-5), 29.4 (C-10), 21.5, 21.4 (2C, –CH<(*C*H$_3$)$_2$). Anal. Calcd for $C_{30}H_{31}NO_6$: C, 71.84; H, 6.23; N, 2.79. Found: C, 71.85; H, 6.15; N, 2.86.

4.2.22. 8-Benzyl-1-hydroxy-4,4-diphenyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one (3ah). R_f=0.45 (chloroform/methanol 97:3 v/v); colorless needles (from chloroform); mp 200 °C; IR ν 3400–3200 (OH), 1626 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.09 (15H, m, arom. H), 4.39 (2H, dd, J=18.7, 14.9 Hz, Ph-CH_2), 3.82 (1H, s, O*H*), 3.38 (1H, dd, J=13.6, 3.9 Hz, H-5), 3.25 (1H, td, J=13.6, 4.4 Hz, H-5), 3.06–2.98 (1H, m, H-9), 2.86 (1 h, dd, J=9.3, 3.9 Hz, H-9), 2.69 (1H, dd, J=13.6, 10.5 Hz, H-6), 1.99–1.84 (2H, m, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (C=O), 144.0, 141.0, 136.4 (3H, arom. C), 128.6, 128.5, 128.1, 127.8, 127.4, 127.1, 126.4, 125.9 (15C, arom. *C*H), 99.8 (C-1), 86.7 (C-4), 50.1 (Ph-*C*H$_2$), 45.0 (C-6), 42.3 (C-9), 34.7 (C-5), 29.3 (C-10). Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37. Found: C, 75.38; H, 5.95; N, 3.39.

4.2.23. 8-Benzyl-1-hydroxy-4,4-bis(4-methylphenyl)-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one (3bh). R_f=0.36 (chloroform/methanol 98:2 v/v); colorless microcrystals (from ethyl acetate); mp 198.0 °C; IR ν 3500–3000 (OH), 1616 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.07 (13H, m, arom. H), 4.46 (1H, d, J=14.9 Hz, Ph-CH_2), 4.33 (1H, d, J=14.9 Hz, Ph-CH_2), 4.19 (1H, s, O*H*), 3.36 (1H, dd, J=13.9, 4.0 Hz, H-5), 3.25 (1H, td, J=8.4, 4.4 Hz, H-9), 3.01 (1H, dt, J=12.1, 4.4 Hz, H-9), 2.86 (1H, dd, J=10.6, 4.0 Hz, H-6), 2.58 (1H, dd, J=13.9, 10.6 Hz, H-5), 2.29 (6H, d, J=12.7 Hz, CH_3×2), 2.03–1.75 (2H, m, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (C=O), 141.5, 138.2, 137.8, 136.7, 136.4 (5C, arom. C), 129.2, 128.7, 128.6, 127.8, 127.4, 126.5, 125.8 (13C, arom. *C*H), 99.8 (C-1), 86.6 (C-4), 50.0 (Ph-*C*H$_2$), 45.1 (C-6), 42.4 (C-9), 35.1 (C-5), 28.9 (C-10), 21.1 (2C, *C*H$_3$×2). Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.46; H, 6.68; N, 2.99.

4.2.24. 8-Benzyl-1-hydroxy-4,4-bis(4-methoxyphenyl)-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one (3ch). A mixture of two stereoisomers; R_f =0.31 (chloroform/methanol 98:2 v/v); colorless microcrystals (from ethyl acetate/hexane); mp 94.5 °C; IR ν 3400–3200 (OH), 1611 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–6.71 (13H, m, arom. H), 4.89 (1H, br s, O*H*), 4.59 (3H, d, J=15.1 Hz, Ph-CH_2, O*H*), 4.44–4.30 (3H, m, Ph-CH_2), 3.85 (3H, s, CH_3), 3.73 (6H, d, J=19.3 Hz, CH_3×2), 3.69 (3H, s, CH_3), 3.45–3.11, 3.02–2.54, 2.00–1.68 (14H, m, H-5, H-6, H-9, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 168.9 (2C, C=O), 159.2, 159.1, 158.6, 158.5, 136.6, 136.4, 136.3, 135.1, 133.6, 133.0 (10C, arom. C), 128.6, 128.2, 128.1, 127.9, 127.8, 127.7, 127.4, 127.3, 113.7, 113.6, 113.4 (26C, arom. *C*H), 99.4, 97.3 (2C, C-1), 87.5, 86.1 (2C, C-4), 55.2, 55.1 (2C, *C*H$_3$), 50.0, 49.8 (2C, Ph-*C*H$_2$), 44.8 (1C, C-6), 43.1 (1C, C-9), 43.0 (1C,

C-6), 42.5 (1C, C-9), 35.0, 30.9 (2C, C-5), 29.1, 28.6 (2C, C-10). Anal. Calcd for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.46; H, 6.01; N, 2.90.

4.2.25. 8-Benzyl-4,4-bis(4-chlorophenyl)-1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one (3dh). R_f=0.34 (chloroform/methanol 98:2 v/v); colorless microcrystals (from ethyl acetate); mp 194.5 °C; IR ν 3500–3150 (OH), 1616 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.06 (13H, m, arom. H), 4.39 (3H, d, J=15.4 Hz, Ph-CH_2, O*H*), 3.29–3.19 (2H, m, H-5, H-9), 3.05–2.99 (1H, m, H-9), 2.83 (1H, dd, J=9.0, 4.2 Hz, H-6), 2.68 (1H, dd, J=13.2, 10.3 Hz, H-5), 2.04–1.99 (1H, m, H-10), 1.88 (1H, dt, J=13.8, 5.1 Hz, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (C=O), 141.8, 139.3, 136.1, 134.3, 133.3 (5C, arom. C), 128.8, 128.7, 128.6, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5, 127.3 (13C, arom. *C*H), 99.5 (C-1), 85.7 (C-4), 50.1 (Ph-*C*H_2), 44.3 (C-6), 42.4 (C-9), 34.2 (C-5), 29.4 (C-10). Anal. Calcd for $C_{26}H_{23}Cl_2NO_4$: C, 64.47; H, 4.79; N, 2.89. Found: C, 64.37; H, 4.97; N, 2.94.

4.2.26. 1-Hydroxy-8-methyl-4,4-diphenyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one (3ai). R_f=0.28 (chloroform/methanol 97:3 v/v); colorless microcrystals (from chloroform); mp 245.3 °C; IR ν 3500–3000 (OH), 1630 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.18 (10H, m, arom. H), 3.60 (1H, br s, O*H*), 3.36–3.05 (4H, m, H-5, H-9), 2.77–2.69 (1H, m, H-9), 2.76–2.69 (1H, m, H-6), 2.75 (3H, s, N-CH_3), 2.08–2.04 (1H, m, H-10), 1.93 (1H, dt, J=13.8, 5.7 Hz, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7 (C=O), 143.5, 141.1 (2C, arom. C), 128.6, 128.1, 128.0, 127.1, 126.4, 126.1 (10C, arom. *C*H), 99.6 (C-1), 86.5 (C-4), 45.1 (C-9), 44.6 (C-6), 34.7 (N-*C*H_3), 34.4 (C-5), 29.5 (C-10). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.83; H, 6.19; N, 4.23.

4.2.27. 8-Ethyl-1-hydroxy-4,4-diphenyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one (3aj). R_f=0.35 (chloroform/methanol 97:3 v/v); colorless microcrystals (from chloroform); mp 203.5 °C; IR ν 3400–3100 (OH), 1618 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.18 (10H, m, arom. H), 3.82 (1H, s, O*H*), 3.33–3.08 (6H, m, H-5, H-9, N-CH_2CH$_3$), 2.75 (1H, s, H-6), 2.07–2.04 (1H, m, H-10), 1.95 (1H, dt, J=13.8, 5.5 Hz, H-10), 0.92 (3H, t, J=7.2 Hz, N-CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C=O), 143.6, 141.3 (2C, arom. C), 128.5, 128.0, 127.0, 126.3, 126.0 (10C, arom. *C*H), 99.5 (C-1), 86.4 (C-4), 44.6 (C-6), 42.4 (C-9), 42.2 (N-*C*H_2CH$_3$), 34.1 (C-5), 29.8 (C-10), 12.0 (N-CH$_2$*C*H_3). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.42; H, 6.30; N, 4.04.

4.2.28. 1-Hydroxy-4,4-diphenyl-8-propyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one (3ak). R_f=0.30 (chloroform/methanol 97:3 v/v); colorless microcrystals (from chloroform); mp 202.5 °C; IR ν 3400–3100 (OH), 1614 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.17 (10H, m, arom. H), 4.53 (1H, br s, O*H*), 3.37–3.28 (2H, m, H-5, H-9), 3.16 (2H, t, J=7.5 Hz, N-CH_2CH$_2$CH$_3$), 3.12 (1H, ddd, J=6.4, 6.4, 5.3 Hz, H-9), 2.79–2.74 (1H, m, H-6), 2.66 (1H, d, J=9.7 Hz, H-5), 2.06–2.02 (1H, m, H-10), 1.94 (1H, dt, J=13.6, 5.3 Hz, H-10), 1.36 (2H, sex, J=7.5 Hz, N-CH$_2$CH_2-CH$_3$), 0.82 (3H, t, J=7.5 Hz, N-CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (C=O), 144.0, 141.2 (2C, arom. C), 128.4, 128.0, 127.9, 127.0, 126.5, 125.9 (10C, arom. *C*H), 99.6 (C-1), 86.5 (C-4), 49.0 (N-*C*H_2CH$_2$CH$_3$), 44.6 (C-6), 43.2 (C-9), 34.7 (C-5), 29.3 (C-10), 20.1 (N-CH$_2$*C*H_2CH$_3$), 11.3 (N-CH$_2$CH$_2$*C*H_3). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.05; H, 6.71; N, 3.85.

4.2.29. 1-Hydroxy-4,4-diphenyl-8-isopropyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one (3al). R_f=0.33 (chloroform/methanol 97:3 v/v); colorless microcrystals (from chloroform); mp 206.0 °C; IR ν 3400–3100 (OH), 1593 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.20 (10H, m, arom. H), 4.61 (1H, sep, J=6.8 Hz, –C*H*<), 3.65 (1H, s, O*H*), 3.24 (1H, dd, J=14.1, 5.1 Hz, H-5), 3.13 (1H, ddd, 12.1, 7.5, 4.8 Hz, H-9), 2.98 (1H, ddd, 12.1, 7.5, 4.8 Hz, H-9), 2.87 (1H, dd, 14.1, 8.1 Hz, H-6), 2.75 (1H, dd, 8.1, 5.1 Hz, H-5), 2.00–1.92 (1H, m, H-10), 1.04 (3H, d, J=6.8 Hz, CH_3), 0.79 (3H, d, J=6.8 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9 (C=O), 143.3, 141.6 (2C, arom. C), 128.4, 128.3, 128.0, 127.9, 127.0, 126.3, 126.2, 125.9 (10C, arom. *C*H), 98.9 (C-1), 86.3 (C-4), 44.7 (C-6), 44.3 (–*C*H<), 35.9 (C-9), 33.7 (C-5), 30.3 (C-10), 19.1, 18.9 (2C, *C*H_3). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.04; H, 6.78; N, 3.88.

4.2.30. 1-Hydroxy-4,4,8-triphenyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one (3am). R_f=0.30 (chloroform/methanol 97:3 v/v); colorless microcrystals (from chloroform); mp 210.5 °C; IR ν 3400–3200 (OH), 1630 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.21 (13H, m, arom. H), 6.82 (2H, d, J=7.5 Hz, arom. H), 3.60–3.53 (2H, m, H-9, O*H*), 3.44 (1H, ddd, J=12.3, 7.5, 4.8 Hz, H-9), 3.27 (1H, dd, J=13.9, 5.5 Hz, H-5), 3.09 (1H, dd, J=13.9, 7.5 Hz, H-5), 2.93 (1H, dd, J=7.5, 5.5 Hz, H-6), 2.24–2.14 (2H, m, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7 (C=O), 142.9, 142.5, 141.6 (3C, arom. C), 129.0, 128.5, 128.1, 128.0, 127.1, 127.0, 126.5, 126.1 (15C, arom. *C*H), 98.9 (C-1), 86.2 (C-4), 46.5 (C-9), 44.8 (C-6), 33.2 (C-5), 31.0 (C-10). Anal. Calcd for $C_{25}H_{23}NO_4 \cdot 2/5H_2O$:C, 73.47; H, 5.87; N, 3.43. Found: C, 73.43; H, 5.48; N, 3.38.

4.3. Oxidation of a mixture of 1,1-disubstituted ethenes 1 and 2,4-piperidinediones 2 with manganese(III) acetate at elevated temperature

An alkene **1** (0.5 mmol), 2,4-piperidinedione **2** (1 mmol), glacial acetic acid (20 mL), and manganese(III) acetate dihydrate (3 mmol) were placed in a 50 mL flask, and the mixture was degassed under reduced pressure using an ultrasonicator followed by argon displacement. The mixture was heated at 50–60 °C or under reflux until the brown color of Mn(III) disappeared (Table 2). The solvent was removed in vacuo, and the residue was triturated with water followed by extraction with chloroform (10 mL×3). The combined extracts were dried over anhydrous magnesium sulfate, and then concentrated to dryness. The products were separated by TLC (wakogel B-10) while eluting with 2% methanol–chloroform or 20% hexane–diethyl ether. The products **4**, **5**, and **6** were further purified by recrystallization from appropriate solvents.

4.3.1. Ethyl 6-acetoxy-3-benzyl-8,8-diphenyl-3-aza-7-oxabicyclo[4.3.0]nonan-2-one-1-carboxylate (4aa). R_f=

0.64 (diethyl ether/hexane 8:2 v/v); colorless oil; IR ν 1747, 1647 (C=O), 1235 (AcO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–6.99 (15H, m, arom. H), 4.73 (1H, d, J=15.1 Hz, Ph-CH_2), 4.23 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 3.81 (1H, d, J=13.8 Hz, H-9), 3.61 (1H, d, J=13.8 Hz, H-9), 3.36 (1H, br d, J=15.1 Hz, Ph-CH_2, H-4), 3.25–3.01 (2H, m, H-4, H-5), 2.52 (1H, td, J=13.0, 6.1 Hz, H-5), 1.69 (3H, s, AcO), 1.25 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9 (C=O), 166.5 (C=O), 165.9 (C=O), 147.1, 143.5, 135.9 (3C, arom. C), 128.3, 128.1, 127.9, 127.8, 127.7, 127.4, 127.2, 127.0, 126.5, 126.3, 125.4, 125.0, 124.2 (15C, arom. *C*H), 107.8 (C-6), 89.7 (C-8), 65.8 (C-1), 61.8 (O*C*H$_2$CH$_3$), 49.2 (Ph-*C*H$_2$), 42.3 (C-4), 41.7 (C-9), 26.7 (C-5), 21.5 (AcO), 13.7 (OCH$_2$*C*H$_3$). FAB MS *m*/*z* (rel intensity), 512 (3, M-1), 454 (100), 382 (15), 247 (13), 191 (9), 91 (98).

4.4. Hydrolysis of 4aa

The acetate **4aa** (45.5 mg) was put in a 30 mL flask and a 10% aqueous solution of sulfuric acid (5 mL) was added. The mixture was then heated under reflux for 30 min. After cooling, the mixture was extracted with chloroform (10 mL×3), and the obtained crude product was purified by TLC using chloroform/methanol (98:2 v/v) as the developing solvent, giving the corresponding hydroxycarboxylate in 74% yield. Surprisingly, the ethoxycarbonyl moiety of **4aa** could not be hydrolyzed under the stated reaction conditions.

4.4.1. Ethyl 3-benzyl-6-hydroxy-8,8-diphenyl-3-aza-7-oxabicyclo[4.3.0]nonan-2-one-1-carboxylate. R_f=0.32 (chloroform/methanol 98:2 v/v); colorless prisms (from ethyl acetate); mp 225.0 °C; IR (neat) ν 3500–3200 (OH), 1742 (C=O), 1634 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.01 (15H, m, arom. H), 4.78 (1H, d, J=15.1 Hz, Ph-CH_2), 4.29–4.16 (2H, m, OCH_2CH$_3$), 3.79 (1H, d, J=14.0 Hz, H-9), 3.52 (1H, br s, O*H*), 3.48 (1H, d, J=14.0 Hz, H-9), 3.01 (1H, d, J=15.1 Hz, Ph-CH_2), 3.01–2.91 (2H, m, H-4), 2.40 (1H, sex, J=6.4 Hz, H-5), 2.17 (1H, br d, J=13.2 Hz, H-5), 1.26 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (C=O), 166.9 (C=O), 147.8, 143.5, 136.4 (3C, arom. C), 128.4, 128.2, 127.9, 127.4, 127.2, 126.8, 125.7, 125.2 (15C, arom. *C*H), 103.6 (C-6), 88.2 (C-8), 65.7 (C-1), 62.0 (OCH$_2$*C*H$_3$), 49.3 (Ph-*C*H$_2$), 42.6 (C-9), 42.4 (C-4), 29.9 (C-5), 13.8 (OCH$_2$*C*H$_3$). Anal. Calcd for $C_{29}H_{29}NO_5$: C, 73.87; H, 6.20; N, 2.97. Found: C, 73.87; H, 6.19; N, 2.99.

4.4.2. Ethyl 6-acetoxy-3-benzyl-8,8-bis(4-methylphenyl)-3-aza-7-oxabicyclo[4.3.0]nonan-2-one-1-carboxylate (4ba). R_f=0.47 (diethyl ether/hexane 8:2 v/v); colorless prisms (from ethanol); mp 174.0 °C; IR ν 1749, 1647 (C=O), 1234 (AcO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.00 (13H, m, arom. H), 4.75 (1H, d, J=14.9 Hz, Ph-CH_2), 4.25 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 3.75 (1H, d, J=13.8 Hz, H-9), 3.56 (1H, d, J=13.8 Hz, H-9), 3.41 (1H, d, J=14.9 Hz, Ph-CH_2), 3.34 (1H, br d, J=11.4 Hz, H-4), 3.14 (1H, dd, J=12.5, 4.0 Hz, H-4), 3.05 (1H, ddd, J=12.5, 6.1, 1.7 Hz, H-5), 2.51 (1H, td, J=13.2, 6.1 Hz, H-5), 2.27 (6H, d, J=9.6 Hz, Ph-CH_3×2), 1.73 (3H, s, AcO), 1.27 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (C=O), 166.7 (C=O), 166.2 (C=O), 144.6, 140.9, 136.5, 136.0 (5C, arom. C), 128.9, 128.8, 128.5, 127.6, 127.3, 125.2, 124.4 (13C, arom. *C*H), 108.0 (C-6), 89.8 (C-8), 66.0 (C-1), 61.8 (O*C*H$_2$CH$_3$), 49.3 (Ph-*C*H$_2$), 42.4 (C-4), 41.8 (C-9), 26.9 (C-5), 21.7 (AcO), 20.8 (2C, Ph-*C*H$_3$), 13.9 (OCH$_2$*C*H$_3$). FAB MS *m*/*z* (rel intensity), 540 (5, M-1), 482 (100), 408 (13), 275 (17), 208 (15), 91 (69). Anal. Calcd for $C_{33}H_{35}NO_6$: C, 73.18; H, 6.51; N, 2.59. Found: C, 73.07; H, 6.56; N, 2.68.

4.4.3. Ethyl 6-acetoxy-3-benzyl-8,8-bis(4-chlorophenyl)-3-aza-7-oxabicyclo[4.3.0]nonan-2-one-1-carboxylate (4da). R_f=0.30 (diethyl ether/hexane 5:5 v/v); colorless oil; IR ν 1749, 1649 (C=O), 1235 (AcO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–6.98 (13H, m, arom. H), 4.66 (1H, d, J=14.9 Hz, Ph-CH_2), 4.26 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 3.75 (1H, d, J=14.0 Hz, H-9), 3.62 (1H, d, J=14.9 Hz, Ph-CH_2), 3.53 (1H, d, J=14.0 Hz, H-9), 3.33 (1H, dt, J=13.2, 2.8 Hz, H-5), 3.12 (2H, br d, J=9.5 Hz, H-4), 2.58–2.47 (1H, m, H-5), 1.74 (3H, s, AcO), 1.29 (3H, t, J=7.16 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (C=O), 166.4 (C=O), 165.8 (C=O), 145.6, 142.0, 135.8, 133.4, 132.9 (5C, arom. C), 128.6, 128.5, 127.6, 127.5, 126.5, 125.8 (13C, arom. *C*H), 108.1 (C-6), 88.9 (C-8), 65.9 (C-1), 62.2 (O*C*H$_2$CH$_3$), 49.8 (Ph-*C*H$_2$), 42.6 (C-4), 41.8 (C-9), 26.7 (C-5), 21.8 (AcO), 14.0 (OCH$_2$*C*H$_3$). FAB MS *m*/*z* (rel intensity), 582 (4, M+1), 522 (77), 450 (9), 273 (10), 229 (5), 154 (15), 91 (100).

4.4.4. Ethyl 6-acetoxy-3-methyl-8,8-diphenyl-3-aza-7-oxabicyclo[4.3.0]nonan-2-one-1-carboxylate (4ab). R_f=0.21 (chloroform/methanol 98:2 v/v); colorless prisms (from ethyl acetate); mp 181.5 °C; IR ν 1744, 1645 (C=O), 1220 (AcO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.15 (10H, m, arom. H), 4.35–4.13 (2H, m, OCH_2CH$_3$), 3.75 (1H, d, J=13.8 Hz, H-9), 3.42 (1H, d, J=13.8 Hz, H-9), 3.39–3.33 (1H, m, H-5), 3.24–3.06 (2H, m, H-4), 2.61 (1H, td, J=13.0, 6.1 Hz, H-5), 2.40 (3H, s, N-CH_3), 1.80 (3H, s, AcO), 1.25 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 (C=O), 166.9 (C=O), 165.7 (C=O), 147.3, 143.3 (2C, arom. C), 128.3, 128.0, 127.2, 126.8, 125.3, 124.4 (10C, arom. *C*H), 108.2 (C-6), 90.0 (C-8), 65.8 (C-1), 62.0 (O*C*H$_2$CH$_3$), 45.4 (C-4), 41.8 (C-9), 34.4 (N-*C*H$_3$), 26.8 (C-5), 21.9 (AcO), 14.1 (OCH$_2$*C*H$_3$). Anal. Calcd for $C_{25}H_{27}NO_6$: C, 68.63; H, 6.22; N, 3.20. Found: C, 68.73; H, 6.12; N, 3.31.

4.4.5. Ethyl 6-acetoxy-3-ethyl-8,8-diphenyl-3-aza-7-oxabicyclo[4.3.0]nonan-2-one-1-carboxylate (4ac). R_f=0.22 (chloroform); colorless oil; IR ν 1747, 1647 (C=O), 1236 (AcO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.12 (10H, m, arom. H), 4.32–4.12 (2H, m, OCH_2CH$_3$), 3.80 (1H, d, J=13.8 Hz, H-9), 3.48 (1H, d, J=13.8 Hz, H-9), 3.45–3.07 (4H, m, N-CH_2CH$_3$, H-4, H-5), 2.83 (1H, dt, J=20.6, 7.2 Hz, H-4), 2.65–2.55 (1H, m, H-5), 1.75 (3H, s, AcO), 1.24 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 0.54 (3H, t, J=7.2 Hz, N-CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4 (C=O), 166.9 (C=O), 165.1 (C=O), 147.6, 143.7 (2C, arom. C), 128.3, 128.2, 127.2, 126.7, 125.2, 124.3 (10C, arom. *C*H), 108.3 (C-6), 89.8 (C-8), 65.8 (C-1), 61.9 (O*C*H$_2$CH$_3$), 43.0 (N-*C*H$_2$CH$_3$), 42.3 (C-4), 41.8 (C-9), 26.9 (C-5), 21.9 (AcO), 14.0 (OCH$_2$*C*H$_3$), 11.0 (N-CH$_2$*C*H$_3$). FAB MS *m*/*z* (rel intensity), 450 (3, M-1), 392 (100), 320 (8), 247 (17), 154 (3).

4.4.6. Ethyl 6-acetoxy-8,8-diphenyl-3-propyl-3-aza-7-oxabicyclo[4.3.0]nonan-2-one-1-carboxylate (4ad). R_f= 0.23 (chloroform); colorless oil; IR ν 1747, 1645 (C=O), 1234 (AcO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.12 (10H, m, arom. H), 4.28–4.12 (2H, m, OCH_2CH$_3$), 3.77 (1H, d, J=13.8 Hz, H-9), 3.50 (1H, d, J=13.8 Hz, H-9), 3.39 (1H, br d, J=12.8 Hz, H-5), 3.26 (1H, td, J=12.5, 3.9 Hz, H-4), 3.12 (1H, ddd, J=12.5, 5.8, 1.5 Hz, H-4), 2.97–2.75 (2H, m, N-CH_2CH$_2$CH$_3$), 2.59 (1H, td, J=12.8, 5.8 Hz, H-5), 1.74 (3H, s, AcO), 1.24 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 1.17–0.85 (2H, m, N-CH$_2$CH_2CH$_3$), 0.68 (3H, t, J=7.3 Hz, N-CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (C=O), 166.8 (C=O), 165.4 (C=O), 147.5, 143.6 (2C, arom. C), 128.2, 128.0, 127.1, 126.6, 125.2, 124.3 (10C, arom. *C*H), 108.1 (C-6), 89.8 (C-8), 65.8 (C-1), 61.8 (O*C*H$_2$CH$_3$), 48.9 (N-*C*H$_2$CH$_2$CH$_3$), 43.4 (C-4), 41.8 (C-9), 26.9 (C-5), 21.8 (AcO), 19.3 (N-CH$_2$*C*H$_2$CH$_3$), 13.9 (OCH$_2$*C*H$_3$), 11.0 (N-CH$_2$CH$_2$*C*H$_3$). FAB MS *m*/*z* (rel intensity), 466 (3, M+1), 406 (100), 334 (7), 247 (13), 154 (11).

4.4.7. Ethyl 6-acetoxy-8,8-diphenyl-3-isopropyl-3-aza-7-oxabicyclo[4.3.0]nonan-2-one-1-carboxylate (4ae). R_f= 0.33 (diethyl ether/hexane 8:2 v/v); colorless prisms (from ethyl acetate); mp 171.0 °C; IR ν 1747, 1636 (C=O), 1236 (AcO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.11 (10H, m, arom. H), 4.42 (1H, sep, J=6.8 Hz, N-C*H*<), 4.29–4.12 (2H, m, OCH_2CH$_3$), 3.80 (1H, d, J=13.8 Hz, H-9), 3.47 (1H, d, J=13.8 Hz, H-9), 3.44–3.39 (1H, m, H-5), 3.10 (1H, sexd, J=6.1, 1.8 Hz, H-4), 3.02 (1H, td, J=12.5, 4.0 Hz, H-4), 2.50 (1H, sex, J=6.1 Hz, H-5), 1.76 (3H, s, Ac), 1.23 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 0.98 (3H, d, J=6.8 Hz, –CH<(CH_3)$_2$), 0.38 (3H, d, J=6.79 Hz, –CH<(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (C=O), 166.7 (C=O), 164.8 (C=O), 147.5, 143.5 (2C, arom. C), 128.0, 127.9, 127.0, 126.4, 125.1, 124.1 (10C, arom. *C*H), 107.8 (C-6), 89.6 (C-8), 65.8 (C-1), 61.5 (O*C*H$_2$CH$_3$), 44.3 (N-*C*H<), 41.5 (C-9), 36.3 (C-4), 26.7 (C-5), 21.6 (AcO), 18.6 (–CH<(*C*H$_3$)$_2$), 17.7 (–CH<(*C*H$_3$)$_2$), 13.7 (OCH$_2$*C*H$_3$). Anal. Calcd for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71; N, 3.01. Found: C, 69.64; H, 6.60; N, 2.95.

4.4.8. Ethyl 6-acetoxy-3,8,8-triphenyl-3-aza-7-oxabicyclo[4.3.0]nonan-2-one-1-carboxylate (4af). R_f=0.23 (chloroform); colorless prisms (from ethyl acetate); mp 198.5 °C; IR ν 1744, 1651 (C=O), 1236 (AcO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.14 (13H, m, arom. H), 6.43–6.42 (2H, m, arom. H), 4.36–4.20 (2H, m, OCH_2CH$_3$), 3.89 (1H, d, J=13.8 Hz, H-9), 3.69 (1H, td, J=12.5, 3.9 Hz, H-4), 3.54 (1H, d, J=13.8 Hz, H-9), 3.51 (1H, br d, J=13.6 Hz, H-5), 3.44 (1H, tdd, 12.5, 5.7, 1.8 Hz, H-4), 2.80 (1H, td, J=13.0, 5.7 Hz, H-5), 1.80 (3H, s, AcO), 1.29 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (C=O), 166.6 (C=O), 165.8 (C=O), 147.5, 143.8, 141.9 (3C, arom. C), 128.9, 128.5, 128.3, 127.3, 127.2, 126.7, 125.9, 125.4, 124.2 (15C, arom. *C*H), 108.1 (C-6), 90.0 (C-8), 66.3 (C-1), 62.0 (O*C*H$_2$CH$_3$), 47.1 (C-4), 41.8 (C-9), 27.3 (C-5), 21.9 (AcO), 14.0 (OCH$_2$*C*H$_3$). Anal. Calcd for $C_{30}H_{29}NO_6$: C, 72.13; H, 5.85; N, 2.80. Found: C, 71.92; H, 5.76; N, 2.97.

4.4.9. 5-Benzyl-2,3,6,7-tetrahydro-2,2-diphenylfuro[3,2-*c*]pyridin-4(5*H*)-one (5ah). R_f=0.40 (chloroform/methanol 98:2 v/v); yellow oil; IR ν 1680 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (15H, m, arom. H), 4.58 (2H, s, Ph-CH_2), 3.67 (2H, t, J=2.2 Hz, H-3), 3.35 (2H, t, J=7.2 Hz, H-6), 2.55 (2H, tt, J=7.2, 2.2 Hz, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 164.7 (2C, C=O, C-7a), 144.8, 137.9 (3C, arom. C), 128.6, 128.4, 128.0, 127.7, 127.3, 125.7 (15C, arom. *C*H), 104.8 (C-3a), 95.4 (C-2), 48.9 (Ph-*C*H$_2$), 44.3 (C-6), 42.0 (C-3), 23.3 (C-7). FAB HRMS (acetone–NBA) calcd for $C_{26}H_{23}NO_2$ 382.1807 (M+1). Found 382.1812.

4.4.10. 5-Benzyl-2,3,6,7-tetrahydro-2,2-bis(4-methylphenyl)furo[3,2-*c*]pyridin-4(5*H*)-one (5bh). R_f=0.44 (chloroform/methanol 98:2 v/v); yellow oil; IR ν 1678 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.10 (13H, m, arom. H), 4.57 (2H, s, Ph-CH_2), 3.63 (2H, t, J=1.5 Hz, H-3), 3.33 (2H, t, J=7.2 Hz, H-6), 2.52 (2H, tt, J=7.16, 1.5 Hz, H-7), 2.29 (6H, s, Ph-CH_3×2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 164.5 (2C, C=O, C-7a), 141.9, 137.8, 137.1 (5C, arom. C), 129.0, 128.6, 128.0, 127.3, 125.7 (13C, arom. *C*H), 104.6 (C-3a), 95.3 (C-2), 48.8 (Ph-*C*H$_2$), 44.1 (C-6), 41.8 (C-3), 23.2 (C-7), 20.8 (Ph-*C*H$_3$). FAB HRMS (acetone–NBA) calcd for $C_{28}H_{28}NO_2$ 410.2120 (M+1). Found 410.2080.

4.4.11. 5-Benzyl-2,3,6,7-tetrahydro-2,2-bis(4-methoxyphenyl)furo[3,2-*c*]pyridin-4(5*H*)-one (5ch). R_f=0.48 (chloroform/methanol 98:2 v/v); yellow oil; IR ν 1674 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.25 (9H, m, arom. H), 6.86 (4H, dd, J=8.6, 1.3 Hz, arom. H), 4.60 (2H, s, Ph-CH_2), 3.79 (6H, d, J=1.3 Hz, OCH_3×2), 3.60 (2H, t, J=1.5 Hz, H-3), 3.39 (2H, t, J=7.3 Hz, H-6), 2.56 (2H, tt, J=7.3, 1.5 Hz, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 164.6 (2C, C=O, C-7a), 158.9, 137.9, 137.1 (5C, arom. C), 128.8, 128.5, 128.0, 127.2, 127.1, 113.5 (13C, arom. *C*H), 104.8 (C-3a), 95.3 (C-2), 55.2 (2C, O*C*H$_3$), 48.9 (Ph-*C*H$_2$), 44.3 (C-6), 42.0 (C-3), 23.4 (C-7). FAB HRMS (acetone–NBA) calcd for $C_{28}H_{28}NO_4$ 442.2018 (M+1). Found 442.2050.

4.4.12. 5-Benzyl-2,2-bis(4-chlorophenyl)-2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(5*H*)-one (5dh). R_f=0.42 (chloroform/methanol 98:2 v/v); colorless microcrystals (from ethyl acetate); mp 172.0 °C; IR ν 1684 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.24 (13H, m, arom. H), 4.59 (2H, s, Ph-CH_2), 3.59 (2H, t, J=2.2 Hz, H-3), 3.40 (2H, t, J=7.2 Hz, H-6), 2.59 (2H, tt, J=7.2, 2.2 Hz, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 164.4 (2C, C=O, C-7a), 142.8, 137.7, 133.7 (5C, arom. C), 128.6, 128.5, 128.0, 127.3, 127.1 (13C, arom. CH), 104.9 (C-3a), 94.3 (C-2), 48.9 (Ph-*C*H$_2$), 44.2 (C-6), 41.8 (C-3), 23.2 (C-7). Anal. Calcd for $C_{26}H_{26}Cl_2NO_2$: C, 69.34; H, 4.70; N, 3.11. Found: C, 69.42; H, 4.59; N, 3.21.

4.4.13. 2,3,6,7-Tetrahydro-5-methyl-2,2-diphenylfuro-[3,2-*c*]pyridin-4(5*H*)-one (5ai). R_f=0.44 (chloroform/methanol 98:2 v/v); yellow oil; IR ν 1682 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.17 (10H, m, arom. H), 3.61 (2H, t, J=2.2 Hz, H-3), 3.46 (2H, t, J=7.3 Hz, H-6), 2.94 (3H, s, N-CH_3), 2.65 (2H, tt, J=7.3, 2.2 Hz, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 164.5 (2C, C=O, C-7a), 144.8 (2C, arom. C), 128.4, 127.7, 125.7 (10C, arom. *C*H), 105.1 (C-3a), 95.4 (C-2), 47.2 (C-6), 41.9 (C-3), 33.7

(N-CH_3), 23.3 (C-7). FAB HRMS (acetone–NBA) calcd for $C_{20}H_{20}NO_2$ 306.1494 (M+1). Found 306.1490.

4.4.14. 5-Ethyl-2,3,6,7-tetrahydro-2,2-diphenylfuro[3,2-*c*]pyridin-4(5*H*)-one (5aj). R_f=0.58 (chloroform/methanol 97:3 v/v); yellow oil; IR ν 1682 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.24 (10H, m, arom. H), 3.61 (2H, t, J=2.2 Hz, H-3), 3.49 (2H, t, J=7.2 Hz, H-6), 3.43 (2H, q, J=7.2 Hz, N-CH_2CH$_3$), 2.64 (2H, tt, J=7.2, 2.2 Hz, H-7), 1.11 (2H, t, J=7.2 Hz, N-CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 164.4 (2C, C=O, C-7a), 144.9 (2C, arom. C), 128.4, 127.6, 125.8 (10C, arom. *C*H), 105.4 (C-3a), 95.4 (C-2), 44.5 (N-*C*H$_2$CH$_3$), 42.0 (C-6), 40.6 (C-3), 23.5 (C-7), 13.0 (N-CH$_2$*C*H$_3$). FAB HRMS (acetone–NBA) calcd for $C_{21}H_{22}NO_2$ 320.1651 (M+1). Found 320.1649.

4.4.15. 2,3,6,7-Tetrahydro-2,2-diphenyl-5-propylfuro[3,2-*c*]pyridin-4(5*H*)-one (5ak). R_f=0.45 (chloroform/methanol 97:3 v/v); yellow oil; IR ν 1682 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.24 (10H, m, arom. H), 3.61 (2H, t, J=2.2 Hz, H-3), 3.48 (2H, t, J=7.2 Hz, H-6), 3.34 (2H, t, J=7.2 Hz, N-CH_2CH$_2$CH$_3$), 2.67 (2H, tt, J=7.2, 2.2 Hz, H-7), 1.54 (2H, sex, J=7.2 Hz, N-CH$_2$CH_2-CH$_3$), 0.90 (2H, t, J=7.2 Hz, N-CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 164.3 (2C, C=O, C-7a), 144.9 (2C, arom. C), 128.3, 127.6, 125.7 (10C, arom. *C*H), 105.3 (C-3a), 95.3 (C-2), 47.5 (N-*C*H$_2$CH$_2$CH$_3$), 45.1 (C-6), 41.9 (C-3), 23.5 (C-7), 21.1 (N-CH$_2$*C*H$_2$CH$_3$), 11.3 (N-CH$_2$CH$_2$-*C*H$_3$). FAB HRMS (acetone–NBA) calcd for $C_{22}H_{24}NO_2$ 334.1807 (M+1). Found 334.1805.

4.4.16. 2,3,6,7-Tetrahydro-2,2-diphenyl-5-isopropylfuro[3,2-*c*]pyridin-4(5*H*)-one (5al). R_f=0.59 (chloroform/methanol 97:3 v/v); yellow oil; IR ν 1682 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.24 (10H, m, arom. H), 4.84 (1H, sep, J=6.8 Hz, N-C*H*<), 3.61 (2H, t, J=2.2 Hz, H-3), 3.38 (2H, t, J=7.2 Hz, H-6), 2.58 (2H, tt, J=7.2, 2.2 Hz, H-7), 1.11 (6H, d, J=6.8 Hz, N-CH<(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 164.2 (2C, C=O, C-7a), 145.0 (2C, arom. C), 128.4, 127.6, 125.8 (10C, arom. *C*H), 105.6 (C-3a), 95.3 (C-2), 42.5 (N-*C*H<), 42.1 (C-6), 38.2 (C-3), 23.7 (C-7), 19.9 (2C, N-CH<(*C*H$_3$)$_2$). FAB HRMS (acetone–NBA) calcd for $C_{22}H_{24}NO_2$ 334.1807 (M+1). Found 334.1803.

4.4.17. 2,3,6,7-Tetrahydro-2,2,5-triphenylfuro[3,2-*c*]pyridin-4(5*H*)-one (5am). R_f=0.41 (chloroform/methanol 98:2 v/v); colorless microcrystals (from ethyl acetate); mp 155.0 °C; IR ν 1676 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.15 (15H, m, arom. H), 3.89 (2H, t, J=7.0 Hz, H-6), 3.67 (2H, t, J=2.0 Hz, H-3), 2.73 (2H, tt, J=7.0, 2.0 Hz, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 164.8 (2C, C=O, C-7a), 144.6, 142.6 (3C, arom. C), 128.6, 128.3, 127.6, 125.6, 125.4, 125.2 (15C, arom. *C*H), 105.6 (C-3a), 95.7 (C-2), 48.0 (C-6), 41.8 (C-3), 23.8 (C-7). Anal. Calcd for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.57; H, 5.55; N, 3.88.

4.4.18. 7-Benzyl-2,3,6,7-tetrahydro-2,2-diphenylfuro[2,3-*b*]pyridin-4(5*H*)-one (6ah). R_f=0.22 (diethyl ether/methanol 97:3 v/v); yellow oil; IR ν 1641 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.19 (15H, m, arom. H), 4.63 (2H, s, Ph-CH_2), 3.67 (2H, s, H-3), 3.41 (2H, t, J=7.3 Hz, H-6), 2.44 (2H, t, J=7.34 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9 (C=O), 168.1 (C-7a), 143.8, 135.6 (3C, arom. C), 128.9, 128.4, 128.0, 127.9, 127.7, 125.7 (15C, arom. *C*H), 95.7 (C-3a), 88.7 (C-2), 52.1 (Ph-*C*H$_2$), 46.8 (C-6), 40.2 (C-3), 35.1 (C-5). FAB HRMS (acetone–NBA) calcd for $C_{26}H_{24}NO_2$ 382.1807 (M+1). Found 382.1820.

4.4.19. 7-Benzyl-2,2-bis(4-chlorophenyl)-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridin-4(5*H*)-one (6dh). R_f=0.23 (chloroform/methanol 98:2 v/v); yellow oil; IR ν 1647 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.15 (13H, m, arom. H), 4.59 (2H, s, Ph-CH_2), 3.59 (2H, s, H-3), 3.44 (2H, t, J=7.2 Hz, H-6), 2.45 (2H, t, J=7.2 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9 (C=O), 167.7 (C-7a), 141.8, 135.5, 134.2 (5C, arom. C), 128.9, 128.7, 128.1, 127.5, 127.2 (13C, arom. *C*H), 94.6 (C-3a), 88.2 (C-2), 52.2 (Ph-*C*H$_2$), 47.0 (C-6), 40.1 (C-3), 35.1 (C-5). FAB HRMS (acetone–NBA) calcd for $C_{26}H_{22}Cl_2NO_2$ 450.1028 (M+1). Found 450.1031.

4.4.20. 2,3,6,7-Tetrahydro-2,2-diphenyl-7-propylfuro[2,3-*b*]pyridin-4(5*H*)-one (6ak). R_f=0.22 (chloroform/methanol 98:2 v/v); colorless needles (from chloroform/hexane); mp 128–129 °C; IR ν 1641 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (10H, m, arom. H), 3.64 (2H, s, H-3), 3.48 (2H, t, J=7.3 Hz, H-6), 3.42 (2H, t, J=7.3 Hz, N-CH_2CH$_2$CH$_3$), 2.46 (2H, t, J=7.3 Hz, H-6), 1.65 (2H, sex, J=7.3 Hz, N-CH$_2$CH_2CH$_3$), 0.94 (3H, t, J=7.3 Hz, N-CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.4 (C=O), 168.3 (C-7a), 143.9 (2C, arom. C), 128.3, 127.8, 125.6 (10C, arom. *C*H), 95.2 (C-3a), 88.0 (C-2), 49.9 (N-*C*H$_2$CH$_2$CH$_3$), 46.8 (C-6), 40.2 (C-3), 35.1 (C-5), 21.2 (N-CH$_2$*C*H$_2$CH$_3$), 11.2 (N-CH$_2$CH$_2$*C*H$_3$). Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.23; H, 6.87; N, 4.21.

4.4.21. 2,3,6,7-Tetrahydro-2,2-diphenyl-7-isopropylfuro[2,3-*b*]pyridin-4(5*H*)-one (6al). R_f=0.27 (chloroform/methanol 97:3 v/v); yellow oil; IR ν 1636 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.20 (10H, m, arom. H), 4.40 (1H, sep, J=6.8 Hz, N-C*H*<), 3.63 (2H, s, H-3), 3.40 (2H, t, J=7.3 Hz, H-6), 2.43 (2H, t, J=7.3 Hz, H-5), 1.26 (6H, d, J=6.8 Hz, N-CH<(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.7 (C=O), 168.0 (C-7a), 144.1 (2C, arom. C), 128.4, 127.9, 125.7 (10C, arom. *C*H), 95.2 (C-3a), 88.8 (C-2), 48.0 (N-*C*H<), 40.7 (C-6), 40.2 (C-3), 35.2 (C-5), 20.2 (2C, N-CH<(*C*H$_3$)$_2$). FAB HRMS (acetone–NBA) calcd for $C_{22}H_{24}NO_2$ 334.1807 (M+1). Found 334.1802.

4.4.22. 2,3,6,7-Tetrahydro-2,2,7-triphenylfuro[2,3-*b*]pyridin-4(5*H*)-one (6am). R_f=0.36 (chloroform/methanol 98:2 v/v); yellow oil; IR ν 1636 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.25 (10H, m, arom. H), 3.96 (2H, t, J=7.0 Hz, H-6), 3.70 (2H, s, H-3), 2.61 (2H, t, J=7.0 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.6 (C=O), 166.2 (C-7a), 143.8, 141.0 (3C, arom. C), 129.0, 128.3, 127.8, 126.0, 125.5, 123.3 (15C, arom. *C*H), 95.6 (C-3a), 90.2 (C-2), 50.1 (C-6), 39.8 (C-3), 35.5 (C-5). FAB HRMS (acetone–NBA) calcd for $C_{25}H_{22}NO_4$ 368.1651 (M+1). Found 368.1648.

4.5. Some reactions of the azabicyclic peroxides

The dioxane **3ca** (0.5 mmol) and acetic acid (20 mL) were placed in a 50 mL flask and the mixture was heated at 100 °C with stirring until **3ca** was completely consumed (21 h). The solvent was removed and the residue was treated with water. The aqueous mixture was extracted with chloroform (10 mL×3). The combined extracts were dried over anhydrous magnesium sulfate, and then concentrated to dryness. The residue was separated by TLC (wakogel B-10) while eluting with 2% methanol–chloroform, giving **7** in quantitative yield. The dioxane **3aa**, **3ca** or **3ch** (0.5 mmol) was also heated in acetic anhydride (20 mL) at 100 °C with stirring in the presence of 4-dimethylaminopyridine (0.5 mmol) until the dioxane was completely consumed (12–25 h). The solvent was removed in vacuo and the residue was triturated with water followed by extraction with chloroform (10 mL×3). The combined extracts were washed with water, a saturated aqueous solution of sodium hydrogencarbonate, dried over anhydrous magnesium sulfate, and then concentrated to dryness. The products were purified by TLC (wakogel B-10) using 2% methanol–chloroform as the developing solvent, and **8**, **9**, and **10** were obtained in 59%, quantitative, and 68% yields, respectively.

4.5.1. Ethyl 1-benzyl-3-[2-(4-methoxyphenyl)-2-oxoethyl]piperidine-2,4-dione-3-carboxylate (7). R_f= 0.51 (chloroform/methanol 98:2 v/v); yellow oil; IR ν 1749, 1717, 1647 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (2H, d, J=8.8 Hz, arom. H), 7.96–7.27 (5H, m, arom. H), 6.91 (2H, d, J=8.8 Hz, arom. H), 4.98 (1H, d, J= 14.9 Hz, Ph-CH_2), 4.52 (1H, d, J=14.9 Hz, Ph-CH_2), 4.36 (1H, d, J=18.0 Hz, CH_2), 4.20 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 4.16 (1H, d, J=18.0 Hz, CH$_2$), 3.84 (3H, s, OCH_3), 3.77–3.67 (2H, m, H-6), 2.97 (2H, ddt, J=35.6, 16.5, 6.2 Hz, H-5), 1.24 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 195.7, 166.7, 165.8 (4C, C=O), 163.9, 136.4 (2C, arom. C), 130.6 (arom. *C*H), 128.7 (arom. C), 128.6, 127.9, 127.6, 113.7 (8C, arom. *C*H), 65.5 (C-3), 62.9 (O*C*H$_2$CH$_3$), 55.5 (O*C*H$_3$), 51.0 (Ph-*C*H$_2$), 43.8 (*C*H$_2$), 42.1 (C-6), 37.5 (C-5), 13.9 (OCH$_2$*C*H$_3$). FAB HRMS (acetone–NBA) calcd for $C_{24}H_{26}NO_6$ 424.1760 (M+1). Found 424.1762.

4.5.2. Ethyl 1-acetoxy-8-benzyl-4,4-diphenyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (8). R_f= 0.64 (diethyl ether/hexane 8:2 v/v); colorless prisms (from ethyl acetate); mp 165.0 °C; IR ν 1761 (C=O), 1744 (C=O), 1643 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63–7.02 (15H, m, arom. H), 4.79 (1H, d, J=15.1 Hz, Ph-CH_2), 4.35–4.22 (2H, m, OCH_2CH$_3$), 3.62 (1H, d, J=14.7 Hz, H-5), 3.44 (1H, d, 14.7 Hz, H-5), 3.05–2.71 (4H, m, Ph-CH_2, H-9, H-10), 2.38–2.12 (1H, m, H-10), 2.07 (3H, s, Ac), 1.27 (3H, t, J=7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 167.6, 165.5 (3C, C=O), 142.5, 139.1, 136.0 (3C, arom. C), 128.4, 128.1, 127.5, 127.4, 127.3, 127.2, 125.7 (15C, arom. *C*H), 100.8 (C-1), 85.0 (C-4), 62.1 (O*C*H$_2$CH$_3$), 54.6 (C-6), 48.9 (Ph-*C*H$_2$), 41.2 (C-9), 33.3 (C-5), 26.4 (C-10), 21.7 (Ac), 13.8 (OCH$_2$*C*H$_3$). Anal. Calcd for $C_{31}H_{31}NO_7$: C, 70.31; H, 5.90; N, 2.64. Found: C, 70.49; H, 5.86; N, 2.70.

4.5.3. Ethyl 7a-acetoxy-5-benzyl-3a,4,5,6,7,7a-hexahydro-2-(4-methoxyphenyl)-4-oxo-furo[3,2-*c*]pyridine-3a-carboxylate (9). R_f=0.33 (chloroform/methanol 98:2 v/v); colorless prisms (from ethyl acetate); mp 146.0 °C; IR ν 1751, 1647 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (2H, d, J=7.5 Hz, arom. H), 7.33–7.21 (5H, m, arom. H), 6.88 (2H, d, J=7.5 Hz, arom. H), 5.76 (1H, s, H-9), 5.04 (1H, d, J=14.9 Hz, Ph-CH_2), 4.33 (2H, q, J=7.0 Hz, OCH_2CH$_3$), 4.16 (1H, d, J=14.9 Hz, Ph-CH_2), 3.83 (3H, s, OCH_3), 3.43 (2H, br d, J=12.7 Hz, H-4, H-5), 3.26–3.20 (1H, br d, J=12.7 Hz, H-4), 2.49–2.39 (1H, m, H-5), 1.99 (3H, s, Ac), 1.36 (3H, t, J=7.0 Hz, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 167.4, 166.4 (3C, C=O), 160.7 (arom. C), 157.0 (C-8), 136.1 (arom. C), 128.6, 127.5, 127.4, 127.2 (7C, arom. *C*H), 121.3 (arom. C), 113.7 (2C, arom. *C*H), 108.7 (C-6), 95.7 (C-9), 69.8 (C-1), 61.8 (O*C*H$_2$CH$_3$), 55.2 (O*C*H$_3$), 49.7 (Ph-*C*H$_2$), 42.5 (C-4), 28.5 (C-5), 21.8 (Ac), 14.1 (OCH$_2$*C*H$_3$). Anal. Calcd for $C_{26}H_{27}NO_7$: C, 67.09; H, 5.85; N, 3.01. Found: C, 67.03; H, 5.88; N, 3.12.

4.5.4. 5-Benzyl-6,7-dihydro-2-(4-methoxyphenyl)furo[3,2-*c*]pyridin-4(5*H*)-one (10). R_f=0.49 (chloroform/methanol 97:2 v/v); Yellow oil; IR ν 1655 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (2H, d, J=8.6 Hz, arom. H), 7.32–7.26 (4H, m, arom. H), 6.92 (2H, d, J=8.6 Hz, arom. H), 6.85 (1H, s, arom. H), 4.71 (2H, s, Ph-CH_2), 3.83 (3H, s, OCH_3), 3.56 (2H, t, J=7.2 Hz, H-6), 2.97 (2H, t, J=7.2 Hz, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (C=O), 159.3, 156.7, 154.4 (3C, arom. C, C-2, C-7a), 137.6 (arom. C), 128.6, 127.4, 127.9, 125.2 (7C, arom. *C*H), 123.1 (1C, arom. C), 117.5 (C-3a), 114.2 (2C, arom. *C*H), 101.4 (C-3), 55.3 (O*C*H$_3$), 49.2 (Ph-*C*H$_2$), 45.4 (C-6), 23.1 (C-7). FAB HRMS (acetone–NBA) calcd for $C_{21}H_{19}NO_3$ 333.1365 (M). Found 333.1360.

4.6. X-ray crystallographic study

All measurements were made using a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo Kα radiation (λ=0.71069 Å). The data reductions were carried out by the PROCESS-AUTO program package, and Lorentz and polarization corrections were performed. Corrections for the secondary extinctions were applied. The structures were solved by the direct method and were refined on SIR-92.[19] The refinements were done by the least-squares full matrix method, with anisotropic displacement parameters for all non-hydrogen atoms. The hydrogen atoms were included but not refined. All calculations were performed using the teXsan[20] crystallographic software package of Molecular Structure Corporation. The crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 272197. 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.

This research was supported by Grants-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' No. 13029088 and No.14044078, from the Ministry of Education, Culture,

Sports, Science and Technology, Japan, and also by Grants-in-Aid for Scientific Research, No. 13640539 and No. 15550039, from the Japan Society for the Promotion of Science. We gratefully acknowledge Professor Teruo Shinmyozu and Dr. Mikio Yasutake, Institute for Materials Chemistry and Engineering, Kyushu University, Japan, for their crystallographic assistance and the measurement of high resolution FAB mass spectrometry.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.09.029. X-ray structural information for **3aa** is collected in Tables 3. Copies of FAB MS, IR, ^{1}H NMR, ^{13}C NMR, and DEPT spectra for **3aa**, **4aa**, **5ah**, and **6ah**.

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Tetrahedron 61 (2005) 11125–11131
Tetrahedron

Facile preparation of organozinc bromides using electrogenerated highly reactive zinc and its use in cross-coupling reaction

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Received 1 August 2005; revised 9 September 2005; accepted 12 September 2005

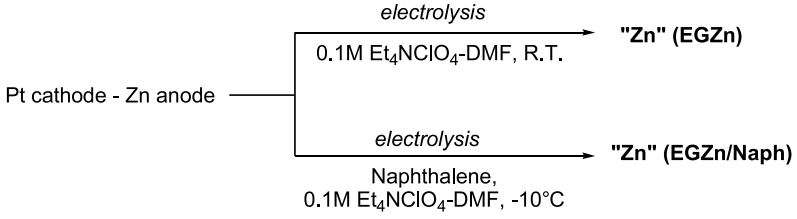
Available online 27 September 2005

Abstract—Highly reactive zinc was readily prepared by electrolysis of a DMF solution containing pyrene as a mediator with a platinum cathode and a zinc anode. Preferential reduction of pyrene occurred to generate the corresponding radical anion, which reduced zinc ions generated from anodic dissolution to give zero valent zinc with high reactivity. The reactive zinc was successfully used for an efficient transformation of bromoalkanes into the corresponding organozinc bromides. Organozinc bromides obtained were further used successfully in Pd-catalyzed cross-coupling reaction with various aryl iodides and bromides.

1. Introduction

Organozinc compounds are very useful organometallic compounds for carbon–carbon bond forming reactions.[1] Organozinc halides can usually be prepared by direct insertion of zinc metal into organic halides,[1b] but commercially available zinc metal is generally poorly reactive. Therefore, activation of the metal is necessary for preparation of organozinc halides. Successful activations such as reduction of zinc salts with alkaline metal or alkali metal naphthalenide have been reported by Rieke et al.[2] Reactive zinc was also prepared by Périchon and his colleagues using electrochemical method.[3] We have also developed a different electrochemical method for preparation of reactive zinc. Our simple preparation method using a platinum cathode and a zinc anode gave an aggregation of fine zinc particles with a large surface area.[4] The electrochemically generated reactive zinc (EGZn) reacts with various functionalized alkyl iodides to give the corresponding organozinc iodides. Subsequent Pd-catalyzed cross-coupling reaction with aryl halides proceeded efficiently to give the corresponding cross-coupled products in high yields.[5] However, organozinc bromides were only obtained in very low yields from the corresponding organic bromides when EGZn was used in the reaction. We have developed a new electrochemical method to prepare zinc metal with much higher reactivity (EGZn/Naph) than that of EGZn by using naphthalene as a mediator (Scheme 1).[6] Reaction of EGZn/Naph with ethyl 2-bromoacrylate efficiently gave the corresponding organozinc bromide, which could be successfully used for palladium-catalyzed cross-coupling reactions with various aryl iodides to give ethyl 2-arylpropenoates.[6]

We carried out a detailed study on preparation of a highly reactive zinc (EGZn/arene) using various arene compounds as mediators and its use in a transformation of bromoalkanes to the corresponding organozinc bromides. In this paper, we



Scheme 1.

Keywords: Electrolysis; Reactive zinc; Coupling reactions; Palladium catalyst.
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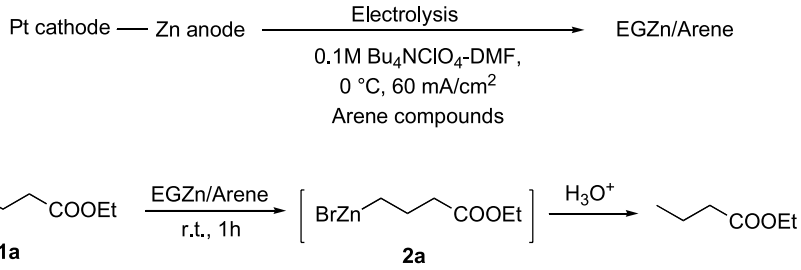
doi:10.1016/j.tet.2005.09.031



Scheme 2.

report those detailed results and also the results on palladium-catalyzed cross-coupling reactions of organozinc bromides with aryl iodides and bromide.

2. Results and discussion

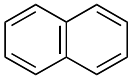
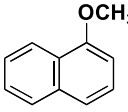
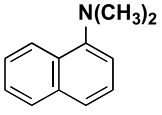
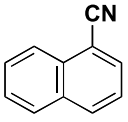
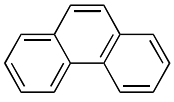
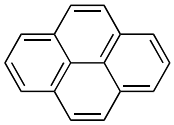
2.1. Preparation and reactivity of electrochemically generated reactive zinc

Electrogenerated zinc was readily prepared by electrolysis of a DMF solution containing 0.1 M Bu_4NClO_4 in the presence of an arene compound in a one-compartment cell fitted with a platinum plate cathode (2×2 cm^2) and a zinc plate anode (2×2 cm^2). Electrolysis was carried out at constant current under a nitrogen atmosphere. Reactivity of the electrogenerated zinc (EGZn/arene) was estimated in the following manner. Ethyl 4-bromobutanoate **1a** (5 mmol) was reacted with the electrogenerated zinc (6 mmol)[7] at rt for 1 h, and unreacted **1a** was determined by GC analysis after quenching of the organozinc bromide **2a** with diluted HCl. Conversion of **1a** into **2a** estimated from the analysis was regarded as a reactivity index of the electrogenerated zinc (Scheme 2).

Effects of arene mediators on the reactivity of electrogenerated zinc are summarized in Table 1. Reactivity of EGZn obtained by electrolysis in the absence of any arene compounds was low, and only 25% of **1a** was transformed into **2a** when the EGZn was used (entry 1). Higher reactivity was observed when EGZn/Naph generated by electrolysis at 0 °C in the presence of naphthalene mediator was used (entry 3). When EGZn/Naph generated by using 2 or 1 equiv of naphthalene to zinc metal was used, **1a** could be converted into **2a** in 95–93% yield (entries 3 and 4). However, a lowering of its reactivity was observed when an electrogenerated zinc was prepared by the use of 0.5 and 0.25 equiv of naphthalene (entries 5 and 6). Similar results were obtained when 1-methoxynaphthalene or 1-(*N*,*N*-dimethylamino)naphthalene was used (entries 7–12). Phenanthrene worked as a mediator (entries 14–16), and the best results were obtained by the use of pyrene. The electrogenerated reactive zinc prepared by electrolysis in the presence of pyrene (EGZn/pyrene) converted **1a** into the corresponding organozinc bromide **2a** in an almost quantitative yield (entry 17). Furthermore, EGZn/pyrene prepared by the use of 0.5 equiv of pyrene to zinc metal was very reactive (entry 18), and its high reactivity was maintained even when 0.25 equiv of pyrene was used as a mediator (entry 20). Consequently, pyrene was found to be the most effective mediator.

We have reported that there is a correlation between the specific surface area of zinc metal and its reactivity in the prenylation of acetophenone. EGZn having a larger specific surface area showed higher reactivity than that having a smaller surface area and was prepared by electrolysis at a smaller current density.[4b] Accordingly, three kinds of EGZn/pyrene were prepared by electrolysis at current densities of 2.5, 37.5 and 60 mA/cm^2. It appeared that the reactivity of EGZn was lowered in the present case when

Table 1. Effects of various arene compounds on the reactivity of EGZn/arene[a]

Entry	Arene compound[b]	Equiv[c]	Conversion (%)[d]
1[e]	None	—	25
2[e]		2.0	52
3		2.0	95
4		1.0	93
5		0.5	74
6		0.25	63
7		1.0	91
8		0.5	77
9		0.25	56
10		1	86
11		0.5	61
12		0.25	72
13		1.0	59
14		1.0	86
15		0.5	72
16		0.25	45
17		1.0	99
18		0.5	99
19		0.4	94
20		0.25	89
21		0.1	30

[a] Electrolysis was carried out at 60 mA/cm^2 in 0.1 M Bu_4NClO_4–DMF (10 mL) using a Pt cathode (2×2 cm^2) and a Zn anode at 0 °C. An electricity of 2 F/mol was passed. The reactive zinc (6 mmol) was reacted with ethyl 4-bromobutanoate (5 mmol) for 1 h at rt.

[b] Reduction potentials were measured by cyclic voltammetry in 0.1 M Bu_4NClO_4–DMF using an Ag/Ag$^+$ reference electrode. Reduction peak potentials of naphthalene, 1-methoxynaphthalene, 1-dimethylaminonaphthalene, 1-cyanonaphthalene, phenanthrene and pyrene were -3.06, <-3.20, -3.07, -2.32, -3.00 and -2.59 V versus Ag/Ag$^+$, respectively.

[c] Equivalent of arene to zinc ion (6 mmol) by dissolution from zinc anode.

[d] Conversions of **1a** into **2a** were estimated by GC of unreacted **1a**.

[e] Electrolysis was carried out at rt.

Table 2. Effect of current density on the reactivity of EGZn/pyrene[a]

Entry	Current density (mA/cm^2)	Conversion (%)[b]
1	2.5	50
2	37.5	79
3	60.0	99

[a] Electrolysis was carried out at 0 °C in 0.1 M Bu_4NClO_4–DMF (10 mL) in the presence of 0.5 equiv of pyrene using a Pt cathode (2×2 cm^2) and a Zn anode. The reactive zinc (6 mmol) was reacted with ethyl 4-bromobutanoate (5 mmol) for 1 h at rt.
[b] Conversions of **1a** into **2a** were estimated by GC of unreacted **1a**.

current density was decreased. Consequently, electrolytic conditions using 0.5 equiv of pyrene with current density of 60 mA/cm^2 at 0 °C were employed as the optimal ones in the present study. EGZn/pyrene thus prepared was completely dispersed in the DMF solution since the zinc particles of EGZn/pyrene could not be collected by filtration. Although the detailed properties and structure of EGZn/pyrene are not clear at the present stage, it seems that EGZn/pyrene is an aggregation of much smaller zinc particles than that of EGZn prepared without addition of any arene mediators (Table 2).

2.2. Generation pathways of EGZn/arene

Probable pathways for generation of the reactive zinc EGZn/arene, EGZn/pyrene as one example in this case, are shown in Figure 1. At the cathode, a one-electron reduction of a pyrene molecule readily occurred to give pyrene radical anions. On the other hand, at the anode, dissolution of the zinc anode occurred to give zinc ions (Zn^{2+}), which were reduced by the pyrene radical anions to give zero-valence highly reactive zinc, EGZn/pyrene (Fig. 1). These pathways are supported by the following experimental results. First, the current density of 60 mA/cm^2 flowed constantly at 0 °C in the presence of arene compounds, although the current flow stopped in a few minutes in the case of electrolysis in the absence of any arene. The formation of pyrene radical anions indicated by a wine-red color appeared at the cathode surface in the initial stage and the color of the electrolyte turned black immediately due to formation of zinc particles.

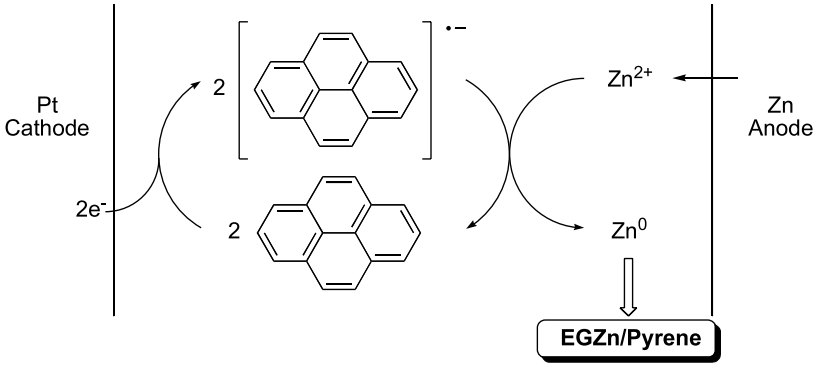


Figure 1.

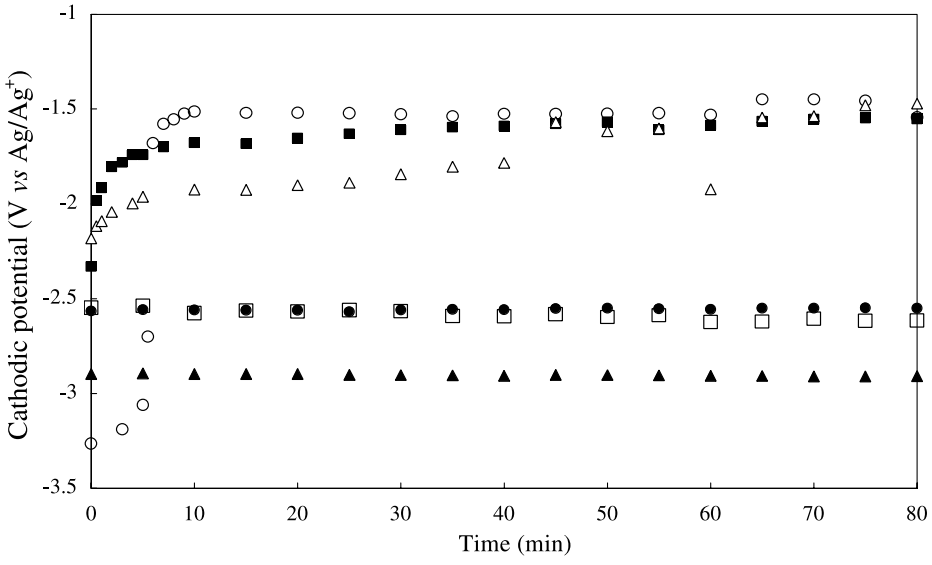
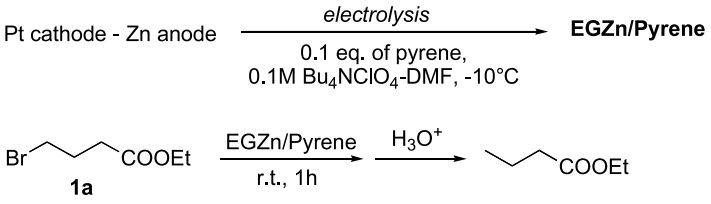


Figure 2. Cathode potential in the electrolysis using a platinum cathode and a zinc anode under various conditions. (○: in the absence of any additive, corresponding to the preparation of EGZn, ■: in the presence of $Zn(ClO_4)_2$ (6 mmol), △: in the presence of $Zn(ClO_4)_2$ (6 mmol) and pyrene (3 mmol), ●: in the presence of pyrene (6 mmol), corresponding to the preparation of EGZn/pyrene (Table 1, entry 17), □: in the presence of pyrene (3 mmol), corresponding to the preparation of EGZn/pyrene (Table 1, entry 18), ▲: in the presence of naphthalene (6 mmol), corresponding to the preparation of EGZn/Naph (Table 1, entry 4)).



Condition of electrolysis	Conversion of **1a** (%)
continueous electrolysis	30
intermittent electrolysis (on: 4 min, off: 2 min)	80
intermittent electrolysis (on: 4 min, off: 6 min)	82

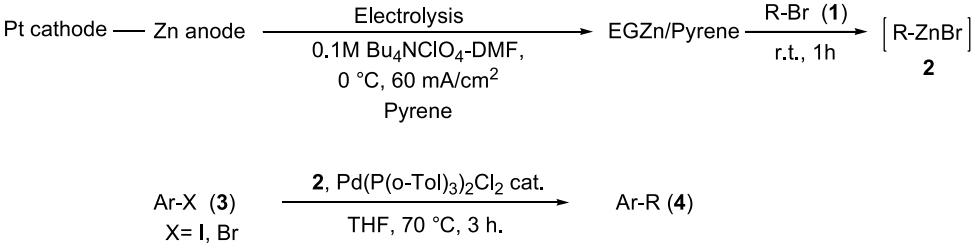
Scheme 3.

Second, a decrease in the amount of arene compound resulted in a lower reactivity of the zinc. Zero-valent zinc generated by direct reduction on the cathode surface showed lower reactivity than that of EGZn/arene (Table 1, entry 1). Third, the efficiency of reduction of pyrene was higher than that of other arene compounds. pyrene has a more positive reductive potential (-2.59 V vs Ag/Ag^+) than naphthalene and phenanthrene, the potentials, of which are nearly -3.0 V or more negative. Fourth, measurements of cathodic potential during various electrolyses are shown in Figure 2. Cathodic reaction in the presence of 1.0 or 0.5 equiv of pyrene to zinc metal (corresponding to the results of entries 17 and 18 in Table 1) proceeded nearly at the reductive potential of pyrene (dotted line with □ and ●). Similar results were obtained in the electrolysis using naphthalene (dotted line with ▲, corresponding to Table 1, entry 4). In contrast, cathodic reaction in the absence of any arene compounds proceeded at a much more positive potential (dotted line with ○). This potential corresponds to a reductive potential of zinc ions, which was confirmed by measurement of cathodic potential in the presence of zinc ions, $Zn(ClO_4)_2$ (dotted line with ■). Therefore, zinc ions from anodic dissolution were reduced by the pyrene radical anion in the bulk of electrolyte (Fig. 1). The reason for preferential reduction of pyrene molecules, in spite of its more negative reduction potential than that of zinc ions, is probably due to the great difference between initial concentrations of pyrene and zinc ion. The initial concentration of zinc ions is very low since they are generated gradually by electrolytic dissolution of the zinc metal anode. When the electrolysis was carried out in the presence of similar concentrations of zinc ions and pyrene, the cathodic potential was maintained at a more positive potential than that of pyrene (Fig. 2, dotted line with △).

Reactivity of EGZn/pyrene prepared by using 0.1 equiv of pyrene was low (Table 1, entry 21). Its reactivity can be drastically improved by intermittent electrolysis. The idea for this method comes from the preparation of Rieke zinc by lithium naphthalenide reduction of zinc chloride using a catalytic amount of naphthalene.[2a] In our case, the electrolysis was stopped and the solution was only stirred at constant intervals in order to completely reduce zinc ions formed by anodic dissolution with pyrene radical anions. Intermittent electrolysis was carried out by repeated electrolysis (4 min) and only stirring (2 min or 6 min) (Scheme 3).

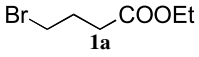
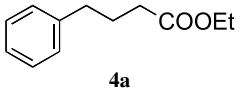
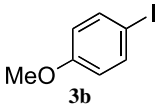
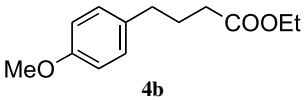
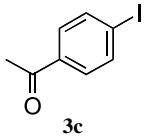
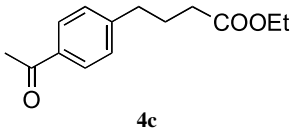
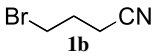
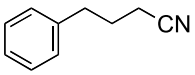
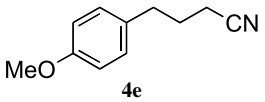
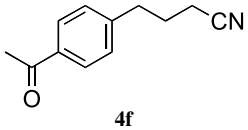
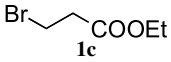
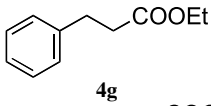
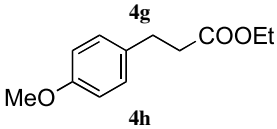
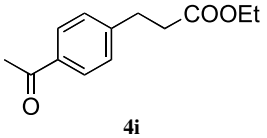
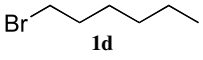
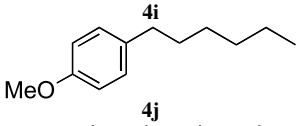
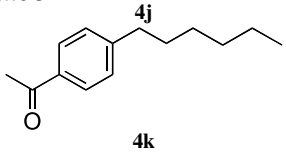
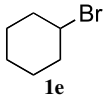
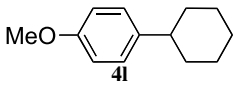
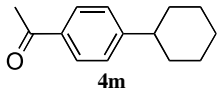
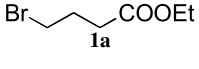
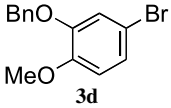
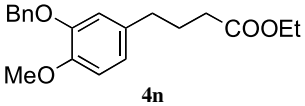
2.3. Use of EGZn/arene in the Pd-catalyzed cross-coupling reaction

Various alkyl bromides (**1**) were efficiently converted to the corresponding organozinc compounds (**2**) by reaction with EGZn/pyrene. Cross-coupling reactions of these organozinc compounds with aryl halides in the presence of a Pd catalyst[8] were examined (Scheme 4). Results are summarized in Table 3. Ethyl 4-bromobutanoate (**1a**), 4-bromobutanenitrile (**1b**) and ethyl 3-bromopropanonate (**1c**) could readily be converted to the corresponding organozinc compounds **2a**, **2b** and **2c** by reaction with EGZn/pyrene. Cross-coupling reaction of these organozinc compounds with iodobenzene itself and iodobenzenes having electron-donating group (**3b**) or electron-withdrawing group (**3c**) gave the desired products (**4a–i**) in 77–92% yields. The reaction of simple alkyl bromides (**1d** and **1e**) with EGZn/Naph and EGZn/pyrene also proceeded efficiently to give **2d** and **2e**, which were reacted with **3b** and **3c** to give the corresponding cross-coupling products (**4j–m**) in 67–85% yields. Transformation of organozinc compounds on a larger scale was also examined. A four-times greater amount of EGZn/pyrene was prepared and the reaction of EGZn/pyrene with a four-times greater amount of **1a** gave the corresponding organozinc compound **2a**, which was used in the cross-coupling reaction to give the desired



Scheme 4.

Table 3. Cross-coupling reaction of alkyl bromides with various aryl halides using electrogenerated highly reactive zinc (EGZn/pyrene)[a]

Entry	Alkyl bromide	Aryl halide	Product	Yield (%)[b]
1	 **1a**	 **3a**	 **4a**	81 (79)[c]
2		 **3b**	 **4b**	83 (75)[d]
3		 **3c**	 **4c**	78 (84)[d]
4	 **1b**	**3a**	 **4d**	83 (89)[d]
5		**3b**	 **4e**	89
6		**3c**	 **4f**	88
7[e]	 **1c**	**3a**	 **4g**	92
8[e]		**3b**	 **4h**	86
9[e]		**3c**	 **4i**	77
10	 **1d**	**3b**	 **4j**	77
11		**3c**	 **4k**	85
12	 **1e**	**3b**	 **4l**	67
13		**3c**	 **4m**	74 (76)[d]
14	 **1a**	 **3d**	 **4n**	80
15[f]				77

[a] A DMF solution of organozinc bromide (6.4 mL, corresponding to 3 mmol of organozinc bromide) was added to a THF solution (20 mL) containing aryl halides (2 mmol) and $Pd(P(o\text{-}Tol)_3)_2Cl_2$ (0.1 mmol) and the reaction mixture was stirred at 70 °C for 3 h.

[b] Isolated yields.

[c] Organozinc compound **2a** was prepared using EGZn/pyrene shown in Scheme 3.

[d] Yields of cross-coupling products using EGZn/Naph are shown in parantheses.

[e] Ethyl 3-bromopropanoate (**1c**) (5 mmol) was reacted at rt for 1 h with EGZn/pyrene (6 mmol).

[f] Ethyl 4-bromobutanoate (**1a**) (20 mmol) was reacted at rt for 1 h with EGZn/pyrene (24 mmol). A DMF solution of organozinc bromide was added to a THF solution containing **3d** (13 mmol) and $Pd(P(o\text{-}Tol)_3)_2Cl_2$ (0.72 mmol).

product **4n** in a yield of 77% (entry 15). EGZn/Naph could be used in the same way (Table 3, entries 2–4, 13). EGZn/pyrene prepared by using a catalytic amount of pyrene (Scheme 3) was also used successfully for the transformation into organozinc compounds, which was shown by the high yields of the product **4a** in the following cross-coupling reaction (Table 3, parenthesis in entry 1).

3. Conclusion

Electrochemical preparation of highly reactive zinc (EGZn/pyrene) could be achieved by using less than 1 equiv of pyrene mediator with a platinum cathode and a zinc anode. The generation mechanism of EGZn/pyrene was proposed on the basis of experimental results: that is, preferential reduction of pyrene occurs to give the radical anion of pyrene, which reduces zinc ion produced by anodic dissolution to generate zero valent zinc with high reactivity. Organozinc compounds were readily obtained from various alkyl bromides by their reaction with EGZn/pyrene under mild conditions. Palladium-catalyzed cross-coupling reaction of these organozinc compounds with aryl halides proceeded successfully to give the corresponding cross-coupling products in high yields.

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 FT NMR spectrometer (^{1}H, 270 MHz; ^{13}C, 67.8 MHz). Chemical shifts were represented as δ-values relative to the internal standard, tetramethylsilane. IR spectra were recorded on a JASCO IR-810 infrared spectrometer. High- and low-resolution mass spectra were determined with a JEOL JMS-AX500 or JEOL JMS-SX102A spectrometer. Thin-layer chromatography was carried out on a Merck Silica gel 60 PF_{254}. Cyclic voltammetry was performed with BAS-50W using an Ag/Ag^+ reference electrode, Pt working electrode and Pt wire counter electrode in 0.1 M Bu_4NClO_4–DMF solution. The reference electrode (RE-6) was purchased from BAS, Inc. and used after filled with 0.01 M $AgNO_3$/0.1 M Bu_4NClO_4/DMF solution. Measurement of cathode potential was carried out using a NICHIA potentio/galvanostat G1051EH.

4.2. Materials

Anhydrous *N*,*N*-dimethylformamide (DMF), functionalized alkylbromides (**1a**–**1d**), iodobenzene (**3a**), 4-iodoanisole (**3b**) and 4-iodoacetophenone (**3c**) were commercially available from Kanto Chemical, Inc. or Acros Organics, Inc. and were used without further purification. Tetrabutylammonium perchlorate (Bu_4NClO_4) was commercially available and was used after recrystallization from hexane and ethyl acetate. A zinc plate was commercially available (NILACO, Inc.) in more than 99.9% purity, and it was washed with 2 N HCl, methanol, and acetone and then dried before electrolysis.

4.2.1. 2-Benzyloxy-4-bromoanisole (3d). Methanesulfonyl chloride (11 mL, 143 mmol) was added at 0 °C to a solution of guaiacol (11 mL, 100 mmol) and pyridine (100 mL). The solution was kept in a refrigerator for 10 h. The reaction mixture was poured onto ice and extracted with Et_2O. The combined organic layers were washed with concentrated HCl, saturated $NaHCO_3$ aqueous solution and brine and then dried over $MgSO_4$. After evaporation of Et_2O, the crude product, (2-methoxyphenyl)methanesulfonate (20 g) was obtained and used without further purification in the next step. ^{1}H NMR ($CDCl_3$) δ 7.33–7.24 (2H, m), 7.02–6.95 (2H, m), 3.90 (3H, s), 3.18 (3H, s).

Bromination of 2-methoxyphenyl methanesulfonate was carried out according to the literature.[9] Recrystallization of the crude product from ethanol and CH_2Cl_2 gave 5-bromo-2-methoxyphenyl methanesulfonate: IR (neat) 1331, 1160, 1125, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (1H, d, J= 2.31 Hz), 7.41 (1H, dd, J=2.31, 8.58 Hz), 6.90 (1H, d, J= 8.58 Hz), 3.88 (3H, s), 3.20 (3H, s); ^{13}C NMR ($CDCl_3$) δ 150.85, 138.53, 131.02, 127.53, 114.14, 112.24, 56.21, 38.46; EIMS *m*/*z* (relative intensity) 282 (26), 280 (26), 203 (66), 201 (68), 94 (100), 79 (24), 57 (21); HRMS Calcd for $C_8H_9SO_4Br$ *m*/*z* 279.9404. Found *m*/*z* 279.9404.

Hydrolysis of 5-bromo-2-methoxyphenyl methanesulfonate was carried out as described below: to 6 N NaOH aqueous solution (50 mL), THF solution (4 mL) of the crude product of (5-bromo-2-methoxyphenyl) methanesulfonate (1 g) was added and reacted for 5 h under reflux. The reaction mixture was extracted with Et_2O after conversion to acidic aqueous solution with 6 N HCl. The combined organic layers were washed with water and brine and then dried over $MgSO_4$. After evaporation of Et_2O, the crude product, 5-bromo-2-methoxyphenol (0.75 g), was obtained and used without further purification in the next step. IR (neat) 3411, 1237, 1038, 623 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.07 (1H, d, J= 2.31 Hz), 6.46 (1H, dd, J=2.31, 8.58 Hz), 6.71 (1H, d, J= 8.58 Hz), 5.65 (1H, s), 3.87 (3H, s).

To a DMF (50 mL) solution of the crude 5-bromo-2-methoxyphenol (0.57 g), K_2CO_3 (0.19 g) and benzyl bromide (11.3 g) were added. The reaction mixture was heated for 12 h at 80 °C (temperature of oil bath). Water was added to dissolve residual K_2CO_3. The reaction mixture was extracted with Et_2O. The combined organic layers were washed with water, 2 N NaOH aqueous solution, saturated $Na_2S_2O_3$ aqueous solution and brine and then dried over $MgSO_4$. After evaporation of Et_2O, the crude product of 2-benzyloxy-4-bromoanisole (0.52 g) was obtained and recrystallized from ethanol: colorless needles; mp 111–112 °C; IR (neat) 1219, 1021, 622 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 7.45–7.31 (5H, m), 7.06–7.02 (2H, m), 6.76 (1H, d, J= 7.6 Hz), 5.11 (1H, s), 3.85 (3H, s); ^{13}C NMR ($CDCl_3$) δ 148.98, 148.93, 136.37, 128.57, 128.36, 128.01, 127.35, 123.94, 117.23, 113.05, 112.60, 112.49, 71.16, 56.10; EIMS *m*/*z* (relative intensity) 294(6), 292(6), 91(100), 65(7); HRMS Calcd for $C_{14}H_{13}O_2Br$ *m*/*z* 292.0098. Found *m*/*z* 292.0084.

4.3. Preparation of electrogenerated highly reactive zinc (EGZn/pyrene)

A one-compartment cell (26 mmol, 150 mm height)

equipped with a magnetic stirrer and two branched necks was used. The solvent and substrate were injected from a rubber septum of one neck. EGZn/pyrene (6 mmol) was prepared by the electrolysis of 0.1M Bu_4NClO_4–DMF solution (10 mL) containing pyrene (3 mmol) in a one-compartment cell fitted with a platinum plate cathode (2×2 cm^2) and a zinc plate anode (2×2 cm^2). Two electrodes were kept in parallel with a distance between them of about 10 mm. Electrolysis was carried out at 0 °C at a current density of 60 mA/cm^2 under nitrogen atmosphere for 80.4 min. The amount of EGZn/pyrene was estimated from the weight of dissolved zinc anode metal. A solution containing EGZn/pyrene was directly used for preparation of organozinc compounds after the zinc anode had been removed from the electrolysis cell.

4.4. General procedure for cross-coupling reaction using EGZn/pyrene

To a DMF solution containing EGZn/pyrene (6 mmol) was added alkyl bromide (**1**) (5 mmol) and the mixture was stirred at rt under nitrogen atmosphere. After 1 h, the DMF solution containing organozinc bromide (6.4 mL, corresponding to 3 mmol of RZnBr) was added to a THF solution of aryl iodide (2 mmol) and $Pd(P(o\text{-}Tol)_3)_2Cl_2$ (0.11 mmol), and the reaction mixture was stirred at 70 °C for 3 h. The resulting mixture was quenched with HCl solution and filtrated. The filtrate was extracted with diethyl ether (50 mL×3), and the combined organic layers were washed with water (100 mL×3), saturated $Na_2S_2O_3$ solution (100 mL×1) and saturated NaCl solution (100 mL×1) and then dried over $MgSO_4$. After evaporation of diethyl ether, the crude product was dissolved into CH_2Cl_2 (2–3 mL). The concentrated CH_2Cl_2 solution was carefully poured into methanol (10 mL). About 70% of pyrene was removed as a solid. After evaporation of the filtrate, the crude product was purified by thin layer chromatography with ethyl acetate–hexane (1/4) to give the corresponding cross-coupling product.

Cross-coupling products (**4a**–**m**) have already been confirmed by spectral data in our previous report.[5]

4.4.1. Ethyl 4-(3-benzyloxy-4-methoxyphenyl)butanoate (4n). Colorless oil; IR (neat) 1724, 1259, 1236, 1159, 1053 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 7.46–7.31 (5H, m), 6.82 (1H, d, J=8.6 Hz), 6.73 (1H, d, J=2.0 Hz), 6.71 (1H, d, J=2.0 Hz), 5.13 (2H, s), 4.12 (2H, q, J=7.3 Hz), 3.86 (3H, s), 2.54 (2H, t, J=7.6 Hz), 2.25 (2H, t, J=7.6 Hz), 1.86 (2H, quint, J=7.6 Hz), 1.25 (3H, t, J=7.3 Hz); ^{13}C NMR($CDCl_3$) δ 173.49, 147.98 (two signals), 137.18, 133.94, 128.43 (two signals), 127.73, 127.31 (two signals), 121.01, 114.72, 111.88, 71.02, 60.18, 56.05, 34.50, 33.48, 26.58, 14.22; EIMS *m/z* (relative intensity) 328(22), 237(8), 191(11), 163(9), 149(9), 91(100); HRMS Calcd for $C_{20}H_{24}O_4$ *m/z* 328.1674. Found *m/z* 328.1679.

References and notes

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The total synthesis and reassignment of stereochemistry of dragonamide

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Received 20 July 2005; revised 9 September 2005; accepted 12 September 2005

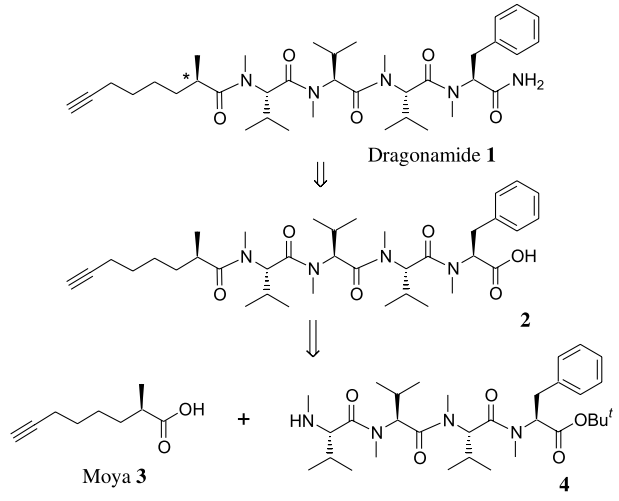
Available online 30 September 2005

Abstract—The first total synthesis of dragonamide is reported. The synthesis has led to a reassignment of the configuration at the stereogenic centre on the alkyne-bearing fragment of the molecule.

1. Introduction

The marine cyanobacteria have provided chemists and biologists with a plethora of natural products, with a wide array of structures and functional groups.[1–4] They have been a fertile source for new bioactive molecules, and many possess potent activity, across a broad spectrum of targets. Their diversity in both biological activity and in chemical complexity has made these secondary metabolites the focus of much work in recent years. We have had a great deal of interest in products isolated from marine cyanobacteria,[5] and given its cytotoxicity against several cell lines it was decided to undertake the synthesis of dragonamide **1** (Scheme 1 and Fig. 1).

Dragonamide **1** was isolated from the marine cyanobacterium *Lyngbya majuscula*, collected at Boca del Drago Beach, Panama, and its structure was determined.[6] It is a structurally unusual natural product insofar as it has the 2-substituted alkynoate unit. The stereochemistry of this unit was assigned by degradation of the peptide chain, isolation and hydrogenation of the acid and correlation to previous work (centre marked * is (*R*) as reported). We would now like to amend the stereochemistry of the alkynoate fragment.



Scheme 1.

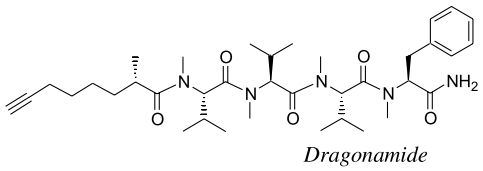


Figure 1.

2. Results and discussion

In our retrosynthetic analysis, dragonamide **1** was deconstructed into two parts: the moya **3** and the protected tetrapeptide **4** (Scheme 1).

Keywords: Stereochemistry; Dragonamide; Tetrapeptide.
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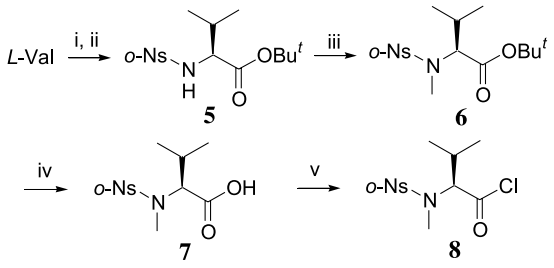
doi:10.1016/j.tet.2005.09.040

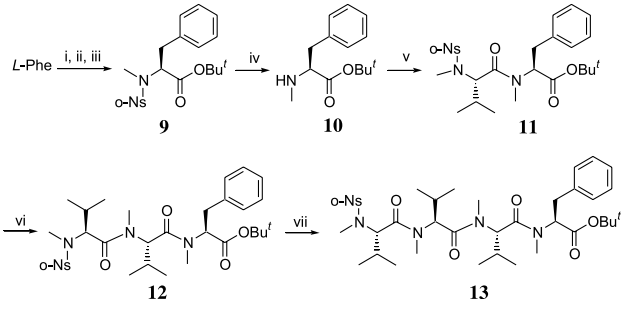
2.1. Synthesis of tetrapeptide 4

The synthesis started with (*S*)-valine, which was converted into its *t*-butyl ester using *tert*-butyl acetate and perchloric acid (Scheme 2).[7] It was then successively protected as its 2-nitrobenzenesulfonamide **5**, by treating it with *o*-nitrobenzenesufonyl chloride in the presence of base.[8] This method of protection was chosen as it allows the nitrogen to be alkylated under mild conditions, and it is readily removable. The alkylation was performed by treating **5** with methyl iodide in DMF with potassium carbonate as base,[9] to furnish **6**. Once the alkylation had been performed, **6** was treated with TFA to produce the free acid **7**, which was readily converted into its acyl chloride **8** by reacting it with oxalyl chloride and DMF in dichloromethane.



Scheme 2. Reagents and conditions: (i) AcOBu^t, $HClO_4$, 91%; (ii) 2-nitrobenzenesufonyl chloride, Et_3N, CH_2Cl_2, 91%; (iii) CH_3I, K_2CO_3, DMF, 77%; (iv) TFA–CH_2Cl_2; (v) $(COCl)_2$, CH_2Cl_2, DMF.

(*S*)-phenylalanine was treated in an analogous manner to (*S*)-valine above and was converted into, sequentially, its *t*-butyl ester, 2-nitrobenzenesulfonamide and *N*-methyl derivative **9**, with all steps proceeding smoothly (Scheme 3). The sulfonamide group was readily removed at this stage by treating **9** with mercaptoacetic acid in DMF under basic conditions, to give amino ester **10**.[10]

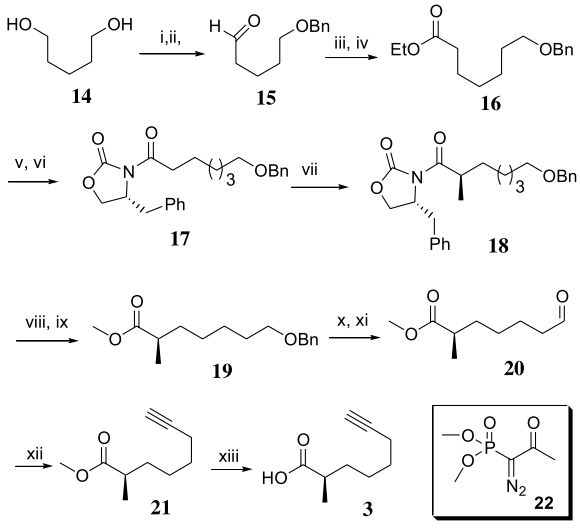


Scheme 3. Reagents and conditions: (i) AcOBu^t, $HClO_4$, 90%; (ii) *o*-nitrobenzenesufonyl chloride, Et_3N, CH_2Cl_2, 93%; (iii) CH_3I, K_2CO_3, DMF, 66%; (iv) LiOH, $HSCH_2COOH$, DMF, 90%; (v) **8**, Et_3N, CH_2Cl_2, 93%; (vi) repeat iv and v, 69%; (vii) repeat iv and v, 79% over two steps.

Fragments **8** and **10** were coupled under mild conditions to yield the protected dipeptide **11**. Compound **11** was then subjected to the same conditions for removal of the 2-nitrobenzenesulfonamide group as compound **9** and the product was coupled with **8** to give tripeptide **12**. Further iteration of this deprotection/coupling procedure led to compound **13** being obtained. These completed the main peptidic portion of the molecule. Our attention then turned towards the novel substituted alkynoate fragment.

2.2. Synthesis of moya 3

This fragment was synthesized via the route shown in Scheme 4. The monoprotection of 1,5-pentanediol **14** was effected by treatment with sodium hydride and benzyl bromide in THF,[11] and Swern oxidation of the remaining alcohol functionality produced aldehyde **15**. This aldehyde was readily olefinated using the commercially available (carbethoxymethylene) triphenylphosphorane to furnish the unsaturated ester in high yield. Hydrogenation using H_2, Pd/C in the presence of Na_2CO_3 in methanol afforded ester **16**.[12] After hydrolysis with LiOH in aqueous THF, **16** was converted into the acyl chloride with oxalyl chloride and DMF in dichloromethane, followed by treatment with (*R*)-4-benzyl-2-oxazolidinone, DMAP and triethylamine to give imide **17**.[13] The α-methylation was smoothly accomplished following the methodology of Evans,[14–15] to give the *R*-configuration at the newly formed centre in **18**. The chiral auxiliary was removed by treating **18** with hydrogen peroxide in aqueous THF, followed by acidification to give an excellent yield of the acid,[16] which was esterified by reacting it with freshly prepared diazomethane to give ester **19**. Cleavage of the benzyl protecting group through catalytic hydrogenation with Pd/C, followed by Swern oxidation produced aldehyde **20**. This was converted to the alkyne **21** in reasonable yield using the Ohira–Bestmann reagent **22**,[17–18] Saponification of alkyne **21** liberated the free acid **3**.

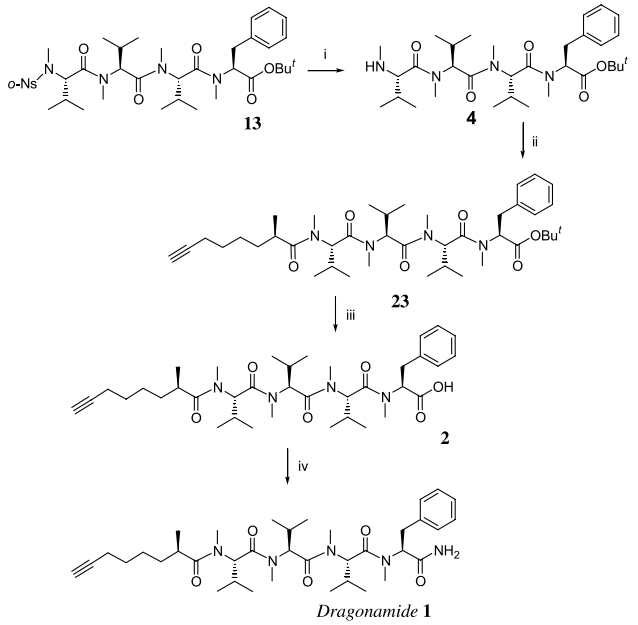


Scheme 4. Reagents and conditions: (i) NaH, BnBr, THF, 83%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 81%; (iii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 91%; (iv) H_2, Pd/C, Na_2CO_3, MeOH, 77%; (v) LiOH, THF–H_2O, 89%; (vi) (a) $(COCl)_2$, DMF, CH_2Cl_2; (b) (*R*)-4-benzyl-2-oxazolidinone, DMAP, Et_3N, CH_2Cl_2, 85% (over two steps); (vii) NaHMDS, MeI, THF, 87%; (viii) LiOH, H_2O_2, THF–H_2O, 91%; (ix) CH_2N_2, Et_2O, 99%; (x) H_2, Pd/C, MeOH, 99%; (xi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 84%; (xii) Ohira–Bestmann reagent **22**, K_2CO_3, MeOH, 78%; (xiii) LiOH, THF–H_2O, 92%.

2.3. Completion of the total synthesis of 1

With fragments **13** and **3** in hand, we next focused on the completion of the synthesis. The sulfonamide was cleaved by treating **13** with mercaptoacetic acid under basic conditions to form the free amine **4**, and it was then coupled with the acid **3** activated by BOPCl to produce **23** in

moderate yield. The final two steps involved cleavage of the *t*-butyl ester of **23** using TFA and formation of the primary amide, which was achieved by activation with PyBOP and treatment with ammonia,[19–20] to produce dragonamide **1**, or so it was assumed (Scheme 5).



Scheme 5. Reagents and conditions: (i) LiOH, $HSCH_2COOH$, DMF; (ii) **3**, BOPCl, DIPEA, CH_2Cl_2, 36% (two steps); (iii) TFA, CH_2Cl_2; (iv), PyBOP, DIPEA, THF, then NH_3 and NH_4OH, 32%.

The material we had made had the same stereochemistry as that reported in the isolation paper; however, both the NMR and optical rotation data of the synthetic material did not match. The main source of doubt about the true structure was the configuration of the novel alkynoate fragment, and it was here that we focused our attention.

Using exactly the same procedure, but this time with (*S*)-4-benzyl-2-oxazolidinone it was possible to make the enantiomer of the substituted alkynoic acid, (*S*)-**3**. This was used to complete the synthesis in exactly the same manner, and it was indeed found that the data for the newly synthesized material was an excellent match for the literature data on dragonamide. Consequently, we can now report that the correct structure for dragonamide is (*S*,*S*,*S*,*S*,*S*) (Fig. 1).

3. Conclusion

The marine cyanobacteria secondary metabolite dragonamide has been synthesized. As a result, the configuration of the moya fragment has been amended.

4. Experimental

4.1. General

All non-aqueous reactions were run under an inert atmosphere (nitrogen) with rigid exclusion of moisture from reagents, and all reaction vessels were oven-dried. Solvents were distilled prior to use: THF from Na/benzophenone; dichloromethane, DMF, triethylamine and diisopropylethylamine from CaH_2; methanol from iodine and magnesium. NMR spectra were recorded on Bruker AV 400 MHz spectrometers. Chemical shifts are reported in parts per million (ppm), relative to the signals due to the solvent. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), coupling constants and integration. High resolution mass spectra were obtained using a Finnigan MAT 95 mass spectrometer, while ESI mass spectra were obtained with a MicroMass Q-Tof-2^{TM} spectrometer. Optical rotations were recorded on a Perkin Elmer 343 Polarimeter. TLC was carried out using precoated sheets (Merck silica gel 60-F_{254}, 0.2 mm) which, after development, were visualized at 254 nm, and/or staining in *para*-anisole, ninhydrin or phosphomolybdic acid solution followed by heating. Flash column chromatography was performed using the indicated solvents (with R_f=0.15–0.20 for the desired component) on E. Merck silica gel 60 (230–400 mesh ASTM).

4.2. Synthesis of tetrapeptide

4.2.1. L-Valine *tert*-butyl ester. To a solution of L-valine (5.89 g, 50.0 mmol) in *tert*-butyl acetate (120 mL) at 0 °C, was added $HClO_4$ (6.5 mL, 75 mmol) slowly. The reaction mixture was stirred at room temperature for 12 h then washed with H_2O (250 mL) and 1.0 mol/L hydrochloric acid (150 mL). The resultant aqueous solution was adjusted to pH 9 by addition of 10% K_2CO_3 solution, and then extracted with dichloromethane (3×50 mL). The combined organic phases were dried with anhydrous sodium sulfate, filtered and concentrated to give an oil. This was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/1) as eluent, to give the title compound (7.9 g, 91%) as a yellow oil. $[\alpha]_D^{20}$ +20.6 (*c* 5.3, EtOAc); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.92 (d, J=7.0 Hz, 3H), 1.00 (d, J=7.0 Hz, 3H), 1.50 (s, 9H), 1.54 (s, 2H), 2.01–2.03 (m, 1H), 3.18 (d, J=4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 16.4, 18.6, 27.4, 31.5, 59.6, 79.8, 174.1; HR-ESIMS calcd for $C_9H_{20}NO_2$ $[M+H]^+$ 174.1494, found 174.1509.

4.2.2. *N-o*-Nitro-benzosulfonyl-L-valine *tert*-butyl ester 5. To a solution of L-valine *tert*-butyl ester (6.3 g, 36.0 mmol) in dichloromethane (120 mL) at 0 °C, was added triethylamine (6.0 mL, 39.6 mmol) and *o*-nitrobenzene-sulfonyl chloride (10.5 g, 45.0 mmol). The reaction mixture was stirred at room temperature overnight and then washed with H_2O (3×15 mL) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/4) as eluent, to produce the title compound (11.7 g, 91%) as a yellow oil. $[\alpha]_D^{20}$ −108.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.94 (d, J=6.9 Hz, 3H), 1.03 (d, J=6.7 Hz, 3H), 1.20 (s, 9H), 2.11–2.17 (m, 1H), 3.88 (q, J=5.0 Hz, 1H), 6.06 (d, J=9.8 Hz, 1H), 7.70–7.73 (m, 1H), 7.86–7.94 (m, 2H), 8.06–8.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.3, 19.0, 27.6, 31.6, 62.6, 82.35, 125.5, 130.4, 132.8, 133.5, 134.4, 136.5, 169.6; HR-ESIMS calcd for $C_{15}H_{22}N_2O_6SNa$ $[M+Na]^+$ 381.1096, found 381.1121.

4.2.3. *N*-*o*-Nitro-benzosulfonyl-*N*-methyl-L-valine *tert*-butyl ester 6. K_2CO_3 (7.7 g, 55.2 mmol) was added to a solution of **5** (9.9 g, 27.6 mmol) in DMF (60.0 mL) at 0 °C under a protective flow of N_2. After 10 min, iodomethane (7.0 mL, 110.4 mmol) was introduced via a syringe. The reaction mixture was then stirred at room temperature overnight prior to being quenched by the addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted with benzene–ethyl acetate (1/3, v/v) (3×80 mL). The combined organic extracts were washed with 0.5 mol/L HCl (2×50 mL) and brine (2×50 mL), dried (Na_2SO_4) and concentrated. The residue was subjected to flash chromatography on silica gel, using ethyl acetate–hexane (1/3) as eluent, affording the title compound (7.9 g, 77%) as a yellow oil. $[\alpha]_D^{20}$ −12.3 (*c* 3.5, $CH_3CO_2C_2H_5$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.98 (d, J=6.8 Hz, 3H), 1.02 (d, J=6.6 Hz, 3H), 1.31 (s, 9H), 2.17–2.23 (m, 1H), 3.08 (s, 3H), 4.04 (d, J=10.1 Hz, 1H), 7.63–7.66 (m, 1H), 7.70–7.76 (m, 2H), 8.04–8.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 19.0, 19.1, 27.5, 27.8, 30.6, 65.5, 81.7, 123.7, 130.8, 131.4, 132.8, 133.4, 147.9, 168.8; HR-ESIMS calcd for $C_{16}H_{24}N_2O_6SNa$ $[M+Na]^+$ 395.1253, found 395.1270.

4.2.4. (2*S*)-3-Methyl-2-(*o*-nitro-benzenesulfonyl-methyl-amino)-butyryl chloride 8. To a solution of **6** (980 mg, 2.6 mmol) in dichloromethane (10 mL) at 0 °C was added TFA (5.0 mL, 67.3 mmol) dropwise and with stirring at 0 °C. The reaction was monitored by TLC and after the starting material had disappeared, the reaction mixture was concentrated to give a dark red oil (**7**).

To a solution of **7** in dichloromethane (10 mL) at 0 °C was added $(COCl)_2$ (0.56 mL, 6.5 mmol) and DMF (20 μL, 0.3 mmol). The reaction was monitored by TLC and after the starting material had disappeared, the reaction mixture was concentrated to give a brown-yellow oil (**8**).

4.2.5. L-Phenylalanine *tert*-butyl ester. This compound was prepared in an analogous manner to compound L-valine *tert*-butyl ester on a 50.0 mmol scale. The yield for the title compound was 90%. $[\alpha]_D^{20}$ +25.1 (*c* 2.8, EtOAc); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.31 (s, 11H), 2.70 (dd, J=7.7, 13.5 Hz, 1H), 2.89 (dd, J=5.8, 13.5 Hz, 1H), 3.47 (dd, J=5.8, 7.7 Hz, 1H), 7.09–7.19 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 27.7, 41.1, 56.1, 80.7, 126.4, 128.2, 129.2, 137.4, 174.1; HR-ESIMS calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$ 222.1494, found 222.1490.

4.2.6. *N*-*o*-Nitro-benzosulfonyl-L-phenylalanine *tert*-butyl ester. This compound was prepared according to the procedures for compound **5** on a 45.1 mmol scale, with a yield of 93%. $[\alpha]_D^{20}$ +88.7 (*c* 3.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.19 (s, 9H), 3.07–3.09 (m, 2H), 4.31–4.36 (m, 1H), 6.06 (d, J=9.0 Hz, 1H), 7.15–7.24 (m, 5H), 7.65–7.70 (m, 1H), 7.82–7.84 (m, 2H), 7.89–8.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 27.4, 39.3, 58.0, 82.6, 125.1, 127.0, 128.3, 129.3, 130.2 132.9, 133.5, 135.0, 136.7, 147.4, 169.1; HR-ESIMS calcd for $C_{19}H_{22}N_2O_6SNa$ $[M+Na]^+$ 429.1096, found 429.1108.

4.2.7. *N*-*o*-Nitro-benzosulfonyl-*N*-methyl-L-phenylalanine *tert*-butyl ester 9. Compound **9** was prepared on a 41.9 mmol scale using the same procedures for compound **6**, with a yield of 66%. $[\alpha]_D^{20}$ +88.5 (*c* 3.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.35 (s, 9H), 3.00 (dd, J=9.2, 14.2 Hz, 1H), 3.06 (s, 3H), 3.36 (dd, J=6.5, 14.2 Hz, 1H), 4.88 (dd, J=6.5, 9.2 Hz, 1H), 7.21–7.27 (m, 5H), 7.53–7.57 (m, 1H), 7.61–7.63 (m, 2H), 7.73–7.75 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 27.3, 30.4, 35.4, 61.0, 81.9, 123.6, 126.5, 128.1, 128.7, 130.2, 131.4, 132.2, 133.2, 136.1, 147.5, 168.5; HR-ESIMS calcd for $C_{20}H_{24}N_2O_6SNa$ $[M+Na]^+$ 443.1253, found 443.1254.

4.2.8. *N*-Methyl-L-phenylalanine *tert*-butyl ester 10. Compound **9** (550 mg, 1.3 mmol) was dissolved in DMF (15 mL) at 0 °C and $LiOH\cdot H_2O$ (570 mg, 13.1 mmol) was added, followed by mercaptoacetic acid (0.19 mL, 2.6 mol). After 2 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (5 mL) and extracted with benzene–ethyl acetate (1/3, v/v) (3×20 mL). The combined organic phase was washed with saturated $NaHCO_3$ (2×60 mL) and brine (2×60 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/3) as eluent, to produce the title compound (280 mg, 90%) as a yellow oil. $[\alpha]_D^{20}$ +22.7 (*c* 3.3, $CH_3CO_2C_2H_5$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.24 (s, 9H), 1.82 (s, 1H), 2.24 (s, 3H), 2.72–2.75 (m, 1H), 2.82 (dd, J=6.4, 13.5 Hz, 1H), 3.17–3.21 (m, 1H), 7.04–7.15 (m, 5H); HR-ESIMS calcd for $C_{14}H_{22}NO_2$ $[M+H]^+$ 236.1651, found 236.1652.

4.2.9. Ns-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu 11. To a solution of **10** (280 mg, 1.2 mmol) in dichloromethane (3 mL) at 0 °C was added Et_3N (0.84 mL, 6 mmol) and **8** (503 mg, 1.5 mmol) dissolved in dichloromethane (3 mL). The reaction mixture was stirred at room temperature overnight, and was washed with 5% HCl (2×30 mL), saturated $NaHCO_3$ (2×30 mL), brine (2×30 mL), dried (Na_2SO_4) and then concentrated. The crude oil was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/2) as eluent, to give the title compound (0.58 g, 92.7%) as a yellow oil. $[\alpha]_D^{20}$ −108.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.66 (d, J=6.6 Hz, 3H), 0.98 (d, J=6.3 Hz, 3H), 1.48 (s, 9H), 2.24–2.31 (m, 1H), 2.98 (dd, J=7.1, 14.3 Hz, 1H), 3.02 (s, 3H), 3.12 (s, 3H), 3.34 (dd, J=5.9, 14.3 Hz, 1H), 4.53 (d, J=10.7 Hz, 1H), 5.31 (dd, J=5.9, 7.1 Hz, 1H), 7.21–7.37 (m, 5H), 7.59–7.72 (m, 3H), 7.91–7.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 18.6, 18.6, 27.9, 28.8, 30.6, 32.8, 34.6, 59.1, 59.3, 81.9, 124.0, 126.5, 128.4, 129.0, 129.8, 131.6, 133.2, 133.3, 137.2, 148.0, 169.6, 170.6; HR-ESIMS calcd for $C_{26}H_{35}N_3O_7SNa$ $[M+Na]^+$ 556.2093, found 556.2007.

4.2.10. (*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu. To a solution of **11** (6.68 g, 12.5 mmol) in DMF (120 mL) at 0 °C was added solid $LiOH\cdot H_2O$ (5.42 g, 125.2 mmol) and mercaptoacetic acid (1.78 mL, 25.0 mol). The reaction mixture was stirred at room temperature for 2 h, quenched by the addition of a saturated NH_4Cl (20 mL) and extracted with benzene–ethyl acetate (1/3, v/v) (3×120 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (2×100 mL) and brine (2×100 mL), dried (Na_2SO_4) and concentrated to give the desired secondary amine as a yellow oil (4.18 g, 96%), which was used in next step without further purification.

4.2.11. Ns-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu 12. To a solution of (*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu (4.18 g, 12 mmol) in dichloromethane (30 mL) at 0 °C was added Et_3N (8.4 mL, 60 mmol), followed by a solution of **8** (5.02 g, 15 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature overnight and then concentrated to dryness. The residue was dissolved in EtOAc (150 mL) and washed with 5% HCl (2×60 mL), saturated $NaHCO_3$ (2×60 mL) and brine (2×60 mL). After being dried (Na_2SO_4), this solution was concentrated to a crude oil, which was subjected to chromatographic purification on silica gel, using ethyl acetate–hexane (1/2) as eluent. The title compound was obtained as a yellow oil (5.60 g, 69.2%, over two steps). $[\alpha]_D^{20}$ −513.8 (*c* 2.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.50 (d, J=6.7 Hz, 3H), 0.55 (d, J=6.7 Hz, 3H), 0.76 (d, J=6.8 Hz, 3H), 0.88 (d, J=6.6 Hz, 3H), 1.39 (s, 9H), 2.03–2.08 (m, 1H), 2.24–2.27 (m, 1H), 2.74 (s, 3H), 2.85 (s, 3H), 2.88 (dd, J=11.2, 15.0 Hz, 1H), 3.06 (s, 3H), 3.30 (dd, J=5.0, 15.0 Hz, 1H), 4.34 (d, J=10.6 Hz, 1H), 5.06 (d, J=10.7 Hz, 1H), 5.36 (dd, J=5.0, 11.2 Hz, 1H), 7.10–7.18 (m, 5H), 7.51–7.54 (m, 1H), 7.59–7.63 (m, 2H), 7.84–7.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.5, 18.4, 18.5, 19.6, 27.4, 27.8, 28.4, 30.0, 30.5, 31.7, 34.1, 57.7, 59.4, 64.0, 81.6, 123.8, 126.4, 128.2, 128.4, 129.7, 131.4, 132.6, 133.4, 136.9, 147.7, 169.4, 170.1, 170.7; HR-ESIMS calcd for $C_{32}H_{46}N_4O_8SNa$ $[M+Na]^+$ 669.2934, found 669.2908.

4.2.12. (*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu. To a solution of **12** (370 mg, 0.57 mmol) in DMF (3 mL) at 0 °C was added solid $LiOH\cdot H_2O$ (0.25 g, 5.7 mmol), followed by mercaptoacetic acid (81 μL, 1.14 mol). The reaction mixture was stirred at room temperature for 2 h and was then quenched by pouring it into saturated NH_4Cl (5 mL) and extracting with benzene–ethyl acetate (1/3, v/v) (3× 5 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (2×10 mL), brine (2×10 mL), dried (Na_2SO_4) and concentrated to give the title compound as a yellow oil, which was used in next steps without further purification.

4.2.13. Ns-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu 13. To a solution of (*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu (1.64 g, 3.6 mmol) in dichloromethane (6 mL) at 0 °C was added Et_3N (3 mL, 21.4 mmol), followed by addition of a solution of **8** (1.34 g, 4 mmol) in dichloromethane (6 mL). The reaction mixture was stirred at room temperature overnight and was then concentrated to dryness. The residue was dissolved in EtOAc (150 mL) and was successively washed with 5% HCl (2×30 mL), saturated $NaHCO_3$ (2×30 mL) and brine (2×30 mL), dried (Na_2SO_4) and concentrated. The resultant residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/1) as eluent, to produce the title compound (2.14 g, 79%, over the last two steps) as a yellow oil. $[\alpha]_D^{20}$ −288.6 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.58 (d, J=6.6 Hz, 3H), 0.67 (d, J=6.8 Hz, 3H), 0.70 (d, J=6.5 Hz, 3H), 0.83 (d, J=6.6 Hz, 3H), 0.87 (d, J=6.8 Hz, 3H), 0.91 (d, J=6.5 Hz, 3H), 1.46 (s, 9H), 2.18–2.29 (m, 3H), 2.60 (s, 3H), 2.87 (s, 3H), 2.92 (dd, J=11.8, 14.9 Hz, 1H), 3.15 (s, 3H), 3.17 (s, 3H), 3.37 (dd, J=4.7, 14.9 Hz, 1H), 4.53 (d, J=10.7 Hz, 1H), 5.02 (d, J=10.8 Hz, 1H), 5.08 (d, J=10.6 Hz, 1H), 5.44 (dd, J=11.8, 4.7 Hz, 1H), 7.14–7.32 (m, 5H), 7.58–7.60 (m, 1H), 7.65–7.71 (m, 2H), 7.93–7.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.6, 18.1, 18.6, 18.6, 19.6, 19.7, 25.6, 27.0, 27.7, 28.0, 29.9, 30.5, 30.8, 30.9, 31.8, 34.2, 57.8, 57.9, 58.1, 59.7, 81.9, 124.0, 126.7, 128.4, 128.7, 130.1, 131.5, 133.0, 133.5, 137.0, 147.9, 169.6, 169.9, 170.4, 171.4; HR-ESIMS calcd for $C_{38}H_{57}N_5O_9SNa$ $[M+Na]^+$ 782.3775, found 782.3776.

4.3. Synthesis of moya

4.3.1. 5-Benzyloxy-pentan-1-ol. To a flask charged with NaH (80% in mineral oil, 0.96 g, 32.0 mmol) at 0 °C, was added pentane-1,5-diol (**14**) (11.0 mL, 105.0 mmol) slowly. After stirring for 6 h at room temperature, the reaction mixture was cooled in an ice-water bath and benzyl bromide (5.0 mL, 42.0 mmol) was added dropwise via a syringe and stirring was continued overnight. The reaction was quenched by slow addition of saturated NH_4Cl (30 mL) and the mixture was extracted with ether (3×30 mL). The combined organic extracts were washed with brine (60 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/2) as eluent, to provide the title compound (6.8 g, 83%) as a clear oil. ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.47–1.54 (m, 2H), 1.59–1.66 (m, 2H), 1.68–1.75 (m, 2H), 3.52–3.55 (m, 2H), 3.60–3.64 (m, 2H), 4.16 (s, 1H), 4.54 (s, 2H), 7.31–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 22.0, 29.0, 32.0, 61.8, 70.0, 72.5, 127.1, 127.3, 128.0, 138.1; HR-ESIMS calcd for $C_{12}H_{19}O_2$ $[M+H]^+$ 195.1385, found 195.1369.

4.3.2. 5-Benzyloxy-pentanal 15. To a solution of $(COCl)_2$ (0.86 mL, 10.0 mmol) in dichloromethane (20 mL) at −78 °C was added DMSO (1.42 mL, 20 mmol) in dichloromethane (5 mL). After 10 min, a pre-cooled solution of 5-benzyloxy-pentan-1-ol (0.97 g, 5 mmol) in dichloromethane (5 mL) was added dropwise. The reaction was kept at −78 °C for 1 h before Et_3N (5.6 mL, 39.8 mmol) was added. The reaction mixture was allowed to warm to −60 °C within 1 h then quenched by slow addition of saturated NH_4Cl. The volatiles were removed under reduced pressure and the remaining solution was extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (60 mL), brine (60 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/5) as eluent, to give the title compound (0.78 g, 81%) as a clear oil. ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.52–1.57 (m, 2H), 1.59–1.65 (m, 2H), 2.32–2.36 (m, 2H), 3.38 (t, J=6.1 Hz, 2H), 4.38 (s, 2H), 7.17–7.24 (m, 5H), 9.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 18.8, 29.0, 43.5, 69.6, 72.8, 127.4, 127.5, 128.3, 138.3, 202.4; HR-ESIMS calcd for $C_{12}H_{16}O_2Na$ $[M+Na]^+$ 215.1048, found 215.1077.

4.3.3. 7-Benzyloxy-hept-2-enoic acid ethyl ester. (Carbethoxymethylene)triphenylphosphorane (3.69 g, 10.6 mmol) was dissolved in dichloromethane (50 mL) at 0 °C and to this was added aldehyde (**15**) (1.94 g, 10.1 mmol) in dichloromethane (10 mL), and the reaction was stirred at room temperature overnight. The triphenylphosphine oxide was removed simply by filtering the reaction mixture

through a pad of silica gel. The filtrate was concentrated to dryness, and the residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/5) as eluent, to give the title compound (2.42 g, 91%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.17 (t, J=7.15 Hz, 3H), 1.43–1.57 (m, 4H), 2.07–2.13 (m, 2H), 3.36 (t, J= 6.2 Hz, 2H), 4.07 (q, J=7.1 Hz, 2H), 4.38 (s, 2H), 5.69–5.74 (m, 1H), 6.82–6.89 (m, 1H), 7.15–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 14.0, 24.5, 29.0, 31.7, 59.8, 69.6, 72.7, 121.3, 127.3, 127.3, 128.1, 138.3, 148.6, 166.3; HR-ESIMS calcd for $C_{16}H_{23}O_3$ $[M+H]^+$ 263.1647, found 263.1636.

4.3.4. 7-Benzyloxy-heptanoic acid methyl ester 16. 7-Benzyloxy-hept-2-enoic acid ethyl ester (0.64 g, 2.4 mmol) and Na_2CO_3 (0.77 g, 7.3 mmol) were placed in a 100 mL round-bottom flask and dissolved in methanol (50 mL). The flask was flushed with nitrogen. A catalytic amount of (10%) Pd/C was added; the flask was sealed tightly and then purged with hydrogen. The reaction mixture was stirred vigorously under a hydrogen atmosphere for 4 h, then filtered through a plug of celite and concentrated. The resultant residue was dissolved in ethyl acetate (150 mL) and washed with brine (30 mL). The solution was then dried (Na_2SO_4) and concentrated to leave a crude oil, which was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1:10) as eluent, to produce the title compound (0.47 g, 77%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.15–1.26 (m, 4H), 1.43–1.51 (m, 4H), 2.13 (t, J=7.5 Hz, 2H), 3.29 (t, J=6.5 Hz, 2H), 3.47 (s, 3H), 4.32 (s, 2H), 7.06–7.17 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 24.3, 25.4, 28.4, 29.1, 33.3, 50.6, 69.7, 72.2, 126.8, 126.9, 127.7, 138.2, 173.2; HR-ESIMS calcd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, found 251.1654.

4.3.5. 7-Benzyloxy-heptanoic acid. To a solution of **16** (0.47 g, 1.9 mmol) in THF–water (8 mL/2 mL) at 0 °C was added solid $LiOH\cdot H_2O$ (130 mg, 2.9 mmol). The reaction mixture was stirred at room temperature for 12 h then extracted with EtOAc (5 ml). The organic layer was discarded. The aqueous phase was acidified to pH 2 with 5%$KHSO_4$ in the presence of EtOAc (20 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (3×20 mL). The combined organic extracts was washed with brine (50 mL), dried (Na_2SO_4) and concentrated to give the title compound (0.39 g, 89%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.23–1.29 (m, 4H), 1.45–1.53 (m, 4H), 2.18 (t, J=7.5 Hz, 2H), 3.33 (t, J= 6.6 Hz, 2H), 4.36 (s, 2H), 7.10–7.20 (m, 5H), 10.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 24.3, 25.5, 28.5, 29.2, 33.7, 69.9, 72.5, 127.2, 127.4, 128.0, 138.2, 179.4; HR-ESIMS calcd for $C_{14}H_{21}O_3$ $[M+H]^+$ 237.1491, found 237.1482.

4.3.6. (4*R*)-3-(7-Benzyloxy-1-oxoheptyl)-4-(benzyl)-2-oxazolidinone 17. To the solution of 7-benzyloxy-heptanoic acid (2.45 g, 10.4 mmol) in dichloromethane (80 mL) at 0 °C, was added $(COCl)_2$ (4.47 mL, 52.1 mmol), followed by DMF (100.5 μL, 1.3 mmol). The reaction was monitored with TLC and after the starting material had been consumed, the mixture was concentrated to provide the corresponding acylchloride as a dark red oil. Meanwhile, in another reaction vessel, (*R*)-4-benzyl-2-oxazolidinone (4.61 g, 26.0 mmol) and DMAP (0.16 g, 1.29 mmol) were dissolved in dichloromethane (80 mL). The solution was cooled to 0 °C and Et_3N (5.48 mL, 39 mmol) added, followed by a solution of the above acylchloride in dichloromethane (10 ml). The reaction was stirred at room temperature for 12 h and concentrated under reduced pressure and the residue was dissolved in EtOAc (100 mL). The solution was successively washed with 3% HCl (100 mL), saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated. The residue, after being purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/5) as eluent, provided the desired compound (3.48 g, 84.9%) as a clear oil. $[\alpha]_D^{20}$ −91.1 (*c* 2.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.33–1.35 (m, 4H), 1.55–1.64 (m, 4H), 2.68 (dd, J=9.6, 13.3 Hz, 1H), 2.82–2.89 (m, 2H), 3.21 (dd, J=2.8, 13.3 Hz, 1H), 3.40 (t, J=6.5 Hz, 2H), 4.06–4.12 (m, 2H), 4.42 (s, 2H), 4.56–4.60 (m, 1H), 7.11–7.27 (m, 10H); ^{130}C NMR ($CDCl_3$, 100 Hz) δ ppm: 24.1, 25.9, 28.9, 29.5, 35.4, 37.9, 55.1, 66.1, 70.3, 72.8, 127.3, 127.4, 127.6, 128.3, 128.9, 129.4, 135.3, 138.6, 153.4, 173.3; HR-ESIMS calcd for $C_{24}H_{30}NO_4$ $[M+H]^+$ 396.2175, found 396.2166.

4.3.7. (2′*R*),4*R*]-3-(7-Benzyloxy-2-methyl-1-oxoheptyl)-4-(benzyl)-2-oxazolidinone 18. To NaHMDS (sodium bis-(trimethylsilyl)amide) (5.8 mL, 9.9 mmol, 1.71 M solution in THF) in THF (70 mL) at −78 °C was added a pre-cooled solution of **17** (3.25 g, 8.22 mmol) in THF (10 mL). After 45 min, iodomethane (2.56 mL, 41.12 mmol) was added slowly via a syringe. After stirring at ×78 °C for 4 h, the reaction mixture was quenched by adding saturated NH_4Cl (50 mL). Volatiles were removed under reduced pressure and the aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic extracts were successively washed with 5% $KHSO_4$ (100 mL), saturated $Na_2S_2O_3$ (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/5) as eluent, to give the title compound (2.92 g, 87%) as a clear oil. $[\alpha]_D^{20}$ −75.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.24 (d, J= 6.9 Hz, 3H), 1.33–1.48 (m, 5H), 1.61–1.68 (m, 2H), 1.77–1.81 (m, 1H), 2.79 (dd, J=9.5, 13.3 Hz, 1H), 3.24–3.27 (m, 1H), 3.48 (t, J=6.5 Hz, 2H), 3.71–3.76 (m, 1H), 4.13–4.16 (m, 2H), 4.51 (s, 2H), 4.65–4.68 (m, 1H), 7.21–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.2, 26.0, 26.9, 29.4, 33.0, 37.4, 37.6, 55.0, 65.7, 70.1, 72.6, 127.1, 127.2, 127.4, 128.1, 128.7, 129.2, 135.1, 138.5, 152.8, 176.9; HR-ESIMS calcd for $C_{25}H_{32}NO_4$ $[M+H]^+$ 410.2331, found 410.2316.

4.3.8. (2*R*)-7-Benzyloxy-2-methyl-heptanoic acid. To a solution of **18** (2.7 g, 6.5 mmol) in THF–water (80 mL/25 mL) at 0 °C was added H_2O_2 (5.3 mL, 52.2 mmol) and after 10 min, $LiOH\cdot H_2O$ (0.56 g, 13.1 mmol) was added. The reaction mixture was stirred at room temperature for 12 h and then cooled to 0 °C before Na_2SO_3 (6.9 g, 53.3 mol) was added. Stirring was continued for another 30 min, then the mixture was washed with EtOAc and the organic extracts were discarded. The aqueous solution was covered with EtOAc (100 mL) and acidified to pH 2 with 5% $KHSO_4$, the layers were separated and the aqueous layer was further extracted with EtOAc (3×100 mL). The

combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4) and concentrated to give the title compound (1.49 g, 91%) as a clear oil. $[\alpha]_D^{20}$ −5.4 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.14 (d, J= 7.0 Hz, 3H), 1.33–1.44 (m, 5H), 1.56–1.70 (m, 3H), 2.37–2.46 (m, 1H), 3.42–3.45 (m, 2H), 4.47 (s, 2H), 7.21–7.31 (m, 5H), 10.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 16.8, 26.0, 26.9, 29.4, 33.4, 39.2, 70.2, 72.7, 127.4, 127.6, 128.3, 138.4, 183.0; HR-ESIMS calcd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, found 251.1647.

4.3.9. (2*R*)-7-Benzyloxy-2-methyl-heptanoic acid methyl ester 19. (2*R*)-7-benzyloxy-2-methyl-heptanoic acid (1.49 g, 5.9 mmol) in ether (20 mL) was treated with freshly prepared diazomethane (large excess) and the reaction was monitored by TLC. When all of the acid had been consumed, a flow of nitrogen was used to bubble the excess CH_2N_2 into a solution of acetic acid. When this was complete, the residue was diluted with ethyl acetate (120 mL), washed with dilute acetic acid, water and brine, dried and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel, using ethyl acetate–hexane (1/5) as eluent, to provide the title compound (1.56 g, 99%) as a clear oil. $[\alpha]_D^{20}$ −9.3 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.15 (d, J= 7.0 Hz, 3H), 1.28–1.45 (m, 5H), 1.59–1.68 (m, 3H), 2.42–2.47 (m, 1H), 3.46 (t, J=6.6 Hz, 2H), 3.66 (s, 3H), 4.50 (s, 2H), 7.27–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.0, 26.0, 27.0, 29.5, 33.7, 39.3, 51.4, 70.2, 72.8, 127.4, 127.5, 128.3, 138.5, 177.2; HR-ESIMS calcd for $C_{16}H_{24}O_3Na$ $[M+Na]^+$ 287.1623, found 287.1595.

4.3.10. (2*R*)-7-Hydroxy-2-methyl-heptanoic acid methyl ester. Compound **19** (1.56 g, 5.92 mmol) was dissolved in methanol (50 mL), a catalytic amount of (10%) Pd/C was added, and the reaction mixture was stirred vigorously under a hydrogen atmosphere for 4 h. The reaction mixture was filtered through a plug of celite and concentrated to give the title compound (1.03 g, 99%) as a clear oil. $[\alpha]_D^{20}$ −15.2 (*c* 0.8, $CHCl_3$);^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.15 (d, J=7.0 Hz, 3H), 1.26–1.47 (m, 5H), 1.52–1.59 (m, 2H), 1.62–1.71 (m, 1H), 2.42–2.48 (m, 1H), 2.79 (s, 1H), 3.60 (t, J=6.6 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 16.4, 25.1, 26.4, 31.8, 33.1, 38.7, 50.8, 61.4, 176.7; HR-ESIMS calcd for $C_9H_{19}O_3$ $[M+H]^+$ 175.1334, found 175.1349.

4.3.11. (2*R*)-2-Methyl-7-oxo-heptanoic acid methyl ester 20. To a solution of $(COCl)_2$ (0.9 mL, 10.5 mmol) in dichloromethane (20 mL) at −78 °C was added DMSO (1.49 mL, 21.0 mmol) in dichloromethane (5 mL). After 10 min, a pre-cooled solution of (2*R*)-7-hydroxy-2-methyl-heptanoic acid methyl ester (0.91 g, 5.3 mmol) in dichloromethane (5 mL) was added dropwise. The reaction was kept at −78 °C for 1 h before Et_3N (5.9 mL, 42.1 mmol) was added. The reaction mixture was warmed up to −60 °C during 1 h, then quenched by slow addition of a saturated aqueous solution of NH_4Cl. The volatiles were removed under vacuum and the remaining solution was extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/5) as eluent, to give the title compound (0.76 g, 84%) as a yellow oil. $[\alpha]_D^{20}$ −24.9 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.13 (d, J= 7.0 Hz, 3H), 1.28–1.33 (m, 2H), 1.34–1.45 (m, 1H), 1.57–1.69 (m, 3H), 2.40–2.46 (m, 3H), 3.65 (s, 3H), 9.74 (t, J= 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.0, 212.8, 26.7, 33.4, 39.2, 43.6, 51.5, 177.0, 202.4; HR-ESIMS calcd for $C_9H_{16}O_3Na$ $[M+Na]^+$ 195.0997, found 195.1028.

4.3.12. (2*R*)-2-Methyl-oct-7-ynoic acid methyl ester 21. To a solution of diethyl 1-diazo-2-oxopropylphosphonate (4.3 g, 19.7 mmol) in methanol (50 mL) at 0 °C was added K_2CO_3. After stirring for 30 min at this temperature, a solution of **20** (0.67 g, 3.9 mmol) in methanol (40 mL) was added slowly and stirring was continued at 0 °C for 1 h then room temperature overnight. The reaction was quenched by adding brine (20 mL), the mixture was concentrated and extracted with dichloromethane (3×100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1:10) as eluent, to give the title compound (0.51 g, 78%) as a yellow oil. $[\alpha]_D^{20}$ −13.3 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.15 (d, J=7.0 Hz, 3H), 1.37–1.49 (m, 3H), 1.51–1.56 (m, 2H), 1.63–1.70 (m, 1H), 1.94 (t, J=2.6 Hz, 1H), 2.16–2.21 (m, 2H), 2.42–2.47 (m, 1H), 3.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.0, 18.1, 26.2, 28.2, 33.1, 39.2, 51.4, 68.3, 84.2, 177.1; HR-ESIMS calcd for $C_{10}H_{17}O_2$ $[M+H]^+$ 169.1229, found 169.1234.

4.3.13. (2*R*)-2-Methyl-oct-7-ynoic acid 3. To a solution of **21** (0.11 g, 0.64 mmol) in THF–water (2 mL/0.5 mL) at 0 °C was added $LiOH\cdot H_2O$ (0.08 g, 1.92 mmol). The reaction mixture was stirred at room temperature for 12 h and then extracted with EtOAc (30 mL). The organic layer was discarded. The aqueous solution was covered with EtOAc (20 mL) and acidified to pH 2 with 5%$KHSO_4$, the layers were separated and the aqueous phase was further extracted with EtOAc (2×20 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated to give the title compound (91 mg, 92%) as a clear oil. $[\alpha]_D^{20}$ −12.9 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 1.18 (d, J=7.0 Hz, 3H), 1.40–1.57 (m, 5H), 1.66–1.73 (m, 1H), 1.93 (t, J=2.6 Hz, 1H), 2.17–2.21 (m, 2H), 2.42–2.50 (m, 1H), 10.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 16.7, 18.2, 26.2, 28.2, 32.8, 39.2, 68.3, 84.2, 183.3; HR-ESIMS calcd for $C_9H_{15}O_2$ $[M+H]^+$ 155.1072, found 155.1091.

4.4. Completion of the total synthesis of 1

4.4.1. (*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu. To a solution of **13** (1.28 g, 1.68 mmol) in DMF (13 mL) at 0 °C was added solid $LiOH\cdot H_2O$ (0.73 g, 16.8 mmol) followed by mercaptoacetic acid (239 μL, 3.36 mol). The reaction mixture was stirred at room temperature for 2 h, quenched by pouring it into saturated NH_4Cl (8 mL) then extracted with benzene–ethyl acetate (1/3, v/v) (3×10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (2×20 mL), brine (2× 20 mL), dried (Na_2SO_4) and concentrated to give the title compound as a yellow oil, which was used in next step without further purification.

4.4.2. (2*R*)-2-Methyl-oct-7-ynoyl-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu 23. Acid moiety **3** (0.25 g, 1.63 mmol) and (*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu (0.92 g, 1.6 mmol) were dissolved in dichloromethane (20 mL). After the solution was cooled to 0 °C, BOPCl (0.84 g, 3.20 mmol) was added with stirring. After 5 min, DIPEA (1.06 mL, 6.4 mmol) was introduced via a syringe. The reaction was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and the solution was successively washed with saturated NH_4Cl (2×20 mL), saturated $NaHCO_3$ (2×20 mL), brine (2×20 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by flash chromatography on silica gel, using ethyl acetate–hexane (1/2) as eluent, to provide the desired compound (0.41 g, 36%) as a yellow oil. $[\alpha]_D^{20}$ −294.8 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.66 (d, J=6.8 Hz, 3H), 0.71 (d, J=6.7 Hz, 3H), 0.74 (d, J=6.4 Hz, 3H), 0.83 (d, J=4.0 Hz, 3H), 0.84 (d, J=3.6 Hz, 3H), 0.90 (d, J=6.3 Hz, 3H), 1.07 (d, J=6.8 Hz, 3H), 1.36–1.42 (m, 3H), 1.46 (s, 9H), 1.49–1.54 (m, 2H), 1.72–1.76 (m, 1H), 1.92 (t, J=2.6 Hz, 1H), 2.16–2.20 (m, 2H), 2.23–2.34 (m, 3H), 2.47 (s, 3H), 2.70–2.71 (m, 1H), 2.86 (s, 3H), 2.91 (dd, J=11.8, 14.8 Hz, 1H), 2.98 (s, 3H), 3.00 (s, 3H), 3.36 (dd, J=4.6, 14.8 Hz, 1H), 4.98 (d, J=10.7 Hz, 1H), 5.04 (d, J=10.6 Hz, 1H), 5.20 (d, J=10.8 Hz, 1H), 5.46 (dd, J=11.8, 4.6 Hz, 1H), 7.13–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm:17.3, 17.5, 17.9, 18.2, 18.3, 19.3, 19.6, 19.7, 26.7, 26.9, 27.0, 27.0, 28.0, 28.4, 29.6, 30.1, 30.2, 31.7, 33.3, 34.2, 36.2, 57.9, 58.1 (3C), 68.3, 81.8, 84.3, 126.7, 128.4, 128.7, 137.1, 169.6, 169.6, 169.8, 170.9, 176.8; HR-ESIMS calcd for $C_{41}H_{67}N_4O_6$ $[M+H]^+$ 711.5061, found 711.5027.

4.4.3. (2*R*)-2-Methyl-oct-7-ynoyl-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-NH_2 1. Compound **23** (135 mg, 0.19 mmol) in dichloromethane (16 mL) was treated with TFA (7 mL) at 0 °C and the reaction was monitored by TLC. After all the starting material was consumed the reaction mixture was concentrated to leave a dark red oil, which was subsequently dissolved in THF (15 mL) and cooled to 0 °C. PyBOP (198 mg, 0.38 mmol) was added under a protective flow of nitrogen and after 5 min DIPEA (94.2 μL, 0.57 mmol) was introduced via syringe. The reaction mixture was then stirred for 20 min at 0 °C and 30 min at room temperature. After cooling to 0 °C again, it was exposed to NH_3 for 25 min and then aqueous ammonia (29 μL, 0.38 mmol) was added. Stirring was continued for 20 min at room temperature, and the reaction was quenched with brine (10 mL). All volatiles were removed under reduced pressure and the residue was extracted with EtOAc (3×20 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was subjected to chromatographic purification, using ethyl acetate–hexane (2/1) as eluent, to give compound 1 (39 mg, 32%, over two steps) as a white solid. $[\alpha]_D^{20}$ −639.6 (*c* 3.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.66 (d, J=6.8 Hz, 3H), 0.71 (d, J=6.6 Hz, 3H), 0.73 (d, J=6.6 Hz, 3H), 0.83 (d, J=6.7 Hz, 3H), 0.84 (d, J=6.5 Hz, 3H), 0.88 (d, J=6.4 Hz, 3H), 1.07 (d, J=6.8 Hz, 3H), 1.32–1.40 (m, 3H), 1.49–1.55 (m, 2H), 1.74–1.76 (m, 1H), 1.92 (t, J=2.6 Hz, 1H), 2.16–2.19 (m, 2H), 2.23–2.34 (m, 3H), 2.44 (s, 3H), 2.69–2.72 (m, 1H), 2.94 (s, 3H), 2.96 (s, 3H), 2.99 (s, 3H), 3.02–3.08 (m, 1H), 3.26 (dd, J=5.4, 15.1 Hz, 1H), 4.94 (d, J=10.7 Hz, 1H), 5.09 (d, J=10.6 Hz, 1H), 5.19 (d, J=10.7 Hz, 1H), 5.54 (s, 1H), 5.58 (dd, J=11.2, 5.4 Hz, 1H), 6.02 (s, 1H), 7.15–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.3, 17.5, 17.9 (2C), 18.2, 19.4, 19.6, 20.0, 26.7, 26.8, 26.9, 27.0, 28.4, 29.6, 30.2, 30.2, 30.6, 30.9, 33.3, 36.2, 56.3, 57.9, 58.0, 58.4, 68.3, 84.3, 126.9, 128.6, 128.7, 136.6, 169.7, 170.9, 171.2, 171.9, 176.8; HR-ESIMS calcd for $C_{37}H_{60}N_5O_5$ $[M+H]^+$ 654.4594, found 654.4580.

4.4.4. (2*S*)-2-Methyl-oct-7-ynoyl-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-*O*-*tert*-Bu. $[\alpha]_D^{20}$ −282.6 (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.66 (d, J=6.8 Hz, 3H), 0.72–0.75 (m, 6H), 0.81 (d, J=7.0 Hz, 3H), 0.83 (d, J=6.9 Hz, 3H), 0.90 (d, J=6.4 Hz, 3H), 1.12 (d, J=6.7 Hz, 3H), 1.30–1.34 (m, 3H), 1.46 (s, 9H), 1.49–1.55 (m, 2H), 1.62–1.78 (m, 1H), 1.94 (t, J=2.7 Hz, 1H), 2.14–2.16 (m, 2H), 2.18–2.35 (m, 3H), 2.46 (s, 3H), 2.69–2.74 (m, 1H), 2.86 (s, 3H), 2.91 (dd, J=11.8, 14.8 Hz, 1H), 2.97 (s, 3H), 2.98 (s, 3H), 3.36 (dd, J=4.6, 14.8 Hz, 1H), 4.99 (d, J=10.7 Hz, 1H), 5.04 (d, J=10.6 Hz, 1H), 5.20 (d, J=10.8 Hz, 1H), 5.46 (dd, J=11.8, 4.6 Hz, 1H), 7.13–7.31 (m, 5H)

4.4.5. (2*S*)-2-Methyl-oct-7-ynoyl-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MeVal-(*S*)-MePhe-NH_2. $[\alpha]_D^{20}$ −237.2 (*c* 2.4, $CHCl_3$); lit.[6] $[\alpha]_D$ −260.8 (*c* 2.6, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 Hz) δ ppm: 0.63 (d, J=6.7 Hz, 3H), 0.67 (d, J=6.5 Hz, 3H), 0.68 (d, J=6.8 Hz, 3H), 0.76 (d, J=6.7 Hz, 3H), 0.79 (d, J=6.4 Hz, 3H), 0.85 (d, J=6.4 Hz, 3H), 1.08 (d, J=6.7 Hz, 3H), 1.25–1.33 (m, 3H), 1.42–1.51 (m, 2H), 1.56–1.78 (m, 1H), 1.89 (t, J=2.5 Hz, 1H), 2.10–2.14 (m, 2H), 2.16–2.32 (m, 3H), 2.40 (s, 3H), 2.63–2.70 (m, 1H), 2.90 (s, 3H), 2.92 (s, 3H), 2.94 (s, 3H), 2.95–2.98 (m, 1H), 3.22 (dd, J=5.3, 15.1 Hz, 1H), 4.91 (d, J=10.7 Hz, 1H), 5.05 (d, J=10.5 Hz, 1H), 5.15 (d, J=10.8 Hz, 1H), 5.32 (s, 1H) 5.54 (dd, J=11.0, 5.3 Hz, 1H), 5.97 (s, 1H), 7.11–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 Hz) δ ppm: 17.3, 17.6, 17.9 (2C), 18.2, 19.4, 19.6, 20.0, 26.7, 26.9, 27.0, 27.0, 28.3, 29.6, 30.1, 30.3, 30.6, 33.1, 33.5, 36.1, 56.2, 57.8 (2C), 58.4, 68.3, 84.1, 126.9, 128.5, 128.6, 136.5, 169.6, 170.7, 171.2, 171.7, 176.7

Acknowledgements

Support from The Shenzhen Graduate School of Peking University and The Hong Kong Polytechnic University was gratefully received.

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Tetrahedron 61 (2005) 11141–11147

Highly regio- and stereocontrolled S_N2' reactions of *gem*-difluorinated vinyloxiranes with monoalkylcopper reagents

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Received 16 August 2005; revised 8 September 2005; accepted 8 September 2005

Available online 23 September 2005

Abstract—Reaction of *gem*-difluorinated vinyloxiranes with RCu(X)Li allowed us to introduce the R group regioselectively at the fluorine-attached terminal carbon atom in an S_N2' manner to afford (*E*)-allylic alcohols exclusively, while homoallylic alcohols with *anti* stereochemical relationship were found to be obtained selectively from higher-ordered cuprates derived from CuCl and RMgBr in a ratio of 1:3.

1. Introduction

Significant requirement of basically artificial fluorine-containing organic compounds have been noticed in many fields due to their unique physical, chemical, and biological properties,[1] and their stereoselective syntheses are quite important issues especially on construction of materials with expecting biological activity.[2]

Recently, we have successfully investigated the novel regio- and stereoselective routes starting from *gem*-difluorinated vinyloxiranes **1** with unique structure (Fig. 1).[3] Hard nucleophiles like RLi realized exclusive S_N2' reactions to furnish various allylic alcohols, where the significantly positive nature of the fluorine-attached carbon atom is responsible for such regiospecificity.[3b] However, this process contained some drawbacks: (1) yields were in a range of moderate to good, and (2) carcinogenic HMPA (usually 0.5 equiv but 5 equiv in the case of MeLi) was necessary to attain exclusive (*E*) preference of the products. To overcome such difficulties, we reexamined the procedure using several types of nucleophiles. Herein, we would like to present our improvement on the S_N2' type alkylations to *gem*-difluorinated vinyloxiranes **1** occurring in highly regio- and stereocontrolled fashions, which were realized by use of soft nucleophiles, lower-ordered cuprates, to afford (*E*)-allylic alcohols as the sole products.

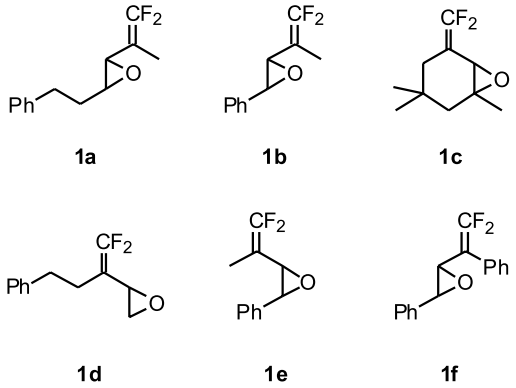

Figure 1. *gem*-Difluorinated vinyloxiranes **1**.

2. Results and discussion

Extensive investigations have been carried out for reactions between non-fluorinated vinyloxiranes and cuprates, which clearly showed their good to excellent S_N2' selectivities in most cases.[4] As described above, in our instance, the terminal sp^2 carbon in *gem*-difluorinated vinyloxiranes **1** was revealed to possess the most electronically positive charge and the largest $2p_z$ orbital coefficient on the basis of our ab initio molecular orbital calculations.[3b] This result allowed us to predict this carbon atom as the actual reaction site on treatment with cuprates,[5] and prompted us to examine regioselectivity of **1** with various types of copper reagents.

Keywords: Cuprate; S_N2' reaction; S_N2 reaction; Inversion; AlR_3; Retention.
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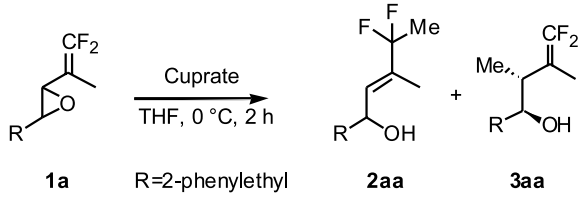
doi:10.1016/j.tet.2005.09.018

Table 1. Reaction of **1a** with cuprates derived from MeMgBr or MeLi



1a R=2-phenylethyl **2aa** **3aa**

Cuprate was prepared from CuX (2.0 equiv) and MeMgBr or MeLi at 0 °C for 1 h stirring.

Entry	CuX	Reagent	Equiv[a]	Yield (%)			Recovery (%)
				2aa	**3aa**	**2aa/3aa**	
1[b]	CuI	MeMgBr	2.0	16	21	43/57	57
2	CuI	MeMgBr	2.0	17	13	57/43	51
3	CuI	MeMgBr	4.0	14	77	15/85	0
4	CuI	MeMgBr	6.0	12	77	13/87	0
5	CuI	MeLi	2.0	91	<1	>99/<1	9
6	CuI	MeLi	4.0	2	16	11/89	0
7	CuI	MeLi	6.0	<1	19	<1/>99	0
8	CuCl	MeMgBr	6.0	11	75	13/87	0
9[c]	CuCl	MeLi	3.0	72	3	96/4	2

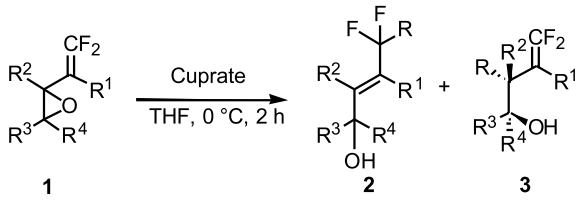
CuI was used after continuous washing with refluxing THF. Yields, ratios and recoveries were determined by ^{19}F NMR.
[a] Equivalent of cuprate.
[b] 0.5 equiv of CuI was used.
[c] 3.0 equiv of CuCl was used.

CuI-catalyzed reaction of **1a** using MeMgBr in THF afforded the desired S_N2' product **2aa** in an excellent *E* selective manner in only low yield and the unexpected S_N2 product **3aa** was formed as the major product (Table 1, entry 1). Because further reactions under several conditions proved that Cu-catalyzed conditions were not effective for our purpose, we decided to employ stoichiometrically prepared cuprates. The product distribution was investigated by fixing the amount of CuI (2.0 equiv) with changing the equiv of MeMgBr as well as MeLi (entries 2–7). It was found out that decrease of the quantity of alkylating reagents tended to improve the S_N2' selectivity. To our satisfaction, when the reaction was carried out with lower-ordered cuprate MeCuILi, (*E*)-**2aa** was obtained exclusively without any trace amount of the corresponding (*Z*) isomer nor the S_N2 product (entry 5). This excellent result was superior to the previous one obtained from the MeLi/HMPA system in terms of better stereoselectivity attained by the absence of calcinogenic HMPA.[3b] Noteworthy is the fact that completely different regioselectivity was observed only by slight modification using cuprates from CuI and MeMgBr in a ratio of 1:3 (entry 4), the S_N2 product **3aa** being formed as a main product. On the other hand, treatment of **1a** with Grignard reagents (MeMgBr, EtMgBr, and PhMgBr) in the absence of CuX resulted in almost recovery of the starting material[6] (Me and Et: no reaction, Ph: 3% of **3af** and 84% of **1a**). These results clearly demonstrated that organocopper reagents generated in situ would be the true reactive species in this reaction. Further examination by changing the reaction conditions and/or copper salt indicated that CuCl without any pretreatment was effective for the S_N2 selective reactions, but somewhat lower yield was obtained for the MeLi-based S_N2' selective reaction (entries 8 and 9).

With optimized reaction conditions in hand, the scope and limitation of **1** as building blocks were examined by treatment with various cuprates (method A for the formation of **2**, method B for **3**). In the case of lower-ordered cuprates for attainment of the selective S_N2' reactions, it was only MeCuILi which furnished the desired products in high yields and other cuprates gave only poor conversions (Table 2, entry 1). This result would imply lower stability of cuprates at this reaction temperature (0 °C). Actually, as our expectation, the lower temperature method worked well for *tert*-BuCuILi (entry 2) while this modification basically gave no effect for cuprates from *n*-BuLi or PhLi. To improve such low reactivity, activation by $BF_3{\cdot}OEt_2$ was attempted,[5a,7] but resulted in decomposition of the starting **1a** possibly due to its sensitivity toward such strongly Lewis acidic circumstance. Various substrates **1** with different structural features were proved to be efficiently employed for this process with showing consistently excellent S_N2' and (*E*) stereoselectivity in all cases (entries 3–7), but not with perfect conversion possibly because of the poor reactivity of monoalkylcopper reagents. The olefinic stereochemistries of the products **2** were assigned by comparison with the authentic samples[3b] as well as by the independent NOESY spectroscopy of **2ad**.

On the other hand, it was clarified that various Grignard-based copper species showed S_N2 selectivity to afford homoallylic alcohols **3** with high to excellent regioselectivity in moderate to good chemical yields. One of the reasons responsible for the lower yields might be defluorination and rearrangement accompanied in the main process (entries 8–17). In the case of bulky *tert*-BuMgCl (entries 13 and 14), 29% of **1a** remained unreacted presumably due to the inherent instability of the cuprate at this reaction temperature (0 °C). On the other hand, this substrate was completely consumed in a range of −40 to −50 °C to exclusively furnish the unexpected S_N2' product **2ad** in much better yield than the ones from *tert*-BuLi itself[3b] or lower-ordered *tert*-BuCuILi (entry 2). This type of temperature dependence was also observed for other

Table 2. Reaction of **1** with various types of cuprates



1 **2** **3**

method A : Cuprate was prepared from CuI (2.0 equiv) and RLi (2.0 equiv) at 0 °C for 1 h stirring.

method B: Cuprate was prepared from CuCl (2.0 equiv) and RMgBr (6.0 equiv) at 0 °C for 1 h stirring.

Entry	[a]	**1**	R	Yield (%)			Recovery (%)
				2	**3**	**2/3**	
1	A	**1a**	Me	87: **2aa**	(<1)	>99/<1	9
2[b]		**1a**	*tert*-Bu	65: **2ad**	(<1)	>99/<1	25
3[c]		**1b**	Me	46: **2ba**	(<1)	>99/<1	17
4[c]		**1c**	Me	69: **2ca**	(<1)	>99/<1	11
5		**1d**	Me	77: **2da**	(<1)	>99/<1	21
6[c]		**1e**	Me	49: **2ba**	(<1)	>99/<1	24
7[c]		**1f**	Me	37: **2fa**	(<1)	>99/<1	43
8	B	**1a**	Me	(12)	66: **3aa**	16/84	0
9		**1a**	Et	(3): **2ab**	45: **3ab**	7/93	3
10[b]		**1a**	Et	(1)	40	3/97	3
11		**1a**	*n*-Bu	(4)	45: **3ac**	9/91	0
12[b]		**1a**	*n*-Bu	(1)	42	2/98	0
13[d]		**1a**	*tert*-Bu	(24)	(<1)	>99/<1	29
14[b,d]		**1a**	*tert*-Bu	98: **2ad**	(<1)	>99/<1	0
15		**1a**	*n*-Octyl	10	45: **3ae**	19/81	0
16[b]		**1a**	*n*-Octyl	(<1)	47	<1/>99	0
17		**1a**	Ph	(13)	(83): **3af**	14/86	5

Yields in parentheses, ratios, and recoveries were determined by ^{19}F NMR.

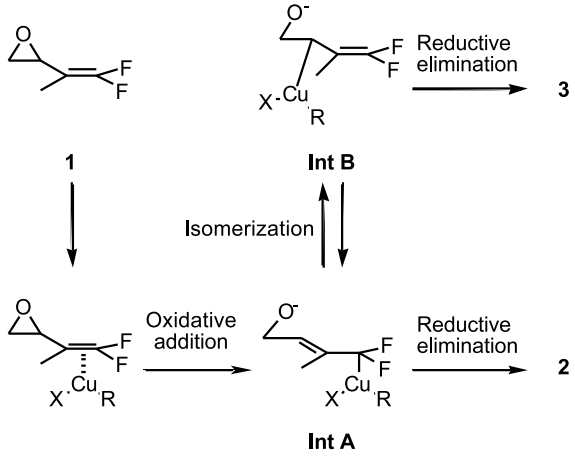
[a] Method.

[b] The cuprate was prepared at −78 °C and the reaction was run at −40 to −50 °C.

[c] Cuprate was prepared from CuCl (3.0 equiv) and MeLi (3.0 equiv).

[d] *tert*-BuMgCl was used.

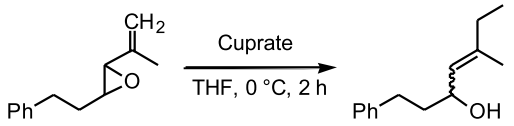
cuprates and slight improvement of regioselectivity was demonstrated along with similar chemical yields in general (entries 10, 12, and 16). The stereochemistries of **3aa** and **3ab** were assigned by their independent cyclization to 2,3-dihydrofuran derivatives, **4aa** and **4ab**, by way of the modified Ichikawa method[8] (yield of **4aa**: 70%, **4ab**: 54%), whose NOE experiments unambiguously indicated that the *anti* isomer was formed exclusively from the reaction of **1** with Grignard-based cuprates.



Scheme 1.

The proposed reaction mechanism of the present process is summarized in Scheme 1. Oxidative addition of cuprates to the model substrate would occur from the side opposite to the cleaving epoxy C–O bond in an S_N2' manner to produce **Int A**. If the rate determining reductive elimination is fast enough, the *anti* S_N2' products **2** would be formed smoothly. However, if this step is relatively slow, the allylic isomerization would become the competing pathway and allow **Int A** to be converted to **Int B**, from which the net S_N2 products **3** might be furnished. Monoalkylcopper reagents (X=Cl or I) are considered to afford S_N2' products exclusively because electron withdrawing halogen ligands are anticipated to cause acceleration of the reductive elimination, while the electron donating alkyl groups would retard this process and the easier isomerization would take place to yield the S_N2 products.[9] Lipshutz and co-workers reported[10] that reductive elimination was affected by the alkyl ligands on copper and the rate was decreased in the order of *sec*-Bu>*n*-Bu≥Et>Me>Ph. This coincided well with our results on the amount of the S_N2 product **3** increasing in the almost opposite order of *tert*-Bu<*n*-Octyl∼*n*-Bu∼Et<Me<Ph which clearly demonstrated the important role of copper ligands in determining regioselectivity.

To understand the effect of fluorine atoms on these regioselective reactions, the corresponding non-fluorinated prototype of **1a** was treated in a similar manner (Scheme 2).

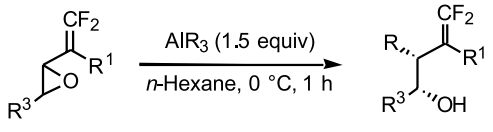


condition (equiv)	isolated yield (%)	*E* / *Z*
CuCl (2.0), MeMgBr (6.0)	79	86 / 14
CuCl (3.0), MeLi (3.0)	92	78 / 22

Scheme 2.

Both reactions with different cuprates demonstrated exclusive S_N2' selectivity, while in the reaction of fluorinated **1a** the S_N2 product **3aa** was obtained as a major product with Grignard-based cuprates (Table 2, entry 8). This regiochemical change may be attributable to the electron-withdrawing effect of a CF_2 group in **Int A** (Scheme 1). Although the first attack by Cu was occurred at the highly electropositive fluorine-possessing carbon atom to produce **Int-A**, the CF_2 group rendered the rate-determining reductive elimination retarded and, as a result, this intermediate followed relatively easy isomerization to **Int B** whose activation energy to the S_N2 product **2** would be lower by attachment of the electron donating alkyl group. On the other hand, when monoalkylcopper reagents were treated with **1**, their inherent fast reductive elimination ability would overwhelm such effect to eventually furnish **2** selectively.

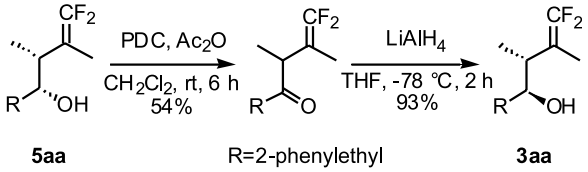
On the other hand, we have found an interesting alkylation by AlR_3 which occurred regiospecifically at the allylic position with, quite interestingly, retention of stereochemistry (Scheme 3). The relative configuration of the homoallylic alcohols **5** was determined as the diastereomers of **3** by the fact that PDC oxidation of **5aa** and the following reduction with $LiAlH_4$ at low temperature exclusively produced stereochemically inverted material at the OH-attached carbon atom in an excellent yield. Physical properties of this product were totally identical to the ones of **3aa** (Scheme 4). Although some structural requirements should be fulfilled for attainment of clean as well as selective formation of **5** like (1) no such activating groups as Ph or vinyl moieties at the δ position of fluorine atoms, or (2) up to disubstitution at the epoxy part, this reaction mode is extremely useful in terms of stereospecific construction of *syn*-**5** which was not attained in a direct manner.



1 **5**

1	AlR_3	yield (%)	product
1a	$AlMe_3$	88	**5aa**
	$AlEt_3$	72	**5ab**
1d	$AlMe_3$	97	**5da**
	$AlEt_3$	74	**5db**

Scheme 3.



5aa R=2-phenylethyl **3aa**

Scheme 4.

3. Conclusion

In summary, we have successfully developed highly regio- and stereoselective reactions of *gem*-difluorinated vinyloxiranes **1** with soft nucleophiles, organocuprates. Thus, monoalkylcopper reagents from CuX (X=I or Cl) and RLi led to the predominant formation of the S_N2' products **2** with excellent (*E*) selectivities. Treatment of the same substrate **1** with higher-ordered cuprates prepared from CuCl (2.0 equiv) and RMgBr (6.0 equiv), on the other hand, afforded the corresponding *anti*-homoallylic alcohols *anti*-**3** as a major product, while their diastereoisomers *syn*-**5** were obtained just by changing the nucleophilic reagents to trialkylaluminum. Thus, judicious choice of nucleophiles enabled us to conveniently select both the reaction sites where an R group is introduced and stereochemistry obtained by the S_N2 mechanisms (retention or inversion), which covers a wide variety of compounds with various structural features starting from the same material **1** just by an easy single-step transformation.

4. Experimental

4.1. General methods

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. All manipulations involving air-sensitive materials were performed under argon, with such materials being exposed only to thoroughly dried and degassed solvents. Anhydrous ether, THF and CH_2Cl_2 were purchased and were used without further purification.

^1H and ^{13}C NMR spectra were recorded with a Varian Mercury (300 and 75 MHz, respectively) and a VXR-500 (500 MHz for ^1H) in $CDCl_3$ unless otherwise noted. Chemical shifts were reported in parts per million (ppm) downfield from internal tetramethylsilane (Me_4Si). ^{19}F NMR spectra were recorded with a Varian Mercury (282 MHz) and a VXR-500 (470 MHz) in $CDCl_3$ unless otherwise noted. Chemical shifts were reported in ppm downfield from internal hexafluorobenzene (C_6F_6). Data were tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sex, sextet; m, multiplet; br, broad peak), number of protons, coupling constants (in hertz). Infrared (IR) spectra were obtained on a JASCO FT/IR-5000 spectrometer or a SHIMADZU IRPrestige-21 as thin films on NaCl plates, and all spectra were reported in wave numbers (cm^{-1}). Melting points, mp, were measured on a MRK MEL-TEMP II without correction. Column chromatography was conducted with silica gel (BW-200) by using a mixture of *n*-hexane and AcOEt (v/v), and before starting separation, it

is recommended to 'wash' silica gel by passing AcOEt for removing the chance of decomposition of epoxy-containing products.

The NMR spectra of **2aa**, **2ad**, **2ba**, and **2ca** were identical to the ones obtained by the reactions of **1** and RLi which, along with the preparation method of the substrates **1** were found in Ref. 3b. Only ^{1}H and ^{19}F NMR spectrums are described for **3af** due to existence of the inseparable impurity.

4.2. Typical procedure for the reaction with cuprate from RLi

The reaction of (*E*)-3,4-epoxy-1,1-difluoro-2-methyl-6-phenylhex-1-ene (**1a**) with CuI and MeLi is described as the representative example. To a flask containing 2.0 equiv of CuI (0.169 g, 0.90 mmol) and 3 mL of dry THF, 2.0 equiv of RLi (0.90 mmol) was added at 0 °C under argon. After 1 h stirring, **1a** (0.10 g, 0.45 mmol) was added with the aid of 2 mL of dry THF and the mixture was kept stirring for 2 h at 0 °C. Then the reaction was quenched with a mixture of saturated NH_4Cl aq and 10% NH_3 aq. The mixture was extracted with ether three times and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of solvents and purification by silica gel column chromatography (*n*-hexane:AcOEt=4:1), the desired product **2aa** was obtained in 87% yield. For the yields of other products, see Table 2.

4.3. Typical procedure for the reaction with cuprate from RMgX

The reaction of (*E*)-3,4-epoxy-1,1-difluoro-2-methyl-6-phenylhex-1-ene (**1a**) with CuCl and MeMgBr is described as the representative example. To a flask containing 2.0 equiv of CuCl (0.089 g, 0.90 mmol) and 3 mL of dry THF, 6.0 equiv of MeMgBr (2.70 mmol) was added at 0 °C under argon. After 1 h stirring, **1a** (0.10 g, 0.45 mmol) was added with the aid of 2 mL of dry THF and the mixture was kept stirring for 2 h at 0 °C. Then the reaction was quenched with a mixture of saturated NH_4Cl aq and 10% NH_3 aq. The mixture was extracted with ether three times and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of solvents and purification by silica gel column chromatography (*n*-hexane:AcOEt=4:1), the desired product **3aa** was obtained in 66% yield. For the yields of other products, see Table 2.

4.3.1. (*E*)-4,4-Difluoro-3-(2-phenylethyl)pent-2-en-1-ol (2da).

^{1}H NMR δ 0.88 (1H, m), 1.77 (3H, t, J=18.4 Hz), 2.44–2.51 (2H, m), 2.74–2.81 (2H, m), 3.91 (2H, tt, J=7.32, 2.47 Hz), 5.96 (1H, tdd, J=7.59, 2.47, 2.20 Hz), 7.17–7.35 (5H, m). ^{13}C NMR δ 23.5 (t, J=24.5 Hz), 28.5 (t, J=2.00 Hz), 35.6, 58.5, 122.5 (t, J=237.3 Hz), 126.0, 128.2, 128.6, 129.8 (t, J=8.59 Hz), 136.4 (t, J=24.1 Hz), 141.0. ^{19}F NMR δ 72.0 (1F, dq, J=18.5, 2.58 Hz), 72.3 (1F, dq, J=18.5, 2.58 Hz). IR (neat) ν 700, 753, 769, 861, 905, 1005, 1048, 1079, 1118, 1172, 1269, 1384, 1455, 1497, 1647, 2346, 2363, 2871, 2942, 3004, 3028, 3064, 3087, 3337 cm^{-1}. Anal. Calcd for $C_{13}H_{16}F_2O$: C, 69.01; H, 7.13. Found: C, 68.83; H, 7.04.

4.3.2. (*E*)-4,4-Difluoro-1,3-diphenylpent-2-en-1-ol (2fa).

^{1}H NMR δ 1.64 (3H, dd, J=18.4, 18.1 Hz), 5.02 (1H, d, J=9.34 Hz), 6.36 (1H, ddd, J=9.34, 2.20, 1.92 Hz), 7.22–7.48 (10H, m). ^{13}C NMR δ 23.6 (t, J=28.9 Hz), 70.7, 120.9 (dd, J=239.9, 239.6 Hz), 126.0, 127.8, 128.2, 128.3, 128.5, 129.6, 132.2 (dd, J=8.30, 8.02 Hz), 137.6 (dd, J=2.86, 2.58 Hz), 138.8 (dd, J=23.8, 23.5 Hz), 142.2 (t, J=1.15 Hz). ^{19}F NMR δ 70.7 (1F, dq, J=245.6, 18.1 Hz), 71.8 (1F, dq, J=245.6, 18.1 Hz). IR (neat) ν 700, 727, 761, 776, 822, 913, 931, 977, 1018, 1074, 1137, 1176, 1234, 1383, 1444, 1493, 1773, 1811, 1890, 1955, 2342, 2360, 2925, 3032, 3061, 3085, 3360, 3584 cm^{-1}. Anal. Calcd for $C_{17}H_{16}F_2O$: C, 74.44; H, 5.88. Found: C, 74.02; H, 5.92.

4.3.3. *anti*-6,6-Difluoro-4,5-dimethyl-1-phenylhex-5-en-3-ol (3aa).

^{1}H NMR δ 1.01 (3H, d, J=7.15 Hz), 1.55 (3H, dd, J=3.30, 3.02 Hz), 1.67 (1H, dtd, J=13.7, 9.89, 5.22 Hz), 1.90 (1H, dddd, J=13.7, 10.4, 6.59, 3.02 Hz), 2.50 (1H, brquint, J=7.14 Hz), 2.68 (1H, ddd, J=13.5, 9.89, 6.60 Hz), 2.87 (1H, ddd, J=13.7, 10.4, 5.22 Hz), 3.49 (1H, m), 7.18–7.34 (5H, m). ^{13}C NMR δ 8.35 (dd, J=2.29, 2.01 Hz), 15.0 (dd, J=2.57, 1.43 Hz), 32.0, 36.5, 37.8 (d, J=2.00 Hz), 72.8 (dd, J=2.29, 2.20 Hz), 86.2 (dd, J=17.2, 16.3 Hz), 125.7, 128.3, 128.3, 142.0, 153.2 (dd, J=283.4, 281.4 Hz). ^{19}F NMR δ 67.2 (1F, dq, J=56.2, 3.39 Hz), 67.5 (1F, brd, J=55.9 Hz). IR (neat) ν 700, 747, 926, 1046, 1125, 1214, 1270, 1389, 1454, 1496, 1603, 1749, 2874, 2933, 3028, 3063, 3457, 3585 cm^{-1}. Anal. Calcd for $C_{14}H_{18}F_2O$: C, 69.98; H, 7.55. Found: C, 69.76; H, 7.80.

4.3.4. *anti*-4-Ethyl-6,6-difluoro-5-methyl-1-phenylhex-5-en-3-ol (3ab).

^{1}H NMR δ 0.84 (3H, dd, J=7.44, 7.33 Hz), 1.31–1.60 (2H, m), 1.55 (3H, t, J=3.18 Hz), 1.71 (1H, dddd, J=13.7, 10.0, 8.91, 5.37 Hz), 1.88 (1H, dddd, J=13.7, 10.3, 6.47, 3.18 Hz), 2.25 (1H, m), 2.68 (1H, ddd, J=13.7, 10.0, 6.47 Hz), 2.85 (1H, ddd, J=13.8, 10.3, 5.37 Hz), 3.57 (1H, m), 7.10–7.40 (5H, m). ^{13}C NMR δ 8.32 (dd, J=2.29, 2.00 Hz), 11.8, 21.3 (dd, J=2.44, 1.58 Hz), 32.0, 36.8, 45.1 (d, J=2.29 Hz), 72.2 (m), 83.9 (dd, J=17.5, 16.0 Hz), 125.6, 128.2, 141.9, 154.2 (dd, J=284.0, 280.9 Hz). ^{19}F NMR δ 67.0 (1F, dd, J=52.7, 2.05 Hz), 68.7 (1F, dsex, J=54.9, 3.05 Hz). IR (neat) ν 700, 749, 814, 902, 1030, 1063, 1140, 1209, 1252, 1382, 1456, 1604, 1746, 2344, 2363, 2876, 2934, 2963, 3028, 3064, 3447, 3587 cm^{-1}. Anal. Calcd for $C_{15}H_{20}F_2O$: C, 70.84; H, 7.93. Found: C, 71.00; H, 7.89.

4.3.5. *anti*-4-(1,1-Difluoroprop-1-en-2-yl)-1-phenyloctan-3-ol (3ac).

^{1}H NMR δ 0.89 (3H, dd, J=7.42, 6.86 Hz), 1.05–1.45 (6H, m), 1.53 (3H, dd, J=3.30, 3.02 Hz), 1.70 (1H, dddd, J=14.0, 9.89, 8.79, 5.49 Hz), 1.87 (1H, m), 2.33 (1H, m), 2.68 (1H, ddd, J=13.7, 9.89, 6.32 Hz), 2.85 (1H, ddd, J=13.7, 10.2, 5.49 Hz), 3.55 (1H, m), 7.15–7.33 (5H, m). ^{13}C NMR δ 8.49 (t, J=2.29 Hz), 14.1, 22.7, 28.1 (dd, J=2.00, 1.71 Hz), 29.5, 32.1, 36.9, 43.3 (d, J=2.00 Hz), 72.4 (dd, J=2.29, 2.00 Hz), 84.3 (dd, J=17.4, 16.0 Hz), 125.7, 128.3, 128.3, 142.0, 154.2 (dd, J=284.0, 280.4 Hz). ^{19}F NMR δ 67.0 (1F, m), 68.6 (1F, dsex, J=55.1, 2.59 Hz). IR (neat) ν 700, 748, 917, 1067, 1132, 1205, 1272, 1388, 1456, 1496, 1746, 2364, 2862, 2933, 3027, 3063, 3481 cm^{-1}. Anal. Calcd for $C_{17}H_{24}F_2O$: C, 72.31; H, 8.57. Found: C, 72.21; H, 8.74.

4.3.6. *anti*-4-(1,1-Difluoroprop-1-en-2-yl)-1-phenyldodecan-3-ol (3ae). ^{1}H NMR δ 0.88 (3H, dd, J=7.08, 6.86 Hz), 1.00–1.60 (14H, m), 1.54 (3H, dd, J=3.27, 3.08 Hz), 1.71 (1H, dddd, J=13.9, 10.0, 8.67, 5.25 Hz), 1.87 (1H, dddd, J=13.8, 10.0, 6.22, 3.30 Hz), 2.33 (1H, m), 2.67 (1H, ddd, J=13.6, 10.0, 6.35 Hz), 2.85 (1H, ddd, J=13.9, 10.2, 5.25 Hz), 3.55 (1H, m), 7.15–7.32 (5H, m). ^{13}C NMR δ 8.36 (dd, J=2.29, 2.00 Hz), 14.1, 22.6, 28.2 (dd, J=2.29, 1.71 Hz), 29.2, 29.4, 29.5, 31.8, 32.0, 36.8, 43.2, 43.2, 72.3 (t, J=2.29 Hz), 84.1 (dd, J=16.2, 16.0 Hz), 125.6, 128.2, 141.2, 154.1 (dd, J=283.9, 280.9 Hz). ^{19}F NMR δ 67.1 (1F, d, J=54.9 Hz), 68.6 (1F, dd, J=55.7, 2.29 Hz). IR (neat) ν 699, 722, 747, 920, 1031, 1077, 1132, 1210, 1273, 1378, 1456, 1496, 1604, 1745, 1870, 1944, 2345, 2856, 2927, 3027, 3063, 3086, 3474 cm^{-1}. Anal. Calcd for $C_{21}H_{32}F_2O$: C, 74.52; H, 9.53. Found: C, 74.20; H, 9.42.

4.3.7. *anti*-6,6-Difluoro-5-methyl-1,4-diphenylhex-5-en-3-ol (3af). ^{1}H NMR δ 1.56 (3H, dd, J=3.30, 3.02 Hz), 1.53–1.68 (1H, m), 1.78 (1H, dddd, J=14.1, 9.61, 7.14, 2.47 Hz), 2.67 (1H, ddd, J=13.7, 9.34, 7.14 Hz), 2.86 (1H, ddd, J=14.0, 9.89, 5.22 Hz), 3.57 (1H, dt, J=9.61, 1.65 Hz), 4.14 (1H, m), 7.07–7.34 (10H, m). ^{19}F NMR δ 67.6 (1F, m), 68.3 (1F, ddt, J=53.4, 5.17, 3.02 Hz).

4.3.8. (*E*)-6,6-Difluoro-5-methyl-1-phenyloct-4-en-3-ol (2ab). ^{1}H NMR δ 0.96 (3H, t, J=7.42 Hz), 1.69 (3H, d, J=1.65 Hz), 1.70–2.03 (4H, m), 2.67 (1H, ddd, J=13.7, 8.79, 6.60 Hz), 2.74 (1H, ddd, J=13.7, 9.07, 6.04 Hz), 4.42 (1H, m), 5.80 (1H, dsex, J=8.51, 1.65 Hz), 7.12–7.36 (5H, m). ^{13}C NMR δ 6.72 (dd, J=5.43, 5.16 Hz), 12.0 (t, J=3.15 Hz), 28.7 (t, J=27.8 Hz), 31.4, 38.5 (t, J=1.15 Hz), 67.4, 123.0 (t, J=241.1 Hz), 125.7, 128.1, 128.2, 131.4 (t, J=8.59 Hz), 132.3 (dd, J=24.1, 23.8 Hz), 141.2. ^{19}F NMR δ 59.0 (1F, dt, J=240.4, 6.37 Hz), 60.0 (1F, dt, J=239.6, 6.37 Hz). IR (neat) ν 700, 747, 881, 970, 1021, 1103, 1173, 1224, 1330, 1387, 1455, 1496, 1604, 1752, 2861, 2942, 2983, 3028, 3063, 3355, 3588 cm^{-1}. Anal. Calcd for $C_{15}H_{20}F_2O$: C, 70.84; H, 7.93. Found: C, 70.42; H, 7.92.

4.4. Typical procedure for 5-*endo-trig* cyclization

The reaction of 6,6-difluoro-4,5-dimethyl-1-phenylhex-5-en-3-ol (**3aa**) is described as the representative example. To a flask containing NaH (0.027 g, 1.13 mmol; 2.5 equiv) and 2 mL of dry DMF, **3aa** (0.11 g, 0.45 mmol) was added with the aid of 3 mL of dry DMF at 0 °C under argon, and the whole mixture was heated to 100 °C. After 3 h stirring, the reaction was quenched with water. The mixture was extracted with ether three times and washed with brine, and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of solvents and purification by silica gel column chromatography (*n*-hexane), the desired product **4aa** was obtained in 70% yield.

4.4.1. *anti*-5-Fluoro-3,4-dimethyl-2-(2-phenylethyl)-2,3-dihydrofuran (4aa). ^{1}H NMR δ 1.06 (3H, dd, J=6.59, 1.37 Hz), 1.50 (3H, dd, J=1.65, 1.10 Hz), 1.86 (1H, ddddd, J=14.0, 10.2, 6.60, 4.40, 2.20 Hz), 2.02 (1H, ddddd, J=13.7, 9.67, 8.51, 5.49, 1.10 Hz), 2.55 (1H, m), 2.69 (1H, ddd, J=13.7, 9.61, 6.59 Hz), 2.81 (1H, ddd, J=13.7, 10.2, 5.49 Hz), 4.03 (1H, dddd, J=8.25, 6.87, 4.40, 1.10 Hz), 7.15–7.34 (5H, m). ^{13}C NMR δ 6.81 (d, J=2.30 Hz), 18.7 (d, J=2.00 Hz), 31.4, 36.9, 44.0 (d, J=3.72 Hz), 78.3 (d, J=14.6 Hz), 85.9 (d, J=1.71 Hz), 125.7, 128.2, 141.2, 154.3 (d, J=269.4 Hz). ^{19}F NMR δ 40.7 (s). IR (neat) ν 699, 748, 904, 1006, 1103, 1144, 1248, 1307, 1361, 1390, 1455, 1496, 1751, 2344, 2364, 2864, 2928, 3028, 3053 cm^{-1}.

4.4.2. *anti*-3-Ethyl-5-fluoro-4-dimethyl-2-(2-phenylethyl)-2,3-dihydrofuran (4ab). ^{1}H NMR δ 0.84 (3H, t, J=7.42 Hz), 1.34 (1H, dq, J=21.4, 7.42 Hz), 1.51 (3H, m), 1.56 (1H, m), 1.81 (1H, ddddd, J=14.0, 10.2, 6.60, 4.12, 2.48 Hz), 2.02 (1H, ddddd, J=14.0, 9.89, 8.82, 4.94, 1.10 Hz), 2.41 (1H, m), 2.69 (1H, ddd, J=13.7, 9.89, 6.86 Hz), 2.82 (1H, ddd, J=13.7, 10.2, 4.94 Hz), 4.15 (1H, dddd, J=8.79, 5.49, 4.12, 1.64 Hz), 7.15–7.34 (5H, m). ^{13}C NMR δ 7.39 (d, J=2.31 Hz), 10.2 (d, J=0.57 Hz), 25.5 (d, J=2.00 Hz), 31.5, 38.1, 50.5 (d, J=3.15 Hz), 76.7 (d, J=14.9 Hz), 83.1 (d, J=2.01 Hz), 125.8, 128.3, 128.3, 141.3, 154.5 (d, J=269.1 Hz). ^{19}F NMR δ 40.8 (s). IR (neat) ν 699, 746, 796, 886, 970, 1016, 1140, 1244, 1288, 1363, 1458, 1497, 1751, 2344, 2362, 2862, 2926, 3027 cm^{-1}.

4.5. General procedure of reaction with AlR_3

The reaction of (*E*)-3,4-epoxy-1,1-difluoro-2-methyl-6-phenylhex-1-ene (**1a**) and $AlMe_3$ is described as the representative example. 1.5 equiv of $AlMe_3$ was added to a solution of **1a** (0.10 g, 0.45 mmol) in 5 mL of dry *n*-hexane at 0 °C under argon, and the mixture was stirred for 1 h at that temperature. Quenching the reaction with 3 N HCl, the mixture was extracted with ether three times and the extracts were dried over anhydrous $MgSO_4$. After removal of solvents and purification by silica gel column chromatography (*n*-hexane:AcOEt=4:1), the desired product **5aa** was obtained in 88% yield. See Scheme 2 for yields of other products.

4.5.1. *syn*-6,6-Difluoro-4,5-dimethyl-1-phenylhex-5-en-3-ol (5aa). ^{1}H NMR δ 1.10 (3H, d, J=7.14 Hz), 1.43 (3H, dd, J=3.30, 3.02 Hz), 1.63 (1H, dtd, J=14.2, 9.34, 5.22 Hz), 1.83 (1H, dddd, J=14.0, 9.88, 7.14, 2.74 Hz), 2.43 (1H, m), 2.65 (1H, ddd, J=13.7, 9.34, 7.14 Hz), 2.85 (1H, ddd, J=14.0, 9.62, 5.22 Hz), 3.47 (1H, m), 7.18–7.35 (5H, m). ^{13}C NMR δ 8.43 (t, J=2.29 Hz), 14.4 (dd, J=2.87, 1.72 Hz), 32.1, 36.8, 38.0 (d, J=2.29 Hz), 73.4 (dd, J=3.73, 2.29 Hz), 87.0 (dd, J=17.8, 16.3 Hz), 125.7, 128.3, 128.3, 141.7, 152.7(dd, J=283.1, 281.1 Hz). ^{19}F NMR δ 66.2 (1F, brd, J=56.1 Hz), 67.2 (1F, m). IR (neat) ν 698, 744, 1037, 1117, 1214, 1268, 1454, 1749, 2873, 2931, 3362 cm^{-1}. Anal. Calcd for $C_{14}H_{18}F_2O$: C, 69.98; H, 7.55. Found: C, 70.01; H, 7.59.

4.5.2. *syn*-4-Ethyl-6,6-difluoro-5-methyl-1-phenylhex-5-en-3-ol (5ab). ^{1}H NMR δ 0.83 (3H, dd, J=7.42, 7.14 Hz), 1.20–1.30 (2H, m), 1.38 (3H, dd, J=3.29, 3.02 Hz), 1.61 (1H, dtd, J=14.3, 9.34, 5.22 Hz), 1.77–1.91 (1H, m), 2.20 (1H, m), 2.66 (1H, ddd, J=13.7, 9.34, 7.29 Hz), 2.86 (1H, ddd, J=14.3, 9.61, 5.22 Hz), 3.47 (1H, m), 7.15–7.33 (5H, m). ^{13}C NMR δ 8.05 (t, J=2.29 Hz), 11.8, 20.8 (dd, J=2.58, 1.72 Hz), 32.0, 37.1,45.7 (d, J=2.00 Hz), 72.8 (dd, J=3.59, 2.15 Hz), 84.3 (dd J=18.0, 17.6 Hz), 125.8, 128.3, 128.3, 141.8, 153.9 (dd, J=283.1, 280.9 Hz). ^{19}F NMR δ 66.8 (1F, m), 67.6 (1F, dsex, J=55,1, 1.29 Hz). IR (KBr) ν

480, 513, 540, 591, 646, 699, 725, 746, 771, 817, 890, 913, 959, 1039, 1059, 1125, 1164, 1206, 1251, 1280, 1322, 1364, 1380, 1458, 1492, 1603, 1654, 1752, 2345, 2363, 2875, 2932, 2956, 3027, 3300 cm^{-1}. Anal. Calcd for $C_{15}H_{20}F_2O$: C, 70.84; H, 7.93. Found: C, 71.03; H, 8.28. mp: 40 °C.

4.5.3. 3-Difluoromethylidene-2-methyl-5-phenylpentan-1-ol (5da). ^1H NMR δ 1.05 (3H, d, $J=7.14$ Hz), 2.24 (2H, m), 2.56 (1H, tqd, $J=7.42$, 7.14, 1.10 Hz), 2.70–2.78 (2H, m), 3.50 (2H, d, $J=7.42$ Hz), 7.15–7.33 (5H, m). ^{13}C NMR δ 15.0 (t, $J=2.29$ Hz), 27.1 (d, $J=2.86$ Hz), 35.0 (t, $J=2.86$ Hz), 35.5 (dd, $J=2.86$, 0.57 Hz), 65.5 (dd, $J=2.86$, 2.57 Hz), 90.1 (dd, $J=15.5$, 14.3 Hz), 126.1, 128.2, 128.3, 141.2, 154.1 (t, $J=286.3$ Hz). ^{19}F NMR δ 69.3 (1F, d, $J=53.9$ Hz), 71.0 (1F, d, $J=53.9$ Hz). IR (neat) ν 669, 699, 750, 835, 890, 956, 1030, 1075, 1092, 1126, 1173, 1211, 1256, 1364, 1454, 1497, 1604, 1696, 1700, 1740, 1803, 1870, 1943, 2342, 2361, 2876, 2934, 2964, 3028, 3064, 3087, 3348 cm^{-1}. Anal. Calcd for $C_{13}H_{16}F_2O$: C, 69.01; H, 7.13. Found: C, 68.93; H, 7.61.

4.5.4. 2-Ethyl-3-difluoromethylidene-5-phenylpentan-1-ol (5db). ^1H NMR δ 0.90 (3H, t, $J=7.42$ Hz), 1.18–1.42 (1H, m), 1.42–1.62 (1H, m), 2.10–2.32 (2H, m), 2.39 (1H, tt, $J=8.79$, 5.77 Hz), 2.75 (2H, m), 3.50 (1H, m), 3.59 (1H, dd, $J=11.0$, 5.77 Hz), 7.15–7.35 (5H, m). ^{13}C NMR δ 12.0, 22.0 (t, $J=2.29$ Hz), 26.8 (d, $J=2.58$ Hz), 34.8 (dd, $J=3.15$, 2.86 Hz), 42.9 (dd, $J=2.58$, 0.86 Hz), 64.2 (t, $J=2.58$ Hz), 88.4 (dd, $J=15.2$, 14.9 Hz), 126.0, 128.1, 128.3, 141.3, 154.7 (dd, $J=286.3$, 286.0 Hz). ^{19}F NMR δ 69.1 (1F, d, $J=52.6$ Hz), 72.2 (1F, d, $J=53.0$ Hz). IR (neat) ν 699, 751, 814, 844, 905, 936, 1008, 1040, 1128, 1171, 1208, 1250, 1381, 1454, 1497, 1381, 1454, 1497, 1604, 1740, 2346, 2362, 2875, 2934, 2963, 3028, 3064, 3087, 3343 cm^{-1}. Anal. Calcd for $C_{14}H_{18}F_2O$: C, 69.98; H, 7.55. Found: C, 69.50; H, 7.28.

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Isoprene-catalyzed lithiation of imidazole: synthesis of 2-(hydroxyalkyl)- and 2-(aminoalkyl)imidazoles

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Received 22 July 2005; revised 6 September 2005; accepted 8 September 2005

Available online 29 September 2005

Abstract—2-Lithioimidazole was prepared by means of a new protocol, which consists of a slight excess of lithium metal in the presence of a substoichiometric amount of isoprene (20 mol%) in THF at room temperature. By reacting this organolithium with carbonyl electrophiles 2-(hydroxyalkyl)imidazoles **3** were obtained, in good yields. As a result of the reaction of the mentioned lithium intermediate with imines **4**, the corresponding 2-(aminoalkyl)imidazoles **5** were isolated in excellent yields.

1. Introduction

Among heterocycles, azoles are important compounds not only because of their abundance in nature but also for their widespread presence in compounds with pharmacological and biological properties.[1] The preparation of 2-substituted 1,3-azoles from different acyclic precursors[2] or by transformation of 1,3-azole systems,[3] is a broad field of interest both for synthetic organic and medicinal chemists.

During the last three decades, lithium and other metalated imidazole derivatives (generally prepared starting from the corresponding lithium precursors) have been very useful intermediates for the introduction of substituents in the heterocyclic system.[2] These compounds have extensive application in organic synthesis.[4] Lithiation reactions and halogen–lithium exchanges have been studied using alkyllithium reagents or lithium amides as lithiating agents.[2,5] In order to prepare these intermediates, reaction conditions usually involving low temperature in an ethereal solvent. An extensive variety of electrophiles have been reacted with these carbanionic compounds allowing the introduction of different substituents at the two position (such as alkyl,[6] alkenyl,[7] hydroxyalkyl,[5,8] halogen,[9] acyl,[10] carboxyl,[11] silyl,[12] sulfanyl[13] or azido[14]). However, the use of imine compounds as electrophiles has not been investigated. Zificsak and Hlasta have very recently reported the use of *N*-protected-imines (mainly as sulfonyl derivatives) as electrophiles for functionalizing imidazole via imidazolium ylides (a non-organometallic compound) as intermediates.[15]

One effective methodology to activate lithium involves using an arene in substoichiometric amount as electron carrier.[16] Lithium metal is a lithiation agent that has been widely used especially for the halogen–lithium exchange, albeit usually it must be activated to permit the preparation of different organolithium intermediates under mild conditions. Different functionalized organolithium reagents[17] have been prepared starting from different substrates (i.e., halogenated or non-halogenated compounds,[18] as well as heterocyclic precursors[19]). In this paper, we describe a new protocol to prepare 2-lithio-imidazole intermediates by using lithium metal and a catalytic amount of isoprene under very mild conditions and their reaction with carbonyl and imine electrophiles in order to produce 2-(hydroxyalkyl)- and 2-(aminoalkyl)imidazole derivatives.

2. Results and discussion

In the course of our recent investigations on dianions[20] derived from carboxylic acids and derivatives,[21] we worked with different bases and found that lithium metal is able to generate 2-lithio-*N*-methylimidazole and used in some cases as a deprotonating agent. Thus, when treating *N*-methylimidazole (NMI, **1**) with lithium powder in THF, the corresponding 2-lithio derivative is generated and can be trapped by deuterium giving the 2-deutero-*N*-methylimidazole (**2**, 75% yield, 87% deuterium incorporation, Scheme 1).

Keywords: Imidazole; Isoprene-catalyzed lithiation; Carbonyl compounds; Imines; Deprotonation.
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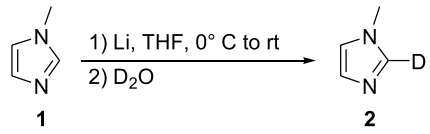
doi:10.1016/j.tet.2005.09.024



Scheme 1.

The reaction conditions for this new procedure to prepare 2-lithio-*N*-methylimidazole and the subsequent reaction with an electrophile was investigated using 3-pentanone (Table 1). When the lithiation and S_E reaction were performed at room temperature, better results were in general obtained than at 0 °C (Table 1, compare entries 1–3 and 4–12). The use of an additive, such as isoprene, was a determining factor to improve the yield of the final product, from 35 to 62% at 0 °C (Table 1, entries 2 and 3) and getting up to 96% of product **3a** when performing the reaction at room temperature (Table 1, entries 5–8). The amount of isoprene could be reduced to 20% without reducing the yield. On the other hand, using diethyl ether as solvent instead of tetrahydrofuran, the yield of the product **3a** was reduced to the half (Table 1, entry 8 and footnote e).

Concerning the role of isoprene in the reaction, it can act both as electron carrier agent[22] and as a hydrogen acceptor.[23] The use of other electron carriers (i.e., 4,4′-di-*tert*-butyl-biphenyl, naphthalene) did not improve the obtained results (Table 1, entries 9 and 10, and footnote d).

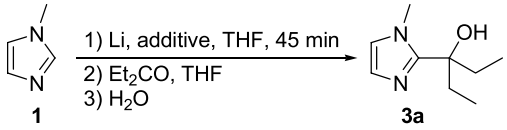
From the above results we concluded that the best conditions to generate the lithium imidazole intermediate are slight excess of lithium together with 20% of isoprene in THF at room temperature. In order to look into the scope of the reaction we submitted different carbonyl compounds to the above described protocol. As shown in Table 2, all the examined electrophiles gave the corresponding 2-(hydroxyalkyl)imidazoles (**3a–i**) with good isolated yields, including aldehydes and ketones with α-protons (Table 2, entries 1–4, 6 and 9). The present procedure allowed the isolation of the final products **3** with comparable or better yields than those already described in the literature.[1,2,5]

The excellent results achieved with carbonyl electrophiles suggested to us the idea of using imines in this reaction. Thus, by employing the synthetic procedure described previously, *N*-benzylideneaniline (**4a**) gave the corresponding amino derivative **5a** in 94% yield (Scheme 2, Table 3, entry 1). Reactions with different aryl aldimines **4b–g** gave the corresponding amine derivatives in good yield (Table 3, entries 2–7), except when nitroaryl imines were used, for which the final product was detected in the crude product in poor yield (Table 3, entries 4 and 5). Ketimine **4h** prepared from acetophenone and aniline did not react with the 2-lithio intermediate. Heating up the reaction gave only traces of product in the reaction mixture (Table 3, entry 8).

4a: R^1 = Ph; R^2 = H; R^3 = Ph
4b: R^1 = 4-MeOC$_6$H$_4$; R^2 = H; R^3 = Ph
4c: R^1 = 4-ClC$_6$H$_4$; R^2 = H; R^3 = Ph
4d: R^1 = 4-O$_2$NC$_6$H$_4$; R^2 = H; R^3 = Ph
4e: R^1 = 3-O$_2$NC$_6$H$_4$; R^2 = H; R^3 = Ph
4f: R^1 = Ph; R^2 = H; R^3 = 4-MeOC$_6$H$_4$
4g: R^1 = Ph; R^2 = H; R^3 = 4-ClC$_6$H$_4$
4h: R^1 = Ph; R^2 = Me; R^3 = Ph
4i: R^1 = Ph; R^2 = H; R^3 = SiMe$_3$
4j: R^1 = Bu^t; R^2 = H; R^3 = SiMe$_3$

Starting imines **4** were prepared according to the literature procedure[24] from the corresponding carbonyl compound

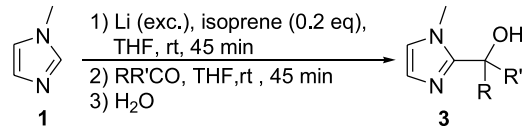
Table 1. Reaction conditions for generating 2-lithio-*N*-methylimidazole[a]

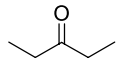
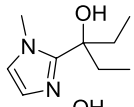
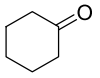
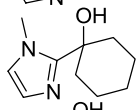
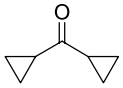
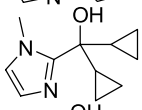
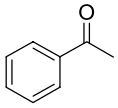
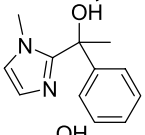
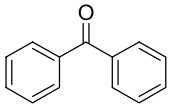
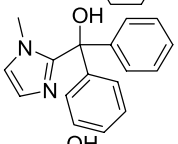
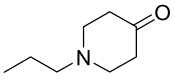
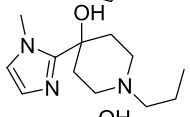
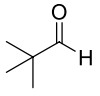
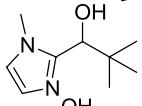
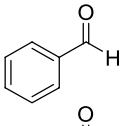
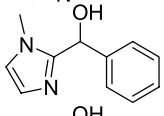
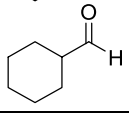
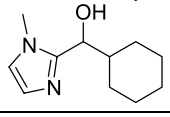


Entry	mmol Li/mmol substrate	Additive (equiv)[b]	*T* (°C)	Yield (%)[c]
1	1.2	—	0	26
2	3	—	0	35
3	3	Isoprene (1)	0	62
4	3	—	25	86
5	3	Isoprene (1)	25	95
6	3	Isoprene (2)	25	96
7	3	Isoprene (0.5)	25	95
8	3	Isoprene (0.2)	25	95 51[e]
9	3	DTBB (0.05)[d]	25	71
10	3	Naphthalene (0.05)[d]	25	84
11	2	—	25	65 63[f]
12	2	Isoprene (0.2)	25	68

[a] Reaction carried out using: NMI (5 mmol), Et_2CO (5.5 mmol), THF (10 mL).
[b] Additive added to the lithium suspension prior the addition of NMI. Equivalents of additive referred to the NMI.
[c] Isolated yield of pure product. Purification was done by recrystallization.
[d] Stirred with lithium in THF until formation of the arene dianion (dark-green solution) before adding the NMI.
[e] Reaction carried out in Et_2O as solvent instead of THF.
[f] Reaction time for lithiation step: 90 min.

Table 2. Reaction of 2-lithio-*N*-methylimidazole with different carbonyl compounds[a]

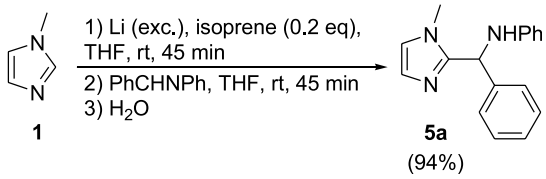


Entry	Electrophile	Product		
		No.		Yield (%)[b]
1		**3a**		95
2		**3b**		95
3		**3c**		>99
4		**3d**		91
5		**3e**		99
6		**3f**		80
7		**3g**		94
8		**3h**		77[c]
9		**3i**		79

[a] Reactions performed with NMI (5 mmol), Li (15 mmol), isoprene (1 mmol), THF (10 mL) and then added electrophile (5.5 mmol).
[b] Isolated yield of pure product. Purification was done by recrystallization.
[c] Purification by column chromatography (pH=6.7–7.3 silica gel, mixtures of hexane and ethyl acetate).

and amine in chloroform in the presence of molecular sieves.

The use of *N*-silylated imines in the reaction shown in Table 3 would allow the preparation of the corresponding primary amine derivatives. Thus, *N*-silylimines **4i** and **4j** (prepared from the corresponding aldehydes and lithium hexamethyldisilazanide)[25] were reacted in situ to yield in good yields after acid/base work-up the corresponding products **5i** and **5j** (Scheme 3).

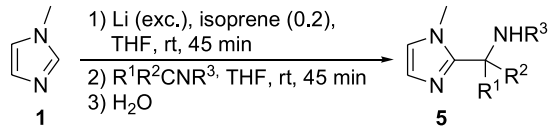


Scheme 2.

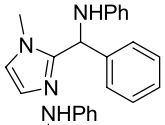
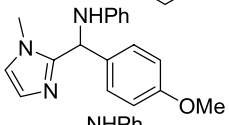
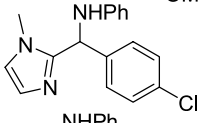
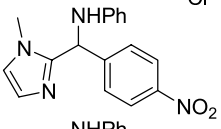
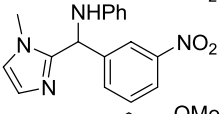
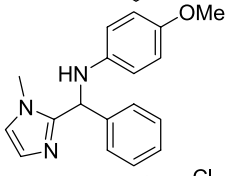
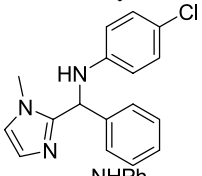
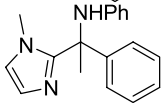
3. Conclusions

In this paper, we have developed a new protocol to prepare 2-lithioimidazole using a slightly excess of lithium metal in the presence of a substoichometric amount of isoprene (20 mol%) at room temperature. The reaction of this intermediate with different carbonyl compounds gave the corresponding 2-(hydroxyalkyl)imidazole derivatives with excellent yields, that were comparable or better than those reported in the literature. The reaction of the organolithium intermediate with imine electrophiles allowed the isolation of new interesting 2-[(*N*-arylamino)benzyl]imidazoles in good yields. Primary amino functionalized imidazoles were obtained by using *N*-silylimines.

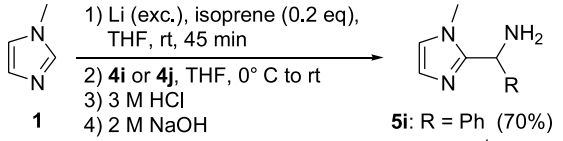
Table 3. Reaction of 2-lithio-*N*-methylimidazole with different imines[a]



1 **5**

Entry	Electrophile	Product		
		No.		Yield (%)[b]
1	**4a**	**5a**		94
2	**4b**	**5b**		92
3	**4c**	**5c**		88
4	**4d**	**5d**		24[c]
5	**4e**	**5e**		25[c]
6	**4f**	**5f**		91
7	**4g**	**5g**		93[d]
8	**4h**	**5h**		—[e]

[a] Reactions performed with NMI (5 mmol), Li (15 mmol), isoprene (1 mmol), THF (10 mL) and then added electrophile (5.5 mmol).
[b] Isolated yield of pure product **5**. Purification was done by recrystallization.
[c] Yield based on GLC, the product **5** was not isolated.
[d] Purification by column chromatography (pH=6.7–7.3 silica gel, mixtures of hexane and ethyl acetate).
[e] Reaction carried out at reflux on THF. Less than 3% of compound **5h** observed by GLC.



1

5i: R = Ph (70%)
5j: R = Bu^t (87%)

Scheme 3.

4. Experimental

4.1. General

All lithiation reactions were carried out under argon atmosphere in oven-dried glassware. All commercially available reagents (Acros, Aldrich, Fluka) were used without further purification, except in the case of liquid electrophiles, which were used freshly distilled. Commercially available anhydrous THF (99.9%, water content $\leq$0.006%, Acros) was used as solvent in all the lithiation reactions. Melting points were obtained with a Reichert Thermovar apparatus. IR spectra were measured with a Nicolet Impact 400 D-FT spectrometer. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are given in δ (ppm) and coupling constants (J) in Hz. Mass spectra (EI) were obtained at 70 eV on an Agilent 5973 spectrometer, fragment ions in m/z with relative intensities (%) in parenthesis and high resolution mass spectra (HRMS) analyses were carried out on a Finnigan MAT95S

spectrometer, when indicated the samples were inserted in the modality of direct insertion probed (DIP). The purity of volatile and the chromatographic analyses (GLC) were determined with an Agilent 6890N instrument equipped with a flame ionization detector and a 30 m capillary column (0.25 mm diameter, 0.25 μm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{injector}=275$ °C, $T_{column}=60$ °C (3 min) and 60–270 °C (15 °C/min); retention times (t_r) are given in minutes under these conditions. Column chromatography was performed using silica gel of 40 μm (J. T. Baker, pH=6.7–7.3 of 10% aqueous suspension). Thin-layer chromatography was carried out on TLC plastic sheets with silica gel 60 F_{254} (Merck). Lithium powder was commercially available (MEDALCHEMY S. L.).

4.2. Procedure for deuteration of 2-lithio-*N*-Methylimidazole

4.2.1. Preparation of 2-deuterio-*N*-Methylimidazole (2). *N*-Methylimidazole (403 μL, 5 mmol) was added to a suspension of lithium powder (105 mg, 15 mmol) in THF (10 mL) at 0 °C. The mixture was stirred for 45 min allowing the reaction to reach room temperature and then deuterium oxide (0.5 mL) was added. Water (15 mL) was added to the reaction mixture and then extracted with diethyl ether (3×15 mL). The organic phase was dried over anhydrous magnesium sulfate and after removal of the solvent under reduced pressure (15 Torr), the desired product **2** was obtained in 75% yield (87% deuterium incorporation): δ_H 3.65 (3H, s, CH_3), 6.86, 7.01 (1H and 1H, 2s, CHCH); δ_C 32.7 (CH_3), 119.6, 128.7 (CHCH), 137.0 (t, $J=31.3$ Hz, CD); *m/z* 84 ($M^+ +1$, 9%), 83 (100), 82 (32), 55 (14), 54 (13).

4.3. General procedure for the preparation of 2-(hydroxylalkyl)imidazoles 3

N-Methylimidazole (403 μL, 5 mmol) was added to a suspension of lithium powder (105 mg, 15 mmol) and isoprene (101 μL, 1 mmol) in THF (10 mL) at room temperature. The mixture was stirred for 45 min and then the corresponding carbonyl compound (5.5 mmol) was added, continuing the stirring during 45 min at the same temperature. The reaction mixture was hydrolyzed with water (15 mL), extracted with ethyl acetate (3×15 mL), and the organic phase was dried over anhydrous magnesium sulfate. After removing the solvent under reduced pressure (15 Torr), the resulting crude was purified by recrystallization (from mixtures of ethyl acetate and *n*-pentane) to yield compounds **3**. Compound **3h** was purified by column chromatography (pH=6.7–7.3 silica gel, mixtures of hexane and EtOAc).

4.3.1. 3-(1-Methyl-1*H*-imidazol-2-yl)pentan-3-ol (3a). Yield 95%; white solid; t_r 10.00; R_f 0.36 (EtOAc/MeOH 8:1); mp 114–116 °C; ν (KBr) 3640–3011 cm^{-1} (OH); δ_H 0.78 (6H, t, $J=7.4$ Hz, 2×CH_2CH_3), 1.86–1.95 (4H, m, 2×CH_2), 3.74 (3H, s, NCH_3), 3.80 (1H, br s, OH), 6.81, 6.89 (1H and 1H, 2s, CHCH); δ_C 7.8 (2C, 2×CH_2CH_3), 32.6 (2C, 2×CH_2), 34.5 (NCH_3), 75.6 (COH), 122.9, 125.5 (CHCH), 150.2 (NCN); *m/z* 168 (M^+, 5%), 140 (10), 139 (100), 83 (58). HRMS calcd for $C_9H_{16}N_2O$ 168.1263, found 168.1266.

4.3.2. 1-(1-Methyl-1*H*-imidazol-2-yl)-cyclohexanol (3b).[8] Yield 95%; white solid; t_r 12.70; R_f 0.37 (EtOAc/MeOH 8:1); mp 165–166 °C; ν (KBr) 3720–2993 cm^{-1} (OH); δ_H 1.26–1.36, 1.59–1.79, 1.92–1.95 (1H, 5H and 4H, 3m, 5×CH_2), 3.86 (3H, s, CH_3), 3.94 (1H, s, OH), 6.79, 6.80 (1H and 1H, 2s, CHCH); δ_C 21.3, 25.2, 36.2 (5C, 5×CH_2), 34.7 (CH_3), 70.8 (COH), 122.6, 125.0 (CHCH), 152.1 (NCN); *m/z* 181 ($M^+ +1$, 7%), 180 (30%), 163 (52), 162 (16), 161 (11), 151 (22), 138 (29), 137 (100), 135 (10), 133 (11), 126 (11), 125 (55), 124 (11), 123 (17), 110 (22), 109 (67), 96 (60), 95 (15), 83 (40), 82 (24), 81 (22), 55 (11).

4.3.3. Dicyclopropyl(1-methyl-1*H*-imidazol-2-yl)-methanol (3c). Yield 99.5%; white solid; t_r 12.42; R_f 0.43 (EtOAc/MeOH 8:1); mp 102–103 °C; ν (KBr) 3690–3039 cm^{-1} (OH); δ_H 0.28–0.42, 0.46–0.55, 0.66–0.74, 1.25–1.34 (4H, 2H, 2H and 2H, 4m, 4×CH_2 and 2×CH ring), 3.85 (3H, s, CH_3), 6.82, 6.85 (1H and 1H, 2s, NCHCHN); δ_C 0.01, 1.6 (4C, 4×CH_2), 18.7 (2C, 2×CH ring), 34.8 (CH_3), 70.8 (COH), 123.0, 125.1 (NCHCHN), 152.4 (NCN); *m/z* 192 (M^+, 8%), 177 (19), 175 (10), 163 (24), 152 (10), 151 (100), 149 (37), 136 (13), 135 (32), 123 (23), 121 (17), 109 (54), 96 (23), 95 (11), 83 (46), 82 (10), 81 (10), 69 (13). HRMS (DIP) calcd for $C_{11}H_{16}N_2O$ 192.1263, found 192.1262.

4.3.4. 1-(1-Methyl-1*H*-imidazol-2-yl)-1-phenylethanol (3d).[8] Yield 91%; pale yellow solid; t_r 13.44; R_f 0.57 (EtOAc/MeOH 8:1); mp 164–165 °C; ν (KBr) 3635–3014 cm^{-1} (OH); δ_H 1.93 (3H, s, CCH_3), 3.04 (1H, br s, OH), 3.29 (3H, s, NCH_3), 6.78, 6.87 (1H and 1H, 2s, NCHCHN), 7.20–7.33 (5H, m, ArH); δ_C 31.6, 34.1 (2×CH_3), 72.9 (COH), 122.7, 124.6, 125.3, 126.9, 128.2 (7C, ArCH and NCHCHN), 145.5 (ArC), 151.1 (NCN); *m/z* 203 ($M^+ +1$, 12%), 202 (89), 201 (45), 188 (13), 187 (100), 185 (17), 184 (13), 183 (26), 125 (35), 111 (12), 109 (41), 105 (36), 83 (27), 77 (29).

4.3.5. (1-Methyl-1*H*-imidazol-2-yl)diphenylmethanol (3e).[26] Yield 99%; white solid; t_r 17.08; R_f 0.74 (EtOAc/MeOH 8:1); mp 191–192 °C; ν (KBr) 3629–2836 cm^{-1} (OH); δ_H 2.87 (1H, br s, OH), 3.30 (3H, s, CH_3), 6.85, 6.90 (1H and 1H, 2s, NCHCHN), 7.25–7.35 (10H, m, ArH); δ_C 34.8 (CH_3), 78.3 (COH), 123.1, 125.8, 127.2, 127.5, 128.0 (12C, ArCH and NCHCHN), 144.3 (2C, ArC), 150.5 (NCN); *m/z* 249 ($M^+ -$Me, 8%), 248 (49), 247 (100), 165 (22), 157 (19). HRMS (DIP) calcd for $C_{17}H_{16}N_2O$ 264.1263, found 264.1240.

4.3.6. 4-(1-Methyl-1*H*-imidazol-2-yl)-1-propylpiperidin-4-ol (3f). Yield 80%; pale yellow solid; t_r 14.78; R_f 0.27 (MeOH); mp 149–151 °C; ν (KBr) 3640–3006 cm^{-1} (OH); δ_H 0.90 (3H, t, $J=7.3$ Hz, CH_2CH_3), 1.45–1.57, 1.73–1.78, 2.03–2.12, 2.28–2.33, 2.40–2.47, 2.59–2.62 (2H, 2H, 2H, 2H, 2H and 2H, 6m, 6×CH_2), 3.85 (3H, s, NCH_3), 5.08 (1H, br s, OH), 6.60, 6.71 (1H and 1H, 2s, CHCH); δ_C 12.0 (CH_2CH_3), 34.6 (NCH_3), 20.1, 35.7, 49.1, 60.6 (6C, 6×CH_2), 68.6 (COH), 122.5, 125.4 (CHCH), 151.4 (NCN); *m/z* 223 (M^+, 5%), 206 (19), 205 (100), 204 (23), 194 (26), 176 (13), 162 (11), 137 (31), 135 (12), 125 (76), 112 (13), 109

(12), 100 (31), 95 (16), 86 (11), 84 (32), 83 (36), 82 (17). HRMS calcd for $C_{12}H_{21}N_3O$ 223.1685, found 223.1668.

4.3.7. 2,2-Dimethyl-1-(1-methyl-1*H*-imidazol-2-yl)propan-1-ol (3g).[27] Yield 94%; white solid; t_r 10.69; R_f 0.37 (EtOAc/MeOH 8:1); mp 83–85 °C; ν (KBr) 3705–3011 cm^{-1} (OH); δ_H 0.97 [9H, s, $C(CH_3)_3$], 3.67 (3H, s, NCH_3), 4.22 (1H, br s, OH), 4.39 (1H, s, C*H*OH), 6.77, 6.92 (1H and 1H, 2s, CHCH); δ_C 25.8 [3C, $C(CH_3)_3$], 33.5 (NCH_3), 37.1 [$C(CH_3)_3$], 74.0 (CHOH), 120.8, 126.7 (CHCH), 148.8 (NCN); *m/z* 168 (M^+, 4%), 112 (45), 111 (100), 83 (10).

4.3.8. (1-Methyl-1*H*-imidazol-2-yl)-phenylmethanol (3h).[28] Yield 77%; amber solid; t_r 13.93; R_f 0.49 (EtOAc/MeOH 8:1); mp 109–110 °C; ν (KBr) 3601–2968 cm^{-1} (OH); δ_H 3.33 (3H, s, CH_3), 5.94 (1H, s, C*H*OH), 6.59, 6.68 (1H and 1H, 2s, NCHCHN), 7.15–7.32 (5H, m, ArH), 8.03 (1H, br s, OH); δ_C 33.0 (CH_3), 68.4 (CHOH), 121.8, 125.5, 125.6, 126.8, 127.9 (7C, ArCH and NCHCHN), 141.0 (ArC), 149.1 (NCN); *m/z* 189 ($M^+ + 1$, 13%), 188 (100), 187 (56), 171 (20), 170 (11), 169 (17), 111 (48), 109 (10), 105 (16), 97 (32), 83 (23), 82 (14), 81 (13), 79 (13), 77 (32).

4.3.9. Cyclohexyl(1-methyl-1*H*-imidazol-2-yl)methanol (3i).[29] Yield 79%; pale yellow solid; t_r 14.15; R_f 0.46 (EtOAc/MeOH 8:1); mp 110–111 °C; ν (KBr) 3690–2994 cm^{-1} (OH); δ_H 0.86–1.29, 1.63–1.66, 1.75–1.87, 2.08–2.13 (6H, 2H, 2H and 1H, 4m, 5×CH_2 and CH ring), 3.68 (3H, s, CH_3), 4.35 (1H, d, J=8.4 Hz, C*H*OH), 4.85 (1H, br s, OH), 6.76, 6.87 (1H and 1H, 2s, CHCH); δ_C 25.7, 25.9, 26.3, 29.2, 29.3 (5×CH_2), 33.0, 43.3 (CH ring and CH_3), 71.4 (CHOH), 121.0, 126.5 (CHCH), 149.6 (NCN); *m/z* 194 (M^+, 3%), 112 (78), 111 (100), 83 (11).

4.4. General procedure for the preparation of imines 4b–h

To a solution of a carbonyl compound (10 mmol) in chloroform (30 mL) was added an amine (12 mmol) and molecular sieve (3.7 g) at room temperature. After being stirred for a certain period of time (TLC), the crude was rinsed with K_2CO_3–brine solution (3×20 mL) and the crude product was concentrated under reduced pressure (15 Torr). Imines **4** were purified by recrystallization from mixtures of ethyl acetate and *n*-pentane. Imines **4b** and **4c** were washed very carefully with cold *n*-pentane due to their solubility. The imine **4h** was purified by distillation.

4.4.1. *N*-(4-Methoxybenzylidene)aniline (4b).[30] Yield 79%; pale yellow solid; t_r 15.80; R_f 0.42 (hexane/EtOAc 8:1); mp 55–56 °C; ν (KBr) 1621 cm^{-1} (C=N); δ_H 3.85 (3H, s, CH_3), 6.96–6.98, 7.18–7.22, 7.35–7.40, 7.83–7.86 (2H, 3H, 2H and 2H, 4m, 9×ArH), 8.37 (1H, s, CHN); δ_C 55.4 (CH_3), 114.1, 120.8, 125.5, 129.1, 130.5 (9C, ArCH), 129.2, 152.2, 162.2 (ArC), 159.7 (CHN); *m/z* 212 ($M^+ + 1$, 12%), 211 (87), 210 (100), 167 (11), 77 (21).

4.4.2. *N*-(4-Chlorobenzylidene)aniline (4c).[30] Yield 82%; pale yellow solid; t_r 15.21; R_f 0.61 (hexane/EtOAc 8:1); mp 60–61 °C; ν (KBr) 1622 cm^{-1} (C=N); δ_H 7.19–7.26, 7.37–7.45, 7.82–7.85 (3H, 4H and 2H, 3m, 9×ArH), 8.41 (1H, s, CHN); δ_C 120.8, 126.2, 129.0, 129.2, 129.9 (9C, ArCH), 134.7, 137.3, 151.6 (ArC), 158.8 (CHN); *m/z* 217 ($M^+ + 2$, 32%), 216 (45), 215 (94), 214 (100), 104 (10), 77 (40), 51 (10).

4.4.3. *N*-(4-Nitrobenzylidene)aniline (4d).[31] Yield 95%; orange solid; t_r 16.97; R_f 0.29 (hexane/EtOAc 8:1); mp 79–80 °C; ν (KBr) 1599 (C=N), 1518, 1344 cm^{-1} (C–NO_2); δ_H 7.24–7.33, 7.40–7.46, 8.05–8.09, 8.29–8.34 (3H, 2H, 2H and 2H, 4m, 9×ArH), 8.55 (1H, s, CHN); δ_C 120.9, 123.9, 127.0, 129.3, 129.4 (9C, ArCH), 141.5, 149.2, 150.8 (ArC), 157.3 (CHN); *m/z* 227 ($M^+ + 1$, 15%), 226 (100), 225 (45), 179 (44), 152 (10), 104 (17), 77 (39), 51 (11).

4.4.4. *N*-(3-Nitrobenzylidene)aniline (4e).[32] Yield 89%; yellow solid; t_r 16.99; R_f 0.31 (hexane/EtOAc 8:1); mp 63–64 °C; ν (KBr) 1613 (C=N), 1529, 1350 cm^{-1} (C–NO_2); δ_H 7.23–7.31, 7.40–7.45, 7.62–7.68, 8.23–8.33 (3H, 2H, 1H and 2H, 4m, 8×ArH), 8.53, 8.73 (1H and 1H, 2s, ArH and CHN); δ_C 120.9, 123.4, 125.5, 126.8, 129.3, 129.7, 134.0 (9C, ArCH), 137.8, 148.6, 150.8 (ArC), 157.1 (CHN); *m/z* 227 ($M^+ + 1$, 15%), 226 (100), 225 (40), 180 (11), 179 (17), 152 (10), 104 (18), 77 (32).

4.4.5. *N*-Benzylidene-4-methoxyaniline (4f).[30] Yield 90%; yellow solid; t_r 15.74; R_f 0.44 (hexane/EtOAc 8:1); mp 70–71 °C; ν (KBr) 1622 cm^{-1} (C=N); δ_H 3.81 (3H, s, CH_3), 6.90–6.94, 7.22–7.25, 7.44–7.46, 7.86–7.90 (2H, 2H, 3H and 2H, 4m, 9×ArH), 8.47 (1H, s, CHN); δ_C 55.4 (CH_3), 114.3, 122.2, 128.5, 128.7, 131.0 (9C, ArCH), 136.4, 144.9, 158.2 (ArC), 158.3 (CHN); *m/z* 212 ($M^+ + 1$, 14%), 211 (88), 210 (14), 197 (15), 196 (100), 167 (21).

4.4.6. *N*-Benzylidene-4-chloroaniline (4g).[30] Yield 92%; pale yellow solid; t_r 15.14; R_f 0.56 (hexane/EtOAc 8:1); mp 60–61 °C; ν (KBr) 1626 cm^{-1} (C=N); δ_H 7.13–7.16, 7.33–7.36, 7.47–7.49, 7.87–7.90 (2H, 2H, 3H and 2H, 4m, 9×ArH), 8.42 (1H, s, CHN); δ_C 122.2, 128.8, 128.9, 129.2, 131.6 (9C, ArCH), 131.4, 135.9, 150.5 (ArC), 160.7 (CHN); *m/z* 217 ($M^+ + 2$, 33%), 216 (44), 215 (100), 214 (99), 138 (11), 111 (25), 75 (15).

4.4.7. *N*-(1-Phenylethylidene)aniline (4h).[30] Yield 87%; amber oil; t_r 14.19; R_f 0.43 (hexane/EtOAc 8:1); ν (film) 1638 cm^{-1} (C=N); δ_H 2.16 (3H, s, CH_3), 6.76–6.79, 7.02–7.07, 7.28–7.33, 7.38–7.40, 7.93–7.96 (2H, 1H, 2H, 3H and 2H, 5m, 10×ArH); δ_C 17.1 (CH_3), 119.2, 123.0, 127.0, 128.2, 128.8, 130.3 (10C, ArCH), 139.3, 151.5 (ArC), 165.2 (C=N); *m/z* 196 ($M^+ + 1$, 8%), 195 (50), 181 (14), 180 (100), 77 (32).

4.5. General procedure for the preparation of 2-(aminoalkyl)imidazoles 5a–g

N-Methylimidazole (403 μL, 5 mmol) was added to a suspension of lithium powder (105 mg, 15 mmol) and isoprene (101 μL, 1 mmol) in THF (7 mL) at room temperature. The mixture was stirred for 45 min and then a solution of the corresponding imine compound (5.5 mmol) in THF (3 mL) was added (except for imines **5c** and **5g** where the resulting solution of the organolithium was filtered to remove the lithium excess and then added to a solution of the imine), continuing the stirring during 45 min at the same temperature. The reaction mixture was

hydrolyzed with water (15 mL), extracted with ethyl acetate (3×15 mL), and the organic phase was dried over anhydrous magnesium sulfate. After removing the solvent under reduced pressure (15 Torr), the resulting crude was purified by recrystallization (from mixtures of ethyl acetate and *n*-pentane) to yield compounds **5**. Compound **5g** was purified by column chromatography (pH=6.7–7.3 silica gel, mixtures of hexane and EtOAc).

4.5.1. [(1-Methyl-1*H*-imidazol-2-yl)-phenylmethyl]-phenyl-amine (5a).[33] Yield 94%; pale yellow solid; t_r 18.51; R_f 0.77 (EtOAc/MeOH 8:1); mp 125–126 °C; ν (KBr) 3377 cm^{-1} (NH); δ_H 3.54 (3H, s, CH_3), 5.24 (1H, br s, NH), 5.61 (1H, s, C*H*NH), 6.64–6.70, 6.77, 7.00, 7.09–7.14, 7.23–7.25, 7.29–7.34, 7.39–7.42 (3H, 1H, 1H, 2H, 1H, 2H and 2H, 7m, 10×ArH and NCHCHN); δ_C 32.9 (CH_3), 55.1 (CHNH), 113.4, 117.8, 121.5, 127.2, 127.3, 127.7, 128.8, 129.1 (12C, ArCH and NCHCHN), 139.9, 146.5, 147.7 (ArC and NCN); *m/z* 264 ($M^+ + 1$, 3%), 263 (16), 172 (14), 171 (100).

4.5.2. *N*-[(4-Methoxyphenyl)(1-methyl-1*H*-imidazol-2-yl)methyl]aniline (5b). Yield 92%; pale yellow solid; t_r 21.27; R_f 0.69 (EtOAc/MeOH 8:1); mp 151–152 °C; ν (KBr) 3397 cm^{-1} (NH); δ_H 3.53, 3.74 (3H and 3H, 2s, 2×CH_3), 5.57 (1H, s, C*H*NH), 6.63–6.69, 6.77, 6.82–6.85, 6.99, 7.08–7.14, 7.30–7.33 (3H, 1H, 2H, 1H, 2H and 2H, 6m, 9×ArH and NCHCHN); δ_C 32.9 (NCH_3), 54.5, 55.2 (CHNH and OCH_3), 113.5, 114.2, 117.7, 121.4, 127.1, 128.5, 129.1 (11C, ArCH and NCHCHN), 131.9, 146.5, 147.9, 159.0 (ArC and NCN); *m/z* 293 (M^+, 9%), 202 (15), 201 (100), 186 (12), 170 (14). HRMS calcd for $C_{18}H_{19}N_3O$ 293.1528, found 293.1527.

4.5.3. *N*-[(4-Chlorophenyl)(1-methyl-1*H*-imidazol-2-yl)methyl]aniline (5c). Yield 88%; beige solid; t_r 20.39; R_f 0.88 (EtOAc/MeOH 8:1); ν (KBr) 3393 cm^{-1} (NH); δ_H 3.57 (3H, s, CH_3), 5.20 (1H, br s, NH), 5.60 (1H, s, C*H*NH), 6.61–6.64, 6.67–6.72, 6.80, 7.00, 7.10–7.15, 7.25–7.30, 7.34–7.37 (2H, 1H, 1H, 1H, 2H, 2H and 2H, 7m, 9×ArH and NCHCHN); δ_C 32.9 (CH_3), 54.3 (CHNH), 113.5, 118.1, 121.6, 127.4, 128.7, 129.0, 129.2, (11C, ArCH and NCHCHN), 133.5, 138.5, 146.2, 147.3 (ArC and NCN); *m/z* 299 ($M^+ + 2$, 6%), 298 (4), 297 (19), 207 (33), 206 (14), 205 (100), 170 (61), 155 (14). HRMS calcd for $C_{17}H_{16}ClN_3$ 297.1033, found 297.1064.

4.5.4. 4-Methoxy-*N*-[(1-methyl-1*H*-imidazol-2-yl)(phenyl)methyl]aniline (5f). Yield 91%; amber oil; t_r 20.93; R_f 0.76 (EtOAc/MeOH 8:1); ν (film) 3690–3169 cm^{-1} (NH); δ_H 3.43, 3.63 (3H and 3H, 2s, 2×CH_3), 4.95 (1H, br s, NH), 5.53 (1H, s, C*H*NH), 6.58–6.61, 6.67–6.71, 6.96, 7.16–7.22, 7.25–7.30, 7.36–7.38 (2H, 3H, 1H, 1H, 2H and 2H, 6m, 9×ArH and NCHCHN); δ_C 32.6 (NCH_3), 55.4, 55.9 (CHNH and OCH_3), 114.5, 114.8, 121.3, 127.0, 127.2, 127.4, 128.5 (11C, ArCH and NCHCHN), 139.9, 140.6, 147.6, 152.1 (ArC and NCN); *m/z* 294 ($M^+ + 1$, 4%), 293 (20), 172 (13), 171 (100). HRMS calcd for $C_{18}H_{19}N_3O$ 293.1528, found 293.1544.

4.5.5. 4-Chloro-*N*-[(1-methyl-1*H*-imidazol-2-yl)(phenyl)methyl]aniline (5g). Yield 93%; yellow oil; t_r 21.13; R_f 0.82 (EtOAc/MeOH 8:1); ν (film) 3690–3179 cm^{-1} (NH); δ_H 3.48 (3H, s, CH_3), 5.42 (1H, br s, NH), 5.53 (1H, s, C*H*NH), 6.54–6.57, 6.75, 6.97–6.98, 7.01–7.04, 7.20–7.24, 7.27–7.32, 7.36–7.39 (2H, 1H, 1H, 2H, 1H, 2H and 2H, 7m, 9×ArH and NCHCHN); δ_C 32.8 (CH_3), 55.1 (CHNH), 114.5, 121.6, 127.1, 127.3, 127.8, 128.8, 129.0, (11C, ArCH and NCHCHN), 122.2, 139.4, 145.0, 147.2 (ArC and NCN); *m/z* 299 ($M^+ + 2$, 4%), 298 (2), 297 (12), 172 (13), 171 (100). HRMS calcd for $C_{17}H_{16}ClN_3$ 297.1033, found 297.1026.

4.6. General procedure for the preparation of 2-(aminoalkyl)imidazoles 5i and 5j

To a solution of hexamethyldisilazane (530 μL, 2.5 mmol) in THF (1.0 mL) was added a 1.6 M solution of *n*-butyllithium in hexane (1.6 mL, 2.6 mmol) at 0 °C and the mixture was stirred for 5 min at the same temperature, and after that, it was added drop-wise to a solution of the corresponding aldehyde (2.2 mmol) in THF (1.0 mL) at 0 °C. Stirring was continued at the same temperature for 30 min. The resulting *N*-trimethylsilylimine solution was used in the synthesis of 2-(aminoalkyl)imidazoles **5i** and **5j** when reacting with the corresponding organolithium derived from *N*-methylimidazole.

N-Methylimidazole (161 μL, 2 mmol) was added to a suspension of lithium powder (42 mg, 6 mmol) and isoprene (40 μL, 0.4 mmol) in THF (4 mL) at room temperature. The resulting mixture was stirred for 45 min at the same temperature. The excess of lithium was filtered off under argon atmosphere and the resulting mixture was added drop-wise to a cooled (0 °C) THF solution of the corresponding *N*-(trimethylsilyl)imine prepared as indicated above. The reaction mixture was allowed to reach room temperature, hydrolyzed with 3 M hydrochloric acid (15 mL) and extracted with ethyl acetate (3×20 mL). The aqueous layer was then basified with 2.5 M sodium hydroxide (25 mL) and extracted with ethyl acetate (3×25 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated (15 Torr). The resulting residue was purified by column chromatography (pH=6.7–7.3 silica gel, mixtures of ethyl acetate and methanol) to yield the compound **5i** or by destillation of the impurities (T= 50 °C, 0.1 Torr) to obtain the product **5j**.

4.6.1. (1-Methyl-1*H*-imidazol-2-yl)(phenyl)methanamine (5i). Yield 70%; yellow oil; t_r 13.90; R_f 0.47 (EtOAc/MeOH 1:1); ν (film) 3710–2960 cm^{-1} (NH_2); δ_H 2.61 (2H, s, NH_2), 3.38 (3H, s, CH_3), 5.17 (1H, s, C*H*NH_2), 6.79, 7.00 (1H and 1H, 2s, NCHCHN), 7.22–7.35 (5H, m, ArH); δ_C 32.6 (CH_3), 53.3 ($CHNH_2$), 121.4, 126.7, 126.8, 127.5, 128.8 (7C, ArCH and NCHCHN), 142.5, 149.5 (ArC and NCN); *m/z* 188 ($M^+ + 1$, 13%), 187 (100), 186 (22), 172 (20), 170 (10), 169 (14), 110 (49), 106 (13), 83 (23), 77 (13). HRMS calcd for $C_{11}H_{13}N_3$ 187.1109, found 187.1113.

4.6.2. 2,2-Dimethyl-1-(1-methyl-1*H*-imidazol-2-yl)propan-1-amine (5j). Yield 87%; yellow oil; t_r 11.18; R_f 0.56 (EtOAc/MeOH 1:1); ν (film) 3720–3029 cm^{-1} (NH_2); δ_H 0.98 [9H, s, $C(CH_3)_3$], 2.03 (2H, br s, NH_2), 3.63 (3H, s, NCH_3), 3.68 (1H, s, C*H*NH_2), 6.77, 6.98 (1H and 1H, 2s, CHCH); δ_C 26.2 [3C, $C(CH_3)_3$], 33.0 (NCH_3), 36.5 [$C(CH_3)_3$], 56.0 ($CHNH_2$), 120.0, 126.9 (CHCH), 150.1

(NCN); *m/z* 167 (M^+, 1%), 110 (100), 83 (13). HRMS calcd for $C_9H_{17}N_3$ 167.1422, found 167.1424.

Acknowledgements

This work was generously supported by the Dirección General de Enseñanza Superior (DGES) of the Spanish Ministerio de Ciencia y Tecnología (MCyT, grant no. CTQ2004-01261) and the Generalitat Valenciana (GV, grant no. GRUPOS 03/135). R. T. thanks the GV for a scholarship.

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Synthesis of all 7αH-guaia-4,11-dien-3-one diastereomers from (+)-dihydrocarvone

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Received 28 June 2005; revised 8 September 2005; accepted 8 September 2005

Available online 27 September 2005

Abstract—All four 7α*H*-guaia-4,11-dien-3-one diastereomers have been synthesized from the common intermediate 1α*H*,10α-acetoxy-7α*H*-guaia-4,11-dien-3-one obtained from (+)-dihydrocarvone. The spectral features of the four diasteromers have been correlated and the structure and absolute configuration of 1β*H*,10β*H*,7α*H*-guaia-4,11-dien-3-one isolated from *Pleocarphus revolutus* has been confirmed.

1. Introduction

The guaianes constitute a large group of natural occurring compounds, which show a wide spectrum of biological activities and are present in both terrestrial and marine organisms.[1,2] A hydroxyl, ester or ether function at C_{10} or a double bond at this position are frequent structural features of this kind of compounds. Nevertheless, some of them are characterized by the presence of hydrogen atoms at C_1 and C_{10} in both cis and trans relative disposition. Other common features are a C_4–C_5 and C_{11}–C_{12} double bond or related oxygenated functions at C_{11}. (Fig. 1).

Compound **1** was first isolated from *Baccharis boliviensis*,[3] and more recently has also been isolated from *Wikstroemia lanceolata*,[4] and its cytotoxicity against P-388 tumour cell lines has been reported.[4] The hydroxy derivative **1a** [(+)-hydroxycolorenone], has been isolated from *Euryops pedunculatus*[5] and *Haplopappus foliosus*.[6] Besides, compound **1a** and its methyl ether **1b** have also been isolated from the indonesian soft coral *Nephthea chabrolii* and the insecticidal activity of **1a** towards *Spodoptera littoralis* has been reported.[7] Compound **2**, the 1β*H*,10β*H* diastereomer of compound **1**, has been isolated by Zdero and Bohlmann from *Pleocarphus revolutus* together with its 6-oxigenated derivatives **2a** and **2b**.[8] These 6-oxygenated compounds had been previously isolated for Silva and col.[9] from the same source but these authors assigned them the structures **3a** and **3b** (*trans*-1β*H*,10α*H*) on the basis that the treatment with Zn–AcOH of the 6-hydroxy derivative afforded a 6-desoxy

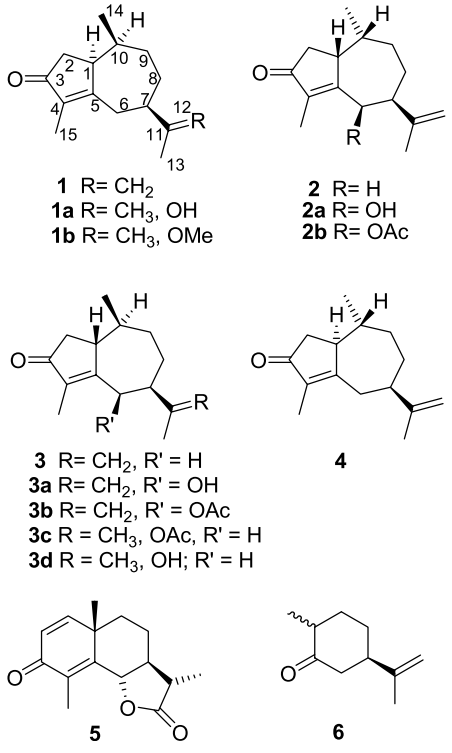

Figure 1.

compound with different spectroscopic features than **2** previously synthesized by Lowenthal and col.[10] Zdero and Bohlmann suggested than most likely the configuration at C_1 had been affected during reduction affording **4**.[8] To our knowledge 1β*H*,10α*H*-*trans*-guaiadienone **3** is not known as a natural product, although its 11-acetyl derivative **3c**

Keywords: Terpene synthesis; Guaiadienones; (+)-Dihydrocarvone; (−)-1,2-Dehydrocyperone; Deoxygenation; Li-amine reduction.
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0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.026

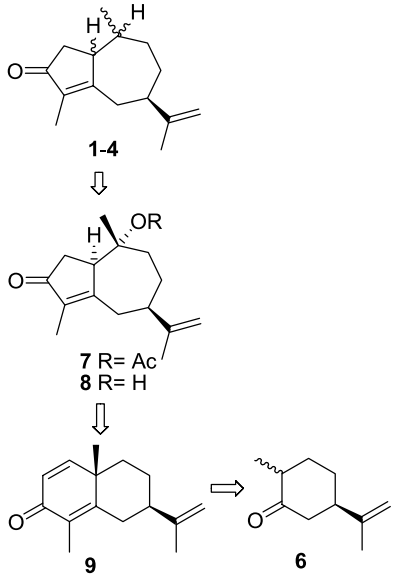
(8-deangeloyloxytorilin) has been recently isolated from the fruits of *Torilis japonica*,[11] a plant used in traditional medicine in China. On the other hand, no 1α*H*,10β*H*-guaiadienone **4** nor related compounds have been reported in the literature.

A common problem in the structural determination of these products is the correct establishment of the spatial disposition of H_1, H_7 and H_{10}. So, the need of an exact knowledge of their structures as well as their interesting biological activities and low availability from natural sources has made them interesting targets for total synthesis. However, the synthesis of the hydroazulene framework with the desired functionalization and stereochemistry presents many difficulties. In fact, only a few successful total syntheses of 1*H*,10*H*-guaianes have been reported in the literature.[12] Recently, Deprés and col. have carried out a stereoselective synthesis of (±)-**1a** and (±)-**3c** from 7-methylcycloheptatriene,[13] whilst our group has carried out the synthesis in enantiomerically pure form of (+)-1α*H*,7α*H*,10α*H*-guaia-4,11-dien-3-one (**1**) and (+)-hydroxycolorenone (**1a**),[14] and Lowenthal's group has described the preparation of (−)-**2** as an intermediate in the synthesis of 1-epicyclocolorenone,[10] starting in both cases from the eudesmanolide santonin (**5**).

As a continuation of our research program on the synthesis of biologically active sesquiterpenoids, we report herein the synthesis of all four 1*H*,10*H*,7α*H*-guaia-4,11-dien-3-one diastereomers (**1**–**4**) from (+)-dihydrocarvone (**6**).

2. Results and discussion

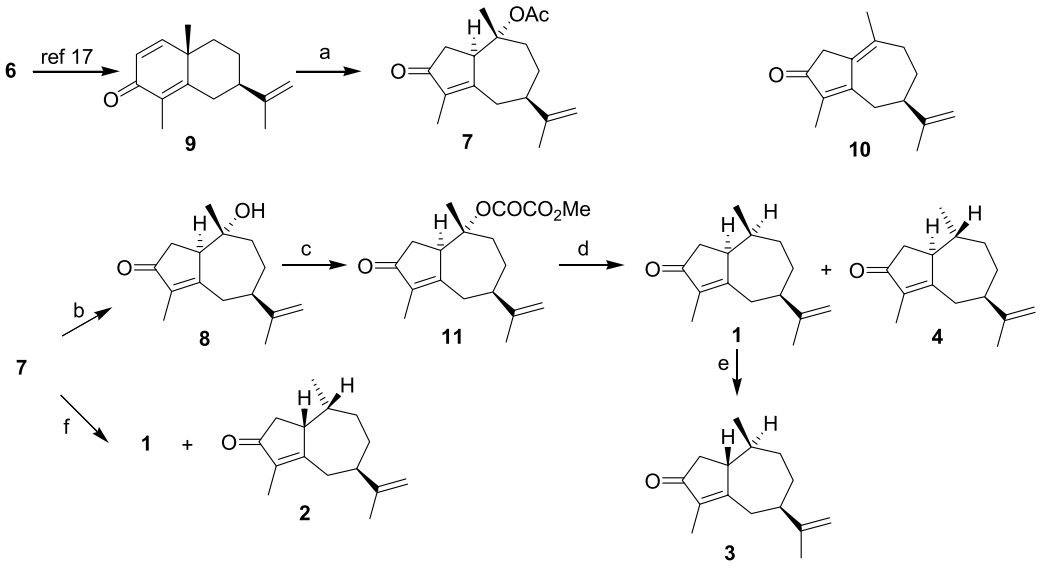
The retrosynthetic analysis is depicted in Scheme 1. It was contemplated that 10α-acetoxy-1αH,7α*H*-guaia-4,11-dien-3-one (**7**) or its parent alcohol **8** could be good intermediates for the preparation of the target compounds. Its selective deoxygenation at C_{10} and epimerization at C_1 would afford diastereomers **1**–**4**.



Scheme 1. Retrosynthetic analysis.

The simplest approach to **7** and **8** was the photochemical rearrangement of (−)-1,2-dehydrocyperone (**9**),[15] whose synthesis from (+)-dihydrocarvone (**6**) has been reported by de Groot's group.[16] The stereochemistry at C_1 and C_{10} in the guaiane framework results from the β-disposition of the C_{10}–Me in the eudesmane framework as has been reported by Piers and Cheng.[15] These authors carried out the photochemical rearrangement of **9** in AcOH–H_2O as solvent to give **8**.[15] However, in our hands complex mixtures of products were obtained from which **8** and its dehydrated derivative **10** [^{1}H NMR δ 1.84 (3H, s), 1.75 (6H, s); ^{13}C NMR δ 167.1, 149.5, 138.0, 136.4, 131.2 (C), 109.4 (CH_2), 23.9, 20.3, 8.3 (CH_3)] were obtained in low yield. In order to improve these results the use of AcOH as solvent was a good option to obtain its 10-acetyl derivative **7**.[17] Besides the addition of a small amount of Ac_2O (10%) improved the results, so that irradiation of **9** for 6 h with an UV lamp afforded acetylguaiadienone **7** in 54% yield. Starting material **9** was recovered (11%) but prolonged reaction times resulted in more complex reaction mixtures (Scheme 2).

For the deoxygenation at C_{10} of **7** the radical deoxygenation of methyl oxalyl esters with *n*-Bu_3SnH–AIBN reported by Dolan and MacMillan,[18] seemed a promising mild method. This deoxygenation has afforded good results with hindered tertiary alcohols even when other methods have failed.[19] The parent alcohol **8** was obtained in 92% yield by basic hydrolysis of **7** with KOH in EtOH–H_2O at room temperature. For the synthesis of methyl oxalate **11** treatment of **8** with methyl oxalyl chloride and DMAP at low temperature (−50 °C) was needed to prevent elimination of oxalate **11** to 7α*H*-guaia-1(10),4,11-trien-3-one (**10**). Direct chromatography of the reaction mixture on silica gel afforded compound **11** in near quantitative yield (95%). Treatment of **11** in toluene at reflux with *n*-Bu_3SnH (2 equiv) and AIBN (1 equiv) in portions for 5–7 h afforded in 80% yield an epimeric mixture of guaia-4,11-dien-3-ones (in 4:1 ratio).[20] Furthermore, these three steps can be carried out without isolation of the intermediate products to give a similar overall yield. The main product was (+)-1α*H*,7α*H*,10α*H*-guaia-4,11-dien-3-one (**1**), which showed the same spectral features and optical rotation sign than the natural compound isolated from *B. boliviensis*[3] and *W. lanceolata*[4] and than the synthetic compound previously reported by us[14] starting from santonin (**5**). For the minor compound, structure **4** was assigned on the basis of the expected stereochemical pathway in the radical deoxygenation. In the reaction conditions only two epimeric 10*H*-guaia-4,11-dien-3-ones could be obtained whose stereochemistry at C_{10} depends on the hydride approach to the intermediate radical by the α or β face to give compounds **1** and **4**, respectively. A 4:1 ratio for the epimeric mixture **1**:**4** points out a more hindered β face as a consequence of its concave shape due to the α disposition of H_1. Outstanding differences between the ^{1}H NMR spectra of **1** and **4** were the signals for H_1 and C_{10}–Me, which appear at 3.15–3.10 δ and 0.65 δ, respectively, for **1** and at 2.63–2.57 δ and 1.03 δ for compound **4**. Unfortunately, the overlapped signals at high field in the ^{1}H NMR spectrum of compound **4** did not allow confirmation of its stereochemistry by NOE experiments. The spectral features in the ^{1}H NMR spectrum and the optical rotation sign of compound **4** agree with those



Scheme 2. Reagents and conditions: (a) hν, AcOH-10% Ac_2O, 6 h; (b) KOH, EtOH–H_2O, 40 min; (c) $ClCOCO_2Me$, DMAP, CH_2Cl_2, −50 °C, 40 min; (d) *n*-Bu_3SnH, AIBN, toluene, reflux, 5–7 h; (e) 3% KOH–EtOH, 40 °C, 3 h; (f) Li, 2:1 *n*-$PrNH_2$–ethylendiamine, 0 °C, 12 min.

reported by Silva and col. for the reduction product of the 6-hydroxy derivative isolated from *P. revolutus*,[9] and supports the epimerization at C_1 in the treatment with Zn–AcOH suggested by Zdero and Bohlmann.[8]

With compound **1** in our hands a straightforward transformation to diastereomer **3** could be carried out by epimerization at C_1, favoured for the γ disposition of H_1 with regard to the enone group. Ishii and col.[21] reported the treatment of 1-*epi*-hydroxycolorenone (**3d**) with 3% KOH–MeOH at reflux for 2 h to afford a 1:1 mixture of **3d** and its C_1 epimer **1a** in 44 and 46% yield, respectively. In these conditions, widespread degradation to more polar compounds was observed for compound **1**, but after several trials best results were obtained (3% KOH–MeOH at 40 °C for 3 h). In these last conditions compound **3** (19%) and starting material **1** (55%) were isolated in near 1:3 ratio, which points out a higher stability of the 1α*H* to the 1β*H* disposition in these guaia-4,11-dien-3-ones.

In a similar way epimerization at C_1 of guaiadienone **4** should afford 1β*H*,10β*H*-guaiadienone **2**, but the low yields of **4** in the deoxygenation step encouraged us to look for other methods. A straightforward approach to its synthesis was the Li-amines reduction of esters reported by Barret and col.[22] In principle, a different stereochemical course could be expected for this deoxygenation as result of the highly polar and basic medium of reaction, which would control the stability and conformation of the radical anion intermediates. After several trials to avoid the concurrent enone reduction, treatment of acetate **7** with Li in a 2:1 mixture of *n*-$PrNH_2$–ethylendiamine at 0 °C afforded **1** and a new guaia-4,11-dien-3-one in 1:3 ratio and 14 and 42% isolated yield, respectively. A small amount of starting

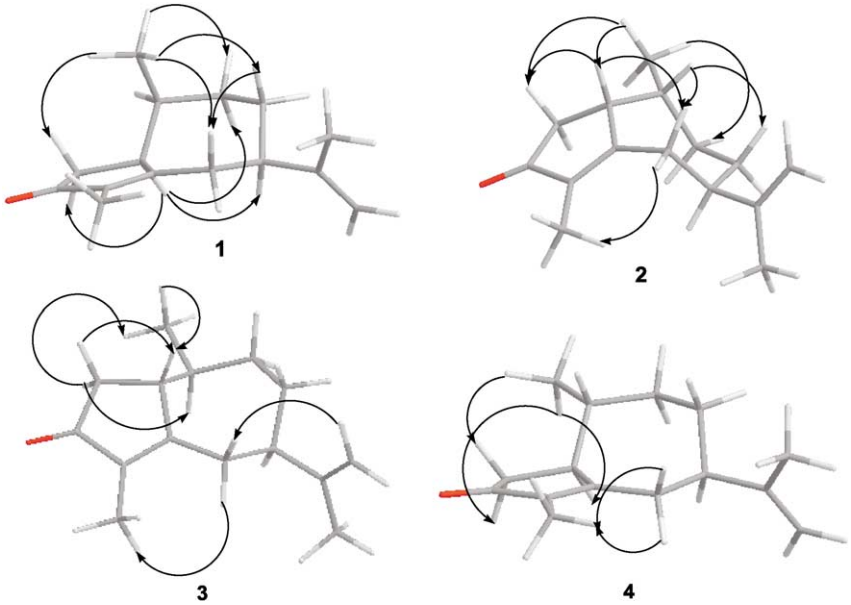
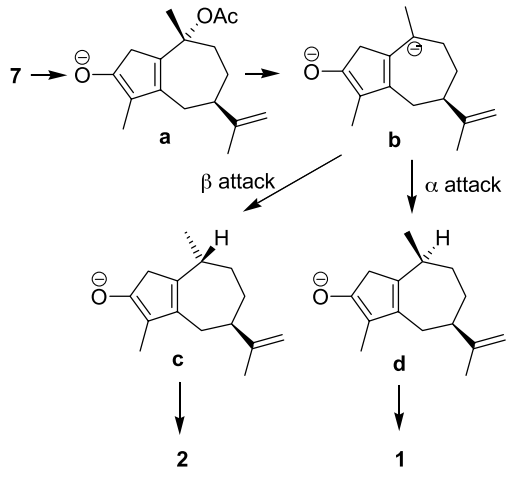


Figure 2. Conformational depictions of diastereomers **1**–**4**. ⇝ = observed NOE (only selected enhancements shown for clarity).



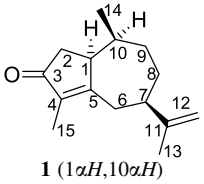
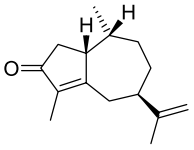
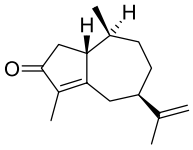
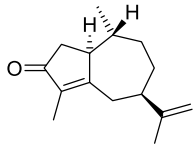
Scheme 3.

material **7** (7%) was also recovered. The structure of the main product had to be **2** with 1β*H*,10β*H* disposition since we had at our disposal the other three 1*H*,10*H*,7α*H*-guaia-4,11-dien-3-ones **1**, **3** and **4**. Besides, its configuration at C_1 and C_{10} was confirmed by NOE experiments (Fig. 2). Positive NOE between $H_{6'}$ and H_1, $H_{8'}$, H_{10} and of $H_{8'}$ with H_{10} shows that all of them are in the same face of the molecule. On the other hand, the conformation of this molecule must be in such a way that H_1 is near to the C_{10}–Me as a small NOE is observed between them. The physical and spectral data of compound **2** were in complete agreement with those reported by Zdero and Bohlmann for the natural product isolated from *P. revolutus*.[8]

It is possible to explain the obtained 3:1 ratio of diastereomers **2** and **1** according to the following mechanistic considerations (Scheme 3). In the polar and basic medium of reaction compound **7** must be in equilibrium with its thermodynamic enolate **a** whose high electronic density protects the dienone system against the reduction conditions of the acetate to give dianion **b**. The favourable protonation of **b** by the β face gives **c** with C_{10}–CH_3 and the isopropenyl side chain in a trans disposition. In a lesser extent protonation of **b** by the α face affords **d** with the side chains in a cis disposition. Further protonation of **c** and **d** at C_1 is favoured *anti* to de C_{10}–Me to give in both cases cis 1*H*,10*H* diastereomers **2** and **1**, respectively.

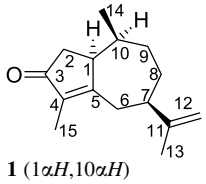
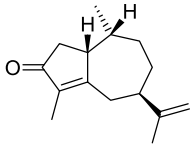
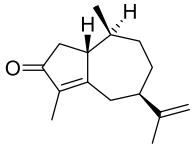
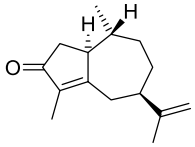
With all four diastereomers **1**–**4** in our hands a comparison of their physical and spectral features was possible (Tables 1 and 2). Some consistent differences could be observed in their NMR spectra. A down field shift of H_1 and H_{10} in the cis diastereomers **1** and **2** compared to their trans isomers **3** and **4**. On the other hand, the carbon atoms C_1 and C_{10} appear at high field in **1** and **2** compared to **3** and **4**. Furthermore, the H_{14} and C_{14} signals in compound **1** appear upfield compared to those of **2**–**4**, which must related to their β disposition overlaying the C_4–C_5 double bond. In compound **2** proton H_7 must be subjected to a similar effect as its signal appears also upfield compared to those of the other diastereomers. Some clear parallelisms could also be observed as the upfield shift of C_6 and C_9 in the 1β*H* diastereomers or of C_8 in the 10α*H* diastereomers. Compound **2** shows some differences with the other isomers in the upfield shift of C_2 and the downfield shift of C_7. These differences and others in the ^{1}H NMR signals must be related to their different conformations and their values are recorded in Table 1.

Table 1. Structures, optical rotations ($CHCl_3$) and ^{1}H NMR data ($CDCl_3$, 400 MHz)[a,b] for diastereomers **1**–**4**

	 **1** (1α*H*,10α*H*)		 **2** (1β*H*,10β*H*)		 **3** (1β*H*,10α*H*)		 **4** (1α*H*,10β*H*)	
$[\alpha]_D^{24}$	+182.8		−95.9		−68.1		+38.1	
	^{1}H NMR [δ_H, m, *J* (Hz) in parentheses]							
H_1	3.51–3.10 m	α	3.02–2.96 m	β	2.40–2.25 m	β	2.63–2.57 m	α
H_2	2.58dd (6.4, 18.8)	α	2.38dd (6.4, 18.0)	β	2.59dd (6.4, 18.4)	β	2.55dd (6.4, 17.6)	
$H_{2'}$	2.03 br d (18.8)	β	2.03dd (3.6, 18.0)	α	2.04dd (2.1, 18.4)	α	2.19 br d (17.6)	
H_6	2.76 br d (19.2)	α	2.73 br d (12.8)	α	2.74dd (2.8, 11.7)	α	2.73 br d (18.4)	
$H_{6'}$	2.45 br dd (12.0, 19.2)	β	2.37dd (11.2, 12.8)	β	2.39t (12.0)	β	2.61 br dd (10.4, 18.4)	
H_7	2.32 br dd (10.8, 12.0)	α	1.96t dd (2.8, 3.6, 11.2)	α	2.40–2.25 m	α	2.36 br td (3.6, 10.4)	α
H_8	1.80–1.70 m	α	1.87–1.79 m	α	1.87–1.77 m		1.95–1.85 m	
$H_{8'}$	1.65–1.50 m	β	1.50t dd (2.4, 11.6, 14.0)	β	1.65–1.50 m		1.45–1.32 m	
H_9	1.87–1.80 m	β	1.33 br dd (6.4, 14.4)	β	1.65–1.50 m		1.95–1.85 m	
$H_{9'}$	1.80–1.70 m	α	1.12dddd (2.0, 9.2, 11.6, 14.4)	α	1.62–1.50 m		1.45–1.32 m	
H_{10}	2.15–2.07 m	α	2.14 br dq (6.8, 8.0)	β	1.31–1.20 m	α	1.45–1.32 m	β
H_{11}	4.74 br s		4.75 br s		4.73 br s		4.73 br s	
H_{12}	4.69t (1.6)		4.73 br s		4.73 br s		4.70 br s	
H_{13}	1.73 br s		1.77 br s		1.76 br s		1.76 s	
H_{14}	0.65d (7.2)	β	0.95d (6.8)	α	1.04d (6.6)	β	1.03d (6.0)	α
H_{15}	1.65d (1.6)		1.70d (2.4)		1.67d (1.9)		1.64 s	

[a] On the basis of ^{1}H–^{1}H decoupling, HSQC and NOE experiments.
[b] Data for compound **3** were obtained at 300 MHz.

Table 2. ^{13}C NMR data in $CDCl_3$ (75 MHz) for diastereomers **1**–**4**[a]

	 **1** (1α*H*,10α*H*)	 **2** (1β*H*,10β*H*)	 **3** (1β*H*,10α*H*)	 **4** (1α*H*,10β*H*)
C_1	45.9	46.8	50.3	48.7
C_2	41.3	37.5	42.4	41.6
C_3	208.2	208.9	208.9	208.0
C_4	137.6	136.8	136.1	136.7
C_5	175.2	176.9	175.7	175.9
C_6	37.9	34.3	33.4	37.2
C_7	44.5	47.9	42.4	43.9
C_8	31.3	35.2	30.3	34.4[b]
C_9	36.7	30.1	31.5	38.5[b]
C_{10}	35.3	34.2	40.9	40.0
C_{11}	150.8	149.5	149.5	150.4
C_{12}	108.9	109.5	109.4	109.1
C_{13}	20.1	20.5	20.5	20.4
C_{14}	12.0	19.8	22.8	22.6
C_{15}	7.9	7.6	7.7	8.1

[a] On the basis of DEPT and HSQC experiments.
[b] Signals could be interchanged.

3. Conclusion

In summary, from 10α-acetoxy-1α*H*,7α*H*-guaia-4,11-dien-3-one (**7**), readily available from (+)-dihydrocarvone (**6**), natural 1α*H*,10α*H*,7α*H*- and 1β*H*,10β*H*,7α*H*-guaia-4,11-dien-3-one (compounds **1** and **2**, respectively) as well as their 1*H*,10*H*-*trans*-diastereomers **3** and **4** have been synthesized. Compound **2** has been synthesized for the first time in an 8% overall yield from (+)-**6** and the structure as well as the absolute configuration of the natural product isolated from *P. revolutus*,[8] has been confirmed. Besides, the syntheses of diastereomers **1**–**4** have allowed us the comparison of their NMR spectral features and correlate them with their configurations at C_1 and C_{10}.

4. Experimental

4.1. General

All reagents are commercially available in analytical grade or were purified by standard procedures prior to use. (+)-1,2-Dehydro-α-cyperone (**9**) was prepared according to the literature.[16] All operations involving air or moisture sensitive materials were performed under an argon atmosphere using syringes, oven-dried glassware, and freshly distilled and dried solvents. Melting points were determined on a Büchi B-545 digital melting point apparatus and are uncorrected. Specific optical rotations were measured using a Perkin-Elmer 243 apparatus in $CHCl_3$ using sodium light (D line 589 nm). Reactions were monitored by TLC analysis using Merck Silica Gel 60 F_{254} thin layer plates. Column chromatography refers to flash chromatography and it was performed on Merck silica gel 60, 230–400 mesh. IR spectra were recorded as thin films on NaCl plates for oils and as KBr discs for solids. NMR spectra were run in $CDCl_3$ at 300 or 400 MHz for ^1H and at 75 or 100 MHz for ^{13}C, and referenced to the solvent as internal standard. Carbon substitution degrees were established by DEPT pulse sequences. A combination of HSQC, ^1H–^1H decoupling and NOE experiments was used in selected cases to aid assignment when necessary. Low and high resolution mass spectra were recorded on an Autospec GC 8000 apparatus by electron impact (EI) at 70 eV.

4.1.1. (−)-10α-Acetoxy-1α*H*,7α*H*-guaia-4,11-dien-3-one (7). A solution of compound **9** (2.0 g, 9.26 mmol) in a mixture of glacial AcOH (100 mL) and Ac_2O (10 mL) under argon was irradiated with a 400 W UV lamp for 6 h. Removal of the solvent at reduced pressure by distillation with hexane afforded an oil, which was chromatographed on silica gel (hexane/EtOAc 9:1–7:3) to give 218 mg (11%) of unreacted starting material **9** and 1.37 g (54%) of **7** as a white solid. Mp 40–42 °C (hexane–EtOAc); $[\alpha]_D^{24}$ −25.6 (*c* 0.93); IR (KBr) ν_{max} 1726, 1689, 1624 cm^{-1}; MS *m*/*z* 276 (M^+, 0.2), 234 (17), 216 (13), 176 (18), 160 (72), 110 (100); HRMS *m*/*z* calcd for $C_{17}H_{24}O_3$ 276.1725. Found: 276.1722; ^1H NMR (300 MHz) δ 4.74 (1H, br s), 4.70 (1H, t, *J*= 1.5 Hz), 4.08 (1H, br s), 2.86–2.70 (1H, m), 2.56 (1H, td, *J*=3.6, 13.4 Hz), 2.48–2.35 (4H, m), 2.15 (1H, ddd, *J*=3.0, 4.7, 11.7 Hz), 1.97 (3H, s), 1.87 (1H, br d, *J*=16.0 Hz), 1.74 (3H, s), 1.64 (3H, d, *J*=1.5 Hz), 1.50–1.32 (1H, m), 1.05 (3H, s); ^{13}C NMR (75 MHz) δ 207.4 (s), 171.5 (s), 170.3 (s), 150.0 (s), 138.3 (s), 109.4 (t), 86.2 (s), 48.6 (d), 43.4 (d), 39.1 (t), 37.4 (t), 37.1 (t), 31.4 (t), 22.4 (q), 20.2 (q), 19.3 (q), 8.2 (q).

4.1.2. (+)-10α-Hydroxy-1α*H*,7α*H*-guaia-4,11-dien-3-one (8). To a solution of compound **7** (493 mg, 1.786 mmol) in EtOH (12.4 mL) was added aqueous 10% KOH (12.4 mL). After stirring for 40 min at room temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with aqueous 2 N HCl, saturated $NaHCO_3$ and brine and dried on anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure afforded 386 mg (92%) of compound **8** as a white solid, which did not need further

purification. Mp 169–171 °C (hexane–EtOAc) [lit.[16] 175–177 C ($CHCl_3$–petroleum ether)]; $[\alpha]_D^{24}$ +47.5 (*c* 0.80); IR (KBr) ν_{max} 3550–3250, 1675, 1608 cm^{-1}; MS *m/z* 234 (M^+, 12), 219 (3), 176 (13), 163 (16), 110 (100); HRMS *m/z* calcd for $C_{15}H_{22}O_2$ 234.1619. Found: 234.1621; ^1H NMR (400 MHz) δ 4.76 (1H, br d), 4.73 (1H, t, J=1.5 Hz), 3.19–3.13 (1H, m), 2.79 (1H, br d, J=17.5 Hz), 2.57 (1H, dd, J=1.9, 19.2 Hz), 2.52–2.34 (3H, m), 2.06–1.97 (1H, m), 1.92–1.75 (2H, m), 1.77 (3H, s), 1.66 (3H, d, J=1.5 Hz), 1.48–1.31 (1H, m), 0.94 (3H, s); ^{13}C NMR (75 MHz) δ 208.2 (s), 172.1 (s), 150.2 (s), 138.1 (s), 109.3 (t), 74.5 (s), 51.9 (d), 46.5 (t), 43.7 (d), 37.6 (t), 37.4 (t), 31.8 (t), 20.8 (q), 20.2 (q), 8.1 (q).

4.1.3. (+)-1α*H*,7α*H*,10α*H*-Guaia-4,11-dien-3-one (1) and (+)-1α*H*,7α*H*,10β*H*-guaia-4,11-dien-3-one (4). *Preparation of methyl oxalate* **11**. To a solution of compound **8** (428 mg, 1.829 mmol) in CH_2Cl_2 (11 mL) at −50 °C and under argon were added DMPA (405 mg, 3.294 mmol) and $ClCOCO_2CH_3$ (260 μL, 2.725 mmol) and the mixture was stirred at −50 °C for 40 min. After this time the reaction mixture was filtered through silica gel eluting with 7:3 hexane/EtOAc. Removal of the solvent afforded **11** (556 mg, 95%) as a colourless oil homogeneous in TLC with the following features: IR (NaCl) ν_{max} 1766, 1739, 1694, 1632, 1209, 1173 cm^{-1}; ^1H NMR (300 MHz) δ 4.74 (1H, br s), 4.71 (1H, br s), 4.03 (1H, br s), 3.84 (3H, s), 2.86–2.72 (1H, m), 2.55–2.26 (6H, m), 1.96–1.86 (1H, m), 1.74 (3H, s), 1.64 (3H, br s), 1.50–1.34 (1H, m), 1.19 (3H, s); ^{13}C NMR (75 MHz) δ 206.6 (s), 169.9 (s), 158.5 (s), 156.5 (s), 149.6 (s), 139.0 (s), 109.6 (t), 90.8 (s), 53.3 (q), 48.6 (d), 43.3 (d), 38.9 (t), 37.2 (t), 37.0 (t), 31.1 (t), 20.2 (q), 18.8 (q), 8.2 (q).

Radical deoxygenation of methyl oxalate **11**. To a solution of compound **11** (530 mg, 1.654 mmol) in toluene (12 mL) under argon at reflux temperature were added AIBN (80 mg, 0.417 mmol) and *n*-Bu_3SnH (231 μL, 0.851 mmol). Three additional portions of the same amount of AIBN and *n*-Bu_3SnH were added at intervals of 1 h 30 min and reflux continued to a total reaction time of 7 h. The reaction mixture was cooled at room temperature, washed with aqueous 1 M Na_2SO_3 and 1 M NaOH, dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residue was purified by column chromatography eluting with hexane–EtOAc (98/2–8/2) to afford the two diastereomeric guaiadienones **4** (60 mg, 16%) and **1** (232 mg, 64%).

Compound **1** had the following features: colourless oil; $[\alpha]_D^{24}$ +182.8 (*c* 0.74) [lit.[3] $[\alpha]_D^{24}$ +63 (*c* 0.23, $CHCl_3$); lit.[4] $[\alpha]_D^{24}$ +63.1 (*c* 0.23, $CHCl_3$); lit.[14] $[\alpha]_D^{24}$ +157.1 (*c* 0.84, $CHCl_3$)]; IR (NaCl) ν_{max} 1703, 1626 cm^{-1}; MS *m/z* 218 (M^+, 100), 203 (25), 175 (13), 161 (27), 109 (15); HRMS *m/z* calcd for $C_{15}H_{22}O$ 218.1671. Found: 218.1672; ^1H NMR data: see Table 1; ^{13}C NMR data: see Table 2.

Compound **4** was obtained as a colourless oil; $[\alpha]_D^{24}$ +38.1 (*c* 1.10); IR (NaCl) ν_{max} 1693, 1630 cm^{-1}; EM *m/z* 218 (M^+, 100), 203 (25), 175 (18), 162 (22), 109 (24); HRMS *m/z* calcd for $C_{15}H_{22}O$ 218.1671. Found: 218.1670; ^1H NMR data: see Table 1; ^{13}C NMR data: see Table 2.

4.1.4. (−)-1β*H*,7α*H*,10α*H*-Guaia-4,11-dien-3-one (3). A solution of 3% KOH–EtOH (36 mL) was added to 96 mg (0.440 mmol) of compound **7** and the mixture was stirred at 40 °C. After 3 h the reaction mixture was cooled at 0 °C, the base neutralized with 2 N HCl and EtOH removed at reduced pressure. The resultant oil was extracted with ether and the combined organic layers were washed with brine and dried on $MgSO_4$. Removal of the solvent at reduced pressure followed by chromatography eluting with hexane–EtOAc (98/2–8/2) separated 52.6 mg (55%) of starting material **7** and 18 mg (19%) of compound **9**: colourless oil; $[\alpha]_D^{24}$ −68.1 (*c* 1.00); IR (NaCl) ν_{max} 1701, 1643 cm^{-1}; MS *m/z* 218 (M^+, 100), 203 (15), 175 (21), 162 (20), 161 (19); HRMS *m/z* calcd for $C_{15}H_{22}O$ 218.1671. Found: 218.1665; ^1H NMR data: see Table 1; ^{13}C NMR data: see Table 2.

4.1.5. (−)-1β*H*,7α*H*,10β*H*-Guaia-4,11-dien-3-one (2). A solution of compound **4** (50 mg, 0.181 mmol) in 1.74 mL of a 2:1 mixture of *n*-$PrNH_2$/$NH_2CH_2CH_2NH_2$ was added to a blue solution of Li (18 mg, 2.520 mmol) in 2:1 *n*-$PrNH_2$/$NH_2CH_2CH_2NH_2$ (2.5 mL) precooled at 0 °C. After stirring for 12 min at 0 °C the reaction was quenched by addition of *t*-BuOH and aqueous NH_4Cl and the mixture was extracted with ether. The combined organic layers were washed with 2 N HCl 2 N, saturated aqueous $NaHCO_3$ and brine and dried on anhydrous $MgSO_4$. Removal of the solvent and careful chromatography eluting with hexane–EtOAc (98/2–8/2) separated 3.5 mg (7%) of recovered starting material **4**, 16.5 mg (42%) of a colourless oil, which was identified as compound **10** and 5.5 mg (14%) of compound **7**.

Compound **10**. Colourless oil; $[\alpha]_D^{24}$ −95.9 (*c* 0.75) [lit.[8] $[\alpha]_D^{24}$ −63 (*c* 0.75, $CHCl_3$); lit.[10] $[\alpha]_D^{24}$ −132 (*c* 1.13),]; IR (NaCl) ν_{max} 1701, 1643 cm^{-1}; EM *m/z* 218 (M^+, 100), 203 (16), 175 (24), 161 (38), 119 (20), 109 (18); HRMS *m/z* calcd for $C_{15}H_{22}O$ 218.1671. Found: 218.1681; ^1H NMR data: see Table 1; ^{13}C NMR data: see Table 2.

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m-Aminobenzoic acid inserted β-turn in acyclic tripeptides: a peptidomimetic design

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Received 17 June 2005; revised 30 August 2005; accepted 8 September 2005

Available online 27 September 2005

Abstract—X-ray diffraction studies show that peptides Boc-Leu-Aib-*m*-ABA-OMe (**I**) (Aib, α-aminoisobutyric acid; *m*-ABA, *meta*-aminobenzoic acid) and Boc-Phe-Aib-*m*-ABA-OMe (**II**) adopt a type-II β-turn conformation, solely stabilized by co-operative steric interactions amongst the amino acid residues. This type of β-turn without any intramolecular hydrogen bonding is generally referred to as an open turn. Although there are some examples of constrained cyclic peptides in which *o*-substituted benzenes have been inserted to mimic the turn region of the neurotrophin, a nerve growth factor, peptides **I** and **II** present novel two examples where *m*-aminobenzoic acid has been incorporated in the β-turn of acyclic tripeptides. The result also demonstrates the first crystallographic evidence of a β-turn structure containing an inserted *m*-aminobenzoic acid, which can be considered as a rigid γ-aminobutyric acid with an all-trans extended configuration.

1. Introduction

A β-turn causes a reversal in the direction of the peptide backbone, which was first recognized in the late 1960s by Venkatachalam.[1] β-Turns also play important roles in stabilizing tertiary structures, initiating folding and facilitating intermolecular recognition.[2] Recently, it has been shown that β-turn structures are subunits for supramolecular β-sheet assembles and amyloid-like fibrils in short model peptides.[3–5] The formation of amyloid-like fibrils is a causative factor for many neurodegenerative diseases including Alzheimer's disease, Huntington's disease and prion-related encephalopathies.[6] Because of their critical importance there has been considerable interest in designing β-turns and β-turn mimetics.

m-Aminobenzoic acid is considered as a rigid γ-aminobutyric acid with an all-trans extended configuration suitable for promoting a β-sheet like structure. It was first introduced in cyclic peptides behaving as an artificial receptor for anions and more recently it has been incorporated into other peptides.[7] Substituted *m*-aminobenzoic acid has also been used as a constrained residue in hetero-duplexes and nanocavities of tunable sizes.[8] A solution phase study by Kunwar et al. shows that designed β-hairpin peptides tolerate insertion of *m*-aminobenzoic acid and also permit accommodation of both enantiomers of Pro-Gly turn motifs.[9] Recently *m*-aminobenzoic acid containing peptides have been exploited to create β-sheet mediated amyloid-like fibrils in the solid state to unfold the mechanistic aspects of various neurodegenerative diseases.[10] Although there are some reports of the utilization of *m*-aminobenzoic acid in peptide design, the generation of β-turns in small peptides by inserting *m*-aminobenzoic acid remains totally unexplored.

Creation of β-turns in small synthetic peptides with non-coded amino acids is an emerging aspect in the field of peptidomimetics. Several reports of type II β-turns in tripeptides, stabilized by intramolecular 10-membered hydrogen bonding, are found in the literature (Fig. 1).[3–5,11] In order to explore the possibility of inserting *m*-aminobenzoic acid in β-turn, we have chosen peptides Boc-Leu-Aib-*m*-ABA-OMe (**I**) (Aib, α-aminoisobutyric acid; *m*-ABA, *meta*-aminobenzoic acid) and Boc-Phe-Aib-*m*-ABA-OMe (**II**). In both the peptides the fragment of chiral α-amino acid, Leu/Phe(1) followed by an achiral amino acid, Aib (2), satisfies the steric requirement for promoting a turn-like structure. It will be interesting to know whether *m*-aminobenzoic acid, equivalent to a rigid γ-aminobutyric acid assists or disrupts the creation of the

Keywords: β-Turn; *meta*-Aminobenzoic acid; α-Aminoisobutyric acid; Peptidomimetic.
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doi:10.1016/j.tet.2005.09.020

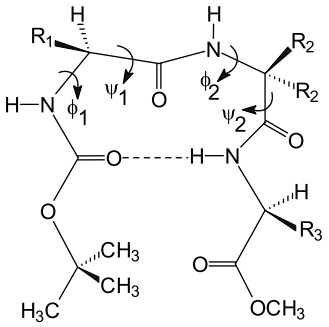

Figure 1. Typical β-turn in tripeptides.

β-turn structure. Peptides **I** and **II** were prepared by conventional solution phase synthesis and their single crystal X-ray diffraction studies are described below.

2. Results and discussion

The crystal structures of peptides Boc-Leu-Aib-*m*-ABA-OMe **I** and Boc-Phe-Aib-*m*-ABA-OMe **II** reveal that both the peptides adopt a folded conformation corresponding to a slightly distorted type II β-turn structure with Leu/Phe(1) and Aib(2) occupying the $i+1$ and $i+2$ positions, respectively (Figs. 2 and 3). Although there are some examples of constrained cyclic peptides by inserting *o*-substituted benzenes to mimic the turn regions of neurotrophin, a nerve growth factor,[12] peptides **I** and **II** present two novel examples where *m*-aminobenzoic acid has been incorporated in the β-turn of acyclic tripeptides. In an ideal type II β-turn, torsion angles of $\phi_{i+1}=-60°, \psi_{i+1}=120°, \phi_{i+2}=80°, \psi_{i+2}=0°$ are expected (Fig. 1).[1] In peptides **I** and **II**, these torsion angles are found to be deviated as ϕ_{i+1} (−71.9/−61.6°), ψ_{i+1} (142.4/142.0°), ϕ_{i+2} (55.8/ 63.6°) and ψ_{i+2} (33.3/22.6°) (Table 1). The torsion angles at the centrally located conformationally constrained Aib (2) residue (**I**: $\phi_2=55.8°$, $\psi_2=33.3°$; **II**: $\phi_2=63.6°$, $\psi_2=22.6°$) deviate appreciably from ideal values for the $i+2$ residue in a type-II β-turn. As a consequence the observed N(1)···O(8) distances between the Boc-CO and *m*-ABA(3)-NH groups are far too long (**I**: 3.89 Å; **II**: 3.87 Å) for an intramolecular 4→1 hydrogen bond. Importantly such β-turns, which do not contain

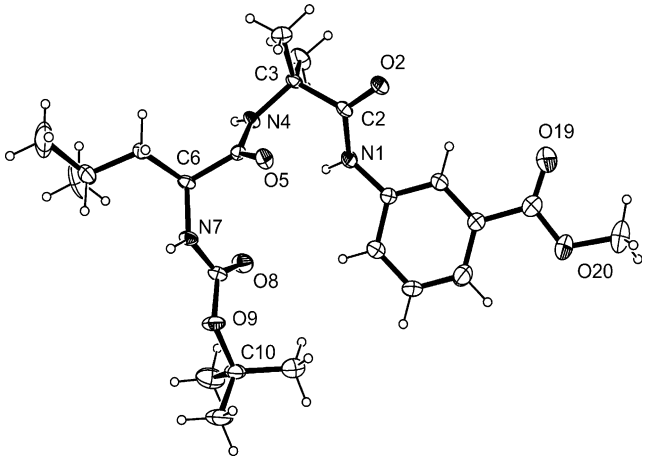

Figure 2. The ORTEP diagram of peptide **I** including the atom numbering scheme. Thermal ellipsoids are shown at the level of 25% probability.

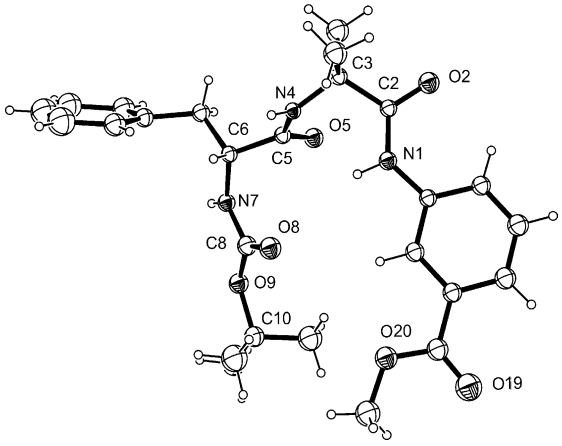

Figure 3. The ORTEP diagram of peptide **II** including the atom numbering scheme. Thermal ellipsoids are shown at the level of 25% probability.

hydrogen bonds are solely stabilized by co-operative steric interactions amongst the amino acids residues and are generally referred to as open turns. It is noteworthy that in both **I** and **II** the peptide bond between Leu/Phe(1) and Aib(2) deviates appreciably from planarity ($\Delta\omega=10.2°$ in **I**, $\Delta\omega=16.7°$ in **II**).

Interestingly, distorted type II β-turns with unusually long intramolecular 4→1 N···O distances of approximately 3.6 Å have also been observed in structures of other acyclic tripeptides (entries b and c, Table 2).[13] The tripeptide Boc-Phe-Aib-Leu-OMe has been reported to form one of the best β-turn structures with an intramolecular 10-membered 4→1 hydrogen bond of 2.35 Å and N···O distance of 3.15 Å (entry a, Table 2).[11d] From a comparative study of various torsion angles (ϕ_1, ψ_1, ϕ_2 and ψ_2) of the peptides in Table 2, it can be concluded that in nonhydrogen-bonded β-turns (entries b–e), the value of the torsion angle ψ_1 (139.9/143.3/142.4/142.0°) is significantly greater than that of hydrogen-bonded β-turns (127.5°). Probably the high value of ψ_1 may be another factor for making the intramolecular 4→1 N···O distances unusually long, so that only very weak hydrogen bonds can be formed (Table 3).

The torsion angles in the backbone of the β-turn structure of peptides **I** and **II** are compared in Table 1 and are found to be almost equivalent. However, it is apparent from Figures 2 and 3 that there is a major difference in the orientation of the $-CO_2Me$ group of the phenyl ring between the two structures. A 180° rotational difference around the N(1)–C(11) bond between peptide **I** and **II** is found, such that the β-turn structure of **I** is open and that of peptide **II** becomes

Table 1. Selected torsion angles (°) for peptides **I** and **II**

	Peptide **I**	Peptide **II**	
N7–C8–O9–C10	171.8(4)	176.2(6)	
C6–N7–C8–O9	179.7(6)	−178.5(6)	ω_0
C5–C6–N7–C8	−71.9(5)	−61.6(7)	ϕ_1
N4–C5–C6–N7	142.4(4)	142.0(4)	ψ_1
C3–N4–C5–C6	169.8(4)	163.3(5)	ω_1
C2–C3–N4–C5	55.8(6)	63.6(7)	ϕ_2
N1–C2–C3–N4	33.3(5)	22.6(7)	ψ_2
C11–N1–C2–C3	−171.9(4)	−171.7(6)	ω_2

Table 2. List of type II β-turn in tripeptides (entries a–e) with torsion angles (°) of the residues at turn, intra-molecular hydrogen bond (HB) distance H···O═C (Å) and N···O distances (Å) between the BocCO and N–H groups of third residues

Entry	Peptides	ϕ_1	ψ_1	ϕ_2	ψ_2	H···O═C	N···O	Ref
	Idealized type II β-turn	−60	120	80	0			1
a	Boc-Phe-Aib-Leu-OMe	−62.0	127.5	61.5	26.6	2.35	3.15	11d
b	Boc-Ala-Dpg-Ala-OMe[a]	−56.1	139.9	66.2	19.3	2.75	3.44	13a
c	Boc-Ala-Dbg-Ala-OMe[a]	−61.5	143.3	66.5	21.1	2.78	3.63	13a
d	Boc-Leu-Aib-*m*-ABA-OMe[b]	−71.9	142.4	55.8	33.3	3.27	3.89	This work
e	Boc-Phe-Aib-*m*-ABA-OMe[b]	−61.6	142.0	63.6	22.6	3.07	3.87	This work

[a] Dpg, α,α-di-*n*-propylglycine; Dbg, α,α-di-*n*-butylglycine.
[b] Aib, α-amino-isobutyric acid; *m*-ABA, *meta*-aminobenzoic acid.

Table 3. Intermolecular hydrogen bonding parameters of peptides **I** and **II**

	N–H···O	H···O (Å)	N···O (Å)	N–H···O (°)
Peptide **I**	N1–H1···O8	3.27	3.892	130.9
	N4–H4···O2[a]	2.12	2.890	148.9
	N7–H7···O5[b]	2.14	2.982	164.7
Peptide **II**	N1–H1···O8	3.08	3.870	153.9
	N4–H4···O2[c]	2.10	2.957	172.7
	N7–H7···O5[d]	2.16	2.945	152.4

[a] Symmetry equivalent $0.5-x$, $0.5+y$, $-0.5-z$.
[b] Symmetry equivalent $1-x$, $1-y$, $-z$.
[c] Symmetry equivalent $x-0.5$, $0.5-y$, z.
[d] Symmetry equivalent $1-x$, $1-y$, $1-z$.

more compact, nearly a close structure. Such a remarkable turn is rarely found in small acyclic peptides. The result also presents the first crystallographic evidence of a β-turn structure containing *m*-aminobenzoic acid, which is considered as a rigid γ-aminobutyric acid with an all-trans extended configuration suitable for β-strand generation. From this study it is evident that *m*-aminobenzoic acid can be effectively utilized in engineering the strand region of β-hairpins.

The molecular packing arrangements of the peptides **I** and **II** are shown in Figs. 4 and 5 and are found to be similar. In peptides **I** and **II**, the molecules are packed as centrosymmetric dimers with two N(7)–H···O(5) hydrogen bonds. In addition each N(4) forms an intermolecular hydrogen bond to the O(2) of a neighbouring molecule, in the case of **I** via a screw axis and in the case of **II** a glide plane. In both structure N(1) does not form any hydrogen bonds.

3. Conclusion and outlook

It has been shown that the incorporation of *m*-aminobenzoic acid, a γ-amino acid, in β-turns of acyclic tripeptides is very well tolerated. The β-turn structure generated from peptide **II** is found to be remarkably close, which is rarely found in turn design. Therefore, peptides **I** and **II** represent a potentially useful way forward for peptidomimetic design. Moreover from the above study it is evident that *m*-aminobenzoic acid could be utilized in rational engineering of the strand region of β-hairpins and multiple antiparallel β-strands.

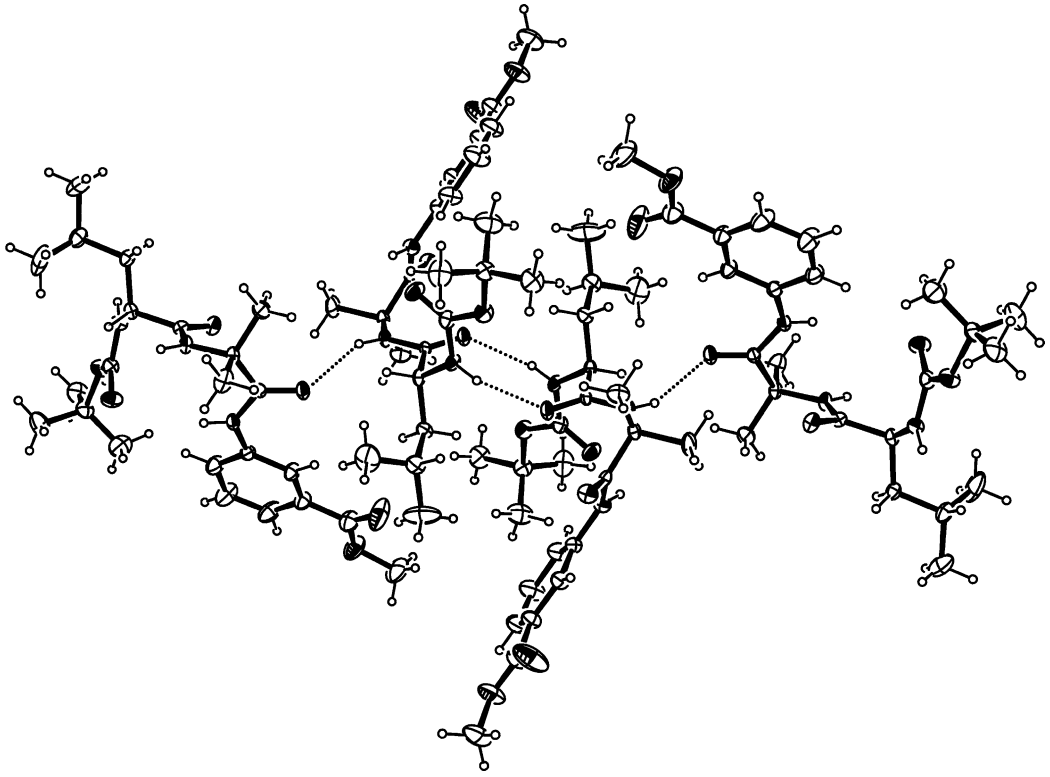

Figure 4. The packing arrangement of peptide **I**. Hydrogen bonds are shown as dotted lines.

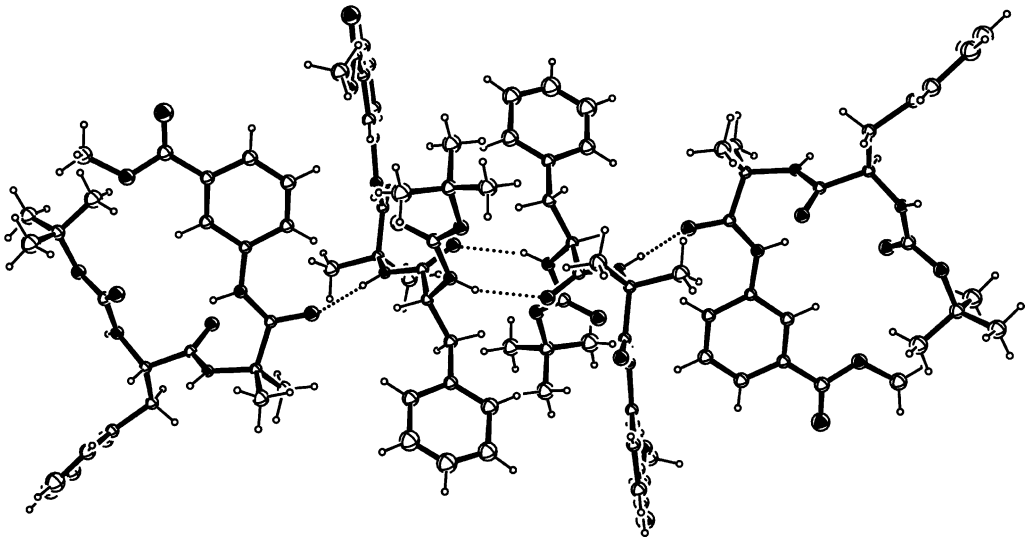

Figure 5. The packing arrangement of peptide **II**. Hydrogen bonds are shown as dotted lines.

4. Experimental

4.1. Synthesis of peptides

The peptides were synthesised by conventional solution phase procedures.[14] The *t*-butyloxycarbonyl and methyl ester groups were used for amino and carboxyl protections and dicyclohexylcarbodiimide (DCC), 1-hydroxybenzotriazole (HOBT) as coupling agents. Methyl ester hydrochlorides of Aib and *m*-ABA were prepared by the thionyl chloride-methanol procedure.[10,11d] All the intermediates obtained were checked for purity by thin-layer chromatography (TLC) on silica gel and used without further purification. All the final peptides were purified by column chromatography using silica gel (100–200 mesh) as the stationary phase and ethyl acetate and petroleum ether mixture as the eluent.

4.1.1. Boc-Leu-Aib-*m*-ABA-OMe (I). *Boc-Leu-Aib-OMe* (**1**). Boc-Leu-OH 1.16 g (5 mmol) was dissolved in dimethylformamide (DMF; 3 mL). 0.59 g (5 mmol) of Aib-OMe obtained from its hydrochloride was added followed by DCC (1.0 g, 5 mmol). The reaction mixture was stirred at room temperature for 3 days. The precipitated dicyclohexylurea (DCU) was filtered and diluted with ethyl acetate (80 mL). The organic layer was washed with excess of water, 1 N HCl (3×30 mL), 1 M Na_2CO_3 solution (3× 30 mL) and again with water. The solvent was then dried over anhydrous Na_2SO_4 and evaporated in vacuo, giving a light brown gum. Yield: 1.99 g (90.0%).

Boc-Leu-Aib-OH (**2**). 0.73 g (2.3 mmol) of **1** was dissolved in methanol (10 mL) and 4 N NaOH (3 mL) was added. The reaction mixture was stirred at room temperature for 2 days. The progress of the reaction was monitered by TLC. After completion of the reaction the methanol was evaporated. The residue obtained was diluted with water and washed with diethylether. The aqueous layer was cooled in ice and neutralised by 2 N HCl and extracted with ethyl acetate. The solvent was evaporated in vacuo to give a brown gum. Yield: 0.57 g, (82.0%).

Boc-Leu-Aib-m-ABA-OMe (**I**). 0.32 g (1 mmol) of **2** was dissolved in DMF (4 mL). *m*ABA-OMe,[10] obtained from it hydrochloride 0.15 g (1 mmol) was added followed by DCC (0.2 g, 1 mmol) and HOBT (0.14 g). The reaction mixture was stirred at room temperature for 5 days. The work-up of the reaction was done as in the case of **1**. Yield: 0.41 g (90.0%). Single crystals were grown from methanol water mixture by slow evaporation and were stable at room temperature. Mp 170–172 °C; IR (KBr): 3293, 2953, 1727, 1675, 1539, 1285, 1162, 757 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$, δ ppm): 9.17 [*m*-ABA NH, 1H, s]; 8.25 [Ha [*m*-ABA], 1H, s]; 7.99 [Hd [*m*-ABA], 1H, d, $J=7.8$ Hz]; 7.75 [Hb [*m*-ABA], 1H, d, $J=7.8$ Hz], 7.36 [Hc [*m*-ABA], 1H, t, $J=7.8$ Hz]; 6.46 [Aib NH, 1H, s]; 4.94 [Leu NH, 1H, d]; 3.94 [$C^{\alpha}H$ of Leu, 1H, m]; 3.88 [–OCH_3, 3H, s]; 1.67–1.72 [$C^{\beta}H$ and $C^{\gamma}H$ of Leu, 2H, m]; 1.59 [$C^{\beta}H$ of Aib, 6H, s]; 1.44 [Boc–CH_3s, 9H, s];0.96 [$C^{\delta}H$ of Leu, 6H, m]. Anal. Calcd for $C_{23}H_{35}N_3O_6$ (449.53): C, 61.45; H, 7.85; N, 9.35. Found: C, 61.56; H, 7.97; N, 9.44.

4.1.2. Boc-Phe-Aib-*m*-ABA-OMe (II). Peptide **II** was synthesised following a similar procedure to that of peptide **I**. Yield: 0.37 g (92.0%). Single crystals were grown from methanol water mixture by slow evaporation and were stable at room temperature. Mp 190–192 °C; IR (KBr): 3312, 2973, 1674, 1538, 1295, 1164, 758 cm^{-1}; ^1H NMR 500 MHz ($CDCl_3$, δ ppm): 9.11[*m*-ABA NH, 1H, s]; 8.24 [Ha [*m*-ABA], 1H, s]; 7.97 [Hd [*m*-ABA], 1H, d, $J=$ 7.9 Hz]; 7.76 [Hb [*m*-ABA], 1H, d, $J=7.9$ Hz]; 7.39 [Hc [*m*-ABA], 1H, t, $J=7.9$ Hz]; 7.20–7.34 [phenyl ring protons]; 6.03 [Aib NH, 1H, s]; 4.98 [Phe NH, 1H, d]; 4.16 [$C^{\alpha}H$ of Phe, 1H, m]; 3.89 [–OCH_3, 3H, s]; 3.08 [$C^{\beta}H$ of Phe, 2H, m]; 1.56 [$C^{\beta}H$ of Aib, 6H, s]; 1.42 [Boc–CH_3s, 9H, s]. Anal. Calcd for $C_{26}H_{33}N_3O_6$ (483.55): C, 64.58; H, 6.87; N, 8.69. Found: C, 64.68; H, 6.96; N, 8.82.

4.2. Single crystal X-ray diffraction study

Peptide **I**. $C_{23}H_{35}N_3O_6$, $M=449.54$, monoclinic, $a=$ 15.405(17) Å, $b=10.778(12)$ Å, $c=16.326(17)$ Å, $\beta=$ 107.53(1)°, $U=2585$ $Å^3$, $Z=4$, space group $P2_1/n$, calcd 1.155 g cm^{-3}.

Peptide **II**. $C_{26}H_{33}N_3O_6$, $M=483.55$, monoclinic, $a=11.483(14)$ Å, $b=19.24(2)$ Å, $c=12.647(14)$ Å, $\beta=105.25(1)^\circ$, $U=2696$ Å^3, $Z=4$, spacegroup $P2_1/a$, calcd 1.191 g cm^{-3}.

Data for the two crystals were measured with Mo Kα radiation using the MAR research Image Plate System. The crystals were positioned at 70 mm from the Image Plate. 100 Frames were measured at 2° intervals with a counting time of 2 min. Data analysis was carried out with the XDS program[15] to provide 44859, 4878 independent reflections. The structure was solved using direct methods with the Shelx86 program.[16] Non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to carbon were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The structures were refined on F^2 using Shelxl[17] to R_1 0.1184, 0.1202, wR_2 0.1989, 0.2181 for 2650, 2283 reflections, respectively, all with $I>2\sigma(I)$. Crystal data has been deposited at the Cambridge Crystallographic Data Centre, reference CCDC 274873 and CCDC 274874.

Acknowledgements

A.D. would like to thank UGC, New Delhi, India, for a Junior Research Fellowship (JRF) and University of Calcutta for financial assistance. We thank EPSRC and the University of Reading, UK for funds for the Image Plate System.

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Arylzinc species by microwave assisted Grignard formation–transmetallation sequence: application in the Negishi coupling

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Received 9 June 2005; revised 30 August 2005; accepted 8 September 2005

Available online 29 September 2005

Abstract—Arylmagnesium species can be efficiently generated from magnesium turnings and aryl chlorides or aryl bromides under dielectric heating conditions. Subsequent microwave assisted transmetallation using $ZnCl_2$–TMEDA afforded the corresponding arylzinc reagents. A sequential microwave assisted arylmagnesium formation–transmetallation–Negishi coupling protocol suitable for automated multiple parallel synthesis has been developed.

1. Introduction

During the last decade microwave dielectric heating has developed into a convenient and widely used tool in organic synthesis.[1] Frequently observed acceleration of reaction speed combined with the apparent ease of automation renders the microwave methodology particularly useful in the development of new drugs. The advantages of dielectric heating in the Negishi C–C bond forming reaction (a powerful means for construction of biaryl bond, which is frequently found in a range of pharmaceuticals, natural products and ligands) have already been demonstrated.[2] However, the organozinc reagents for the desired Negishi coupling have usually been prepared under conventional conditions. Therefore, fast and operationally simple microwave assisted arylzinc preparation procedure for the subsequent Negishi cross-coupling is highly desirable, especially for automated multiple parallel synthesis.

Recently, Kappe has demonstrated the microwave assisted preparation of arylzinc species from Rieke zinc.[3] The methodology benefits from short reaction times and utilizes aryl bromides along with aryl iodides as the starting materials. However, the necessity to employ the highly reactive Rieke zinc suspension hampers its use in automated microwave systems, especially in those, equipped with liquid handling tools. Moreover, aryl chlorides apparently are unreactive under the reported conditions. As an alternative, we reported the generation of arylzinc species under microwave conditions using readily available and air-stable Zn–Cu couple.[4] Unfortunately, our approach is limited to the use of aryl iodides, as aryl bromides and chlorides do not react with Zn–Cu couple. To expand the scope of substrates in a microwave assisted synthesis, we considered the use of a more reactive metal such as magnesium. Transmetallation of the resulting organomagnesium reagent would afford organozinc species. Herein, we report a convenient synthesis of arylzinc species from aryl chlorides and bromides via a microwave assisted Grignard generation[5]–transmetallation sequence.

2. Microwave assisted generation of aryl magnesium bromides

The formation of the Grignard reagents usually proceeds by reaction of magnesium with the corresponding halide. The success of the reaction depends critically on its initiation and prior activation of magnesium surface usually is necessary to start the reaction. Among various magnesium activation methods, the most frequently employed are overnight dry stirring in inert atmosphere,[6] addition of iodine or dibromoethane,[7] chemical generation of activated magnesium from Mg–anthracene complex[8] as well as in situ reduction of magnesium chloride using potassium.[9] Notably, under microwave dielectric heating conditions, Grignard species were readily formed from aryl bromides without prior activation of magnesium.[10] Thus, microwave heating of bromobenzene and magnesium turnings[11] in THF[12] at 80 °C for 10 min resulted in the formation of characteristic metallic-gray solution of phenylmagnesium bromide. Carbon dioxide was used as a quenching agent to

Keywords: Microwaves; Grignard reagents; Organozinc reagents; Transmetallation; Negishi coupling.
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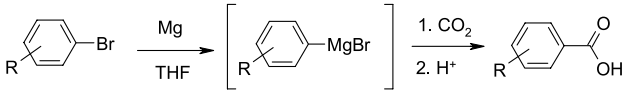
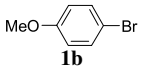
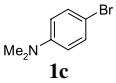
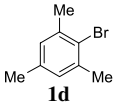
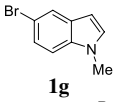
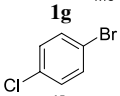
doi:10.1016/j.tet.2005.09.022

Table 1. Microwave assisted preparation of arylmagnesium bromides



1 2

Entry	Aryl halide	Time (min)	Temperature (°C)	Yield of $ArCO_2H$ **2** (%)[a]
1	 **1a**	10	80	88 (**2a**)
2	 **1b**	20	80	88 (**2b**)
3	 **1c**	20	80	71 (**2c**)
4	 **1d**	20	80	74 (**2d**)
5	 **1e**	20	80	83 (**2e**)
6	 **1f**	15	80	87 (**2f**)
7	 **1g**	30	120	84 (**2g**)
8	 **1h**	10	80	88 (**2h**)

[a] Reactions were carried out using 2.2 mmol of Mg turnings and 2.0 mmol of aryl bromide in dry THF (2.0 mL); isolated yields represent an average of two runs.

establish yields of the formed Grignard reagent.[13] After extractive workup, benzoic acid was isolated in 88% yield (Table 1, entry 1).

Concentration of the aryl bromide was found to be critical and the best yields of phenylmagnesium bromide were obtained using ca. 1 M solution of the starting bromide in THF. The use of lower concentrations (0.25 M) required elevated temperature (up to 160 °C) and prolonged time (30 min) to bring about the formation of arylmagnesium species. Furthermore, the Grignard formation suffered from low reproducibility.

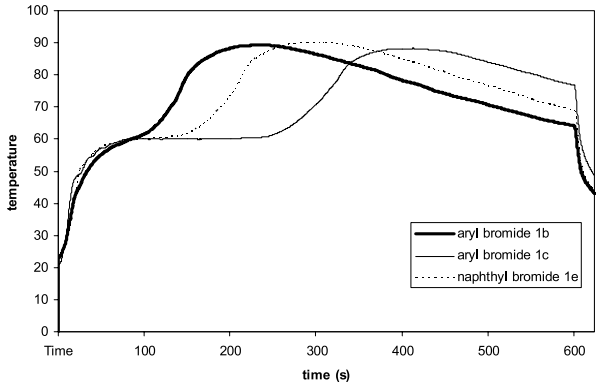


Figure 1. Temperature profiles for the Grignard formation from aryl bromides **1b–c** and **1e** (see entries 2, 3, and 5, Table 1) in THF at 60 °C.

Table 1 illustrates the scope of the procedure. Generally, a temperature of 60 °C was sufficient to initiate the exotherm of the Grignard formation (see Fig. 1 for a typical temperature profile at 60 °C). Upon initiation of the exotherm, the temperature rose to 30 °C above the adjusted 60 °C and the microwave power was instantaneously cut-off by the temperature control system.[14] The subsequent formation of Grignard reagent occurred without microwave irradiation until the temperature decreased back to 60 °C, whereupon it was maintained by the dielectric heating. As seen from Figure 1, temperature control during the reaction allows to estimate time, necessary to initiate the Grignard reaction. Thus, the exotherm of Grignard formation started already after ca. 80 s at 60 °C in the case of aryl bromide **1b**, while the less reactive substrate **1c** required microwave heating for ca. 240 s to initiate the reaction. Consequently, reluctant electron-rich aryl bromides were employed to demonstrate the advantages of dielectric heating. Thus, Grignard reagents were readily formed from aryl bromides **1b–c** possessing electron donating substituents (entries 2 and 3) after microwave heating for 10–20 min at 80 °C.[15] Higher temperature and longer time was necessary in the case of even less reactive 5-bromoindole **1g** (entry 7). Selective formation of 4-chloro-phenylmagnesium bromide

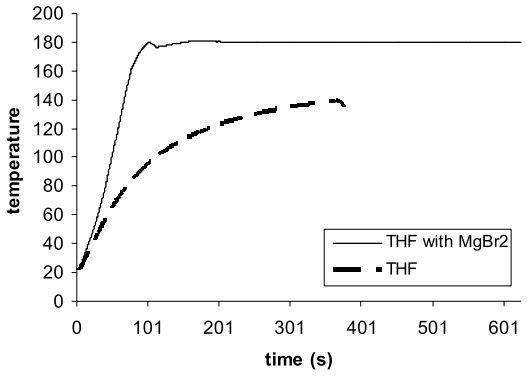


Figure 2. Dielectric heating profiles for a 1 M solution of chlorobenzene **3a** in THF with and without added 0.5 M $MgBr_2$ in THF.

(entry 8) was possible, as aryl chloride was completely unreactive at 80 °C.

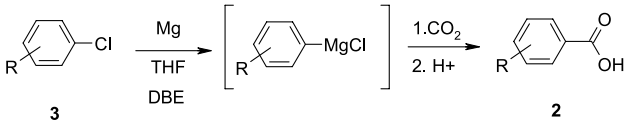
3. Microwave assisted preparation of Grignard regents from aryl chlorides

High temperatures (140–180 °C) were initially applied to bring about the reaction of non-activated magnesium turnings with aryl chlorides. Unfortunately, heating above 140 °C of a 1 M solution of chlorobenzene **3a** in a relatively non-polar THF as a solvent[16] required prolonged application of the maximum irradiation power (300 W). This frequently resulted in the overheating of the microwave equipment and subsequent cut-off of the microwave energy. Meantime, the use of salt additives was shown to substantially improve the absorption of microwave energy by the non-polar solvent.[17] Indeed, addition of 0.5 M THF solution of $MgBr_2$[18] to a 1 M solution of chlorobenzene **3a** in THF resulted in much faster heating rate compared to the analogous process without the salt additive (see Fig. 2).[19]

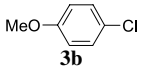
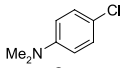
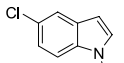
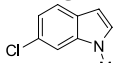
Disappointingly, non-activated magnesium turnings did not react with aryl chlorides even after 15 min at 180 °C suggesting that activation of metal surface is necessary to bring about the oxidative magnesiation of aryl chlorides. Among various activation methods examined, the use of 1,2-dibromoethane (DBE) was the most advantageous. The addition of DBE resulted not only in the activation of magnesium surface,[7] but also in the in situ formation of $MgBr_2$ solution in THF. The presence of salt substantially improved absorption of microwaves by the reaction media, thus allowing to perform reactions at temperatures up to 200 °C.

Aryl chlorides possessing electron donating substituents (substrates, which traditionally are regarded as difficult substrates for the direct oxidative addition to magnesium)[20] where chosen to demonstrate the scope of the developed procedure. Carbon dioxide was used as a quenching agent and yields of isolated benzoic acids represented yields of the formed Grignard reagent.[13] As seen from Table 2, arylmagnesium species were efficiently formed from reluctant aryl chlorides (entries 1 and 2, Table 3) as well as from thienyl chloride **3f** (entry 4).[21] Indolyl chlorides **3g** and **3i** (entries 5 and 6) and aryl chloride **3c** (entry 3) required heating at 200 °C for 30 min to form the Grignard species. The most important side reaction was formation of biaryls.

Table 2. Microwave assisted preparation of arylmagnesium chlorides

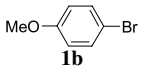
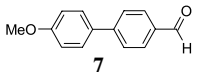
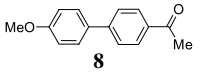
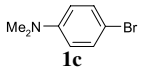
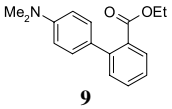
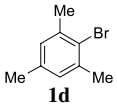
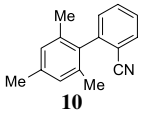
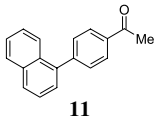
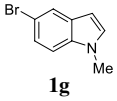
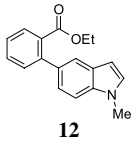
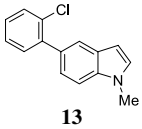
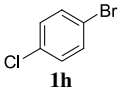
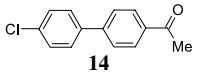
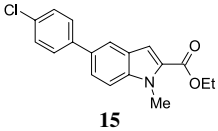
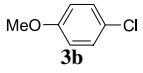
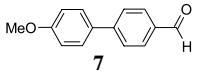
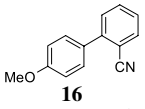
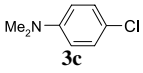
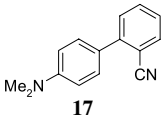
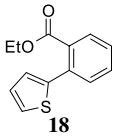
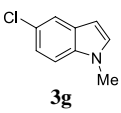
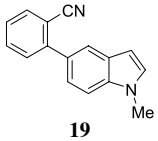
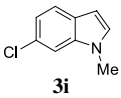
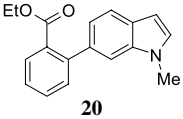


3 **2**

Entry	Aryl chloride	Time (min)	Temperature (°C)	Yield of $ArCO_2H$ **2** (%)[a]
1	 **3a**	15	180	81 (**2a**)
2	 **3b**	15	180	70 (**2b**)
3	 **3c**	30	200	72 (**2c**)
4	 **3f**	15	180	82 (**2f**)
5	 **3g**	30	200	48 (**2g**)
6	 **3i**	30	200	76 (**2i**)

[a] Reactions were carried out in THF (2.0 mL) using 3.5 mmol of Mg turnings, 2.0 mmol of aryl chloride and 1.0 mmol of 1,2-dibromoethane as additive; yields of isolated products represent an average of two runs.

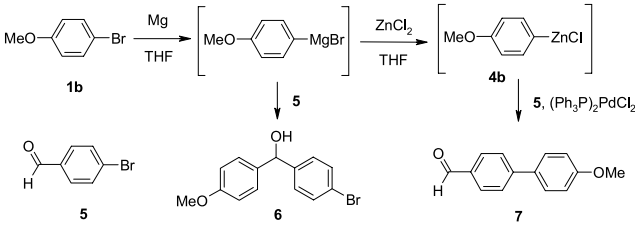
Table 3. Microwave assisted preparation of arylzinc reagents and the Negishi cross-coupling

Entry	Arylzinc source	Product	Solvent	Conditions	Yield (%)[a]
1	 **1b**	 **7**	THF	5 min, rt	81
2		 **8**	THF/DMF 1:1	2 min, 80 °C	76
3	 **1c**	 **9**	THF	2 min, 80 °C	88
4	 **1d**	 **10**	THF	2 min, 120 °C	86
5	 **1e**	 **11**	THF/DMF 1:2	10 min, 80 °C	82
6	 **1g**	 **12**	THF	2 min, 80 °C	73
7		 **13**	THF	3 min, 120 °C	83
8	 **1h**	 **14**	THF/DMF 1:1	2 min, 80 °C	68
9		 **15**	THF	30 min, 80 °C	83
10	 **3b**	 **7**	THF	5 min, rt	87
11		 **16**	THF	2 min, 120 °C	92
12	 **3c**	 **17**	THF	2 min, 120 °C	81
13	 **3f**	 **18**	THF	2 min, 80 °C	92
14	 **3g**	 **19**	THF	2 min, 120 °C	70
15	 **3i**	 **20**	THF	2 min, 80 °C	64

[a] Yields of isolated products were calculated based on cross-coupling partner—bromo-arene (0.7 mmol). 1.1 mL of arylzinc reagent (0.7–0.9 mmol) was employed in the Negishi cross-coupling reaction.

4. Transmetallation of arylmagnesium to arylzinc species

With efficient protocol for arylmagnesium generation in hand, the transmetallation to the arylzinc species was addressed. In a model study, phenylmagnesium bromide **1b** was transmetallated to phenylzinc reagent **4b** (Scheme 1). Given that the Negishi cross-coupling reaction of arylzinc species with bromoarenes could be performed highly chemoselectively in the presence of an aldehyde moiety[22] the transmetallation reaction mixture was treated with 4-bromobenzaldehyde **5** (1 equiv) and $(Ph_3P)_2PdCl_2$ (3 mol%) at room temperature for 5 min. Yields of biphenyl aldehyde **7** reflected the chemical outcome of the transmetallation product **4**, while the amount of the remaining Grignard reagent could be determined based on the yields of alcohol **6**.[23]



Scheme 1. Model study of the transmetallation reaction.

Reaction of Grignard reagent with $ZnCl_2$[24] resulted in the complete transmetallation after dielectric heating at 80 °C for 15 min. However, the separation of the resulting solution of phenylzinc chloride **4** from bulk precipitate of inorganic salts was difficult. Meanwhile, the use of $ZnCl_2$–TMEDA complex[25] also brought about the quantitative formation of arylzinc chloride after 15 min at 80 °C. In this case, the phenylzinc reagent was obtained as a slightly cloudy solution and therefore could be easily handled. Consequently, all transmetallation reactions were carried out using $ZnCl_2$–TMEDA complex.

5. The Negishi cross-coupling

To demonstrate the suitability of the developed methodology for automated multiple parallel synthesis, the design of a sequential microwave assisted arylmagnesium formation—transmetallation—Negishi coupling protocol was carried out. The Negishi cross-coupling between arylzinc reagent **4b** and bromobenzaldehyde **5** readily occurred at room temperature (see the transmetallation step above; see also entries 1 and 10, Table 3).[26] The cross-coupling with other aryl bromides, however, required higher temperatures. Thus, the formation of esters **9**, **12**, and **18** (entries 3, 6, 13, and 15) was completed after heating at 80 °C for 2 min, while biaryl nitriles **10**, **16**, **17** and **19** (entries 4, 11, 12, and 14) required microwave heating at 120 °C for 2 min. Aryl chlorides did not react under the Negishi conditions and 2-chloro-bromobenzene selectively cross-coupled via bromide, affording 5-aryl indole **13** (entry 7). Formation of indole-2-carboxylic ester required prolonged heating (30 min) at 80 °C (entry 9). In case of bromo-ketones (entries 2, 5, and 8), the use of THF–DMF mixture as solvent was found to be beneficial because in pure THF the reaction did not go to completion.

6. Conclusions

In summary, we have shown that arylmagnesium species can be efficiently generated directly from magnesium turnings and aryl chlorides or aryl bromides under dielectric heating conditions. Grignard species were readily formed from aryl bromides without prior activation of magnesium. Generation of arylmagnesium reagents from aryl chloride required activation of magnesium surface by in situ addition of dibromoethane. A convenient procedure for microwave-assisted generation of arylzinc species from aryl bromides and aryl chlorides via Grignard formation–transmetallation sequence has been developed. The methodology complements previously reported approach for arylzinc generation from aryl iodides and Zn–Cu couple in a microwave environment.[4] To demonstrate the suitability of the developed methodology for parallel high-throughput organic synthesis, a sequential arylzinc formation–Negishi cross coupling protocol has been designed.

7. Experimental

7.1. General

Microwave heating was performed on a purpose-built Smith Synthesizer by Personal Chemistry (Uppsala, Sweden) with a monomode cavity and temperature control. Melting points were obtained on an OptiMelt apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were observed on Varian Mercury 200 spectrometer with tetramethylsilane as an internal standard. Column chromatography was performed with Acros silica gel, (0.06–0.2 mm). Reactions were monitored by thin-layer chromatography on Merck Kieselgel 60_{F254}.

7.2. General procedure for the generation of Grignard reagents from aryl bromides

An oven dried Emrys™ MW process vial (2–5 mL) equipped with a Teflon-coated stirring bar was charged with magnesium turnings (Acros, 53.5 mg, 2.2 mmol) and aryl bromide (if solid at room temperature, 2.0 mmol), flushed with argon and closed using an aluminum open-top seal with PTFE-faced septum. Dry THF (2 mL) and aryl bromide (if liquid at room temperature, 2.0 mmol) were introduced via a syringe and the reaction mixture was microwave-irradiated for the appropriate time and temperature, affording intensely colored (usually metallic gray or brown) solution of the Grignard reagent.

7.3. General procedure for preparation of Grignard reagents from aryl chlorides

An oven dried Emrys™ MW process vial (2–5 mL) equipped with a Teflon-coated stirring bar was charged with magnesium turnings (85.1 mg, 3.5 mmol) and aryl chloride (if solid at room temperature, 2.0 mmol), flushed with argon and closed using an aluminum open-top seal with

PTFE-faced septum. Dry THF (2 mL) and aryl chloride (if liquid at room temperature, 2.0 mmol) were introduced via syringe, followed by 1,2-dibromoethane (86 μL, 1.0 mmol). The reaction mixture was microwave-irradiated for the appropriate time and temperature, affording intensely colored (usually metallic gray or brown) solution of the Grignard reagent.

7.4. General procedure for isolation of arylcarboxylic acids

Sealed Emrys™ MW process vial containing solution of arylmagnesium halide was cooled to 1 °C (crushed ice) and a stream of dry CO_2 (generated from 'dry ice' and dried by passing through concentrated sulfuric acid) was introduced via cannula for 5 min. Then, 4 N HCl (1.0 mL) was added to the resulting mixture (caution! intense evolution of hydrogen!) and after the gas evolution was ceased, the reaction mixture was poured into 20 mL of 1 N HCl and extracted with MeOtBu (4×10 mL). Combined organic extracts were washed with 1 N NaOH solution (3×10 mL) and basic extracts were acidified by careful addition of concentrated HCl to pH∼1.[27] After extraction with MeOtBu (3×10 mL), washing with brine and drying (Na_2SO_4), solvent was removed in vacuo (aspirator) to afford crystalline residue. After additional drying in vacuo (0.1 Torr) for 1 h, analytically pure product was obtained.

7.5. Characterization data for representative carboxylic acids

7.5.1. 1-Methyl-1*H*-indole-5-carboxylic acid (2g). Brown crystals, mp 214–215 °C (decomp.) 200 MHz ^{1}H NMR (DMSO-d_6, ppm) δ 12.44 (1H, br s) 8.22 (1H, d, J=1.4 Hz) 7.75 (1H, dd, J=8.6, 1.4 Hz) 7.48 (1H, d, J=8.6 Hz) 7.41 (1H, d, J=3.0 Hz) 6.56 (1H, d, J=3.0 Hz) 3.80 (3H, s).

7.5.2. 1-Methyl-1*H*-indole-6-carboxylic acid (2i). Yellow solid, mp 189–190 °C (decomp.); 200 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 12.20 (1H, br s) 7.90 (1H, dd, J=8.4, 0.9 Hz) 7.68 (1H,d, J=8.4 Hz) 7.25 (1H, d, J=2.8 Hz) 6.55 (1H, dd, J=2.8, 0.9 Hz) 3.89 (3H, s).

7.6. General procedure for transmetallation-Negishi cross-coupling

An oven dried Emrys™ MW process vial (2–5 mL) equipped with a Teflon-coated stirring bar was charged with $ZnCl_2$–TMEDA (518 mg, 2.05 mmol), flushed with argon and closed using an aluminum open-top seal with PTFE-faced septum. A solution of Grignard reagent (prepared as described above) was added via cannula to the $ZnCl_2$–TMEDA and the resulting mixture was heated by microwaves at 80 °C for 15 min yielding slightly cloudy solution of arylzinc reagent.

An oven dried Emrys™ MW process vial (2–5 mL) equipped with a Teflon-coated stirring bar was charged with $Pd(PPh_3)_2Cl_2$ (21 mg, 0.03 mmol), aryl bromide (0.7 mmol) and solvent (1.0 mL; see Table 3 for the appropriate solvent), flushed with argon and closed using an aluminum open-top seal with PTFE-faced septum. The contents of the vial were stirred intensely for 2 min whereupon the arylzinc solution (1.1 mL) from above was introduced via cannula. The reaction was stirred at room temperature or heated by microwaves (see Table 3), then diluted with EtOAc (5 mL) and filtered through a Celite plug (2×2 cm) with an EtOAc rinse. After solvent removal (rotary evaporator) the residue was purified by flash column chromatography on silica gel.

4′-Methoxy-biphenyl-4-carbaldehyde (**7**) was isolated via the sulfite adduct.

7.6.1. 4′-Methoxy-biphenyl-4-carbaldehyde (7). EtOH (0.5 mL) and saturated $NaHSO_3$ solution (0.5 mL) was added to the reaction mixture and after vigorous shaking (vortex) for 5 min, the formed precipitate was filtered off and washed with EtOH (5 mL). The wet solid was suspended in 4 N HCl (20 mL) and EtOAc (30 mL) and stirred until clear biphasic solution formed. Layers were separated and acidic solution was washed with EtOAc (3× 15 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). Filtration and solvent removal (aspirator) afforded aldehyde **8** (122 mg, 81%) as white crystals, mp 101–102 °C. (lit. 101.5–102 °C).[28] Analytical TLC on silica gel, 9:1 petroleum ether/EtOAc, R_f=0.24; IR (Nujol, cm^{-1}) 1688 C=O; 200 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 10.04 (1H, s) 7.96–7.90 (2H, m) 7.74–7.69 (2H, m) 7.63–7.56 (2H, m) 7.05–6.97 (2H, m) 3.87 (3H, s); GC–MS *m/z* (% relative intensity, ion): 212 (100, M) 197 (15) 169 (18) 152 (14) 139 (48) 115 (39).

7.6.2. 1-(4′-Methoxy-biphenyl-4-yl)-ethanone (8). Following general procedure, 1-bromo-4-methoxy-benzene **1b** was converted into arylzinc reagent and cross-coupled with 1-(4-bromo-phenyl)-ethanone. Purification of the crude product by column chromatography (75 mL silica gel, column i.d. 30 mm) using 10% EtOAc in petroleum ether afforded 122 mg (76%) of white solid; analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, R_f=0.30. Pure material was obtained by crystallization from EtOAc/ petroleum ether, mp 156–158 °C, colorless plates (lit.[29] 153.5–155 °C); IR (Nujol, cm^{-1}) 1678 C=O; 200 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 8.05–7.96 (2H, m) 7.69–7.53 (4H, m) 7.05–6.95 (2H, m) 3.86 (3H, s) 2.62 (3H, s); GC–MS *m/z* (% relative intensity, ion): 226 (50, M) 211 (100, M−CH_3) 183 (10) 168 (30) 152 (24) 140 (40) 139 (76).

7.6.3. 4′-Dimethylamino-biphenyl-2-carboxylic acid ethyl ester (9). Following general procedure, 4-bromo-*N*,*N*-dimethylaminobenzene **1c** was converted into arylzinc reagent and cross-coupled with 2-bromo-benzoic acid ethyl ester. Purification of the crude product by column chromatography (150 mL silica gel, column i.d. 50 mm) using CH_2Cl_2 afforded 165 mg (88%) of pale yellow liquid; analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, R_f=0.30; IR (Nujol, cm^{-1}) 1720 C=O; 200 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.78–7.70 (1H, m) 7. 53–7. 18 (5H, m) 6.86–6.72 (2H, m) 4.18 (2H, q) 3.00 (6H, s) 1.12 (3H, t); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 169.7, 150.1, 142.5, 131.6, 131.2, 130.7, 129.7, 129.4, 126.4, 112.5, 61.0, 40.8, 14.2; GC–MS *m/z* (% relative intensity, ion): 269 (100, M) 240 (40, M−C_2H_5) 224 (11) 180 (10) 152 (22).

7.6.4. 2′,4′,6′-Trimethyl-biphenyl-2-carbonitrile (10). Following general procedure, 2-bromo-1,3,5-trimethyl-benzene **1d** was converted into arylzinc reagent and cross-coupled with 2-bromo-benzonitrile. Purification of the crude product by column chromatography (100 mL silica gel, column i.d. 30 mm) using gradient elution from 2% EtOAc/petroleum ether to 10% EtOAc/petroleum ether afforded 133 mg (86%) of solid material; analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, R_f=0.60. Pure material was obtained by crystallization from EtOAc/petroleum ether, mp 91–92 °C, colorless prisms; IR ($CHCl_3$ thin film, cm^{-1}) 2220 C≡N; 200 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.76 (1H, dd, J=7.7, 1.4 Hz) 7.65 (1H, ddd, J=7.7, 7.7, 1.4 Hz) 7.45 (1H, ddd, J=7.7, 7.7, 1.1 Hz) 7.28 (1H, dd, J=7.7, 1.1 Hz, overlapped with $CHCl_3$) 2.34 (s, 3H) 1.98 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 145.7, 138.3, 135.8, 135.1, 133.2, 133.1, 130.8, 128.7, 127.6, 118.1, 113.5, 21.4, 20.5; GC–MS *m/z* (% relative intensity, ion): 221 (100, M) 220 (32) 206 (57, M−CH_3) 190 (35) 179 (57). Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.86; H, 6.89; N, 6.27.

7.6.5. 1-(4-Naphthalen-1-yl-phenyl)-ethanone (11). Following general procedure, 1-bromo-naphthalene **1e** was converted into arylzinc reagent and cross-coupled with 1-(4-bromo-phenyl)-ethanone. Purification of the crude product by column chromatography (75 mL silica gel, column i.d. 30 mm) using gradient elution from 2% EtOAc/petroleum ether to 4% EtOAc/petroleum ether afforded 142 mg (82%) of solid material; analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, R_f=0.43. Pure material was obtained by crystallization from EtOAc/petroleum ether, mp 102–103 °C, colorless prisms; IR (Nujol, cm^{-1}) 1685 C=O; 200 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 8.14–8.06 (2H, m) 7.96–7.81 (3H, m) 7.65–7.40 (6H, m) 2.69 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 198.1, 146.0, 139.2, 136.2, 134.0, 131.4, 130.6, 128.7, 128.6, 127.2, 126.6, 126.2, 125.8, 125.6, 26.9; GC–MS *m/z* (% relative intensity, ion): 246 (53, M), 231 (75, M−CH_3) 203 (35) 202 (100) 201 (25) 200 (28) 176 (10) 150 (10). Anal. Calcd for $C_{18}H_{14}O$: C, 87.78; H, 5.73. Found: C, 87.59; H, 5.69.

7.6.6. 2-(1-Methyl-1*H*-indol-5-yl)-benzoic acid ethyl ester (12). Following general procedure, 5-bromo-1-methyl-1*H*-indole **1g** was converted into arylzinc reagent and cross-coupled with 2-bromo-benzoic acid ethyl ester. Purification of the crude product by column chromatography (100 mL silica gel, column i.d. 35 mm) using gradient elution from 15% CH_2Cl_2/petroleum ether to 50% CH_2Cl_2/petroleum ether afforded 143 mg (73%) pale yellow liquid; analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, R_f=0.23; IR (neat, cm^{-1}) 1719 C=O; 200 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.81–7.75 (1H, m) 7.60–7.16 (6H, m) 7.09–7.06 (1H, m) 6.51–6.47 (1H, m) 4.08 (2H, q, J=7.2 Hz) 3.82 (3H, s) 0.96 (3H, t, J=7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 169.8, 143.6, 136.3, 132.8, 132.1, 131.4, 131.1, 129.6, 128.7, 126.7, 122.8, 120.8, 101.5, 109.0, 61.1, 33.2, 14.1; GC–MS *m/z* (% relative intensity, ion): 279 (100, M) 251 (24, M−C_2H_4) 234 (68) 219 (23) 207 (65) 190 (36) 178 (19) 165 (75).

7.6.7. 5-(2-Chloro-phenyl)-1-methyl-1*H*-indole (13). Following general procedure, 5-bromo-1-methyl-1*H*-indole **1g** was converted into arylzinc reagent and cross-coupled with 1-bromo-2-chlorobenzene. Purification of the crude product by column chromatography (100 mL silica gel, column i.d. 35 mm) using gradient elution from 0.5% CH_2Cl_2/petroleum ether to 25% CH_2Cl_2/petroleum ether afforded 140 mg (83%) pale yellow solid; analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, R_f=0.48. Pure material was obtained by crystallization from EtOAc/petroleum ether, mp 141–143 °C, pale yellow pyramidal crystals; 200 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.69 (1H, dd, J=1.5, 0.8 Hz) 7.52–7.21 (6H, m) 7.10 (1H, d, J=3.1 Hz) 6.54 (1H, d, J=2.9 Hz) 3.84 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 142.0, 136.3, 133.2, 132.2, 131.0, 130.1, 129.7, 128.5, 128.2, 127.0, 123.6, 122.1, 108.9, 101.6, 33.2; GC–MS *m/z* (% relative intensity, ion): 241 (100, M) 204 (14) 190 (16) 165 (19) 163 (14). Anal. Calcd for $C_{15}H_{12}ClN$: C, 74.53; H, 5.00; N, 5.79. Found: C, 74.32; H, 4.84; N, 5.50.

7.6.8. 1-(4′-Chloro-biphenyl-4-yl)-ethanone (14). Following general procedure, 1-bromo-4-chloro-benzene **1h** was converted into arylzinc reagent and cross-coupled with 1-(4-bromo-phenyl)ethanone. Purification of the crude product by column chromatography (75 mL silica gel, column i.d. 30 mm) using 4% EtOAc/petroleum ether afforded 109 mg (68%) of solid material; analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, R_f=0.31. Pure material was obtained by crystallization from EtOAc/petroleum ether, mp 100–101 °C, colorless needles (lit.[30] 102–103 °C); IR (Nujol, cm^{-1}) 1678 C=O; 200 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 8.07–7.99 (2H, m) 7.68–7.40 (6H, m) 2.64 (3H, s); GC–MS *m/z* (% relative intensity, ion): 230 (35, M) 215 (98, M−CH3) 152 (100).

7.6.9. 5-(4-Chloro-phenyl)-1-methyl-1*H*-indole-2-carboxylic acid ethyl ester (15). Following general procedure, 1-bromo-4-chloro-benzene **1h** was converted into arylzinc reagent and cross-coupled with 5-bromo-1-methyl-1*H*-indole-2-carboxylic acid ethyl ester. Purification of the crude product by column chromatography (100 mL silica gel, column i.d. 35 mm) using gradient elution from 15% CH_2Cl_2/petroleum ether to 30% CH_2Cl_2/petroleum ether afforded 183 mg (83%) of solid material; analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, R_f=0.38. Pure material was obtained by crystallization from EtOAc/petroleum ether, mp 128–129 °C, colorless plates; IR ($CHCl_3$ thin film, cm^{-1}) 1712 C=O; 200 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.85–7.82 (1H, m) 7.61–7.32 (7H, m) 4.39 (2H, q, J=7.0 Hz) 4.11 (3H, s) 1.42 (3H, t, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 162.3, 140.5, 139.4, 132.94, 132.88, 129.1, 128.7, 126.5, 124.7, 120.8, 110.9, 110.5, 60.8, 32.1, 14.5; GC–MS *m/z* (% relative intensity, ion): 313 (100, M) 285 (87, M−C_2H_4) 268 (15) 241 (24) 204 (18) 199 (59) 190 (31) 163 (22). Anal. Calcd for $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14; N, 4.46. Found: C, 68.39; H, 4.94; N, 4.14.

7.6.10. 4′-Methoxy-biphenyl-2-carbonitrile (16). Following general procedure, 1-chloro-4-methoxybenzene **3b** was converted into arylzinc reagent and cross-coupled with 2-bromo-benzonitrile. Purification of the crude product by column chromatography (75 mL silica gel, column i.d. 30 mm) using gradient elution from 2.5% EtOAc/petroleum

ether to 10% EtOAc/petroleum ether yielded 134 mg (92%) of solid material; analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, $R_f=0.33$. Pure material was obtained by crystallization from EtOAc/petroleum ether, mp 83–84 °C, colorless needles (lit.[31] 81–82 °C); IR (Nujol, cm^{-1}) 2213 C≡N; 200 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.77–7.35 (6H, m) 7.06–6.97 (2H, m) 3.86 (3H, s); GC–MS *m/z* (% relative intensity, ion): 209 (83, M) 194 (25, M−CH_3) 166 (100) 140 (93) 113 (34) 63 (37).

7.6.11. 4′-Dimethylamino-biphenyl-2-carbonitrile (17). Following general procedure, 4-chloro-*N*,*N*-dimethylaminobenzene **3c** was converted into arylzinc reagent and cross-coupled with 2-bromo-benzonitrile. Purification of the crude product by column chromatography (100 mL silica gel, column i.d. 50 mm) using gradient elution from 2% EtOAc/petroleum ether to 10% EtOAc/petroleum ether afforded 90 mg (81%) brown solid; analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, $R_f=0.33$. Pure material was obtained by crystallization from EtOAc/petroleum ether, mp 106–107 °C, brownish parallelepiped crystals; IR ($CHCl_3$ thin film, cm^{-1}) 2213 C≡N; 200 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.75–7.68 (1H, m) 7.64–7.45 (4H, m) 7.39–7.29 (1H, m) 6.87–6.77 (2H, m) 3.02 (6H, s); ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ 150.3, 145.7, 133.5, 132.3, 129.29, 129.31, 129.31, 126.1, 125.6, 112.09, 112.10, 119.4, 110.9, 40.2; GC–MS *m/z* (% relative intensity, ion): 222 (100, M) 205 (15) 178 (18) 151 (19). Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.00; H, 6.38; N, 12.73.

7.6.12. 2-Thiophen-2-yl-benzoic acid ethyl ester (18). Following general procedure, 2-chloro-thiophene **3d** was converted into arylzinc reagent and cross-coupled with 2-bromo-benzoic acid ethyl ester. Purification of the crude product by column chromatography (100 mL silica gel, column i.d. 30 mm) using gradient elution from 2% EtOAc/petroleum ether to 4% EtOAc/petroleum ether gave 149 mg (92%) of colorless oil, analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, $R_f=0.55$; IR (neat, cm^{-1}) 1718 C=O; 200 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.77–7.70 (1H, m) 7.51–7.32 (4H, m) 7.08–7.00 (2H, m) 4.18 (2H, q, $J=7.2$ Hz) 1.13 (3H, t, $J=7.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 169.0, 142.4, 134.4, 132.5, 131.4, 131.1, 129.6, 128.0, 127.3, 126.5, 126.0, 61.5, 14.0; GC–MS *m/z* (% relative intensity, ion): 232 (70, M) 187 (87) 160 (27) 115 (100).

7.6.13. 2-(1-Methyl-1*H*-indol-5-yl)-benzonitrile (19). Following general procedure, 5-chloro-1-methyl-1*H*-indole **3e** was converted into arylzinc reagent and cross-coupled with 2-bromo-benzonitrile. Purification of the crude product by column chromatography (80 mL silica gel, column i.d. 35 mm) using gradient elution from 15% CH_2Cl_2/petroleum ether to 50% CH_2Cl_2/petroleum ether afforded 113 mg (70%) of brownish solid; analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, $R_f=0.20$. Pure material was obtained by crystallization from EtOAc/petroleum ether, mp 106–107 °C, brownish parallelepiped crystals; IR ($CHCl_3$ thin film, cm^{-1}) 2220 C≡N; 200 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.84–7.72 (2H, m) 7.67–7.54 (2H, m) 7.47–7.34 (3H, m) 7.11 (1H, d, $J=3.1$ Hz) 6.57 (1H, d, $J=3.1$ Hz) 3.83 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 147.2, 137.0, 133.9, 132.9, 130.7, 130.1, 129.8, 128.9, 126.9, 122.7, 121.7, 119.7, 111.6, 109.7, 101.9, 30.1; GC–MS *m/z* (% relative intensity, ion): 232 (100, M) 190 (17). Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.65; H, 5.04; N, 12.11.

7.6.14. 2-(1-Methyl-1*H*-indol-6-yl)-benzoic acid ethyl ester (20). Following general procedure, 6-chloro-1-methyl-1*H*-indole **3f** was converted into arylzinc reagent and cross-coupled with 2-bromo-benzoic acid ethyl ester. Purification of the crude product by column chromatography (80 mL silica gel, column i.d. 30 mm) using gradient elution from 15% CH_2Cl_2/petroleum ether to 50% CH_2Cl_2/petroleum ether yielded 126 mg (64%) of yellow oil; analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, $R_f=0.23$; IR ($CHCl_3$ film, cm^{-1}) 1720 C=O; 200 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.82–7.76 (1H, m) 7.65–7.34 (4H, m) 7.31–7.28 (1H, m) 7.11–7.04 (2H, m) 6.50 (1H, dd, $J=3.3$, 0.7 Hz) 4.07 (2H, q, $J=7.0$ Hz) 3.80 (3H, s) 0.92 (3H, t, $J=7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ 169.8, 143.5, 136.9, 135.2, 132.2, 131.2, 131.1, 129.62, 129.55, 127.9, 126.9, 120.8, 120.6, 109.2, 101.1, 61.2, 33.1, 13.8; GC–MS *m/z* (% relative intensity, ion): 279 (100, M) 251 (35) 234 (37) 219 (26) 207 (41) 190 (26) 178 (15) 165 (35).

Acknowledgements

This work has been partly supported by the European Social Fund within the National Programme 'Support for the carrying out doctoral study programm's and post-doctoral researches' project 'Support for the development of doctoral studies at Riga Technical University'. The financial support of the Latvian Science Council (Grants 05.1775 and 05.1782) is also acknowledged.

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10. Inert atmosphere and moisture free conditions, necessary for the Grignard generation can be easily realized in a Emrys™ microwave process vial closed with aluminum open-top seal with PTFE-faced septum.
11. Magnesium turnings were purchased from Acros. Initially, we made certain that the microwave irradiation of magnesium in organic solvents can be carried out safely. Thus, dielectric heating of magnesium turnings at various temperatures was performed in THF and in Et_2O, which are a routinely used medium for preparation of Grignard reagents. We were pleased to find that temperature and pressure profiles of the heating did not show any unusual behavior such as quick rise of temperature or sudden change of pressure, demonstrating that microwave irradiation of magnesium turnings under the tested conditions is safe and reliable procedure.
12. THF was distilled from sodium benzophenone ketyl under argon prior to use.
13. Prepared from 'dry ice' and dried by passing through concentrated sulfuric acid. Carbon dioxide has been frequently used as trapping agent to determine yields of organometallic species: see: Schlosser, M. In *Organoalkali Chemistry*; Schlosser, A., Ed.; Organometallics in Synthesis: a Manual; Wiley: Chichester, 2002; pp 1–353.
14. During several 100 experiments performed, the pressure never exceeded 2 bar and none of over pressurization incidents were observed (the maximum pressure that could be employed in the system is 20 bar).
15. The use of 80 °C (vs 60 °C) resulted in higher reproducibility of the Grignard formation.
16. Dielectric constant of THF: 7.5 (at 22 °C); dielectric constant of chlorobenzene: 5.7 (at 22 °C); see: *CRC Handbook of Chemistry and Physics*; Lide, D. R., Ed.; CRC, 2000; pp 6–149.
17. Ionic liquids are among the most frequently employed additives; see, for example: Leadbeater, N. E.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145.
18. Prepared by the reaction of excess magnesium with 1,2-dibromoethane, followed by removal of unreacted metal, then evaporation of solvent and, finally, drying of the solid residue in vacuo (0.1 Torr).
19. The use of less concentrated $MgBr_2$ solution (0.1 M) did not improve the heating rate. If more concentrated $MgBr_2$ solution (1.0 M) was employed, precipitation of magnesium salts was observed.
20. For relative rates of the formation of various arylmagnesium species see: Rogers, H. R.; Rogers, R. J.; Mitchell, H. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 231.
21. Dielectric heating at 180 °C developed 13–19 bar pressure inside the Emrys™ microwave process vial. However, we never observed any of over pressurization incidents (the maximum pressure that could be employed in the system is 20 bar).
22. Okamoto, Y.; Yoshioka, K.; Yamana, T.; Mori, H. *J. Organomet. Chem.* **1989**, *369*, 285.
23. Ca. 5% of alcohol **6** was formed when 4-bromobenzaldehyde **5** was reacted with arylzinc chloride **4b** in the absence of Pd catalyst after 5 min at room temperature (yields of alcohol **6** and biphenyl aldehyde **7** were determined by GC–MS assay). On the other hand, none of the alcohol **6** was formed in the presence of $(Ph_3P)_2PdCl_2$, thus demonstrating the high chemoselectivity of the Negishi coupling over the 1,2-addition.
24. The solution of $ZnCl_2$ in Et_2O (1 M) (Aldrich) and 0.5 M solution of $ZnCl_2$ in THF (Aldrich) was employed.
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26. Elevated temperature (120 °C for 5 min) was applied in a previous work (see Ref. 4) to bring the Negishi cross-coupling of various arylzinc iodides with 4-bromobenzaldehyde **5** to completion. However, back then, arylzinc iodides were generated directly from aryl iodides and Zn–Cu couple and therefore did not contain inorganic salts. Herein, apparently, the presence of Mg salts (from transmetallation step) in the solution of arylzinc reagent facilitates the palladium catalyzed cross-coupling with aryl bromides. In a control experiment, phenylzinc iodide was prepared from iodobenzene and Zn–Cu couple in the presence of $MgCl_2$ (0.5 M solution in THF). Subsequent Negishi coupling with 4-bromobenzaldehyde **5** was completed at room temperature after 5 min (GC–MS assay). Further work is in progress to establish the role of Mg salts in the cross-coupling reaction.
27. In the case of 4-dimethylamino-benzoic acid **2c** the combined basic extracts were acidified with 1 M HCl to pH ~ 4. 0.1 M HCl was employed to acidify the basic extracts in the case of indoles **2g** and **2i**.
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Functionalization of saturated hydrocarbons. High temperature bromination of octahydropentalene. Part 19☆

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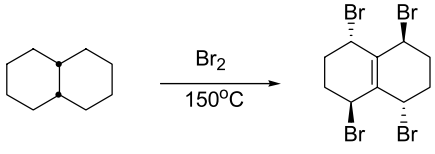
Received 7 June 2005; revised 30 August 2005; accepted 8 September 2005

Available online 28 September 2005

Abstract—The synthesis and thermal bromination of octahydropentalene was studied. The reaction afforded 1a,3a,4b,6b-tetrabromo-1,2,3,4,5,6-hexahydropentalene (**14**) with remarkable regio- and stereospecificity. The structure of the product was determined by ^{1}H and ^{13}C NMR data and single X-ray structural analysis. The treatment of octahydropentalene with tenfold bromine gave the octabromopentalene derivative. The formation mechanism of the products is discussed.

1. Introduction

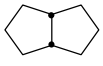
The bromination of hydrocarbons involves important processes because it leads to a variety of useful synthetic intermediates.[2] Recently we have reported that the bromination of decalin **1**, gave 1a,4b,5a,8b-tetrabromo-3,5,7,9-tetrabromooctalin (**2**), as the major product along with smaller amounts of bromonaphthalene derivatives (Scheme 1).[3] It was remarkable to notice that the reaction proceeded with regio- and stereospecificity. The exclusive formation of **2**, which is only one of the five possible diastereomeric tetrabromides, could be the result of the fact that **2** is formed faster than other isomers (kinetic control). Alternatively, **2** may simply be the most stable one of the five possible diastereomers (thermodynamic control).



1 **2**

Scheme 1.

Inspired by encouraging results with decalin, we have decided to investigate the scope and limitations of the reaction in view of other bicyclic hydrocarbons. We have envisaged that the bromination of octahydropentalene (**3**),[4] would afford the analogue tetrabromide regio- and stereospecifically. Herein, we wish to describe the conditions under, which the high-temperature bromination[5] of **3** proceeds with remarkable regio- and stereospecificity.



3

2. Results and discussion

In order to obtain the desired hydrocarbon skeleton we started with *cis*,*cis*-1,5-cyclooctadiene (COD), (**4**). Uemura et al.[6] reported that the treatment of COD with iodine smoothly gave **5** and **6**[7] via a transannular cyclization along with the three unidentified minor products.[8] Repetition of the reaction according to the reported conditions afforded a mixture consisting of **5**, **6**, **7**, **8**, and **9** in a ratio of 20:20:6:2:1, respectively (Scheme 2).

The major products, **5** and **6**, were isolated by the crystallization of the reaction mixture from hexane in a

☆ See Ref. 1

Keywords: Bromination; Hydrocarbons; Pentalene; Substitution.
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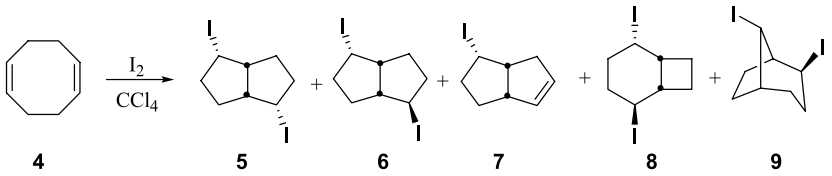
‡ To whom correspondence concerning the X-ray analysis of **20** should be sent.

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.019

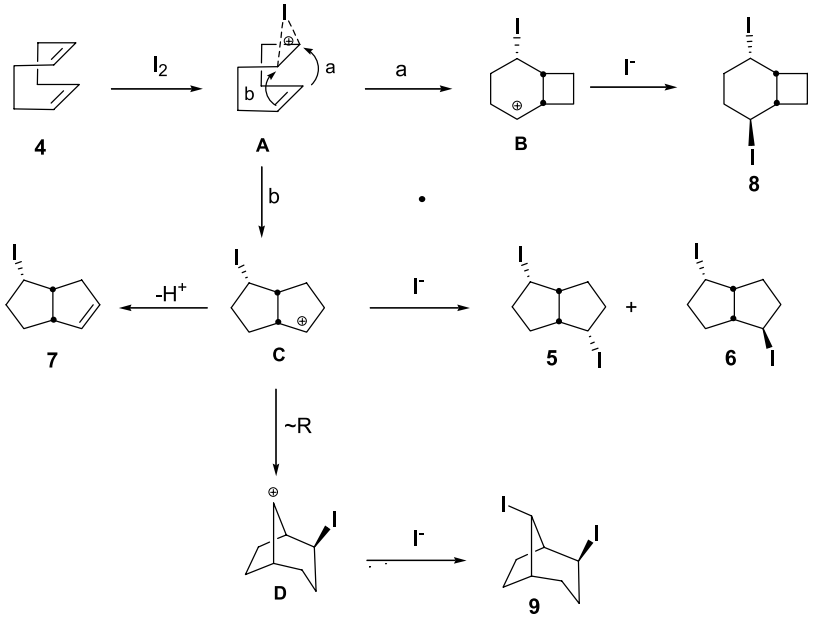


Scheme 2.

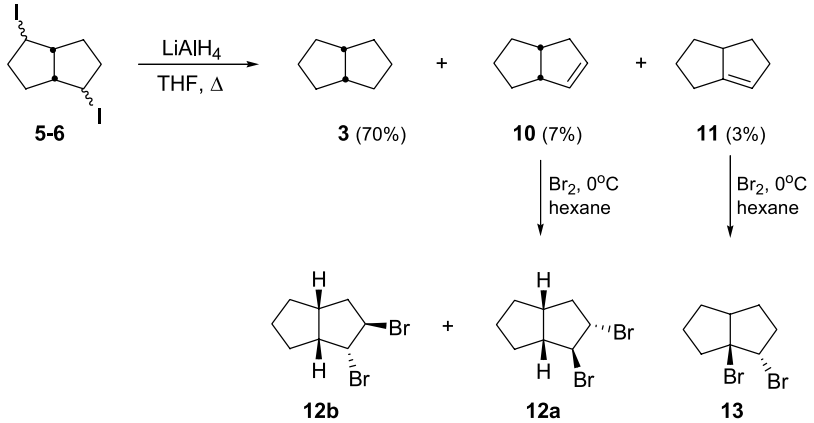
yield of 67%. This mixture was subjected to column chromatography to give **5** and **6** separately as white solids in an approximately equal amount. The spectral data for **5** and **6** was in full agreement with the those previously reported.[5] After the removal of **5** and **6**, the residue was subjected to repeated column chromatography, and three compounds were also isolated: 3-iodo-1,2,3,3a,4,6a-hexahydropentalene (**7**), *trans*-2,5-diiodo-bicyclo[4.2.0]octane (**8**), and 2,8-diiodo-bicyclo[3.2.1]octane (**9**). The structures of all the compounds were determined by ^{1}H, ^{13}C NMR and 2-D experiments (DEPT, COSY, HMQC, HMBC).

A plausible mechanism for the formation of the products is summarized in Scheme 3. The addition of iodine to one of the double bonds first gives the iodonium intermediate **A**, which then rearranges to two different carbocations, **B** and **C** via two possible transannular π participations. The attack of iodine on the formed carbocations, **B** and **C**, affords **8** and **5**, **6**, respectively. However, intermediate **C** may also eliminate hydrogen to give **7**, or may further rearrange to **D**, of which a substitution gives **9**.

Reduction of the mixture of **5** and **6** with $LiAlH_4$ in refluxing THF afforded octahydropentalene (**3**) as the major product in 70% yield with smaller amounts of **10** and **11** in a ratio of 20:2:1, respectively (Scheme 4). Compounds **10** and



Scheme 3.

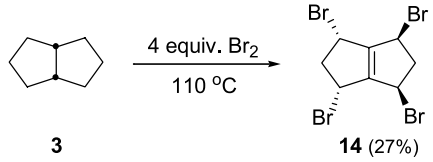


Scheme 4.

11 probably arise from the competing elimination path under the given reaction conditions. Unfortunately, all of our initial attempts to separate the mixture by fractional distillation failed.

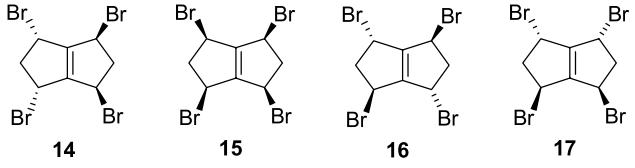
Then the mixture consisting of **3**, **10**, and **11** was treated with bromine at 0 °C in the dark (Scheme 4), in which the hydrocarbon **3** was successfully separated from the formed dibromides **12** and **13** by column chromatography or simple distillation in 70% yield.

The treatment of octahydropentalene (**3**) with 4 equiv of bromine at 110 °C over a period of 1.5 h afforded the tetrabromide **14** in a yield of 27% (Scheme 5).



Scheme 5.

The ^{1}H and ^{13}C NMR studies of the tetrabromide showed the formation of a highly symmetrical compound. The ^{13}C NMR spectrum consisted of three distinct carbon resonances indicating high symmetry in the molecule. This could be in agreement with four possible diastereomeric structures **14**, **15**, **16**, and **17**.



The ^{1}H NMR spectrum of the isolated compound shows three sets of signals. The methine protons appear as a doublet of doublets at 5.04 ppm ($J=7.0$, 1.5 Hz) and the methylene protons appear as an AB system as two doublets of triplets at 3.76 ppm (A-part of AB system, $J=16.5$, 7.1 Hz) and 3.15 ppm (B-part of AB system, $J=16.5$, 1.5 Hz). In the case of **16** and **17** the methylenic protons are equal and would not give rise to the formation of an AB-system. Therefore, the structures **16** and **17** were excluded. However, on the basis of NMR data alone, we were not able to distinguish between the possible symmetrical tetrabromides **14** and **15**. Attempts to carry out reactions (epoxidation, bromination) with the central double bond, which would allow one to distinguish between those isomers, resulted only in the formation of unreacted starting material. Apparently steric effects associated with the adjacent bromine atoms preclude a reaction with the central double bond. Finally, the structure of tetrabromide **14** was unambiguously shown by the X-ray crystallographic analysis (Fig. 1).

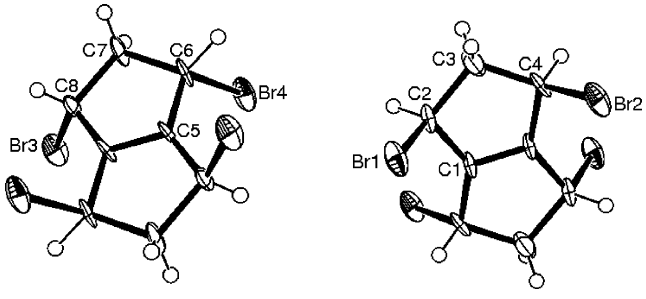
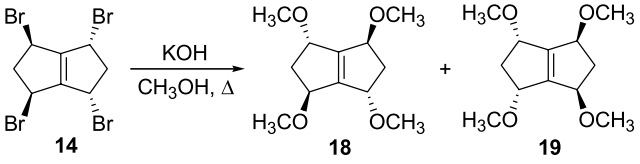


Figure 1. The X-ray crystal structure of **14**.

AM1 and MM+ molecular mechanics calculations show that the isomer **14** and **16** are close in energy and they are approximately 2–4 kcal/mol more stable than the other isomers. According to these values it was expected that the isomer **16** should also be formed. Careful examination of the reaction mixture did not reveal the formation of any trace of the isomer **16**, to where we assume that **14** is favored kinetically (Table 1).

For further functionalization of the isomer **14** it was treated with KOH in refluxing MeOH, in which the reaction afforded tetramethoxy compounds **18** and **19** in a ratio of 2:1, respectively (Scheme 6). The stereochemical outcome of the reaction was also noteworthy that the bromine atoms are converted into methoxy groups, perhaps via an S_N1 type mechanism.

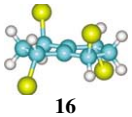
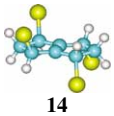
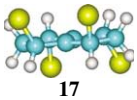
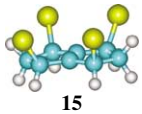


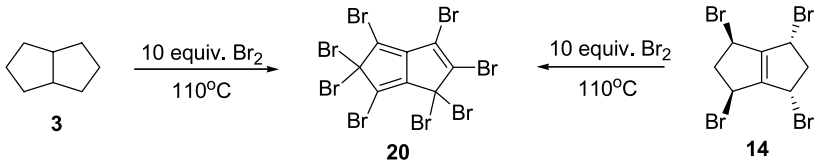
Scheme 6.

The ^{1}H NMR spectrum of **18** shows three sets of signals. The methoxyl protons give sharp singlet at 3.34 ppm whereas the protons adjacent to methoxyl group appear as a triplet at 4.53 ppm ($J=5.0$ Hz). The fact that the methylenic protons also appear as a triplet at 2.44 ppm ($J=5.0$ Hz) indicate the all-trans-configuration. A four-line ^{13}C NMR spectrum is also in agreement with the structure.

On the other hand, the ^{1}H NMR spectrum of **19** consists of a doublet of doublets at 4.38 ppm ($J=7.0$, 3.6 Hz), a sharp singlet at 3.38 ppm and an AB system at 2.92 (A-part of AB-system, $J=14.1$, 7.0 Hz) and 2.03 ppm (B-part of

Table 1. The AM1 calculated heats of formation and MM+ relative strain energies in kcal/mol of diastereomeric tetrabromides **14–17**

Tetrabromides	 **16**	 **14**	 **17**	 **15**
AM1	0.00	0.04	1.83	2.41
MM+	0.00	0.25	4.16	3.25



Scheme 7.

AB-system, $J=14.1$, 3.7 Hz), which strongly indicates the cis-orientation of the methoxyl groups as of the bromines in the case of tetrabromo compound **14**.

Octahydropentalene **3** or tetrabromide **14** was treated with 10 equiv of bromine under the same reaction conditions as reported for the synthesis of **14** (Scheme 7). Fractional crystallization and ^{1}H and ^{13}C NMR spectral studies indicated the formation of a product, which did not contain any protons. The ^{13}C NMR spectrum showed eight distinct signals indicating the presence of an asymmetric structure. The exact structure of this compound was solved by X-ray analysis, indicating the presence of eight bromine atoms (Fig. 2).

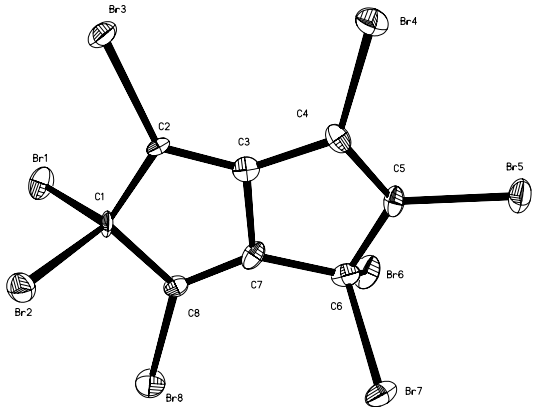


Figure 2. The X-ray crystal structure of **20**.

In view of the mechanism, we assume that octahydropentalene (**3**) reacts with bromine radical to give the monobromide **21**, from which HBr elimination affords the alkene **22** (Scheme 8). This alkene would undergo sequential allylic bromination reactions to furnish tetrabromide **14** with remarkable regio- and stereospecificity. The formation of the octabromo **20** compound can be rationalized by tandem HBr elimination followed by bromine addition. Attempts to trap the intermediates failed. We assume that the formed intermediates such as penta- hexa- and heptabromides are unstable under the reaction conditions. The octa-bromide is probably the most stable one.

In summary, the bromination of octahydropentalene (**3**) carried out at high temperatures takes place with remarkable stereo- and regiospecificity to give **14**. This methodology can be applied to functionalize bicyclic hydrocarbons. Efforts to elucidate the scope and the limitations of a high temperature bromination reaction of saturated hydrocarbons are still in progress.

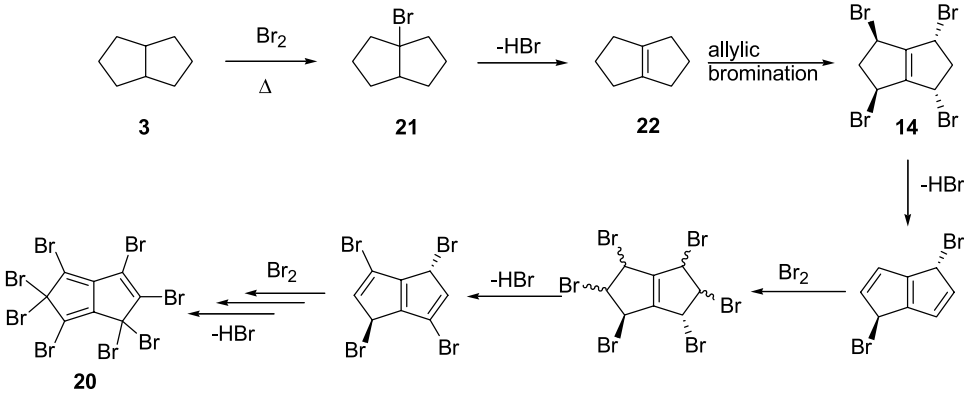
3. Experimental

3.1. General

Melting points were determined on a Büchi model 530 apparatus and are uncorrected. Infrared spectra were recorded on a Mattson model 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on 400 (100) MHz spectrometers. Mass spectra (electron impact) were recorded at 70 eV. Column chromatography was performed on silica gel (60–200 mesh) from the Merck Company. TLC was carried out on Merck 0.2 mm silica gel 60 F254 analytical aluminum plates.

3.2. Iodination of *cis*,*cis*-1,5-cyclooctadiene (4)

A solution of iodine (17.8 g, 70 mmol) and *cis*,*cis*-cycloocta-1,5-diene **4** (5.04 g, 46.7 mmol) in CCl_4 (100 mL) was stirred at 25 °C for 24 h. The mixture was then washed with aqueous $Na_2S_2O_3$ to remove excess iodine, washed with brine, and dried over $MgSO_4$. Evaporation of the solvent in vacuo and crystallization from hexane left a pale yellow solid mixture of **5** and **6**. The



Scheme 8.

crystals were subjected to column chromatography on silica gel with hexane as eluent to give each of pure 1,4-diiodooctahydropentalene **5** (5.7 g, 31.5 mmol, 34%), and **6** (5.6 g, 31.5 mmol, 34%) as white solids, the former being eluted first. Then the repeated column chromatographic separations of the remaining mixture on silica gel with hexane as an eluent also gave **7** (1.71 g, 9.5 mmol, 11%), **8** (0.57 g, 3.15 mmol, 4%), and **9** (0.29 g, 1.6 mmol, 2%).

3.2.1. (1*S*(*R*),3a*R*(*S*),4*S*(*R*),6a*R*(*S*))-1,4-Diiodooctahydropentalene (5)[6] White needle crystals from hexane, mp 67–68 °C (lit. mp 60–62 °C[6]); ν_{max} ($CHCl_3$) 3007, 2965, 2930, 2839, 1448, 1280, 1252, 1182, 1085, 1015, 910, 819, 791, 749 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.92 (2H, m, H_1 and H_4); 3.08 (2H, m, H_{3a} and H_{6a}); 2.16 (2H, m, H_3 and H_6); 2.03 (4H, m, H_2 and H_5); 1.26 (2H, m, $H_{3'}$ and $H_{6'}$); δ_C (100 MHz, $CDCl_3$) 56.2 (C_{3a}, C_{6a}), 39.2 (C_2, C_5), 32.2 (C_1, C_4), 31.9 (C_3, C_6); *m*/*z* (EI) 362 (0.5), 236 (12), 235 (−HI, 84), 234 (20), 108 (27), 107 (−2HI, 65), 106 (19), 79 (100).

3.2.2. (1*R*(*S*),3a*R*(*S*),4*S*(*R*),6a*R*(*S*))-1,4-Diiodooctahydropentalene (6)[6] White needle crystals from hexane, mp 79–80 °C (lit. mp 77 °C[6]); ν_{max} ($CHCl_3$) 2951, 2930, 2846, 1455, 1343, 1259, 1210, 1175, 1064, 910, 791, 756 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.92 (1H, m, H_4); 3.82 (1H, m, H_1); 2.87 (1H, m, H_{3a}); 2.69 (1H, m, H_{6a}); 2.13–2.14 (2H, m, H_2 and H_5); 1.97–1.87 (3H, m, $H_{2'}$, $H_{5'}$ and H_6); 1.66 (1H, m, H_3); 1.44 (2H, m, $H_{3'}$ and $H_{6'}$); δ_C (100 MHz, $CDCl_3$) 55.1 (C_{3a}), 48.4 (C_{6a}), 40.3 (C_2), 37.4 (C_5), 34.9 (C_6), 32.1 (C_4), 31.2 (C_1), 31.1 (C_3); *m*/*z* (EI) 362 (0.3), 236 (26), 235 (−HI, 100), 234 (62), 108 (55), 107 (−2HI, 85), 106 (48), 79 (95).

3.2.3. (3*R*(*S*),3a*S*(*R*),6a*R*(*S*))-3-Iodo-1,2,3,3a,4,6a-hexahydropentalene (7). Colorless liquid; ν_{max} ($CHCl_3$) 3107, 3093, 3065, 3051, 3037, 3024, 3010, 2996, 2982, 2940, 2927, 2885, 2844, 1557, 1529, 1494, 1391, 1335, 1218, 1211, 1204, 1038, 934, 865, 830, 789, 775, 768, 754, 657, 629 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.65 (2H, br s, H_5 and H_6); 4.10 (1H, q, J=5.2 Hz, H_3); 3.35 (1H, m, H_{6a}); 3.25 (1H, m, H_{3a}); 2.74 (1H, ddd, A-part of AB-system, J=17.2, 9.4, 1.5 Hz, H_4); 2.27–2.14 (2H, m, H_1 and H_2); 2.14–2.00 (2H, m, $H_{1'}$ and $H_{4'}$); 1.52 (1H, m, H_2); δ_C (100 MHz, $CDCl_3$) 134.5 (C_6), 128.6 (C_5), 54.4 (C_{3a}), 49.6 (C_{6a}), 39.9 (C_4), 38.3 (C_2), 36.6 (C_3), 31.1 (C_1). Anal. Calcd for $C_8H_{11}I$: C, 41.05; H, 4.74. Found: C, 41.01; H, 4.81; *m*/*z* (EI) 234 (6), 108 (26) 107 (−HI, 94) 106 (51) 79 (100).

3.2.4. *trans*-2,5-Diiodo-bicyclo[4.2.0]octane (8). Colorless liquid; ν_{max} ($CHCl_3$) 3032, 2877, 2729, 1650, 1458, 1378, 1218, 1146, 1038, 984, 954, 908, 878, 789, 763, 748, 648, 532, 516 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.00 (1H, qui, J=6.2 Hz, H_5); 3.72 (1H, h, J=6.0 Hz, H_2); 2.72 (1H, dqui, J=6.3, 1.5 Hz, H_1); 2.54–2.45 (1H, m, H_4); 2.43–2.38 (2H, m, $H_{4'}$ and H_6); 2.15–2.09 (1H, m, H_7); 2.05–1.97 (1H, m, $H_{7'}$); 1.78–1.69 (1H, m, H_3); 1.62–1.52 (2H, m, $H_{3'}$ and H_8); 1.50–1.40 (1H, m, $H_{8'}$); δ_C (100 MHz, $CDCl_3$) 49.3 (C_4), 49.2 (C_3), 48.9 (C_1), 41.5 (C_6), 36.1 (C_7), 32.7 (C_8), 28.1 (C_5), 19.2 (C_2). Anal. Calcd for $C_8H_{12}I_2$: C, 26.54; H, 3.34. Found: C, 26.48; H, 3.44; *m*/*z* (EI) 362 (0.4), 236 (8), 235 (−HI, 47), 234 (21), 108 (12), 107 (−2HI, 37), 106 (12), 79 (100).

3.2.5. 2-*exo*,9-*exo*-2,9-Diiodo-bicyclo[3.2.1]octane (9). Colorless liquid; ν_{max} ($CHCl_3$) 3107, 3037, 2996, 2982, 2954, 2871, 1619, 1543, 1446, 1391, 1328, 1252, 1169, 809, 802, 796, 789,775, 761, 747, 733, 719, 706, 692, 678, 657, 643, 609 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.33 (1H, dd, J=11.4, 5.8 Hz, H_2); 4.11 (1H, s, H_9); 2.82 (1H, br d, J=3.3 Hz, H_1); 2.54 (1H, br s, H_5); 2.23–2.14 (3H, m, H_3, H_6 and H_7); 2.02 (1H, dt, J=12.6, 6.0 Hz, $H_{3'}$); 1.94 (1H, t, J=10.4–Hz, $H_{7'}$); 1.64 (1H, dt, J=13.4, 5.0 Hz, H_4); 1.51 (1H, br t, J=9.3 Hz, $H_{6'}$); 1.39 (1H, ddt, J=13.4, 5.0, 1.2 Hz, $H_{4'}$); δ_C (100 MHz, $CDCl_3$) 55.9 (C_1), 44.9 (C_5), 36.1 (C_8), 36.0 (C_4), 31.6 (C_2), 31.5 (C_3), 26.8 (C_6), 25.3 (C_7). Anal. Calcd for $C_8H_{12}I_2$: C, 26.54; H, 3.34. Found: C, 26.51; H, 3.40; *m*/*z* (EI) 362 (5), 236 (45), 235 (−HI, 100), 234 (85), 233 (40), 108 (84), 107 (−2HI, 100), 106 (60), 79 (100).

3.3. Reduction of 5 and 6 with $LiAlH_4$

To a suspension of $LiAlH_4$ (3.5 g, 92 mmol) in 100 mL THF was dropwise added a mixture of **5** and **6** (16 g, 44 mmol) in 50 mL THF and the mixture was heated under reflux during 20 h. After cooling to room temperature, excess $LiAlH_4$ was destroyed with saturated NH_4Cl solution (300 mL), then the mixture was extracted with ether (3×150 mL), washed with brine (500 mL), dried over $MgSO_4$ and the solvent was simply distilled to give a 4 g mixture of **3**, **10** and **11**, in a ratio of 20:2:1, respectively (80%). This mixture was directly treated with bromine in the following step.

3.4. Bromination of the mixture of 3, 10, and 11 at 0 °C

Bromine (1.6 g, 10 mmol) in 10 mL hexane was added dropwise to a solution of **3**, **10**, **11** (4 g, 36 mmol) in 20 mL hexane at 0 °C in the dark during 30 min. The mixture was directly subjected to column chromatography on silica gel with pentane as an eluent to give each pure **3** (3.5 g, 31.6 mmol, 70%), **12a** and **12b** (0.84 g, 3.1 mmol, 7%), and **13** (0.4 g, 1.6 mmol, 4%).

3.4.1. Octahydropentalene (3). Volatile colorless liquid bp 125–130 °C; ν_{max} ($CHCl_3$) 3154, 3034, 3000, 2901, 1622, 1559, 1470, 1380, 1237, 1161, 1095, 915 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.20–2.25 (2H, m, H_{3a} and H_{6a}); 1.60 1.68 (4H, m, H_1, H_3, H_4, H_6); 1.49–1.54 (2H, m, H_2 and H_5); 1.36–1.40 (2H, m, $H_{2'}$ and $H_{5'}$); 1.15–1.21 (4H, m, $H_{1'}$, $H_{3'}$, $H_{4'}$, $H_{6'}$); δ_C (100 MHz, $CDCl_3$) 43.5 (C_{3a}, C_{6a}), 34.7 (C_1, C_3, C_4, C_6), 26.7 (C_2, C_5). Anal. Calcd for C_8H_{14}: C, 87.19; H, 12.81. Found: C, 87.01; H, 12.91.

3.4.2. (1*R*(*S*),2*R*(*S*),3a*S*(*R*),6a*S*(*R*))-1,2-Dibromooctahydropentalene (12a). Colorless liquid; ν_{max} ($CHCl_3$) 3097, 3019, 2864, 2758, 2622, 2253, 1519, 1374, 1215, 1014, 908, 848, 792, 764, 747, 728, 670, 624 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.51 (1H, t, J=5.8 Hz, H_1); 4.46 (1H, q, J=5.0 Hz, H_2); 2.99–2.92 (1H, m, H_{6a}); 2.88–2.78 (1H, m, H_{3a}); 2.24–2.17 (1H, m, H_3); 2.14–2.07 (1H, m, $H_{3'}$); 1.86–1.78 (1H, m, H_4); 1.75–1.73 (3H, m, H_5, H_6 and $H_{6'}$); 1.57–1.53 (1H, m, $H_{5'}$); 1.41–1.34 (1H, m, $H_{4'}$); δ_C (100 MHz, $CDCl_3$) 63.3 (C_1), 57.4 (C_2), 46.5 (C_{6a}), 42.4 (C_{3a}), 41.1 (C_3), 33.8 (C_4), 30.1 (C_6), 27.9 (C_5). Anal. Calcd for $C_8H_{12}Br_2$: C, 35.85; H, 4.51. Found: C, 35.81; H, 4.50; *m*/*z* (EI) 269/267/265 (10, 20, 10), 187/185 (43, 41), 106 (53), 105 (100), 104 (53), 79 (85).

3.4.3. (1*S*(*R*),2*S*(*R*),3a*S*(*R*),6a*S*(*R*))-1,2-Dibromooctahydropentalene (12b). Colorless liquid; ν_{max} ($CHCl_3$) 3107, 3024, 2968, 2954, 2940, 2927, 2913, 2885, 2857, 1598, 1543, 1453, 1398, 1301, 1218, 1162, 906, 892, 885, 872, 858, 844, 830, 816, 782, 754, 740, 726, 719, 706, 678, 602 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.06–3.98 (1H, m, H_2); 3.64 (1H, t, $J=8.8$ Hz, H_1); 2.75–2.68 (1H, m, H_{6a}); 2.61–2.50 (2H, m, H_3 and H_{3a}); 1.72–1.63 (5H, m, H_4, H_5, $H_{5'}$, H_6, and $H_{6'}$); 1.59 1.50 (2H, m, $H_{3'}$ and $H_{4'}$); δ_C (100 MHz, $CDCl_3$) 62.0 (C_1), 54.3 (C_2), 53.0 (C_{6a}), 42.6 (C_3), 41.1 (C_{3a}), 33.9 (C_4), 31.8 (C_6), 25.1 (C_5). Anal. Calcd for $C_8H_{12}Br_2$: C, 35.85; H, 4.51. Found: C, 35.81; H, 4.50; *m/z* (EI) 269/267/265 (8, 20, 12), 187/185 (48, 48), 106 (65), 105 (100), 104 (58), 79 (87).

3.4.4. 1,6a-Dibromooctahydropentalene (13). Colorless liquid; ν_{max} ($CHCl_3$) 3079, 3012, 2959, 2869, 1452, 1297, 1261, 1216, 1180, 1070, 946, 921, 888, 828, 770, 753, 733, 704, 669, 580 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.52 (1H, dd, $J=10.9$, 6.5 Hz, H_1); 2.93 (1H, ddd, $J=9.5$, 9.1, 2.7 Hz, H_{3a}); 2.26–2.09 (4H, m); 1.95–1.92 (2H, m); 1.84–1.74 (2H, m); 1.41–1.39 (1H, m); 1.34–1.26 (1H, m); δ_C (100 MHz, $CDCl_3$) 78.0 (C_{6a}), 62.4 (C_1), 54.4 (C_{3a}), 44.4 (C_2), 36.0 (C_6), 35.0 (C_4), 30.5 (C_3), 26.3 (C_5) Anal. Calcd for $C_8H_{12}Br_2$: C, 35.85; H, 4.51. Found: C, 35.81; H, 4.50; *m/z* (EI) 189/187 (M^+-Br, 49, 53), 188/186 (M^+-HBr, 30, 24), 108 (35), 107 (97), 79 (100).

3.5. Bromination of octahydropentalene (3) at 110 °C

To 1.0 g (9 mmol) of octahydropentalene (**3**) was added dropwise 2 mL of (40 mmol) bromine at 110 °C over 1.5 h while stirring. The resulting solution was stirred at the same temperature for an additional 15 min. After cooling to room temperature, the mixture was treated with 30 mL of CH_2Cl_2 and the solvent was removed by rotary evaporation. The distillation of the reaction mixture allowed us to recover the starting material in 39% yield. Then 20 mL of hexane was added and the mixture was allowed to stand one night at room temperature to give solid **14**. Recrystallization from hexane gave pure tetrabromide **14** (1.03 g, 27% (isolated yield), 46% based on the consumed material).

3.5.1. (1*R*(*S*),3*S*(*R*),4*S*(*R*),6*R*(*S*))-1,3,4,6-Tetrabromo-1,2,3,4,5,6-hexahydropentalene (14). White crystals from CH_2Cl_2, mp 182 °C (decomposition); ν_{max} ($CHCl_3$) 3075, 3020, 2939, 1501, 1215, 1210, 1071, 782, 764, 747, 670, 508 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.04 (1H, dd, $J=7.1$, 1.5 Hz, H_1); 3.76 (1H, dt, A-part of AB-system, $J=16.5$, 7.1 Hz, H_2); 3.15 (1H, dt, B-part of AB-system, $J=16.5$, 1.5 Hz, $H_{2'}$); δ_C (100 MHz, $CDCl_3$) 154.2 (C_3), 51.3 (C_1), 43.3 (C_2). Anal. Calcd for $C_8H_8Br_4$: C, 22.67; H, 1.90. Found: C, 22.61; H, 1.95.

3.6. Treatment of 14 with KOH

A solution of 0.3 g (0.7 mmol) of **14** in 40 mL methanol was dropwise added to a solution of 0.1 g (1.5 mmol) KOH in 50 mL methanol and the flask was heated up to reflux during 15 h. After cooling to room temperature, the mixture was diluted with water and extracted with CH_2Cl_2 (3×150 mL), dried over $MgSO_4$ and the solvent was evaporated to give 110 mg crude product (77%). The residue was subjected to repeated column chromatography using hexane–ethyl acetate as an eluent (10/1) to give **18** (50 mg, 0.22 mmol, 38%), **19** (25 mg, 0.11 mmol, 19%).

3.6.1. (1*R*(*S*),3*R*(*S*),4*R*(*S*),6*R*(*S*))-1,3,4,6-Tetramethoxy-1,2,3,4,5,6-hexahydropentalene (18). Colorless liquid; ν_{max} IR ($CHCl_3$) 3057, 3019, 2976, 2834, 2763, 2377, 2224, 1451, 1391, 1369, 1331, 1271, 1255, 1216, 1184, 1086, 1015, 901, 743 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.53 (4H, t, $J=5.0$ Hz); 3.34 (12H, s); 2.44 (4H, t, $J=5.0$ Hz); δ_C (100 MHz, $CDCl_3$) 155.0 (=C), 80.5 (OCH_3), 56.9 (CH), 42.9 (CH_2). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.04; H, 8.91; *m/z* (EI) 228, (M^+, 1), 196 (M^+-OCH_3, 5), 180 (5), 169 (100), 150 (15), 138 (55), 126 (30), 108 (25), 94 (30), 74 (95), 62 (10), 44 (30).

3.6.2. (1*R*(*S*),3*S*(*R*),4*S*(*R*),6*R*(*S*))-1,3,4,6-Tetramethoxy-1,2,3,4,5,6-hexahydropentalene (19). Colorless liquid; ν_{max} ($CHCl_3$) 3144, 3046, 3030, 2986, 2436, 2393, 2246, 1516, 1418, 1271, 1249, 1189, 911, 797, 754 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.38 (2H, dd, $J=7.0$, 3.6 Hz, H_1); 3.38 (12H, s, OCH_3); 2.92 (2H, dt, A-part of AB system, $J=14.1$, 7.0 Hz, H_2); 2.03 (2H, dt, B-part of AB system, $J=14.1$, 3.7 Hz, $H_{2'}$); δ_C (100 MHz, $CDCl_3$) 155.0 (=C), 80.9 (OCH_3), 57.0 (CH), 41.8 (CH_2). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.04; H, 8.91; *m/z* (EI) 196 (M^+-OCH_3, 10), 180 (10), 169 (100), 150 (20), 138 (60), 126 (25), 108 (30), 94 (25), 74 (95), 62 (15), 44 (35).

3.7. Bromination of octahydropentalene (3) at 110 °C with 10 equiv bromine

To 1.0 g (9 mmol) of octahydropentalene (**3**) was added dropwise 5 mL of (80 mmol) bromine at 110 °C over 3 h while stirring. The resulting solution was stirred at the same temperature for an additional 15 min. After cooling to room temperature, the mixture including unreacted hydrocarbon was treated with 30 mL of CH_2Cl_2 and the solvent was removed by rotary evaporation. Then 20 mL of hexane was added and the mixture was allowed to stand one night at room temperature to give octabromide **20**, which was recrystallized from *n*-hexane–CH_2Cl_2 (1.6 g, 2.2 mmol, 48%).

3.7.1. 1,1,2,3,4,5,5,6-Octabromo-1,5-dihydropentalene (20). Yellow crystals from *n*-hexane–CH_2Cl_2, mp 212 °C (decomposition); ^{13}C NMR (100 MHz) 145.7, 138.7, 134.8, 125.7, 118.4, 117.7, 64.4, 45.7; IR (KBr, cm^{-1}): 2972, 2930, 2860, 1275, 1266, 1224, 1189, 1106, 1057, 775, 756, 728, 609. Anal. Calcd for C_8Br_8: C, 13.07. Found: C, 13.05.

3.8. X-ray structure determination of compound 20 and 14

The molecular structure of **20** was established by X-ray diffraction analysis (Fig. 2). All data were collected on a Bruker SMART™ 1000 CCD-based diffractometer at 213(2) and wavelength 0.71073 Å *P*2(1)/*n*; crystal data for compound **20**: C_8Br_8, space group: monoclinic, *P*2(1)/*n*; unit cell dimensions: $a=10.1019(14)$ Å, $b=9.1835(13)$ Å, $c=16.060(2)$ Å, $\alpha=90°$, $\beta=95.491(2)°$, $\gamma=90°$; volume: 1483.1(4) $Å^3$; *Z*, 2; calculated density: 3.293 mg/m^3; absorption coeffecient: 21.601 mm^{-1}; *F*(000): 1312; crystal

size: $0.09\times0.07\times0.06\ mm^3$; θ range for data collection 2.29–28.28°; completeness to θ:28.28, 97.3%; refinement method: full-matrix least-square on F^2; data/restraints/parameters: 3455/0/146; goodness-of-fit on F^2: 0.725; final R indices [$I>2\sigma(I)$]: $R_1=0.0369$, $wR_2=0.0481$; R indices (all data): $R_1=0.0982$, $wR_2=0.0578$; extinction coefficient: 0.00008(4); largest diff. peak and hole: 0.718 and $-0.689\ e\text{Å}^{-3}$.

The X-ray diffraction measurement of **14** was made on Enraf Nonius CAD4 diffractometer at temperature 293(2) K and wavelength 1.54184 Å. Crystal data for compound **14**: $C_8H_8Br_4$, $f_w=423.74$, crystal system, space group: triclinic, P-1; unit cell dimensions: $a=7.6236(12)$ Å, $b=8.5814(11)$ Å, $c=8.9047(13)$ Å, $\alpha=90.267(11)°$, $\beta=106.405(13)°$, $\gamma=104.141(12)°$; volume: 540.20(14) Å^3; $Z=2$; calculated density: $2.605\ mg/m^3$; absorption coeffecient: $1.774\ mm^{-1}$; $F(000)$: 392; crystal size: $0.20\times0.10\times0.10\ mm^3$; θ range for data collection: 9.23–74.19°; completeness to 2θ: 100.0%; refinement method: full-matrix least-square on F^2; data/restraints/parameters: 1777/0/118; goodness-of-fit on F^2: 0.992; final R indices [$I>2\sigma(I)$]: $R_1=0.0464$, $wR_2=0.1088$; R indices (all data): $R1=0.0633$, $wR2=0.1194$; extinction coefficient: 0.0031(4); largest diff. peak and hole: 1.136 and $-0.802\ e\text{Å}^{-3}$.

Crystallographic data for the structural analysis of compound **20** and **14** has been deposited with the Cambridge Crystallographic Data Center (CCDC) under the number 273699 and 273574, respectively. Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Acknowledgements

The authors are indebted to TUBITAK (Scientific and Technical Research Council of Turkey) and TUBA (Turkish Academy of Sciences) for their financial support of this research. D. D. G. would also like thank the TUBITAK for awarding a scholarship.

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Tetrahedron 61 (2005) 11184–11191

Synthesis and reactivity profiles of phosphinated poly(alkyl aryl ether) dendrimers

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Received 3 June 2005; revised 23 August 2005; accepted 8 September 2005

Available online 10 October 2005

Abstract—Poly(alkyl aryl ether) dendrimers were utilized to synthesize a series of new triphenylphosphine functionalized dendrimers. Zero, first, second and third generation dendrimers, carrying 3, 6, 12 and 24 triphenylphosphine units, were prepared and characterized. The new triphenylphosphine containing dendrimers were assessed for their reactivity profiles and in this instance, the dendrimers were used as reagents to mediate Mitsunobu etherification reaction between phenol and various primary, secondary and benzylic alcohols. In addition, dendritic poly-phenols were also tested in an *O*-benzylation reaction. A monomeric methoxy group attached triphenylphosphine acted as a control for comparison of reactivity profiles of dendrimers. It was observed that the etherification reaction was mediated efficiently by the dendritic reagent, and in addition, the dendritic phosphine oxide reagents could be recovered quantitatively by precipitation methods. The recovered dendritic phosphine oxides were reduced subsequently to the corresponding phosphines and used as reagents for the Mitsunobu reaction, repetitively.

1. Introduction

Hyperbranched macromolecules with uniform branches at every branching location are referred generally as dendritic macromolecules. Ever since their prominence in the literature,[1] dendritic macromolecules have been explored in detail as to their synthesis, physical and chemical properties.[2] Uniform branching throughout the structure is one of the unique structural features of dendrimers. This particular structural feature leads to uniform distribution of chain ends within the molecule and it is of immediate interest to find out whether this uniform distribution of chain ends is beneficial for exploring the dendritic architectures further in conjunction with other functional entities of chemical, biological and material relevance. Thus, dendrimers of various constitutions have been functionalized or modified with different types of functional entities.[2] The evolution of the so-called 'dendritic effect' has been observed in few instances, providing credibility to properties arising due to dendritic architecture.[3] Organometallic catalysis is one of the beneficiaries of dendritic structures and many different organometallic complexes have been synthesized and studied extensively.[4] Dendritic catalysts most often react under homogeneous reaction conditions and the reaction kinetics and product selectivities are comparable or better in comparison to the reactions conducted with monomeric catalysts. Phosphination of dendrimers provides an easy access to dendritic organometallic complexes and various phosphinated dendrimers and their metal complexes have thus been prepared and their catalytic properties studied.[5] We were interested in the synthesis and studies of triphenylphosphine containing dendrimers, in view of the manifold reactions known to involve triphenylphosphine as a reagent, apart from its use as a ligand for metal complexations. Here, we describe the synthesis and an assessment of the reactivity profiles of a series of triphenylphosphine containing dendrimers. One of the phenyl groups of triphenylphosphine was involved for covalent attachment at the peripheries of dendrimers and dendrimers carrying 3, 6, 12 and 24 triphenylphosphine units were thus installed at the peripheries of poly(alkyl aryl ether) dendrimers. Following the preparation, these dendrimers were assessed for their reactivity profiles as reagents for Mitsunobu etherification reaction. Details of synthesis and studies are presented herein.

2. Results and discussion

2.1. Synthesis of triphenylphosphine functionalized monomer

The dendrimers of choice for functionalization with

Keywords: Alkylation; Dendrimers; Etherification; Mitsunobu reaction; Triphenyl phosphine.
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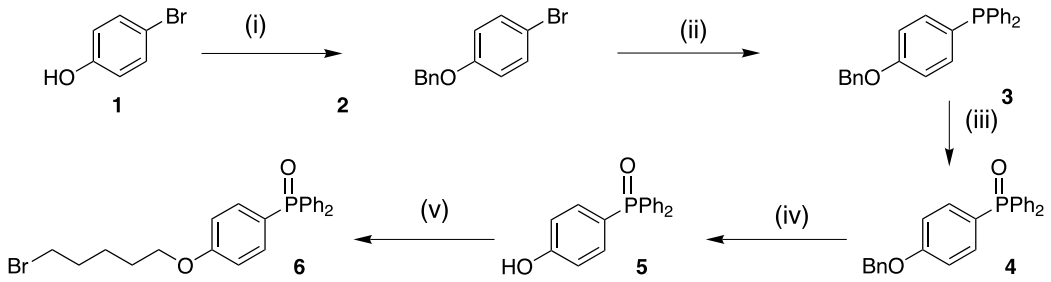
doi:10.1016/j.tet.2005.09.021

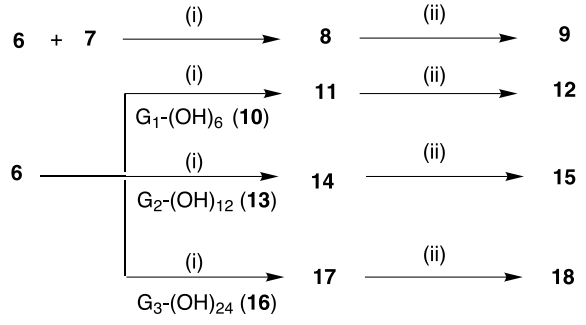


Scheme 1. (i) BnBr, K_2CO_3, 18-Crown-6 (cat.), Me_2CO, reflux, 7 h, 89%; (ii) (a) Mg, I_2 (cat.), THF, reflux, 1 h; (b) $ClPPh_2$, THF, 0 °C to rt, 15 h, 60%; (iii) 30% H_2O_2, Me_2CO, reflux, 1 h, 70%; (iv) Pd–C, EtOH, H_2 (60 bar), 60 °C, 48 h, 72%. (v) 1,5-dibromopentane, K_2CO_3, 18-Crown-6 (cat.), DMF, 70 °C, 7 h, 86%.

triphenylphosphine moiety were the phloroglucinol based poly(alkyl aryl ether) dendrimers, reported recently.[6] Phenolic hydroxyl groups present at the peripheries of these dendrimers were utilized to alkylate a phosphine oxide containing monomer unit (**6**). The monomer **6** was obtained by following a sequence of (i) *O*-benzylation of 4-bromophenol (**1**) to afford **2**; (ii) phosphination with chlorodiphenyl phosphine to **3**; (iii) oxidation of phosphine to phosphine oxide (**4**); (iv) benzyl group deprotection to **5** and (v) alkylation of **5** with dibromopentane to afford **6**, in an overall 23% yield (Scheme 1).

2.2. Synthesis of triphenylphosphine functionalized dendrimer

A three-fold *O*-alkylation of **5** with 1,3,5-tris(5-bromopentyloxy)benzene (**7**)[6] led to the isolation of zero generation triphenylphosphine oxide containing dendrimer (**8**). *O*-Alkylations of first (G_1-$(OH)_6$) (**10**), second (G_2-$(OH)_{12}$) (**13**) and third G_3-$(OH)_{24}$ (**16**) generation dendrimers with the monomer **6**, in the presence of K_2CO_3 and 18-C-6, afforded the corresponding 6 (**11**), 12 (**14**) and 24 (**17**) phosphine oxide containing dendrimers, respectively (Scheme 2). The phosphine oxide containing dendrimers were purified (SiO_2) and were obtained as glassy substances soluble in common organic solvents. Reduction of the phosphine oxide to phopshine was conducted using $CeCl_3$/LAH reagent system[7] in THF (Scheme 2) and the reduction reaction afforded the desired products in nearly quantitative yields. The molecular structures of the phosphinated dendrimers **9**, **12**, **15** and **18** are presented in Figures 1–3. The phosphinated dendrimers were freely soluble in $CHCl_3$, CH_2Cl_2, THF and PhMe. In terms of loading, the triphenylphosphine content was calculated to be 2.58, 2.15, 2.36 and 2.49 mmol/g for the zero (**9**), first (**12**), second (**15**) and third (**18**) generation dendrimers, respectively.



Scheme 2. (i) K_2CO_3, 18-C-6 (cat.), DMF, reflux; (ii) $CeCl_3$, $LiAlH_4$, THF, 60 °C, 5 h.

2.3. Characterization

The purities of new synthesized dendrimers were examined by gel permeation chromatography (GPC) (Phenogel 500 Å, 300×7.80 mm), eluting with THF (flow rate: 1 mL/min., UV–vis detector set at 254 nm). The GPC chromatograms of each phosphine oxide functionalized dendrimers

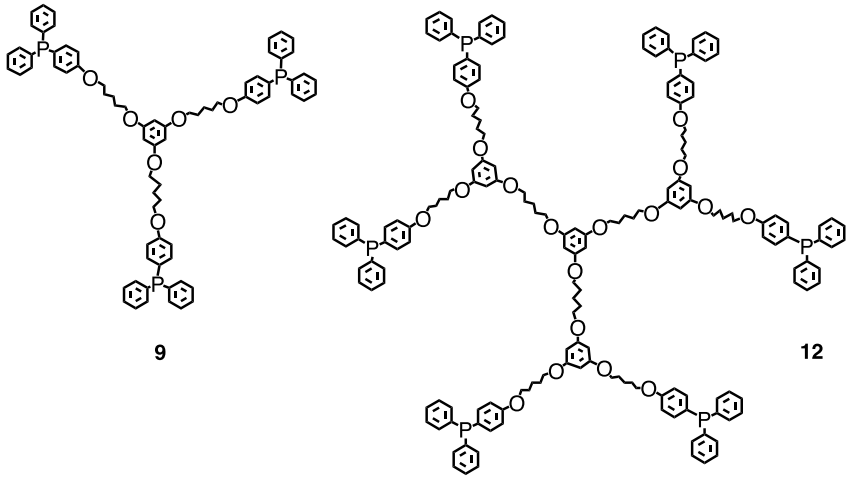


Figure 1. Molecular structures of zero (**9**) and first (**12**) generation phopshinated poly(alkyl aryl ether) dendrimers.

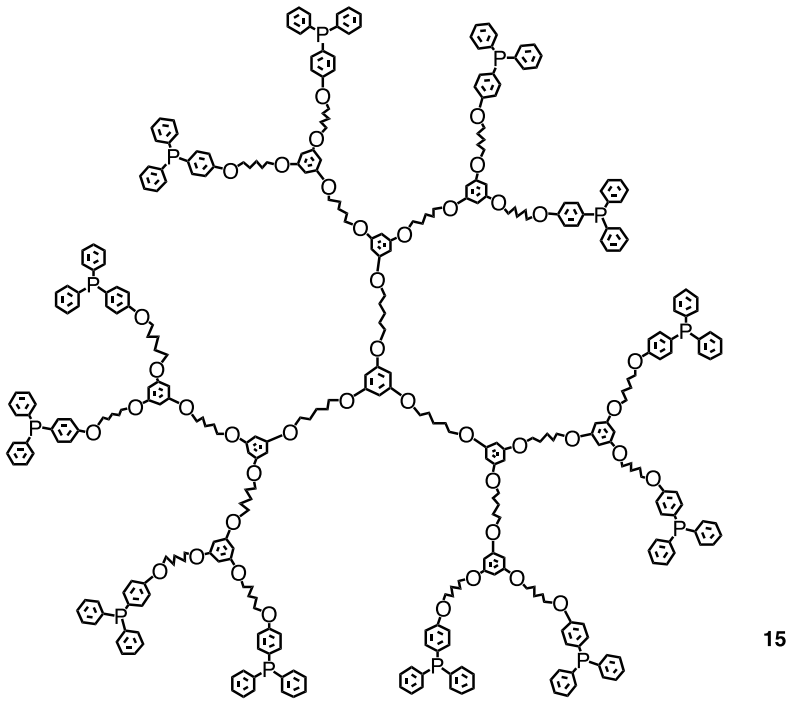


Figure 2. Molecular structure of the second generation phopshinated dendrimer **15**.

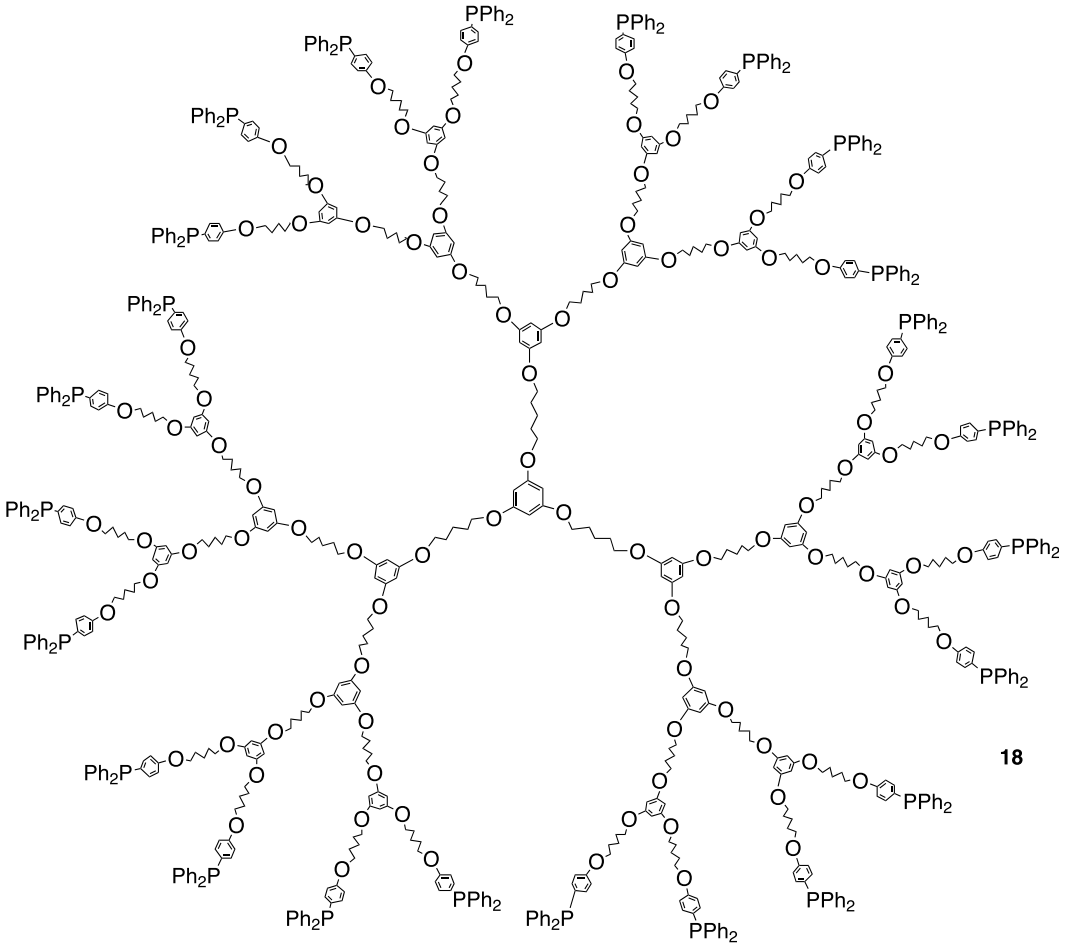


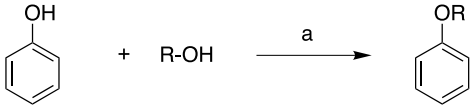
Figure 3. Molecular structure of third generation phosphinated dendrimer **18**.

exhibited decreasing retention times centered at: **8**: 9.31 min, **11**: 8.26 min, **14**: 7.75 min and **17**: 7.58 min.

The phosphine oxide and the phosphinated dendrimers were characterized by ^{1}H, ^{13}C, ^{31}P NMR spectroscopies and elemental composition analysis. Mass spectral characterization was possible for the smaller molecular weight compounds, that of larger molecular weight dendrimers, ionizations by either FAB-MS or MALDI-TOF MS or ES-MS were not successful. In the ^{1}H NMR spectra, the triphenylphosphine oxide unit appeared as multiplets between 7.70 and 7.40 ppm, whereas in the corresponding triphenylphosphine unit in dendrimers, the aromatic rings of the phosphine unit appeared as multiplets between 7.30 and 7.20 ppm. The ^{31}P NMR signals for the phosphine oxide and phosphine moieties in all the compounds were observed at 29.0 and −7.0 ppm, respectively. Elemental composition analyses confirmed further the constitution of each compound.

2.4. Assessment of the reactivity profiles of the phosphinated dendrimers

The reactivities of the phosphinated dendrimers were tested, by involving them as a reagent in an etherification reaction, namely, the Mitsunobu reaction.[8] The reaction of phenol with various alcohols was conducted using diisopropylazidodicaboxylate (DIAD) and dendritic phosphines. The Mitsunobu reaction is prominent in etherification and esterification, in which phosphonium adduct formation between DIAD and phosphine initiates the reaction, leading to an ester or ether depending on the substrate. A systematic mechanistic study has previously been performed[9] on the Mitsunobu reaction, as have reactions involving modified phosphines and azidodicarboxylates.[10] In the etherification reaction performed herein, DIAD and dendritic phosphines (1.1 M equiv, on per phosphine unit basis) were used with respect to phenol and the alcohols (each 1 M equiv) (Scheme 3). Results of the Mitsunobu reaction are presented in Table 1. A good conversion of the alcohols to aryl ethers was observed, for all the dendritic phosphines and the yields were comparable to that of the monomer phosphine reagent, namely, 4-methoxyphenyldiphenyl phosphine **19**.[11]



Scheme 3. Phenol (1.0 M equiv), alcohol (1.0 M equiv), DIAD (1.1 M equiv) and monomeric or dendritic phosphines **9**, **12**, **15** and **18** (1.1 M equiv on a per phosphine unit basis), CH_2Cl_2, room temperature.

Table 1. Mitsunobu etherification of phenol with different alcohols

Alcohol	*n*-Butanol (% Yield)	2-Propanol (% Yield)	Allyl alcohol (% Yield)	Benzyl alcohol (% Yield)
19	84	85	89	90
9	100	77	86	80
12	82	93	73	74
15	92	93	90	78
18	88	87	79	82

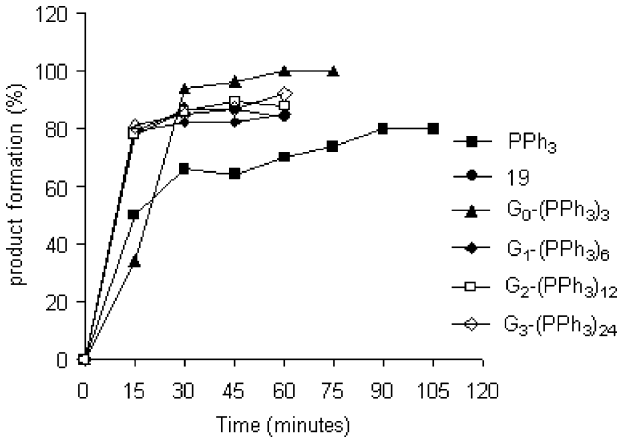
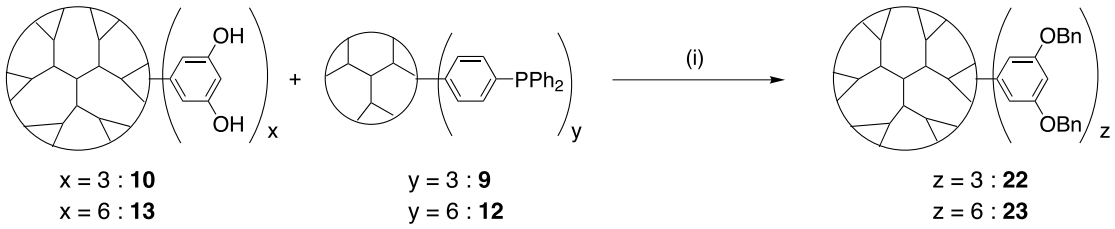


Figure 4. Formation of *n*-butyl phenyl ether with dendritic phosphines.

The time course versus product formation was also monitored by HPLC and the results are presented in Figure 4, for the reaction between phenol and *n*-butanol, mediated by DIAD and dendritic phosphines. The etherification involving these two substrates was facile with the dendritic phosphines, as well as with the monomer **19**. Reaction mediated by PPh_3 was also tested, however, the product formation was sluggish with this reagent. In the case of the dendritic phosphines and the monomer **19**, the reaction was almost complete within the first 15 min and 75–90% of the product formed within this period. In comparison, PPh_3 reaction required 90 min for 75% formation of the product. Very similar reactivity profiles of dendritic phosphines (**9**, **12**, **15** and **18**) and the monomeric phosphine **19** indicate that each phosphine unit on the dendritic scaffold act independently and in an unconnected manner. Upon completion of the reaction, solvents were removed and Et_2O was added to the residue, which solubilized the aryl ether product and the reduced DIAD, leaving the phosphine oxide to be separated from the solution. The Et_2O solution was evaporated and the resulting residue was added to petroleum ether, which solubilized the aryl ether product, leaving the reduced DIAD un-dissolved. In this manner, the aryl ether products were obtained in excellent yields and purities, devoid of reduced DIAD and phosphine oxide reagents. Further purification by column chromatography was required in order to remove un-reacted phenol and the alcohol.

The reactivities of the dendritic phosphines were also tested in the alkylations of different generations of dendritic phenols. Thus poly-benzylation of the phenolic hydroxyl group functionalized poly(alkyl aryl ether) dendrimer was performed in the presence of dendritic phosphines (Scheme 4). 5-Benzyloxy resorcinol (**20**) and **19** were used as monomeric analogs of phenol and phosphine, respectively. Compounds, **10**, **13** and **20** were thus *O*-benzylated, by utilizing **9**, **12** and **19** to afford tri-*O*-benzylated phloroglucinol (**21**), G_1-$(OBn)_6$ (**22**) and G_2-$(OBn)_{12}$ (**23**), respectively (Fig. 5). The time course versus product formation was monitored by HPLC and the results are presented in Table 2, for the reaction between polyphenols and benzyl alcohol, mediated by DIAD and the dendritic/monomeric phosphines. Di-*O*-benzylation of 5-benzyloxy-resorcinol led to the isolation of the



Scheme 4. (i) Dendritic phenol (1 M equiv) (**10** or **13**), triphenylphosphine (1.1 M equiv on per phosphine basis) (**9** or **12**), BnOH (1 M equiv), DIAD (1.1 M equiv), THF, room temperature.

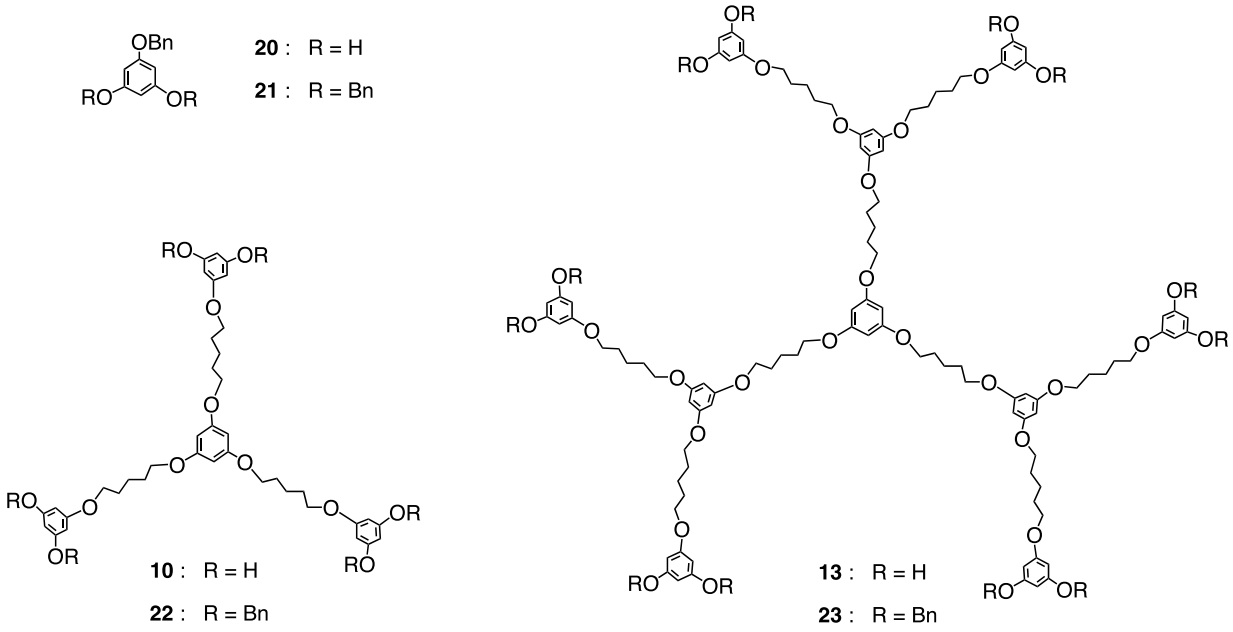


Figure 5. Molecular structures of monomeric (**20**), dendritic phenols (**10** and **13**) and their corresponding benzylated derivatives (**21**, **22** and **23**).

Table 2. Polybenzyl ether formation with dendritic phosphines

Entry	Phenol	Phosphine	Time (h)	Yield (%)
1	**10**	**9**	2.5	77
2	**13**	**9**	3.0	75
3	**20**	**9**	1.0	74
4	**10**	**12**	2.5	75
5	**13**	**12**	3.0	77
6	**20**	**12**	1.0	87
7	**10**	**19**	2.5	82
8	**13**	**19**	3.0	79
9	**20**	**19**	0.75	94

corresponding tri-*O*-benzylated phloroglucinol in good yield within 45 min. Polybenzylation of **10** and **13** afforded moderate yield (70–77%) of product in 3 h and prolonged reaction time did not improve the yield.

After securing the triphenylphosphine oxide by the solvent treatments (vide supra), reduction to the corresponding triphenylphosphines was conducted using $CeCl_3$/LAH, in quantitative yield. The reduced reagents were used again for the Mitsunobu reaction and the reaction could be conducted efficiently as that of first cycle reagents. The oxidation of the dendritic phosphine to mediate the etherification reaction, the reduction of the resulting phosphine oxide to the phosphine and subjecting the phosphine in the etherification reaction could be conducted several times, without any loss in efficiency of the reactions (Table 3).

Table 3. Percentage recovery of the phopshine oxide functionalized dendrimers after each cycle of reduction and reuse of the resulting phosphine in etherification reactions

Dendrimer	Cycle			
	1	2	3	4
8	92	92	93	93
11	>95	>95	>95	95
14	Quant.	Quant.	Quant.	Quant.
17	Quant.	Quant.	Quant.	Quant.

3. Conclusion

The scope and wide application of the Mitsunobu reaction is well documented.[8] The generic trialkyl and triaryl phosphines have led to the development of modified reagents, which assist in simplifying the purification of the reaction mixtures. Several modified phosphines, polymeric phosphines and fluorous phosphines have been developed to make the Mitsunobu reaction a more versatile approach for several etherification, esterification and amidation reactions.[10] The dendritic regents that we have presented

herein are a useful addition as a new types of triarylphosphine reagent.

4. Experimental

4.1. General remarks

4.1.1. Compound 2. To a solution of 4-bromophenol (25.0 g, 144.4 mmol) in Me_2CO (100 mL), BnBr (24.71 g, 144.5 mmol), K_2CO_3 (19.9 g, 144.5 mmol), 18-C-6 (cat.) were added and refluxed for 7 h. The reaction mixture was filtered, solvents removed in vacuo, the resulting residue dissolved in $CHCl_3$ (150 mL), washed with water (2× 150 mL), the organic portion dried (Na_2SO_4) and concentrated to afford **2**, as a white solid (34.0 g, 89%). TLC: R_f 0.65 (Hexane/EtOAc=98:2). Mp: 59–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.99 (s, 2H), 6.83 (d, J=6.9 Hz, 2H), 7.34–7.38 (m, 7H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 70.1, 113.1, 116.6, 127.4, 128.1, 128.6, 132.2, 136.5, 157.8. Anal. Calcd for $C_{13}H_{11}BrO$: C, 59.34; H, 4.21; found: C, 59.46; H, 4.35.

4.1.2. Compound 3. To a suspension of Mg (1.01 g, 41.65 mmol) in THF (7 mL) and I_2 (25 mg), **2** (10.0 g, 37.9 mmol) in THF (20 mL) was added dropwise, refluxed for 1 h and cooled to 0 °C. Chlorodiphenyl phosphine (9.61 g, 43.6 mmol) in THF (5 mL) was added over a period of 10 min and stirred for 15 h at room temperature. The reaction mixture was quenched with aq. HCl (5%), washed with $CHCl_3$ (200 mL), followed by H_2O (2×100 mL), dried (Na_2SO_4), concentrated and purified to afford phosphine, **3**, as a colorless solid (8.4 g, 60%). TLC: R_f 0.72 (PhMe). Mp: 48–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.99 (s, 2H), 6.93 (d, J=7.5 Hz, 2H), 7.23–7.39 (m, 17H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 69.8, 115.0 (d, J=6.8 Hz), 127.42, 127.9 (d, J=9.8 Hz), 128.4 (d, J=7.6 Hz), 128.5, 129.4, 133.4 (d, J=18.1 Hz), 135.5 (d, J=21.1 Hz), 136.6, 137.8 (d, J=11.3 Hz), 158.7, 159.5; ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ: −7.0; HR-MS *m/z*: calcd for $C_{25}H_{21}OP$ $[M+1]^+$: 369.1408; found: 369.1413 (50%). Anal. Calcd for $C_{25}H_{21}OP$: C, 81.5; H, 5.75; found: C, 81.42; H, 5.96.

4.1.3. Compound 4. Aq. H_2O_2 (30%) (3.33 g, 97.8 mmol) was added cautiously to an ice-cooled solution of **3** (18.0 g, 48.9 mmol) in Me_2CO (75 mL) and refluxed for 1 h. The solvent was removed in vacuo. PhMe (100 mL) and aq. NaOH (10%, 70 mL) were added to the resulting residue and stirred for 1 h at room temperature. The organic layer was separated, washed with brine (2×150 mL), dried (Na_2SO_4), concentrated. Upon addition of Et_2O (70 mL), **4** precipitated, as a white solid (13.2 g, 70%). TLC: R_f 0.5 (EtOAc/PhMe=7:3). Mp: 121–122 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.06 (s, 2H), 7.02 (d, J=6.9 Hz, 2H), 7.26–7.69 (m, 17H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 69.8, 114.7 (d, J=12.9 Hz), 127.2, 127.9, 128.2 (d, J=11.9 Hz), 128.4, 131.6, 131.8 (d, J=9.9 Hz), 133.7 (d, J=11.2 Hz), 135.9, 161.5; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz,) δ: 27.8; HR-MS *m/z*: calcd for $C_{25}H_{21}O_2P$ $[M+1]^+$: 385.1357; found: 385.1364 (100%). Anal. Calcd for $C_{25}H_{21}O_2P$: C, 78.11; H, 5.51; found: C, 78.02; H, 5.59.

4.1.4. Compound 5. A solution of **4** (20 g, 52.1 mmol) in EtOH (100 mL) was admixed with Pd–C (10%, 2.0 g), stirred under H_2 blanket (60 atm) at 60 °C in an autoclave for 48 h. The reaction mixture was filtered, concentrated and dried in vacuo to afford **5** as a white solid (11.1 g, 72%). TLC: R_f 0.27 (PhMe/EtOAc=7:3). Mp: 240 °C. IR (KBr, cm^{-1}): 3437.5; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.94 (dd, $^3J_{HH}$=8.7 Hz, $^4J_{PH}$=2.1 Hz, 2H), 7.40–7.67 (m, 12H), 10.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 115.3 (d, J=13.6 Hz), 127.8 (d, J=12.1 Hz), 131.3 (d, J=10.6 Hz), 131.6, 133.0, 133.3 (d, J=10.6 Hz), 160.7; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ: 29.8; HR-MS *m/z*: calcd for $C_{18}H_{15}O_2P$ $[M+1]^+$: 295.0888; found: 295.0874 (100%). Anal. Calcd for $C_{18}H_{15}O_2P$: C, 73.46; H, 5.14; found: C, 73.35; H, 5.25.

4.1.5. Compound 6. To a solution of **5** (10.0 g, 34.01 mmol) in DMF (25 mL), 1,5-dibromopentane (23.0 g, 102 mmol), K_2CO_3 (5.64 g, 40 mmol) and 18-crown-6 (cat.) were added and stirred at 70 °C for 7 h. Solvents were removed in vacuo and the resulting crude mixture dissolved in $CHCl_3$ (100 mL), washed with H_2O (2×100 mL), dried (Na_2SO_4), concentrated and purified (SiO_2) to afford **6**, as a brown oil (12.9 g, 86%). TLC: R_f 0.38 (PhMe/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.62 (m, 2H), 1.78 (m, 2H), 1.93 (m, 2H), 3.43 (t, J=6.6 Hz, 2H), 4.00 (t, J=6.0 Hz, 2H), 6.95 (d, $^3J_{HH}$=7.5 Hz, 2H), 7.45–7.69 (m, 12H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 24.7, 28.2, 32.3, 33.5, 67.6, 114.5 (d, J=13.0 Hz), 128.4 (d, J=11.9 Hz), 131.8, 132.0 (d, J=10.0 Hz), 133.4, 133.9 (d, J=11.2 Hz), 162.0; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ: 28.0; HR-MS *m/z*: calcd for $C_{23}H_{24}BrO_2P$ $[M+Na]^+$: 465.0595; found: 465.0595 $[M+Na]^+$(100%), 467.0618 $[M+Na+2]^+$(98%). Anal. Calcd for $C_{23}H_{24}BrO_2P$: C, 62.31; H, 5.46; found: C, 61.91; H, 5.57.

4.1.6. Compound 8. A mixture of **7**[6] (0.41 g, 0.71 mmol), **5** (0.75 g, 2.55 mmol), K_2CO_3 (0.15 g, 1.1 mmol) and 18-crown-6 (cat.) in DMF (20 mL) was stirred at 70 °C for 12 h. Solvents were then removed in vacuo, the resulting residue dissolved in CH_2Cl_2, washed with water, dried, concentrated and purified (SiO_2, $CHCl_3$/MeOH=95:5) to afford **8**, as colorless oil (0.9 g, 92%). TLC: R_f 0.59 ($CHCl_3$/MeOH=96:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62 (m, 6H), 1.86 (m, 12H), 3.93 (t, J=6.3 Hz, 6H), 4.01 (t, J=6.0 Hz, 6H), 6.07 (s, 3H), 6.95 (dd, $^3J_{HH}$=8.7 Hz, $^4J_{PH}$=1.8 Hz, 6H), 7.42–7.69 (m, 36H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 28.8, 28.9, 67.7, 67.9, 93.8, 114.5 (d, J=12.8 Hz), 128.4 (d, J=11.3 Hz), 131.8, 132.0 (d, J=9.8 Hz), 132.2, 133.6, 133.9 (d, J=11.3 Hz), 160.9, 161.9, 162.0; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: 29.4; MALDI-TOF-MS *m/z*: calcd for $C_{75}H_{75}O_9P_3$: 1213; found: 1213 $[M]^+$(15%), 1235.5 $[M+Na]^+$(100%), 1251.6 $[M+K]^+$(70%). Anal. Calcd for $C_{75}H_{75}O_9P_3$: C, 74.24; H, 6.23; found: C, 73.77; H, 7.1.

4.1.7. Compound 9. To a stirred suspension of $CeCl_3$ (0.29 g, 1.16 mmol) in THF (6 mL), $LiAlH_4$ (0.059 g, 1.55 mmol) and **8** (0.312 g, 0.26 mmol) in THF (3 mL) were added and warmed at 60 °C for 4 h. The reaction mixture was quenched with water, filtered, concentrated and purified by passing through a pad of SiO_2 (2% EtOAc/PhMe) to afford compound **9**, as colorless oil (0.3 g, 98%). TLC R_f 0.65 (PhMe/EtOAc=98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.63 (m, 6H), 1.83 (m, 12H), 3.95 (m, 12H), 6.06

(s, 3H), 6.87 (d, J=7.8 Hz, 6H), 7.23–7.30 (m, 36H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 28.9, 67.6, 67.7, 93.8, 114.7 (d, J=7.6 Hz), 128.4 (d, J=7.6 Hz), 133.4 (d, J=19.6 Hz), 135.6 (d, J=21.1 Hz), 137.9 (d, J=9.8 Hz) 159.8, 160.8; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: −6.9. Anal. Calcd for $C_{75}H_{75}O_6P_3$: C, 77.3; H, 6.49; found: C, 77.2, H, 6.51.

4.1.8. Compound 11. A mixture of **10**[6] (0.22 g, 0.31 mmol), **6** (1.0 g, 2.25 mmol), K_2CO_3 (0.311 g, 2.25 mmol) and 18-crown-6 (cat.) in DMF (10 mL) was heated at 70 °C for 48 h. Solvents were then removed in vacuo and the resulting residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4) and concentrated. Excess of **6** was removed by triturating with Et_2O washings and the residue was purified further (SiO_2, $CHCl_3$/MeOH=95:5) to afford **11**, as a brown foamy material (0.69 g, 76%). TLC R_f 0.52 ($CHCl_3$/MeOH=96:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62 (br, 18H), 1.82 (br, 36H), 3.92 (br, 24H), 4.01 (t, J=5.7 Hz, 12H), 6.06 (s, 12H), 6.94 (dd, $^3J_{HH}$=8.4 Hz, $^4J_{PH}$=1.8 Hz, 12H), 7.44–7.67 (m, 72H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.6, 28.7, 28.8, 28.9, 67.6, 67.7, 93.7, 114.4 (d, J=13.1 Hz), 128.3 (d, J=11.8 Hz), 131.7, 131.8, 131.9 (d, J=10.0 Hz), 132.2, 133.5, 133.8 (d, J=11.9 Hz), 160.7, 161.9; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: 28.0; ES-MS m/z: calcd for $C_{177}H_{186}O_{24}P_6$: 2883.2; found: 1442.2 $[M]^{2+}$(93%). Anal. Calcd for $C_{177}H_{186}O_{24}P_6\cdot 3H_2O$: C, 72.32; H, 6.54; found: C, 72.36; H, 7.01.

4.1.9. Compound 12. To a stirred suspension of $CeCl_3$ (0.20 g, 0.82 mmol) in THF (6 mL), $LiAlH_4$ (0.041 g, 1.08 mmol) was added and stirred for 1 h at room temperature. A solution of **11** (0.26 g, 0.09 mmol) in THF (5 mL) was added and refluxed at 60 °C for 5 h. The reaction mixture was quenched with water, filtered and concentrated. The crude reaction mixture was purified by passing through a pad of SiO_2 (2% EtOAc/PhMe) to afford **12**, as a colorless oil (0.24 g, 96%). TLC R_f 0.58 (PhMe/EtOAc=98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.61 (m, 18H), 1.85 (m, 36H), 3.99 (m, 36H), 6.07 (s, 12H), 6.88 (d, J=6.3 Hz, 12H), 7.25–7.32 (m, 72H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 25.6, 28.9, 67.7, 67.9, 93.8, 114.7 (d, J=7.6 Hz), 128.4 (d, J=7.6 Hz), 133.4 (d, J=19.6 Hz), 135.6 (d, J=21.1 Hz), 137.8, 159.8, 160.9; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: −7.0. Anal. Calcd for $C_{177}H_{186}O_{18}P_6$: C, 76.27; H, 6.73; found: C, 76.02, H, 6.51.

4.1.10. Compound 14. A mixture of **13**[6] (0.2 g, 0.11 mmol), **6** (0.68 g, 1.54 mmol), K_2CO_3 (0.212 g, 1.53 mmol) and 18-C-6 (cat.) in DMF (10 mL) was heated at 70 °C for 72 h. Solvents were then removed in vacuo and the resulting residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4), concentrated and purified (SiO_2, $CHCl_3$/MeOH=8:2) to afford **14**, as a brown oil (0.45 g, 68%). TLC R_f 0.47 ($CHCl_3$/MeOH=92:8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.65 (br, 42H), 1.81 (br, 84H), 3.91 (br, 60H), 3.97 (t, J=6.6 Hz, 24H), 6.05 (s, 30H), 6.93 (d, $^3J_{HH}$=8.4 Hz, 24H), 7.43–7.68 (br, 144H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.0, 22.7, 28.8, 29.0, 67.8, 67.9, 68.0, 93.4, 114.6 (d, J=13.6 Hz), 128.5 (d, J=12.1 Hz), 129.3, 131.9, 132.1 (d, J=9.8 Hz), 134.0 (d, J=11.3 Hz), 160.9, 162.1; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: 29.3. Anal. Calcd for $C_{381}H_{408}O_{54}P_{12}$: C, 73.54; H, 6.61; found: C, 73.43; H, 7.12.

4.1.11. Compound 15. To a stirred suspension of $CeCl_3$ (0.086 g, 0.35 mmol) in THF (6 mL), LAH (0.025 g, 0.69 mmol) was added and stirred for 1 h at room temperature. Dendrimer **14** (0.12 g, 0.019 mmol) in THF (5 mL) was added and refluxed at 60 °C for 5 h. The reaction mixture was quenched with water, filtered and concentrated. The crude product was purified by passing through a pad of SiO_2 (5% EtOAc/PhMe) to afford **15**, as a colorless oil. TLC: R_f 0.41 (PhMe/EtOAc=98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62 (br, 42H), 1.83 (br, 84H), 3.93 (m, 84H), 6.06 (s, 30H), 6.94 (d, J=8.4 Hz, 24H), 7.23–7.67 (br, 144H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 29.0, 29.7, 67.6, 67.7, 93.8, 114.7 (d, J=7.6 Hz), 128.4 (d, J=7.6 Hz), 133.4 (d, J=15.9 Hz), 133.5, 135.6 (d, J=21.1 Hz), 137.9 (d, J=10.6 Hz), 159.9, 160.9; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: −7.0. Anal. Calcd for $C_{381}H_{408}O_{42}P_{12}$: C, 75.88; H, 6.82; found: C, 75.84; H, 6.54.

4.1.12. Compound 17. A mixture of **16**[6] (0.058 g, 0.014 mmol), **6** (0.183 g, 0.414 mmol), K_2CO_3 (0.046 g, 0.33 mmol) and 18-crown-6 (cat.) in DMF (15 mL) was heated at 70 °C for 6 days. Solvents were removed in vacuo and the resulting residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4) and concentrated. Excess **6** was removed by triturating with Et_2O and the residue was purified further (SiO_2, EtOAc/MeOH=95/5) to afford **17** as a brown oil (0.098 g, 55%). TLC R_f 0.42 ($CHCl_3$/MeOH=95:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.57 (br, 90H), 1.81 (br, 180H), 3.71–4.12 (br, 180H), 6.04 (s, 66H), 6.95 (dd, $^3J_{HH}$=8.4 Hz, $^4J_{PH}$=1.8 Hz, 48H), 7.42–7.69 (br, 288H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.6, 28.7, 29.0, 67.8, 68.0, 93.9, 114.6 (d, J=13.6 Hz), 128.3, 128.4 (d, J=12.1 Hz), 129.1, 131.8, 132.0 (d, J=9.8 Hz), 134.0 (d, J=11.3 Hz), 160.9, 161.8; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: 29.3. Anal. Calcd for $C_{789}H_{852}O_{114}P_{24}$: C, 73.45; H, 6.66; found: 73.23; H, 7.11.

4.1.13. Compound 18. To a stirred solution of **17** (47 mg, 0.006 mmol), $CeCl_3$ (0.033 g, 0.131 mmol) in THF (4 mL)/DMF (0.1 mL), LAH (0.075 g, 1.97 mmol) was added and refluxed for 24 h. The reaction mixture was quenched with water, filtered, concentrated and dried. The crude product was purified by passing through a pad of SiO_2 (10% EtOAc/PhMe) to afford **18**, as a brown oil (0.038 g, 84%). TLC: R_f 0.30 (PhMe/EtOAc=90:10). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.57 (br, 90H), 1.83 (br, 180H), 3.94 (m, 180H), 6.05 (s, 66H), 6.87 (d, J=8.1 Hz, 48H), 7.23–7.30 (br, 288H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.8, 29.0, 29.7, 67.7, 67.8, 93.8, 114.7 (d, J=7.6 Hz), 128.4 (d, J=7.6 Hz), 133.4 (d, J=19.6 Hz), 135.6 (d, J=21.1 Hz), 137.9, 159.9, 160.9; ^{31}P{^{1}H} NMR ($CDCl_3$, 162.0 MHz) δ: −7.0. Anal. Calcd for $C_{789}H_{852}O_{90}P_{24}$: C, 75.7; H, 6.86; found: C, 75.29; H, 6.52.

4.2. General procedure for the alkyl aryl ether formation

To a solution of phenol (1.0 M equiv), alcohol (1.0 M equiv) and phosphine (1.1 M equiv on per phosphine unit basis) in CH_2Cl_2 (1.5 mL), DIAD (1.1 M equiv) was added and the reaction mixture was stirred at room

temperature for 1 h, under N_2 atmosphere. Solvents were removed in vacuo and Et_2O was added to precipitate the phosphine oxide. Et_2O portion was separated, concentrated and the resulting residue was added with petroleum ether. Petroleum ether portion was filtered from un-dissolved reduced DIAD and solvents were removed in vacuo and purified further. For monitoring the reaction, an aliquot of petroleum ether was injected into a normal phase (SiO_2) semi-preparative column, attached to a HPLC. Elution was carried out with EtOAc/pet. ether (3:1), at a rate of 1 mL/min. and monitored at 254 nm. The retention times for the starting materials and products were, benzyl alcohol: 22.5 min; phenol: 17.4 min; phenyl butyl ether: 16.4 min; phenyl isopropyl ether: 16.5 min; phenyl allyl ether: 16.7 min; phenyl benzyl ether: 16.0 min.

Acknowledgements

We are grateful to Council of Scientific and Industrial Research (CSIR), New Delhi, for financial support. J.N. thanks CSIR for a research fellowship.

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Enantiospecific synthesis, separation and olfactory evaluation of all diastereomers of a homologue of the sandalwood odorant Polysantol®

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Received 27 May 2005; revised 2 September 2005; accepted 8 September 2005

Available online 27 September 2005

Dedicated to Professor Joaquín Plumet on the occasion of his 60th birthday with admiration and friendship.

Abstract—The four stereoisomers of (5*E*)-4,4-dimethyl-6-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)-hex-5-en-3-ol, a homologue of the valuable sandalwood-type odorant Polysantol®, were enantiospecifically synthesized from (+)- and (−)-α-pinene, through (−)- and (+)-campholenic aldehyde, by aldol condensation with 3-pentanone, deconjugative α-methylation and reduction. The mixtures of epimeric alcohols obtained after reduction were separated by means of derivatization with (−)-(1*S*)-camphanic chloride. The enantiomerically pure final products were evaluated organoleptically.

1. Introduction

Since olfactory receptors (OR) are peptides consisting of L-amino acids, fragrance science frequently deals with the phenomenon of chirality. Very often, diastereomers, and enantiomers exhibit different olfactory profiles and intensities.[1] The optical purity and diastereomeric composition of a mixture of chiral fragrances can also influence the odour greatly. Enantiomeric chiral molecules interact differently with other chiral molecules present in the different ORs types since such interactions are diastereomeric.[2] However, it is often difficult to obtain large amounts of optically pure chiral odour materials. Synthetic chemicals are often racemic, or have a specific ratio of stereoisomers that is related to either the optical purity of the starting material, the stereoselectivity of the reaction, or both. The growing awareness of the importance of chirality in fragrance chemistry has resulted in both the development of asymmetric synthesis of chiral chemicals and the search for optically active natural starting materials.

East India sandalwood oil belongs to the most appreciated but unfortunately scarce perfumery raw materials.[3] The main constituents of sandalwood oil are unsaturated alcohols, aldehydes and ketones consisting of a bulky polycyclic hydrophobic moiety separated from the oxygenated function by a 4–5 C-atoms chain (e.g., **I**–**III**, Fig. 1).[4]

The search for their efficient synthetic substitutes has been carried out over the last 50 years and, until now, the best ones found are trimethylcyclopentenyl alkenols **IV**–**VII**[5,6] (Fig. 1) derived from campholenic aldehyde (**1**). However, not much is known about the structure–odour relationship (SOR) of single stereoisomers of sandalwood-smelling mixtures because the structures of the specific ORs and the corresponding mechanism of interaction between the receptor protein and the odour molecules remain more or less unknown. Nevertheless, some authors[7] have postulated, for the sandalwood-type odour, the importance of at least three binding centres together with the relative position of these points, that is, the distance among binding sites and the stereospecificity is crucial for eliciting this specific type of odour.

As a continuation of our previous studies on the synthesis of odorants,[8] we had contributed to develop a collection of several substitutes of sandalwood scent.[6] In that report, we attained Polysantol® (**V**) and other analogous molecules, taking the exact position of the binding site in consideration,[7] based on a selective and efficient magnesium-

Keywords: α-Campholenic aldehyde derivatives; α-Pinene; Enantiospecific synthesis; Organoleptic evaluation; Sandalwood; Odorants.
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doi:10.1016/j.tet.2005.09.023

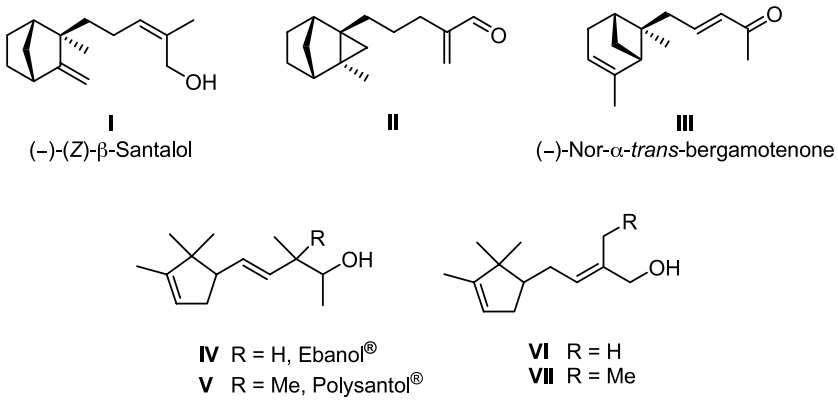
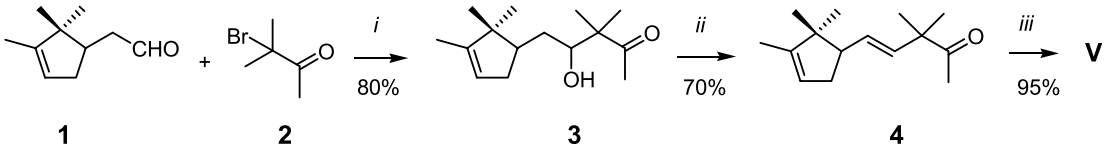


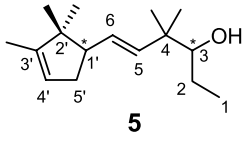
Figure 1.



Scheme 1. Synthesis of Polysantol®(**V**) from campholenic aldehyde (**1**). (i) Mg, Et_2O, △; (ii) MsCl, Py, 0 °C to rt; LiBr, Li_2CO_3, DMF, 150 °C; (iii) $NaBH_4$, MeOH, 0 °C to rt.

mediated aldol reaction of technical-grade campholenic aldehyde and different α-bromoketones, dehydration of the resulting secondary alcohols, and reduction of the carbonyl group (Scheme 1).

Among the whole range of compounds structurally related to Polysantol® prepared by us,[6] the perfumers pointed out compound **5** due to its interesting olfactory properties. Even though, as a mixture of stereoisomers, compounds **5** showed woody, leathery and spicy notes with a slight sweetness, surprisingly, it was almost devoid of sandalwood scent. Since great differences in the odour impression of enantiomers often exist,[9] it was of interest to synthesize all the possible stereoisomers and evaluate their odour separately.



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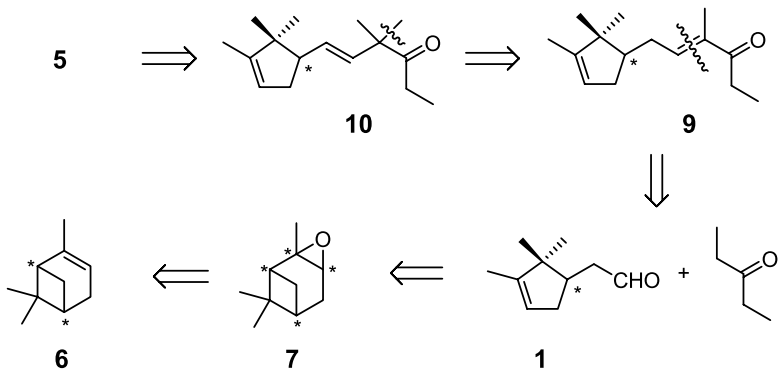
According to this, an approach based on the development of an enantiospecific synthesis of the two enantiomeric ketones, precursors of **5**, was chosen. In this way, the reduction of these ketones and esterification of the resulting alcohols with an enantiomerically pure chiral reagent, the subsequent chromatographic isolation of these new diastereomeric derivatives and, finally, the removing of the chiral auxiliary moiety, led to the enantiomerically pure final products.

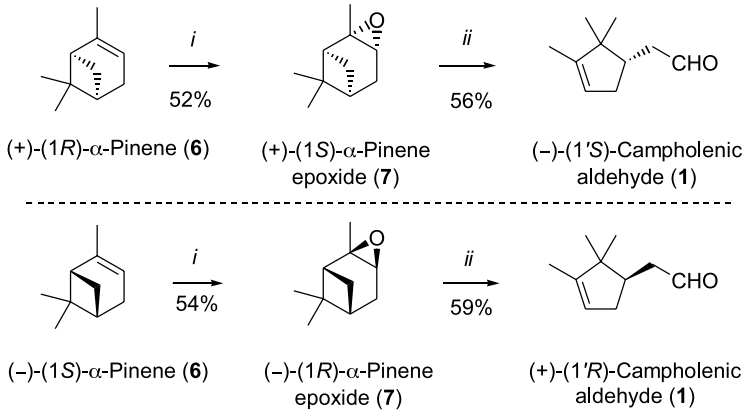
2. Results and discussion

2.1. Synthesis

In the following, we describe the syntheses of the two C-1′ epimers of (5*E*)-4,4-dimethyl-6-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)-hex-5-en-3-ones (**10**), which are suitable to be transformed to alcohols **5** (Scheme 2). Starting with the epoxidation and rearrangement of (+)- and (−)-α-pinene (**6**) to afford the two enantiomers of campholenic aldehyde (**1**) separately (as they are not optically pure commercially available), we continued by aldol condensation of each one with 3-pentanone, deconjugative



Scheme 2. Retrosynthetic approach to (5*E*)-4,4-dimethyl-6-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)-hex-5-en-3-ol (**5**).



Scheme 3. Syntheses of (−)- and (+)-campholenic aldehydes (**1**). (i) AcOOH, NaOAc, CH_2Cl_2, 0 °C; (ii) $ZnBr_2$, toluene, △.

α-methylation of the respective enones (**9**) and reduction of **10** (in analogy to the route described by Firmenich,[5b] Scheme 2) to achieve the two pairs of isomers **5**, separately.

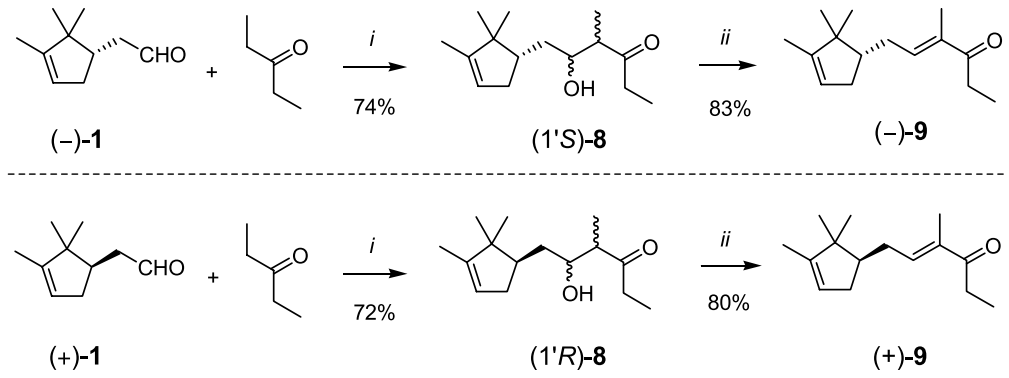
In the synthesis of compounds **5** according to the above described reactions, the configuration of the campholenic aldehyde starting material depends on that of the α-pinene used, which fixes the final product configuration at C-1′. When (+)-(1*R*)-α-pinene (91% ee) is used to produce campholenic aldehyde via pinene epoxide, the product is (−)-(1′*S*)-campholenic aldehyde (Scheme 3). These processes involve an epoxidation of α-pinene (**6**) and a stereospecific rearrangement of the epoxide **7** to campholenic aldehyde (**1**) in the well-known modified Arbuzov preparation,[10,11] in the presence of a catalytic amount of $ZnBr_2$ in refluxing toluene.

The epoxidation of **6** (AcOOH/NaOAc/CH_2Cl_2)[12] is a diastereoface-selective reaction. The electrophilic reagent normally reacts on the sterically less hindered face. Consequently, the reaction afforded the epoxide **7** with excellent diastereofacial selectivity, in both α-pinenes (Scheme 3). Under the latter condition, the oxidation reagent peracetic acid prompts the newly formed α-pinene oxide (**7**) to the rearrangement into α-campholenic aldehyde (**1**) as well. A 10% amount of **1** was detected by GC, as a by-product of the epoxidation. Since the flash chromatography attempted led to the degradation of the α-pinene oxide (**7**), a viable alternative based on the vacuum distillation technique was tried. Nevertheless, the differences in boiling points between both oxygenated monoterpenes, **7** and **1**, are not sufficient to allow a complete separation of them. As a result, the spectra set and $[\alpha]_D$ were performed with the distilled mixture of **7** and **1**. However, these spectroscopic data are in accordance with those already described.[13]

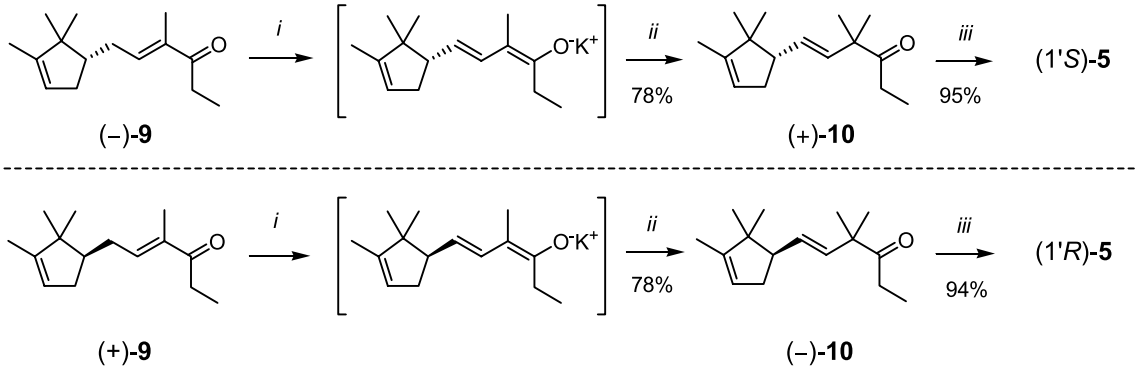
With regard to the rearrangement of the two α-pinene epoxide isomers (**7**), the reaction of these with $ZnBr_2$ yielded, in both cases, the corresponding campholenic aldehyde ((−)-(1′*S*)-**1**, 56% and (+)-(1′*R*)-**1**, 59%) with a small amount of pinocamphone as by-product (11:1, in favour of **1**, detected by GC).[13]

The two aldehydes, (−)-(1′*S*)-**1** and (+)-(1′*R*)-**1**, derived from the two optically pure α-pinene samples (**6**), were reacted with 3-pentanone, separately, using potassium hydroxide as catalyst (Scheme 4).[14] In both cases, the direct aldol reaction was carried out without low temperature conditions, because of the symmetry of 3-pentanone does not lead to the formation of regioisomers in the enolate ion of the ketone. The mixtures of the β-hydroxyketone isomers (1′*S*)-**8** and (1′*R*)-**8** were identified by mass spectrometry.

Without previous purification, the crude products of the aldol addition directly underwent dehydration by azeotropic distillation in dry toluene and *p*-toluenesulfonic acid. Thus, the α,β-unsaturated ketones **9** obtained were purified by reduced pressure distillation to afford (−)-(1′*S*)-**9** (61%



Scheme 4. Aldol reaction of (−)- and (+)-campholenic aldehydes (**1**) with 3-pentanone and dehydration to the α,β-unsaturated ketones (−)-**9** and (+)-**9**. (i) KOH, MeOH; (ii) *p*-TsOH, toluene, △.



Scheme 5. Deconjugative α-methylation of **9** and reduction of **10** to **5**. (i) K^{t}BuO, DMF, 20 °C, 30 min; (ii) MeI, 0 °C, 10 min; (iii) $NaBH_4$, MeOH, 0 °C to rt.

addition-dehydration yield, $[\alpha]_D$ −1.6) and (+)-(1′*R*)-**9** (58% addition–dehydration yield, $[\alpha]_D$ +1.5). The examination of the ^{1}H NMR and ^{13}C NMR spectra of both enantiomers (**9**), where two new sets of signals were detected at δ (^{1}H) 1.10 (t) and 2.68 (q) together with δ (^{13}C) 8.87 and 30.32 for C-1 and C-2, proved the presence of the ethylketone moiety. Besides, the α,β-unsaturation (Δ^4) could be unequivocally assigned as a result of the two signals detected at δ 136.92 and 141.87 in ^{13}C NMR.

Once the ketones **9** were obtained, they could be converted to the β,δ-unsaturated ketones **10** by deconjugative α-methylation reaction.[15] This step relies on the initial formation of an enolate, using a slight stoichiometric excess of potassium *t*-butoxide, followed by the methylation of this ion under conditions that provided the kinetically favoured product in excess over the thermodynamically favoured product. A 10 M excess of cool iodomethane was added quickly over the cooled (0 °C) solution of the referred enolate in *N*,*N*-dimethylformamide. This procedure provided the two new chiral enones (+)-(1′*S*)-**10** ($[\alpha]_D$ +28.5, 78%) and (−)-(1′*R*)-**10** ($[\alpha]_D$ −26.6, 78%) (Scheme 5).

Finally, the β,δ-unsaturated ketones **10** could be converted into the corresponding homoallylic alcohols by reducing the carbonyl group with sodium borohydride. As expected, a mixture of diastereoisomeric alcohols **5** in 55:45 ratio was obtained (95 and 94%) in both cases. The existence of the diastereoisomeric pair was only revealed by their NMR spectra and was especially clear in their camphanoate ester derivatives gas chromatogram (vide infra).

At that moment, a direct chromatography separation of the pair of diastereoisomers (3*S*/3*R*,1′*S*)-**5** and (3*S*/3*R*,1′*R*)-**5** was envisaged. Unfortunately, these attempts were fruitless. Different alternatives to the above more straightforward method of separation of **5** were attempted, like the preparation of acetate or benzoate esters. Nevertheless, only the preparation of the camphanoate derivatives,[16a] allowed us to separate them by chromatography. Hence, the mixture of (3*S*/3*R*,1′*S*)-**5** was reacted with (1*S*)-(−)-camphanic chloride,[16b] using DMAP as nucleophilic catalyst and proton scavenger. The mixture of the camphanoate diastereoisomers **11a/11b** was obtained in 86% yield (Fig. 2). Two successive chromatographies with flash silica gel were necessary, because of the scarce

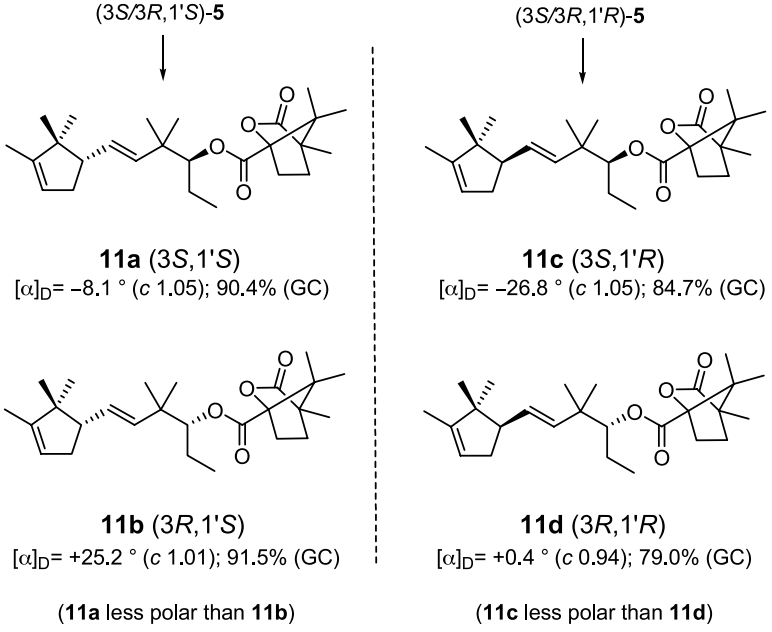


Figure 2. Diastereoisomers **11a–11d** prepared by esterifying (1′*S*)-**5** and (1′*R*)-**5** with (−)-(1*S*)-camphanic chloride, and specific rotations measured for each one after chromatographic purification.

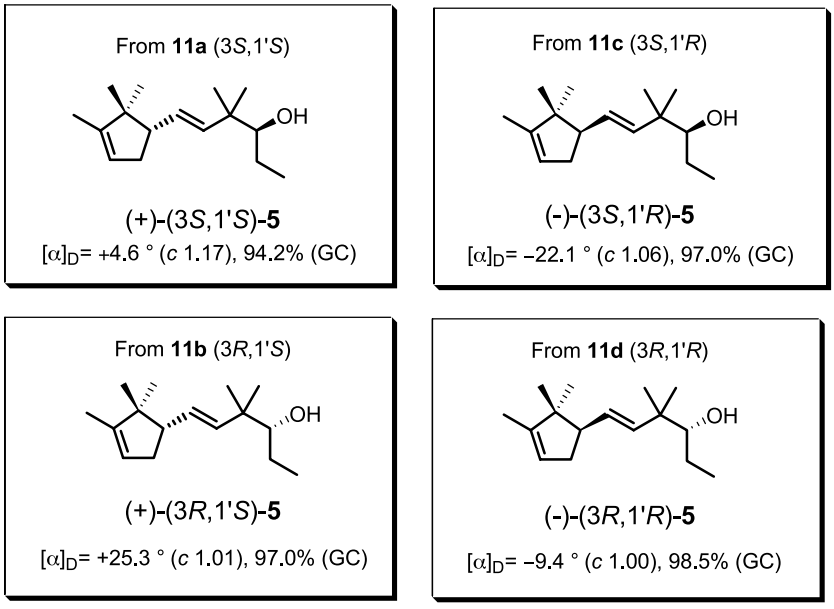


Figure 3. Isomers **5** obtained by reduction of **11** with $LiAlH_4$, and specific rotations measured for each one after chromatographic purification.

difference in polarity exhibited by the two diastereomers (**11a/11b**). The less polar product was **11a**-(3*S*,1′*S*). Both compounds could not be obtained entirely pure but as a mixture in a 9:1 ratio. Similar results over compounds (3*S*/3*R*,1′*R*)-**5** were obtained yielding the stereoisomer compounds **11c/11d** (Fig. 2). The behaviour of these products on the silica-gel chromatography and their retention times when analyzed by GC clearly show that the separation is possible due to the diastereomeric relationship between the camphanoate moiety and the C-3 centre, the stereochemical configuration at C-1′ being irrelevant for this purpose.

These four compounds were structurally assigned by standard spectroscopic analytical techniques (IR, MS, ^{1}H NMR, ^{13}C NMR, 2D NMR). Their absolute configurations at C-3 were deduced latter, after establishing those of the four stereoisomers of **5**.

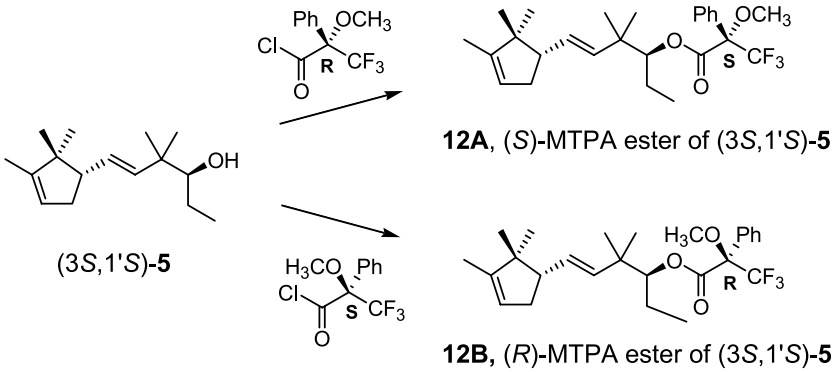
Next, we attempted the saponification of the esters **11** with KOH in MeOH. Nevertheless, the strict condition of this saponification (reflux for 4–5 days) was not enough to complete the ester hydrolysis. We, therefore, decided to liberate the pure enantiomers of **5** by reducing **11a–11d**, separately, with $LiAlH_4$[17] in THF at room temperature for 2 h (91% yield after silica-gel purification) (Fig. 3).

The stereoisomers of **5** were characterized by their NMR and MS data. No spectroscopic differences were found between the data corresponding to the separated isomers and the initial mixtures of them, except the disappearance of some duplicate signals in NMR.

To determine the absolute configuration of enantiomers **5**, the modified Mosher's method[18] was selected. The isomer **5** obtained from **11a** was treated with (−)-(2*R*)-MTPA chloride and (+)-(2*S*)-MTPA chloride, separately, affording the esters **12A** and **12B** (Scheme 6).

After assigning the ^{1}H NMR signals of **12A** and **12B**, and obtaining $\Delta\delta$ [$\delta(S)-\delta(R)$] values for the protons, the absolute configuration was then accomplished following the typical procedure referred in the literature.[18] The results, which support the assignment are summarized in Table 1.

Consequently, the absolute configuration at C-3 of the



Scheme 6. Esterification of (+)-(3*S*,1′*S*)-**5** with (−)-(2*R*)- and (+)-(2*S*)-MTPA chlorides.

Table 1. Differences in the ^{1}H NMR chemical shifts of the (*S*) and (*R*)-MTPA esters of (3*S*,1′*S*)-**5** to define the stereochemistry at C-3

δ(*S*)-MTPA (ppm)	δ(*R*)-MTPA (ppm)	$\Delta\delta$ [δ(*S*)-MTPA − δ(*R*)-MTPA] (Hz)	Assignation
0.79	0.87	−24	H-1
0.99	0.96	+9	Me-4
1.00	0.97	+9	Me′-4
1.41–1.54	1.46–1.58	ca. −15	H-2
1.63–1.73	1.64–1.78	ca. −9	H′-2

alcohol **5** prepared from **11a** is *S*, and accordingly, the configuration of the isomer of **5** obtained from **11b** on C-3 was necessarily *R*. Eventually, the absolute configuration at the carbon C-3 of the two isomers of **5** obtained from **11c** and **11d**, were assigned as *S* and *R*, respectively, by comparison of the ^{13}C NMR spectra data of them with those of **11a** and **11b**.

2.2. Odour evaluation

The independent odour evaluation of each individual optically active isomer **5** (over 98.5% of purity according to GC) was carried out by a group of perfumers using two different protocols.

(a) Compounds **5** were smelt at three moments from blotting paper strips impregnated with them, previously diluted with Et_2O, at the beginning, after Et_2O evaporation (top note), after 3 h (heart note) and finally after 24 h (base note):
- (+)-(3*S*,1′*S*)-**5**: top notes: phenolic, leather, styrax, sandalwood and woody. Heart notes: very clean sandalwood and sandela scents. Base note: almost odourless.
- (+)-(3*R*,1′*S*)-**5**: top notes: smoky, tarry, phenolic, guaiacol, woody on cedar, sandal and benjui notes. Heart notes: sandalwood and burnt scents. Base note: weak sandalwood odour.
- (−)-(3*S*,1′*R*)-**5**: top notes: sandalwood, polysantol-type, woody and dry. Heart notes: sandalwood and sandela very intense. Base note: mild but clear sandalwood note.
- (−)-(3*R*,1′*R*)-**5**: top notes: weak spicy, sandalwood, woody and dry. Heart notes: weak spicy and sandalwood. Base note: almost odourless.

(b) Compounds **5** were odour evaluated after injecting them, separately, on a GC fitted with sniffing port. The results achieved by this way are depicted on Table 2.

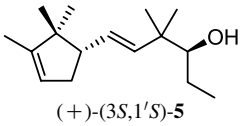
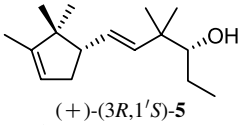
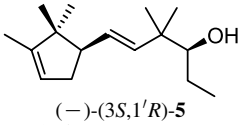
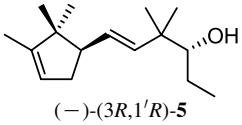
Therefore, the profile of the stereoisomer (−)-(3*S*,1′*R*)-**5** was positioned as the most stimulating and full of interesting qualities among the four diastereomers, though its odour is not as intense as that of Polysantol® (**V**). It is also interesting to emphasize that in the case of Polysantol® (**V**), the diastereomer, which triggers the strongest and most substantive sandalwood type odour is that with the absolute configuration alike to (−)-(3*S*,1′*R*)-**5** on the same carbon atoms.[9b] From this analogy, that somehow can be extended to Ebanol® (**IV**), some useful conclusions could be put forward regarding the structure–odour relationship among the derivatives of campholenic aldehyde sandalwood-type odorants.

3. Experimental

3.1. General experimental conditions

GC analyses were performed on a Varian CP-3800 gas chromatograph fitted with a methyl silicone (CP-Sil 8 CB) capillary column (30 m×0.25 mm×0.25 μm); carrier gas: He; flow rate: 1 mL/min; oven temperature program: 50–200 °C at a rate of 3 °C/min, then 200–290 °C at a rate of 12 °C/min, holding the final temperature for 5 min; injector temperature: 250 °C; flame ionization detector temperature: 300 °C; retention times (R_t) are expressed in

Table 2. Odour evaluation of compounds **5** using a GC fitted with sniffing port

Isomer	Odour
 (+)-(3*S*,1′*S*)-**5**	Sandalwood pure note
 (+)-(3*R*,1′*S*)-**5**	Very clean but less intense sandalwood scent than (+)-(3*S*,1′*S*)-**5**, with woody, borneol and cashmeran notes at the end
 (−)-(3*S*,1′*R*)-**5**	Very clean sandalwood odour, with a waxy note at the end
 (−)-(3*R*,1′*R*)-**5**	Sandalwood pure note, with a waxy note at the end

minutes. Sample size for each injection was approximately 1 μL in a 1:50 split mode. HRMS were obtained on a trisector EBE Waters Micromass AutoSpect NT spectrometer using EI (70 eV). Unless otherwise specified, the other general aspects and instrumentation used on these experiences and those previous reported by us on this same journal[8a,b] are alike.

3.2. Starting materials

(+)-(1*R*)-α-pinene (**6**) ((1*R*,5*R*)-2,6,6-trimethyl-bicyclo[3.1.1]hept-2-ene): $[\alpha]_D$ +47.1 (neat), 91% ee, Aldrich, 98%. (−)-(1*S*)-α-pinene (**6**) ((1*S*,5*S*)-2,6,6-trimethyl-bicyclo[3.1.1]hept-2-ene): $[\alpha]_D$ −45.0 (neat), 87% ee, Aldrich, 99%. (−)-(1*S*)-camphanic chloride ((1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyl chloride): $[\alpha]_D$ −18.0, 99% ee, Aldrich, 98%. (−)-(2*R*)-MTPA chloride ((−)-(2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride): $[\alpha]_D$ −137.0, 99% ee, FLUKA, 99%. (+)-(2*S*)-MTPA chloride ((+)-(2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride): $[\alpha]_D$ +137.0, 99% ee, FLUKA, 99%.

3.3. Epoxidation of α-pinene to give 7

A mixture of AcOOH (60 mL, 30%, 236.8 mmol) and anhydrous NaOAc (1.56 g) was added dropwise to a stirred solution of (+)-(1*R*)-α-pinene ((+)-**6**) (30.75 g, 223.4 mmol) and anhydrous NaOAc (28.19 g, 343.6 mmol) in CH_2Cl_2 (250 mL) at 0 °C for 45 min. After the addition was completed, the mixture was allowed to warm to room temperature and stirring was continued for another 2 h. Then, the organic solution was washed with saturated aqueous Fe_2SO_4 solution (4×100 mL), brine (3×100 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation gave 27.78 g of a crude, which was purified by reduced pressure distillation (bp at 0.05 Torr: 22–28 °C) to afford (+)-(1*S*)-α-pinene epoxide ((+)-**7**) (18.6 g, 52% yield). GC analysis showed a 10% amount of (−)-**1** as well. In the same way, (−)-α-(1*R*)-pinene epoxide ((−)-**7**) was obtained from (−)-(1*S*)-α-pinene ((−)-**6**) in a 54% yield.

3.3.1. (1*S*,2*S*,4*R*,6*S*)-2,7,7-Trimethyl-3-oxatricyclo[4.1.1.0.^{2,4}]octane, (+)-7 Colourless liquid (lit.[13a,b]); R_t 13.62; $[\alpha]_D$ +95.4 (*c* 1.18); 89.5% (GC purity); 91% ee; IR (neat) *ν* 2978 (CH), 1267, 857 and 767 (COC); ^{1}H NMR *δ* 0.94 (3H, s, Me-7), 1.29 (3H, s, Me′-7), 1.31 (3H, s, Me-2), 1.62 (1H, d, *J*=9.1 Hz, H-1), 1.68–1.76 (1H, m, H-6), 1.85–2.05 (4H, m, H-5+H-8) and 3.07 (1H, dd, *J*=4.0, 1.2 Hz, H-4); ^{13}C NMR *δ* 45.04 (C-1), 60.24 (C-2), 56.83 (C-4), 27.59 (C-5), 39.71 (C-6), 40.48 (C-7), 25.82 (C-8), 20.12 (Me-7), 22.36 (Me-2) and 26.67 (Me′-7); MS *m*/*z* 152 (M^+, 0.3%), 137 (M^+−Me, 16), 119 (M^+−Me–H_2O, 4), 109 (M^+−C_2H_3O, 28), 95 (18), 83 (34), 67 (100), 55 (37) and 41 (90).

3.3.2. (1*R*,2*R*,4*S*,6*R*)-2,7,7-Trimethyl-3-oxatricyclo[4.1.1.0.^{2,4}]octane, (−)-7 All spectroscopic properties were identical to those of (+)-**7**, except for $[\alpha]_D$ −108.8 (*c* 1.24); 95.3% (GC purity); 87% ee.

3.4. Preparation of campholenic aldehyde (1)

A solution of (+)-**7** (30.12 g, 198.2 mmol) in dry toluene (10 mL) was added dropwise to a refluxing solution of $ZnBr_2$ (44 mg, 0.19 mmol) in dry toluene (50 mL) for 10 min. The reaction flask was fitted with a Dean–Stark apparatus to remove any trace of water. After that, reflux was continued for a further 1 h. The solution was cooled down to room temperature, diluted with Et_2O (200 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3×100 mL), 1 N AcOH solution (100 mL) and brine (3×100 mL). The resulting organic solution was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude oil (28.13 g) was purified by reduced pressure distillation (bp at 0.3 Torr: 43–49 °C) to afford (−)-(1′*S*)-campholenic aldehyde ((−)-**1**) (16.76 g, 56%). In the same way, (+)-(1′*R*)-campholenic aldehyde ((+)-**1**) was obtained from (−)-**7** in a 59% yield.

3.4.1. [(1′*S*)-(2′,2′,3′-Trimethylcyclopent-3′-en-1′-yl)]-acetaldehyde, (−)-1. Colourless liquid (lit.[9a,13a]); R_t 14.80; $[\alpha]_D$ −5.0 (*c* 1.08); 96.5% (GC purity); 91% ee; IR (neat) *ν* 2716 (CHO), 1727 (C=O), 3040, 800 (C=C) and 1438 (CH_3–C=C); ^{1}H NMR *δ* 0.80 (3H, s, Me_{ax}-2′), 1.01 (3H, s, Me_{eq}-2′), 1.62 (3H, br s, Me-3′), 1.83–1.96 (1H, m, H-1′), 2.23–2.46 (3H, m, H-5′+H-2), 2.53 (1H, ddd, *J*=15.4, 4.1, 2.2 Hz, H′-2), 5.24 (1H, br s, H-4′) and 9.80 (1H, t, *J*=2.2 Hz, H-1); ^{13}C NMR *δ* 202.93 (C-1), 45.07 (C-2), 44.18 (C-1′), 46.88 (C-2′), 147.93 (C-3′), 121.52 (C-4′), 35.48 (C-5′), 19.98 (Me_{ax}-2′), 25.58 (Me_{eq}-2′) and 12.55 (Me-3′); MS *m*/*z* 152 (M^+, 1%), 137 (M^+−Me, 1), 119 (M^+−Me–H_2O, 5), 108 (M^+−C_2H_4O, 100), 93 (108^+−Me, 86), 77 (20), 67 (32), 53 (14) and 41 (30).

3.4.2. [(1′*R*)-(2′,2′,3′-Trimethylcyclopent-3′-en-1′-yl)]-acetaldehyde, (+)-1. All spectroscopic properties were identical to those of (−)-**1**, except for $[\alpha]_D$ +3.0 (*c* 1.06); 97.5% (GC purity); 87% ee.

3.5. Aldol reaction of 1 to give 8

The aldehyde (−)-**1** (22.98 g, 151.2 mmol) was added dropwise to a stirred solution of 3-pentanone (53.04 g, 603.5 mmol) and KOH (499 mg, 7.6 mmol) in MeOH (12 mL) at 0 °C for 1 h. Then, the mixture was allowed to warm to room temperature and stirring was continued for a further 3 h. The reaction was quenched with a 1 N AcOH aqueous solution (100 mL), the solvent was then partially evaporated in vacuo and the resulting crude diluted with Et_2O (25 mL) and washed with 1 N AcOH solution (25 mL) and brine (3×25 mL). The crude was dried over anhydrous Na_2SO_4 and evaporated to yield 26.52 g (74%) of a yellow residue, which was used in the next reaction without further purification. The mixture of diastereoisomeric aldols (1′*S*)-**8** was analyzed by mass spectrometry. In the same way, the reaction of (+)-**1** with 3-pentanone yielded a mixture of aldols (1′*R*)-**8** in a 72% yield.

3.5.1. (4*R*/*S*,5*R*/*S*)-5-Hydroxy-4-methyl-6-[(1′*S*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hexan-3-one, (1′*S*)-8. R_t: 37.14, 37.39 and 37.52 (three peaks); MS *m*/*z* (peak R_t 37.14) 238 (M^+, 2%), 220 (M^+−H_2O, 5), 209 (M^+−Et, 1), 205 (M^+−H_2O–Me, 0.9), 162 (2), 153 (2), 149 (2), 137 (3), 128 (2), 122 (39), 108 (79), 93 (55), 86 (13), 79 (17), 67 (18), 57 (100) and 41 (41); MS *m*/*z* (peak R_t 37.39) 238

(M^+, 2%), 220 (M^+-H_2O, 6), 209 (M^+−Et, 1), 205 (M^+-H_2O–Me, 0.9), 162 (2), 153 (2), 149 (2), 137 (3), 128 (4), 122 (28), 108 (78), 93 (53), 86 (15), 79 (15), 67 (19), 57 (100) and 41 (34); MS *m/z* (peak R_t 37.52) 238 (M^+, 3%), 220 (M^+-H_2O, 5), 209 (M^+−Et, 2), 205 (M^+-H_2O–Me, 1), 162 (2), 153 (3), 149 (2), 137 (4), 128 (7), 122 (28), 108 (90), 93 (55), 86 (18), 79 (18), 67 (22), 57 (100) and 41 (49).

3.5.2. (4*R*/*S*,5*R*/*S*)-5-Hydroxy-4-methyl-6-[(1′*R*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hexan-3-one, (1′*R*)-8. The GC analysis and mass spectra were identical to those of (1′*S*)-**8**.

3.6. Dehydration of aldol 8 to give 9

A Dean–Stark apparatus was fitted to a flask containing a solution of (1′*S*)-**8** (25.68 g, 107.9 mmol) and $TsOH\cdot H_2O$ (282 mg, 1.4 mmol) in dry toluene (40 mL), and the mixture was refluxed for 30 min. Then, the solution was allowed to cool down and washed with an aqueous saturated $NaHCO_3$ solution (3×25 mL), 1 N AcOH solution (25 mL) and brine (3×25 mL). The solution was dried over anhydrous Na_2SO_4 and evaporated in vacuo to yield an oil (22.07 g), which was purified by reduced pressure distillation (bp at 0.06 Torr: 78–86 °C) to afford (−)-**9** (14.55 g, 61% from (−)-**1**).[†] In the same way, (+)-**9** was obtained from (1′*R*)-**8** in a 58% yield (from (+)-**1**).

3.6.1. (4*E*)-4-Methyl-6-[(1′*S*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-4-en-3-one, (−)-9. Colourless liquid; R_t 35.38; $[\alpha]_D$−1.6 (*c* 1.02); 93.1% (GC purity); 91% ee; IR (neat) *ν* 1673, 1641 (C=O), 3039, 798 (C=C), 1461 (CH_3–C=C); ^{1}H NMR *δ* 0.83 (3H, s, Me_{ax}-2′), 1.02 (3H, s, Me_{eq}-2′), 1.10 (3H, t, *J*=7.4 Hz, H-1), 1.61 (3H, br s, Me-3′), 1.80 (3H, br s, Me-4), 1.81–1.99 (2H, m, H-5′+H-1′), 2.15–2.42 (3H, m, H′-5′+H-6), 2.68 (2H, q, *J*=7.4 Hz, H-2), 5.23 (1H, br s, H-4′) and 6.68 (1H, td, *J*=7.3, 1.4 Hz, H-5); ^{13}C NMR *δ* 8.87 (C-1), 30.32 (C-2), 202.49 (C-3), 136.92 (C-4), 141.87 (C-5), 29.78 (C-6), 49.82 (C-1′), 46.90 (C-2′), 148.43 (C-3′), 121.48 (C-4′), 35.56 (C-5′), 11.47 (Me-4), 19.76 (Me_{ax}-2′), 25.89 (Me_{eq}-2′) and 12.59 (Me-3′); MS *m/z* 220 (M^+, 4%), 205 (M^+−Me, 12), 191 (M^+−Et, 4), 177 (5), 163 (M^+−EtCO, 3), 159 (3), 150 (13), 138 (5), 121 (20), 112 (39), 93 (39), 79 (28), 67 (47), 57 (60) and 41 (100).

3.6.2. (4*E*)-4-Methyl-6-[(1′*R*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-4-en-3-one, (+)-9. All spectroscopic properties were identical to those of (−)-**9**, except for $[\alpha]_D$+1.5 (*c* 1.16); 98.8% (GC purity); 87% ee.

3.7. Deconjugative α-methylation of 9 to give 10

A solution of (−)-**9** (13.31 g, 60.5 mmol) in dry DMF (4 mL) was added dropwise to a stirred solution of K^{t}BuO (6.98 g, 61.0 mmol) in dry DMF (30 mL) at room temperature for 30 min. After the addition was completed, the reaction was stirred for 10 min and then cooled to 0 °C. Pre-cooled MeI (22.81 g, 160.7 mmol) was added quickly and stirred at that temperature for 10 min and the mixture was allowed to warm to room temperature. Brine (10 mL) and 1 N AcOH solution (10 mL) were added and the crude was extracted with hexane/Et_2O 1:1 (75 mL). The resulting organic solution was washed with 1 N AcOH solution (2× 30 mL) and brine (3×30 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford 13.49 g of crude (+)-**10**. An aliquot sample of this crude (621 mg) was chromatographed on flash silica gel (eluent hexane/Et_2O 95:5) to afford pure (+)-**10** (484 mg, 78% yield). The rest of the crude was used in the following reaction without further purification. In the same way, (−)-**10** was obtained from (+)-**9** in a 78% yield.

3.7.1. (5*E*)-(4,4-Dimethyl-6-[(1′*S*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-one, (+)-10. Colourless liquid; R_t 32.58; $[\alpha]_D$+28.5 (*c* 1.16); 95.7% (GC purity); 91% ee; IR (neat) *ν* 1712 (C=O), 3038, 798 (C=C) and 1463 (CH_3–C=C); ^{1}H NMR *δ* 0.74 (3H, s, Me_{ax}-2′), 0.95 (3H, s, Me_{eq}-2′), 1.01 (3H, t, *J*=7.3 Hz, H-1), 1.23 (6H, s, Me-4), 1.61 (3H, br s, Me-3′), 2.02–2.14 (1H, m, H-5′), 2.20–2.31 (1H, m, H′-5′), 2.38 (1H, dt, *J*=9.1, 7.3 Hz, H-1′), 2.49 (2H, q, *J*=7.3 Hz, H-2), 5.23 (1H, br s, H-4′), 5.50 (1H, d, *J*=15.6 Hz, H-5) and 5.58 (1H, dd, *J*=15.6, 7.3 Hz, H-6); ^{13}C NMR *δ* 8.39 (C-1), 30.46 (C-2), 214.21 (C-3), 49.97 (C-4), 135.20 (C-5), 131.17 (C-6), 54.10 (C-1′), 48.31 (C-2′), 147.95 (C-3′), 121.41 (C-4′), 35.29 (C-5′), 24.29 (Me-4), 20.48 (Me_{ax}-2′), 25.42 (Me_{eq}-2′) and 12.62 (Me-3′); MS *m/z* 234 (M^+, 0.8%), 219 (M^+−Me, 0.1), 177 (M^+−EtCO, 14), 161 (0.9), 149 (2), 135 (4), 126 (20), 109 (33), 91 (9), 79 (7), 69 (100), 57 (33) and 41 (53).

3.7.2. (5*E*)-4,4-Dimethyl-6-[(1′*R*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-one, (−)-10. All spectroscopic properties were identical to those of (+)-**10**, except for $[\alpha]_D$−26.6 (*c* 1.04); 97.7% (GC purity); 87% ee.

3.8. Reduction of 10 with $NaBH_4$ to give 5

Solid $NaBH_4$ (2.77 g, 71.8 mmol) was added portionwise to a stirred solution of crude (+)-**10** (12.80 g, ca. 54.7 mmol) in MeOH (50 mL) at 0 °C. After 15 min the crude was allowed to warm to room temperature and left to react for 45 min. Then, the solvent was partially evaporated under reduced pressure and the resulting suspension was diluted with hexane/Et_2O 1:2 (75 mL), cooled again to 0 °C and neutralized with 1 N AcOH solution. The organic layer was washed again with 1 N AcOH solution (50 mL) and brine (3×50 mL), then dried over anhydrous Na_2SO_4 and the solvent evaporated in vacuo to yield 12.64 g of a crude, which was purified by reduced pressure distillation (bp at 0.15 Torr: 89–90 °C) to afford (1′*S*)-**5** ((3*R*/*S*,5*E*)-4,4-dimethyl-6-[(1′*S*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-ol) (9.58 g, 95% yield). (1′*S*)-**5** is a mixture of diastereoisomers in ca. 1:1 ratio as its NMR spectra showed. Colourless liquid; R_t 33.28; 98.5% (GC purity). In the same way, a (1′*R*)-**5** mixture was obtained from (−)-**10**

[†] The synthesis of (−)-**9** was also performed working with crude products without further purification in order to avoid losing weight by evaporation of the very volatile compounds **7** and **1**. In that case, a four-step overall yield of 36% from α-pinene was obtained (77% averaged yield per reaction).

in a 94% yield, showing the same retention time in GC and identical NMR spectra.

3.9. Esterification of 5 with (−)-(1*S*)-camphanic chloride

Solid (−)-(1*S*)-camphanic chloride (1.08 g, 4.9 mmol) was added to a stirred solution of (1′*S*)-**5** (807 mg, 3.42 mmol) and DMAP (595 mg, 4.8 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C under argon. The reaction crude was allowed to reach room temperature and, after 2 h, the crude was diluted with Et_2O (50 mL) and washed with 1 N AcOH solution (3× 25 mL), saturated aqueous $NaHCO_3$ solution (2×25 mL) and brine (2×25 mL). The resulting organic solution was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to yield 1.31 g of a mixture of the diastereoisomers **11a/11b**. The mixture was flash chromatographed on silica gel (eluent hexane to hexane/Et_2O 9:1) to obtain 188 mg of **11a** (less polar product), 853 mg of a **11a/11b** mixture and 177 mg of **11b** (more polar product) (total recovered mass after column chromatography: 1218 mg, 86% reaction yield). In the same way, (1′*R*)-**5** was esterified with the same acid chloride to yield a mixture of the diastereoisomers **11c/11d** (84% yield), which were also isolated using the same separation technique, the less polar product being **11c** and the more polar one **11d**.

3.9.1. (1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid, (3*S*,5*E*)-4,4-dimethyl-6-[(1′*S*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-yl ester, 11a.[‡] Colourless crystals; mp 90.9–92.2 °C (hexane); R_t 56.88; $[\alpha]_D$ −8.1 (*c* 1.05); 90.4% (GC purity; 9.6% of **11b**); IR (KBr) ν 1793, 1741, 1173 (COO), 3040 and 979 (C=C); ^{1}H NMR δ 0.74 (3H, s, Me_{ax}-2′), 0.87 (3H, t, *J*=7.3 Hz, H-1), 0.94 (3H, s, Me_{eq}-2′), 1.01 (3H, s, Me-7_{camp}), 1.037 (3H, s, Me-4), 1.044 (3H, s, Me′-4), 1.11 (3H, s, Me′-7_{camp}), 1.12 (3H, s, Me-4_{camp}), 1.42–1.57 (1H, m, H-2), 1.61 (3H, br s, Me-3′), 1.65–1.76 (2H, m, H′-2+H-5_{camp}), 1.93 (1H, ddd, *J*=13.2, 10.7, 4.4 Hz, H′-5_{camp}), 1.99–2.12 (2H, m, H-5′+H-6_{camp}), 2.16–2.28 (1H, m, H′-5′), 2.30–2.37 (1H, m, H-1′), 2.43 (1H, ddd, *J*=13.2, 10.7, 4.4 Hz, H′-6_{camp}), 4.89 (1H, dd, *J*=10.6, 2.3 Hz, H-3), 5.23 (1H, br s, H-4′) and 5.39–5.53 (2H, m, H-5+H-6); ^{13}C NMR δ 11.03 (C-1), 22.78 (C-2), 83.56 (C-3), 40.15 (C-4), 136.74 (C-5), 129.66 (C-6), 54.19 (C-1′), 48.18 (C-2′), 148.01 (C-3′), 121.38 (C-4′), 35.55 (C-5′), 23.34 (Me-4), 24.24 (Me′-4), 20.44 (Me_{ax}-2′), 25.34 (Me_{eq}-2′) and 12.65 (Me-3′), signals for the camphanoate moiety: 91.35 (C-1), 178.35 (C-3), 54.82* (C-4), 28.92 (C-5), 31.08 (C-6), 53.77* (C-7), 167.53 (COO-1), 9.64 (Me-4), 16.79 (Me-7) and 16.87 (Me′-7) (*these signals may be interchanged); MS *m*/*z* 218 (M^+ −CampOH, 6%), 203 (M^+ −CampOH–Me, 6), 189 (M^+ −CampOH–Et, 3), 177 (M^+ −CampO-CHEt, 67), 161 (8), 149 (8), 135 (5), 121 (37), 109 (56), 97 (20), 83 (57), 69 (100), 55 (58) and 41 (64).

[‡] In order to avoid confusion, identification numbers for hydrogen and carbon atoms in NMR are the same than in **5**. Carbon atoms of the camphanoate moiety are separately numbered from 1 to 7, following the IUPAC nomenclature, with the subscript 'camp'. Despite this, note that in IUPAC nomenclature the camphanoate moiety is the main part of the molecule. In the MS, 'camp' means (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyl. This moiety has a formula weight of 181 amu.

3.9.2. (1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid, (3*R*,5*E*)-4,4-dimethyl-6-[(1′*S*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-yl ester, 11b. Colourless crystals; mp 104.6–106.1 °C (hexane); R_t 56.97; $[\alpha]_D$ +25.2 (*c* 1.01); 91.5% (GC purity; 8.5% of **11a**); IR (KBr) ν 1793, 1741, 1172 (COO), 3031 and 977 (C=C); ^{1}H NMR δ 0.74 (3H, s, Me_{ax}-2′), 0.89 (3H, t, *J*=7.3 Hz, H-1), 0.95 (3H, s, Me_{eq}-2′), 1.02 (3H, s, Me-7_{camp}), 1.03 (6H, s, Me-4), 1.10 (3H, s, Me′-7_{camp}), 1.12 (3H, s, Me-4_{camp}), 1.42–1.56 (1H, m, H-2), 1.61 (3H, br s, Me-3′), 1.65–1.76 (2H, m, H′-2+H-5_{camp}), 1.94 (1H, ddd, *J*=13.3, 10.7, 4.5 Hz, H′-5_{camp}), 2.01–2.13 (2H, m, H-5′+H-6_{camp}), 2.16–2.29 (1H, m, H′-5′), 2.30–2.37 (1H, m, H-1′), 2.43 (1H, ddd, *J*=13.3, 10.7, 4.5 Hz, H′-6_{camp}), 4.88 (1H, dd, *J*=10.4, 2.5 Hz, H-3), 5.23 (1H, br s, H-4′), 5.42 (1H, d, *J*=15.8 Hz, H-5) and 5.49 (1H, dd, *J*=15.8, 6.7 Hz, H-6); ^{13}C NMR δ 11.14 (C-1), 23.10 (C-2), 83.70 (C-3), 40.02 (C-4), 136.24 (C-5), 129.67 (C-6), 54.15 (C-1′), 48.02 (C-2′), 147.98 (C-3′), 121.42 (C-4′), 35.30 (C-5′), 23.16 (Me-4), 25.03 (Me′-4), 20.45 (Me_{ax}-2′), 25.35 (Me_{eq}-2′) and 12.65 (Me-3′), signals for the camphanoate moiety: 91.32 (C-1), 178.18 (C-3), 54.84* (C-4), 28.98 (C-5), 31.12 (C-6), 53.84* (C-7), 167.41 (COO-1), 9.63 (Me-4), 16.84 (Me-7) and 16.91 (Me′-7) (*these signals may be interchanged); MS *m*/*z* 218 (M^+ −CampOH, 12%), 203 (M^+ −CampOH–Me, 9), 189 (M^+ −CampOH–Et, 3), 177 (M^+ −CampO-CHEt, 100), 161 (11), 149 (8), 135 (14), 121 (25), 109 (42), 97 (13), 83 (37), 69 (61), 55 (37) and 41 (40).

3.9.3. (1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid, (3*S*,5*E*)-4,4-dimethyl-6-[(1′*R*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-yl ester, 11c. Colourless crystals; mp 67.6–72.2 °C (hexane); R_t 56.85; $[\alpha]_D$ −26.8 (*c* 1.05 in $CHCl_3$); 84.7% (GC purity; 8.5% of **11d**); IR (KBr) ν 1791, 1742, 1173 (COO), 3040 and 979 (C=C); ^{1}H NMR δ 0.74 (3H, s, Me_{ax}-2′), 0.86 (3H, t, *J*=7.4 Hz, H-1), 0.95 (3H, s, Me_{eq}-2′), 1.01 (3H, s, Me-7_{camp}), 1.03 (3H, s, Me-4), 1.04 (3H, s, Me′-4), 1.11 (3H, s, Me′-7_{camp}), 1.12 (3H, s, Me-4_{camp}), 1.43–1.56 (1H, m, H-2), 1.61 (3H, br s, Me-3′), 1.63–1.75 (2H, m, H′-2+H-5_{camp}), 1.92 (1H, ddd, *J*=13.3, 10.7, 4.4 Hz, H′-5_{camp}), 1.99–2.13 (2H, m, H-5′+H-6_{camp}), 2.15–2.27 (1H, m, H′-5′), 2.30–2.37 (1H, m, H-1′), 2.43 (1H, ddd, *J*=13.3, 10.7, 4.4 Hz, H′-6_{camp}), 4.88 (1H, dd, *J*=10.4, 2.2 Hz, H-3), 5.23 (1H, br s, H-4′) and 5.39–5.54 (2H, m, H-5+H-6); ^{13}C NMR δ 11.11 (C-1), 22.94 (C-2), 83.77 (C-3), 40.11 (C-4), 136.36 (C-5), 129.66 (C-6), 54.15 (C-1′), 48.06 (C-2′), 148.06 (C-3′), 121.46 (C-4′), 35.30 (C-5′), 23.17 (Me-4), 24.98 (Me′-4), 20.49 (Me_{ax}-2′), 25.39 (Me_{eq}-2′) and 12.70 (Me-3′), signals for the camphanoate moiety: 91.40 (C-1), 178.42 (C-3), 54.87* (C-4), 28.96 (C-5), 31.09 (C-6), 53.81* (C-7), 167.59 (COO-1), 9.69 (Me-4), 16.83 (Me-7) and 16.92 (Me′-7) (*these signals may be interchanged); MS *m*/*z* 218 (M^+ −CampOH, 4%), 203 (M^+ −CampOH–Me, 3), 189 (M^+ −CampOH–Et, 1), 177 (M^+ −CampO-CHEt, 37), 161 (4), 149 (4), 135 (7), 121 (16), 109 (26), 97 (10), 83 (26), 69 (75), 55 (69) and 41 (100).

3.9.4. (1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid, (3*R*,5*E*)-4,4-dimethyl-6-[(1′*R*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-yl ester, 11d. Colourless crystals; mp 106.2–109.4 °C (hexane); R_t 56.99; $[\alpha]_D$ +0.4 (*c* 0.94); 79.0% (GC purity;

8% of **11c**); IR (KBr) ν 1793, 1741, 1172 (COO), 3065 and 980 (C=C); ^{1}H NMR δ 0.74 (3H, s, Me_{ax}-2′), 0.89 (3H, t, J=7.4 Hz, H-1), 0.94 (3H, s, Me_{eq}-2′), 1.02 (3H, s, Me-7$_{camp}$), 1.03 (3H, s, Me-4), 1.04 (3H, s, Me′-4), 1.10 (3H, s, Me′-7$_{camp}$), 1.12 (3H, s, Me-4$_{camp}$), 1.44–1.57 (1H, m, H-2), 1.61 (3H, br s, Me-3′), 1.63–1.77 (2H, m, H′-2+H-5$_{camp}$), 1.93 (1H, ddd, J=13.3, 10.7, 4.4 Hz, H′-5$_{camp}$), 2.00–2.11 (2H, m, H-5′+H-6$_{camp}$), 2.17–2.29 (1H, m, H′-5′), 2.30–2.37 (1H, m, H-1′), 2.44 (1H, ddd, J=13.3, 10.7, 4.4 Hz, H′-6$_{camp}$), 4.89 (1H, dd, J=10.4, 2.2 Hz, H-3), 5.23 (1H, br s, H-4′) and 5.38–5.53 (2H, m, H-5+H-6); ^{13}C NMR δ 11.15 (C-1), 23.00 (C-2), 83.56 (C-3), 40.15 (C-4), 136.70 (C-5), 129.71 (C-6), 54.24 (C-1′), 48.20 (C-2′), 148.05 (C-3′), 121.44 (C-4′), 35.58 (C-5′), 23.29 (Me-4), 24.41 (Me′-4), 20.48 (Me_{ax}-2′), 25.38 (Me_{eq}-2′) and 12.69 (Me-3′), signals for the camphanoate moiety: 91.36 (C-1), 178.25 (C-3), 54.90* (C-4), 29.02 (C-5), 31.16 (C-6), 53.89* (C-7), 167.45 (COO-1), 9.68 (Me-4), 16.85 (Me-7) and 16.91 (Me′-7) (*these signals may be interchanged); MS *m/z* 218 (M^+−CampOH, 4%), 203 (M^+−CampOH–Me, 3), 189 (M^+−CampOH–Et, 1), 177 (M^+−CampO-CHEt, 36), 161 (4), 149 (4), 135 (7), 121 (15), 109 (26), 97 (9), 83 (31), 69 (80), 55 (65) and 41 (100).

3.10. Reduction of 11 with $LiAlH_4$ to give 5

Solid $LiAlH_4$ (320 mg, 8.43 mmol) was added portionwise to a stirred solution of **11a** (270 mg, 0.65 mmol) in dry THF (15 mL) at 0 °C, and then allowed to react at room temperature for 2 h. Then, the mixture was diluted wih Et_2O (25 mL). The remaining hydride was destroyed by adding brine (10 mL) and the aqueous solution neutralized with 1 N HCl solution. The aqueous layer was extracted with Et_2O (2×25 mL) and the resulting organic solution was washed with 5% $NaHCO_3$ solution (25 mL) and brine (2×25 mL), then dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to afford 250 mg of a crude, which was purified by silica-gel flash chromatography (eluent hexane/Et_2O 85:15) to yield (+)-(3*S*,1′*S*)-**5** (140 mg, 0.59 mmol, 91%). In the same way, by reduction of **11b**, **11c** and **11d**, separately, (+)-(3*R*,1′*S*)-**5**, (−)-(3*S*,1′*R*)-**5** and (−)-(3*R*,1′*R*)-**5** were obtained, respectively.

3.10.1. (3*S*,5*E*)-4,4-Dimethyl-6-[(1′*S*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-ol, (+)-(3*S*,1′*S*)-5. Obtained from **11a**, colourless liquid; R_t 33.28; $[\alpha]_D$+4.6 (*c* 1.17); 94.2% (GC purity); 66% de;[§] IR (neat) ν 3412 (OH), 1102 (C–O), 3036, 977 (C=C) and 1463 (CH_3–C=C); ^{1}H NMR δ 0.75 (3H, s, Me_{ax}-2′), 0.96 (3H, s, Me_{eq}-2′), 0.97–1.04 (9H, m, Me-4+H-1), 1.15–1.32 (1H, m, H-2), 1.53–1.70 (1H, m, H′-2), 1.62 (3H, br s, Me-3′), 2.02–2.15 (1H, m, H-5′), 2.19–2.32 (1H, m, H′-5′), 2.37 (1H, q, J=8.2 Hz, H-1′), 3.14 (1H, d, J=10.2 Hz, H-3), 5.24 (1H, br s, H-4′), 5.40 (1H, d, J=15.9 Hz, H-5) and 5.50 (1H, dd, J=15.9, 7.7 Hz, H-6); ^{13}C NMR δ 11.66 (C-1), 24.27 (C-2), 80.15 (C-3), 41.02 (C-4), 137.77 (C-5), 130.20 (C-6), 54.28 (C-1′), 48.03 (C-2′), 148.02 (C-3′), 121.50 (C-4′), 35.48 (C-5′), 22.66 (Me-4), 23.94 (Me′-4), 20.52 (Me_{ax}-2′), 25.38 (Me_{eq}-2′) and 12.70 (Me-3′); MS *m/z* 221 (M^+−Me, 0.1%), 218 (M^+−H_2O, 0.1), 207 (M^+−Et, 0.3), 203 (M^+−H_2O–Me, 0.2), 178 (M^+−CH_3CH_2COH, 20), 163 (178$^+$−Me, 14), 149 (4), 135 (14), 121 (26), 109 (48), 93 (16), 79 (12), 69 (100), 59 (23) and 41 (62). HRMS *m/z*, calcd for $C_{16}H_{28}O$, 236.2140 (M^+), found 236.2116.

3.10.2. (3*R*,5*E*)-4,4-Dimethyl-6-[(1′*R*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-ol, (−)-(3*R*,1′*R*)-5. Obtained from **11d**. All spectroscopic properties were identical to those of (+)-(3*S*,1′*S*)-**5**, except for $[\alpha]_D$−9.4 (*c* 1.00); 98.5% (GC purity); 66% de.

3.10.3. (3*R*,5*E*)-4,4-Dimethyl-6-[(1′*S*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-ol, (+)-(3*R*,1′*S*)-5. Obtained from **11b**, colourless liquid; R_t 33.28; $[\alpha]_D$+25.3 (*c* 1.26); 97.7% (GC purity); 64% de; IR (neat) ν 3413 (OH), 1103 (C–O), 3037, 977 (C=C) and 1463 (CH_3–C=C); ^{1}H NMR δ 0.75 (3H, s, Me_{ax}-2′), 0.95 (3H, s, Me_{eq}-2′), 0.97–1.05 (9H, m, Me-4+H-1), 1.15–1.31 (1H, m, H-2), 1.51–1.69 (1H, m, H′-2), 1.61 (3H, br s, Me-3′), 2.01–2.15 (1H, m, H-5′), 2.20–2.31 (1H, m, H′-5′), 2.37 (1H, dt, J=8.9, 7.7 Hz, H-1′), 3.14 (1H, d, J=10.4 Hz, H-3), 5.24 (1H, br s, H-4′), 5.41 (1H, d, J=15.8 Hz, H-5) and 5.50 (1H, dd, J=15.8, 7.7 Hz, H-6); ^{13}C NMR δ 11.66 (C-1), 24.28 (C-2), 80.25 (C-3), 41.00 (C-4), 137.74 (C-5), 130.26 (C-6), 54.37 (C-1′), 48.03 (C-2′), 148.00 (C-3′), 121.50 (C-4′), 35.56 (C-5′), 22.68 (Me-4), 24.01 (Me′-4), 20.53 (Me_{ax}-2′), 25.45 (Me_{eq}-2′) and 12.70 (Me-3′); MS *m/z* 221 (M^+−Me, 0.1%), 219 (M^+−OH, 0.1), 207, (M^+−Et, 0.3), 203 (M^+−H_2O–Me, 0.2), 178 (M^+−CH_3CH_2COH, 23), 163 (178$^+$−Me, 15), 149 (4), 135 (11), 122 (25), 109 (48), 93 (16), 79 (11), 69 (100), 59 (24) and 41 (62).

3.10.4. (3*S*,5*E*)-4,4-Dimethyl-6-[(1′*R*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-ol, (−)-(3*S*,1′*R*)-5. Obtained from **11c**. All spectroscopic properties were identical to those of (+)-(3*R*,1′*S*)-**5**, except for $[\alpha]_D$−22.1 (*c* 1.06); 97.0% (GC purity); 64% de. HRMS *m/z*, calcd for $C_{16}H_{28}O$, 236.2140 (M^+), found 236.2144.

3.11. Esterification of (+)-(3*S*,1′*S*)-5 with (−)-(2*R*)- and (+)-(2*S*)-MTPA chloride

A solution of (−)-(2*R*)-MTPA chloride (0.3 mL, 10%, 0.12 mmol) in dry CH_2Cl_2 was added to a stirred solution of (+)-(3*S*,1′*S*)-**5** (13.5 mg, 0.057 mmol) and DMAP (23 mg, 3.3 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C under argon. Then, the reaction crude was allowed to warm to room temperature overnight. After that, the crude was diluted with Et_2O (25 mL) and the organic solution was washed with 1 N AcOH solution (2×10 mL), saturated aqueous $NaHCO_3$ solution (15 mL) and brine (2×15 mL). The resulting organic solution was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to yield 32 mg of a crude that was flash chromatographed on silica gel (eluent hexane/Et_2O 95:5) to obtain pure **12A** (23 mg, 89% yield). In the same way, the (*R*)-MTPA ester (**12B**) was obtained after reacting (+)-(3*S*,1′*S*)-**5** with (+)-(2*S*)-MTPA chloride in an 89% yield.

[§] Diastereomeric excess calculated through the integration of the duplicate ^{13}C NMR signals assigned to C-3, C-1′, C-5′ and Me′-4, for (+)-(3*S*,1′*S*)-**5** (major component) and its diastereomer (+)-(3*R*,1′*S*)-**5** (minor component).

3.11.1. (2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionic acid, (3*S*,5*E*)-4,4-dimethyl-6-[(1′*S*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-yl ester, 12A.[¶] Colourless liquid; R_t 54.90; 94% (GC purity); ^{1}H NMR δ 0.72 (3H, s, Me_{ax}-2′), 0.79 (3H, t, J=7.6 Hz, H-1), 0.93 (3H, s, Me_{eq}-2′), 0.99 (3H, s, Me-4), 1.00 (3H, s, Me′-4), 1.41–1.54 (1H, m, H-2), 1.60 (3H, br s, Me-3′), 1.63–1.73 (1H, m, H′-2), 1.99–2.09 (1H, m, H-5′), 2.15–2.28 (1H, m, H′-5′), 2.28–2.38 (1H, m, H-1′), 3.54 (3H, br s, OMe), 4.93 (1H, dd, J= 10.2, 2.5 Hz, H-3), 5.23 (1H, br s, H-4′), 5.36–5.51 (2H, m, H-5+H-6), 7.36–7.43 (3H, m, *o*,*p*-Ph), 7.57–7.62 (2H, m, *m*-Ph); ^{13}C NMR δ 10.91 (C-1), 23.17 (C-2), 85.33 (C-3), 40.33 (C-4), 136.64 (C-5), 129.66* (C-6), 54.19 (C-1′), 48.16 (C-2′), 148.06 (C-3′), 121.45 (C-4′), 35.42 (C-5′), 23.41 (Me-4), 24.37 (Me′-4), 20.44 (Me_{ax}-2′), 25.35 (Me_{eq}-2′), 12.69 (Me-3′), signals for the MTPA moiety: 166.52 (C-1), 84.50 (C-2), 125.35 (CF_3), 55.33 (OMe), 131.95 (C-1_{Ph}), 129.51* (C-2_{Ph}), 128.31 (C-3_{Ph}), 127.81 (C-4_{Ph}) (*these signals may be interchanged).

3.11.2. (2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid, (3*S*,5*E*)-4,4-dimethyl-6-[(1′*S*)-(2′,2′,3′-trimethylcyclopent-3′-en-1′-yl)]-hex-5-en-3-yl ester, 12B. Colourless liquid; R_t 54.85; 95% (GC purity); ^{1}H NMR δ 0.72 (3H, s, Me_{ax}-2′), 0.87 (3H, t, J=7.6 Hz, H-1), 0.93 (3H, s, Me_{eq}-2′), 0.96 (3H, s, Me-4), 0.97 (3H, s, Me′-4), 1.46–1.58 (1H, m, H-2), 1.60 (3H, br s, Me-3′), 1.64–1.78 (1H, m, H′-2), 1.97–2.10 (1H, m, H-5′), 2.13–2.24 (1H, m, H′-5′), 2.27–2.37 (1H, m, H-1′), 3.57 (3H, br s, OMe), 4.93 (1H, dd, J=9.7, 2.3 Hz, H-3), 5.23 (1H, br s, H-4′), 5.35–5.50 (2H, m, H-5+H-6), 7.37–7.44 (3H, m, *o*,*p*-Ph), 7.58–7.64 (2H, m, *m*-Ph); ^{13}C NMR δ 11.24 (C-1), 23.44 (C-2), 85.38 (C-3), 40.30 (C-4), 136.34 (C-5), 129.76* (C-6), 54.22 (C-1′), 48.14 (C-2′), 148.05 (C-3′), 121.46 (C-4′), 35.41 (C-5′), 22.87 (Me-4), 24.68 (Me′-4), 20.44 (Me_{ax}-2′), 25.36 (Me_{eq}-2′), 12.69 (Me-3′), signals for the MTPA moiety: 166.44 (C-1), 85.00 (C-2), 125.37 (CF_3), 55.38 (OMe), 132.13 (C-1_{Ph}), 129.49* (C-2_{Ph}), 128.28 (C-3_{Ph}), 127.62 (C-4_{Ph}) (*these signals may be interchanged).

3.12. Sensory evaluation

Blotting paper strips were impregnated with compounds **5a–5d**, previously diluted with Et_2O (25 mg/200 μL) and smelt by perfumers at that moment, 3 h later, and 24 h later. The olfactory description in each session, therefore, corresponded to the top, heart and base notes, respectively.

3.13. GC sniffing analysis

Odour assessment by a group of perfumers was achieved using a Hewlett–Packard Model 5890 Series II gas chromatograph equipped with a thermal conductivity detector (TCD) and a handmade sniffing port. Separation was done with a 10% Carbowax 20M over Chromosorb W/AW 80–100 mesh packed column (1.8 m×6 mm OD× 2.2 mm ID); injector temperature: 250 °C; detector temperature: 250 °C; oven temperature program: 60 °C (0 min) to 240 °C (20 min) at a rate of 4 °C/min. Sample size for each injection was approximately 1 μL.

[¶] In order to avoid confusion, identification numbers for hydrogen and carbon atoms in NMR are the same than in **5**. Carbon atoms of the MTPA moiety are separately numbered, following the IUPAC nomenclature. Despite this, note that in IUPAC nomenclature the MTPA moiety is the main part of the molecule.

Acknowledgements

We wish to thank the Spanish Ministerio de Ciencia y Tecnología for financial support (R+D project PPQ2000-1665; partial financial support from the FEDER funds of the European Union) and the Ministerio de Educación, Cultura y Deporte for a fellowship to J.M.C. We also greatly thank to Carles Ibáñez, Fina Caballer and Meritxell Antich of Lucta S. A. (Barcelona, Spain) for the odour evaluation.

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Tetrahedron

Palladium mediated synthesis of isoindolinones and isoquinolinones

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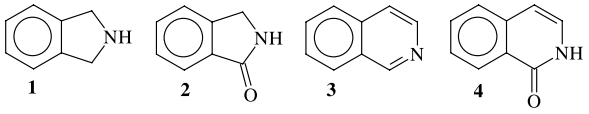
Received 12 May 2005; revised 31 August 2005; accepted 8 September 2005

Available online 10 October 2005

Abstract—The palladium-catalyzed reactions of 2-iodo-*N*-substituted benzamides **5–10** with acrylic esters **11–14** led to *N*-substituted-3-alkylisoindolinone esters **15–22** in good yields. The esters of isoindolinones **15–22** underwent hydrolysis reactions yielding the *N*-aryl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid **26–31** in good yields.

1. Introduction

Isoindoline (2,3-dihydro-1*H*-isoindole) **1** and isoindolinone or 2,3-dihydro-1*H*-isoindol-1-one (phthalimidine) **2** moieties are an integral part of some biologically active compounds and naturally occurring products.[1] Isoindolinones and their derivatives have gained considerable attention due to their profound physiological and chemotherapeutic properties. Many compounds containing the isoindolinone skeleton have shown antiviral, antileukemic, antiinflammatory, antipsychotic and antiulcer properties.[2] Isoindolinones are useful for the synthesis of various drugs[3] and naturally occurring compounds.[4] Isoquinolines **3** and isoquinolinones (1-oxo-1,2-dihydroisoquinoline) **4** are an integral part of many naturally occurring substances[5] and a class of fused heterocycles that are of increasing interest in synthetic and pharmaceutical chemistry.[6–8]



1 2 3 4

There are several methods available for the synthesis of isoindolinones based on the Gabriel method,[9] Grignard procedure,[10] lithiation process,[11] Diels–Alder reaction,[12] Wittig reaction,[13] reduction reactions,[14] rearrangement processes[15] and photochemical reactions.[16] Methods are also known for the synthesis of 1(2*H*)-isoquinolones[17–22] and 1,2,3,4-tetrahydro-1-(2*H*)-isoquinolones.[23–25]

Only a few methods have utilized palladium catalysis. Palladium catalyzed[26] reactions have been extensively used for carboannulation[27] and heteroannulation[28] processes. Several research groups have reported the synthesis of aromatic heterocycles via palladium-catalyzed annulation of internal alkynes.[29] Others have shown that palladium-catalyzed cyclizations are valuable synthetic tools for the preparation of a wide variety of heterocycles[30] using vinylic compounds, terminal alkynes, allenes and other substrates. In recent years, our group has developed methods for the synthesis of benzofused heterocyclic compounds, for example, isobenzofurans[31] and isoindolinones[32] by palladium-catalyzed reactions with terminal alkynes and acid chloride. In this paper, a novel approach to 3-alkylisoindolinone acetate and isoquinolinone-3-carboxylic acid is described.

2. Results and discussion

A new strategy for the synthesis of *N*-substituted-3-alkyl isoindolinone acetate **15–22** through palladium-catalyzed reaction of 2-iodo-*N*-substituted benzamides **5–10** with terminal alkene (acrylic ester) **11–14** and preparation of isoquinolinone-3-carboxylic acids **26–31** by the hydrolysis of the ester of isoindolinones **15–22** is reported as shown in the Table 1, Scheme 1.

The reactions were usually carried out by heating a mixture of 2-iodo-*N*-aryl (alkyl) benzamides **5–10** and terminal alkenes (acrylic ester) **11–14** (3 equiv) in DMF (10 mL) at 80 °C for 24 h in the presence of $(Ph_3P)_2PdCl_2$ (3.5 mol%) and triethylamine (4 equiv) under nitrogen atmosphere.[33] After usual workup and separation by column

Keywords: Palladium; Benzamides; Quinoline; Isoindolinone; Isoquinolinone.
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doi:10.1016/j.tet.2005.09.032

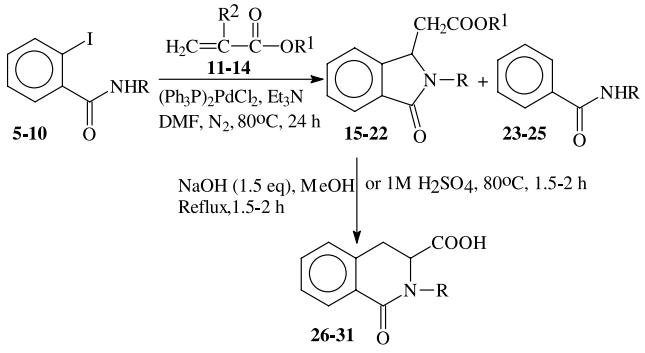
Table 1. Synthesis of isoindolinone and isoquinolinone

Entry	2-Iodo-*N*-substituted benzamide (**5**–**10**)	R	**11**–**14**	R^1	R^2	**15**–**22** Isoindolinone	**26**–**31** Isoquinolinone	Yield %[a]
1	**5**	C_6H_5	**11**	Butyl	H	**15**	**26**	(75) 54
2	**6**	$C_6H_4CH_3$-*p*	**11**	Butyl	H	**16**	**27**	(76) 68
3	**7**	$C_6H_4OCH_3$-*p*	**11**	Butyl	H	**17**	**28**	(80) 72
4	**8**	C_6H_4Cl-*p*	**11**	Butyl	H	**18**	**29**	(77) 69
5	**9**	CH_3	**11**	Butyl	H	—	**30**	(—) 60
6	**10**	$CH_2C_6H_4Cl$-*p*	**11**	Butyl	H	—	**31**	(—) 65
7	**6**	$C_6H_4CH_3$-*p*	**12**	Ethyl	H	**19**	**27**	(70) 64
8	**7**	$C_6H_4OCH_3$-*p*	**12**	Ethyl	H	**20**	**28**	(72) 66
9	**6**	$C_6H_4CH_3$-*p*	**13**	Methyl	H	**21**	**27**	(65) 58
10	**7**	$C_6H_4OCH_3$-*p*	**13**	Methyl	H	**22**	**28**	(67) 61
11[b]	**5**	C_6H_5	**14**	Methyl	CH_3	—	—	—
12[b]	**6**	$C_6H_4CH_3$-*p*	**20**	Acrylonitrile H_2C=CHCN		—	—	—
13[c]	**7**	$C_6H_4OCH_3$-*p*	**21**	Acrolein H_2C=CHCHO		—	**25**	—

[a] Yield% inside the bracket is the yield of isoindolinone and outside the bracket is of isoquinolinone based on 2-iodo-*N*-substituted benzamides.
[b] The entry 11, 12 afforded mixture of deiodinated and cyclic product.
[c] The entry 13 afforded only deiodinated product **24**.

chromatography on silica gel, the crude mass afforded 3-alkyl isoindolinone acetate **15**–**22** and some amount deiodinated benzamide **23**–**25** (10–15%). The 3-alkyl isoindolinone acetate **15**–**22** (1 mmol) were converted to the corresponding acid of isoquinolinone **26**–**31** by refluxing with NaOH (1.5 equiv) in MeOH (10 mL) for 1.5–2 h. The hydrolysis was also carried out using 1 M H_2SO_4 acid (4 equiv) in H_2O under reflux condition for 1.5–2 h to afford the corresponding acid of isoquinolinones. The yield was similar in each case. The palladium-catalyzed reaction between 2-iodo-*N*-phenylbenzamide and methyl methacrylate under the same conditions afforded a mixture of the ester of isoindolinone and deiodinated products in lower yield.

An alternative approach towards the synthesis of the acid of isoindolinone utilizing palladium-catalyzed olefination with acrylonitrile has been attempted, although a mixture of the ester of isoindolinone and deiodinated product were obtained in lower yield. In the case of acrolein, only deiodinated benzamide has been isolated.



Scheme 1. 5, **26** R=CH_3, **6**, **27** R=$CH_2C_6H_4Cl$-*p*, **7**, **23**, **28** R=C_6H_5, **8**, **24**, **29** R=$C_6H_4CH_3$-*p*, **9**, **25**, **30** R=$C_6H_4OCH_3$-*p*, **10**, **31** R=C_6H_4Cl-*p*; **11**–**14** R^1(R^2)=C_4H_9(H), C_2H_5(H), CH_3(H), CH_3(CH_3); **15**–**22** R(R^1)=C_6H_5(C_4H_9), $C_6H_4CH_3$-*p*(C_4H_9), $C_6H_4OCH_3$-*p*(C_4H_9), C_6H_4Cl-*p*(C_4H_9), $C_6H_4CH_3$-*p*(C_2H_5), $C_6H_4OCH_3$-*p*(C_2H_5), $C_6H_4CH_3$-*p*(CH_3), $C_6H_4OCH_3$-*p*(CH_3).

It was observed that the vinylic group required activation through conjugation with an ester or a nitrile group for the reaction to take place. Conjugated aldehyde (acrolein) led only to deiodinated products and methyl methaacrylate gave a mixture of the ester of isoindolinone and the deiodinated product. It was also found that the yield of the ester of isoindolinone and the acid of isoquinolinone was found higher and easily separable when *n*-butyl acrylate was used as the terminal alkene.

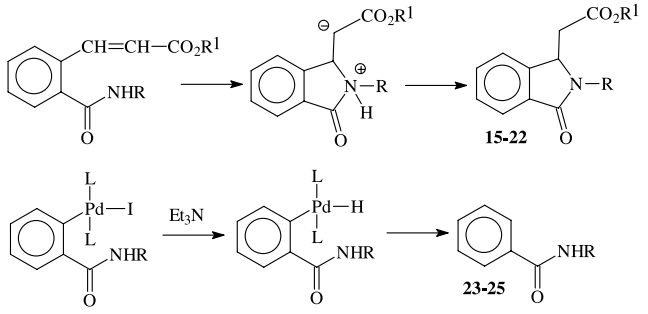
3. Characterization of products

The heteroannulation of 2-iodo-*N*-substituted benzamides with terminal alkenes (acrylic ester) in the presence of $(Ph_3P)_2PdCl_2$ and Et_3N in DMF afforded 3-alkyl isoindolinone acetate, which were later hydrolyzed with 1 M NaOH in MeOH or 1 M H_2SO_4 solution to yield the corresponding acid of isoquinolinone exclusively. All the isoindolinones and isoquinolinones were well characterized by their satisfactory spectroscopic (IR, UV, ^{1}H NMR and ^{13}C NMR) and analytical data. The data of isoquinolinones were also compatible with those reported by Kundu et al.[33]

3.1. Mechanism of palladium-catalyzed reactions of 2-iodo-*N*-substituted benzamide with terminal alkenes (acrylates)

Although the detailed mechanism of the reaction is yet to be clarified, it can be perceived that the reactions proceed according to Scheme 2. From our observations it was clear that the presence of palladium catalyst and base was very essential for the success of the heteroannulation reactions. The key steps of the plausible mechanism were based on the following observations. It could be suggested that Pd(0)

could be the intermediate involved in the catalytic process. The reduction of Pd(II) to Pd(0) in the presence of Et_3N and terminal alkenes took place. The Heck reaction produced the expected products, presumably by the classic catalytic cycle. Then the 2-alkenyl benzamides underwent the Michael addition, then protonation to give the kinetic 5-membered ring products **15–22** (Scheme 2).



Scheme 2.

4. Conclusion

We have described a convenient, general and facile method for the preparation of *N*-aryl(alkyl)-3-alkyl isoindolinone acetate from the reaction of 2-iodo-*N*-substituted benzamides with acrylic esters by a $(Ph_3P)_2PdCl_2$ Et_3N system. The ester of the isoindolinones was converted to *N*-aryl-(alkyl) isoquinolinone-3-carboxylic acid by base/acid hydrolysis. The reaction is highly regioselective in the case of the palladium-catalyzed and hydrolysis type reactions. A variety of functional groups can be introduced at the 2- and 3-positions of the isoquinolinones moiety. Through this methodology biologically important derivatives of isoindolinone and isoquinolinone could be synthesized.

5. Experimental

Melting points were determined in open capillary tubes on Gallenkamp (England) melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR spectrophotometer and UV spectra were recorded in dry EtOH with a Shimadzu visible spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrophotometer (400 MHz) using tetramethylsilane as internal reference. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60F-254 (E. Merck), and the spots were visualized with UV light. Column chromatography was performed on silica gel (60–120 mesh). Elemental analyses (C, H, N) were carried out on a Perkin-Elmer 240C Analyser. Bis(triphenylphosphine)palladium(II) chloride, acrylic esters, and other reagents were purchased from E. merck (Germany) and Fluka (Switzerland).

5.1. Synthesis of 2-iodo-*N*-substituted benzamides 5–10

2-Iodo-*N*-substituted benzamides **5–10** were prepared from 2-iodobenzoic acids obtained through Sandmeyer iodination reaction of anthranilic acid.[34] 2-Iodobenzoic acid was converted to 2-iodobenzoylchloride by heating with PCl_5 at 80 °C for 2 h. 2-Iodobenzoyl chloride (3.0 g) was dissolved in dry benzene (20 mL) under nitrogen atmosphere and cooled under ice bath. To the resulting solution was added a solution of primary amine (2.0 equiv) in dry benzene (10 mL) slowly with stirring. The residue obtain by filtration was washed with dilute HCl (3×50 mL), saturated $NaHCO_3$ solution (3×50 mL) and distilled water (3×50 mL) and finally the residue was washed with ether (2×25 mL). The crystallization was done from ethanol to yield 2-iodo-*N*-substituted benzamide **5–10**. Some of the 2-iodo-*N*-substituted benzamides were identical to the reported compound in the literature.[32]

5.1.1. 2-Iodo-*N*-*p*-chlorobenzyl benzamide 6. Colourless needle; mp 164–165 °C; IR: ν_{max} (KBr) 3276.8, 3059.9, 3029.0, 2921.0, 2845, 1647.1, 1584.4, 1488.9 cm^{-1}; UV (EtOH): λ_{max} 326.4, 305.2, 275.4, 227.6 and 208.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 (d, 2H, J=4.08 Hz, –CH_2), 6.16 (br s, 1H–NH), 7.10 (d, 1H, J=7.09 Hz, Ar-H), 7.26–7.37 (m, 6H, Ar-H) and 7.85 (d, 1H, J=7.49 Hz, Ar-H). Anal. Calcd for $C_{14}H_{11}NOClI$: C, 45.25; H, 2.98; N, 3.76. Found: C, 45.01; H, 3.12; N, 3.95.

5.1.2. 2-Iodo-*N*-*p*-chlorophenyl benzamide 10. Colourless needles; mp 141–142 °C; IR: ν_{max} (KBr) 3351.1, 1653.8, 1595.0, 1516.9, 1493.8 cm^{-1}; UV (EtOH): λ_{max} 272 and 223.8 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09–7.93 (m, 9H). Anal. Calcd for $C_{13}H_9NOClI$: C, 43.54; H, 2.53; N, 3.91. Found: C, 43.25; H, 2.67; N, 4.22.

5.2. Synthesis of *N*-substituted-3-alkyl isoindolinone esters 15–22

A mixture of 2-iodo-*N*-substituted benzamide **5–10** (0.5 g, 1.55 mmol), bis(triphenyl phosphine)palladium(II) chloride (0.038 g, 3.5 mol%) and triethylamine (0.625 g, 4 equiv) was stirred in DMF (10 mL) under nitrogen atmosphere for 1 h. Then alkyl acrylate **11–14** (0.57 g, 3 equiv) was added to the reaction mixture. The solution was heated at 80 °C for 23 h. The progress of the reaction was monitored by TLC(*n*-hexane/chloroform 1:1). After completion of the reaction, the mixture was then evaporated to dryness under reduced pressure and the residue was extracted with chloroform (3×50 mL). The combined chloroform extracts were washed with distilled water (3×50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain reddish gum. The latter was purified by chromatography on a column of silica gel (60–120 mesh) with *n*-hexane/chloroform 1:3 and chloroform. *N*-substituted-3-alkyl isoindolinone esters **15–22** and small amount of deiodinated product **23–25** were obtained.

5.2.1. *N*-phenyl-3-butyl isoindolin-1-one acetate 15. Colourless solid; mp 90–91 °C; IR: ν_{max} (KBr) 1740.6, 1678.0, 1597.9, 1493.8, 1464.8, 1391.5 and 1301.9 cm^{-1}; UV (EtOH): λ_{max} 273.00 (log ε 3.810), 236.60, (log ε 3.766), 229.60 (log ε 3.697) and 211.60 (log ε 3.664) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, J=7.26, 14.66 Hz, –CH_3), 1.30 (m, 2H, –CH_2), 1.52 (m, 2H, –CH_2), 2.51 (dd, 1H, J=8.45, 16.05 Hz, H-2′), 2.95 (dd, 1H, J=3.87, 16.08 Hz, H-2′), 4.05 (m, 2H, –OCH_2), 5.60 (dd, 1H, J=3.94, 8.34 Hz, H-3), 7.23–7.60 (m, 8H, Ar-H), and 7.91 (d, 1H, J=7.80 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

13.63 (CH_3), 19.03 (–CH_2–), 30.47 (–CH_2–), 37.75 (C-2′), 57.58 (C-3), 64.97 (–O–CH_2), 122.57, 123.89, 124.29, 125.95, 128.90, 129.30, 131.96, 132.30, 136.50, 144.28, (Ar-C), 166.90 (CON) and 170.49 (–CO_2–). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.29; H, 6.54; N, 4.33. Found: C, 74.50; H, 6.65; N, 4.58.

5.2.2. *N*-*p*-methyl phenyl-3-butyl isoindolin-1-one acetate 16. Light yellow liquid; IR: ν_{max} (CCl_4) 1734.9, 1707.8, 1550.7, 1515.0, 1467.7, 1376.1 and 1306.7 cm^{-1}; UV (EtOH): λ_{max} 243.60 (log ε 3.828) and 208.40 (log ε 3.664) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H, J=7.33, 14.70 Hz, –CH_3), 1.27 (m, 2H, –CH_2), 1.47 (m, 2H, –CH_2), 2.35 (s, 3H, Ar-CH_3), 2.51 (dd, 1H, J=8.45, 16.05 Hz, H-2′), 2.94 (dd, 1H, J=4.09, 16.08 Hz, H-2′), 4.03 (m, 2H, –OCH_2), 5.54 (dd, 1H, J=4.07, 8.34 Hz, H-3), 7.24 (t, 1H, J=2.38, 8.05 Hz, Ar-H), 7.42 (d, 2H, J=8.24 Hz, Ar-H), 7.49–7.58 (m, 4H, Ar-H), and 7.92 (d, 1H, J=7.74 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.63 (CH_3), 19.09 (–CH_2–), 21.02 (Ar-CH_3), 30.47 (–CH_2–), 37.76 (C-2′), 57.75 (C-3), 64.93 (O–CH_2), 122.55, 124.07, 124.26, 124.22, 129.89, 132.07, 132.15, 133.82, 135.88, 144.31, (Ar-C), 166.84 (CON) and 170.53 (–CO_2–). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.76; H, 6.87; N, 4.15. Found: C, 74.80; H, 6.65; N, 4.38.

5.2.3. *N*-*p*-methoxy phenyl-3-butyl isoindolin-1-one acetate 17. Colourless solid; mp 166–167 °C; IR: ν_{max} (CCl_4) 1734.9, 1706.9, 1549.7, 1514.0, 1249.8, 1217.0 and 1106.1 cm^{-1}; UV (EtOH): λ_{max} 234.60 (log ε 3.848) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (m, 3H, CH_3), 1.29 (m, 2H, –CH_2), 1.51 (m, 2H, –CH_2), 2.51 (dd, 1H, J=8.22, 16.03 Hz, H-2′), 2.89 (dd, 1H, J=4.39, 16.05 Hz, H-2′), 3.81 (s, 3H, ArOCH_3), 4.03 (m, 2H, –OCH_2), 5.47 (dd, 1H, J=4.35, 8.09 Hz, H-3), 6.97 (d, 2H, J=8.90 Hz, Ar-H), 7.40–7.58 (m, 5H, Ar-H) and 7.91 (d, 1H, J=7.20 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.62 (CH_3), 19.02 (–CH_2–), 30.45 (–CH_3–), 37.79 (C-2′), 55.50 (Ar-OCH_3), 58.17 (C-3), 64.92 (O–CH_2), 114.58, 122.53, 124.16, 126.05, 128.81, 129.18, 132.02, 132.08, 144.27, 157.90, (Ar-C), 166.94 (CON) and 170.49 (–CO_2–). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.38; H, 6.56; N, 3.96. Found: C, 71.60; H, 6.65; N, 4.28.

5.2.4. *N*-*p*-chlorophenyl-3-butyl isoindolin-1-one acetate 18. Light yellow liquid; IR: ν_{max} (CCl_4) 1732.9, 1711.7, 1550.7, 1494.7, 1373.2, 1253.6, 1217.0 and 1173.6 cm^{-1}; UV (EtOH): λ_{max} 258.20 (log ε 3.854), 226.40 (log ε 3.696) and 209.60 (log ε 3.684) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (m, 3H, CH_3), 1.29 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 2.51 (dd, 1H, J=8.24, 16.10 Hz, H-2′), 2.92 (dd, 1H, J=4.04, 16.10 Hz, H-2′), 5.56 (dd, 1H, J=3.98, 8.11 Hz, H-3), 7.41 (d, 2H, J=8.72 Hz, Ar-H), 7.50–7.61 (m, 5H, Ar-H), and 7.92 (d, 1H, J=7.19 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.62 (CH_3), 19.02 (CH_2), 30.54 (CH_2), 37.63 (C-2′), 57.46 (C-3), 65.06 (–O–CH_2), 122.57, 124.33, 124.85, 129.00, 129.39, 131.27, 131.63, 132.53, 135.10, 144.10 (Ar-C), 166.82 (CON) and 170.28 (–CO_2–). Anal. Calcd for $C_{20}H_{20}NO_3Cl$: C, 67.14; H, 5.63; N, 3.92. Found: C, 67.00; H, 5.75; N, 4.18.

5.2.5. *N*-*p*-methyl phenyl-3-ethyl isoindolin-1-one acetate 19. Colourless crystalline solid; mp 97–98 °C; IR: ν_{max} (KBr) 1728.1, 1682.8, 1515 and 1370.3 cm^{-1}; UV (EtOH): λ_{max} 247.80 (log ε 3.791) and 210.00 (log ε 3.642) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, 3H, J=7.20, 14.40 Hz, –CH_3), 2.36 (s, 3H, Ar-CH_3), 2.52 (dd, 1H, J=8.40, 16.41 Hz, H-2′), 2.92 (dd, 1H, J=4.0, 16.0 Hz, H-2′), 4.07 (dd, 2H, J=2.0, 7.20 Hz, –OCH_2), 5.30 (dd, 1H, J=4.00, 8.4 Hz, H-3), 7.23 (d, 2H, J=8.00 Hz, Ar-H), 7.41 (d, 2H, J=8.40 Hz, Ar-H), 7.49–7.59 (m, 3H, Ar-H), and 7.92 (d, 1H, J=6.80 Hz, Ar-H). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.78; H, 6.19; N, 4.53. Found: C, 74.00; H, 6.35; N, 4.78.

5.2.6. *N*-*p*-methoxy phenyl-3-ethyl isoindolin-1-one acetate 20. Light yellow liquid; IR: ν_{max} (CCl_4) 1735.8, 1707.8, 1548.7, 1513.1 and 1248.8 cm^{-1}; UV (EtOH): λ_{max} 243.80 (log ε 3.813) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, 3H, J=7.13, 14.28 Hz, CH_3), 2.50 (dd, 1H, J=8.20, 16.14 Hz, H-2′), 2.88 (dd, 1H, J=4.42, 16.04 Hz, H-2′), 3.81 (s, 3H, OCH_3), 4.07 (dd, 2H, J=2.08, 7.17 Hz, O–CH_2), 5.4 (dd, 1H, J=4.41, 8.08 Hz, H-3), 6.97 (d, 2H, J=8.96 Hz, Ar-H), 7.39–7.67 (m, 5H, Ar-H) and 7.91 (d, 1H, J=8.18 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.02 (–CH_3), 37.80 (C-2′), 55.50 (OCH_3), 58.16 (C-3), 60.97 (–OCH_2), 114.56, 122.54, 124.13, 126.06, 128.54, 128.80, 129.18, 132.06, 144.24, 157.89, (Ar-C), 166.92 (CON) and 170.35 (–CO_2–). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.15; H, 5.89; N, 4.31. Found: C, 70.30; H, 5.65; N, 4.38.

5.2.7. *N*-*p*-methyl phenyl-3-methyl isoindolin-1-one acetate 21. Light yellow liquid; IR: ν_{max} (CCl_4) 1739.7, 1707.8, 1550.7, 1515.9 and 1380.9 cm^{-1}; UV (EtOH): λ_{max} 245.80 (log ε 3.771) and 206.20 (log ε 3.631) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H, Ar-CH_3), 2.50 (dd, 1H, J=8.52, 16.06 Hz, H-2′), 2.92 (dd, 1H, J=4.1, 16.14 Hz, H-2′), 3.60 (s, 3H, OCH_3), 5.52 (dd, 1H, J=4.02, 8.4 Hz, H-3), 7.22 (d, 2H, J=8.9 Hz, Ar-H), 7.40 (d, 2H, J=8.16 Hz, Ar-H), 7.47–7.58 (m, 3H, Ar-H) and 7.91 (d, 1H, J=7.45 Hz, Ar-H). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.21; H, 5.80; N, 4.74. Found: C, 73.50; H, 5.65; N, 4.88.

5.2.8. *N*-*p*-methoxy phenyl-3-methyl isoindolin-1-one acetate 22. Light yellow liquid; IR: ν_{max} (CCl_4) 1740.6, 1707.8, 1550.7, 1514.0 cm^{-1}; UV (EtOH): λ_{max} 273.40 (log ε 3.674), 235.20 (log ε 3.742) and 206.00 (log ε 3.652) nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (dd, 1H, J=8.39, 16.09 Hz, H-2′), 2.91 (dd, 1H, J=4.46, 16.08 Hz, H-2′), 3.60 (s, 3H, –OCH_3), 3.81 (s, 3H, Ar-OCH_3), 5.48 (dd, 1H, J=4.42, 8.31 Hz, H-3), 6.95–7.67 (m, 7H, Ar-H), and 7.90 (d, 1H, J=7.40 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.69 (C-2′), 51.96 (C-3), 55.51 (Ar-O–C), 58.11 (O–CH_2), 114.59, 122.50, 124.19, 126.04, 128.86, 129.16, 131.96, 132.12, 144.21, 157.90 (Ar-C), 166.89 (CON) and 170.88 (–CO_2–). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.45; H, 5.50; N, 4.50. Found: C, 69.70; H, 5.65; N, 4.78.

5.2.9. *N*-*p*-phenyl benzamide 23. Colourless crystalline solid; mp 134–135 °C; IR: ν_{max} (KBr) 3273.3, 3013.6, 1653.8, 1641.3, 1618.2, 1598.9, 1598.9, 1488.0 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04–7.89 (m, 10H, Ar-H), 8.96 (br s, 1H, N–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.90, 124.46, 127.16, 128.13, 128.89, 129.72, 130.21, 136.04, 137.86, 139.05 (Ar-C), 168.28 (C=O). Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.28; H, 5.65; N, 7.38.

5.2.10. *N*-*p*-methyl phenyl benzamide 24. Colourless crystalline solid; mp 146–147 °C; IR: ν_{max} (KBr) 3307.7, 1648.1, 1597.9, 1513.1, 1500.0 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H, Ar-CH_3), 7.04–7.67 (m, 9H, Ar-H), 8.83 (br s, 1H, N–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.87 (Ar-CH_3), 119.97, 127.13, 128.04, 129.34, 130.05, 134.08, 135.31, 136.14, 139.06 (Ar-C), 168.15 (C=O). Anal. Calcd for $C_{14}H_{13}NO$: C, 79.20; H, 6.32; N, 6.75. Found: C, 79.46; H, 6.68; N, 6.88.

5.2.11. *N*-*p*-methoxy phenyl benzamide 25. Colourless crystalline solid; mp 166–167 °C; IR: ν_{max} (KBr) 3236.3, 1653.7, 1593.1, 1533.3, 1488.9, 1396.4, and 1321.1 cm^{-1}; UV (EtOH): λ_{max} 279.80 (log ε 3.115), 225.00 (log ε 3.198) and 203.40 (log ε 3.456) nm; ^1H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H, Ar-CH_3), 6.90 (d, 2H, J=8.91 Hz, Ar-H), 7.44–753 (m, 5H, Ar-H), 7.77 (br s, 1H, N–H) and 7.85 (d, 2H, J=7.18 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.40 (Ar-OCH_3), 121.77, 121.77, 127.23, 128.44, 129.88, 131.13, 132.13, 132.07, 136.18, 139.10 (Ar-C), 168.19 (CO). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.16. Found: C, 74.20; H, 5.65; N, 6.38.

5.3. Synthesis of *N*-substituted-1,2,3,4-tetrahydro-1-oxo isoquinoline-3-carboxylic acids

The mixture of *N*-substituted-3-alkyl isoindolin-1-one acetate **15**–**22** (200 mg) and NaOH (1.5 equiv) in MeOH (10 mL) was heated under refluxing condition for 1.5 h. After removal of solvent from the mixture, the residue was diluted with water (25 mL) and filtered. The filtrate upon neutralization with dilute HCl acid and extracted with chloroform (3×50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and crystallization from *n*-hexane/ethyl acetate to obtain a colourless solid compound **26**–**31** in good yield.

5.3.1. *N*-phenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 26. Compound **26** was prepared from **15**. Colourless solid; mp 184–185 °C; IR: ν_{max} (KBr) 1730, 1650, 1600, 1500 and 1420 cm^{-1}; UV (EtOH): λ_{max} 274.8 (log ε 4.01) and 228.6 (log ε 4.12) nm; ^1H NMR (400 MHz, d_6-DMSO): 2.60 (dd, 1H, J=8.00, 16.00 Hz, H-4 ax), 2.92 (dd, 1H, J=4.00, 16.00 Hz, H-4 eq), 5.72 (dd, 1H, J=4, 8 Hz, H-3), 7.16–8.12 (m, 9H, Ar-H) and 12.40 (br s, 1H, CO_2H); ^{13}C NMR (100 MHz, d_6-DMSO): 36.82 (C-4), 57.91 (C-3), 123.79, 124.08, 124.76, 126.32, 129.42, 129.79, 132.55, 133.13, 137.50, 145.57 (Ar-C), 167.01, (CON) and 171.82 (CO_2H). Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.77; H, 5.03; N, 5.36.

5.3.2. *N*-*p*-methyl phenyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 27. Compound **27** was prepared from **16**, **19** and **21** utilizing the above procedure. Colourless needles; mp 193–194 °C; IR: ν_{max} (KBr) 1718.5, 1651.9, 1617.2, 1603.7, 1516.9, 1427.2 and 1404.1 cm^{-1}; UV (EtOH): λ_{max} 257.20 (log ε 3.747), 240.00 (log ε 3.719) and 205.80 (log ε 3.574) nm; ^1H NMR (400 MHz, d_6-DMSO): δ 2.32 (s, 3H, Ar-CH_3), 2.55 (dd, 1H, J=7.30, 16.33 Hz, H-4 ax), 2.88 (dd, 1H, J=3.77, 16.34 Hz, H-4 eq), 5.61 (dd, 1H, J=3.71, 7.08 Hz, H-3) and 7.24–7.77 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 20.58 (Ar-CH_3), 36.08 (C-4) 57.23 (C-3), 122.90, 123.14, 124.03, 128.52, 129.40, 131.79, 132.13, 134.06, 134.83, 144.72 (Ar-C), 166.10 (CON) and 170.95 (CO_2H). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38; N, 4.9. Found: C, 72.59; H, 5.63; N, 5.26.

5.3.3. *N*-*p*-methoxy phenyl-1,2,3,4-tetrahydro-1-oxo-isoquinoline-3-carboxylic acid 28. Compound **28** was prepared from **17**, **20** and **22** following the above procedure. It was also prepared by hydrolysis with 1 M H_2SO_4 (4 equiv) in H_2O. Colourless crystalline solid; mp 216–217 °C; IR: ν_{max} (KBr) 1718.5, 1653.8, 1517.9, 1419.5 and 1402 cm^{-1}; UV (EtOH): λ_{max} 280.60 (log ε 3.033), 275.00 (log ε 3.027), 226.80 (log ε 3.264) and 204.80 (log ε 3.536) nm; ^1H NMR (400 MHz, d_6-DMSO): δ 2.54 (dd, 1H, J=7.20, 16.42 Hz, H-4 ax), 2.85 (dd, 1H, J=3.98, 16.38 Hz, H-4 eq), 3.78 (s, 3H, $ArOCH_3$), 5.56 (dd, 1H, J=3.99, 6.87 Hz, H-3), 7.01 (d, 2H, J=8.78 Hz, Ar-H) and 7.43–7.76 (m, 6H, Ar-H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 36.23 (C-4) 55.29 (OCH_3), 57.69 (C-3), 114.17, 122.90, 123.08, 126.15, 128.49, 129.35, 131.81, 132.02, 144.77, 157.18, (Ar-C), 166.12 (CON) and 171.03 (CO_2H). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.35; H, 5.25; N, 4.69.

5.3.4. *N*-*p*-chlorophenyl-1,2,3,4-tetrahydro-1-oxo-isoquinoline-3-carboxylic acid 29. Compound **29** was prepared from **18** by following the above procedure. Light yellow solid; mp 183–184 °C; IR: ν_{max} (KBr) 1724.2, 1664.5, 1617.2, 1595.0, 1496.2, 1470.6 and 1390.6 cm^{-1}; UV (EtOH): λ_{max} 274.40 (log ε 3.553), 231.00 (log ε 3.556) and 208.00 (log ε 3.598) nm; ^1H NMR (400 MHz, d_6-DMSO): δ 2.61 (dd, 1H, J=6.96, 16.32 Hz, H-4 ax), 2.91 (dd, 1H, J=3.71, 16.34 Hz, H-4 eq), 5.69 (dd, 1H, J=3.74, 6.56 Hz, H-3), and 7.51–7.79 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 35.97 (C-4), 57.13 (C-3), 122.97, 123.29, 125.46, 128.62, 128.87, 129.52, 131.41, 132.45, 135.64, 144.67 (Ar-C) 166.27 (CON) and 170.86 (CO_2H). Anal. Calcd for $C_{16}H_{12}ClNO_3$: C, 63.69; H, 4.01; N, 4.64. Found: C, 63.52; H, 4.27; N, 4.70.

5.3.5. *N*-methyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 30. Bis(triphenyl phosphine) palladium(II) chloride (0.047 g, 3.5 mol%), triethyl amine (0.77 g, 4 equiv) and butyl acrylate **11** (0.74 g, 3 equiv) were added to the solution of 2-iodo-*N*-methyl benzamide **10** (0.50 g, 1.915 mmol) in DMF (10 mL) by following the procedure described above for the compound **15** and then hydrolysis with NaOH (1.5 equiv) in MeOH by following the procedure described above for the compound **26**. After usual work-up, it was crystallized from *n*-hexane/ethyl-acetate, light yellow solid compound **30** was obtained; mp 165–166 °C; IR: ν_{max} (KBr): 1700, 1660, 1450 and 1400 cm^{-1}; UV: λ_{max} (EtOH): 279.2 (log ε 3.24) and 239.8 (log ε 3.82) nm; ^1H NMR (400 MHz, d_6-DMSO): 2.71 (dd, 1H, J=8.00, 16.30 Hz, H-4 ax), 2.87 (dd, 1H, J=4.20, 16.00 Hz, H-4 eq), 3.13 (s, 3H, N–CH_3), 4.83 (dd, 1H, J=4, 8.00 Hz, H-3) and 7.53–7.73 (m, 4H, Ar-H). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.37; H, 5.40; N, 6.83. Found: C, 64.05; H, 5.44; N, 6.88.

5.3.6. *N*-*p*-chlorobenzyl-1,2,3,4-tetrahydro-1-oxoisoquinoline-3-carboxylic acid 31. Compound **31** was prepared from 2-iodo-*N*-*p*-chlorobenzyl benzamide **6** and

butyl acrylate **11** by following the above procedure. After usual work-up, it was crystallized from the mixture of *n*-hexane and ethyl acetate to obtain a colourless solid compound **31**; mp 163–164 °C; IR: ν_{max} (KBr) 1721.3, 1648.1, 1618.2, 1497, 1440.7, 1420.5, and 1409.9 cm^{-1}; UV (EtOH): λ_{max} 223.60 (log ε 3.522) and 206.20 (log ε 3.630) nm; ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.68 (dd, 1H, J=6.87, 16.42 Hz, H-4 ax), 2.97 (dd, 1H, J=4.86, 16.43 Hz, H-4 eq), 4.46 (d, 1H, J=15.69 Hz, NCH_2), 4.74 (dd, 1H, J=6.01, 11.49 Hz, H-3), 5.01 (d, 1H, J=15.69 Hz, –NCH_2) and 7.28–7.738 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, d_6-DMSO): δ 20.59 (N–CH_2), 36.08 (C-4), 57.24 (C-3), 122.90, 123.15, 124.04, 128.52, 129.41, 131.80, 132.14, 134.07, 134.83, 144.72 (Ar-C), 166.11 (CON) and 170.98 (CO_2H). Anal. Calcd for $C_{17}H_{14}NO_3Cl$: C, 64.67; H, 4.46; N, 4.43. Found: C, 64.45; H, 4.44; N, 4.58.

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Electron transfer-initiated asymmetric photocyclization of chiral auxiliary-substituted *N*-acyl-α-dehydro(1-naphthyl)alaninamides to the corresponding 3,4-dihydrobenzo[*f*]quinolinone derivatives

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Received 25 July 2005; accepted 5 September 2005

Available online 5 October 2005

Abstract—Photoinduced electron transfer reactions of the title *N*-acyl-α-dehydronaphthylalaninamides [(*Z*)-**1**] with (*S*)-1-phenylethylamino and (*S*)-alaninamide auxiliary groups in methanol containing a tertiary amine were shown to form (*R*,*S*)- and (*S*,*S*)-3,4-dihydrobenzo[*f*]quinolinone derivatives (**2**) in excess at rt, respectively. The magnitude of diastereomeric excess (de) was varied in the range of −5–26% for (*R*,*S*)-**2** and 16–92% for (*S*,*S*)-**2**, depending on the chiral auxiliary and reaction temperature. The mechanism of asymmetric induction in the photocyclization process eventually affording diastereomeric **2** was discussed based on solvent, tertiary amine, chiral auxiliary and temperature effects on the de value as well as on MM2 and PM5 calculations for the diastereomeric enol intermediates.

1. Introduction

Organic photochemistry has continued to contribute to the development of efficient and selective transformations for the preparation of complicated molecules, which could not have been synthesized by conventional methods.[1] While modern synthetic methods have also contributed to the enhancement of enantio- and diastereoselectivities in many asymmetric photoreactions,[2–5] there have been only a few enantio- and diastereodifferentiating photochemical reactions of synthetic utilities, particularly in liquid phase. Much attention has recently been devoted to developing novel photoinduced electron transfer reactions of aromatic olefins having a conjugated C=C double bond in a given molecule, owing to the fact that many of these reactions enable the efficient construction of various heterocyclic rings.[6] In the course of our systematic study regarding photoinduced electron transfer reactions of *N*-acyl-α-dehydronaphthylalanine derivatives, we found that electron transfer-initiated photocyclizations of these naphthyl-substituted α-dehydroamino acids in methanol give racemic 3,4-dihydrobenzo[*f*]quinolinones with an excellent degree of selectivity.[7] This finding stimulated us to incorporate a chiral auxiliary into the starting α-dehydronaphthylalanine derivative and to develop a novel asymmetric photocyclization enabling the construction of the chiral dihydrobenzoquinolinone ring, which is strongly expected to exhibit pharmacological and physiological activities.[8] As described in the previous paper,[9] the presence of an (*S*)-alanine methyl ester auxiliary induced the asymmetric photocyclization to the (*S*,*S*)-dihydrobenzoquinolinone derivative, which proceeded in a moderate diastereoselectivity. Analysis of solvent and tertiary amine effects on the magnitude of diastereomeric excess (de) revealed the essential role of hydrogen bonding and electrostatic interactions between a given enol intermediate and a tertiary amine in the observed asymmetric photocyclization. Our previous finding suggests that the de value strongly depends upon the structure and conformation of a chiral auxiliary group incorporated and, hence, the effect of this group on the diastereodifferentiating ability may shed much more light on the mechanism of the novel asymmetric photocyclization eventually giving diastereomeric 3,4-dihydrobenzo[*f*]quinolinone derivatives. In order to obtain further mechanistic information regarding the electron transfer-initiated asymmetric photocyclization of *N*-acyl-α-dehydronaphthylalaninamides found by us, we designed and synthesized (*Z*)-*N*-acyl-α-dehydro(1-naphthyl)alaninamide derivatives [(*Z*)-**1a**–**h**] bearing (*S*)-1-phenylethylamino (**1a**,**b**), (*S*)-alaninalkylamide (**1c**–**e**) and (*S*)-alaninarylamide (**1f**–**h**) auxiliary groups and investigated the effects of chiral auxiliary, solvent, tertiary amine and temperature on the magnitude of de in more detail.

Keywords: Amino acids and derivatives; Photochemistry; Electron transfer; Asymmetric cyclization; Dihydrobenzoquinolinones.
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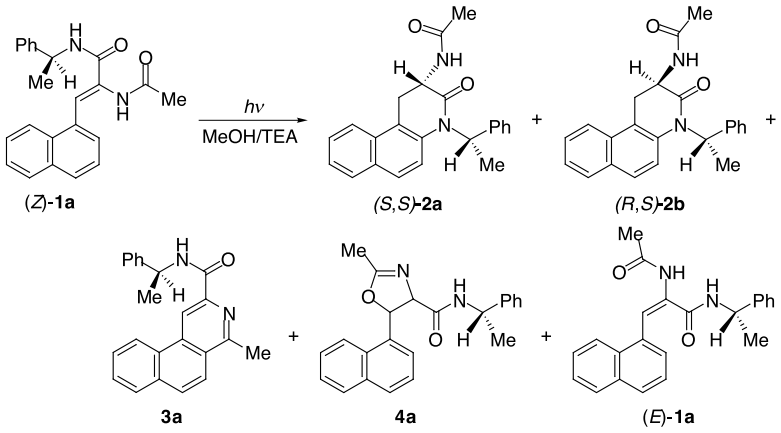
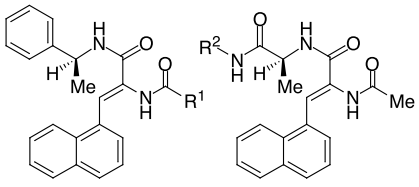
doi:10.1016/j.tet.2005.09.042



Scheme 1.



R^1 = Me (**1a**), Ph (**1b**)
R^2 = Me (**1c**), H (**1d**), *t*-Bu (**1e**), Ph (**1f**), 4-$MeOC_6H_4$ (**1g**), 4-CNC_6H_4 (**1h**)

2. Results and discussion

The starting (*Z*)-α-dehydroalaninamides [(*Z*)-**1a**–**h**] were prepared in good yields by the ring-opening reactions of (*Z*)-1-naphthyl-substituted oxazolones with (*S*)-1-phenylethylamine (**1a**,**b**) and (*S*)-alaninamide derivatives (**1c**–**h**).[10]

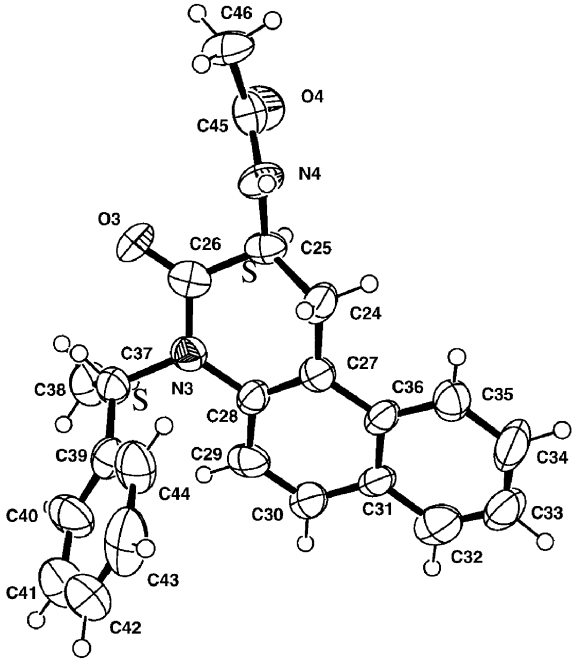


Figure 1. ORTEP drawing of (*S*,*S*)-**2a**.

After a nitrogen-saturated methanol solution of (*Z*)-**1a** (3.75×10^{-3} mol dm^{-3}) containing TEA (0.10 mol dm^{-3}) was irradiated with Pyrex-filtered light (>280 nm) from a 400 W high-pressure Hg lamp for 70 min at room temperature (rt), the product mixture obtained was subjected to column chromatography over silica gel, which allowed us to isolate (*E*)-**1a** (5%), a diastereomeric mixture of (*S*,*S*)-**2a** and (*R*,*S*)-**2a** (30%) and benzo[*f*]isoquinoline derivative (**3a**) (24%) at the 81% conversion of **1a** (Scheme 1). Though there was a detectable amount of *cis*-4,5-dihydrooxazole derivative (**4a**) in this reaction mixture (^{1}H NMR spectral analysis), no attempt was made to isolate the minor product. The structures of isolated products were determined based on their spectroscopic and physical properties and were confirmed by the ^{1}H–^{1}H and ^{13}C–^{1}H COSY spectra of these products. The same product distribution was obtained also by the 70 min irradiation of (*Z*)-**1c** (3.75×10^{-3} mol dm^{-3}, conversion: 86%): (*E*)-**1c** (5%), diastereomeric mixtures of **2c** (38%) and **3c** (18%) were isolated by usual workup of the **1c**-derived reaction mixture. The very low ^{1}H NMR yield of **4c** (1%) made its isolation virtually impossible. Similar results were obtained with (*Z*)-**1b** and (*Z*)-**1d**–**h**, which were irradiated under the same conditions. The diastereomeric mixture of (*S*,*S*)-**2** and (*R*,*S*)-**2** could be separated by repeated preparative TLC (silica gel). From a ^{1}H NMR

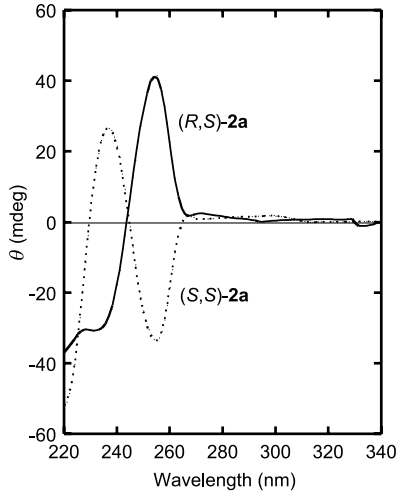


Figure 2. Circular dichroism spectra of (*S*,*S*)-**2a** and (*R*,*S*)-**2a** (4.0×10^{-5} mol dm^{-3}) in MeOH at room temperature.

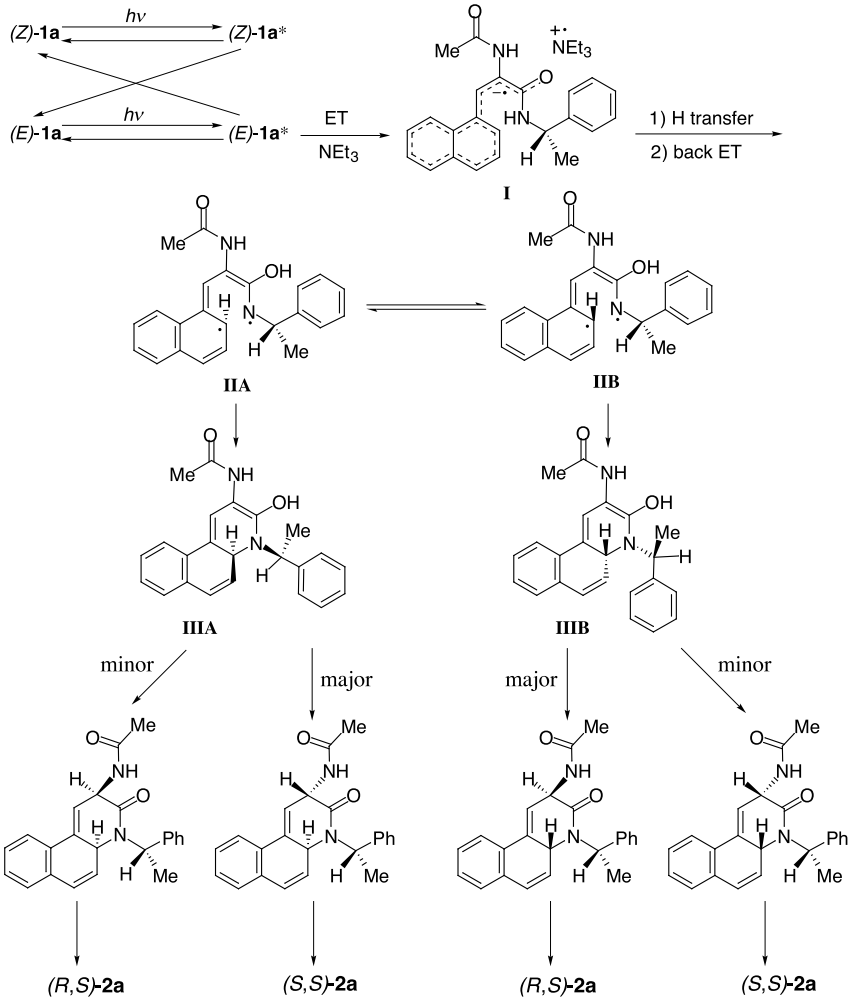
spectral analysis of each diastereomer of **2** we see that the methine proton signals in the chiral auxiliary of each diastereomer (**2a**–**g**) and the dihydroquinolinone-ring proton signals at the 3-position for **2h**-derived diastereomers are detected at different positions (for example, 6.05 and 6.30 ppm for **2a**; 5.04 and 5.43 ppm for **2b**; 4.65 and 4.73 ppm for **2h**). An X-ray structural analysis of single crystal derived from the diastereomer of **2a** (showing its methine proton signal at 6.05 ppm) established that the asymmetric carbon in the dihydroquinolinone ring has the (*S*)-configuration (Fig. 1). Furthermore, a comparison of the circular dichroism (CD) spectra of (*S*,*S*)-**2a** and (*R*,*S*)-**2a** confirmed that the dihydroquinolinone ring having (*S*)- and (*R*)-configurations gives CD bands of negative and positive signs at 250 nm, respectively (Fig. 2). Thus, the absolute configuration of the asymmetric carbon in the ring can be definitely determined by the ^{1}H NMR and CD spectral analysis and, additionally, the area ratio of the methine or the quinolinone-ring proton signals for given diastereomers allows us to estimate the magnitude of de.

In Table 1 are summarized conversion of (*Z*)-**1a**,**b**, selectivity for **2a**,**b**, % de and configuration of a major diastereomer, obtained after the 1 h irradiation made under several reaction conditions. As already described in the previous study,[9] the electron transfer-initiated photocyclization of (*Z*)-**1** with an (*S*)-alanine methyl ester auxiliary group in methanol–acetonitrile preferentially gave the corresponding (*S*,*S*)-3,4-dihydrobenzo[*f*]quinolinone derivative, the de value of which was varied from 0 to 55% depending on the properties of tertiary amine and solvent employed without undergoing temperature effects. Based on this finding it was suggested that the hydrogen bonding/electrostatic interaction between the amine and the enol intermediate is a major factor for governing the magnitude of de. However, analysis of the data given in Table 1 demonstrates that *N*-acyl substituent, steric bulkiness about the tertiary amino nitrogen and solvent property (e.g., hydrogen-bonding solvation ability) exert only very small effects on the de value. These results form a striking contrast to those obtained for (*Z*)-**1** having an (*S*)-alanine methyl ester auxiliary and, hence, suggest that the hydrogen bonding/electrostatic interaction described above makes a negligible contribution to the asymmetric induction observed in the photocyclization process of (*Z*)-**1a**,**b**. It is very likely that a mechanism by which the asymmetric photocyclization of (*Z*)-**1** proceeds is strongly dependent on the structure of chiral auxiliary introduced. Further inspection of Table 1 provides us an intriguing information that on lowering temperature the de value for (*R*,*S*)-**2a** is decreased and then the diastereomer formed in excess is changed to (*S*,*S*)-**2a** at −78 °C. In order to explain the reason why de for (*R*,*S*)-**2a** is changed depending on temperature, we accept the reaction pathway previously suggested for formation of **2** as shown in Scheme 2 and discuss the temperature dependence of this de.[7,9] The observation that tertiary amine and solvent exert negligible effects on the de value suggests that relative rate for tautomerization in **IIIA** and **IIIB** is nearly equal to unity and also influenced by temperature to only a small extent[9] and then this temperature dependence is not a major factor that determines the magnitude of de. In addition, interconversions of **IIIA** and **IIIB** and of the **III**-derived tautomerized intermediates are unlikely to take place during the asymmetric cyclization, and hence we were led to assume that the relative composition of **IIIA** (or **IIIB**) plays a pivotal role in determining the magnitude of de. Taking into account that conformations of the biradicals **IIA** and **IIB** as precursors of **IIIA** and **IIIB** can be approximated by those of the corresponding latter intermediates,[11] we interpret the temperature dependence of de for (*R*,*S*)-**2a** in terms of a preequilibrium between the former intermediates as demonstrated in Scheme 2. In other words, the relative composition of **IIA** (or **IIB**), which must be formed via hydrogen transfer and the subsequent back electron transfer within the ion radical pair **I**, is nearly equal to that of **IIIA** (or **IIIB**) and steric repulsion between the hydrogen at the 2-position on the naphthalene ring of **III** and the methyl hydrogens in the chiral auxiliary may control the configuration of major diastereomer formed. Because it is significant to understand the temperature dependence of the composition of **IIIA** relative to **IIIB**, we attempted to generate all conformations of low energies by using MM2 calculations and to determine the energy-minimized conformations of **IIIA** and **IIIB** based on their heats of formation (ΔH_f) estimated by PM5 calculations. Close inspection of these two conformations depicted in Figure 3 confirms that both the ring hydrogen at the 2-position and

Table 1. Substituent, solvent, tertiary amine and temperature effects on the conversion of (*Z*)-**1**, selectivity of **2** and de for **2**, obtained by the 1 h irradiation of (*Z*)-**1** with an (*S*)-1-phenylethylamino auxiliary group (3.75×10^{-3} mol dm^{-3})

(*Z*)-**1**	Solvent	Amine	Temperature (°C)	Conversion (%)[a]	Selectivity (%)[b]	de (%)	Major diastereomer
1a	MeOH	TEA	rt	63	46	17	(*R*,*S*)-**2a**
1a	MeOH	TMA[c]	rt	71	44	20	(*R*,*S*)-**2a**
1a	MeOH	MP[d]	rt	53	44	20	(*R*,*S*)-**2a**
1a	MeOH	PEP[e]	rt	48	59	15	(*R*,*S*)-**2a**
1b	MeOH	TEA	rt	29	39	18	(*R*,*S*)-**2b**
1a	MeOH–MeCN (1/9 v/v)	TEA	rt	20	21	14	(*R*,*S*)-**2a**
1a	MeOH	TEA	50	36	31	26	(*R*,*S*)-**2a**
1a	MeOH	TEA	−78	73	83	5	(*S*,*S*)-**2a**

[a] Estimated by subtracting the sum of the composition of (*Z*)-**1** and (*E*)-**1** from 100.
[b] Evaluated by dividing the composition of **2** by the sum of the composition of **2**, **3**, and **4**. Because the photocyclization of (*Z*)-**1** proceeds without accompanying any side reactions, this selectivity value can be regarded as ^{1}H NMR yield of the corresponding dihydrobenzoquinolinone derivative.
[c] Trimethylamine.
[d] 1-Methylpiperidine.
[e] *N*-Isopropyl-*N*-ethylisopropylamine.

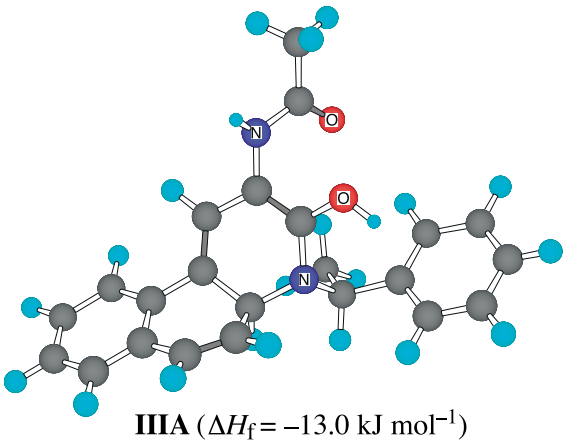


Scheme 2.

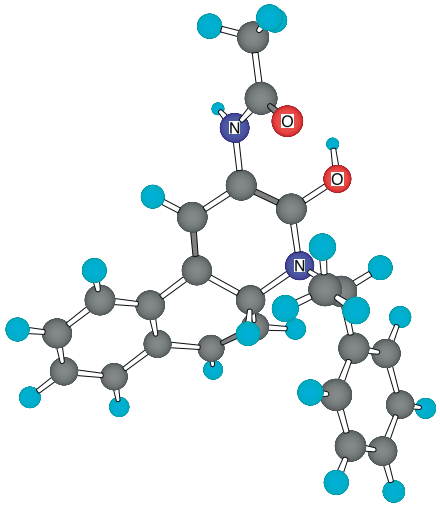
the auxiliary-group methyl hydrogens are situated in the *si* face for **IIIA** ($\Delta H_f = -13.0$ kJ mol^{-1}) and in the *re* face for **IIIB** ($\Delta H_f = -9.3$ kJ mol^{-1}). Then a comparison of these ΔH_f values shows that the former stereoisomer is thermodynamically more stable than the latter isomer. Because tautomerization in the enol intermediate **IIIB** preferentially takes place from the *si* face to afford (*R*,*S*)-**2a** as a major diastereomer owing to the above-mentioned steric repulsion (Scheme 2), the finding that this diastereomer is obtained in 15–20% de at rt (25 ± 2 °C) substantiates the shift of a given preequilibrium to the **IIB** side. In addition, on lowering temperature the equilibrium should be shifted to the more stable intermediate **IIA**, so that it is possible to enhance de for (*S*,*S*)-**2a** as observed. In this connection, it was found that energy-minimized conformations of the (*S*)-alanine methyl ester auxiliary-substituted intermediates with structures corresponding to those of **IIIA** and **IIIB** give virtually the same ΔH_f values (-462.4 vs -462.7 kJ mol^{-1}). This finding is consistent with the temperature-independent de value for the system studied previously,[9] thus providing additional evidence for the preequilibrium between **IIA** and **IIB**.

On the other hand, there is another pathway of **III** to **2**: the hydrogen shift in **III** (re-aromatization) takes place at first to give the intermediate **IV** depicted in Figure 4, the tautomerization of which forms **2** as the thermodynamically more stable product. The energy-minimized conformation of **IV** with a given chiral auxiliary group in the *si* face demonstrates that on account of the steric hindrance caused by this group the tautomerization occurs preferentially from the *re* face to generate (*S*,*S*)-**2a**, being inconsistent with the result obtained. These considerations, therefore, led us to conclude that the tautomerization of the enol intermediate **III** takes place prior to its re-aromatization, as shown in Scheme 2.

Our attention is now given to the electron transfer-initiated asymmetric photocyclization of (*Z*)-**1c**–**h** bearing an (*S*)-alaninamide auxiliary group. We have already stated that the irradiation of (*S*)-alanine methyl ester auxiliary-substituted (*Z*)-**1** in the presence of TEA results in a preferential formation of the corresponding dihydrobenzoquinolinone derivative with the (*S*,*S*)-configuration and also de for this diastereomer is fairly sensitive to both tertiary amine and solvent.[9] As can be seen from Table 2, which summarized experimental data for (*Z*)-**1c**–**h**, reaction temperature exerts a great effect on the extent of de whereas its value undergoes only a slight change depending on tertiary amine and solvent examined. Because these results correspond well to those obtained for (*Z*)-**1a**,**b**, the relative compositions of diastereomeric biradical and cyclized enol

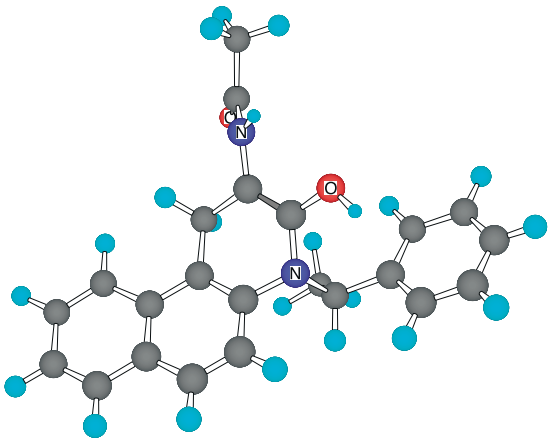


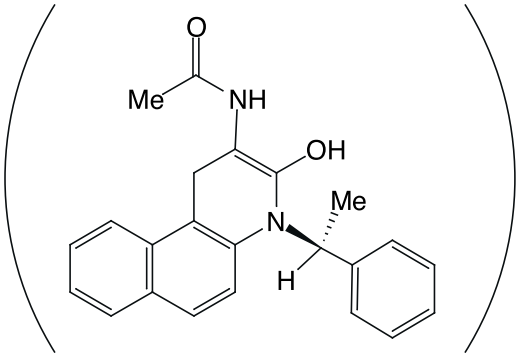
IIIA ($\Delta H_f = -13.0$ kJ mol^{-1})



IIIB ($\Delta H_f = -9.3$ kJ mol^{-1})

Figure 3. Energy-minimized conformations and heats of formation for **IIIA** and **IIIB**.





IV

Figure 4. Energy-minimized conformation of **IV**.

intermediates (see **II** and **III** in Scheme 2), as well as stereoelectronic interactions in the latter intermediate, are considered to play central roles in inducing asymmetric photocyclizations of (*Z*)-**1c** and related derivatives. In order to discuss temperature and substituent (chiral auxiliary) effects on the de value estimated in the presence of TEA, energy-minimized conformations for the (*Z*)-**1c**-derived

Table 2. Substituent, solvent, tertiary amine and temperature effects on the conversion of (*Z*)-**1**, selectivity of **2** and diastereomeric excess for **2**, obtained by the 1 h irradiation of (*Z*)-**1** with an (*S*)-alaninamide auxiliary group (3.75×10^{-3} mol dm^{-3})

(*Z*)-**1**	Solvent	Amine	Temperature (°C)	Conversion (%)[a]	Selectivity (%)[b]	de (%)	Major diastereomer
1c	MeOH	TEA	50	31	41	16	(*S*,*S*)-**2c**
1c	MeOH	TEA	rt	40	71	34	(*S*,*S*)-**2c**
1c	MeOH	TEA	−78	65	95	72	(*S*,*S*)-**2c**
1c	MeOH	MP[c]	rt	36	71	40	(*S*,*S*)-**2c**
1c	MeOH	PEP[d]	rt	39	73	34	(*S*,*S*)-**2c**
1c	MeOH–MeCN (1/9 v/v)	TEA	rt	13	18	32	(*S*,*S*)-**2c**
1d	MeOH	TEA	rt	43	68	38	(*S*,*S*)-**2d**
1d	MeOH	TEA	−78	55	87	68	(*S*,*S*)-**2d**
1e	MeOH	TEA	rt	29	41	33	(*S*,*S*)-**2e**
1e	MeOH	TEA	−78	37	95	66	(*S*,*S*)-**2e**
1f	MeOH	TEA	rt	32	54	52	(*S*,*S*)-**2f**
1f	MeOH	TEA	−78	39	94	80	(*S*,*S*)-**2f**
1g	MeOH	TEA	rt	31	53	57	(*S*,*S*)-**2g**
1g	MeOH	TEA	−78	38	95	76	(*S*,*S*)-**2g**
1h	MeOH	TEA	rt	30	67	70	(*S*,*S*)-**2h**
1h	MeOH	TEA	−78	42	97	92	(*S*,*S*)-**2h**

[a] Estimated by subtracting the sum of the composition of (*Z*)-**1** and (*E*)-**1** from 100.
[b] Evaluated by dividing the composition of **2** by the sum of the composition of **2**, **3**, and **4**. Because the photocyclization of (*Z*)-**1** proceeds without accompanying any side reactions, this selectivity value can be regarded as ^{1}H NMR yield of the corresponding dihydrobenzoquinolinone derivative.
[c] 1-Methylpiperidine.
[d] *N*-Isopropyl-*N*-ethylisopropylamine.

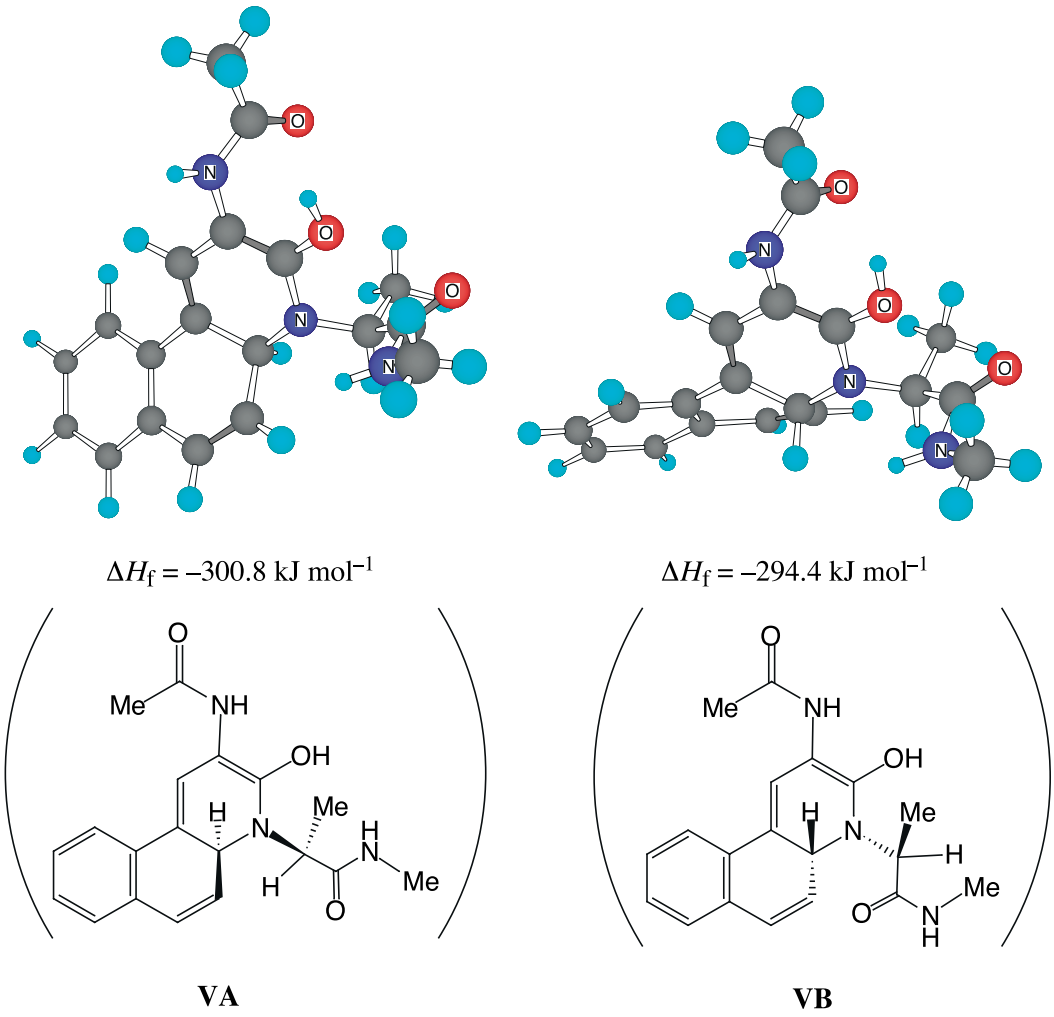
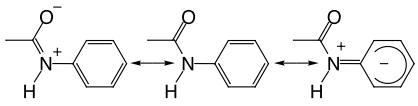


Figure 5. Energy-minimized conformations and heats of formation for **VA** and **VB**.

enol intermediates **VA** and **VB** were similarly determined along with their heats of formation based on MM2 and PM5 calculations (Fig. 5). Intriguing findings are that the methyl hydrogens in chiral auxiliary groups of the stereoisomers **VA** and **VB** are both situated in the *si* face and then the former stereoisomer is thermodynamically more stable than the latter by 6.4 kJ mol^{-1}. It is thus very likely that steric repulsion between these methyl hydrogens/the ring hydrogen at the 2-position and the enol hydroxy hydrogen particularly accelerates the tautomerization (that proceeds from the *re* face in **VA**) to eventually give (*S*,*S*)-**2c** in a moderate de. In addition, the finding that **VA** is a more stable intermediate than **VB** provides a good explanation for the de value for this diastereomer, which is increased as temperature is lowered, as already discussed based on the temperature-dependent de of (*R*,*S*)-**2a** or (*S*,*S*)-**2a**. In closing, we should discuss substituent effects on the de value for (*S*,*S*)-**2** (Table 2). Comparison of the data obtained for (*S*,*S*)-**2a**–**c** reveals that an increase in the steric bulkiness of *N*′-alkyl substituent (R: H→Me→*t*-Bu) has a negligible effect on the extent of the observed asymmetric induction at rt and −78 °C. Thus, the observation that replacement of methyl (**2a**) by phenyl (**2f**) as the substituent *R* increases de by 18% at rt confirms that the magnitude of de is influenced by an electronic factor of this substituent but not by its steric factor. Interestingly, the introduction of a 4-cyanophenyl group into the chiral alaninamide moiety enabled the progress of highly diastereoselective photocyclization of (*Z*)-**1h** to (*S*,*S*)-**2h** (de=92%). If we take into account the possibility of intramolecular hydrogen bonding between the enol hydroxy hydrogen and the chiral auxiliary-group amide carbonyl oxygen in the intermediate **V**, as well as the amide resonance forms shown in Scheme 3, the role of the 4-cyanophenyl substituent is considered to weaken this hydrogen bonding to a much greater extent than does the phenyl one. The weakened hydrogen bonding may contribute to accelerating proton transfer (tautomerization) from the *re* face of **V** and, hence, enhancing de for (*S*,*S*)-**2** as observed.



Scheme 3.

3. Conclusions

It was found that the irradiation of *N*-acyl-α-dehydronaphthylalaninamides having (*S*)-1-phenylethylamino and (*S*)-alaninamide auxiliaries in methanol containing tertiary

amine preferentially gives (*R*,*S*)- and (*S*,*S*)-dihydrobenzoquinolinones at rt, respectively. While amine base and solvent exerted their negligible effects on de, the drop in temperature resulted in a substantial increase in its value for the (*S*,*S*)-diastereomer in any cases. The introduction of a 4-cyanophenyl-substituted (*S*)-alaninamide auxiliary enhanced de for this diastereomer up to 92%. Analyses of tertiary amine, solvent, substituent (chiral auxiliary) and temperature effects on the magnitude of de substantiated the participation of a preequilibrium between the diastereomeric enol-type biradical intermediates, the relative composition of which may be a dominating factor of de. A molecular modeling study for the diastereomeric cyclized enol intermediates led us to propose that steric repulsion between the enol hydroxy hydrogen and the methyl hydrogens or hydrogen attached to the asymmetric carbon should also play a central role in generating either of given diastereomers in excess.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR and IR spectra were taken with a JEOL JNM-A500 spectrometer and a Shimadzu IRPrestige-21 infrared spectrophotometer, respectively. Chemical shifts were determined using tetramethylsilane as an internal standard. UV absorption spectra were recorded on a Hitachi U-3300 spectrophotometer. A cell with a 10 mm pathlength was used. Circular dichroism spectra were recorded on a Nihonbunko J-600 spectropolarimeter. Optical rotations were measured on a Nihonbunko P-1020 polarimeter. Elemental analyses were performed on a Perkin-Elmer PE2400 series II CHNS/O analyzer. MeOH and MeCN were purified according to the standard procedures and freshly distilled prior to use. TEA was fractionally distilled from sodium hydroxide. All other reagents used were obtained from commercial sources and were of the highest grade available. MM2 and PM5 calculations were accomplished by using CAChe 5.0 for Windows available from Fujitsu Ltd, 2002.

4.2. General procedure for the synthesis of (*S*)-*N*-benzyloxycarbonyl-*N*′-(alkyl- or aryl-substituted) alaninamides

Aliphatic or aromatic primary amine (0.016 mol) was added to a $CHCl_3$ solution (15 mL) of (*S*)-*N*-benzyloxycarbonylalanine succinimido ester (0.016 mol) and the resulting mixture was stirred for 1 h at rt. After removal of the solvent under reduced pressure, water (100 mL) was added to the residue and the solid separated out was collected by filtration with suction and washed with water and then dry hexane to give colorless powder or syrup (90–95%).

4.2.1. (*S*)-*N*-Benzyloxycarbonyl-*N*′-methylalaninamide. Mp 114.0–115.0 °C. IR (KBr): 3300, 1686, 1651 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.37 (3H, d, J=6.9 Hz), 2.8 (3H, d, J=4.8 Hz), 4.21 (1H, dq, J=6.8, 6.9 Hz), 5.08 (1H, d, J=12.4 Hz), 5.12 (1H, d, J=12.4 Hz), 5.38 (1H, br s), 6.17 (1H, br s), 7.31–7.37 (5H, m).

4.2.2. (*S*)-*N*-Benzyloxycarbonyl-*N*′-(*tert*-butyl)alaninamide. Syrup. IR (KBr): 3319, 1724, 1659 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.32 (9H, s), 1.34 (3H, d, J=6.9 Hz), 4.13 (1H, dq, J=6.9, 6.9 Hz), 5.10 (1H, s), 5.46 (1H, d, J=6.9 Hz), 5.92 (1H, s), 7.29–7.37 (5H, m).

4.2.3. (*S*)-*N*-Benzyloxycarbonyl-*N*′-phenylalaninamide. Mp 154.5–156.0 °C. IR (KBr): 3296, 1686, 1660 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (3H, d, J=6.9 Hz), 3.78 (3H, s), 4.39 (1H, br s), 5.10 (1H, d, J=11.7 Hz), 5.14 (1H, d, J=11.7 Hz), 5.45 (1H, br s), 6.82 (2H, d, J=8.9 Hz), 7.31–7.34 (5H, m), 7.37 (2H, d, J=8.9 Hz), 8.15 (1H, s).

4.2.4. (*S*)-*N*-Benzyloxycarbonyl-*N*′-(4-methoxyphenyl) alaninamide. Mp 161.5–162.5 °C. IR (KBr): 3327, 1688, 1678 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 (3H, d, J=6.9 Hz), 4.39 (1H, dq, J=5.5, 6.9 Hz), 5.14 (1H, d, J=12.3 Hz), 5.17 (1H, d, J=12.3 Hz), 5.25 (1H, br s), 7.32–7.38 (5H, m), 7.55–7.59 (4H, m), 8.77 (1H, s).

4.3. Procedure for the synthesis of (*S*)-*N*-benzyloxycarbonyl-*N*′-(4-cyanophenyl)alaninamide

(*S*)-*N*-Benzyloxycarbonylalanine succinimido ester (0.016 mol) and 4-cyanoaniline (0.016 mol) was dissolved in 1,4-dioxane (50 mL) and the resulting solution was heated at 80 °C for 2 h with stirring in the presence of *N*,*N*-dimethylaminopyridine (0.016 mol). After removal of the solvent under reduced pressure, the residue obtained was subjected to column chromatography over silica gel (230 mesh, Merck) eluting with EtOAc–$CHCl_3$ (1/2 v/v). The second fraction was concentrated to dryness in vacuo to give (*S*)-*N*-benzyloxycarbonyl-*N*′-(4-cyanophenyl)alaninamide as colorless powder (66%).

4.3.1. (*S*)-*N*-Benzyloxycarbonyl-*N*′-(4-cyanophenyl)alaninamide. Mp 144.5–145.0 °C. IR (KBr): 3337, 3304, 2241, 1694, 1678 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 (3H, d, J=6.9 Hz), 4.39 (1H, dq, J=5.5, 6.9 Hz), 5.14 (1H, d, J=12.3 Hz), 5.17 (1H, d, J=12.3 Hz), 5.25 (1H, br s), 7.32–7.38 (5H, m), 7.55–7.59 (4H, m), 8.77 (1H, s).

4.4. General procedure for the synthesis of (*S*)-*N*′-(alkyl- or aryl-substituted)alaninamides

(*S*)-*N*-Benzyloxycarbonyl-*N*′-(alkyl- or aryl-substituted) alaninamide (0.020 mol) was dissolved in MeOH and treated with H_2 in the presence of 10% Pd/C (1.0 g) for 0.5–1.5 h at rt. After Pd/C was removed by filtration, the filtrate obtained was concentrated to dryness in vacuo to quantitatively give colorless syrup.

4.4.1. (*S*)-*N*′-Methylalaninamide. Syrup. IR (KBr): 3292, 1657 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.10 (3H, d, J=6.9 Hz), 1.85 (2H, br s), 2.58 (3H, d, J=4.8 Hz), 3.20 (1H, q, J=6.9 Hz), 7.74 (1H, br s).

4.4.2. (*S*)-*N*′-(*tert*-Butyl)alaninamide. Syrup. IR (KBr): 3273, 1658 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.07 (3H, d, J=6.9 Hz), 1.25 (9H, s), 1.80 (2H, br s), 3.13 (1H, q, J=6.9 Hz), 7.39 (1H, s).

4.4.3. (*S*)-*N*′-Phenylalaninamide. Syrup. IR (KBr): 3298, 1665 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.43 (3H, d, $J=6.9$ Hz), 1.79 (2H, br s), 3.63 (1H, q, $J=6.9$ Hz), 7.10 (1H, dd, $J=7.6$, 7.6 Hz), 7.33 (2H, dd, $J=7.6$, 8.3 Hz), 7.60 (2H, d, $J=8.3$ Hz), 9.46 (1H, br s).

4.4.4. (*S*)-*N*′-(4-Methoxyphenyl)alaninamide. Syrup. IR (KBr): 3298, 1655 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.43 (3H, d, $J=6.9$ Hz), 1.59 (2H, br s), 3.61 (1H, q, $J=6.9$ Hz), 3.79 (3H, s), 6.87 (1H, d, $J=8.9$ Hz), 7.51 (2H, d, $J=8.9$ Hz), 9.32 (1H, s).

4.4.5. (*S*)-*N*′-(4-Cyanophenyl)alaninamide. Syrup. IR (KBr): 3283, 2224, 1686 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.45 (3H, d, $J=7.6$ Hz), 1.58 (2H, br s), 3.65 (1H, q, $J=7.6$ Hz), 7.62 (2H, d, $J=8.9$ Hz), 7.74 (2H, d, $J=8.9$ Hz), 9.85 (1H, s).

4.5. General procedure for the synthesis of (*Z*)-2-methyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone and (*Z*)-4-(1-naphthylmethylene)-2-phenyl-5(4*H*)-oxazolone

N-Acetylglycine or *N*-benzoylglycine (0.087 mol), 1-naphthaldehyde (16.1 g, 0.103 mol), and sodium aceate (5.3 g, 0.067 mol) were added to acetic anhydride (100 mL) and the resulting mixture was heated at 75–85 °C for 6 h (*N*-acetylglycine) or 1 h (*N*-benzoylglycine) with stirring. The mixture was cooled with ice and the solid separated out was collected by filtration with suction and washed with water, small amounts of cold EtOH and then with dry hexane. After the crude product had been air-dryed at rt, it was recrystallized from hexane–$CHCl_3$ to give yellow crystals (40–50%).

4.5.1. (*Z*)-2-Methyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone. Mp 159.0–160.0 °C. IR (KBr): 1760, 1650, 1260 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.43 (3H, s), 7.54 (1H, dd, $J=7.3$, 7.9 Hz), 7.58 (1H, dd, $J=7.3$, 8.6 Hz), 7.61 (1H, dd, $J=7.3$, 8.6 Hz), 7.88 (1H, d, $J=7.9$ Hz), 7.93 (1H, d, $J=8.6$ Hz), 8.02 (1H, s), 8.24 (1H, d, $J=8.6$ Hz), 8.75 (1H, d, $J=7.3$ Hz).

4.5.2. (*Z*)-4-(1-Naphthylmethylene)-2-phenyl-5(4*H*)-oxazolone. Mp 166.0–167.0 °C. IR (KBr): 1797, 1647, 1167 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (2H, dd, $J=7.3$, 7.6 Hz), 7.55 (1H, dd, $J=8.6$, 8.6 Hz), 7.62 (1H, dd, $J=7.3$, 7.3 Hz), 7.63 (1H, dd, $J=8.6$, 8.6 Hz), 7.64 (1H, dd, $J=6.7$, 8.6 Hz), 7.90 (1H, d, $J=8.6$ Hz), 7.97 (1H, d, $J=8.6$ Hz), 8.13 (1H, s), 8.21 (2H, d, $J=7.6$ Hz), 8.31 (1H, d, $J=8.6$ Hz), 9.03 (1H, d, $J=6.7$ Hz).

4.6. General procedure for the synthesis of (*Z*)-2-acetylamino-3-(1-naphthyl)-*N*-[(*S*)-1-phenylethyl]-2-propenamide [(*Z*)-1a] and (*Z*)-2-benzoylamino-3-(1-naphthyl)-*N*-[(*S*)-1-phenylethyl]-2-propenamide [(*Z*)-1b]

(*Z*)-2-Methyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone (for **1a**, 0.010 mol) or (*Z*)-4-(1-naphthylmethylene)-2-phenyl-5(4*H*)-oxazolone (for **1b**, 0.010 mol) was added to dry $CHCl_3$ (10 mL) containing (*S*)-1-phenylethylamine (0.010 mol) and the resulting mixture was refluxed for 1 h. The reaction mixture was concentrated to dryness in vacuo affording crystalline solid. On recrystallization from EtOAc, (*Z*)-**1a**,**b** slowly precipitated as colorless crystals (60–70%).

4.6.1. (*Z*)-2-Acetylamino-3-(1-naphthyl)-*N*-[(*S*)-1-phenylethyl]-2-propenamide [(*Z*)-1a]. Mp 169.5–170.5 °C. IR (KBr): 3256, 3052, 2974, 1656, 1624 cm^{-1}. $[\alpha]_D^{25}$ +9.6 (*c* 0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.47 (3H, d, $J=7.3$ Hz), 1.85 (3H, s), 5.11 (1H, dq, $J=8.6$, 7.3 Hz), 7.24 (1H, dd, $J=7.9$, 7.9 Hz), 7.34 (2H, dd, $J=7.9$, 7.3 Hz), 7.44 (2H, d, $J=7.3$ Hz), 7.46 (1H, s), 7.57–7.52 (3H, m), 7.60 (1H, d, $J=7.3$ Hz), 7.91 (1H, d, $J=7.9$ Hz), 7.99–7.95 (2H, m), 8.48 (1H, d, $J=8.6$ Hz), 9.25 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.1, 22.7, 48.3, 123.6, 124.3, 125.5, 126.0, 126.2 (2C), 126.3, 126.4, 126.5, 128.1 (2C), 128.4, 128.5, 131.0, 131.4, 132.8, 133.2, 144.7, 164.3, 169.4. Anal. Calcd (found) for $C_{23}H_{22}N_2O_2$: C, 77.07 (76.97); H, 6.19 (6.27); N, 7.82% (7.66%).

4.6.2. (*Z*)-2-Benzoylamino-3-(1-naphthyl)-*N*-[(*S*)-1-phenylethyl]-2-propenamide [(*Z*)-1b]. Mp 166.0–167.0 °C. IR (KBr): 3240, 3056, 2976, 1642, 1610 cm^{-1}. $[\alpha]_D^{25}$ +32.4 (*c* 0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.49 (3H, d, $J=6.7$ Hz), 5.15 (1H, dq, $J=8.6$, 6.7 Hz), 7.24 (1H, dd, $J=7.3$, 7.3 Hz), 7.35 (2H, dd, $J=7.3$, 7.3 Hz), 7.42 (2H, dd, $J=7.3$, 7.3 Hz), 7.45 (1H, dd, $J=8.6$, 7.3 Hz), 7.46 (2H, d, $J=7.3$ Hz), 7.51 (1H, dd, $J=7.3$, 7.3 Hz), 7.55 (1H, dd, $J=7.3$, 7.3 Hz), 7.57 (1H, dd, $J=7.9$, 7.3 Hz), 7.66 (1H, d, $J=7.3$ Hz), 7.72 (1H, s), 7.83 (2H, d, $J=7.3$ Hz), 7.86 (1H, d, $J=8.6$ Hz), 7.94 (1H, d, $J=7.3$ Hz), 8.05 (1H, d, $J=7.9$ Hz), 8.63 (1H, d, $J=8.6$ Hz), 9.72 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.1, 48.3, 124.3, 125.4, 125.6, 126.0, 126.2 (3C), 126.3, 126.5, 127.8 (2C), 128.1 (4C), 128.4 (2C), 131.1, 131.45, 131.51, 132.6, 133.2, 133.9, 144.7, 164.2, 166.1. Anal. Calcd (found) for $C_{28}H_{24}N_2O_2$: C, 79.98 (79.70); H, 5.75 (5.80); N, 6.66% (6.50%).

4.7. General procedure for the synthesis of (*Z*)-2-acetylamino-*N*-[*N*-(alkyl- or aryl-substituted)-(*S*)-2-propionamido]-3-(1-naphthyl)-2-propenamide [(*Z*)-1c–h]

To a DMF solution (15 mL) of (*S*)-*N*′-(alkyl- or aryl-subustituted)alaninamide derivative (for **1c**,**e**–**h**, 0.010 mol) or (*S*)-alaninamide hydrochloride (for **1d**, 0.010 mol) containing triethylamine (for **1d**, 0.010 mol) was added (*Z*)-2-methyl-4-(1-naphthylmethylene)-5(4*H*)-oxazolone (0.010 mol) and the resulting mixture was stirred for 12 h at rt. The reaction mixture was dissolved in $CHCl_3$ (50 mL) and the solution was washed with water (50 mL) and then dried over $MgSO_4$. After removal of the solvent under reduced pressure, the solid obtained was recrystallized from EtOAc–hexane (**1c**–**g**) or EtOAc–$CHCl_3$ (**1h**) affording colorless crystals (40–60%).

4.7.1. (*Z*)-2-Acetylamino-*N*-[(*S*)-*N*-methyl-2-propionamido]-3-(1-naphthyl)-2-propenamide [(*Z*)-1c]. Mp 107.5–108.5 °C. IR (KBr): 3314, 3254, 1660, 1651, 1634 cm^{-1}. $[\alpha]_D^{25}$ +50.6 (*c* 0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.30 (3H, d, $J=6.9$ Hz), 1.87 (3H, s), 2.60 (3H, d, $J=4.1$ Hz), 4.31 (1H, dq, $J=6.9$, 7.6 Hz), 7.36 (1H, s), 7.51–7.57 (4H, m), 7.71 (1H, q, $J=4.1$ Hz), 7.90 (1H, d, $J=7.6$ Hz), 7.93–7.95 (2H, m), 8.32 (1H, d, $J=7.6$ Hz), 9.52 (1H, s). ^{13}C NMR (125 MHz,

DMSO-d_6): δ 17.4, 22.7, 25.7, 48.9, 122.9, 124.3, 125.5, 126.1, 126.4, 126.6, 128.5 (2C), 131.0, 131.1, 132.4, 133.2, 164.7, 170.5, 172.4. Anal. Calcd (found) for $C_{19}H_{21}N_3O_3$: C, 67.24 (67.25); H, 6.24 (6.14); N, 12.38% (12.42%).

4.7.2. (*Z*)-2-Acetylamino-*N*-[(*S*)-2-propionamido]-3-(1-naphthyl)-2-propenamide [(*Z*)-1d]. Mp 138.0–139.0 °C. IR (KBr): 3420, 3235, 1660, 1641, 1631 cm^{-1}. $[\alpha]_D^{25}$ +46.5 (*c* 0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.33 (3H, d, J=7.3 Hz), 1.89 (3H, s), 4.23 (1H, dq, J=7.3, 7.9 Hz), 7.12 (1H, s), 7.28 (1H, s), 7.40 (1H, s), 7.54–7.59 (4H, m), 7.93 (1H, d, J=7.9 Hz), 7.96–7.99 (2H, m), 8.31 (1H, d, J=7.9 Hz), 9.53 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.4, 22.5, 48.6, 122.8, 124.2, 125.5, 126.0, 126.3, 126.4, 128.4 (2C), 130.9, 131.0, 132.4, 133.1, 164.5, 170.3, 174.3. Anal. Calcd (found) for $C_{18}H_{19}N_3O_3$: C, 66.45 (66.70); H, 5.89 (5.77); N, 12.91% (13.20%).

4.7.3. (*Z*)-2-Acetylamino-*N*-[(*S*)-*N*-(*tert*-butyl)-2-propionamido]-3-(1-naphthyl)-2-propenamide [(*Z*)-1e]. Mp 147.5–148.5 °C. IR (KBr): 3523, 3251, 1663, 1653, 1626 cm^{-1}. $[\alpha]_D^{25}$ +71.6 (*c* 0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.29 (3H, d, J=6.9 Hz), 1.30 (9H, s), 1.90 (3H, s), 4.31 (1H, dq, J=6.9, 7.6 Hz), 7.27 (1H, s), 7.42 (1H, s), 7.54–7.59 (4H, m), 7.92 (1H, d, J=8.2 Hz), 7.95–7.98 (2H, m), 8.16 (1H, d, J=7.6 Hz), 9.49 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.9, 22.6, 28.4 (3C), 49.0, 50.1, 123.2, 124.1, 125.5, 126.0, 126.3, 126.4, 128.4 (2C), 130.9, 131.0, 132.4, 133.1, 164.2, 170.1, 171.3. Anal. Calcd (found) for $C_{22}H_{27}N_3O_3$: C, 69.27 (69.02); H, 7.13 (7.06); N, 11.02% (11.02%).

4.7.4. (*Z*)-2-Acetylamino-*N*-[(*S*)-*N*-phenyl-2-propionamido]-3-(1-naphthyl)-2-propenamide [(*Z*)-1f]. Mp 128.0–129.0 °C. IR (KBr): 3273, 3051, 1672, 1661, 1601 cm^{-1}. $[\alpha]_D^{25}$ +100.8 (*c* 0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.44 (3H, d, J=7.6 Hz), 1.96 (3H, s), 4.53 (1H, dq, J=7.4, 7.6 Hz), 7.08 (1H, dd, J=7.5, 7.5 Hz), 7.34 (2H, dd, J=7.4, 7.5 Hz), 7.45 (1H, s), 7.55–7.58 (3H, m), 7.62 (1H, d, J=6.9 Hz), 7.78 (2H, d, J=7.4 Hz), 7.94 (1H, d, J=8.6 Hz), 7.97–7.99 (2H, m), 8.56 (1H, d, J=7.4 Hz), 9.59 (1H, s), 9.66 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.4, 22.8, 49.7, 119.3 (2C), 123.2, 123.4, 124.3, 125.6, 126.1, 126.4, 126.6, 128.47, 128.54, 128.7 (2C), 131.0 (2C), 132.2, 133.2, 138.9, 164.8, 170.9, 171.1. Anal. Calcd (found) for $C_{24}H_{23}N_3O_3$: C, 71.80 (71.75); H, 5.77 (5.67); N, 10.47% (10.36%).

4.7.5. (*Z*)-2-Acetylamino-*N*-[(*S*)-*N*-(4-methoxyphenyl)-2-propionamido]-3-(1-naphthyl)-2-propenamide [(*Z*)-1g]. Mp 150.0–151.0 °C. IR (KBr): 3277, 1670, 1657, 1630 cm^{-1}. $[\alpha]_D^{25}$ +96.4 (*c* 0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.43 (3H, d, J=7.6 Hz), 1.96 (3H, s), 3.73 (3H, s), 4.51 (1H, dq, J=7.6, 7.6 Hz), 6.91 (2H, d, J=8.9 Hz), 7.44 (1H, s), 7.56–7.58 (3H, m), 7.62 (1H, d, J=7.6 Hz), 7.68 (2H, d, J=8.9 Hz), 7.94 (1H, d, J=8.3 Hz), 7.97–7.98 (2H, m), 8.53 (1H, d, J=7.6 Hz), 9.46 (1H, s), 9.65 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.4, 22.8, 49.5, 55.1, 113.8 (2C), 120.8 (2C), 123.1, 124.3, 125.6, 126.1, 126.4, 126.7, 128.49, 128.55, 131.0 (2C), 132.0, 132.3, 133.3, 155.3, 164.7, 170.5, 170.9. Anal. Calcd (found) for $C_{25}H_{25}N_3O_4$: C, 69.59 (69.25); H, 5.84 (5.69); N, 9.74% (9.46%).

4.7.6. (*Z*)-2-Acetylamino-*N*-[(*S*)-*N*-(4-cyanophenyl)-2-propionamido]-3-(1-naphthyl)-2-propenamide [(*Z*)-1h]. Mp 134.0–135.0 °C. IR (KBr): 3277, 2224, 1690, 1678, 1667 cm^{-1}. $[\alpha]_D^{25}$ +98.7 (*c* 0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.44 (3H, d, J=6.9 Hz), 1.96 (3H, s), 4.53 (1H, dq, J=6.9, 6.9 Hz), 7.44 (1H, s), 7.56–7.59 (3H, m), 7.62 (1H, d, J=7.6 Hz), 7.82 (2H, d, J=8.9 Hz), 7.95 (1H, d, J=8.3 Hz), 7.96–7.99 (2H, m), 7.97 (2H, d, J=8.9 Hz), 8.65 (1H, d, J=6.9 Hz), 9.69 (1H, s), 9.97 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.1, 22.8, 50.0, 105.2, 119.0, 119.3 (2C), 123.3, 124.2, 125.6, 126.1, 126.4, 126.7, 128.5, 128.6, 130.9, 131.0, 132.1, 133.3 (3C), 143.0, 164.9, 171.0, 172.1. Anal. Calcd (found) for $C_{25}H_{22}N_4O_3$: C, 70.41 (70.39); H, 5.20 (5.02); N, 13.14% (13.10%).

4.8. General procedure for the irradiation of (*Z*)-1a–h

For the purpose of analyzing the effects of chiral auxiliary, tertiary amine, solvent and temperature on the magnitude of de, a MeOH or a MeOH–MeCN solution (50 mL) of (*Z*)-**1** (3.75×10^{-3} mol dm^{-3}) containing tertiary amine (0.10 mol dm^{-3}) was irradiated under nitrogen with Pyrex-filtered light from a 400 W high-pressure Hg lamp at 50, rt (25±2) or −78 °C. After 1 h irradiation, an appropriate amount of the solution (10 mL) being irradiated was pipetted off and concentrated to dryness in vacuo. The resulting residue was dissolved in DMSO-d_6 and subjected to ^1H NMR spectral analysis.

On the other hand, a solution (500 mL) of (*Z*)-**1a–h** (3.75×10^{-3} mol dm^{-3}) in MeOH containing TEA (0.10 mol dm^{-3}), placed in a Pyrex vessel, was irradiated for a given period of time under nitrogen with Pyrex-filtered light from a 400 W high-pressure Hg lamp at rt. After 5 h irradiation, an appropriate amount of the solution (5 mL) being irradiated was pipetted off and concentrated to dryness in vacuo giving the residue, which was subjected to ^1H NMR spectral analysis in DMSO-d_6. The remaining solutions of **1a–h** were concentrated to dryness under reduced pressure and the resulting residues were subjected to column chromatography over silica gel (230 mesh, Merck) eluting with EtOAc–hexane. For the purpose of isolating each diastereomer of **2a–h**, preparative TLC plate (silica gel) was also used. Physical and spectroscopic properties of (*E*)-**1a**,**c**, (*S*,*S*)-**2a–h**, (*R*,*S*)-**2a–h**, **3a–g** and diastereo mers of *cis*-**4b** are as follows.

4.8.1. Compound (*E*)-1a. Mp 144.0–146.0 °C. IR (KBr): 3268, 3052, 2974, 2932, 1680, 1626 cm^{-1}. $[\alpha]_D^{25}$ +19.6 (*c* 0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.05 (3H, d, J=6.7 Hz), 2.03 (3H, s), 4.84 (1H, dq, J=8.6, 6.7 Hz), 7.00–6.99 (2H, m), 7.14–7.12 (3H, m), 7.25 (1H, dd, J=7.9, 7.3 Hz), 7.32 (1H, d, J=7.3 Hz), 7.45 (1H, s), 7.52 (1H, dd, J=7.3, 6.7 Hz), 7.55 (1H, dd, J=7.3, 6.7 Hz), 7.78 (1H, d, J=7.9 Hz), 7.91 (1H, d, J=7.3 Hz), 8.02 (1H, d, J=7.3 Hz), 8.23 (1H, d, J=8.6 Hz), 9.78 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.2, 23.3, 47.5, 112.5, 124.6, 125.3, 125.6, 125.7, 125.8, 126.0 (2C), 126.2, 126.9, 127.8 (2C), 128.1, 131.2, 132.3, 133.0, 134.9, 143.6, 163.7, 168.4. Anal. Calcd (found) for $C_{23}H_{22}N_2O_2$: C, 77.07 (77.02); H, 6.19 (6.00); N, 7.82% (7.88%).

4.8.2. Compound (*E*)-1c. Mp 220.5–221.5 °C. IR (KBr): 3356, 3242, 1663, 1650, 1625 cm^{-1}. $[\alpha]_D^{25}$ −403.5 (*c* 0.05, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 0.81 (3H, d, *J*=7.6 Hz), 2.04 (3H, s), 2.51 (3H, d, *J*=4.8 Hz), 4.05 (1H, dq, *J*=7.6, 8.3 Hz), 7.06 (1H, s), 7.38 (1H, d, *J*=6.9 Hz), 7.41 (1H, dd, *J*=6.9, 8.3 Hz), 7.52 (1H, dd, *J*=6.9, 7.6 Hz), 7.55 (1H, dd, *J*=6.9, 8.2 Hz), 7.57 (1H, q, *J*=4.8 Hz), 7.82 (1H, d, *J*=8.3 Hz), 7.91 (1H, d, *J*=7.6 Hz), 8.00 (1H, d, *J*=8.2 Hz), 8.15 (1H, d, *J*=8.3 Hz), 10.14 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.3, 23.0, 25.6, 48.0, 114.0, 124.5, 125.2, 125.6, 125.9, 126.1, 127.6, 128.3, 131.2, 131.5, 133.1, 133.4, 164.1, 168.7, 171.8. Anal. Calcd (found) for $C_{19}H_{21}N_3O_3$: C, 67.24 (66.82); H, 6.24 (6.08); N, 12.38% (12.09%).

4.8.3. (3*S*)-3-Acetylamino-3,4-dihydro-1-[(*S*)-1-phenylethyl]-2(1*H*)-benzo[*f*]quinolinone [(*S*,*S*)-2a]. Mp 204.0–205.0 °C. IR (KBr): 3304, 3058, 2926, 1680, 1659 cm^{-1}. $[\alpha]_D^{25}$ −93.2 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ −1111. ^1H NMR (500 MHz, DMSO-d_6): δ 1.91 (3H, d, *J*=7.3 Hz), 1.95 (3H, s), 3.10 (1H, dd, *J*=15.3, 14.6 Hz), 3.66 (1H, dd, *J*=15.3, 5.5 Hz), 4.60 (1H, ddd, *J*=14.6, 7.9, 5.5 Hz), 6.05 (1H, q, *J*=7.3 Hz), 7.14 (1H, d, *J*=9.2 Hz), 7.18 (1H, dd, *J*=7.3, 7.3 Hz), 7.29 (2H, dd, *J*=7.3, 7.3 Hz), 7.32 (2H, d, *J*=7.3 Hz), 7.41 (1H, dd, *J*=7.9, 7.3 Hz), 7.54 (1H, dd, *J*=8.5, 7.3 Hz), 7.63 (1H, d, *J*=9.2 Hz), 7.80 (1H, d, *J*=7.9 Hz), 8.02 (1H, d, *J*=8.5 Hz), 8.39 (1H, d, *J*=7.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 18.0, 22.6, 27.0, 48.8, 53.0, 117.6, 119.6, 128.2, 124.7, 126.2 (2C), 126.6, 126.9, 127.1, 128.1, 128.4 (2C), 129.5, 130.6, 136.1, 140.4, 168.9, 169.3. Anal. Calcd (found) for $C_{23}H_{22}N_2O_2$: C, 77.07 (76.73); H, 6.19 (6.25); N, 7.82% (8.13%).

4.8.4. (3*S*)-3-Benzoylamino-3,4-dihydro-1-[(*S*)-1-phenylethyl]-2(1*H*)-benzo[*f*]quinolinone [(*S*,*S*)-2b]. Mp 103.0–105.0 °C. IR (KBr): 3322, 3058, 2926, 1690, 1641 cm^{-1}. $[\alpha]_D^{25}$ −122.0 (*c* 0.5, MeOH). ^1H NMR (500 MHz, DMSO-d_6): δ 1.95 (3H, d, *J*=6.7 Hz), 3.36 (1H, dd, *J*=15.3, 14.6 Hz), 3.75 (1H, dd, *J*=15.3, 5.5 Hz), 4.88 (1H, ddd, *J*=14.6, 8.6, 5.5 Hz), 6.09 (1H, q, *J*=6.7 Hz), 7.17 (1H, d, *J*=9.2 Hz), 7.18 (1H, dd, *J*=7.9, 7.9 Hz), 7.30 (2H, d, *J*=7.9, 7.3 Hz), 7.34 (2H, d, *J*=7.3 Hz), 7.42 (1H, dd, *J*=7.9, 7.9 Hz), 7.53 (2H, dd, *J*=7.6, 7.3 Hz), 7.53 (1H, dd, *J*=8.6, 7.9 Hz), 7.59 (1H, dd, *J*=7.3, 7.3 Hz), 7.63 (1H, d, *J*=9.2 Hz), 7.81 (1H, d, *J*=7.9 Hz), 7.97 (2H, d, *J*=7.6 Hz), 8.07 (1H, d, *J*=8.6 Hz), 8.91 (1H, d, *J*=8.6 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 18.0, 26.8, 49.2, 53.1, 117.7, 119.6, 123.2, 124.7, 126.3 (2C), 126.6, 126.9, 127.1, 127.4 (2C), 128.1, 128.35 (2C), 128.38 (2C), 129.5, 130.5, 131.5, 134.1, 136.1, 140.3, 166.1, 169.0. Anal. Calcd (found) for $C_{28}H_{24}N_2O_2$: C, 79.98 (80.00); H, 5.75 (6.08); N, 6.66% (6.64%).

4.8.5. (3*S*)-3-Acetylamino-3,4-dihydro-1-[(*S*)-*N*-methyl-2-propionamido]-2(1*H*)-benzo[*f*]quinolinone [(*S*,*S*)-2c]. Mp 136.0–137.0 °C. IR (KBr): 3321, 1678, 1660, 1643 cm^{-1}. $[\alpha]_D^{25}$ +7.1 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ −1087. ^1H NMR (500 MHz, DMSO-d_6): δ 1.51 (3H, d, *J*=6.9 Hz), 1.93 (3H, s), 2.53 (3H, d, *J*=4.1 Hz), 3.05 (1H, dd, *J*=14.4, 15.1 Hz), 3.59 (1H, dd, *J*=6.2, 15.1 Hz), 4.62 (1H, ddd, *J*=6.2, 7.6, 14.4 Hz), 5.09 (1H, q, *J*=6.9 Hz), 7.33 (1H, d, *J*=8.9 Hz), 7.44 (1H, dd, *J*=6.9, 8.2 Hz), 7.55 (1H, dd, *J*=6.9, 8.3 Hz), 7.78 (1H, q, *J*=4.1 Hz), 7.84 (1H, d, *J*=8.9 Hz), 8.89 (1H, d, *J*=8.2 Hz), 8.00 (1H, d, *J*=8.3 Hz), 8.30 (1H, d, *J*=7.6 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.0, 22.6, 26.1, 26.9, 48.5, 54.4, 116.7, 119.3, 123.1, 124.7, 127.0, 127.6, 128.2, 129.7, 130.7, 136.7, 168.5, 169.3, 170.0. Anal. Calcd (found) for $C_{19}H_{21}N_3O_3$: C, 67.24 (67.17); H, 6.24 (6.05); N, 12.38% (12.52%).

4.8.6. (3*S*)-3-Acetylamino-3,4-dihydro-1-[(*S*)-2-propionamido]-2(1*H*)-benzo[*f*]quinolinone [(*S*,*S*)-2d]. Mp 148.5–150.0 °C. IR (KBr): 3489, 3200, 1690, 1678, 1662 cm^{-1}. $[\alpha]_D^{25}$ +17.6 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ −1074. ^1H NMR (500 MHz, DMSO-d_6): δ 1.50 (3H, d, *J*=6.9 Hz), 1.94 (3H, s), 3.10 (1H, dd, *J*=14.5, 15.1 Hz), 3.59 (1H, dd, *J*=6.2, 15.1 Hz), 4.63 (1H, ddd, *J*=6.2, 7.6, 14.5 Hz), 5.14 (1H, q, *J*=6.9 Hz), 7.07 (1H, s), 7.35 (1H, d, *J*=8.9 Hz), 7.36 (1H, s), 7.45 (1H, dd, *J*=6.9, 8.3 Hz), 7.56 (1H, dd, *J*=6.9, 8.3 Hz), 7.86 (1H, d, *J*=8.9 Hz), 7.89 (1H, d, *J*=8.3 Hz), 8.00 (1H, d, *J*=8.3 Hz), 8.29 (1H, d, *J*=7.6 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.0, 22.6, 26.9, 48.4, 53.9, 116.7, 119.1, 123.1, 124.6, 126.9, 127.5, 128.2, 129.7, 130.7, 136.5, 168.4, 169.2, 171.7. Anal. Calcd (found) for $C_{18}H_{19}N_3O_3$: C, 66.45 (66.64); H, 5.89 (5.92); N, 12.91% (13.27%).

4.8.7. (3*S*)-3-Acetylamino-1-[(*S*)-*N*-(*tert*-butyl)-2-propionamido]-3,4-dihydro-2(1*H*)-benzo[*f*]quinolinone [(*S*,*S*)-2e]. Mp 212.0–213.0 °C. IR (KBr): 3433, 3290, 1693, 1665, 1650 cm^{-1}. $[\alpha]_D^{25}$ −31.4 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ −1630. ^1H NMR (500 MHz, DMSO-d_6): δ 1.05 (9H, s), 1.49 (3H, d, *J*=6.9 Hz), 1.94 (3H, s), 3.14 (1H, dd, *J*=14.4, 15.1 Hz), 3.59 (1H, dd, *J*=6.2, 15.1 Hz), 4.50 (1H, ddd, *J*=6.2, 7.6, 14.4 Hz), 5.19 (1H, q, *J*=6.9 Hz), 7.11 (1H, s), 7.28 (1H, d, *J*=8.9 Hz), 7.42 (1H, dd, *J*=6.9, 8.3 Hz), 7.54 (1H, dd, *J*=6.9, 8.9 Hz), 7.80 (1H, d, *J*=8.9 Hz), 7.87 (1H, d, *J*=8.3 Hz), 7.99 (1H, d, *J*=8.9 Hz), 8.13 (1H, d, *J*=7.6 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.3, 22.6, 26.6, 28.2 (3C), 48.7, 50.3, 53.7, 116.8, 119.2, 123.1, 124.6, 126.9, 127.2, 128.2, 129.7, 130.6, 136.1, 168.5, 168.6, 169.4. Anal. Calcd (found) for $C_{22}H_{27}N_3O_3$: C, 69.27 (69.40); H, 7.13 (7.02); N, 11.02% (10.86%).

4.8.8. (3*S*)-3-Acetylamino-3,4-dihydro-1-[(*S*)-*N*-phenyl-2-propionamido]-2(1*H*)-benzo[*f*]quinolinone [(*S*,*S*)-2f]. Mp 146.0–147.0 °C. IR (KBr): 3304, 1682, 1661, 1636 cm^{-1}. $[\alpha]_D^{25}$ −94.6 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ −1393. ^1H NMR (500 MHz, DMSO-d_6): δ 1.55 (3H, d, *J*=6.2 Hz), 1.95 (3H, s), 3.13 (1H, dd, *J*=14.4, 15.1 Hz), 3.65 (1H, dd, *J*=6.2, 15.1 Hz), 4.71 (1H, ddd, *J*=6.2, 7.6, 14.4 Hz), 5.35 (1H, q, *J*=6.2 Hz), 7.01 (1H, dd, *J*=7.6, 7.6 Hz), 7.24 (2H, dd, *J*=7.6, 8.9 Hz), 7.45 (1H, dd, *J*=6.9, 7.6 Hz), 7.51 (2H, d, *J*=8.9 Hz), 7.53 (1H, d, *J*=9.0 Hz), 7.57 (1H, dd, *J*=6.9, 8.2 Hz), 7.88 (1H, d, *J*=9.0 Hz), 7.89 (1H, d, *J*=7.6 Hz), 8.02 (1H, d, *J*=8.2 Hz), 8.30 (1H, d, *J*=7.6 Hz), 9.67 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.9, 22.6, 26.9, 48.5, 54.8, 116.8, 119.4, 120.4 (2C), 123.2, 123.3, 124.7, 127.0, 127.7, 128.2, 128.3 (2C), 129.8, 130.7, 136.6, 138.9, 168.6, 168.7, 169.3. Anal. Calcd (found) for $C_{24}H_{23}N_3O_3$: C, 71.80 (72.00); H, 5.77 (5.84); N, 10.47% (10.08%).

4.8.9. (3*S*)-3-Acetylamino-3,4-dihydro-1-[(*S*)-*N*-(4-methoxyphenyl)-2-propioamido]-2(1*H*)-benzo[*f*]quinolinone [(*S*,*S*)-2g]. Mp 128.0–129.5 °C. IR (KBr): 3302, 1690, 1674, 1659 cm^{-1}. $[\alpha]_D^{25}$ −82.8 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ −1679. ^1H NMR (500 MHz, DMSO-d_6): δ 1.56 (3H, d, J=6.9 Hz), 1.96 (3H, s), 3.13 (1H, dd, J=14.4, 14.1 Hz), 3.65 (1H, dd, J=5.5, 14.3 Hz), 3.68 (3H, s), 4.69 (1H, ddd, J=5.5, 7.6, 14.1 Hz), 5.34 (1H, q, J=6.9 Hz), 6.82 (2H, d, J=8.9 Hz), 7.37 (2H, d, J=8.9 Hz), 7.44 (1H, dd, J=6.9, 8.2 Hz), 7.50 (1H, d, J=8.9 Hz), 7.56 (1H, dd, J=6.9, 8.8 Hz), 7.87 (1H, d, J=8.9 Hz), 7.89 (1H, d, J=8.2 Hz), 8.02 (1H, d, J=8.8 Hz), 8.30 (1H, d, J=7.6 Hz), 9.54 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.9, 22.6, 26.9, 48.5, 54.6, 55.1, 113.5 (2C), 116.8, 119.4, 122.1 (2C), 123.2, 124.7, 127.0, 127.6, 128.2, 129.7, 130.7, 131.8, 136.6, 155.4, 168.2, 168.6, 169.3. Anal. Calcd (found) for $C_{25}H_{25}N_3O_4$: C, 69.59 (69.85); H, 5.84 (6.26); N, 9.74% (9.44%).

4.8.10. (3*S*)-3-Acetylamino-1-[(*S*)-*N*-(4-cyanophenyl)-2-propionamido]-3,4-dihydro-2(1*H*)-benzo[*f*]quinolinone [(*S*,*S*)-2h]. Mp 166.0–167.0 °C. IR (KBr): 3319, 2224, 1708, 1689, 1656 cm^{-1}. $[\alpha]_D^{25}$ −144.4 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ −1246. ^1H NMR (500 MHz, DMSO-d_6): δ 1.50 (3H, d, J=6.9 Hz), 1.93 (3H, s), 3.09 (1H, dd, J=14.4, 15.1 Hz), 3.65 (1H, dd, J=5.5, 15.1 Hz), 4.73 (1H, ddd, J=5.5, 8.3, 14.4 Hz), 5.34 (1H, q, J=6.9 Hz), 7.46 (1H, dd, J=7.6, 7.6 Hz), 7.57 (1H, dd, J=7.6, 8.3 Hz), 7.59 (1H, d, J=8.9 Hz), 7.72 (2H, d, J=8.9 Hz), 7.78 (2H, d, J=8.9 Hz), 7.90 (1H, d, J=8.9 Hz), 7.91 (1H, d, J=7.6 Hz), 8.03 (1H, d, J=8.3 Hz), 8.32 (1H, d, J=8.3 Hz), 10.05 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.6, 22.6, 27.0, 48.3, 55.2, 104.9, 117.0, 119.0, 119.5, 120.0 (2C), 123.2, 124.8, 127.1, 127.8, 128.3, 129.8, 130.7, 132.9 (2C), 136.6, 143.4, 168.7, 169.3, 169.5. Anal. Calcd (found) for $C_{25}H_{22}N_4O_3$: C, 70.41 (70.66); H, 5.20 (5.31); N, 13.14% (12.80%).

4.8.11. (3*R*)-3-Acetylamino-3,4-dihydro-1-[(*S*)-2-phenylethyl]-2(1*H*)-benzo[*f*]quinolinone [(*R*,*S*)-2a]. Mp 112.0–114.0 °C. IR (KBr): 3292, 3064, 2926, 1677, 1659 cm^{-1}. $[\alpha]_D^{25}$ −144.8 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ +1377. ^1H NMR (500 MHz, DMSO-d_6): δ 1.71 (3H, d, J=7.3 Hz, Hl), 1.97 (3H, s), 3.04 (1H, dd, J=15.3, 14.3 Hz), 3.69 (1H, dd, J=15.3, 5.8 Hz), 4.67 (1H, ddd, J=14.3, 7.6, 5.8 Hz), 6.30 (1H, q, J=7.3 Hz), 7.00 (1H, d, J=8.9 Hz), 7.29 (1H, dd, J=7.3, 7.3 Hz), 7.36 (2H, d, J=7.3 Hz), 7.40 (2H, dd, J=7.3, 7.3 Hz), 7.45 (1H, dd, J=7.3, 7.3 Hz), 7.56 (1H, dd, J=7.9, 7.3 Hz), 7.70 (1H, d, J=8.9 Hz), 7.84 (1H, d, J=7.9 Hz), 8.05 (1H, d, J=8.6 Hz), 8.38 (1H, d, J=7.6 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.5, 22.6, 26.9, 48.4, 50.8, 117.7, 120.3, 123.2, 124.8, 125.5 (2C), 126.7, 126.9, 127.0, 128.2, 128.6 (2C), 129.6, 130.6, 135.2, 141.5, 169.1, 169.3. Anal. Calcd (found) for $C_{23}H_{22}N_2O_2$: C, 77.07 (76.95); H, 6.19 (6.50); N, 7.82% (7.41%).

4.8.12. (3*R*)-3-Benzoylamino-3,4-dihydro-1-[(*S*)-2-phenylethyl]-2(1*H*)-benzo[*f*]quinolinone [(*R*,*S*)-2b]. Mp 121.0–124.0 °C. IR (KBr): 3334, 3058, 2926, 1680, 1650 cm^{-1}. $[\alpha]_D^{25}$ −119.0 (*c* 0.02, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ +1558. ^1H NMR (500 MHz, DMSO-d_6): δ 1.72 (3H, d, J=7.3 Hz), 3.32 (1H, dd, J=15.3, 14.3 Hz), 3.76 (1H, dd, J=15.3, 6.1 Hz), 5.00 (1H, ddd, J=14.3, 8.5, 6.1 Hz), 6.38 (1H, q, J=7.3 Hz), 7.00 (1H, d, J=9.2 Hz), 7.31 (1H, dd, J=7.3, 7.3 Hz), 7.39 (2H, d, J=7.6 Hz), 7.42 (2H, dd, J=7.6, 7.3 Hz), 7.46 (1H, dd, J=7.9, 7.6 Hz), 7.53 (2H, dd, J=8.0, 7.3 Hz), 7.57 (1H, dd, J=8.5, 7.9 Hz), 7.59 (1H, dd, J=7.3, 7.3 Hz), 7.71 (1H, d, J=9.2 Hz), 7.85 (1H, d, J=7.6 Hz), 7.98 (2H, d, J=8.0 Hz), 8.10 (1H, d, J=8.5 Hz), 8.90 (1H, d, J=8.5 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.5, 26.7, 48.8, 50.6, 117.8, 120.3, 123.3, 124.9, 125.6 (2C), 126.8, 126.98, 127.02, 127.4 (2C), 128.2, 128.4 (2C), 128.7 (2C), 129.7, 130.7, 131.5, 134.0, 135.1, 141.5, 166.1, 169.3. Anal. Calcd (found) for $C_{28}H_{24}N_2O_2$: C, 79.98 (80.15); H, 5.75 (6.16); N, 6.66% (6.80%).

4.8.13. (3*R*)-3-Acetylamino-3,4-dihydro-1-[(*S*)-*N*-methyl-2-propionamido]-2(1*H*)-benzo[*f*]quinolinone [(*R*,*S*)-2c]. Mp 222.0–223.0 °C. IR (KBr): 3254, 1686, 1660, 1639 cm^{-1}. $[\alpha]_D^{25}$ −91.5 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ +1733. ^1H NMR (500 MHz, DMSO-d_6): δ 1.38 (3H, d, J=7.6 Hz), 1.95 (3H, s), 2.62 (3H, d, J=4.8 Hz), 2.97 (1H, dd, J=14.4, 15.1 Hz), 3.64 (1H, dd, J=6.2, 15.1 Hz), 4.79 (1H, ddd, J=6.2, 8.3, 14.4 Hz), 5.47 (1H, q, J=7.6 Hz), 7.07 (1H, d, J=8.9 Hz), 7.45 (1H, dd, J=7.6, 8.3 Hz), 7.55 (1H, dd, J=7.6, 8.3 Hz), 7.85 (1H, d, J=8.9 Hz), 7.88 (1H, d, J=8.3 Hz), 7.91 (1H, q, J=4.8 Hz), 8.02 (1H, d, J=8.3 Hz), 8.37 (1H, d, J=8.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.1, 22.6, 26.1, 27.0, 48.2, 51.4, 117.3, 119.9, 123.2, 124.9, 127.0, 127.3, 128.2, 129.7, 130.7, 134.9, 169.19, 169.25, 170.5. Anal. Calcd (found) for $C_{19}H_{21}N_3O_3$: C, 67.24 (67.47); H, 6.24 (6.02); N, 12.38% (12.26%).

4.8.14. (3*R*)-3-Acetylamino-3,4-dihydro-1-[(*S*)-2-propionamido]-2(1*H*)-benzo[*f*]quinolinone [(*R*,*S*)-2d]. Mp 187.5–189.0 °C. IR (KBr): 3320, 3180, 1694, 1674, 1650 cm^{-1}. $[\alpha]_D^{25}$ −76.0 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ +1633. ^1H NMR (500 MHz, DMSO-d_6): δ 1.38 (3H, d, J=6.9 Hz), 1.96 (3H, s), 2.98 (1H, dd, J=14.5, 15.1 Hz), 3.64 (1H, dd, J=6.2, 15.1 Hz), 4.78 (1H, ddd, J=6.2, 6.9, 14.5 Hz), 5.48 (1H, q, J=6.9 Hz), 7.16 (1H, d, J=9.7 Hz), 7.23 (1H, s), 7.46 (1H, dd, J=7.6, 8.3 Hz), 7.53 (1H, s), 7.56 (1H, dd, J=8.3, 8.9 Hz), 7.87 (1H, d, J=9.7 Hz), 7.90 (1H, d, J=7.6 Hz), 8.02 (1H, d, J=8.9 Hz), 8.34 (1H, d, J=6.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.1, 22.6, 27.0, 48.2, 51.3, 117.4, 119.7, 123.1, 124.8, 127.0, 127.2, 128.2, 129.7, 130.7, 134.9, 169.1, 169.2, 172.3. Anal. Calcd (found) for $C_{18}H_{19}N_3O_3$: C, 66.45 (66.73); H, 5.89 (6.05); N, 12.91% (12.73%).

4.8.15. (3*R*)-3-Acetylamino-1-[(*S*)-*N*-(*tert*-butyl)-2-propionamido]-3,4-dihydro-2(1*H*)-benzo[*f*]quinolinone [(*R*,*S*)-2e]. Mp 215.0–216.0 °C. IR (KBr): 3497, 3319, 1692, 1676, 1661 cm^{-1}. $[\alpha]_D^{25}$ −66.8 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ +1228. ^1H NMR (500 MHz, DMSO-d_6): δ 1.27 (9H, s), 1.35 (3H, d, J=7.6 Hz), 1.94 (3H, s), 2.98 (1H, dd, J=14.4, 15.1 Hz), 3.62 (1H, dd, J=6.2, 15.1 Hz), 4.70 (1H, ddd, J=6.2, 8.3, 14.4 Hz), 5.43 (1H, q, J=7.6 Hz), 7.16 (1H, s), 7.24 (1H, d, J=8.9 Hz), 7.44 (1H, dd, J=7.6, 8.3 Hz), 7.54 (1H, dd, J=7.6, 8.3 Hz), 7.84 (1H, d, J=8.9 Hz), 7.88 (1H, d, J=8.3 Hz), 8.01 (1H, d, J=8.3 Hz), 8.33 (1H, d, J=8.3 Hz).

^{13}C NMR (125 MHz, DMSO-d_6): δ 14.7, 22.6, 26.9, 28.4 (3C), 48.4, 50.7, 52.0, 117.8, 120.0, 123.2, 124.8, 127.0, 127.1, 128.2, 129.8, 130.7, 135.0, 169.3 (2C), 169.7. Anal. Calcd (found) for $C_{22}H_{27}N_3O_3$: C, 69.27 (69.20); H, 7.13 (7.13); N, 11.02% (10.81%).

4.8.16. (3*R*)-3-Acetylamino-3,4-dihydro-1-[(*S*)-*N*-phenyl-2-propionamido]-2(1*H*)-benzo[*f*]quinolinone [(*R*,*S*)-2f]. Mp 193.5–194.5 °C. IR (KBr): 3310, 1682, 1665, 1659 cm^{-1}. $[\alpha]_D^{25}$ −112.3 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ +1166. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.53 (3H, d, *J*=6.9 Hz), 1.95 (3H, s), 3.06 (1H, dd, *J*=14.3, 15.3 Hz), 3.66 (1H, dd, *J*=5.6, 15.3 Hz), 4.75 (1H, ddd, *J*=5.6, 8.0, 14.3 Hz), 5.50 (1H, q, *J*=6.9 Hz), 7.07 (1H, dd, *J*=7.4, 7.4 Hz), 7.30 (2H, dd, *J*=7.4, 7.6 Hz), 7.33 (1H, d, *J*=9.2 Hz), 7.47 (1H, dd, *J*=6.9, 7.5 Hz), 7.58 (1H, dd, *J*=6.9, 8.6 Hz), 7.59 (2H, d, *J*=7.6 Hz), 7.90 (1H, d, *J*=9.2 Hz), 7.91 (1H, d, *J*=7.5 Hz), 8.06 (1H, d, *J*=8.6 Hz), 8.41 (1H, d, *J*=8.0 Hz), 9.73 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.4, 22.6, 27.0, 48.4, 53.1, 117.1, 120.0, 120.7 (2C), 123.2, 123.6, 124.8, 127.0, 127.5, 128.2, 128.4 (2C), 129.8, 130.7, 135.5, 138.7, 169.1, 169.2 (2C). Anal. Calcd (found) for $C_{24}H_{23}N_3O_3$: C, 71.80 (71.38); H, 5.77 (5.51); N, 10.47% (10.24%).

4.8.17. (3*R*)-3-Acetylamino-3,4-dihydro-1-[(*S*)-*N*-(4-methoxyphenyl)-2-propionamido]-2(1*H*)-benzo[*f*]quinolinone [(*R*,*S*)-2g]. Mp 131.0–132.0 °C. IR (KBr): 3310, 1690, 1674, 1659 cm^{-1}. $[\alpha]_D^{25}$ −121.8 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ +1237. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.50 (3H, d, *J*=6.9 Hz), 1.95 (3H, s), 3.04 (1H, dd, *J*=14.5, 15.2 Hz), 3.66 (1H, dd, *J*=6.2, 15.2 Hz), 3.72 (3H, s), 4.78 (1H, ddd, *J*=6.2, 7.6, 14.5 Hz), 5.55 (1H, q, *J*=6.9 Hz), 6.88 (2H, d, *J*=8.9 Hz), 7.29 (1H, d, *J*=8.9 Hz), 7.45 (2H, d, *J*=8.9 Hz), 7.47 (1H, dd, *J*=7.6, 8.2 Hz), 7.58 (1H, dd, *J*=6.9, 7.6 Hz), 7.89 (1H, d, *J*=8.9 Hz), 7.91 (1H, d, *J*=6.9 Hz), 8.05 (1H, d, *J*=8.2 Hz), 8.40 (1H, d, *J*=7.6 Hz), 9.62 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.4, 22.6, 27.0, 48.4, 55.1 (2C), 113.6 (2C), 117.2, 120.0, 122.6 (2C), 123.2, 124.8, 127.0, 127.5, 128.2, 129.8, 130.8, 131.6, 135.4, 155.6, 168.8, 169.26, 169.30. Anal. Calcd (found) for $C_{25}H_{25}N_3O_4$: C, 69.59 (69.66); H, 5.84 (5.87); N, 9.74% (9.42%).

4.8.18. (3*R*)-3-Acetylamino-1-[(*S*)-*N*-(4-cyanophenyl)-2-propionamido]-3,4-dihydro-2(1*H*)-benzo[*f*]quinolinone [(*R*,*S*)-2h]. Mp 168.0–169.0 °C. IR (KBr): 3399, 2226, 1710, 1678, 1665 cm^{-1}. $[\alpha]_D^{25}$ −104.4 (*c* 0.5, MeOH). CD (4.0×10^{-5} mol dm^{-3}, MeOH) $[\theta]_{250}$ +1254. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.56 (3H, d, *J*=6.9 Hz), 1.92 (3H, s), 3.08 (1H, dd, *J*=14.4, 15.1 Hz), 3.65 (1H, dd, *J*=5.5, 15.1 Hz), 4.65 (1H, ddd, *J*=5.5, 7.6, 14.4 Hz), 5.33 (1H, q, *J*=6.9 Hz), 7.38 (1H, d, *J*=8.9 Hz), 7.47 (1H, dd, *J*=6.9, 7.6 Hz), 7.58 (1H, dd, *J*=6.9, 8.2 Hz), 7.76 (2H, d, *J*=8.9 Hz), 7.83 (2H, d, *J*=8.9 Hz), 7.92 (1H, d, *J*=8.9 Hz), 7.92 (1H, d, *J*=7.6 Hz), 8.07 (1H, d, *J*=8.2 Hz), 8.42 (1H, d, *J*=7.6 Hz), 10.10 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.2, 22.5, 26.9, 48.4, 54.0, 105.1, 116.6, 119.0, 119.9, 120.2 (2C), 123.2, 124.8, 127.1, 127.7, 128.3, 129.8, 130.7, 133.0 (2C), 135.9, 143.3, 169.1, 169.3, 169.6. Anal. Calcd (found) for $C_{25}H_{22}N_4O_3$: C, 70.41 (70.39); H, 5.20 (5.14); N, 13.14% (13.00%).

4.8.19. 4-Methyl-2-[(*S*)-*N*-(1-phenylethyl)aminocarbonyl]benzo[*f*]isoquinoline (3a). Mp 182.5–183.0 °C. IR (KBr): 3352, 2926, 1692, 1650 cm^{-1}. $[\alpha]_D^{25}$ −144.0 (*c* 0.2, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.11 (1H, s), 9.02 (1H, d, *J*=8.5 Hz), 8.91–8.89 (1H, m), 8.17 (1H, d, *J*=9.2 Hz), 8.12–8.11 (1H, m), 7.83–7.79 (2H, m), 7.47 (2H, d, *J*=7.3 Hz), 7.34 (2H, dd, *J*=7.3, 7.3 Hz), 7.24 (1H, dd, *J*=7.3, 7.3 Hz), 5.28 (1H, dq, *J*=8.5, 7.3 Hz), 3.04 (3H, s), 1.59 (3H, d, *J*=7.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.0, 22.6, 48.3, 113.3, 122.8, 123.8, 126.2 (2C), 126.4, 126.8, 128.0, 128.3 (2C), 128.6, 128.7, 129.1, 129.7, 132.9, 134.6, 144.1, 144.3, 157.2, 163.4. Anal. Calcd (found) for $C_{23}H_{20}N_2O$: C, 81.15 (80.87); H, 5.92 (5.99); N, 8.23% (7.91%).

4.8.20. 4-Methyl-2-[(*S*)-*N*-methyl-2-propionamidoaminocarbonyl]benzo[*f*]isoquinoline (3c). Mp 221.5–222.5 °C. IR (KBr): 3404, 3341, 1680, 1649 cm^{-1}. $[\alpha]_D^{25}$ −19.6 (*c* 0.5, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.40 (3H, d, *J*=6.9 Hz), 2.63 (3H, d, *J*=4.1 Hz), 3.02 (3H, s), 4.58 (1H, dq, *J*=6.9, 8.3 Hz), 7.80–7.83 (2H, m), 8.11–8.13 (2H, m), 8.11 (1H, d, *J*=9.6 Hz), 8.17 (1H, d, *J*=9.6 Hz), 8.87 (1H, d, *J*=8.3 Hz), 8.90–8.91 (1H, m), 9.11 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 19.2, 22.6, 25.6, 48.3, 113.2, 122.8, 123.8, 126.4, 128.0, 128.6, 128.7, 129.1, 129.8, 132.9, 134.5, 143.7, 157.2, 163.3, 172.2. Anal. Calcd (found) for $C_{19}H_{19}N_3O_2$: C, 71.01 (70.75); H, 5.96 (5.82); N, 13.03% (12.94%).

4.8.21. 4-Methyl-2-[(*S*)-2-propionamidoaminocarbonyl]benzo[*f*]isoquinoline (3d). Mp 257.0–258.0 °C. IR (KBr): 3401, 3341, 1676, 1655 cm^{-1}. $[\alpha]_D^{25}$ −16.0 (*c* 0.05, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.43 (3H, d, *J*=6.9 Hz), 3.05 (3H, s), 4.58 (1H, dq, *J*=6.9, 7.5 Hz), 7.24 (1H, s), 7.83 (1H, s), 7.82–7.85 (2H, m), 8.14–8.16 (1H, m), 8.15 (1H, d, *J*=9.2 Hz), 8.20 (1H, d, *J*=9.2 Hz), 8.87 (1H, d, *J*=7.5 Hz), 8.93–8.95 (1H, m), 9.15 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 19.3, 22.6, 48.0, 113.1, 122.8, 123.8, 126.4, 128.0, 128.6, 128.7, 129.1, 129.7, 132.9, 134.6, 143.8, 157.3, 163.3, 173.8. Anal. Calcd (found) for $C_{18}H_{17}N_3O_2$: C, 70.34 (70.04); H, 5.58 (5.52); N, 13.67% (13.81%).

4.8.22. 2-[(*S*)-*N*-(*t*-Butyl)-2-propionamidoaminocarbonyl]-4-methylbenzo[*f*]isoquinoline (3e). Mp 199.0–199.5 °C. IR (KBr): 3331, 1680, 1651 cm^{-1}. $[\alpha]_D^{25}$ −32.6 (*c* 0.5, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.28 (9H, s), 1.36 (3H, d, *J*=6.9 Hz), 2.99 (3H, s), 4.59 (1H, dq, *J*=6.9, 7.6 Hz), 7.77–7.81 (2H, m), 7.83 (1H, m), 8.08 (1H, d, *J*=8.9 Hz), 8.08–8.11 (1H, m), 8.13 (1H, d, *J*=8.9 Hz), 8.83 (1H, d, *J*=7.6 Hz), 8.86–8.87 (1H, m), 9.08 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 19.9, 22.7, 28.4 (3C), 48.3, 50.2, 113.1, 122.8, 123.8, 126.4, 127.9, 128.6, 128.7, 129.1, 129.7, 132.9, 134.5, 143.7, 157.2, 163.0, 171.3. Anal. Calcd (found) for $C_{22}H_{25}N_3O_2$: C, 72.70 (72.86); H, 6.93 (6.70); N, 11.56% (11.37%).

4.8.23. 4-Methyl-2-[(*S*)-*N*-phenyl-2-propionamidoaminocarbonyl]benzo[*f*]isoquinoline (3f). Mp 219.0–222.0 °C. IR (KBr): 3331, 1680, 1651 cm^{-1}. $[\alpha]_D^{25}$ −126.3 (*c* 0.05, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.56 (3H, d, *J*=7.6 Hz), 3.06 (3H, s), 4.84 (1H, dq, *J*=7.6, 7.6 Hz), 7.09 (1H, dd, *J*=7.6, 7.6 Hz), 7.35 (2H, dd, *J*=7.6,

8.3 Hz), 7.67 (2H, d, J=8.3 Hz), 7.81–7.85 (2H, m), 8.12–8.14 (1H, m), 8.13 (1H, d, J=8.9 Hz), 8.18 (1H, d, J=8.9 Hz), 8.91–8.92 (1H, m), 8.96 (1H, d, J=7.6 Hz), 9.14 (1H, s), 10.29 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 19.1, 22.6, 49.1, 113.3, 119.3 (2C), 122.8, 123.5, 123.8, 126.5, 128.0, 128.6, 128.7, 128.8 (2C), 129.1, 129.8, 132.9, 134.5, 138.7, 143.6, 157.3, 163.5, 170.9. Anal. Calcd (found) for $C_{24}H_{21}N_3O_2$: C, 75.18 (74.95); H, 5.52 (5.17); N, 10.96% (10.91%).

4.8.24. 2-[(*S*)-*N*-(4-Methoxyphenyl)-2-propionamido-aminocarbonyl]-4-methylbenzo[*f*]isoquinoline (3g). Mp 262.0–263.0 °C. IR (KBr): 3402, 3267, 1686, 1667 cm^{-1}. $[\alpha]_D^{25}$ −152.0 (c 0.01, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.55 (3H, d, J=6.9 Hz), 3.05 (3H, s), 3.74 (3H, s), 4.82 (1H, dq, J=6.9, 8.2 Hz), 6.93 (2H, d, J=9.6 Hz), 7.58 (2H, d, J=9.6 Hz), 7.81–7.85 (2H, m), 8.11–8.13 (1H, m), 8.12 (1H, d, J=8.9 Hz), 8.17 (1H, d, J=8.9 Hz), 8.90–8.91 (1H, m), 8.95 (1H, d, J=8.2 Hz), 9.13 (1H, s), 10.16 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 19.2, 22.6, 49.0, 55.1, 113.2, 113.9 (2C), 120.9 (2C), 122.8, 123.8, 126.4, 128.0, 128.6, 128.7, 129.1, 129.8, 131.8, 132.9, 134.5, 143.6, 155.4, 157.2, 163.4, 170.3. Anal. Calcd (found) for $C_{25}H_{23}N_3O_3$: C, 72.62 (72.43); H, 5.61 (5.38); N, 10.16% (9.99%).

4.8.25. 2-[(*S*)-*N*-(4-Cyanophenyl)-2-propionamido-aminocarbonyl]-4-methylbenzo[*f*]isoquinoline (3h). Mp 207.0–208.0 °C. IR (KBr): 3367, 3267, 2226, 1707, 1657 cm^{-1}. $[\alpha]_D^{25}$ −201.2 (c 0.5, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.55 (3H, d, J=6.9 Hz), 3.08 (3H, s), 4.81 (1H, dq, J=6.9, 7.6 Hz), 7.81 (2H, d, J=8.9 Hz), 7.82 (2H, d, J=8.9 Hz), 7.82–7.86 (2H, m), 8.15–8.16 (1H, m), 8.17 (1H, d, J=9.6 Hz), 8.23 (1H, d, J=9.6 Hz), 8.94–8.96 (1H, m), 8.98 (1H, d, J=7.6 Hz), 9.17 (1H, s), 10.69 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ 18.6, 22.6, 49.5, 105.2, 113.4, 119.0, 119.4 (2C), 122.8, 123.9, 126.5, 128.0, 128.6, 128.7, 129.2, 129.9, 132.9, 133.3 (2C), 134.6, 143.0, 143.5, 157.3, 163.8, 171.8. Anal. Calcd (found) for $C_{25}H_{20}N_4O_2$: C, 73.51 (73.29); H, 4.94 (4.75); N, 13.72% (13.76%).

4.8.26. (4*S,5*S**)-5-(1-Naphthyl)-2-phenyl-4-[(*S*)-*N*-(1-phenylethyl)aminocarbonyl]-4,5-dihydrooxazole [(*S*,*S*,*S*)-4b or (*R*,*R*,*S*)-4b].** Mp 159.0–160.0 °C. IR (KBr): 3216, 3072, 2936, 1650, 1602 cm^{-1}. $[\alpha]_D^{25}$ +393.6 (c 0.5, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.09–8.07 (1H, m), 8.07 (2H, d, J=8.2 Hz), 7.99–7.97 (1H, m), 7.92 (1H, d, J=8.2 Hz), 7.86 (1H, d, J=8.2 Hz), 7.65 (1H, dd, J=7.3, 7.3 Hz), 7.59 (1H, d, J=7.6 Hz), 7.59–7.54 (2H, m), 7.57 (2H, dd, J=8.2, 7.3 Hz), 7.43 (1H, dd, J=8.2, 7.6 Hz), 7.05 (1H, dd, J=7.3, 7.3 Hz), 6.99 (2H, dd, J=7.3, 7.3 Hz), 6.79 (1H, d, J=10.4 Hz), 6.50 (2H, d, J=7.3 Hz), 5.45 (1H, d, J=10.4 Hz), 4.35 (1H, dq, J=8.2, 7.0 Hz), 1.01 (3H, d, J=7.0 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.2, 46.9, 73.2, 80.5, 123.8, 123.9, 125.1, 125.4 (2C), 125.6, 126.1, 126.2, 127.3, 127.8 (2C), 128.1, 128.3 (2C), 128.4, 128.7 (2C), 130.1, 132.0, 132.4, 132.9, 143.1, 164.9, 166.6. Anal. Calcd (found) for $C_{28}H_{24}N_2O_2$: C, 79.98 (80.00); H, 5.75 (5.66); N, 6.66% (6.79%).

4.8.27. (4*R,5*R**)-5-(1-Naphthyl)-2-phenyl-4-[(*S*)-*N*-(1-phenylethyl)aminocarbonyl]-4,5-dihydrooxazole [(*S*,*S*,*S*)-4b or (*R*,*R*,*S*)-4b].** Mp 185.0–186.0 °C. IR (KBr): 3292, 3060, 2976, 1658, 1602 cm^{-1}. $[\alpha]_D^{25}$ −590.4 (c 0.5, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.12 (1H, d, J=7.6 Hz), 8.06 (2H, d, J=7.3 Hz), 7.95 (1H, d, J=8.5 Hz), 7.88 (1H, d, J=8.5 Hz), 7.87 (1H, d, J=7.9 Hz), 7.63 (1H, dd, J=7.3, 7.3 Hz), 7.59 (1H, dd, J=7.6, 6.7 Hz), 7.55–7.58 (4H, m), 7.46 (1H, dd, J=7.9, 7.9 Hz), 7.20 (2H, dd, J=7.3, 7.3 Hz), 7.14 (1H, dd, J=7.3, 7.3 Hz), 6.94 (2H, d, J=7.3 Hz), 6.78 (1H, d, J=10.4 Hz), 5.51 (1H, d, J=10.4 Hz), 4.15 (1H, dq, J=8.5, 7.3 Hz), 0.32 (3H, d, J=7.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.5, 47.2, 72.8, 80.5, 123.5, 124.1, 125.1, 125.5, 125.9 (3C), 126.5, 127.2, 127.8, 128.0 (2C), 128.1 (2C), 128.2, 128.7 (2C), 129.9, 131.9, 132.7, 132.8, 143.6, 164.3, 166.2. Anal. Calcd (found) for $C_{28}H_{24}N_2O_2$: C, 79.98 (79.83); H, 5.75 (5.72); N, 6.66% (6.66%).

4.9. X-ray crystallographic analysis of (*S*,*S*)-2a

A colorless crystal (of the molecular formula $C_{23}H_{22}N_2O_2$) having approximate dimensions of 0.18×0.18×0.05 mm was mounted on a glass fiber in a random orientation. Preliminary examination and data collection were performed with Mo Kα radiation (λ=0.71069 Å) on a Rigaku RAXIS-RAPID equipped with an imaging plate. Data collection and cell refinement: MSC/AFC diffractometer control. Data reduction: teXsan for windows version 1.06.[12] Structure solution: SIR92.[13] Refinement: SHELXL97.[14]

4.10. Crystal data for (*S*,*S*)-2a

Crystal data for (*S*,*S*)-**2a**. $C_{23}H_{22}N_2O_2$, f_w=358.43; Orthorhombic, space group $P2_12_12_1$; a=17.1392(13) Å, b=19.9116(13) Å, c=11.3231(9) Å, V=3864.2(5) Å^3; Z=8; D_{calcd}=1.232 g cm^{-3}; R=0.0661, $wR(F^2)$=0.2204. Crystallographic data (excluding these structure factors) for the structure in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 267308. 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).

Acknowledgements

This research was partially supported by a 'High-Tech Research Project' from the Ministry of Education, Sports, Culture, Science and Technology, Japan.

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A novel cis-chelated Pd(II)–NHC complex for catalyzing Suzuki and Heck-type cross-coupling reactions

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Received 22 July 2005; revised 1 September 2005; accepted 5 September 2005

Available online 23 September 2005

Abstract—A novel Pd(II)–NHC complex, which has a 'normal' cis-chelating, bidentate structure is fairly effective in Suzuki and Heck-type cross-coupling reaction to give the products in good to excellent yields in most cases.

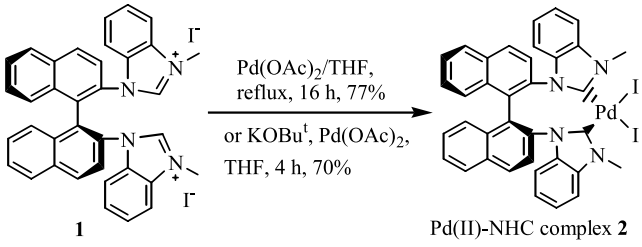
1. Introduction

In 1968, Öfele and Wanzlick concurrently prepared the first described metal complexes of *N*-heterocyclic carbenes (NHC).[1] However, these reports received little attention until Arduengo III synthesized stable free carbenes.[2] Herrmann's group further expanded this field by preparing numerous NHCs and their metal complexes, and applying these complexes in homogeneous catalysis.[3] Recently, numerous papers concerning this topic have appeared, and complexes of NHCs have been applied as catalysts in a broad range of reactions. Significantly, a number of Pd–NHC complexes have emerged as effective catalysts for a variety of coupling reaction.[4,5]

Previously, we reported the synthesis of a novel axially chiral Rh(III)–NHC complex derived from binaphthyl-2,2′-diamine (BINAM) and its application in the enantioselective hydrosilylation of methyl ketones.[5] In this paper, we wish to report the synthesis of a novel cis-chelating, Pd(II)–NHC complex and the application in the Suzuki and Heck-type cross-coupling reaction.[6]

2. Results and discussion

The synthesis of the novel cis-chelated, Pd(II)–NHC complex **2** is shown in Scheme 1. Reaction of dibenzimidazolium iodide (NHC precursor) **1**[5] with $Pd(OAc)_2$ either under reflux in THF or by treatment with a base such as potassium *tert*-butoxide in THF affords the desired complex **2** in 77 and 70% yields, respectively. Its crystal structure was determined by X-ray diffraction (Fig. 1).[7,8]



1 Pd(II)-NHC complex **2**

Scheme 1. Preparation of a novel Pd(II)–NHC complex.

Structural features. The single crystals of this complex suitable for X-ray crystal structure analysis were grown from dichloromethane/petroleum ether 1:2 solution. This is a NHC cis-chelating, bidentate Pd(II) complex. The bite angle of C–Pd–C is slightly more than 90° (94.4°). The bond length of C–Pd is 1.981(10)–1.982(9) Å, which is slightly contracted in comparison to those in the Herrmann's diiodide complexes.[3e,f] The bond length of the Pd–I bond trans to the carbene is 2.6617(10)–2.6658(10) Å and the bite angle of Pd–I–Pd is slightly more than 90° [94.87(4)°], which is resulted from the different steric effects of the terminal iodine atom and the NHC ligand.

The use of **2** as a catalyst for Suzuki cross-coupling reactions was examined where both solvent and base effects were carefully examined in the reaction of phenylboronic acid with bromobenzene under ambient atmosphere. The

Keywords: Pd(II)–NHC complex; Suzuki–Miyaura cross-coupling reaction; Heck reaction.
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doi:10.1016/j.tet.2005.09.010

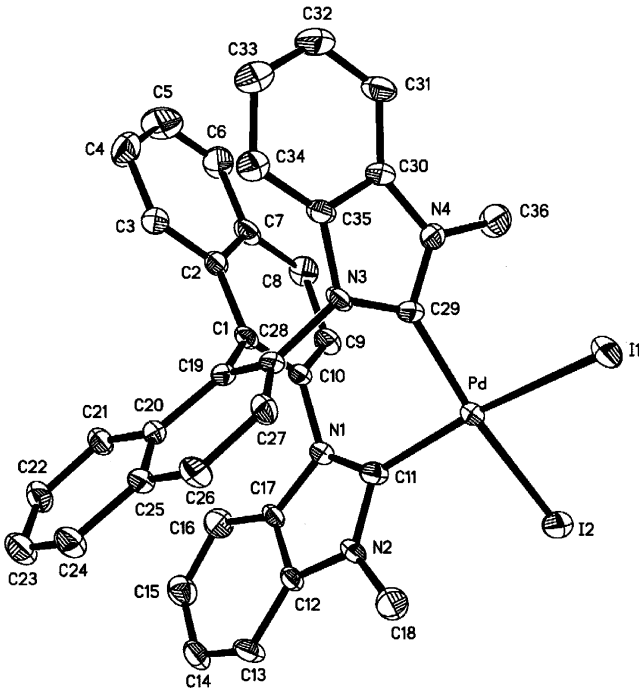
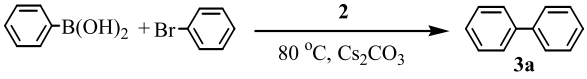


Figure 1. The ORTEP draw of Pd(II)–NHC complex **2**.

results are summarized in Tables 1 and 2, respectively. We found that using Cs_2CO_3 as the base in *N*,*N*-dimethylacetamide (DMA) or THF at 80 °C gave the coupled product **3a** in 66 and 70% yield, respectively (Table 1, entries 6 and 8). Increasing the reaction temperature to 100 °C in DMA with Cs_2CO_3 gave **3a** in 98% yield after 24 h (Table 2, entry 1). Thus, DMA is the solvent of choice and Cs_2CO_3 is the preferred base for this reaction. Using these optimized reaction conditions, the Suzuki cross-coupling reactions of a variety of aryl halides, including aryl bromides, aryl chlorides and iodobenzene, with phenylboronic acid were examined. The results are summarized in Table 3. As can be seen, aryl bromides and iodobenzene afforded coupling products **3** in 75–99% yield under ambient atmosphere (Table 3, entries 1–6 and 9). Aryl chlorides afforded moderate yields of the coupling products **3** (Table 3, entries 7 and 8). Under argon atmosphere, the isolated yields of **3a** and **3d** from chlorobenzene and 4-chloroacetophenone with phenylboronic acid could reach 54 and 80%, respectively (Table 3, entries 7 and 8). This is because aryl chlorides involved in a slower oxidative addition with Pd(0)–carbene complex might be more reactive under argon atmosphere, which increases the probability to have a Pd(0) complex rather than an unreactive Pd(II) complex.

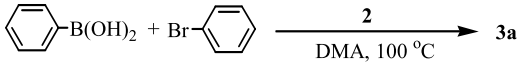
Table 1. Pd(II)–NHC complex **2** catalyzed Suzuki coupling reaction between phenylboronic acid (1.2 mmol) with bromobenzene (1.0 mmol) in various solvents



Entry	Solvent	Time (h)	Yield (%) **3a**[a]
1	1,4-Dioxane	24	40
2	DMSO	24	14
3	DMF	24	36
4	CH_2ClCH_2Cl	24	22
5	DME	24	65
6	DMA	24	66
7	CH_3CN	24	40
8	THF	24	70

[a] Isolated yields.

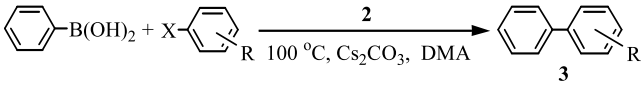
Table 2. Pd(II)–NHC complex **2** catalyzed Suzuki coupling reaction between phenylboronic acid (1.2 mmol) with bromobenzene (1.0 mmol) in the presence of various bases



Entry	Base	Time (h)	Yield (%) **3a**[a]
1	CS_2CO_3	24	98
2	Na_2CO_3	24	56
3	K_2CO_3	24	67
4	KF	24	85
5	$K_3PO_4 \cdot 3H_2O$	24	77
6	$KOBu^t$	24	6

[a] Isolated yields.

Table 3. Pd(II)–NHC complex **2** catalyzed Suzuki coupling reaction between phenylbronic acid (1.2 mmol) and arylhalides (1.0 mmol) under optimized conditions

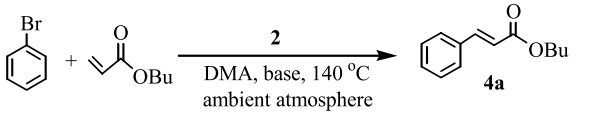


Entry	X	R	Time (h)	Yield (%) **3**[a]
1	Br	*o*-Me	24	**3b**, 95
2	Br	*p*-Me	24	**3c**, 75
3	Br	*p*-COMe	24	**3d**, 90
4	Br	*p*-OMe	24	**3e**, 86
5	Br	*o*-Cl	24	**3f**, 95
6	Br	3,5-Me,Me	24	**3g**, 89
7	Cl	H	24	**3a**, 40 (54)[b]
8	Cl	*p*-COMe	24	**3d**, 45 (80)[b]
9	I	H	24	**3a**, 99

[a] Isolated yields.
[b] Isolated yield under argon atmosphere.

Heck coupling reactions were also examined in DMA by the reaction of bromobenzene with butyl acrylate in the presence of various bases (Table 4, entries 1–7). We found that KF afforded the best results for this reaction and offered the coupling product **4a** in 53% under ambient

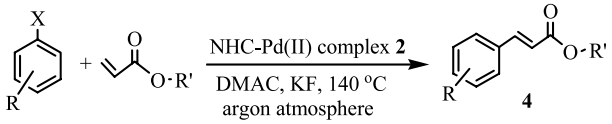
Table 4. Pd(II)–NHC complex **2** catalyzed Heck coupling of bromobenzene with *n*-butyl acrylate under ambient or argon atmosphere



Entry	Base	Time (h)	Yield (%) **4a**[a]
1	Na_2CO_3	30	38
2	K_2CO_3	30	40
3	KF	30	53 (98)[b]
4	$K_3PO_4 \cdot 3H_2O$	30	31
5	NaOAc	30	9
6	$KOBu^t$	30	Trace
7	NaOAc[c]	30	48

[a] Isolated yields.
[b] Under argon atmosphere.
[c] Bu_4NBr (0.2 mmol) was added to the reaction solution.

Table 5. Pd(II)–NHC complex **2** catalyzed Heck coupling of aryl halides with butyl acrylate under argon atmosphere



Entry	X	R	R′	Time (h)	Yield (%) **4**[a]
1	Br	*o*-Me	*n*-Bu	30	**4b**, 86
2	Br	*p*-Me	*n*-Bu	30	**4c**, 84
3	Br	*p*-COMe	*n*-Bu	30	**4d**, 99
4	Br	*p*-OMe	*n*-Bu	30	**4e**, 28
5	Br	*o*-Cl	*n*-Bu	30	**4f**, 90
6	Br	3,5-Me,Me	*n*-Bu	30	**4g**, 70
7	Br	H	*n*-Bu	30	**4a**, 98
8	Cl	*p*-COMe	*n*-Bu	30	**4d**, 50
9	Br	H	Me	30	**4h**, 76
10	Br	*p*-CHO	Me	30	**4i**, 83

[a] Isolated yields.

atmosphere (Table 4, entry 3). Using an argon atmosphere, the yield of **4a** was improved to 98% (Table 4, entry 3).

Using these reaction conditions, we next examined the Heck coupling of a variety of aryl halides with butyl and methyl acrylate. The results are summarized in Table 5. We found that the Heck reaction products **4** were obtained in good to high yields in most cases when an argon atmosphere was used (Table 5, entries 1–3 and 5–10). For electron rich 4-bromoanisole, the reaction was sluggish and product **4e** was obtained in only 28% yield under the same conditions (Table 5, entry 4). Product structures were determined by ^{1}H and ^{13}C NMR spectroscopy and HRMS or microanalyses (for ^{1}H NMR charts see Supporting information).

We believe that the cis-chelated configuration of **2** is responsible for allowing it to be an effective catalyst in these coupling reactions since the 1,1-reductive elimination from a cis-oriented coordination site is favored.[9] Moreover, carbene ligands are less likely to dissociate than the corresponding phosphine[10] or bis-pyridine[11] systems, so the catalysis via less saturated intermediates is disfavored.[12]

In conclusion, we disclosed novel cis-chelating, Pd(II)–NHC complex **2**, which has a 'normal' bidentate structure and is an effective catalyst for Suzuki and Heck cross-coupling reactions. Efforts are underway to elucidate the mechanistic details of these C–C bond forming reactions and the use of **2** to catalyze other C–C bond forming transformations.

3. Experimental

3.1. General remarks

^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard; *J* values are in Hz. Mass spectra were recorded with a HP-5989 instrument. THF and toluene were distilled from Na under Ar atmosphere. All of the solid compounds reported in this paper gave satisfactory CHN microanalyses with a Carlo-Erba 1106 analyzer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure.

3.1.1. 1,1′-(1,1′-Binaphthyl)-3,3′-dimethyldibenzimidazolium diiodide 1. This is a known compound.[5] The synthesis of **1** has been summarized in Supporting information.

3.1.2. Preparation of Pd(II)–NHC complex. The compound **1** (154 mg, 0.20 mmol) and $Pd(OAc)_2$ (44 mg, 0.20 mmol) was refluxed in THF (10 mL) for 16 h. The solvent was removed under reduced pressure and the residue was separated by silica gel chromatography to give Pd(II)–NHC complex **2** (134 mg, 77%) as a yellow solid [eluent: CH_2Cl_2/ethyl acetate 0:1–1:1]. The single crystal for X-ray diffraction was obtained by recrystallization from CH_2Cl_2/petroleum ether. Mp>300 °C; IR (KBr): ν 3538, 1583, 1509, 1382, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 3.82 (6H, s, CH_3), 6.66 (2H, d, J=8.1 Hz, ArH), 6.73–6.93 (10H, m, ArH), 7.19–7.24 (2H, m, ArH), 7.70 (2H, d, J=8.7 Hz, ArH), 8.03–8.10 (4H, m, ArH); MS (ESI) *m/e* 747.0 ($M^{+}-I$). Anal. Calcd for $C_{36}H_{26}I_2N_4Pd\cdot H_2O$ requires: C, 48.43; H, 3.16; N, 6.27%. Found: C, 48.27; H, 3.24; N, 6.15%.

3.2. General procedure for the Suzuki reactions of aryl bromides with boronic acids

A typical procedure is given below on the reaction expressed in entry 3 of Table 3. Complex **2** (8.7 mg, 0.01 mmol), cesium carbonate (646 mg, 2.0 mmol), 4-bromoacetophenyl (198 mg, 1.0 mmol), phenylboronic acid (148 mg, 1.2 mmol), and DMA (2.0 mL) were introduced to an Schlenk tube under ambient atmosphere. The mixture was stirred at 100 °C for 24 h. The reaction mixture was diluted with H_2O (15 mL) and Et_2O (15 mL), followed by extraction twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude product. The pure product was isolated by column chromatography (eluent: hexane/ethyl acetate 15:1) on silica gel to give 176 mg (90%) of 4-acetylbiphenyl as a

colorless solid, which was analyzed by ^{1}H NMR and IR spectroscopy.

3.2.1. Compound 3a. A white solid, mp 70.5–72.0 °C; IR (KBr): ν 3037, 1569, 1480, 1429, 729, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 7.35–7.37 (2H, m, ArH), 7.42–7.47 (4H, m, ArH), 7.59–7.62 (4H, m, ArH).

3.2.2. Compound 3b. A colorless oil; IR (KBr): ν 3059, 3020, 2933, 1590, 1479, 1439, 1372, 1010, 774, 748, 726, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.27 (3H, s, CH_3), 7.23–7.61 (9H, m, ArH).

3.2.3. Compound 3c. A white solid, mp 45.0–50.0 °C; IR (KBr): ν 3029, 1486, 1398, 823, 755, 735, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.40 (3H, s, CH_3), 7.24–7.60 (9H, m, ArH).

3.2.4. Compound 3d. A white solid, mp 120.4–121.3 °C; IR (KBr): ν 3050, 1680, 1600, 1570, 1450, 1394, 1353, 1261, 958, 835, 765, 721, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.65 (3H, s, CH_3), 7.40–7.48 (3H, m, ArH), 7.62–7.71 (4H, m, ArH), 8.04 (2H, d, J=7.2 Hz, ArH).

3.2.5. Compound 3e. A white solid, mp 91.1–92.3 °C; IR (KBr): ν 3050, 2956, 2837, 1605, 1520, 1486, 1446, 1283, 1269, 1180, 1035, 834, 760, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 3.87 (3H, s, OCH_3), 6.97–7.00 (2H, m, ArH), 7.26–7.30 (1H, m, ArH), 7.39–7.44 (2H, m, ArH), 7.52–7.57 (4H, m, ArH).

3.2.6. Compound 3f. A yellow solid, mp 32.5–33.5 °C; IR (KBr): ν 3059, 3031, 2924, 1380, 1498, 1467, 1425, 1128, 1075, 1036, 1009, 770, 748, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 7.24–7.61 (9H, m, ArH).

3.2.7. Compound 3g. A white solid, mp 22.2–23.1 °C; IR (KBr): ν 3059, 3031, 2919, 1603, 1577, 1482, 1380, 850, 761, 737, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 2.37 (6H, s, CH_3), 6.99–7.61 (8H, m, ArH).

3.3. Typical reaction procedure for Heck reaction

In a Schlenk tube fitted with a septum and a reflux condenser were placed aryl halide (1.0 mmol), butyl acrylate (1.5 mmol), potassium fluoride (116 mg, 2.0 mmol), tetrabutylammonium bromide (64.4 mg, 0.20 mmol), and *N*,*N*-dimethylacetamide (DMAC, 2.0 mL). After repeated degassing by oil pump vacuum and flushing with argon, complex **2** (8.7 mg, 0.01 mmol) was added under an argon atmosphere. The mixture was stirred at 140 °C for 30 h. The reaction mixture was diluted with H_2O (15 mL) and Et_2O (15 mL), followed by extraction twice with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give crude product. A pure product was isolated by column chromatography (eluent: hexane/ethyl acetate 15:1) on silica gel. The purified product was analyzed by ^{1}H NMR and IR spectroscopy.

3.3.1. Compound 4a. A yellow liquid; IR (KBr): ν 3020, 2960, 2874, 1714, 1638, 1571, 1500, 1450, 1380, 979, 768, 711 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 0.96 (3H, t, J=7.2 Hz, CH_3), 1.37–1.50 (2H, m, CH_2), 1.64–1.74 (2H, m, CH_2), 4.21 (2H, t, J=7.2 Hz, OCH_2), 6.44 (1H, d, J=15.9 Hz, =CH), 7.36–7.38 (3H, m, ArH), 7.50–7.53 (2H, m, ArH), 7.68 (1H, d, J=15.9 Hz, =CH).

3.3.2. Compound 4b. A yellow liquid; IR (KBr): ν 3070, 3020, 2959, 2867, 1713, 1634, 1600, 1520, 1461, 1380, 1313, 1275, 1173, 981, 763, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 0.97 (3H, t, J=7.2 Hz, CH_3), 1.38–1.50 (2H, m, CH_2), 1.64–1.75 (2H, m, CH_2), 2.44 (3H, s, CH_3), 4.22 (2H, t, J=7.2 Hz, OCH_2), 6.36 (1H, d, J=15.9 Hz, =CH), 7.19–7.30 (3H, m, ArH), 7.54–7.57 (1H, m, ArH), 7.98 (1H, d, J=15.9 Hz, =CH).

3.3.3. Compound 4c. A yellow liquid; IR (KBr): ν 3020, 2956, 2859, 1713, 1638, 1605, 1520, 1464, 1380, 1310, 1256, 1204, 1168, 983, 813 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 0.88 (3H, t, J=7.2 Hz, CH_3), 1.29–1.42 (2H, m, CH_2), 1.57–1.66 (2H, m, CH_2), 2.28 (3H, s, CH_3), 4.21 (2H, t, J=7.2 Hz, OCH_2), 6.31 (1H, d, J=15.6 Hz, =CH), 7.09 (2H, d, J=7.2 Hz, ArH), 7.34 (2H, d, J=7.2 Hz, ArH), 7.58 (1H, d, J=15.6 Hz, =CH).

3.3.4. Compound 4d. A yellow liquid; IR (KBr): ν 3020, 2941, 2852, 1715, 1685, 1638, 1601, 1560, 1460, 1380, 1312, 1265, 1174, 982, 827 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 0.97 (3H, t, J=7.2 Hz, CH_3), 1.40–1.48 (2H, m, CH_2), 1.68–1.73 (2H, m, CH_2), 2.62 (3H, s, CH_3), 4.23 (2H, t, J=7.2 Hz, OCH_2), 6.53 (1H, d, J=15.9 Hz, =CH), 7.61 (2H, d, J=8.4 Hz, ArH), 7.69 (1H, d, J=15.9 Hz, =CH), 7.97 (2H, d, J=8.4 Hz, ArH).

3.3.5. Compound 4e. A yellow liquid; IR (KBr): ν 3070, 3020, 2959, 2852, 1710, 1635, 1604, 1564, 1513, 1464, 1387, 1251, 1170, 1031, 983, 828 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 0.89 (3H, t, J=7.2 Hz, CH_3), 1.32–1.40 (2H, m, CH_2), 1.56–1.63 (2H, m, CH_2), 3.76 (3H, s, OCH_3), 4.12 (2H, t, J=7.2 Hz, OCH_2), 6.24 (1H, d, J=15.6 Hz, =CH), 6.81–6.84 (2H, m, ArH), 7.39–7.42 (2H, m, ArH), 7.57 (1H, d, J=15.6 Hz, =CH).

3.3.6. Compound 4f. A yellow liquid; IR (KBr): ν 3070, 3020, 2960, 2934, 2873, 1717, 1637, 1591, 1520, 1471, 1443, 1380, 1315, 1269, 1202, 1176, 1053, 980, 760, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 0.97 (3H, t, J=7.2 Hz, CH_3), 1.42–1.48 (2H, m, CH_2), 1.55–1.74 (2H, m, CH_2), 4.22 (2H, t, J=7.2 Hz, OCH_2), 6.43 (1H, d, J=15.6 Hz, =CH), 7.25–7.31 (2H, m, ArH), 7.38–7.41 (1H, m, ArH), 7.59–7.62 (1H, m, ArH), 8.08 (1H, d, J=15.6 Hz, =CH).

3.3.7. Compound 4g. A yellow liquid; IR (KBr): ν 3020, 2959, 2867, 1714, 1637, 1594, 1442, 1380, 1285, 1254, 1164, 982, 843, 678 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ 0.97 (3H, t, J=7.2 Hz, CH_3), 1.40–1.48 (2H, m, CH_2), 1.66–1.71 (2H, m, CH_2), 2.33 (6H, s, CH_3), 4.20 (2H, t, J=7.2 Hz, OCH_2), 6.42 (1H, d, J=15.6 Hz, =CH), 7.02 (1H, s, ArH), 7.15 (2H, s, ArH), 7.62 (1H, d, J=15.6 Hz, =CH).

3.3.8. Compound 4h. A white solid, mp 35.8–36.5 °C; IR (KBr): ν 3050, 3020, 2944, 1717, 1638, 1576, 1496, 1450, 1380, 1314, 1275, 1200, 1170, 980, 768, 712 cm^{-1}; ^{1}H

NMR ($CDCl_3$, 300 MHz, TMS): δ 3.81 (3H, s, OCH_3), 6.45 (1H, d, $J=15.6$ Hz, =CH), 7.38–7.41 (3H, m, ArH), 7.51–7.55 (2H, m, ArH), 7.70 (1H, d, $J=15.6$ Hz, =CH).

3.3.9. Compound 4i. A white solid, mp 82.1–83.0 °C; IR (KBr): ν 3020, 2958, 2840, 2740, 1712, 1691, 1637, 1602, 1540, 1425, 1392, 1315, 1203, 1163, 984, 820, 796 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS): δ 3.84 (3H, s, OCH_3), 6.57 (1H, d, $J=15.9$ Hz, =CH), 7.69 (2H, d, $J=8.0$ Hz, ArH), 7.73 (1H, d, $J=15.9$ Hz, =CH), 7.91 (2H, d, $J=8.0$ Hz, ArH), 10.04 (1H, s, HC=O).

Acknowledgements

We thank the State Key Project of Basic Research (project 973) (no. G2000048007), Shanghai Municipal Committee of Science and Technology, and the National Natural Science Foundation of China (203900502, 20472096 and 20272069) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.09.010. The spectroscopic charts of coupling products **3** and **4** as well as the synthesis of 1,1′-(1,1′-binaphthyl)-3,3′-dimethyldibenzimidazolium diiodide **1** and the X-ray crystal data of NHC–Pd(II) complex **2**.

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Tetrahedron

Synthetic studies related to diketopyrrolopyrrole (DPP) pigments. Part 3: Syntheses of tri- and tetra-aryl DPPs☆

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Received 29 June 2005; revised 15 August 2005; accepted 1 September 2005

Available online 5 October 2005

Abstract—Novel synthetic methodologies leading towards 2,3,5-triaryl- and 2,3,5,6-tetraaryl-2,5-dihydropyrrolo[3,4-*c*]pyrrole-1,4-diones (tri- and tetra-aryl-DPPs) and their derivatives have been investigated. Direct arylation of 3,6-diphenyl-DPP was possible using 1-fluoro-2,4-dinitrobenzene. Acylation of ethyl 2-aryl-4,5-dihydro-5-oxopyrrole-3-carboxylates with *N*-arylbenzimidoyl chlorides in the presence of a strong base gives the novel 2,3,6-triaryl-DPPs together with the corresponding uncyclised enamines. A new and simple method for the synthesis of ethyl 1,2-diaryl-4,5-dihydro-5-oxopyrrole-3-carboxylates has led to an alternative route to triaryl-DPPs via reaction with benzonitrile under basic conditions, and combination of this with the benzimidoyl chloride methodology has enabled the synthesis of variously substituted 2,3,5,6-tetraphenyl-DPPs.

1. Introduction

The synthesis of derivatives of the 3,6-diphenyl-2*H*,5*H*-pyrrolo[3,4-*c*]pyrrole-1,4-dione **1** (diketopyrrolopyrrole or DPP) ring system may be accomplished by several different routes, for example, reaction of dialkyl succinates or of alkyl 4,5-dihydro-5-oxo-2-phenylpyrrole-3-carboxylates (e.g., **2a**) with aromatic nitriles in the presence of a strong base such as sodium *t*-amyloxide.[1,2] Those DPPs in which both nitrogen atoms are unsubstituted (e.g., **1**) find commercial application as red pigments, not only because of their colour strength and brightness, but also because of their very low solubility in most common solvents. The low solubility results in part from the solid-state arrangement of molecules in parallel sheets, with strong intermolecular hydrogen-bonding between adjacent molecules, and the colour derives not only from the fundamental chromophore but also from π–π stacking:[3] for example, a DPP derivative such as **1** (R = Ph), which is red in the solid state, is yellow (and fluorescent) in very dilute solution in DMSO.

Similarly *N*,*N*′-disubstitution, which removes the possibility of intermolecular hydrogen bonding, not only increases the solubility but also changes the perceived colour of the solid. Dialkylation at the two nitrogens[4,5] is possible (Scheme 1), and these dialkyl derivatives **3** are fluorescent and relatively soluble in organic solvents. Direct arylation of DPPs has not until now been recorded, although *N*,*N*′-diaryl-DPPs **4** may be obtained in certain cases from the corresponding furo[3,4-*c*]furans **5** by reaction with aniline derivatives,[6] by the cyclisation of bis-anilides **6**[7] or by oxidation of a tetrahydro-DPP precursor **7**[4] with DDQ (Scheme 1). The isomeric *N*,*N*′-diarylpyrrolo[3,2-*b*]pyrroles **8** are known, and can be synthesised from arylacetic esters using bis-imidoyl chlorides as electrophiles.[8] The bis-*N*-arylimidoyl chlorides **9** react with 2 equiv of ester anions, to give the bis-imines **10a** or bis-enamines **10b**, which are cyclised to the *N*,*N*′-diaryl-pyrrolopyrroles **8**. In particular, unsymmetrical derivatives can be made via the corresponding unsymmetrical bis-imidoyl chlorides.[9] All of these methods should be adaptable to provide routes to unsymmetrically diarylated DPPs. Mono-*N*-arylated DPPs, in which the other nitrogen is unsubstituted, constitute a class of DPP derivatives which are hitherto uninvestigated. Mono-*N*-aryl-DPPs might be expected to have properties intermediate between those of the di-*NH*- and the di-*N*-aryl-DPPs, to the extent that they retain the potential to exhibit intermolecular hydrogen bonding, perhaps to form dimers in the solid state. In Part

☆ Part 2, see Ref. 10.

Keywords: Pigments; Heterocycles; Pyrrolopyrroles; Cyclisation; Enamines; Microwaves.
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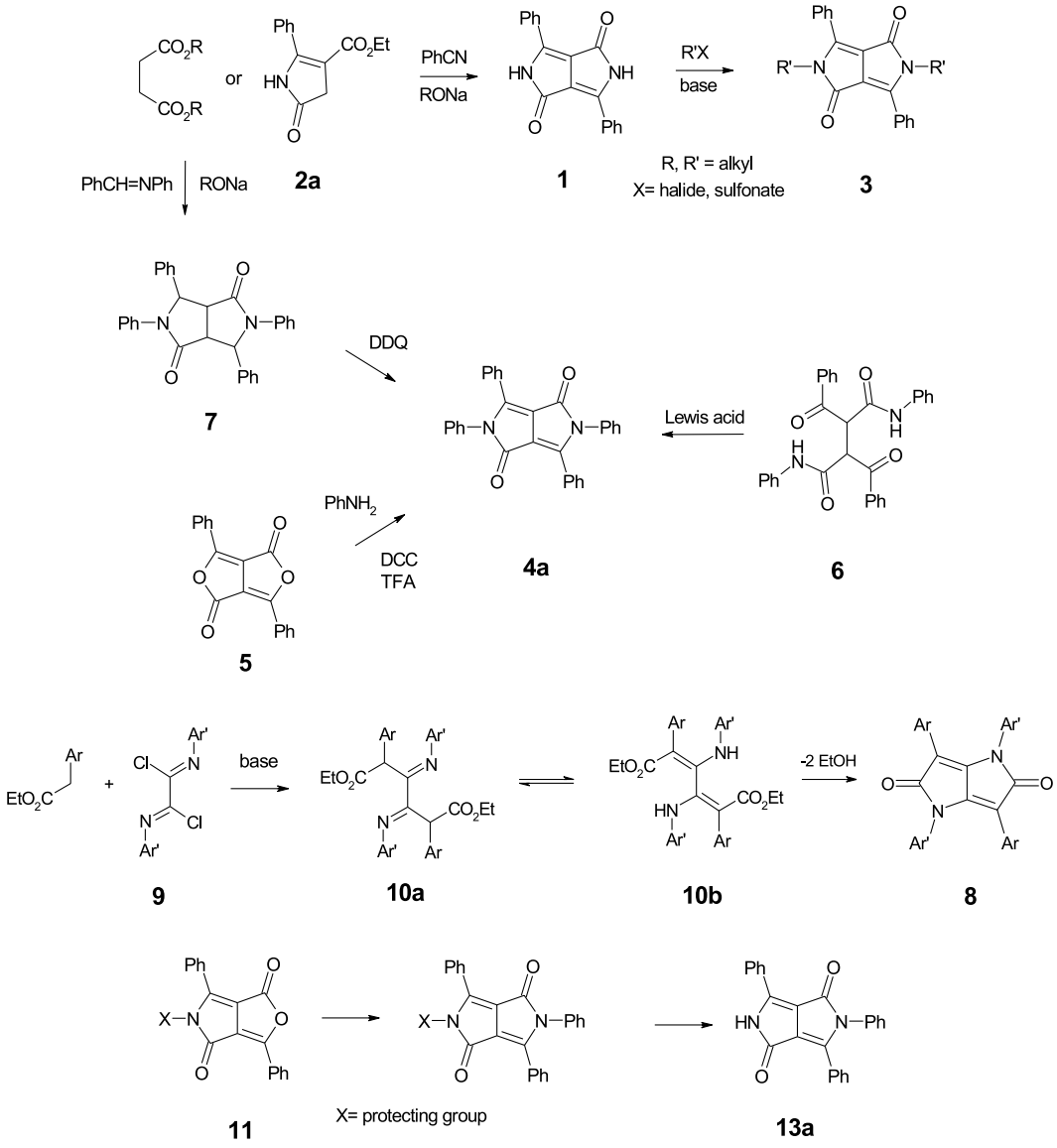
doi:10.1016/j.tet.2005.09.005



Scheme 1.

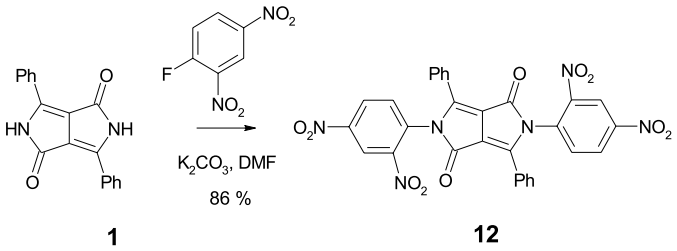
2[10] we have described what is potentially an indirect route to such compounds, although the ring-opening/ring-closure sequence which converts the furopyrrolediones **11** into DPPs requires that the nitrogen of the former be substituted,[10] and *N*-protection and deprotection would represent additional steps in such a synthesis (Scheme 1).

2. Results and discussion

2.1. Direct arylation of 3,6-diphenyl-DPP

In contrast to alkylation, direct *N*-arylation of amides is not readily accomplished without using highly electron-deficient aryl electrophiles such as 1-fluoro-2,4-dinitrobenzene. It was found that diphenyl-DPP **1** reacted with 1-fluoro-2,4-dinitrobenzene and potassium carbonate in DMF at room temperature to give the *N*,*N*′-bis-(2,4-dinitrophenyl)-DPP **12** as an orange crystalline solid in high yield (Scheme 2). It is noteworthy that this reaction typically requires reaction times of several days, and this time cannot be reduced by heating as this causes significant decomposition. The structure of compound **12** was confirmed by X-ray crystallography, which shows that the molecule crystallises with two molecules of DMF (Fig. 1). Despite the simplicity and high yields of this reaction, the four nitro groups strongly quench the fluorescence properties, rendering these compounds unsuitable for any fluorescence-based application.

In agreement with earlier observations by workers within Ciba,[11] no reaction was observed at all between compound **1** and less electrophilic arylating agents—even 1-fluoro-4-nitrobenzene. Similarly, treatment of both DPPs **1** and **13a** (see below) with iodobenzene and either copper[12,13] or palladium[14,15] catalysts under a variety of conditions and solvents gave none of the *N*-arylated products; only starting materials were recovered, presumably because of the insolubility of these substrates.



Scheme 2.

2.2. Mono-*N*-aryl-DPPs

Mono-*N*-aryl-DPPs, in which the other nitrogen is unsubstituted, have not hitherto been reported. The present paper describes two methods for the synthesis of triaryl-DPPs, the combination of which enables the synthesis of tetraaryl-DPPs in which all four aryl groups can vary independently of one another.

2.2.1. *N*-arylbenzimidoyl chlorides as electrophiles. The tetrahydro-DPPs referred to above are obtained when a Schiff base replaces the nitrile in a standard DPP synthesis. For example, the use of *N*-benzylideneaniline, PhCH=NPh, leads to compound **7**. If on the other hand the nitrile is replaced by an *N*-arylbenzimidoyl chloride, ArC(Cl)=NAr′, the mono-*N*-arylated DPP may be obtained directly. These *N*-arylbenzimidoyl chlorides, for example, **14a**–**d**, are most conveniently obtained from the corresponding benzanilides and thionyl chloride or phosphorus pentachloride.

Reaction of the ester **2a** with a strong base (sodium hydride or sodium hexamethyldisilazide) and *N*-phenylbenzimidoyl chloride **14a** in tetrahydrofuran gave a mixture of two products. The insoluble orange compound was identified by NMR and mass spectrometry as the DPP derivative **13a**, whereas work-up of the reaction solution yielded a beige compound, identified as the enamine **15a**. The corresponding reactions of compound **2a** and of its *p*-chloro-analogue **2b** with a range of *N*-arylbenzimidoyl chlorides **14a**–**d** led to a series of mono-*N*-aryl-DPPs **13a**–**d** and enamines **15a**–**d**.

Treatment of the 2,3,6-triaryl-DPPs **13a**–**d** with methyl *p*-toluenesulfonate and potassium carbonate in DMF gave the corresponding *N*-methyl analogues **16a**–**d**; likewise, treatment with benzyl bromide under the same conditions gave the *N*-benzyl derivatives **17a**–**d**. Due to the breakdown of any hydrogen bonding ability, these *N*-alkyl compounds are markedly more soluble than the *N*-unsubstituted precursors, and similarly are highly coloured and fluorescent. The triaryl derivatives **13b**,**d** also reacted with 1-fluoro-2,4-dinitrobenzene to give novel tetra-aryl-DPPs **18b**,**d**. These reactions were significantly faster than that of the unsubstituted analogue, with high yields generated after relatively short periods of time. These compounds are summarised in Table 1 and Scheme 3.

It was demonstrated in Part 2[10] that the 4-acyl derivatives of the esters **2a**,**b**, which exist substantially as the enol tautomers, underwent thermal cyclisation, either in a high-boiling solvent or in a microwave reactor, to give furo[3,4-*c*]pyrrolediones, even if the preferred geometry of the enol was *Z*. The enamines **15a**–**d**, however, were resistant to thermal cyclisation under analogous conditions: it therefore seems a reasonable hypothesis that these enamines have the *Z*-configuration. This assignment is supported, as in the enol series, by the anomalously low chemical shift ($\delta_H \sim 3.2$) of

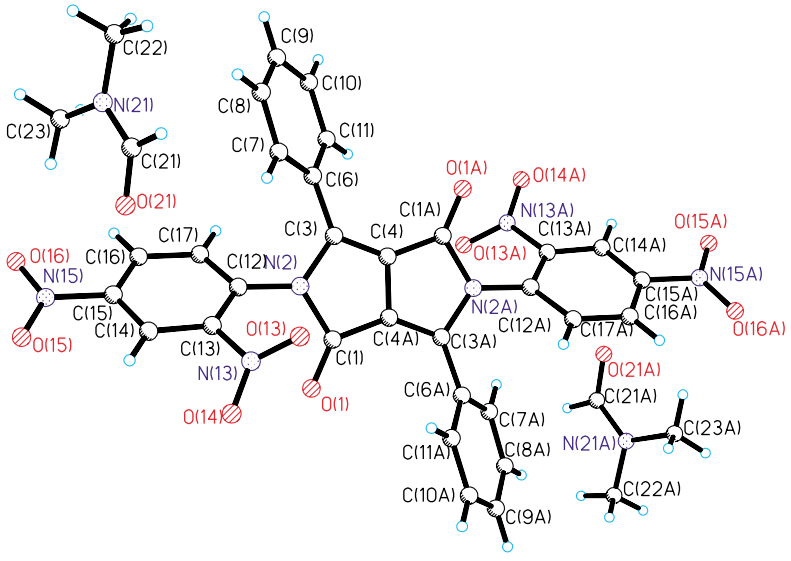
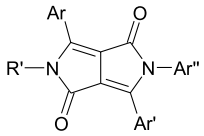


Figure 1. X-ray structure of compound **12**. Selected bond lengths (Å): C(1)–N(2), 1.439(3); N(2)–C(3), 1.413(3); C(3)–C(4), 1.371(4); C(1)–C(4A), 1.449(4); N(2)–C(12), 1.404(3); C(3)–C(6), 1.447(4); C(4)–C(4A), 1.404(5). Selected interbond angles (°): C(1)–N(2)–C(3), 111.6(2); C(1)–N(2)–C(12), 121.4(2); N(2)–C(3)–C(4), 106.1(2); C(3)–C(4)–C(1A), 140.5(2); C(4)–C(4A)–C(1), 109.0(3). Selected torsion angles (°): C(1)–N(2)–C(12)–C(13), 50.6(3); N(2)–C(3)–C(6)–C(7), 43.2(4).

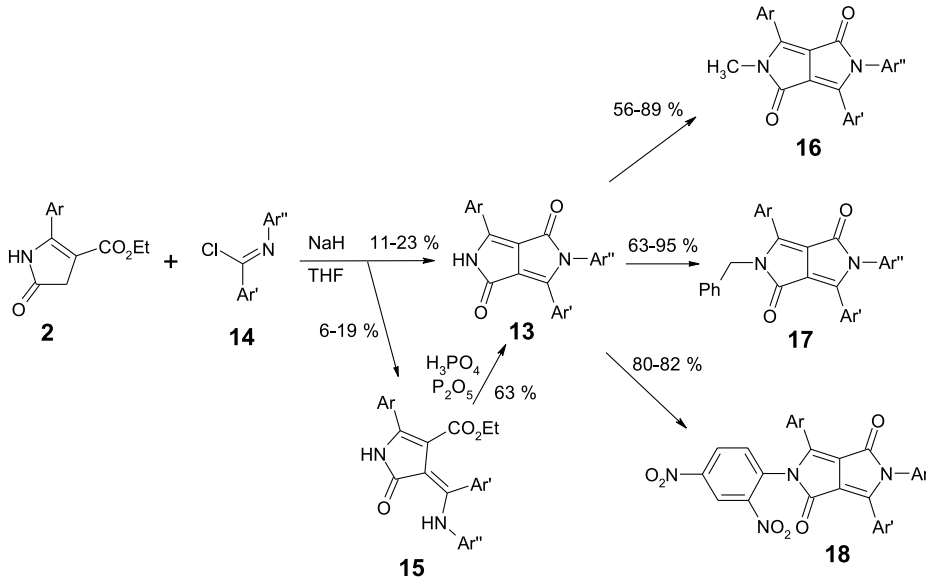
Table 1. Various DPP derivatives synthesised



Compound number	R′	Ar	Ar′	Ar″	λ_{max} abs	Log ε	Solvent	λ_{max} em	Quantum yield (%)
12	*o*/*p*-$(NO_2)_2C_6H_3$	Ph	Ph	*o*/*p*-$(NO_2)_2C_6H_3$	470	4.33	DMSO	516	2
13a	H	Ph	Ph	Ph	498	4.23	DMSO	520	44
					470	4.21			
13b	H	Ph	Ph	*p*-$MeOC_6H_4$	500	4.20	DMSO	521	3
					472	4.17			
13c	H	Ph	Ph	*p*-$F_3CC_6H_4$	493	4.19	DMSO	519	43
					467	4.17			
13d	H	*p*-ClC_6H_4	*p*-BrC_6H_4	*p*-$MeOC_6H_4$	511	4.46	DMSO	532	9
					481	4.43			
16a	CH_3	Ph	Ph	Ph	468	4.11	DCM	521	43
16b	CH_3	Ph	Ph	*p*-$MeOC_6H_4$	471	4.19	DCM	522	23
16c	CH_3	Ph	Ph	*p*-$F_3CC_6H_4$	470	4.11	DCM	520	48
16d	CH_3	*p*-ClC_6H_4	*p*-BrC_6H_4	*p*-$MeOC_6H_4$	487	4.18	DCM	533	15
17a	CH_2Ph	Ph	Ph	Ph	468	4.11	DCM	519	42
17b	CH_2Ph	Ph	Ph	*p*-$MeOC_6H_4$	470	4.27	DCM	522	27
17c	CH_2Ph	Ph	Ph	*p*-$F_3CC_6H_4$	468	4.12	DCM	518	43
17d	CH_2Ph	*p*-ClC_6H_4	*p*-BrC_6H_4	*p*-$MeOC_6H_4$	488	4.28	DCM	532	5
18b	*o*/*p*-$(NO_2)_2C_6H_3$	Ph	Ph	*p*-$MeOC_6H_4$	470	4.26	DMSO	515	0
18d	*o*/*p*-$(NO_2)_2C_6H_3$	*p*-ClC_6H_4	*p*-BrC_6H_4	*p*-$MeOC_6H_4$	483	4.43	DMSO	513	0
4a	Ph	Ph	Ph	Ph	488	4.27	*o*-$Cl_2C_6H_4$	524	29
4b	Ph	Ph	Ph	*p*-$MeOC_6H_4$	490	4.24	*o*-$Cl_2C_6H_4$	520	12
4c	Ph	Ph	Ph	*p*-$F_3CC_6H_4$	486	4.29	*o*-$Cl_2C_6H_4$	520	32

the ester methylene protons, and was confirmed unambiguously for **15b**,**d** by X-ray crystallography (see Figs. 4 and 5). It seems also reasonable to suggest that the reaction of the esters **2a**,**b** with the imidoyl chlorides **14a–d** gives initially both *E* and *Z*-enamines, that the former undergo spontaneous cyclisation to the DPPs **13a–d** and that the enamines undergo *Z*→*E* transformation much less easily than the corresponding enols. Cyclisation of the enamines **15a–d** was, however, promoted by treatment with polyphosphoric acid.

These triaryl-DPPs **13a–d** appear amorphous to the naked eye when crystallisation is attempted from most solvents; however, in the case of the *N*-*p*-methoxyphenyl-DPP **13b**,



13-18: a) Ar = Ar′ = Ar″ = Ph
b) Ar = Ar′ = Ph, Ar″ = *p*-$MeOC_6H_4$
c) Ar = Ar′ = Ph, Ar″ = *p*-$CF_3C_6H_4$
d) Ar = *p*-ClC_6H_4, Ar′ = *p*-BrC_6H_4, Ar″ = *p*-$MeOC_6H_4$

Scheme 3.

crystals suitable for X-ray analysis were obtained from acetic acid. These did not contain dimers, but showed hydrogen bonding between the amidic moiety of the DPP and the carboxyl group of acetic acid (Fig. 2). The compound was efflorescent, however, solvent being lost from the surface molecules during the drying process in vacuo, so that the analytical sample contained a non-stoichiometric proportion of acetic acid. The crystal structure of the *N*-methyl analogue **16b** could also be solved (Fig. 3). Similarly, when the enamine **15d** was crystallised from acetic acid, the crystal structure showed hydrogen bonding between the amide and acetic acid (Fig. 4). However, when the enamine **15b** was crystallised from ethanol, the crystal structure showed that there was hydrogen bonding between two molecules resulting in a dimeric structure (Fig. 5). The crystal structures of both these enamines showed the geometry of the enamine double bond to be *Z*, that is, with hydrogen bonding of the enamine N–H to the ring carbonyl oxygen.

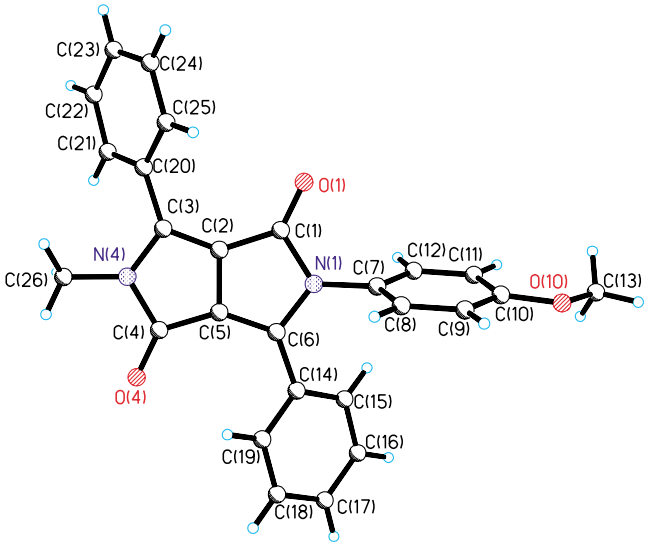


Figure 3. X-ray structure of compound **16b**. Selected bond lengths (Å): C(1)–C(2), 1.4522(17); C(1)–O(1), 1.2169(16); C(1)–N(1), 1.4360(16); C(2)–C(3), 1.3782(17); C(2)–C(5), 1.4248(18); C(3)–C(20), 1.4653(18); C(3)–N(4), 1.3917(16); N(4)–C(26), 1.4564(15). Selected interbond angles (°): C(1)–C(2)–C(3), 141.28(12); C(1)–N(1)–C(6), 111.24(10); C(1)–C(2)–C(5), 108.60(11); C(3)–N(4)–C(26), 127.55(10). Selected torsion angles (°): C(1)–N(1)–C(7)–C(12), −86.42(16); C(2)–C(3)–C(20)–C(25), −31.1(2); C(5)–C(6)–C(14)–C(19), −33.7(2).

2.2.2. Syntheses from *N*-arylpyrrolinones. All the previous reactions in our DPP-related investigations have started with pyrrolinones **2a**,**b**, and access to the *N*-aryl analogues of these would in principle enable the synthesis of tetra-aryl-DPP derivatives. According to Caballero and co-workers,[16] enamines analogous to **19** undergo reaction with glyoxal, at room temperature in methanol, to give cyclised pyrrolin-5-ones. Accordingly, the enamine **19** was prepared by condensation of ethyl benzoylacetate with aniline (Scheme 4), and X-ray crystallography showed this to have the *Z*-configuration (Fig. 6). However, in our hands no reaction at all was observed between **19** and glyoxal or glyoxal trimeric hydrate in various solvents and temperatures, but the enamine **19** reacted successfully with oxalyl chloride in ether, as reported in the literature, to give the known pyrroledione **20**.[17] Reaction of the enamine **19** with chloroacetyl chloride did not, however, give a pyrrolinone; only one of the chlorines was displaced and the product had spectroscopic properties consistent with its formulation as **21** (or its *Z*-isomer). Despite the fact[18] that *N*-alkyl analogues of **21** are cyclised in base to pyrrol-4-ones, attempts to effect the cyclisation of **21** to **22**, either thermally or in the presence of acid or base, were unsuccessful.

The corresponding oxygen analogue of the required pyrrolinones, ethyl 5-oxo-2-phenyl-4,5-dihydrofuran-3-carboxylate **23**, is known in the literature, and is synthesised by cyclisation of the acid **24** formed by alkylating ethyl benzoylacetate with bromoacetic acid.[27] This furanone **23** reacted with aniline to give a crystalline solid, whose structure was determined by X-ray crystallography (Fig. 7) to be the ring-opened amide, ethyl 2-benzoyl-*N*-phenylsuccinamate **25**. In Part 2,[10] we reported that reaction of aniline with 3,6-diphenylfuro[3,4-*c*]pyrrole-1,4-dione gave a

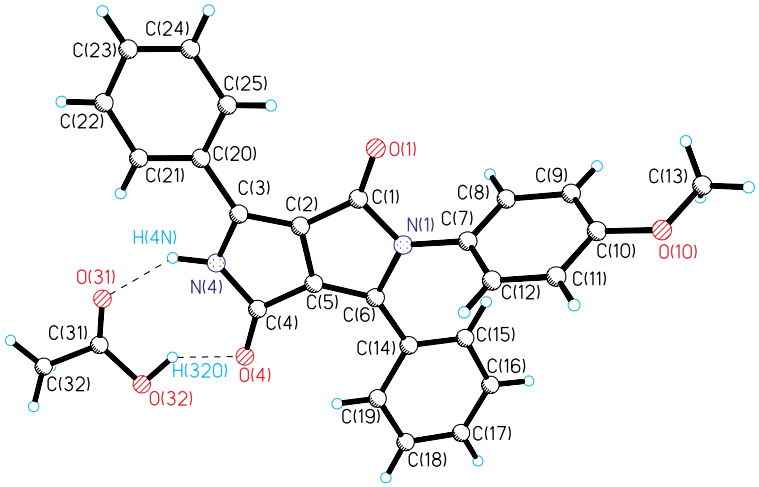


Figure 2. X-ray structure of compound **13b**. Selected bond lengths (Å): C(1)–C(2), 1.454(18); C(1)–O(1), 1.237(16); C(1)–N(1), 1.440(17); C(2)–C(3), 1.364(16); C(2)–C(5), 1.399(16); C(3)–C(20), 1.457(18); C(3)–N(4), 1.325(18); N(4)–O(31), 2.849(14); O(4)–O(32), 2.585(14); C(31)–O(31), 1.171(19); C(31)–O(32), 1.308(19). Selected interbond angles (°): C(1)–C(2)–C(3), 142.8(16); C(1)–N(1)–C(6), 111.9(12); C(1)–C(2)–C(5), 106.7(12). Selected torsion angles (°): C(1)–N(1)–C(7)–C(8), −75.2(16); C(2)–C(3)–C(20)–C(21), −179.6(15); C(5)–C(6)–C(14)–C(15), 149.6(16).

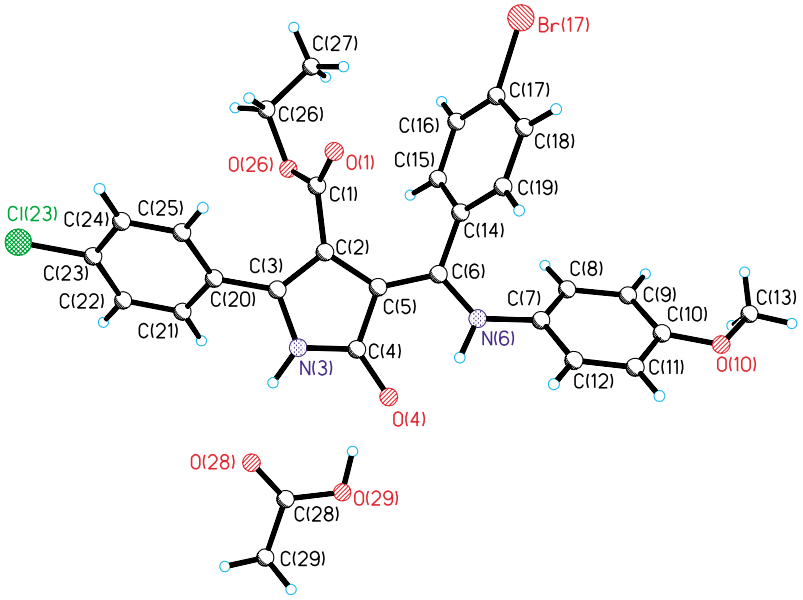


Figure 4. X-ray structure of compound **15d**. Selected bond lengths (Å): C(2)–C(3), 1.373(17); C(2)–C(5), 1.435(17); C(5)–C(6), 1.392(18); C(6)–N(6), 1.332(16); N(6)–O(4), 2.670(14); N(3)–O(28), 2.813(14); O(4)–O(29), 2.571(12). Selected interbond angles (°): N(3)–C(3)–C(2), 108.0(11); C(2)–C(5)–C(6), 134.5(11); C(5)–C(6)–N(6), 119.2(12); C(6)–N(6)–C(7), 132.3(11). Selected torsion angles (°): C(2)–C(3)–C(20)–C(21), 140.5(13); O(4)–C(4)–C(5)–C(6), 3(2); O(1)–C(1)–C(2)–C(3), 121.8(14); C(5)–C(6)–C(14)–C(15), −47.9(18); C(6)–N(6)–C(7)–C(8), −41(2).

ring-opened and decarboxylated product, indicating that attack of aniline takes place at the alkene carbon. This is in contrast to the product reported here, which clearly indicates aniline attack at the lactone carbonyl. It was found that treatment of this acyclic amide with acid promoted cyclisation to the corresponding ethyl 4,5-dihydro-5-oxo-1,2-diphenylpyrrole-3-carboxylate **26a**, and in fact treatment of furanone **23** with aniline in acetic acid gives the *N*-phenylpyrrolinone **26a** directly (Scheme 5). The structure of this compound was confirmed by X-ray crystallography (Fig. 8), which indicates clearly the presence of a localised C(2)–C(3) double bond and a C(3)–C(4) single bond in the ring system. The furanone **23** was also reacted with *p*-anisidine and *p*-aminobenzotrifluoride to give two further pyrrolinones **26b**,**c**.

Like the *N*-unsubstituted pyrrolinones **2a**,**b**, the novel *N*-phenylpyrrolinone **26a** may be readily *C*-acylated by

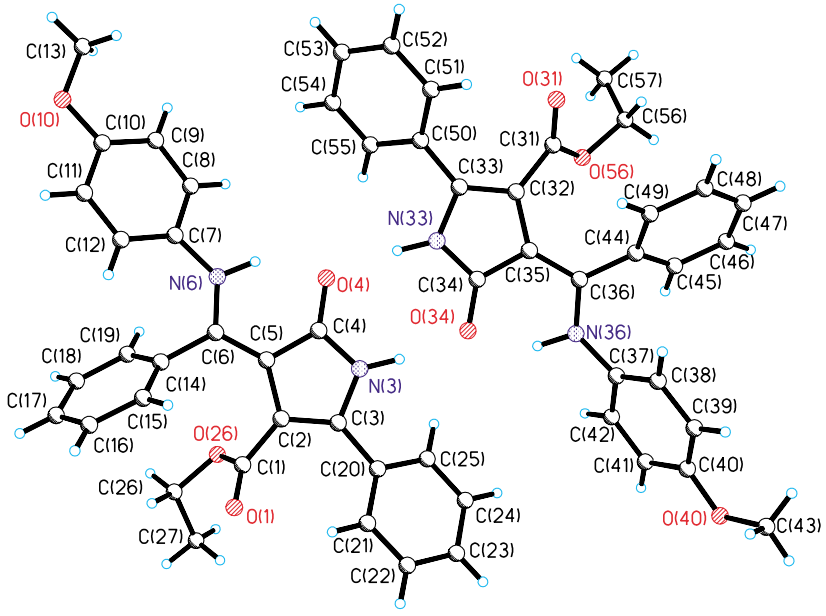
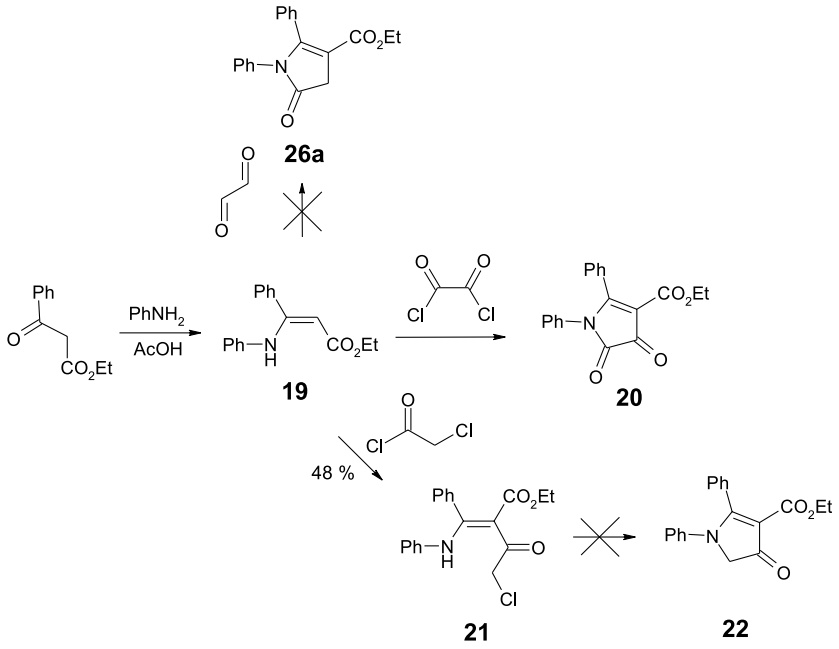


Figure 5. X-ray structure of compound **15b**. Selected bond lengths (Å): C(2)–C(3), 1.376(4); C(2)–C(5), 1.460(4); C(5)–C(6), 1.399(4); C(6)–N(6), 1.350(3); N(3)–O(34), 2.808(3); N(6)–O(4), 2.654(3). Selected interbond angles (°): N(3)–C(3)–C(2), 108.0(2); C(2)–C(5)–C(6), 132.2(2); C(5)–C(6)–N(6), 116.9(2); C(6)–N(6)–C(7), 132.2(2). Selected torsion angles (°): C(2)–C(3)–C(20)–C(21), −41.9(5); O(4)–C(4)–C(5)–C(6), −0.1(5); O(1)–C(1)–C(2)–C(3), 60.6(4); C(5)–C(6)–C(14)–C(15), 57.0(4); C(6)–N(6)–C(7)–C(8), −160.9(3).



Scheme 4.

treatment with benzoyl chloride and lithium hexamethyldisilazide to give the acylated product **27**, which presumably adopts the same *Z*-enol configuration as in the *N*-unsubstituted series (methylene chemical shift of ~3.5 ppm). This acylated compound may then be cyclised to the corresponding furopyrrole **28** by heating to around 200 °C in a microwave reactor. This furopyrrole has been synthesised previously, albeit in very low yield, by Langhals and co-workers[6] using a different method: this new method represents a far more efficient synthetic route to the same compound, which in turn can be converted into the tetraphenyl-DPP **4** (Scheme 6). This overall strategy for tetra-aryl DPP synthesis constitutes a versatile method, in which all four aryl groups can be selected independently from one another. Similarly to the furopyrroles reported in Part 2, in the absence of any carbodiimide coupling reagent the furopyrrole **27** undergoes attack of aniline at the alkenyl carbon, giving the decarboxylated product **29**.

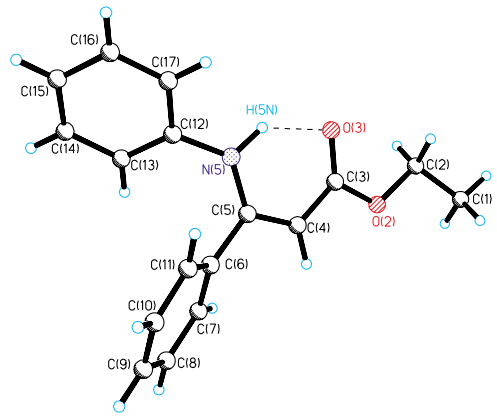


Figure 6. X-ray structure of compound **19**.

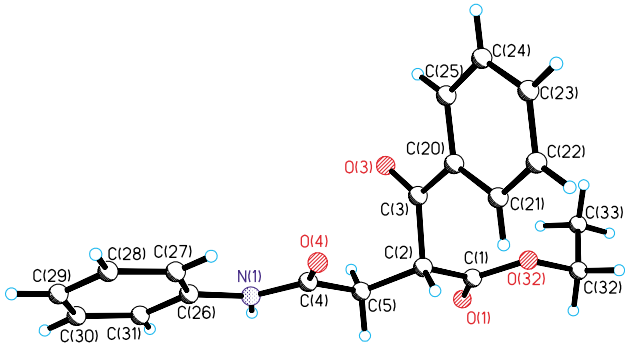


Figure 7. X-ray structure of compound **25**. Selected bond lengths (Å): C(1)–C(2), 1.5249(17); C(2)–C(3), 1.5481(17); C(3)–O(3), 1.2180(15).

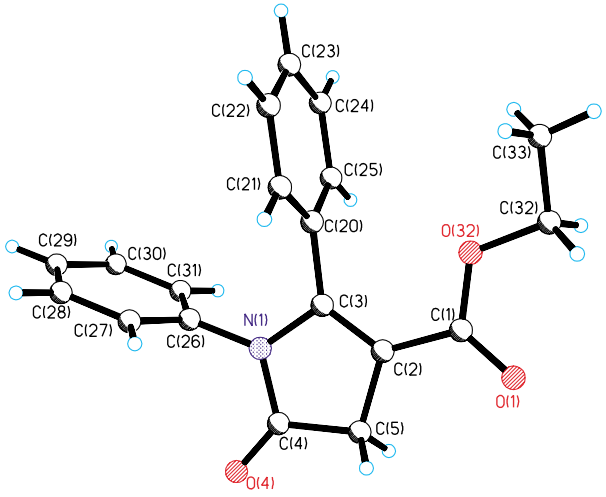
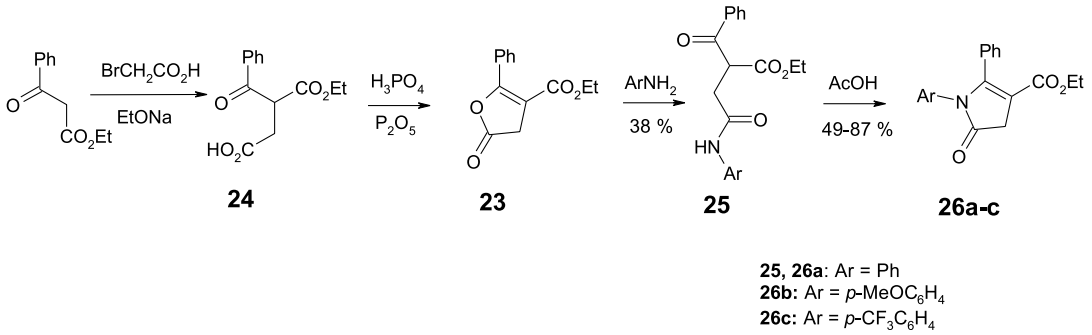


Figure 8. X-ray structure of compound **26a**. Selected bond lengths (Å): C(1)–C(2), 1.459(2); C(2)–C(3), 1.348(2); N(1)–C(3), 1.414(2); N(1)–C(4), 1.387(2); C(4)–C(5), 1.508(2); C(2)–C(5), 1.506(2). Selected interbond angles (°): C(3)–C(2)–C(5), 109.30(14); N(1)–C(4)–C(5), 107.02(14); C(4)–C(5)–C(2), 103.16(13); C(4)–N(1)–C(3), 110.64(13); N(1)–C(3)–C(2), 109.88(14). Selected torsion angles (°): C(3)–N(1)–C(26)–C(27), −95.7(2); C(2)–C(3)–C(20)–C(21), −94.8(2); C(5)–C(2)–C(1)–O(1), −4.5(2).



Scheme 5.

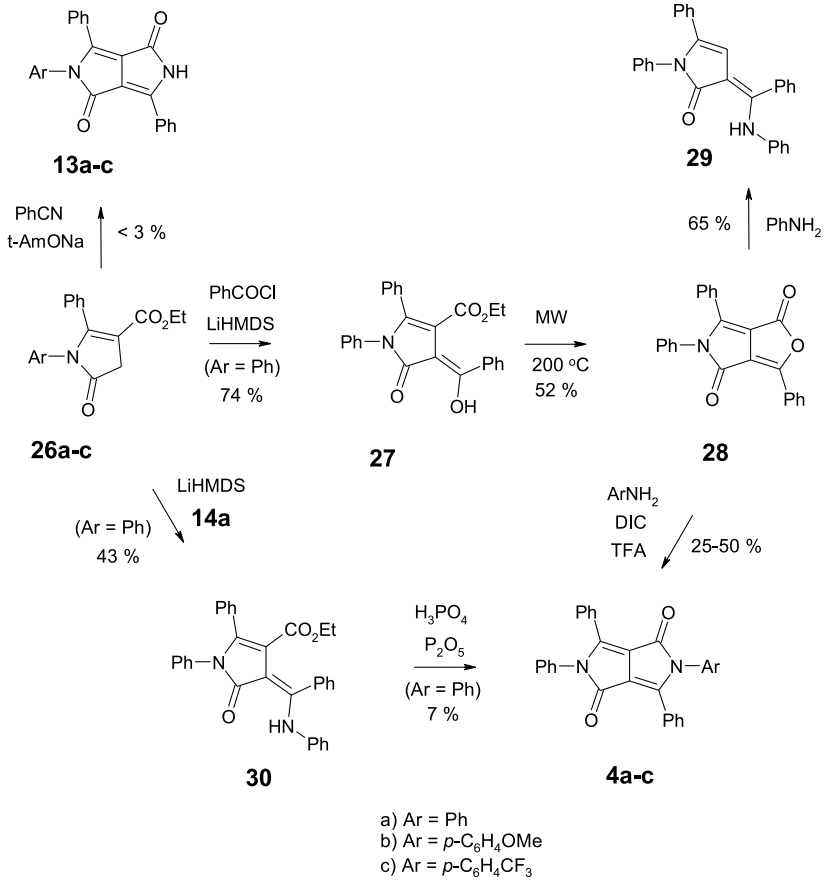
In the standard synthesis of DPPs, either a dialkyl succinate or the pyrrolinone **2a** is reacted with an aromatic nitrile and a strong base such as sodium *t*-amyloxide. Similarly, the *N*-phenylpyrrolinone **26a** when treated with benzonitrile and heated with sodium *t*-amyloxide in *t*-amyl alcohol, gave the triphenyl-DPP **13a**, albeit in low yield. This same method using *N*-arylpyrrolinones **26b**,**c** gave the triaryl-DPPs **13b**,**c**, identical with those obtained as in Section 2.2.1. Although product **13b** could be identified by TLC, yields were so low that the product could not be isolated.

2.3. Reaction of *N*-arylpyrrolinones with imidoyl chlorides to give tetraaryl-DPPs

Similarly to the reaction of pyrrolinones **2a**,**b**, the *N*-phenylpyrrolinone **26a** reacts with *N*-phenylbenzimidoyl chloride and sodium hexamethyldisilazide to give the uncyclised enamine **30**. Unlike the reactions of the pyrrolinone **2a**,**b**, however, no DPP was detected in this reaction mixture and cyclisation of **30** could not be promoted by treatment with base or by heating (either conventionally or by microwave irradiation). However, cyclisation to the tetraphenyl-DPP **4** did occur by heating in the presence of polyphosphoric acid (Scheme 6).

3. Spectroscopic properties of these compounds

A variety of both symmetrical and unsymmetrical *N*-substituted DPPs have been synthesized in the present work. Analysis of the visible absorption spectra of these compounds gives some interesting results. A comparison



Scheme 6.

of compounds **13a–d** reveals that substitution of the *N*-phenyl ring with either an electron-donating methoxy substituent or electron-withdrawing trifluoromethyl substituent does little to change either the absorption wavelength maximum or the extinction coefficient, values differing by only 2–6 nm from those of the unsubstituted **13a** (498 and 470 nm). This is in contrast to values reported in Part 2 of this series, where it was reported that substitution on the *C*-aryl ring resulted in shifts of up to 30 nm. This clearly implies that the *N*-phenyl rings are not nearly as conjugated to the chromophore as the *C*-aryl rings, their substitution affecting absorption wavelengths only marginally. This is repeated in compounds **16a–d**, **17a–d** and **18b**,**d**, again showing that the strongly electron-withdrawing 2,4-dinitrophenyl group does little to change the absorption maxima. Additionally, the fluorescence emission maxima change only marginally upon *N*-aryl substitution, although quantum yields decrease markedly upon the introduction of electron-donating (*p*-OMe) or highly electron-withdrawing groups [*o*,*p*-$(NO_2)_2$].

4. Conclusion

We have reported herein various methods for the synthesis of both symmetrical and unsymmetrical *N*-arylated DPPs. *N*-arylbenzimidoyl chlorides have been used as electrophiles in a two-step, one-pot synthesis of novel triaryl-DPPs. *N*-arylpyrrolinones have been produced via the corresponding furanones, thus providing new routes to *N*-aryl- and *N*,*N*′-diaryl-DPPs, via the corresponding furopyrrole and enamine intermediates. Using these methods it is now possible for the first time to synthesise DPPs with a diverse range of *N*- and *C*-aryl substituents.

5. Experimental

5.1. General

Melting points in excess of 300 °C were recorded using differential scanning calorimetry (DSC). FT-IR spectra of solids were recorded for Nujol mulls, and those of liquids were recorded for thin films; frequencies are expressed in cm^{-1}. Unless otherwise indicated, UV–visible spectra were recorded (wavelengths expressed in nm) for solutions in dichloromethane, and ^1H and ^{13}C NMR spectra were obtained at 300 and 75.4 MHz, respectively, for solutions in $CDCl_3$ (or, where indicated, DMSO-d_6). Chemical shifts (δ) are expressed relative to $SiMe_4$ ($\delta_H=\delta_C=0$) and coupling constants (J) in Hz. ^{13}C assignments were supported, where necessary, using the PENDANT sequence. Mass spectra and accurate mass measurements were obtained using electron impact (EI) ionisation at 70 eV, or electrospray ionization (ESI) with a Micromass LCT instrument. The microwave reactor was a CEM Discover™ model, with a circular single mode cavity design and a maximum operating power of 300 W; the samples were contained in sealed glass tubes, whereby the pressure was allowed to increase to a maximum of 2.07 MPa (300 psi). 'Ether' refers to diethyl ether and 'petrol' to the fraction of bp 40–60 °C. Ethyl 4,5-dihydro-5-oxo-2-phenylpyrrole-3-carboxylate **2a**[2] and its *p*-chlorophenyl analogue **2b**[10] were prepared as previously described. Fluorescence quantum yields were measured relative to perylene-3,4,9,10-tetracarboxylic acid tetrapotassium salt[19] (compounds **12**, **4a–c**), with quantum yield 1.0 or *N*,*N*′-bis(butylpentyl)-3,4,9,10-perylenebis(dicarboximide)[20] (compounds **13a–d**, **16a–d**, **17a–d**, **18b**,**d**), assumed quantum yield of 100%.

5.1.1. 2,5-Bis-(2,4-dinitrophenyl)-DPP 12. DPP **1** (200 mg, 0.69 mmol) was stirred with potassium carbonate (383 mg, 2.77 mmol) and 1-fluoro-2,4-dinitrobenzene (517 mg, 349 μl, 2.77 mmol) in DMF (20 cm^3) for 4 days at room temperature. Water was added, and the precipitate filtered off and washed with water. Recrystallisation from DMF gave the DPP **12** as an orange solid (369 mg, 86%), mp 373–376 °C. (Found: C, 56.35; H, 3.65; N, 14.6. $C_{36}H_{30}N_8O_{12}$ (+2 DMF) requires C, 56.4; H, 3.9; N, 14.6%). υ_{max} 1710 (C=O), 1670 (DMF C=O), 1530 and 1350 (NO_2). δ_H (DMSO-d_6) 7.32–7.64 (10H, m, Ph), 7.80 and 7.88 (2×1H, d, $J=8.6$ Hz, 6-Ar-H), 8.51 and 8.60 (2×1H, dd, $J=8.6$, 2.6 Hz, 5-Ar-H), 8.84 and 8.90 (2×1H, d, $J=2.6$ Hz, 3-Ar-H).

5.1.2. *N*-Phenylbenzimidoyl chloride 14a. Benzanilide (1.0 g, 5.08 mmol) and thionyl chloride (8.19 g, 5.0 cm^3) were stirred at 65 °C for 2 h, and the excess of thionyl chloride was then removed by distillation. The crude product was then heated with hexane, filtered, and the filtrate evaporated, to give the imidoyl chloride, mp 38–39 °C (lit.[21]: 38–40 °C), in almost quantitative yield. δ_H 6.91–6.96 (2H, m), 7.09–7.15 (1H, m), 7.25–7.50 (5H, m), and 8.05–8.11 (2H, m). The imidoyl chloride was used in subsequent reactions without further purification.

5.1.3. *N*-(*p*-Methoxyphenyl)benzimidoyl chloride 14b. This was similarly obtained from *N*-(*p*-methoxyphenyl)-benzamide[22] (1.0 g, 4.4 mmol) and thionyl chloride (8.15 g, 5.0 cm^3), and had mp 58–60 °C (lit.,[23] 58.5–59.5 °C) δ_H 3.84 (3H, s, OCH_3), 6.95 and 7.08 (each 2H, AA′BB′, *p*-$MeOC_6H_4$), 7.43–7.57 (3H, m, *m*- and *p*-Ph-H), and 8.14–8.18 (2H, m, *o*-Ph-H).

5.1.4. *N*-(*p*-Trifluoromethylphenyl)benzimidoyl chloride 14c. This was similarly obtained from *N*-(*p*-trifluoromethylphenyl)benzamide, mp 207–210 °C (from ethanol; lit.,[24] 205–206 °C) (2.0 g, 7.55 mmol), phosphorus pentachoride (1.57 g, 7.55 mmol) and thionyl chloride (20 cm^3), mp 100–103 °C (known,[25] but no lit. mp recorded). δ_H 7.08 (2H, half of AA′BB′, Ar-H), 7.46–7.62 (3H, m, Ph-*m*/*p*-H), 7.67 (2H, half of AA′BB′, Ar-H) and 8.19 (2H, m, Ph-*o*-H).

5.1.5. *N*-(*p*-Methoxyphenyl)-*p*-bromobenzimidoyl chloride 14d. This was similarly obtained from *N*-(*p*-methoxyphenyl)-*p*-bromobenzamide[26] (2.0 g, 6.54 mmol) and thionyl chloride (10 cm^3) and was used without further purification, mp 104–107 °C. υ_{max} 1735 (C=N). δ_H 3.77 (3H, s, CH_3), 6.88 and 7.01 (each 2H, AA′BB′, *p*-$MeOC_6H_4$), 7.53 and 7.95 (each 2H, AA′BB′, *p*-BrC_6H_4). δ_C 157.9 (quat), 141.0 [C(Cl)=N],[†] 140.2 (quat), 135.1 (quat), 132.0 (2×CH), 131.2 (2×CH), 127.1 (quat), 123.0 (2×CH), 114.5 (2×CH) and 55.8 (CH_3).

[†] Provisional assignment.

5.1.6. 2,3,6-Triphenyl-DPP 13a. (a) The pyrrolinone ester **2a** (1.0 g, 4.33 mmol) was added to sodium hydride (866 mg, 21.7 mmol) in THF (50 cm^3), and the mixture was stirred at room temperature for 30 min. To this was added the imidoyl chloride **14a** (0.93 g, 4.33 mmol), the mixture stirred at room temperature overnight, then acidified (HCl) and the orange precipitate filtered off, to give 2,3,6-triphenyl-DPP **13a** (362 mg, 23%).

(b) The *N*-phenylpyrrolinone ester **26a** (see below) (663 mg, 2.16 mmol) and benzonitrile (446 mg, 440 μl, 4.3 mmol) were added successively to a solution of sodium *t*-amyloxide [from sodium (150 mg, 6.5 mmol) and *t*-amyl alcohol (4.0 cm^3)], and the mixture heated to reflux for 6 h. The mixture was then cooled, acidified (HCl), and extracted with dichloromethane. The organic extracts were then dried and the solvent evaporated. Precipitation from methanol followed by filtration gave the triphenyl-DPP as a bright orange solid (18 mg, 3%).

(c) The enamine **15a** (200 mg, 0.549 mmol) was mixed with polyphosphoric acid (5.0 cm^3), and the mixture heated to 120 °C for 1 h. Water was added and the precipitate filtered and washed with ethanol, to give the pyrrolopyrrole (111 mg, 63%), mp 389 °C. (Found: C, 79.0; H, 4.3; N, 7.7. $C_{24}H_{16}N_2O_2$ requires C, 79.1; H, 4.4; N, 7.7%). υ_{max} 3160 (NH), 1670 (C=O), 1610; δ_H (DMSO-d_6) 7.29–7.33 (2H, m, Ar-H), 7.38–7.54 (6H, m, Ar-H), 7.57–7.67 (5H, m, Ar-H), 8.49–8.53 (2H, m, Ar-H), 11.54 (1H, s, NH). *m/z* (ESI −ve): 364 (30%, $M^{+\cdot}$) and 363 [100%, $(M-H)^+$].

5.1.7. 2-(*p*-Methoxyphenyl)-3,6-diphenyl-DPP 13b. NaHMDS (67 cm^3 of 1 M THF solution, 67 mmol) and the pyrrolinone ester **2a** (4.83 g, 20.9 mmol) in THF (200 cm^3) were stirred at room temperature for 30 min. The solid imidoyl chloride **14b** (5.13 g, 20.9 mmol) was then added, and the mixture stirred at room temperature overnight, then acidified (HCl) and the orange precipitate filtered off, to give **13b** as an orange solid (1.42 g, 18%), mp 368 °C (from *o*-$Cl_2C_6H_4$). [Found: C, 73.6; H, 4.0; N, 6.65. $C_{25}H_{18}N_2O_3$ (4:1 ratio with *o*-$C_6H_4Cl_2$) requires C, 73.8; H, 4.4; N, 6.5%.] $\upsilon_{max.}$3150 (NH), 1680 (C=O), 1620 (C=C). δ_H (DMSO-d_6) 3.85 (3H, s, OCH_3), 7.01 and 7.21 (each 2H, AA′BB′, C_6H_4), 7.36–7.45 (3H, m, Ar-H), 7.57–7.63 (5H, m, Ar-H), 8.49–8.54 (2H, m, Ar-H) and 11.52 (1H, s, NH). *m/z* (ESI −ve): 394 (30%, $M^{+\cdot}$) and 393 [100%, $(M-H)^+$].

5.1.8. 3,6-Diphenyl-2-(*p*-trifluoromethylphenyl)-DPP 13c. To sodium hydride (1.69 g, 70.5 mmol) was added THF (300 cm^3), followed by the pyrrolinone **2a** (4.07 g, 17.6 mmol), and the mixture was stirred at room temperature for 30 min. To this was added the imidoyl chloride **14c** (5.0 g, 17.6 mmol), and the mixture stirred at room temperature for 1 week. The mixture was then acidified (HCl) and the precipitate filtered off, to give the triaryl-DPP **13c** as an orange solid (854 mg, 11%), mp 377 °C. (Found: C, 69.6; H, 3.8; N, 6.3. $C_{25}H_{15}F_3N_2O_2$ requires C, 69.4; H, 3.5; N, 6.5%). δ_H (DMSO-d_6) 7.36–7.64 (10H, m, Ar-H), 7.78–7.84 (2H, m, Ar-H) 8.46–8.51 (2H, m, Ar-H) and 11.56 (1H, s, NH). *m/z* (ESI −ve): 432 (28%, $M^{+\cdot}$) and 431 [100%, $(M-H)^+$].

5.1.9. 3-*p*-Bromophenyl-6-*p*-chlorophenyl-2-*p*-methoxyphenyl-DPP 13d. To sodium hydride (0.79 g, 19.75 mmol) was added THF (200 cm^3), followed by the pyrrolinone ester **2b** (1.64 g, 6.17 mmol), and the mixture was stirred at room temperature for 30 min. To this was added the imidoyl chloride **14d** (2.00 g, 6.17 mmol), and the mixture stirred at room temperature for 48 h. The mixture was then acidified (HCl) and the precipitate filtered, to give the triaryl-DPP **13d** as an orange solid (452 mg, 15%), mp 372 °C. (Found: C, 59.2; H, 3.1; N, 5.6. $C_{25}H_{16}BrClN_2O_3$ requires C, 59.1; H, 3.2; N, 5.5%). δ_H (DMSO-d_6) 3.59 (3H, s, OCH_3), 6.80 and 6.99 (each 2H, AA′BB′, Ar-H), 7.28 and 7.42 (each 2H, AA′BB′, Ar-H), 7.49 and 8.30 (each 2H, AA′BB′, Ar-H) and 11.33 (1H, s, NH). *m/z* (EI): 506/508/510 (27/100/74%, $M^{+\cdot}$) and 288/290 (71/63%).

5.1.10. Ethyl 2-phenyl-4-[1-phenyl-1-(phenylamino)-methylidene]-4,5-dihydro-5-oxopyrrole-3-carboxylate 15a. The filtrate from **13a** [procedure (a) above] was concentrated in vacuo, and gave the uncyclised enamine **15a** (177 mg, 10%), mp 263 °C (from ethanol). (Found: C, 76.4; H, 5.6; N, 6.8. $C_{26}H_{22}N_2O_3$ requires C, 76.1; H, 5.4; N, 6.8%.). υ_{max} 3000–3200 (lactam NH), 2720 (H-bonded enamine NH), 1700 (ester C=O), 1650 (lactam C=O), 1620 (C=C) and 1550 (NH bend). δ_H (DMSO-d_6): 0.81 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 3.22 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 6.76–6.91 (2H, m, Ar-H), 6.98–7.04 (1H, m, Ar-H), 7.11–7.19 (2H, m, Ar-H), 7.25–7.48 (10H, m, Ar-H), and 11.00 and 12.10 (each 1H, s, NH; exchangeable with D_2O). *m/z* (EI): 410 (100%, $M^{+\cdot}$), 365 [$(M-EtOH)^{+\cdot}$: possibly the triphenyl-DPP **13a**], 180 $(PhC{=}NHPh)^+$ and 91 (C_6H_5N).

5.1.11. Ethyl 2-phenyl-4-[1-phenyl-1-(*p*-methoxyphenylamino)methylidene]-4,5-dihydro-5-oxopyrrole-3-carboxylate 15b. The filtrate from the above preparation of **13b** was cooled with ice, and the precipitated uncyclised enamine **15b** filtered off, to give an orange solid (0.78 g, 9%), mp 244.5–248 °C (from ethanol). (Found: C, 73.3; H, 5.4; N, 6.4. $C_{27}H_{24}N_2O_4$ requires C, 73.6; H, 5.5; N, 6.4%). δ_H (DMSO-d_6) 0.71 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 3.12 (2H, q, OCH_2CH_3), 3.58 (3H, s, OCH_3), 6.61–6.73 (4H, m, Ar-H), 7.17–7.38 (8H, m, Ar-H), 7.48–7.54 (2H, m, Ar-H), 10.77 (1H, s, NH) and 11.92 (1H, s, NH).

5.1.12. Ethyl 2-phenyl-4-[1-phenyl-1-(*p*-trifluoromethylphenylamino)methylidene]-4,5-dihydro-5-oxopyrrole-3-carboxylate 15c. The filtrate from the above preparation of **13c** was cooled with ice, and the precipitated uncyclised enamine **15c** filtered off, to give a beige solid (541 mg, 6%), mp 264.5–265.5 °C (from ethanol). (Found: C, 67.5; H, 4.1; N, 5.7. $C_{27}H_{21}F_3N_2O_3$ requires C, 67.8; H, 4.4; N, 5.85%). δ_H (DMSO-d_6) 0.79 (3H, t, $J=7.2$ Hz, CH_2CH_3), 3.22 (2H, q, $J=7.2$ Hz, OCH_2), 6.86–6.94 (2H, m, Ar-H), 7.31–7.54 (12H, m, Ar-H), 10.94 (1H, s, NH) and 11.84 (1H, s, NH).

5.1.13. Ethyl 4-[1-*p*-bromophenyl-1-(*p*-methoxyphenylamino)methylidene]-2-chlorophenyl-4,5-dihydro-5-oxopyrrole-3-carboxylate 15d. The filtrate from the above preparation of **13d** was cooled with ice, and the precipitated uncyclised enamine **15d** filtered off, to give a beige solid (660 mg, 19%), mp 265–266 °C (from AcOH). (Found: C, 56.8; H, 4.0; N, 4.85. $C_{27}H_{22}BrClN_2O_4$ (+AcOH) requires

C, 56.7; H, 4.3; N, 4.6%). υ_{max} 3120 (NH), 1710 (ester C=O), 1630 (lactam C=O). δ_H (DMSO-d_6) 0.84 (3H, t, J=7.2 Hz, CH_2CH_3), 2.10 (3H, s, AcOH), 3.31 (2H, q, J=7.2 Hz, OCH_2) 3.67 (3H, s, OMe), 6.76 and 6.84 (each 2H, AA′BB′, p-$MeOC_6H_4$), 7.44 (4H, s, Ar), 7.22 and 7.57 (each 2H, AA′BB′, Ar), 10.93 (1H, s, NH) and 11.92 (1H, s, NH). δ_C 14.0 (CH_3), 55.7 (OCH_3), 60.2 (OCH_2), 102.6 (quat), 107.3 (quat), 114.5 (2×CH), 125.9 (2×CH), 127.7 (2×CH), 128.8 (4×CH), 129.8 (2×CH), 131.1 (2×quat), 132.1 (2×quat), 132.4 (quat), 133.4 (quat), 157.1 (quat), 157.4 (quat), 165.6 and 168.8 (2×CO).

5.1.14. 5-Methyl-2,3,6-triphenyl-DPP 16a. The triphenyl-DPP **13a** (500 mg, 1.37 mmol) was stirred with methyl p-toluenesulfonate (383 mg, 2.06 mmol), potassium carbonate (380 mg, 2.75 mmol) and DMF (40 cm^3) overnight. Water was added, and the organic component extracted with DCM. The solvent was evaporated and washing with water then methanol gave the DPP **16a** as an orange solid (290 mg, 56%), mp 267–269 °C. (Found: C, 79.4; H, 5.0; N, 7.3. $C_{25}H_{18}N_2O_2$ requires C, 79.35; H, 4.8; N, 7.4%). δ_H 3.42 (3H, s, NCH_3), 7.15–7.20 (2H, m, Ar) 7.28–7.41 (6H, m, Ar), 7.51–7.56 (3H, m, Ar), 7.62–7.68 (2H, m, Ar), 7.91–7.95 (2H, m, Ar). m/z (ESI +ve): 402 [28%, $(M+Na+1)^+$], 401 [100%, $(M+Na)^+$] and 379 [14%, $(M+1)^+$].

5.1.15. 2-(p-Methoxyphenyl)-5-methyl-3,6-diphenyl-DPP 16b. The triaryl-DPP **13b** (1.23 g, 3.12 mmol), methyl p-toluenesulfonate (1.13 g, 6.08 mmol) and potassium carbonate (0.841 g, 6.08 mmol) were heated to 120 °C in DMF (40 cm^3) for 2 h. The mixture was cooled to room temperature, water was added and the organic component extracted with DCM. Evaporation of the solvent and recrystallisation from toluene gave the methylated compound **16b** (0.99 g, 80%), mp 252–254 °C. (Found: C, 76.15; H, 4.9; N, 6.9. $C_{26}H_{20}N_2O_3$ requires C, 76.45; H, 4.9; N, 6.9%). δ_H 3.53 (3H, s, NCH_3), 3.93 (3H, s, OCH_3), 7.00 and 7.21 (each 2H, AA′BB′, p-$MeOC_6H_4$), 7.41–7.50 (3H, m, Ar-H), 7.61–7.67 (3H, m, Ar-H), 7.77–7.82 (2H, m, Ar-H), and 8.02–8.07 (2H, m, Ar-H). δ_C 30.0 (NCH_3), 55.9 (OCH_3), 114.7 (2×CH), 128.1 (2×C quat), 128.2 (2×quat), 128.7 (2×CH), 129.0 (2×quat), 129.2 (2×CH), 129.4 (2×CH), 129.6 (2×CH), 130.1 (2×CH), 131.4 (CH), 131.8 (CH), 147.6 (quat), 149.2 (quat), 159.3 and 162.6 (2×C=O)[‡] and 163.2 (quat). m/z (ESI +ve): 447 [10%, $(M+K+H)^+$], 446 (27%, M+K), 431 [100%, $(M+Na)^+$] and 409 [35%, $(M+1)^+$].

5.1.16. 5-Methyl-3,6-diphenyl-2-p-trifluoromethylphenyl-DPP 16c. A mixture of the DPP **13c** (200 mg, 0.463 mmol), methyl p-toluenesulfonate (129 mg, 0.695 mmol), potassium carbonate (128 mg, 0.93 mmol) and DMF (10 cm^3) was stirred at room temperature overnight, added to water and extracted with DCM. Evaporation of the solvents followed by washing with water then methanol gave the pyrrolopyrrole **16c** as an orange solid (184 mg, 89%), mp 237.5–238.5 °C. (Found: C, 69.9; H, 3.7; N, 6.1. $C_{26}H_{17}F_3N_2O_2$ requires C, 69.95; H, 3.8; N, 6.3%). δ_H 7.94–7.87 (2H, m, Ph-H), 7.67–7.51 (7H, m, Ph-H), 7.45–7.27 (5H, m, Ar-H) and 3.42 (3H, s, N–CH_3).

[‡] Provisional assignment.

5.1.17. 3-p-Bromophenyl-6-p-chlorophenyl-2-p-methoxyphenyl-5-methyl-DPP 16d. A mixture of DPP **13d** (100 mg, 0.2 mmol), methyl p-toluenesulfonate (75.1 mg, 0.404 mmol), potassium carbonate (70 mg, 0.51 mmol) and DMF (10 cm^3) was heated to 100 °C for 3 h, cooled to room temperature, added to water and extracted with DCM. Evaporation of the solvents followed by washing with water then methanol gave the pyrrolopyrrole **16d** as a red-orange solid (81 mg, 79%), mp 262–264 °C. (Found: C, 59.5; H, 3.3; N, 5.3. $C_{25}H_{16}BrClN_2O_3$ requires C, 59.1; H, 3.3; N, 5.5%). υ_{max} 1670 (C=O) and 1610; δ_H 3.31 (3H, s, NCH_3), 3.75 (3H, s, OCH_3), 6.83 and 7.01 (each 2H, AA′BB′, NC_6H_4OMe), 7.37 and 7.47 (each 2H, AA′BB′, p-Ar), 7.41 and 7.80 (each 2H, AA′BB′, p-Ar). δ_C 30.1 (NCH_3) 55.9 (OCH_3) 114.9 (2×C, Ar-H), 126.2 (2×C, quat), 126.4 (quat), 126.8 (quat), 128.5 (2×C, quat), 129.3 (2×C, Ar), 129.6 (2×C, Ar), 130.9 (2×C, Ar) 131.4 (2×C, Ar), 132.1 (2×C, Ar), 138.1 (quat), 146.6 (quat), 148.1 (quat), 159.6 (2×C, quat) and 162.9 (quat). m/z (EI): 520/522/524 (27/100/78%, M^+) and 288/290 (60/61%).

5.1.18. 5-Benzyl-2,3,6-triphenyl-DPP 17a. The triphenyl-DPP **13a** (500 mg, 1.37 mmol) was stirred with benzyl bromide (352 mg, 245 µl, 2.06 mmol), potassium carbonate (380 mg, 2.75 mmol) and DMF (40 cm^3) overnight. Water was added, and the organic component extracted with DCM. The solvent was evaporated and washing with water and then methanol gave the pyrrolopyrrole **17a** as an orange solid (548 mg, 93%), mp 262–264 °C. (Found: C, 81.9; H, 4.8; N, 6.2. $C_{31}H_{22}N_2O_2$ requires C, 81.9; H, 5.0; N, 6.2%). υ_{max} 1680 (CO), 1590; δ_H 5.05 (2H, s, $PhCH_2N$), 7.16–7.24 (4H, m, Ar-H), 7.27–7.50 (12H, m, Ar-H), 7.66–7.70 (2H, m, Ar-H) and 7.74–7.79 (2H, m, Ar-H). δ_C 46.1 (CH_2), 127.1 (2×CH), 127.8 (CH), 128.0 (2×quat), 128.1 (quat), 128.2 (2×CH), 128.3 (CH), 128.7 (2×CH), 129.2 (4×CH), 129.4 (2×CH), 129.5 (2×CH), 130.2 (2×CH), 131.6 (CH), 131.9 (CH), 136.1 (quat), 137.8 (quat), 147.9 (quat), 149.7 (quat), 162.3 and 163.3 (2×CO).

5.1.19. 5-Benzyl-2-p-methoxyphenyl-3,6-diphenyl-DPP 17b. The triaryl-DPP **13b** (100 mg, 0.254 mmol), benzyl bromide (118 mg, 83 µl, 0.66 mmol) and potassium carbonate (100 mg, 0.71 mmol) were heated to 120 °C in DMF (10 cm^3) for 2 h. The mixture was cooled to room temperature, water was added and the organic component extracted with DCM. Evaporation of the solvent from the dried extract gave the benzylated compound **17b** (108 mg, 88%), mp 263–264 °C (from AcOH). [Found: C, 76.2; H, 4.8; N, 5.6. $C_{32}H_{24}N_2O_3$ (3:2 ratio with AcOH) requires C, 76.3; H, 5.1; N, 5.3%]. δ_H 2.10 (3H, s, AcOH), 3.74 (3H, s, OCH_3), 4.97 (2H, s, NCH_2), 6.82 and 7.04 (each 2H, AA′BB′, p-$MeOC_6H_4$), 7.11–7.41 (6H, m, Ar-H), and 7.61–7.71 (4H, m, Ar-H). δ_C 46.1 (CH_2), 55.9 (OCH_3), 114.8 (CH), 127.0 (CH), 127.8 (CH), 128.0 (quat), 128.1 (2×quat), 128.7 (CH), 129.2 (2×CH), 129.4 (CH), 129.5 (CH), 130.2 (CH), 131.5 (CH), 131.8 (CH), 137.8 (quat), 148.0 (quat), 149.4 (quat), 159.4 (2×C=O),[‡] 162.6 (quat) and 163.3 (quat). m/z (ESI +ve): 508 [34%, $(M+Na+1)^+$], 507 [100, $(M+Na)^+$] and 485 [8, $(M+1)^+$].

5.1.20. 5-Benzyl-3,6-diphenyl-2-(p-trifluoromethylphenyl)-DPP 17c. A mixture of the triaryl-DPP **13c** (200 mg, 0.46 mmol), benzyl bromide (119 mg, 83 µl, 0.695 mmol),

potassium carbonate (128 mg, 0.93 mmol) and DMF (10 cm^3) was stirred at room temperature overnight, added to water and extracted with DCM. Evaporation of the solvents followed by washing with methanol gave the pyrrolopyrrole **17c** as an orange solid (151 mg, 63%), mp 254.5–256.5 °C (from toluene). (Found: C, 73.3; H, 3.8; N, 5.2. $C_{32}H_{21}F_3N_2O_2$ requires C, 73.6; H, 4.05; N, 5.4%). δ_H 5.05 (2H, s, PhCH_2N), 7.17–7.22 (2H, m, Ar-H), 7.27–7.54 (11H, m, Ar-H), 7.60–7.67 (4H, m, Ar-H) and 7.71–7.76 (2H, m, Ar-H).

5.1.21. 5-Benzyl-3-*p*-bromophenyl-6-*p*-chlorophenyl-2-*p*-methoxyphenyl-DPP 17d. A mixture of the triaryl-DPP **13d** (2.0 g, 3.95 mmol), benzyl bromide (1.0 g, 0.7 cm^3, 5.92 mmol), K_2CO_3 (1.1 g, 7.9 mmol) and DMF (50 cm^3) was stirred at room temperature overnight, added to water and extracted with DCM. Evaporation of the solvents followed by washing with methanol gave the pyrrolopyrrole **17d** as a red-orange solid (2.25 g, 95%), mp 215–217 °C. (Found: C, 64.6; H, 3.4; N, 4.6. $C_{32}H_{22}BrClN_2O_3$ requires C, 64.3; H, 3.7; N, 4.7%). δ_H 3.76 (3H, s, NCH_3), 4.95 (2H, s, PhCH_2N), 6.85 and 7.04 (4H, AA′BB′, Ar-H), 7.10–7.16 (2H, m, *o*-Ph), 7.21–7.28 (3H, m, *m*/*p*-Ph), 7.15 and 7.33 (4H, AA′BB′, Ar-H) and 7.39 and 7.64 (4H, AA′BB′, Ar-H).

5.1.22. 2-(*p*-Methoxyphenyl)-5-(2,4-dinitrophenyl)-3,6-diphenyl-DPP 18b. The triaryl-DPP **13b** (100 mg, 0.25 mmol), 1-fluoro-2,4-dinitrobenzene (94 mg, 0.51 mmol) and potassium carbonate (70 mg, 51 mmol) were stirred in DMF (20 cm^3) at room temperature for 5 h. Water was then added, and the orange precipitate filtered. Recrystallisation from DMF gave the pyrrolopyrrole **18b** as an orange crystalline solid (117 mg, 82%), mp 293–295 °C. (Found: C, 66.2; H, 3.2; N, 10.1. $C_{31}H_{20}N_4O_7$ requires C, 66.4; H, 3.6; N, 10.0%). υ_{max} 1690 (C=O), 1600; δ_H (DMSO-d_6) 3.60 (3H, s, OCH_3), 7.10 and 7.40 (each 2H, AA′BB′, *p*-MeOC_6H_4), 7.50–7.80 [11H, m, Ph+Ar-H(6)], 8.60 [1H, dd, J=8.6 l, 2.6 Hz, Ar-H(5)] and 8.90 [1H, d, J=2.6 Hz, Ar-H(3)]. δ_C 55.7 (CH_3), 107.5 (quat), 112.3 (quat), 114.7 (2×CH), 121.6 (CH), 126.6 (quat), 127.1 (quat), 127.9 (quat), 128.7 (3×CH), 128.8 (2×CH), 129.3 (CH), 129.4 (2×CH), 129.9 (4×CH), 132.2 (CH), 132.3 (CH), 133.9 (quat), 144.5 (quat), 145.8 (quat), 146.7 (quat), 150.1 (quat), 159.3 (quat), 159.7 and 161.7 (2×CO).†

5.1.23. 3-(*p*-Bromophenyl)-6-(*p*-chlorophenyl)-5-(2,4-dinitrophenyl)-2-(*p*-methoxyphenyl)-DPP 18d. The triaryl-DPP **13d** (300 mg, 0.59 mmol), 1-fluoro-2,4-dinitrobenzene (220 mg, 1.18 mmol) and potassium carbonate (245 mg, 1.77 mmol) were stirred in DMF (40 cm^3) at room temperature for 5 h. This was acidified (HCl), and the organic component extracted with DCM. Evaporation of the solvent and recrystallisation from acetic acid gave the pyrrolopyrrole **18d** as an orange-red crystalline solid (320 mg, 80%), mp 290–293 °C. (Found: C, 55.2; H, 2.6; N, 8.4. $C_{31}H_{18}BrClN_4O_7$ requires C, 55.3; H, 2.7; N, 8.3%). δ_H (DMSO-d_6) 3.60 (3H, s, OCH_3), 6.82 and 7.04 (each 2H, AA′BB′, Ar-H) 7.35 and 7.43 (each 2H, AA′BB′, Ar-H), 7.43 [2H, d, J=8.7 Hz, Ar-H(6)], 7.24 and 7.46 (each 2H, AA′BB′, Ar-H) 8.37 [1H, dd, J=2.6, 8.7 Hz, Ar-H(5)] and 8.69 [1H, d, J=2.6 Hz, Ar-H(3)].

5.1.24. Ethyl 2-(1-phenyl-1-aminophenylmethylidene)-3-oxo-4-chlorobutanoate 21. Chloroacetyl chloride (220 mg, 2.0 mmol) was added dropwise to a solution of the enamine **19** (240 mg, 0.9 mmol) in ether (5 cm^3) at −50 °C. The reaction mixture was stirred at −45 to −35 °C for 2 h, then at room temperature for a further 2 h. Evaporation of the solvent and column chromatography (silica gel, eluent: 1:6 ethyl acetate/hexane) gave the enamine as a white crystalline solid (133 mg, 48%), mp 122.5–123.5 °C (from ethanol). (Found: C, 66.4; H, 5.05; N, 4.0. $C_{19}H_{18}ClNO_3$ requires C, 66.4; H, 5.3; N, 4.1%). ν_{max} 1545, 1600, 1690 (CO_2Et or C=O), 3165 (NH) δ_H 0.67 (3H, t, J=7.2 Hz, CH_3), 3.70 (2H, q, J=7.2 Hz, OCH_2), 4.64 (2H, s, CH_2), 6.70–6.76 (2H, m, *o*-N-Ph), 7.01–7.15 (3H, m, *m*/*p*-Ph-H), 7.22–7.17 (2H, m, *o*-Ph-H) and 7.25–7.38 (3H, m, *m*/*p*-Ph-H). δ_C 13.7 (CH_3), 48.9 (CH_2Cl), 60.9 (OCH_2), 125.0 (2×CH), 126.3 (CH), 128.7 (2×CH), 128.8 (2×CH), 129.2 (2×CH), 130.1 (CH), 134.8 (quat), 138.1 (quat), 166.7 (CO_2) and 190.5 (CO). *m*/*z* (ESI +ve): 366/368 [100%, $(M+Na)^+$], 330 [95%, $(M-Cl+Na)^+$] and 308 [75%, $(M-Cl)^+$].

5.1.25. Ethyl 2-benzoyl-*N*-phenylsuccinamate 25. A solution of the furanone **23**[27] (100 mg, 0.43 mmol) and aniline (51 mg, 50 μl, 0.55 mmol) in toluene (2.0 cm^3) was heated to 120 °C (using microwave irradiation) for 10 min. The solution was then cooled, and the solvent evaporated. Recrystallisation from ethanol gave the amide **25** as a colourless crystalline solid (53 mg, 38%), mp 106–106.5 °C. (Found: C, 69.9; H, 5.6; N, 4.3. $C_{19}H_{19}NO_4$ requires C, 70.1; H, 5.9; N, 4.3%). υ_{max} 1670 (amide CO), 1685 (ketone CO), 1735 (ester CO) and 3340 (NH). δ_H 1.16 (3H, t, J=7.2 Hz, $COCH_2CH_3$), 3.09 (2H, d, J=6.9 Hz, $CHCH_2CONH$), 4.15 (2H, q, J=7.2 Hz, CH_2CH_3), 5.06 (1H, t, J=6.9 Hz, $COCHCO_2Et$), 7.05–7.13 (1H, m, Ar-H), 7.26–7.33 (2H, m, Ar-H), 7.43–7.53 (4H, m, Ar-H), 7.57–7.64 (1H, m, Ar-H) and 8.05–8.10 (2H, m, Ar-H). δ_C 14.3 (CH_3), 36.7 (CH_2), 50.3 (CH), 62.4 (OCH_2), 120.2 (2×CH), 124.8 (CH), 129.2 (2×CH), 129.4 (2×CH), 129.5 (2×CH), 134.2 (CH), 136.1 (quat), 138.0 (quat), 168.7 and 169.6 (2×CO) and 195.2 (ketone CO).

5.1.26. Ethyl 4,5-dihydro-5-oxo-1,2-diphenylpyrrole-3-carboxylate 26a. Aniline (2.65 g, 2.59 cm^3, 28.5 mmol) was added to a solution of the furanone **23** (6.0 g, 25.9 mmol) and acetic acid (100 cm^3), and the solution heated to reflux for 3 h. The solution was then cooled, diluted with water and extracted with ether. The organic extracts were dried and concentrated. Column chromatography (silica gel, eluent: DCM) gave the pyrrolinone **26a** as a colourless solid (6.9 g, 87%), mp 129–130 °C. (Found: C, 74.1; H, 5.6; N, 4.5. $C_{19}H_{17}NO_3$ requires C, 74.25; H, 5.6; N, 4.6%). υ_{max} 1725 (ester C=O), 1690 (amide C=O), 1590 (C=C). δ_H 1.11 (3H, t, J=6.9 Hz, OCH_2CH_3), 3.67 (2H, s, CH_2), 4.08 (2H, q, J=6.9 Hz, OCH_2CH_3), 6.93–6.98 (2H, m, *o*-Ph-N) and 7.15–7.32 (8H, m, Ar-H). δ_C 14.5 (CH_3), 38.0 (CH_2), 60.5 (OCH_2), 128.0 (4×CH), 128.1 (CH), 129.3 (2×CH), 129.8 (CH), 130.0 (2×CH), 134.6 (2×quat), 154.8 (NC=C), 163.6 (amide CO) and 175.5 (ester CO).

5.1.27. Ethyl 4,5-dihydro-1-(*p*-methoxyphenyl)-5-oxo-2-phenylpyrrole-3-carboxylate 26b. This was prepared similarly to **26a** from *p*-anisidine (5.83 g, 47.40 mmol),

furanone **23** (10.00 g, 43.10 mmol) and acetic acid (150 cm^3). Recrystallisation from diethyl ether gave the pyrrolinone **26b** as a colourless solid (7.4 g, 49%), mp 149.5–151.5 °C. (Found: C, 70.9; H, 5.7; N, 4.0. $C_{20}H_{19}NO_4$ requires C, 71.2; H, 5.7; N, 4.15%). δ_H 1.10 (3H, t, J=7.2 Hz, CH_3), 3.64 (2H, s, CH_2), 3.73 (3H, s, OCH_3), 4.07 (2H, q, J=7.2 Hz, OCH_2), 6.75 and 6.88 (each 2H, AA′BB′, p-$MeOC_6H_4$) and 7.31–7.16 (5H, m, Ph).

5.1.28. Ethyl 4,5-dihydro-5-oxo-2-phenyl-1-(*p*-trifluoromethylphenyl)pyrrole-3-carboxylate 26c. This was prepared similarly to **26a** from p-aminobenzotrifluoride (7.63 g, 47.40 mmol), furanone **23** (10.00 g, 43.10 mmol) and acetic acid (150 cm^3). Recrystallisation from a mixture of ether and hexane gave the pyrrolinone **26c** as a light beige solid, mp 131–132 °C. (Found: C, 64.05; H, 4.0; N, 3.6. $C_{20}H_{16}F_3NO_3$ requires C, 64.0; H, 4.3; N, 3.7%). δ_H 1.12 (3H, t, J=7.2 Hz, CH_3), 3.69 (2H, s, CH_2), 4.09 (2H, q, J=7.2 Hz, OCH_2), 7.16–7.22 (2H, m, o-Ph), 7.25–7.38 (3H, m, m/p-Ph), and 7.07 and 7.49 (each 2H, AA′BB′, p-$F_3CC_6H_4$).

5.1.29. Ethyl 4-benzoyl-4,5-dihydro-5-oxo-1,2-diphenylpyrrole-3-carboxylate 27. A solution of the pyrrolinone ester **26a** (1.76 g, 5.74 mmol) in tetrahydrofuran (100 cm^3) was cooled to −78 °C, and a 1.0 M solution of lithium hexamethyldisilazide (17.2 cm^3, 17.2 mmol) in THF was added. After 5 min, benzoyl chloride (0.97 g, 0.79 cm^3, 6.89 mmol) was added, and the solution stirred for 30 min. Methanol was added, and the solution warmed to room temperature. The mixture was acidified (HCl) and extracted with ether. The ether extracts were concentrated, and chromatography (silica gel, eluent DCM) gave the enol **27** as a yellow solid (1.74 g, 74%), mp 137–139 °C. (Found: C, 75.8; H, 4.9; N, 3.3. $C_{26}H_{21}NO_4$ requires C, 75.9; H, 5.1; N, 3.4%). υ_{max} 1720 (ester C=O), 1650 (sh), 1625; δ_H 0.65 (3H, t, J=7.2 Hz, CH_3), 3.54 (2H, q, J=7.2 Hz, CH_2) 7.07–7.14 (2H, m, Ar), 7.19–7.34 (8H, m, Ar), 7.44–7.54 (3H, m, Ar) and 7.68–7.75 (2H, m, Ar). δ_C 13.6 (CH_3), 61.0 (OCH_2), 103.2 (*C*–CON), 108.8 (*C*–CO_2), 127.8 (2×CH), 127.9 (CH), 128.1 (2×CH), 128.8 (2×CH), 129.4 (2×CH), 129.5 (quat), 130.5 (CH), 131.0 (2×CH), 131.9 (CH), 134.5 (quat), 136.0 (quat), 140.1 (quat), 164.5 (COH), 168.9 (CO_2) and 176.15 (CON).

5.1.30. 3,5,6-Triphenyl-1*H*-furo[3,4-*c*]pyrrole-1,4(5*H*)-dione 28. The benzoylpyrrolinone ester **27** (74 mg) was irradiated with microwave radiation (at 300 W) without solvent, heating to 200 °C for 10 min. The crude product was then allowed to cool, methanol was added and the solid filtered off and washed with methanol. This gave the furopyrrole as an orange solid (34 mg, 52%), mp 230–232 °C (lit.[6] 230–232 °C). δ_H 7.20–7.61 (13H, m, Ar-H) and 8.42–8.48 (2H, m, Ar-H).

5.1.31. 1,2-Diphenyl-4-[1-phenyl-1-(phenylamino)-methylidene]-4,5-dihydropyrrol-5-one 29. The furopyrrole **28** (50 mg, 0.14 mmol), aniline (14 mg, 14 µl, 0.15 mmol) and toluene (2.0 cm^3) were heated to 120 °C for 10 min under microwave irradiation. The mixture was cooled, and evaporation of the solvent and recrystallisation from ethanol gave the pyrrolinone as an orange solid (37 mg, 65%), mp 212.5–214.5 °C. (Found: C, 83.7; H, 5.4; N, 6.8. $C_{29}H_{22}N_2O$ requires C, 84.0; H, 5.35; N, 6.8%). υ_{max} 1630 (C=O), 1590 (C=C or NH bending). δ_H 5.94–5.97 (1H, s, C=C–CH), 6.69–6.75 (2H, m, o-N-Ph-H), 6.91–7.01 (1H, m, p-N-Ph-H), 7.03–7.18 (7H, m, Ph-H), 7.19–7.30 (3H, m, Ph-H), 7.32–7.40 (2H, m, Ph-H), 7.40–7.47 (5H, m, Ph-H), and 11.88 (1H, s, NH). δ_C 104.3 (CH), 104.9 (OC*C*=CN), 122.7 (2×CH), 124.3 (CH), 126.9 (CH), 127.5 (CH), 127.6 (2×CH), 128.5 (2×CH), 129.1 (4×CH), 129.2 (2×CH), 129.7 (4×CH), 130.2 (CH), 132.7 (quat), 133.5 (2×quat), 134.2 (quat), 136.5 (quat), 153.8 (quat) and 168.7 (CO).

5.1.32. Ethyl 1,2-diphenyl-4-[1-phenyl-1-(phenylamino)-methylidene]-4,5-dihydro-5-oxopyrrole-3-carboxylate 30. A solution of the pyrrolinone **26a** (200 mg, 0.862 mmol) in THF (20 cm^3) was cooled to −78 °C, and sodium hydride (62 mg, 2.59 mmol) was added, followed by the imidoyl chloride **13a** (557 mg, 2.59 mmol). The solution was left to warm to room temperature overnight, then acidified (HCl). The organic component was extracted with DCM and the extract evaporated. Recrystallisation from ethanol gave the enamine **30** as a yellow solid (180 mg, 43%), mp 237–239 °C. (Found: C, 78.9; H, 5.7; N, 5.8. $C_{32}H_{26}N_2O_3$ requires C, 79.0; H, 5.4; N, 5.8%). υ_{max} 1715 (ester C=O), 1625 (lactam C=O), 1590 (C=C or NH bend). δ_H, 0.81 (3H, t, J=7.2 Hz, CH_3), 3.35 (2H, q, J=7.2 Hz, OCH_2), 6.75–6.69 (2H, m, Ar-H), 7.02–6.96 (2H, m, Ar-H), 7.44–7.05 (16H, m, Ar-H) and 12.22 (1H, s, NH). δ_C 14.1 (CH_3), 60.9 (CH_2), 105.3 (quat), 112.4 (quat), 118.9 (quat), 121.8 (quat), 123.8 (2×CH), 125.1 (CH), 127.5 (CH), 128.0 (2×CH), 128.1 (3×CH), 128.6 (CH), 129.0 (2×CH), 129.1 (2×CH), 129.2 (2×CH), 129.7 (2×CH), 130.4 (2×CH), 134.0 (quat), 136.2 (quat), 139.1 (2×quat), 157.8 (CO) and 177.4 (CO).

5.1.33. 2,3,5,6-Tetraphenyl-DPP 4a. (a) A solution of the furopyrrole **28** (100 mg, 0.274 mmol), aniline (38 mg, 37 µl, 0.411 mmol), *N*,*N*′-diisopropylcarbodiimide (69 mg, 85 µl, 0.548 mmol) trifluoroacetic acid (one drop) and DCM (5 cm^3) was stirred at room temperature for 14 days. Filtration of the formed precipitate, followed by washing with methanol and DCM gave the pyrrolopyrrole **4a** as an orange solid (30 mg, 25%); no mp was observed by DSC up to 400 °C (lit.[6] >360 °C).

(b) The enamine **30** (50 mg, 0.114 mmol) was mixed with polyphosphoric acid (2.0 cm^3) and the mixture heated to 175 °C for 5 min. Water was added, and the precipitate filtered and washed with methanol, to give the pyrrolopyrrole (3 mg, 7%). m/z (EI TOF): 441 [37%, $(M+1)^+$], 440 (100%, M^+), 439 [43%, $(M-1)^+$], 364 [57%, $(M-Ph)^+$] and 180 (59%, PhC–NPh). An accurate NMR spectrum could not be obtained due to very low solubility.

5.1.34. 2-*p*-Methoxyphenyl-3,5,6-triphenyl-DPP 4b. A solution of the triphenyl-furopyrrole **28** (100 mg, 0.27 mmol), p-anisidine (67 mg, 0.55 mmol), *N*,*N*′-diisopropylcarbodiimide (69 mg, 85 µl, 0.55 mmol), DMAP (67 mg, 0.55 mmol), HOBT (74 mg, 0.55 mmol) and DCM (10 cm^3) was stirred at room temperature for 24 h. The formed precipitate was filtered and washed with DCM, methanol and acetone, to give the tetraaryl-DPP as an orange solid (63 mg, 48%), mp 374–376 °C (from o-$Cl_2C_6H_4$). [Found: C, 78.0; H, 4.4; N, 5.55. $C_{31}H_{22}N_2O_3$

(6:1 ratio with o-$Cl_2C_6H_4$) requires C, 77.6; H, 4.6; N, 5.7%]. m/z (ES +ve): 494 [12%, $(M+Na+1)^+$], 493 [100%, $(M+Na)^+$] and 471 [5%, $(M+1)^+$]. An accurate NMR spectrum could not be obtained due to very low solubility.

5.1.35. 3,5,6-Triphenyl-2-*p*-trifluoromethylphenyl-DPP 4c. A solution of the furopyrrole **28** (100 mg, 0.27 mmol), *p*-aminobenzotrifluoride (88 mg, 69 μl, 0.55 mmol), *N*,*N*′-diisopropylcarbodiimide (69 mg, 85 μl, 0.55 mmol), dimethylaminopyridine (67 mg, 0.55 mmol) and *N*-hydroxybenzotriazole (74 mg, 0.55 mmol) in DCM (10.0 cm^3) was stirred for 2 weeks at room temperature. The precipitate was filtered and washed with further DCM and hot ethanol, to give the tetraaryl-DPP as an orange solid (70 mg, 50%), mp 363–364.5 °C. (Found: C, 71.7; H, 3.5; N, 5.0. $C_{31}H_{19}F_3N_2O_2$ (4:1 ratio with o-$Cl_2C_6H_4$) requires C, 71.6; H, 3.7; N, 5.1%). m/z (ESI +ve): 532 [12%, $(M+Na+1)^+$] and 531 [100%, $(M+Na)^+$]. An accurate NMR spectrum could not be obtained due to very low solubility.

6. X-ray crystallography

The intensity data for compounds **15b** and **15d** were recorded at 93 K using a Rigaku MM007/Mercury diffractometer (rotating anode, confocal optics Mo-Kα radiation), and for **12** and **19** at 125 K using a Bruker SMART diffractometer (sealed tube graphite-monochromated Mo Kα radiation). In **12**, two molecules of DMF were included in the lattice, in **15b** two crystallographically independent molecules were present in the asymmetric unit and in **15d** an acetic acid molecule and disordered water in two locations were present in the asymmetric unit. All data were corrected for Lorentz, polarisation and absorption effects (multiple equivalent reflection method). Structures were solved by direct methods and refined by full-matrix least-squares against F^2 (SHELXTL). All N–H hydrogen atoms in compounds **15b** and **19** were refined isotropically subject to a distance constraint (N–H=0.98 Å). In **15d**, due to the poorer data quality the N–H was refined in an idealised position at a fixed distance of 0.98 Å and with a riding isotropic thermal parameter. All remaining hydrogen atoms were assigned riding isotropic displacement parameters and constrained to idealised geometries.

CCDC-276105-276112 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).

Acknowledgements

We thank Dr. I. Fraser (Ciba), Prof. A. Mills and Mr. J. Hepburn (University of Strathclyde) for help with fluorescence spectroscopy, Mrs. S. Williamson for microanalyses and DSC measurements, Mrs. C. E. R. Horsburgh (EI and CI) and Dr. C. H. Botting (ESI) for mass spectra, and Ciba Specialty Chemicals Inc. (Basel) and the Royal Society (London) for financial support.

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Tetrahedron 61 (2005) 11244–11252
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Preparation of novel 3*H*-trifluoromethyldiazirine-based photoactivatable potassium channel antagonists

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Received 24 June 2005; revised 11 August 2005; accepted 1 September 2005

Available online 28 September 2005

Abstract—The preparation of a series of photoactivatable precursors for use in photoaffinity labelling of potassium channels is described. 3*H*-Diazirine functionalities were incorporated into the previously described potassium channel antagonists **1**–**3**. The ability to perform enantioselective reductions and Wittig reactions in the presence of 3*H*-diazirines was central to this work.

1. Introduction

Ion channels are macromolecular protein complexes within cell membranes that mediate and regulate crucial electrical functions throughout the body. They are drug targets for a number of therapeutic agents aimed at treating a variety of disorders including hypertension, arrhythmias, seizures, pain, stroke, and diabetes. It has become evident that there are a multitude of channels, each having a highly evolved structure.

Much attention has been paid to the determination of the structure of voltage-activated (K_V) potassium channels as they are amongst the most functionally diverse of all the ion-channels, playing major roles in the control of cell excitability across a wide range of cell types.[1] Such structural information is important for the development of channel-specific antagonists (blockers) targeted to the brain, offering the potential to treat a number of currently untreatable or difficult to manage diseases such as multiple sclerosis.[2] Elegant structural studies have revealed much of the details concerning the structure and function of these channels.[3] They consist of tetrameric bundles of proteins, each of which is composed of six transmembrane helices (S1–S6).[4] The first four, and particularly S4, are responsible for detecting changes in membrane potential, S5, S6, and the connecting loop provide the ion-selectivity filter (Fig. 1).

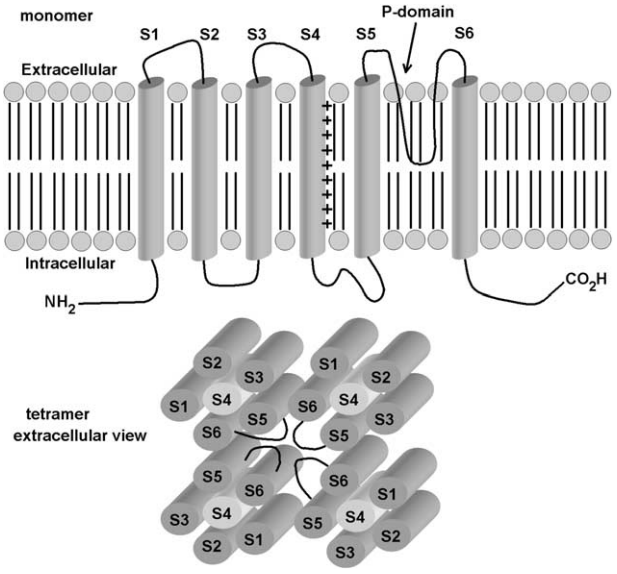

Figure 1.

Although many peptidic toxins show a high activity in the brain as K_V channel blockers, producing marked physiological responses,[5] to date there are few non-peptidic blockers targeted towards these channels. Among those described[6,7] is a series of open channel blockers of which **1**–**3** (Fig. 2) show a particularly interesting activity towards brain $K_V1.1$ channels, with IC_{50} values in the range 60–600 μM.

Photoaffinity labelling is a powerful tool for probing the structure of membrane proteins to elucidate otherwise

Keywords: Photoreactive; Photolabile; Antagonist; Stereoselective; Diazirine.
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doi:10.1016/j.tet.2005.09.007

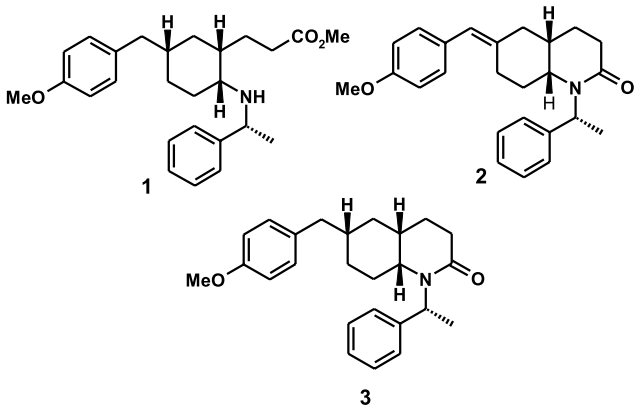


Figure 2.

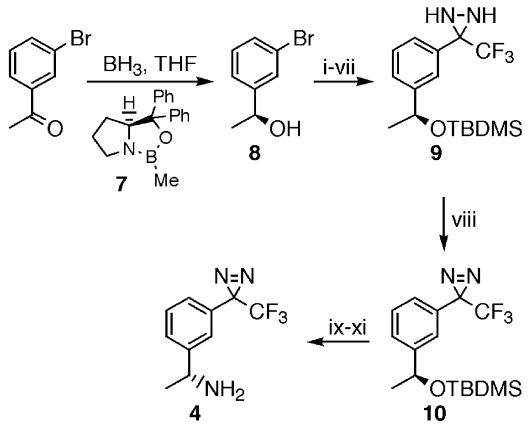
difficult to obtain structural information, such as the details of antagonist binding sites.[8] Various functional groups have been utilised as photocrosslinkable units for the study of biological systems, notably aryl ketones,[9] and azides.[8] Amongst these, the 3*H*-trifluoromethyl diazirines are particularly attractive due to their thermal stability and ability to release a highly reactive trifluoromethyl carbene upon photolysis at around 350 nm.[10–16] As the small molecule K_V channel blockers such as **1**–**3** (Fig. 2) offered the potential for investigating the possibility of these binding within the narrow part of the channel pore,[17] which is inaccessible to the larger peptidic blockers, it was highly desirable to prepare a number of photoactivatable derivatives of these molecules, incorporating 3*H*-trifluoromethyl diazirines to enable labelling studies to be performed on the brain $K_V1.1$ channel.

Despite their demonstrated potential as photolabile moieties, syntheses of non-peptidic 3*H*-trifluoromethyldiazirine-labelled substrates are few and there is presently only a limited knowledge of their behaviour under various chemical conditions. We therefore describe below the synthesis of a range of diazirine-based photoreactive antagonists, which illustrate the chemical robustness of this versatile photolabile moiety.

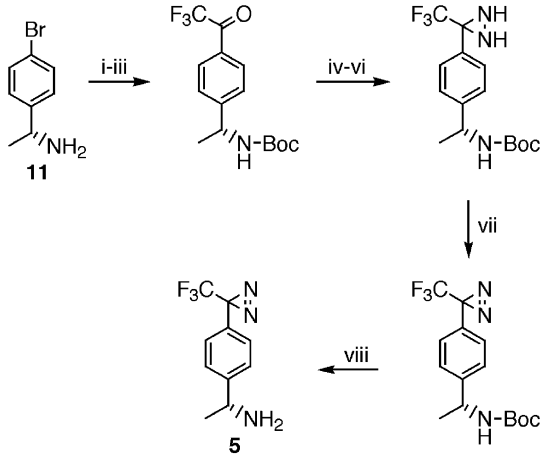
2. Results and discussion

In order to prepare photoactivatable analogues of **1**, our initial synthetic targets were chiral amines **4** and **5** (Schemes 1 and 2) to be used in the reductive amination of ketone **6** (Scheme 3). A high yielding preparation of chiral amine **4** was subsequently developed (Scheme 1). Thus, 3-bromoacetophenone was reduced to chiral alcohol **8** with borane in the presence of Corey's chiral oxazaborolidine **7**.[18] This was then protected as the *tert*-butyldimethylsilyl (TBDMS) ether by reaction of the sodium salt of the alcohol with TBDMS chloride in the presence of a catalytic amount of 15-crown-5 (Scheme 1).

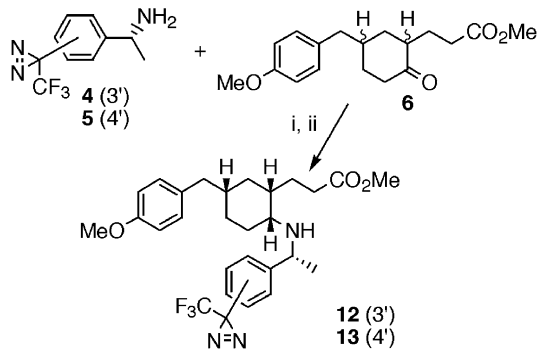
Diaziridine **9** was prepared from the silyl ether via a sequence involving formation of a trifluoromethyl ketone, oximation, and cyclisation of the *O*-tosylated oxime with ammonia.[19] During the course of this and other work, it became apparent to us that oxidation of trifluoromethyl



Scheme 1. Reagents and conditions: (i) NaH, 15-crown-5, DCM; (ii) TBDMS–Cl, 78%; (iii) *n*BuLi, THF, −78 °C; (iv) Et_2NCOCF_3, −78 °C, 91%; (v) $NH_2OH{\cdot}HCl$, pyridine, 99%; (vi) TsCl, DIEA, DMAP, DCM, 82%; (vii) NH_3, Et_2O, −78 °C, 79%; (viii) PCC, pyridine, DCM, 96%; (ix) TBAF, THF, H_2O, 2 h, 82%; (x) phthalimide, Ph_3P, DEAD, 50%; (xi) NH_2NH_2, MeOH, 83%.



Scheme 2. Reagents and conditions: (i) BOC–ON, DCM, 72%; (ii) *n*BuLi (2 equiv), THF; (iii) Et_2NCOCF_3, −78 °C, 82%; (iv) $NH_2OH{\cdot}HCl$, pyridine, Δ, 96%; (v) TsCl, DIEA, DMAP, DCM, 77%; (vi) NH_3, Et_2O, −78 °C, 95%; (vii) PCC, DCM, pyridine, 82%; (viii) HCOOH, Δ, 75%.



Scheme 3. Reagents and conditions: (i) AcOH (1.1 equiv), 3 Å sieves, DCE, 18 h; (ii) $NaBH(OAc)_3$, 4 h, 23% (**13**) 5% (**12**).

diaziridines such as **9** to yield the corresponding diazirine proceeds sluggishly using silver oxide, often requiring the addition of further quantities of freshly prepared reagent to the reaction. It was found, however, that this conversion could be readily achieved in excellent yield using PCC in DCM, being complete within 5 min. The addition of pyridine to the reaction mixture enabled diazirine **10** to be obtained without loss of the silyl protecting group; a problem described elsewhere[20] with PCC.

Following fluoride ion mediated removal of the silyl protecting group to give the alcohol; the corresponding protected amine was prepared, with inversion of stereochemistry,[21] using a Mitsunobu reaction with phthalimide. The phthaloyl group was subsequently removed using hydrazine in methanol. Chiral amine **5** was prepared in good yield from commercially available amine **11** as outlined in Scheme 2. Boc-protection of the amine and subsequent conversion to the diazirine proceeded smoothly. Final deprotection was achieved in good yield using formic acid to produce **5**.

Our initial strategy involved a nickel catalysed reductive amination of ketone **6**[6] with amines **4** and **5**. It was found, however, that the diazirine moiety was not stable under these conditions and reduction to a mixture of the corresponding trifluoromethyl hydrazone and 2,2,2-trifluoroethyl substituted system was observed. Sodium triacetoxyborohydride on the other hand, was found to be a suitably mild reducing agent, and by careful control of reaction conditions the *para*-substituted benzylamine **5** gave the desired stereoisomer **13** in modest yield but crucially, with the diazirine ring intact (Scheme 3).

It is interesting that, despite the rather modest yield, **13** was obtained as a single diastereoisomer, and no other isomeric amines were detected in the crude reaction mixtures (NMR), diazirine **13** being easily purified using column chromatography.

Stereochemical assignment was made by comparison of the NMR spectra of **13** to those of authentic samples of antagonist **1** and the stereoisomeric compounds **A–C** (Fig. 3).[22] In particular, comparison of the ^{13}C resonances revealed a close correspondence with those in the ^{13}C NMR spectrum of **1**, (Fig. 3).

A likely explanation for the observed stereocontrol is the differences in the rates of reduction of the various imine intermediates (Fig. 4). As the starting material **6** is a racemic mixture containing both cis- and trans-isomers, condensation with optically pure amine can yield up to four diastereoisomeric imines, reduction of which creates a fourth stereocentre yielding eight possible diastereoisomeric amines. The observed stereocontrol can be explained in terms of kinetic resolution of the imine corresponding to the desired product. It has already been demonstrated[23a–d] that bulky borohydride reducing agents favour equatorial attack from the least hindered face of 2-substituted exocyclic cyclohexylimine, producing an axial amine as the product (Fig. 4A). This mechanism operates due to the hindrance of axial attack resulting from the presence of the 3- and 5- axial hydrogens. As a

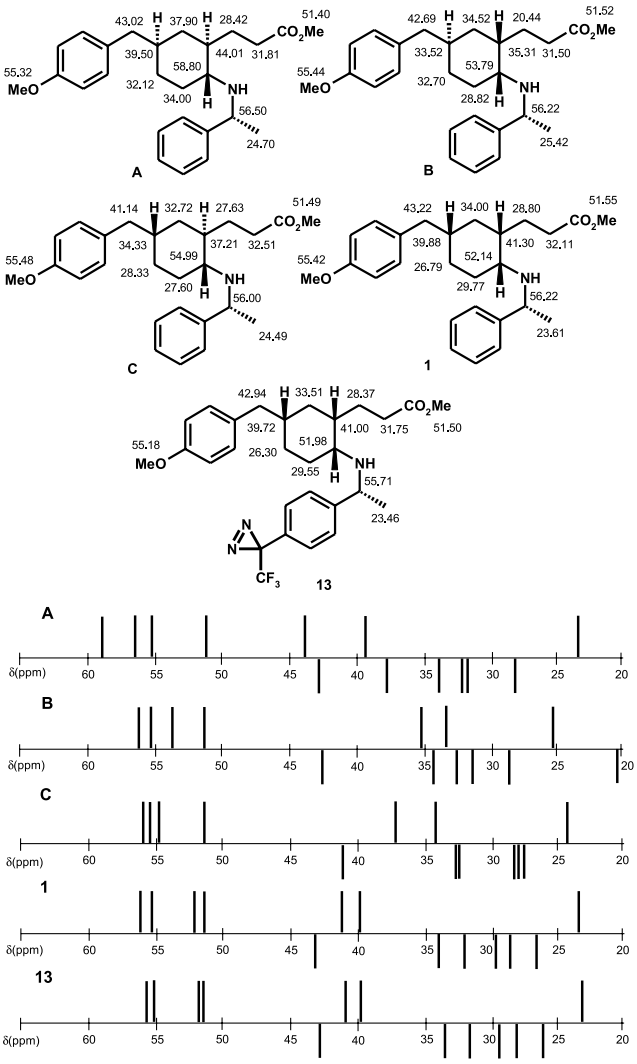


Figure 3. Schematic comparison of ^{13}C spectra (only high-field signals shown). Methine resonances identified using DEPT and are shown as inverted signals.

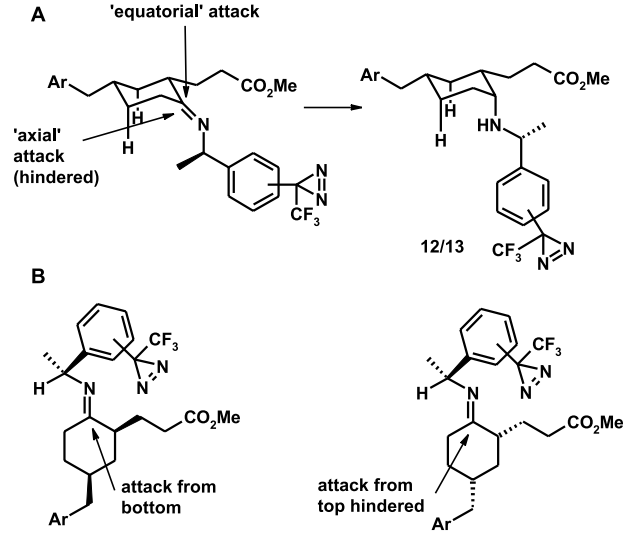


Figure 4.

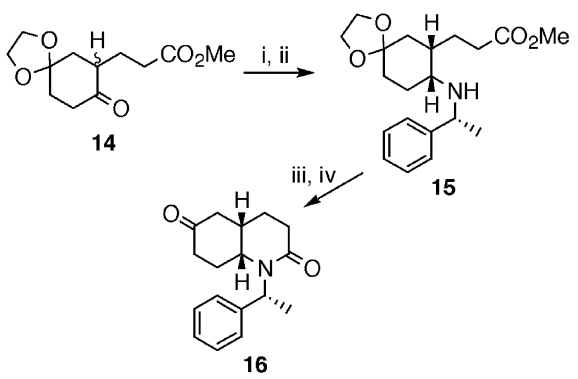
consequence, assuming that the 2-propionyl group is always equatorial, reduction by triacetoxyborohydride will always result in a cis relative sterochemical relationship with the amino group in the product. It is furthermore noteworthy that the 4-methoxybenzyl substituent is equatorial in the imines corresponding to the products **12** and **13**. The corresponding imine with the 4-substituent of opposite stereochemistry would have this substituent located axially, which would partially hinder equatorial attack by the borohydride, and also favour a high population of the chair conformation with the axially-located 2-substituent also blocking equatorial attack. The central issue to resolve is the selectivity observed between the two imines of opposing ring stereochemistry, which would both produce an all cis substitution pattern upon imine reduction (Fig. 4B). This is accounted for by the chirality of the methylbenzyl group. In both imines, this group is expected to be in the *E* conformation, with the methylbenzyl group directed away from the 2-propionyl substituent.

At the same time, however, the methylbenzyl substituent occupies conformations in which the aromatic ring and the methyl group partially obstruct attack on the imine carbon. In the case of the imine corresponding to **12** and **13**, the top face of the ring as seen in Figure 4B is obstructed. This is not significant, however, as equatorial attack occurs from the bottom face in this case.

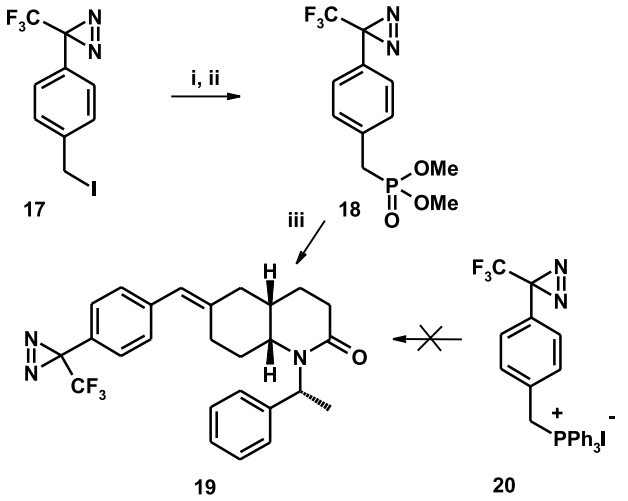
For the imine corresponding to the 'wrong' stereoisomer, the top face of the ring is still obstructed, and equatorial attack also occurs from this face. As a result, presumably, the rate of reduction of this imine is markedly decreased.

Although very low yielding, the *para*-subtituted benzylamine **4** similarly reacted with ketone **6** to give **12** as the sole product of reductive amination. In this case, stereochemistry was assigned via spectral comparison of the ^{1}H NMR spectrum to that of compound **13**.

In order to prepare a photoactivatable analogue of antagonist **2**, ketone **16** (Scheme 4) was prepared by the reductive amination of **14**[6] to give **15**, followed by lactamisation and acetal deprotection. Wittig–Horner reaction of this ketone with phosphonate **18**, prepared by reaction of benzyl iodide **17**[19] with trimethylphosphite, gave target olefin **19** in moderate yield (Scheme 5). Our initial



Scheme 4. Reagents and conditions: (i) *R*(+)-α-methylbenzylamine, TsOH, PhMe, Δ; (ii) Ni/H_2, 74%; (iii) AcOH, PhMe, Δ, 64%; (iv) AcOH, H_2O, Δ, 82%.



Scheme 5. Reagents and conditions: (i) $P(OMe)_3$ (10 equiv), PhMe; (ii) Δ, 18%; (iii) **16**, NaH, THF, 18 h, 27%.

intention to use phosphonium salt **20** for this reaction was unsuccessful as **20** proved to be too unreactive in the presence of ketone **16**, although it was observed to undergo reaction with simple aldehydes such as benzaldehyde (79% yield).

3. Conclusions

We have described the preparation of a number of reagents with important applications in photoaffinity labelling studies of voltage-activated potassium channels. This work has further explored the scope and limitations of reactions involving diazirine-containing substrates. In particular, the potential for use of the diazirine group in the preparation of photolabile substrates has been expanded by the preparation of diazirines of application in the derivatisation, via Wittig reaction, of aldehydes and ketones. Furthermore, a modest stability of the diazirine moiety in the presence of reducing agents has been demonstrated.

4. Experimental

4.1. General

Infrared spectra were recorded using a Perkin Elmer 1420 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on General Electric QE 300 or Bruker AMX400 spectrometers using tetramethylsilane as the internal standard. Coupling constants (*J*) are quoted in Hertz. Low and high-resolution mass specta were recorded on an VG Autospec using either chemical ionisation (CI), electron impact (EI), or fast atom bombardment (FAB) ionisation techniques. All accurate mass measurements were performed using EI on signals of greater than 1% relative intensity. Optical rotations were determined at 30 °C using an Optical Activity AA1000 polarimeter with cells of path lengths 0.25 or 1 dm. Melting points were determined using a Reichert hot stage and are uncorrected. Microanalyses were performed by the University of Leeds Microanalytical service using an Elemental Analyser 1106. Flash column chromatography

was carried out using Merck Kieselgel 60 (230–400 mesh). Solvents were either obtained dry from commercial sources or dried prior to use using standard methods.

4.1.1. (*S*)-1-(3-Bromophenyl)ethyl alcohol (8). To a stirred solution of 3-bromoacetophenone (4.90 g, 24.6 mmol) and (*R*)-(+)-2-methyl-CBS-oxazaborolidine (0.74 g, 2.5 mmol) in THF (20 ml) under argon was added BH_3 (1.0 M in THF; 14.8 ml, 14.8 mmol) over 10 min. After stirring for a further 15 min the mixture was cooled to 0 °C and diluted with MeOH (60 ml). After 30 min HCl/Et_2O (60 ml) was added and the solution concentrated in vacuo. The resulting oily solid was washed with Et_2O (100 ml), the washings evaporated in vacuo and the oily residue chromatographed (hexane/Et_2O; 4:1) to give the title compound (2.63 g, 53%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.48 (3H, d, J=6.6 Hz, Me), 1.96 (1H, br, OH), 4.88 (1H, q, J=6.6 Hz, Me-C*H*(Ar)-OH), 7.19–7.39 (2H, m, Ar), 7.43 (1H, d, J=8.3 Hz, Ar), 7.55 (1H, d, J=9.6 Hz, Ar). ν/cm^{-1} (liquid film) 3370 (s), 2900 (s), 1600 (m), 1570 (s), 1430 (s), 1200 (s), 1070 (s), 905 (m), 785 (s), 700 (s). $[\alpha]_D^{30}$ −19 (*c* 0.9, $CHCl_3$). *m*/*z* (EI, %): 202 (20, M^+, ^{81}Br), 77 (100).

4.1.2. (*S*)-1-(3-Bromophenyl)ethyl alcohol-*O*-(*tert*-butyldimethylsilyl) ether. A solution of alcohol (**8**) (1.86 g, 9.3 mmol) in DCM (10 ml) was added dropwise to a stirred suspension of NaH (60% suspension in mineral oil; 0.64 g, 16.0 mmol) in DCM (10 ml) under argon at room temperature over a 10 min period. Following stirring for a further 10 min, a mixture of TBSMS–Cl (3.48 g, 23.1 mmol) and 15-crown-5 (0.2 g, 0.9 mmol) in DCM (10 ml) was added dropwise over 10 min. After stirring for a further 55 min, the reaction was quenched by the addition of ^{i}PrOH (50% aq, 45 ml) and the mixture diluted with DCM (60 ml). The organic layer was then washed with water (2× 100 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification using chromatography (hexane) gave the title compound (2.28 g, 78%) as a colourless liquid. ^{1}H NMR (200 MHz, $CDCl_3$); δ −0.02 (3H, s, Me-Si–), 0.93 (9H, s, ^{t}Bu), 1.40 (3H, d, J=6.4 Hz, *Me*-CH(Ar)-OSi), 4.84 (1H, q, J=6.2 Hz, Me-C*H*(Ar)-OSi), 7.15–7.29 (2H, m, Ar), 7.34–7.39 (1H, m, Ar), 7.49–7.50 (1H, m, Ar). ν/cm^{-1} (liquid film) 2960 (s), 1600 (m), 1570 (m), 1470 (s), 1260 (s), 1200 (s), 1120 (s), 1100 (s), 840 (s), 780 (s), 700 (s). $[\alpha]_D^{30}$ −23 (*c* 0.9, $CHCl_3$). *m*/*z* (CI (NH_3) %): 334 (1, $M^+ + NH_4$, ^{81}Br), 332 (0.8, $M^+ + NH_4$, ^{79}Br), 317 (1, $M^+ + H$, ^{81}Br), 315 (1, $M^+ + H$, ^{79}Br), 276 (11, ^{81}Br), 274 (14, ^{79}Br), 202 (47, ^{81}Br), 200 (50, ^{79}Br), 196 (27), 122 (100). $C_{14}H_{23}BrOSi$ requires: C, 53.3; H, 7.35. Found: C, 53.5; H, 7.37.

4.1.3. (*S*)-3-[1-(*tert*-Butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone. To a stirred solution of (*S*)-1-(3-bromophenyl)ethyl alcohol-*O*-(*tert*-butyldimethylsilyl) ether (2.68 g, 8.5 mmol) at −78 °C under argon in THF (30 ml) was added ^{n}BuLi (1.6 M in hexane: 6.2 ml, 9.9 mmol) dropwise over 10 min. After stirring at −78 °C for a further 75 min, a solution of *N*,*N*-diethyltrifluoroacetamide (1.9 g, 11 mmol), in THF (6 ml) was added dropwise over 1 h. After stirring for a further 75 min at −78 °C, ammonium chloride (half satd aq solution; 30 ml) was added and the stirred mixture allowed to warm to room temperature. Diethyl ether (50 ml) was added and the organic layer separated and washed successively with ammonium chloride (satd aq; 2×50 ml) and water (3× 50 ml). Following drying ($MgSO_4$) of the combined organic solutions, filtration and removal of the solvents in vacuo, chromatography (hexane/EtOAc; 6:1) of the resulting yellow oil gave the title compound (2.57 g, 91%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ −0.02 (3H, s, *Me*-Si–), 0.09 (3H, s, *Me*-Si–), 0.93 (9H, s, ^{t}Bu), 1.44 (3H, d, J=6.4 Hz, *Me*-CH(Ar)-OSi), 4.96 (1H, q, J=6.2 Hz, Me-C*H*(Ar)-OSi), 7.51 (1H, t, J=7.8 Hz, Ar), 7.68–7.72 (1H, m, Ar), 7.94–7.98 (1H, m, Ar), 8.09 (1H, m, Ar). ν/cm^{-1} (liquid film) 2960 (s), 2920 (s), 1729 (s), 1605 (w), 1220 (s), 1200 (s), 1155 (s), 950 (m), 840 (s), 780 (m), 740 (m). $[\alpha]_D^{30}$ −23 (*c* 1.2, $CHCl_3$). *m*/*z* (EI, %): 332 (0.02, M^+), 276 (3), 263 (2), 225 (100), 131 (42), 103 (14), 75 (79). $C_{16}H_{23}F_3O_2Si$ requires: C, 57.03; H, 7.03. Found: C, 57.06; H, 7.09.

4.1.4. (*S*)-3-[1-(*tert*-Butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone oxime. (*S*)-3-[1-(*tert*-butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone (2.5 g, 7.56 mmol) and hydroxylamine hydrochloride (2.5 g, 7.56 mmol) were stirred together in a mixture of pyridine (27 ml) and EtOH (12 ml) at 80 °C for 4 h. Following removal of the solvents in vacuo, the residue was treated with Et_2O (70 ml) and washed with water (4×35 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (hexane/ether; 4:1) of the residue gave the title compound (2.61 g, 99%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ −0.02 (3H, s, *Me*-Si–), 0.05 (3H, s, *Me*-Si–), 0.90 (9H, s, ^{t}Bu), 1.41 and 1.44 (3H, d, J=6.4 Hz, *Me*-CH(Ar)-OSi, E/Z oxime), 4.90 (1H, q, J=6.4 Hz, Me-C*H*(Ar)-OSi), 7.35–7.48 (4H, m, Ar), 8.42 (1H, br, –OH). ν/cm^{-1} (liquid film) 3300 (m), 2970 (s), 2920 (s), 1260 (m), 1230 (m), 1170 (s), 1100 (m), 835 (s), 780 (m). $[\alpha]_D^{30}$ −22 (*c* 0.6, $CHCl_3$). *m*/*z* (CI (NH_3), trimethylsilyl derivative, %): 420 (52, $M^+ + H$), 352 (3), 332 (100), 305 (15), 288 (12). $C_{16}H_{24}F_3NO_2Si$ requires: C, 55.3; H, 6.96; N, 4.0. Found: C, 57.06; H, 6.65; N, 3.5.

4.1.5. (*S*)-3-[1-(*tert*-Butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone-*O*-(4-toluenesulphonyl)oxime. 4-Toluenesulphonyl chloride (1.4 g, 7.4 mmol) was added portion-wise to a stirred solution of (*S*)-3-[1-(*tert*-butyldimethylsiloxy)ethyl]-2,2,2-trifluoro acetophenone oxime (2.58 g, 7.4 mmol), DIEA (1.4 ml, 8.3 mmol) and DMAP (70 mg, 0.56 mmol) in DCM (12.5 ml) at 0 °C. The stirred mixture was allowed to warm to room temperature over 40 min and was washed with water (3×15 ml) and dried ($MgSO_4$). Following filtration and concentration in vacuo, chromatography (DCM/petrol; 3:4) gave the title compound (3.07 g, 82%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ −0.03 and −0.04 (3H, s, *Me*-Si–, E/Z oxime), 0.06 (3H, s, *Me*-Si–), 0.89 (9H, s, ^{t}Bu), 1.38 and 1.40 (3H, d, J=6.4 Hz, *Me*-CH(Ar)-OSi, E/Z oxime), 2.46 and 2.48 (3H, s, *Me*-PhSO_2–, E/Z oxime), 4.88 (1H, m, Me-C*H*(Ar-OSi), 7.24–7.50 (6H, m, Ar), 7.86–7.93 (2H, m, Ar). ν/cm^{-1} (liquid film) 2970 (m), 2920 (m), 1600 (w), 1390 (s), 1200 (s), 1180 (s), 1095 (m), 830 (s), 780 (s). $[\alpha]_D^{30}$ −15 (*c* 0.6, $CHCl_3$). *m*/*z* (CI (NH_3), %): 519 (1, $M^+ + NH_4$), 351 (11), 332 (100), 219 (5), 204 (10).

4.1.6. (*S*)-3-Trifluoromethyl-3-{3-[1-(*tert*-butyl dimethylsiloxy)ethyl]phenyl}diaziridine (9). To a stirred solution of (*S*)-3-[1-(*tert*-butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone -*O*-(4-toluenesulphonyl) oxime (2.95 g,

5.9 mmol), in ether (12 ml) at −78 °C in a 3-neck flask fitted with a CO_2/acetone condenser and potassium carbonate guard tube, was added ammonia (36 ml) by direct distillation from sodium over an 8 h period and this solution then stirred at −78 °C for 2 h. The ammonia was then allowed to evaporate via allowing the solution to warm to room temperature over a 7 h period. The ethereal solution was filtered and the solvent removed in vacuo to give the title compound (1.61 g, 79%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ −0.04 (3H, s, *Me*-Si–), 0.07 (3H, s, *Me*-Si–), 0.88 (9H, s, ^{t}Bu), 2.22 (1H, d, J=8.7 Hz, –N*H*–NH–), 2.80 (1H, d, J=8.7 Hz, –NH–N*H*–), 1.42 (3H, d, J=6.4 Hz, *Me*-CH(Ar)-OSi), 4.86 (1H, q, J=6.5 Hz, Me-C*H*(Ar)-OSi), 7.29–7.62 (4H, m, Ar). ν/cm^{-1} (liquid film) 3260 (m), 2920 (s), 1720 (w), 1460 (m), 1250 (m), 1170 (s), 1140 (s), 970 (m), 830 (s), 770 (m). $[\alpha]_D^{30}$ −24 (*c* 1.0, $CHCl_3$). *m*/*z* (EI, %): 346 (0.1, M^+), 331 (0.5), 274 (9), 224 (22), 208 (13), 130 (44), 75 (100). $C_{16}H_{25}F_3N_2OSi$ requires: C, 55.5; H, 7.3; N, 8.1. Found: C, 55.4; H, 7.0; N, 7.8.

4.1.7. (*S*)-1-[3-(3-Trifluoromethyl-3*H*-diazirin-3-yl)-phenyl]ethyl alcohol-*O*-*tert*-butyldimethylsilyl ether (10). To a stirred solution of (*S*)-3-trifluoromethyl-3-{3-[1-(*tert*-butyldimethylsiloxy)ethyl]phenyl}diaziridine (0.99 g, 2.8 mmol) and pyridine (2.5 ml) in DCM (25 ml) was added PCC (0.92 g, 2.8 mmol) over 10 min. Following dilution with ether (25 ml), the mixture was filtered through a pad of silica and concentrated in vacuo. Chromatography (hexane/ether; 4:1) gave the title compound (0.94 g, 96%) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ −0.04 (3H, s, *Me*-Si–), 0.05 (3H, s, *Me*-Si–), 0.90 (9H, s, ^{t}Bu), 1.38 (3H, d, J=6.3 Hz, *Me*-CH(Ar)-OSi), 4.86 (1H, q, J=6.3 Hz, Me-C*H*(Ar)-OSi), 7.02–7.04 (1H, m, Ar), 7.20 (1H, br s, Ar), 7.28–7.35 (2H, m, Ar). ν/cm^{-1} (liquid film) 2960 (s), 2930 (s), 1610 (m), 1250 (s) 1200 (s), 1150 (s), 950 (m), 830 (s), 780 (m), 700 (m). $[\alpha]_D^{30}$ −24 (*c* 1.2, $CHCl_3$). *m*/*z* (EI, %): 344 (0.1, M^+), 259 (3), 149 (20), 81 (61), 69 (100). $C_{16}H_{23}F_3N_2OSi$ requires: C, 55.79; H, 6.73; N, 8.13. Found: C, 55.64; H, 7.20; N, 8.05.

4.1.8. (*S*)-1-[3-(3-Trifluoromethyl-3*H*-diazirin-3-yl)-phenyl]ethyl alcohol. (*S*)-1-[3-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethyl alcohol-*O*-*tert*-butyldimethylsilyl ether (0.29 g, 0.83 mmol) was treated with a solution of TBAF (1.6 M in THF; 6.8 ml, 10.9 mmol) containing 5% water for 2 h at 20 °C. Following dilution with ether (20 ml), the mixture was washed with water (2×20 ml) and dried ($MgSO_4$). Following filtration and evaporation in vacuo, chromatography (ether) gave the title compound (0.16 g, 82%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.48 (3H, d, J=6.6 Hz, *Me*-CH(Ar)-OH), 1.85 (1H, br, –OH), 4.90 (1H, q, J=6.6 Hz, Me-C*H*(Ar)-OH), 7.13–7.16 (2H, m, Ar), 7.34–7.45 (2H, m, Ar). ν/cm^{-1} (liquid film) 3350 (s), 2980 (m), 2910 (m), 1610 (m), 1240 (s), 1200 (s), 1160 (s), 900 (m), 800 (m), 700 (m). $[\alpha]_D^{30}$ −25 (*c* 0.9, $CHCl_3$). *m*/*z* (EI, %): 230 (0.5, M^+), 206 (6), 187 (27), 159 (32), 137 (43), 109 (57), 91 (100). $C_{10}H_9F_3N_2O$ requires: C, 52.2; H, 3.9; N, 12.2. Found: C, 52.4; H, 4.0; N, 11.9.

4.1.9. (*R*)-*N*-{1-[3-(3-Trifluoromethyl-3*H*-diazirin-3-yl)-phenyl]ethyl}phthalimide. To a stirred solution of (*S*)-1-[3-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethyl alcohol (0.26 g, 1.1 mmol), triphenylphosphine (0.36 g, 1.4 mmol), and phthalimide (0.22 g, 1.5 mmol) in THF (25 ml) under argon, was added DEAD (0.22 ml, 1.4 mmol) dropwise over 2 min. After stirring the resulting pale yellow solution at room temperature for 4 days, the solvent was removed in vacuo and the residue chromatographed (pentane/ether; 4:1) to give the title compound (0.21 g, 50%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.90 (3H, d, J=7.2 Hz, *Me*-CH(Ar)-N–), 5.54 (1H, q, J=7.4 Hz, Me-C*H*(Ar)-N), 7.17 (1H, d, J=6.2 Hz, Ar), 7.30–7.39 (2H, m, Ar), 7.57–7.59 (1H, m, Ar), 7.69–7.72 (2H, m, Ar), 7.79–7.84 (2H, m, Ar). ν/cm^{-1} (liquid film) 3080 (m), 2940 (m), 1710 (s), 1610 (m), 1390 (s), 1245 (s), 1200 (s), 1145 (s), 900 (m), 875 (m), 795 (m), 725 (s), 700 (s). $[\alpha]_D^{30}$ −17 (*c* 0.3, $CHCl_3$). *m*/*z* (EI, %): 359 (0.7, M^+), 331 (36), 316 (16), 262 (67), 220 (26), 205 (85), 183 (58), 43 (100). $C_{18}H_{12}F_3N_3O_2$ requires: C, 60.17; H, 3.37; N, 11.69. Found: C, 60.31; H, 3.66; N, 11.66.

4.1.10. (*R*)-1-[3-(3-Trifluoromethyl-3*H*-diazirin-3-yl)-phenyl]ethylamine (4). A solution of (*R*)-*N*-{1-[3-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethyl} phthalimide (0.1 g, 0.28 mmol) in MeOH (5 ml) was treated with hydrazine (2.0 M solution in MeOH; 5 ml, 10 mmol) and this mixture stirred at room temperature for 17 h before the solvent was removed in vacuo. The residue was treated with chloroform and filtered before being washed with water (2×20 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo to give the title compound (0.05 g, 83%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.36 (3H, d, J=6.6 Hz, *Me*-CH(Ar)–NH_2), 4.13 (1H, q, J=6.3 Hz, Me-C*H*(Ar)–NH_2), 7.12–7.16 (1H, m, Ar), 7.31–7.43 (3H, m, Ar). ν/cm^{-1} (liquid film) 3480 (w), 3225 (w), 2920 (s), 2845 (s), 1545 (w), 1465 (m), 1440 (m), 1165 (s), 1125 (s), 790 (m), 700 (m). $[\alpha]_D^{30}$ −8 (*c* 0.05, $CHCl_3$). *m*/*z* (EI, %): 229 (0.8, M^+), 216 (8), 201 (33), 183 (100), 167 (29), 149 (78), 108 (28). $C_{10}H_{10}F_3N_3$ requires: 229.082682. Found: 229.083022.

4.1.11. (*R*)-*N*-(*tert*-Butoxycarbonyl)-1-(4-bromophenyl) ethylamine. To a solution of (*R*)-1-(4-bromophenyl) ethylamine (**11**) (3.07 g, 15.3 mmol) and triethylamine (3 ml, 21.5 mmol) in DCM (15 ml) was added 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (4.06 g, 16.5 mmol) at room temperature. The mixture was stirred for 70 min and was then diluted with DCM and the organic extracts dried ($MgSO_4$), filtered, and the solvents removed in vacuo. Recrystallisation from EtOAc/hexane gave the title compound (3.32 g, 72%) as a colourless solid, mp 131–135 °C. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.40–1.44 (12H, br m, ^{t}Bu and Me, E/Z Boc-NH), 4.65–4.80 (2H, br m, Me-C*H*(Ar)-NH-Boc and -N*H*-Boc, E/Z Boc-NH), 7.17 (2H, d, J=8.4 Hz, Ar), 7.43–7.47 (2H, m, Ar, E/Z Boc-NH). ν/cm^{-1} (liquid film) 3380 (s), 1680 (s), 1520 (s), 1250 (s), 1170 (s), 1060 (s), 830 (s). $[\alpha]_D$ −48 (*c* 0.9, $CHCl_3$). *m*/*z* (CI, (NH_3), %): 319 (2, $M^+ + NH_4$, ^{81}Br), 317 (2, $M^+ + NH_4$, ^{79}Br), 263 (38, ^{81}Br), 261 (37, ^{79}Br), 219 (21, ^{82}Br), 217 (23, ^{79}Br), 202 (98, ^{81}Br), 200 (100, ^{79}Br). $C_{13}H_{18}BrNO_2$ requires: C, 52.0; H, 6.0; N, 4.7. Found: C, 51.9; H, 6.0; N, 4.6.

4.1.12. (*R*)-*N*-(*tert*-Butoxycarbonyl)-4-[(1-amino)ethyl]-2,2,2-trifluoroacetophenone. The title compound was prepared from (*R*)-*N*-(*tert*-butoxycarbonyl)-1-(4-bromophenyl)ethylamine (2.0 g, 6.7 mmol) using the method

described above (Section 4.1.3) for the preparation of (*S*)-3-[1-(*tert*-butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone. Purification using chromatography (hexane/ether; 4:1) gave the title compound (1.69 g, 84%) as a pale yellow solid, mp 75–76 °C. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.40–1.47 (12H, br m, ^{t}Bu and Me, E/Z Boc-NH), 4.72–5.00 (2H, br m, Me-C*H*(Ar)-NHBoc and –N*H*-Boc, E/Z Boc-NH), 7.48 (2H, d, J=8.2 Hz, Ar), 8.05 (2H, d, J=8.0 Hz, Ar). ν/cm^{-1} (nujol mull) 3380 (s), 1730 (s), 1680 (s), 1530 (s), 1220 (s), 1180 (s), 1130 (s), 1060 (s), 950 (s), 870 (m), 770 (m), 730 (m). $[\alpha]_D^{30}$ −44 (*c* 0.9, $CHCl_3$). *m*/*z* (EI, %): 302 (0.2, M^+), 262 (10), 246 (12), 202 (23), 201 (14), 57 (100). $C_{15}H_{18}F_3NO_3$ requires: C, 56.8; H, 5.7; N, 4.4. Found: C, 56.8; H, 6.0; N, 4.7.

4.1.13. (*R*)-*N*-(*tert*-Butoxycarbonyl)-4-[(1-amino)ethyl]-2,2,2-trifluoroacetophenone oxime. The title compound was prepared from (*R*)-*N*-(*tert*-butoxycarbonyl)-4-[(1-amino)ethyl]-2,2,2-trifluoroacetophenone (0.75 g, 2.4 mmol) using the method described above for the preparation of (*S*)-3-[1-(*tert*-butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone oxime (Section 4.1.4) but replacing ether for ethyl acetate in the work-up. Purification using chromatography ($CHCl_3$/MeOH; 20:1) gave the title compound (0.76 g, 96%) as a pale yellow solid, mp 86–89 °C. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.41–1.43 (12H, br m, ^{t}Bu and Me, E/Z Boc-NH), 4.65–4.95 (2H, br m, Me-C*H*(Ar)-NHBoc and –N*H*-Boc, E/Z Boc-NH), 7.26–7.47 (4H, m, Ar), 8.91 and 9.27 (1H, br, OH, E/Z oxime). ν/cm^{-1} (nujol mull) 3390 (s), 3280 (br m), 1680 (s), 1520 (s), 1210 (s), 1180 (s), 1170 (s), 1060 (s), 950 (s), 830 (m), 730 (m). $[\alpha]_D^{30}$ −49 (*c* 0.7, $CHCl_3$). *m*/*z* (CI (NH_3), %): 334 (0.2, M^++2H), 278 (13), 243 (15), 219 (52), 217 (100), 202 (56), 200 (56), 122 (96). $C_{15}H_{19}F_3N_2O_3$ requires: C, 54.2; H, 5.8; N, 8.4. Found: C, 54.4; H, 5.8; N, 8.4.

4.1.14. (*R*)-*N*-(*tert*-Butoxycarbonyl)-4-[(1-amino)ethyl]-2,2,2-trifluoroacetophenone-*O*-(4-toluenesulphonyl) oxime. The title compound was prepared from (*R*)-*N*-(*tert*-butoxycarbonyl)-4-[(1-amino)ethyl]-2,2,2-trifluoroacetophenone oxime (0.71 g, 2.13 mmol) using the method described above for (*S*)-3-[1-(*tert*-butyldimethylsiloxy) ethyl]-2,2,2-trifluoroacetophenone-*O*-(4-toluenesulphonyl) oxime (Section 4.1.5). Purification using chromatography (hexane/ether; 3:2) gave the title compound (0.79 g, 77%) as a colourless solid, mp 146–149 °C. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.41–1.44 (12H, br m, ^{t}Bu and Me, E/Z Boc-NH), 2.47 and 2.48 (3H, s, *Me*$PhSO_2$, E/Z oxime), 4.71–4.86 (2H, br m, Me-C*H*(Ar)-NHBoc and –N*H*-Boc, E/Z Boc-NH), 7.31–7.43 (6H, m, Ar), 7.87 and 7.92 (2H, m, Ar). ν/cm^{-1} (nujol mull) 3380 (s), 1680 (s), 1530 (s), 1395 (s), 1190 (s), 1180 (s), 1060 (m), 880 (m), 820 (m), 730 (m). $[\alpha]_D^{30}$ −31 (*c* 1.0, $CHCl_3$) *m*/*z* (CI (NH_3), %): 504 (1.5, $M^+ + NH_4$), 448 (2), 317 (41), 261 (66), 243 (100), 217 (85), 204 (48), 122 (52). $C_{22}H_{25}F_3N_2O_5S$ requires: C, 54.3; H, 5.2; N, 5.8. Found: C, 54.6; H, 5.5; N, 5.7.

4.1.15. (*R*)-4-{*N*-(*tert*-Butoxycarbonyl)-(1-amino)ethyl}-3-trifluoromethyl diaziridine. The title compound was prepared from (*R*)-*N*-(*tert*-butoxycarbonyl)-4-[(1-amino) ethyl]-2,2,2 trifluoro acetophenone-*O*-(4-toluenesulphonyl) oxime (0.50 g, 1.03 mmol) using the method described above for (*S*)-3-trifluoromethyl-3-{3-[1-(*tert*-butyldimethylsiloxy)ethyl]phenyl}diaziridine (**9**) (Section 4.1.6). Purification using chromatography (hexane/ether; 3:2) gave the title compound (0.32 g, 95%) as a colourless solid, mp 117–118 °C. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.40–1.45 (12H, br m, ^{t}Bu and Me, E/Z Boc-NH), 2.20 (1H, d, J= 8.8 Hz, N*H*-NH), 2.78 (1H, d, J=8.8 Hz, NH-N*H*), 4.70–4.88 (2H, br m, Me-C*H*(Ar)-NHBoc and –N*H*-Boc, E/Z Boc-NH), 7.33–7.37 (2H, m, Ar), 7.58 (2H, d, J=8.2 Hz, Ar). ν/cm^{-1} (nujol mull) 3380 (s), 3270 (m), 1680 (s), 1520 (s), 1250 (s), 1220 (s), 1170 (s), 1140 (s), 1070 (m), 950 (m), 830 (s), 705 (m). $[\alpha]_D^{30}$ −40 (*c* 0.7, $CHCl_3$). *m*/*z* (EI, %): 331 (0.3, M^+), 316 (3), 274 (76), 215 (80), 187 (66), 145 (44), 57 (100). $C_{15}H_{20}F_3N_3O_2$ requires: C, 54.4; H, 6.1; N, 12.7. Found: C, 54.8; H, 6.2; N, 12.6.

4.1.16. (*R*)-*N*-(*tert*-Butoxycarbonyl)-1-[4-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethylamine. The title compound was prepared from (*R*)-4-{*N*-(*tert*-butoxycarbonyl)-(1-amino)ethyl}-3-trifluoro methyl diaziridine 0.30 g, 0.9 mmol) using the method described above for (*S*)-1-[3-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethyl alcohol-*O*-*tert*-butyldimethyl silyl ether (Section 4.1.7). The crude yellow solid was recrystallised from EtOAc/pentane to give the title compound (0.24 g, 82%) as a colourless solid, mp 163–167 °C (dec). ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.39–1.43 (12H, br m, ^{t}Bu and Me, E/Z Boc-NH), 4.67–4.82 (2H, br m, Me-C*H*(Ar)-NHBoc and –N*H*-Boc, E/Z Boc-NH), 7.16 (2H, d, J=8.0 Hz, Ar), 7.33 (2H, d, J=8.1 Hz, Ar). ν/cm^{-1} (nujol mull) 3390 (s), 1680 (s), 1520 (s), 1240 (m), 1200 (s), 1150 (s), 1070 (m), 940 (m). $[\alpha]_D^{30}$ −38 (*c* 0.16, $CHCl_3$). *m*/*z* (EI, %): 329 (0.4, M^+), 314 (0.3), 301 (4), 272 (7), 245 (74), 200 (62), 57 (100). $C_{15}H_{28}F_3N_3O_2$ requires: C, 54.7; H, 5.5; N, 12.8. Found: C, 54.9; H, 5.5; N, 12.7.

4.1.17. (*R*)-1-[4-(3-Trifluoromethyl-3*H*-diazirin-3-yl)-phenyl]ethylamine (5). (*R*)-*N*-(*tert*-butoxycarbonyl)-1-[4-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethylamine (0.1 g, 0.3 mmol) was treated with formic acid (5 ml) and the mixture stirred for 2.5 h at room temperature before being concentrated in vacuo and diluted with ether (20 ml). The ethereal solution was treated with sodium bicarbonate solution (1 M aq) until effervescence ceased and the aqueous layer adjusted to pH 14 with KOH solution (10 M aq). After separation, the organic layer was washed with NaCl solution (satd aq; 20 ml), dried (K_2CO_3), filtered and concentrated in vacuo to give a yellow oil. Purification using column chromatography ($CHCl_3$/MeOH/20: 1) gave the title compound (0.052 g, 75%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.36 (3H, d, J=6.6 Hz, Me), 4.15 (1H, q, J=6.6 Hz, Me-C*H*(Ar)-NH_2), 7.16 (2H, d, J= 8.0 Hz, Ar), 7.39 (2H, d, J=8.0 Hz, Ar). ν/cm^{-1} (liquid film); 3370 (m), 3300 (m), 2980 (m), 1620 (m), 1345 (s), 1230 (s), 1180 (s), 1160 (s), 930 (s), 820 (s). $[\alpha]_D^{30}$ −20 (*c* 0.3, $CHCl_3$). *m*/*z* (EI, %): 229 (6, M^+), 202 (42), 186 (97), 184 (100), 162 (21). $C_{10}H_{10}F_3N_3$ requires: 229.082682. Found: 229.081616.

4.1.18. Methyl(1′*R*,1*S*,2*R*,5*S*)-5-[(4-methoxyphenyl) methyl]-2-{1′-[4-(3-trifluoromethyl-3*H*-diazirin-3-yl) phenyl]ethylamino}cyclohexanepropionate (13). A mixture of (±)-3-[2-oxo-5-(4-methoxybenzyl)cyclohexyl]-propionic acid methyl ester (**6**) (0.134 g, 0.44 mmol), (*R*)-1-[4-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethylamine

(**5**) (0.100 g, 0.44 mmol), AcOH (25 μl, 0.44 mmol) and 3 Å molecular sieves (powdered; 3 g) in DCE (4 ml) was stirred under argon at room temperature for 17 h before the addition of $NaBH(OAc)_3$ (0.120 g, 0.57 mmol). After stirring for a further 5.5 h, the mixture was filtered through a porosity three sinter, and the sieves washed with $CHCl_3$ (2×10 ml). The combined organic extracts were then washed successively with NaOH solution (1 M aq; 25 ml) and H_2O (2×25 ml) before being dried (K_2CO_3), filtered and concentrated in vacuo to give a green oil. Purification using flash column chromatography (pentane/Et_2O; 4:1) gave the title compound (0.051 g, 23%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$); δ 0.89–1.08 (4H, m), 1.24–1.80 (10H, m), 2.26–2.45 (4H, m), 2.79–2.80 (1H, m), 3.66 (3H, s, $-CO_2Me$), 3.73–3.79 (4H, m, *Me*OPh– and Me-C*H*(Ar)-NH–), 6.80 (2H, d, $J=8.5$ Hz, Ar), 7.01 (2H, d, $J=8.1$ Hz, Ar), 7.13 and 7.24 (2H, d, $J=8.3$ Hz, Ar), 7.39 and 7.42 (2H, d, $J=8.3$ Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$); δ 23.46, 26.30, 28.37, 29.55, 31.75, 33.51, 39.72, 41.00, 42.94, 51.50, 51.98, 55.18, 55.71, 113.46, 122.02 (q, $J=$ 67.8 Hz, $-CF_3$), 126.38, 127.11, 128.40, 129.87, 131.28, 132.91, 149.32, 157.62, 174.40. ν/cm^{-1} (liquid film) 3350 (w), 2920 (s), 1730 (s), 1610 (s), 1505 (s), 1445 (s), 1240 (s), 1180 (s), 1040 (m), 940 (m), 825 (m). $[\alpha]_D^{30}$ +7 (*c* 0.1, $CHCl_3$). *m*/*z* (EI, %): 517 (4, M^+), 489 (20), 474 (13), 240 (20), 200 (22), 185 (25), 149 (33), 121 (100). $C_{28}H_{34}F_3N_3O_3$ requires: 517.255227. Found: 517.254865.

4.1.19. Methyl(1′*R*,1*S*,2*R*,5*S*)-5-[(4-methoxyphenyl) methyl]-2-{1′-[3-(3-trifluoromethyl-3*H*-diazirin-3-yl) phenyl]ethylamino}cyclohexanepropionate (12). The title compound was prepared from (*R*)-1-[3-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethylamine (**4**) (0.040 g, 0.175 mmol) and (±)-3-[2-oxo-5-(4-methoxybenzyl)cyclohexyl]propionic acid methyl ester (**6**) (0.054 g, 0.177 mmol) using the method described above for the preparation of amine (**13**) (Section 4.1.8). Purification of the crude product using flash column chromatography (pentane/Et_2O; 4:1) gave the title compound (0.023 g, 5%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$); δ 0.90–1.11 (4H, m), 1.22–1.70 (10H, m), 2.30–2.49 (4H, m), 2.79–2.80 (1H, m), 3.63 (3H, s, $-CO_2Me$), 3.72–3.80 (4H, m, *Me*OPh– and Me-C*H*(Ar)-NH–), 6.81 (2H, d, $J=8.2$ Hz, Ar), 7.03 (2H, d, $J=$ 8.5 Hz, Ar), 7.06–7.20 (1H, m, Ar), 7.31 and 7.40 (3H, m, Ar). ν/cm^{-1} (liquid film) 3350 (w), 2910 (s), 2850 (m), 1740 (s), 1615 (w), 1515 (s), 1250 (s), 1160 (s). $[\alpha]_D^{30}$ −9 (*c* 0.1, $CHCl_3$). *m*/*z* (EI, %): 517 (6, M^+), 489 (5), 304 (5), 268 (21), 240 (12), 185 (24), 149 (34), 121 (100). $C_{28}H_{33}F_3N_3O_3$ requires: 517.255227. Found: 517.254469.

4.1.20. Methyl(1′*R*,1*S*,2*R*)-5-[spiro-(2,5-oxa)cyclopentyl]-2-[1′-(phenylethyl)amino]cyclohexanepropionate (15). A mixture of 4-toluenesulphonic acid (0.05 g, 0.3 mmol), (±) methyl (2,5-oxo)-5-[spiro-(2,5-oxa)cyclopentyl]cyclohexane propionate (5.0 g, 20.6 mmol) and *R*(+)-α-methylbenzylamine (2.62 g, 23.3 mmol) in toluene (60 ml) was heated at reflux with a Dean-Stark water separator for 23 h, before the solvent was removed in vacuo and the residue dissolved in ethanol. To this was added Raney nickel (prepared from 1 g of a slurry in water) and the mixture stirred under an atmosphere of hydrogen for 6 days. Following filtration of the mixture through a pad of silica, the residue was concentrated in vacuo and purified using chromatography to give the title compound (5.23 g, 74%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$); δ 1.31 (3H, d, $J=6.6$ Hz, *Me*-CH(Ar)-NH–), 1.42–1.83 (7H, m), 1.91–2.12 (1H, m), 2.35–2.41 (3H, m), 2.60–2.82 (2H, m), 3.70 (3H, s, $-CO_2Me$), 3.76 (1H, q, $J=6.5$ Hz, Me-C*H*(Ar)-NH–), 3.91 (4H, br m, $-OCH_2CH_2O-$), 7.22–7.36 (5H, m, Ar). ν/cm^{-1} (liquid film); 3430 (w), 2960 (s), 1745 (s), 1440 (s), 1360 (s), 1160 (s), 1100 (s), 760 (m), 700 (s). $[\alpha]_D^{30}$ +6 (*c* 0.4, $CHCl_3$). *m*/*z* (EI, %): 347 (1, M^+), 332 (11), 246 (5), 187 (100), 105 (63). $C_{20}H_{29}NO_4$ requires: C, 69.1; H, 8.4; N, 4.0. Found: C, 68.7; H, 8.3; N, 3.8.

4.1.21. (1′*R*,4a*S*,8a*R*)-3,4,4a,5,7,8,8a-Septahydro-6-[spiro-(2,5-oxa)cyclopentyl]-1-[(1′phenyl)ethyl]quinolin-2(1*H*)-one. A solution of methyl (1′*R*,1*S*,2*R*)-5-[spiro-(2,5-oxa)cyclopentyl]-2-[1′-(phenylethyl)amino]cyclohexanepropionate **15** (5.0 g, 14.4 mmol) in toluene (60 ml) and acetic acid (20 ml) was heated at 70 °C for 15 h before the solvents were removed in vacuo and the residue dissolved in toluene (20 ml). After washing the organic solution successively with sodium bicarbonate solution (satd aq; 20 ml), and water (2×20 ml), the solution was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification using chromatography (ether) gave the title compound (2.9 g, 64%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$); δ 1.21 (1H, t, $J=6.9$ Hz), 1.25–1.72 (5H, m), 1.83–2.02 (3H, m), 2.32–2.60 (4H, m), 2.96–3.03 (1H, m), 3.48 (1H, q, $J=7.8$ Hz), 3.85 (2H, br d, $J=5.5$ Hz, $-OCH_2CH_2-$O–), 3.91 (2H, br d, $J=5.5$ Hz, $-OCH_2CH_2O-$), 5.81 (1H, q, $J=7.2$ Hz, Me-C*H*(Ar)-NH–), 7.21–7.39 (5H, m, Ar). ν/cm^{-1} (liquid film) 2950 (m), 1630 (s), 1440 (m), 1380 (w), 1130 (s), 1100 (s), 945 (w), 700 (m). $[\alpha]_D^{30}$ +38 (*c* 0.5, $CHCl_3$). *m*/*z* (EI, %): 315 (83, M^+), 270 (8), 224 (14), 205 (14), 120 (31), 105 (100), 101 (73). $C_{19}H_{25}NO_3$ requires: C, 72.3; H, 8.0; N, 4.4. Found: C, 72.3; H, 8.1; N, 4.3.

4.1.22. (1′*R*,4a*S*,8a*R*)-3,4,4a,5,7,8,8a-Heptahydro-1-[(1′-phenyl)ethyl]quinolin-2,6(1*H*)-dione (16). A solution of (1′*R*, 4a*S*, 8a*R*)-3,4,4a,5,7,8,8a-septa hydro-6-[spiro-(2,5-oxa)cyclopentyl]-1-[(1′phenyl)ethyl]quinolin-2(1*H*)-one (2.5 g, 7.9 mmol) in acetic acid (40 ml) and water (40 ml) was heated at 80 °C for 16 h before the solvents were removed in vacuo and the residue dissolved in ether (20 ml). After washing the organic layer successively with sodium bicarbonate solution (satd aq; 20 ml) and water (2×20 ml), the solution was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification using chromatography (ether) gave the title compound (1.77 g, 82%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$); δ 1.25–1.44 (1H, m), 1.63 (3H, d, $J=7.3$ Hz, *Me*-CH(Ar)–NH–), 1.76 (1H, t, $J=7.9$ Hz), 1.98–2.08 (1H, m), 2.14–2.32 (5H, m), 2.41–2.48 (1H, m), 2.55–2.61 (2H, m), 3.41–3.45 (1H, m), 6.04 (1H, q, $J=$ 7.1 Hz, Me-C*H*(Ar)-NH–), 7.27–7.44 (5H, m, Ar). ν/cm^{-1} (liquid film) 2960 (s), 1715 (s), 1625 (s), 1445 (m), 1285 (m), 1205 (m), 700 (m). $[\alpha]_D^{30}$ +33 (*c* 0.6, $CHCl_3$). *m*/*z* (EI, %): 271 (100, M^+), 256 (7), 174 (20), 160 (34), 105 (90). $^{12}C_{16}C^{13}H_{21}NO_2$ requires: 272.160584. Found: 272.161027.

4.1.23. Dimethyl[4-(3-trifluoromethyl-3*H*-diazirin-3-yl) phenyl]methyl phosphonate (18). A solution of 3-(α-iodo-4-tolyl)-3-(trifluoromethyl)-3*H*-diazirine (**17**) (0.500 g, 1.53 mmol) in toluene (10 ml) and trimethylphosphite (2 ml,

17.0 mmol) was stirred under argon at room temperature for 15 h. After stirring for a further 2 h at 75 °C, the solution was concentrated in vacuo and the residue purified using preparative TLC ($CHCl_3$/MeOH; 5:1) to give the title compound (0.077 g, 18%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$); δ 3.17 (2H, d, $J=22.0$ Hz, Ar-CH_2-P), 3.68 (6H, d, $J=10.9$ Hz, (MeO)$_2$P), 7.15 (2H, d, $J=8.0$ Hz, Ar), 7.33 (2H, dd, $J=8.4$, 2.2 Hz, Ar). ν/cm^{-1} (liquid film); 2950 (m), 2920 (m), 1610 (w), 1340 (m), 1230 (s), 1185 (s), 1155 (s), 1030 (s), 935 (m). *m/z* (%): 309 (2, M^+), 280 (100), 248 (12), 184 (13), 170 (34), 151 (48), 109 (45), 93 (49). $C_{11}H_{13}F_3N_2O_3P$ requires: 309.061591. Found: 309.062951.

4.1.24. (1′*R*,4a*S*,8a*R*)-3,4,4a,5,7,8,8a-Heptahydro-6-[4-(3-trifluoromethyl-3*H*-diazirin-3-yl)benzylidene]-1-[(1′-phenyl)ethyl]quinolin-2(1*H*)-one (19). To a stirred solution of dimethyl[4-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]methyl phosphonate **18** (50.0 mg, 162 μmol) in THF (0.5 ml) was added NaH (60% dispersion in mineral oil; 7.9 mg, 198 μmol) in one portion, producing an instant black colouration. After stirring at room temperature under argon for 1 h, a solution of (1′*R*,4a*S*,8a*R*)-3,4,4a,5,7,8,8a-heptahydro-1-[(1′-phenyl)ethyl]quinolin-2,6(1*H*)-dione (**16**) (58.6 mg, 0.32 mmol) in THF (1 ml) was added and the mixture stirred for a further 24 h at room temperature, during which time the black colouration faded. The solution was then diluted with Et_2O (10 ml) and washed with H_2O (2×10 ml) before being dried (Na_2SO_4), filtered and concentrated in vacuo. Purification using flash column chromatography (Et_2O) gave the title compound (22.4 mg, 27%) as a viscous yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.23–2.15 (9H, m), 2.26–2.83 (4H, m), 3.09–3.20 (2H, m), 5.93 (1H, m, Me-C*H*(Ar)-NH–), 6.19 and 6.34 (1H, s, Ar-C*H*=C–, E/Z), 7.06–7.20 (4H, m, Ar), 7.28–7.40 (5H, m, Ar). ν/cm^{-1} (liquid film); 2920 (s), 1740 (w), 1720 (w), 1635 (m), 1615 (s), 1350 (m), 1185 (s), 1160 (s), 935 (m), 700 (m). $[\alpha]_D^{30}$ −28 (*c* 0.1, $CHCl_3$). *m/z* (EI, %): 453 (12, M^+), 427 (5), 331 (5), 209 (7), 149 (12), 120 (19), 105 (100). $C_{26}H_{26}F_3N_3O$ requires: 453.202797. Found: 453.200569.

Acknowledgements

The authors would like to thank the MRC and Wyeth Research (UK) for funding (J. M. S) and R. Crossley, A. Opalko and K. Heatherington for help and advice.

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Design, synthesis and biological evaluation of novel 1α,25-dihydroxyvitamin D_3 analogues possessing aromatic ring on 2α-position

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Received 5 July 2005; accepted 29 August 2005

Available online 10 October 2005

Abstract—In the present study, we describe the synthesis of new analogues of 1α,25-dihydroxyvitamin D_3 (**1**), which possess hydrophobic aromatic ring on the 2α position. Among these analogues, 2α-benzyl analogue showed the highest potency in the affinity for the wild type vitamin D receptor (VDR) and induction of HL-60 cell differentiation as well as transcriptional activity. Affinity for the mutant VDR related to hereditary vitamin D-resistant rickets (R274L) was also examined.

1. Introduction

1α,25-Dihydroxyvitamin D_3 (1α,25-$(OH)_2D_3$, **1**) is known as the active metabolite of vitamin D_3 and regulates a wide variety of biological activities, such as intestinal calcium absorption, bone resorption and mineralization.[1] In addition, **1** has been found to induce cell differentiation and proliferation in culture and in vivo.[2] These biological activities are mediated by ligand binding to the nuclear vitamin D receptor (VDR), a ligand-dependent transcription factor.[3] In order to improve the biological profile of **1** for a therapeutic application, numerous analogues of **1** have been synthesized and developed for biological studies and clinical trials, most of which have modified side chain of **1**.[4]

We have synthesized A-ring modified analogues of **1**, in which the 2α-alkyl or the 2α-hydroxyalkyl group was introduced to **1**, to study the A-ring conformation- and structure-activity relationships (Fig. 1).[5–8] The resulting analogues exhibited interesting biological activities, in particular, 2α-methyl and 2α-(3-hydroxypropyl) analogues (**2** and **3**) showed much higher potency than **1** with respect to binding affinity for the bovine thymus VDR, elevation of serum calcium in rats, and induction of HL-60 cell differentiation. Among 2α-substituted analogues, 2α-methyl analogue **2** is worthy of comment, that is, only a small structural modification on the 2α position leads to 4-fold increase in VDR affinity and 2-fold increase in induction of HL-60 cell differentiation. Based on the X-ray crystallographic analysis of the truncated VDR ligand binding domain (LBD) occupied by the natural hormone,[9] we could see that the A-ring of **1** is surrounded by hydrophobic amino acid residues Tyr143, Tyr147, Phe150 and Tyr236 (Fig. 2). We considered that the affinity of the

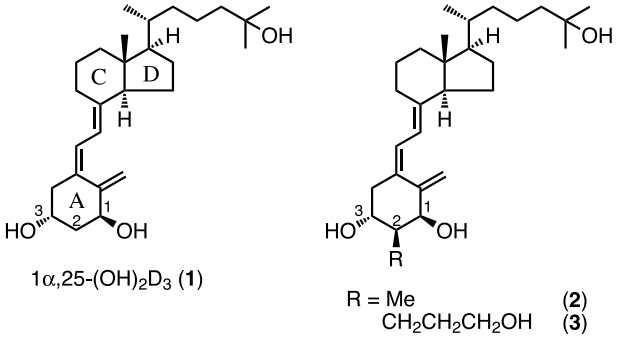

Figure 1. 1α,25-Dihydroxyvitamin D_3 and its analogues.

Keywords: Vitamin D receptor; Aromatic ring; Ligand binding domain.
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doi:10.1016/j.tet.2005.08.116

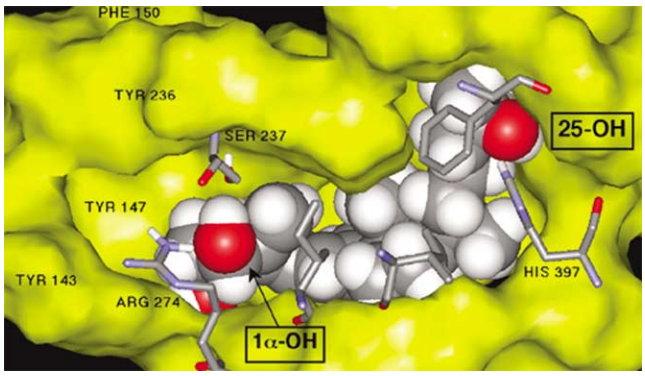


Figure 2. X-ray structure of VDR ligand binding domain with **1** by Moras et al.[9]

2α-methyl analogue (**2**) for the VDR should increase because of hydrophobic interaction between 2α-methyl group and this hydrophobic pocket. In the present study we examined the hypothesis that the affinity for VDR would increase if a larger hydrophobic group, for example, the phenyl group, could interact with the hydrophobic pocket. In order to elucidate this assumption, we synthesized novel analogues that have aromatic groups at the 2α-position. That is, we prepared 2α-phenyl-(**4**), 2α-benzyl-(**5**) and 2α-phenethyl-1α,25-$(OH)_2D_3$ (**6**) and evaluated their affinity for VDR and their ability to induce differentiation of HL-60 cells (Fig. 3).

2. Synthesis

Retrosynthetic analysis of the analogues is shown in Scheme 1. We adapted the convergent synthetic method developed by Trost et al.[10] This method utilized bromoolefin **7**[10] and enyne **8** as reaction substrates and these were coupled in the presence of a palladium catalyst. CD ring bromoolefin **7** was synthesized from vitamin D_3 and A-ring enyne **8** was synthesized from sugar epoxide **11**, easily derived from D-glucose.[11] 2α-Substituents could be introduced by the reaction of **11** with corresponding Grignard reagents, which was reported from our laboratory quite recently.[12]

Summary of the synthesis of enynes **8a–c** is shown in Scheme 2. In short, the ring opened products **10a–c** were subjected to NBS in the presence of $BaCO_3$ to give

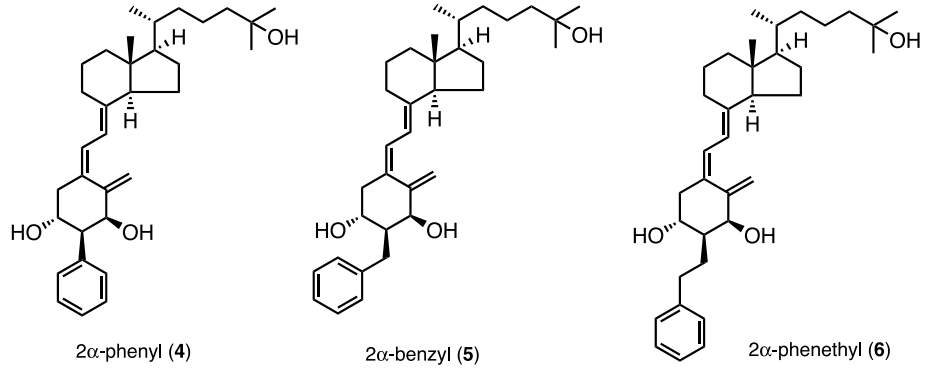
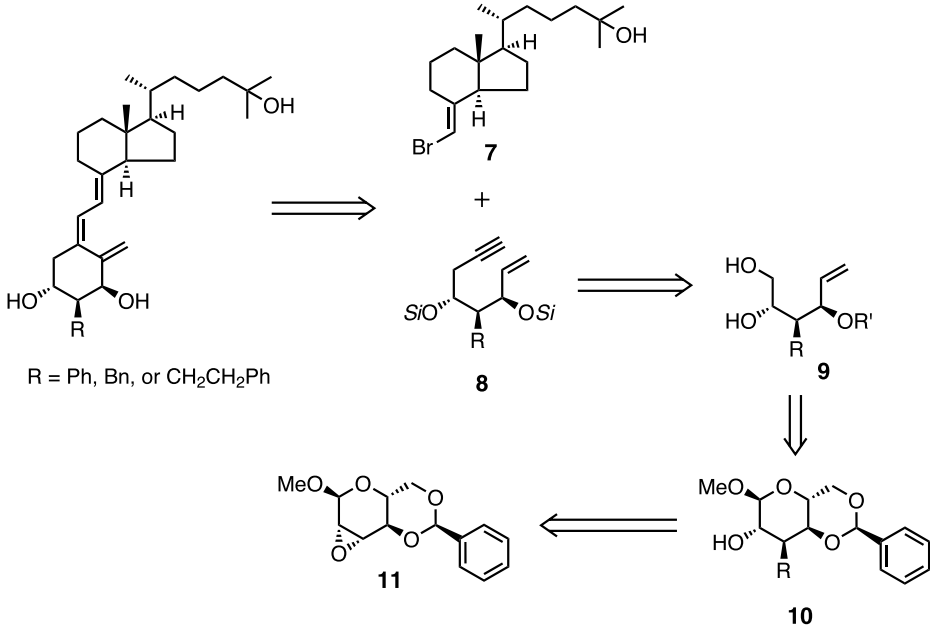
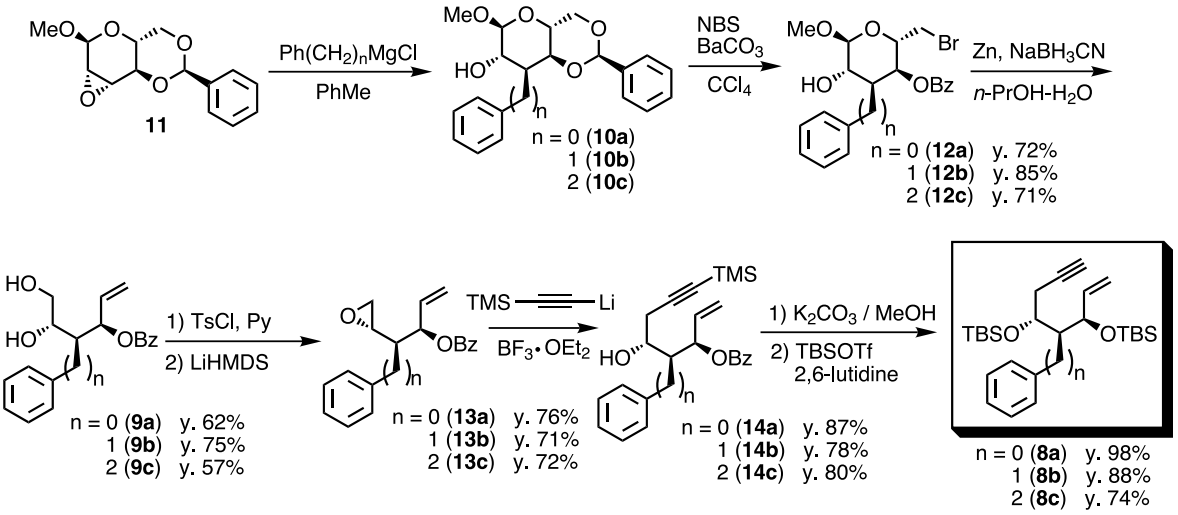


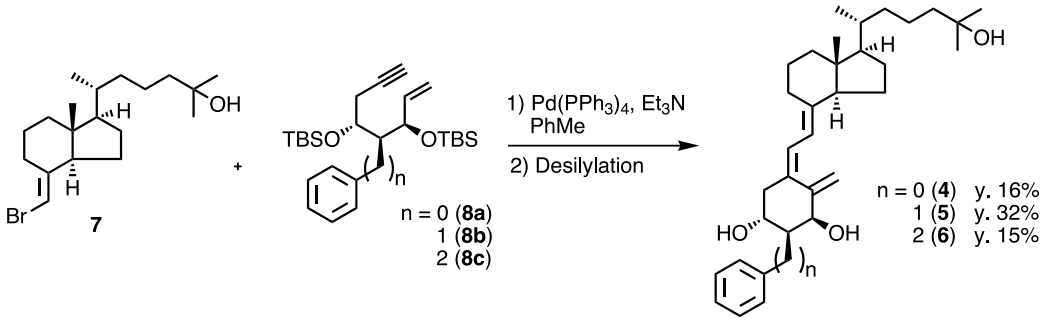
Figure 3. Structures of 2α-aromatic substituted analogues.



Scheme 1. Retrosynthetic analysis of **4–6**.



Scheme 2. Synthetic route toward the A-ring precursors of 2α-aromatic analogues **4**–**6**.



Scheme 3. Palladium-catalyzed coupling reaction.

bromides **12a**–**c**, which upon reaction with activated zinc powder and sodium cyanoborohydride gave diols **9a**–**c**. These diols were transformed to epoxides **13a**–**c** via monotosylates. Epoxides were converted to enynes **8a**–**c** through reaction with lithium acetylide followed by treatment with K_2CO_3 and persilylation. Palladium catalyzed coupling reaction of CD ring bromoolefin **7** with **8**, followed by deprotection gave the 2α-aromatic substituted vitamin D derivatives **4**–**6** (Scheme 3). These derivatives were purified for biological assays by recycling reverse-phase HPLC.

3. Results and discussions

The new analogues were first examined for their affinity for the bovine thymus VDR, by using competition assay.[13] We found that these analogues had lower affinity compared with the natural hormone, 1α,25-$(OH)_2D_3$. In fact, 2α-phenyl, 2α-benzyl and 2α-phenethyl substituted analogues (**4**, **5** and **6**, respectively) showed 7, 15 and 1% affinities, respectively, when compared with the natural hormone (Table 1). These results would suggest that aromatic groups of 2α-substituents would be so large that these could not fit well to the pocket around the A-ring of vitamin D in the LBD, contrary to our hypothesis. In addition to the steric bulkiness of the aromatic ring, tendencies of the aromatic substituents to adopt the equatorial position[14] would lower the affinities for VDR due to the partial conformational changes in the A-ring from the β-form, suitable for hydrogen bonding, to the unsuitable α-form.[6a] Indeed, if the aromatic ring would be forced to accommodate in the pocket, the analogue molecules should shift their atomic positions largely in order to form hydrogen bonds (see Figs. 4 and 5).

Table 1. Biological activities of analogues prepared

	VDR affinity[a,b]	HL-60 cell differentiation[a]
2α-phenyl (**4**)	7	220
2α-benzyl (**5**)	15	460
2α-phenethyl (**6**)	1	140

[a] Activities of 1α,25-$(OH)_2D_3$ were normalized to 100.
[b] Bovine thymus.

Surprisingly, when HL-60 cell differentiating activities were measured, the analogues were as potent or even higher than the natural hormone. Above all, 2α-benzyl analogue **5** was 4.6-fold more potent than the natural hormone (Table 1).

To further elucidate the origin of the discrepancies between VDR binding profiles of the analogues and their cellular responses, we considered the possibility that the bovine VDR (calf thymus) and the human VDR (in HL-60 cells) have different binding properties to these analogues. Therefore, we used recombinant human VDR to perform additional assays including a protease sensitivity assay and transactivation assay.[15] The protease sensitivity assay has

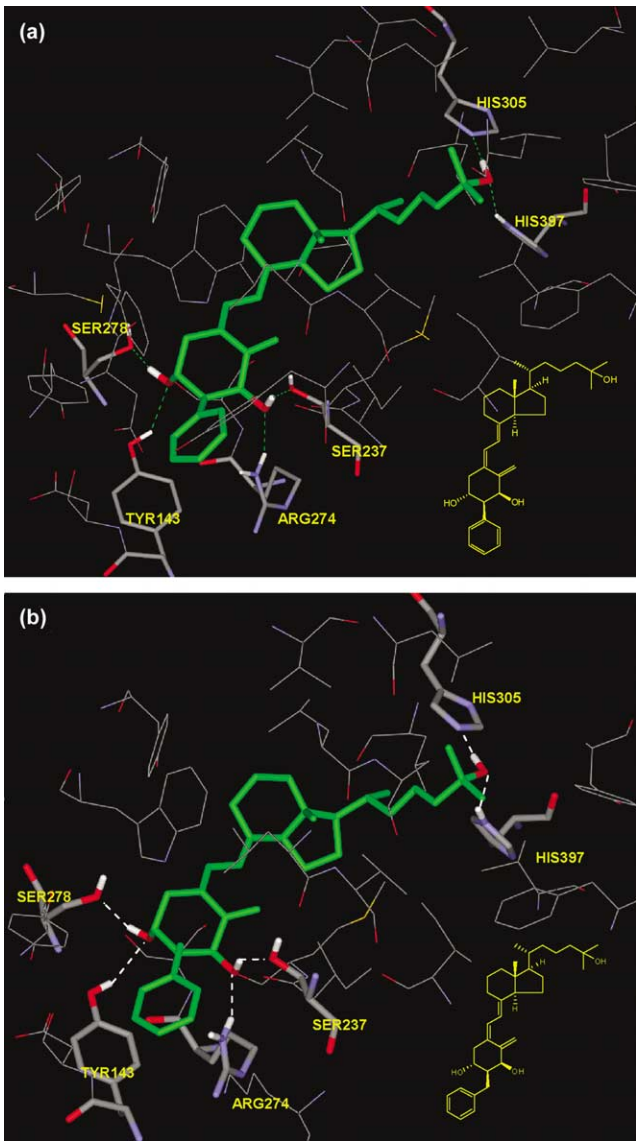


Figure 4. Hypothetical models for the structure of the VDR's LBD bound to 2α-phenyl analogue **4** (a) and 2α-benzyl analogue **5** (b). Hydrogen bonds are drawn as dotted lines.

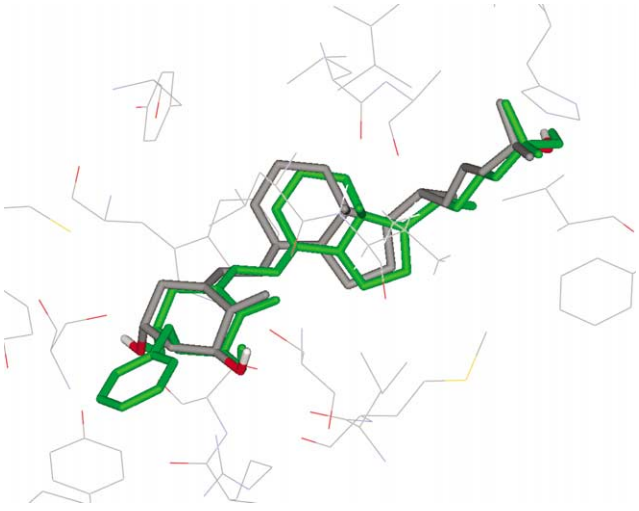


Figure 5. An overlay of the modeled VDR-2α-benzyl analogue **5** complex with VDR-**1** structure in the LBD. Ligands **1** and **5** are drawn in gray and green, respectively.

Table 2. Biological activities of the analogues with recombinant human VDR

	Protease sensitivity[a]	Transcriptional activity[a,b]
2α-phenyl (**4**)	0.02	25
2α-benzyl (**5**)	20	250
2α-phenethyl (**6**)	0.2	77

[a] Activities of 1α,25-$(OH)_2D_3$ were normalized to 100.
[b] Co-transfection of wild type human VDR and osteocalcin VDRE-TK-GH reporter gene.

been used to determine the effect of ligand on VDR's conformation, as reflected by the size of VDR fragments that become resistant to trypsin digestion after ligand binding. The assay, in some cases, also reflects transcriptional potency of an analogue because ability to stabilize VDR conformation in vitro may correlate with transcriptional activity of the analogue in cultured cells.[15] The protease sensitivity assay was performed with in vitro synthesized ^{35}S-labeled VDR treated with different concentrations of the analogues and digested with trypsin. Then protease-resistant fragments were analyzed by SDS-PAGE and autoradiography of the dried gels.[15] We found that the three analogues stabilized a VDR conformation similar to that stabilized by the natural hormone (data not shown). However, we also found similar results (Table 2) to the competitive assay with bovine thymus VDR (Table 1). That is, aromatic ring-substituted analogues **4–6** had lower ability to stabilize human VDR conformation against trypsin digestion than the natural hormone **1**, and 2α-benzyl substituted analogue **5** had the highest potency among this group of derivatives. In contrast, transcriptional activities of the analogues were similar to that of the natural hormone (Table 2), as in the case of HL-60 cell differentiation (Table 1). The reason for restoring potency to induce cell differentiation and transcriptional activity is not clear, but it may suggest that cellular modifications of the analogue-bound VDR or interaction of the analogue-bound VDR with dimerization partners or coactivators of transcription change the mode of interaction of these analogues with VDR in the cells and lead to an increase in their transcriptional potency and cellular activities which is not proportional to their receptor binding properties in vitro. Our laboratory is now developing such a high-throughput assay system that could examine coactivator-dependent ligand binding with VDR.[16] The origin of discrepancies shown here could be clarified utilizing this assay system.

As the hydrophobic properties of the 2α-substituents of the analogues **4–6** were considered, we anticipated that the analogues **4–6** could be used to restore defective ligand binding activity of the mutant VDR, Arg274Leu, which causes hereditary vitamin D-resistant rickets (HVDRR). HVDRR is caused by mutations to the VDR gene, which lead to resistance to 1α,25-$(OH)_2D_3$ (**1**) under physiological condition.[17] Clinically, HVDRR is associated with hypocalcemia, secondary hyperparathyroidism, and relatively high concentration of 1α,25-$(OH)_2D_3$ (**1**) in serum. Over 20 mutations that cause HVDRR have been reported. Most of these mutations occur at the DNA binding domain, but a few are localized at the LBD. We have focused our attention to the mutated VDR whose Arg-274 is substituted to Leu, Arg274Leu.[18] The Arg-274 residue locates in the ligand

binding domain of the VDR and forms hydrogen bond with the 1α-hydroxy group of **1** (Fig. 2). The mutation causes a 1000-fold decrease in the affinity for **1**, thus the vitamin D action should be disrupted. Vitamin D derivatives that bind specifically to a mutated VDR of this type would be a candidate for therapeutic agent against HVDRR.[15] A few research groups have reported such designs of ligand for the mutant VDR. Peleg et al. have demonstrated the rationale for using A ring-modified analogues to restore loss of binding and transcriptional activity of the Arg274Leu mutant.[15] Koh et al. developed derivatives whose 1α-hydroxy group is protected by a substituted benzyl group.[19] On the other hand, we have approached to the issue by using 2α-hydroxypropylated **1** (**3**).[20] In this case, we have shown that **3** would form hydrogen bonding with Asp144 of the mutant VDR through the terminal hydroxy group of the 2α-substituent, thus could restore its complex formation ability with the mutant VDR.

We hypothesized that analogues possessing hydrophobic substituent at the 2α-position could fit the hydrophobic pocket formed by the mutation and restore ligand-mediated VDR action. Our modeling studies imply that the hydrophobic pocket around the 2α-position of **1** would be extended by the mutation of bulkier Arg to sterically less demanding Leu. Because of this, the aromatic ring on the 2α-substituent could be accommodated more comfortably in the pocket of the mutant receptor than that of the wild type receptor, which would make the complex more stable (Fig. 6). So, we decided to assay the analogues **4**–**6** for their binding to the mutant VDR, Arg274Leu.

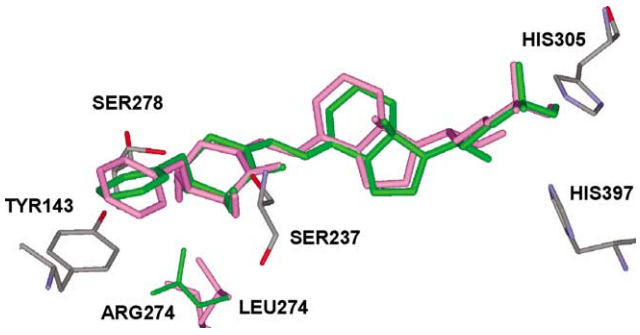


Figure 6. Superposition of modeled structures of **5** in the LBD of wild type VDR (green) and mutant VDR (Arg274Leu, purple).

Because competition assays cannot be used with this mutant due to its low affinity for the natural hormone, we used instead the protease sensitivity assay to assess binding of the analogues to the human VDR, in vitro.[15] Contrary to our expectation, these analogues showed poor ability to stabilize the conformation of the mutant VDR, and only the 2α-benzyl analogue induced detectable stabilization of the mutant VDR (Table 3).

Table 3. Binding affinity of the analogues with mutant VDR (Arg274Leu)

	Protease sensitivity[a]
1α,25-$(OH)_2D_3$	0.1
2α-phenyl (**4**)	ND[b]
2α-benzyl (**5**)	0.1
2α-phenethyl (**6**)	ND[b]

[a] Affinity of 1α,25-$(OH)_2D_3$ to wild type VDR is normalized to 100.
[b] Not detectable.

In all cases where biological activities were assayed, the 2α-benzyl analogue (**5**) was the most potent in the aromatic analogue series, that is, one methylene group appeared the most appropriate to link the A-ring of the natural hormone with the phenyl group.

In summary, we prepared novel analogues of **1** that possess the aromatic ring on the 2α position. Data of biological assays showed that these analogues induce HL-60 cell differentiation and transcriptional activities as much potent as **1**, whereas the affinity for VDR was less than 10% relative to the natural hormone. Further studies are now on the way to elucidate the discrepancies between binding affinity of the analogues for VDR in vitro and their potencies in the cellular assays, including studies on metabolism by CYP27A1 and CYP24A1.[21]

Transcriptional assay for the mutant VDR (Arg274Leu) is now planning and the result will be reported elsewhere.

4. Experimental

4.1. General procedure

^1H and ^{13}C NMR spectra were recorded on a JEOL GSX-400 or AL-400 NMR (400 MHz) or ECP-600 NMR (600 MHz). ^1H NMR spectra taken in $CDCl_3$ were referenced to tetramethylsilane (δ 0.00) as an internal standard. ^{13}C NMR spectra taken in $CDCl_3$ (δ 77.0) were referenced to the residual solvents. Melting points were determined with Yanagimoto micro melting point apparatus without correction. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. IR spectra were measured on a JASCO FT/IR-8000 spectrophotometer. Low- and high-resolution MS spectra were recorded on a JEOL JMS-SX-102A spectrometer. Merck silica gel 60 (230–400 mesh) was employed for flash column chromatography. The ratios of solvent mixtures for chromatography are shown in volume/volume.

Syntheses of **10a**–**c** have been reported elsewhere.[12]

4.1.1. Methyl 4-*O*-Benzoyl-6-*C*-bromo-3,6-dideoxy-3-*C*-phenyl-α-D-altropyranoside (12a). Under an Ar atmosphere, **10a** (144.9 mg, 0.423 mmol) was dissolved in CCl_4 (5 mL, passed through alumina pad before use), and to this solution were added *N*-bromosuccinimide (90 mg, 0.51 mmol) and $BaCO_3$ (46.7 mg, 0.24 mmol). After refluxed for 40 min, the mixture was allowed to cool to room temperature, diluted with AcOEt (10 mL) and washed with saturated aqueous Na_2SO_3 (10 mL). Layers were separated and organic layer was washed successively with water (5 mL), saturated aqueous $NaHCO_3$ solution (5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography (toluene–AcOEt (20/1–18/1)) gave the product **12a** (128 mg, 72%) as a white foam.

^1H NMR (400 MHz, $CDCl_3$) δ 1.97 (1H, d, J=2.9 Hz), 3.32

(1H, dd, J=4.1, 11.5 Hz), 3.59 (3H, s), 3.72 (1H, dd, J=4.1, 11.0 Hz), 4.25 (1H, dt, J=3.9, 7.3 Hz), 4.44 (1H, ddd, J=3.8, 5.4, 11.5 Hz), 4.77 (1H, d, J=5.4 Hz), 5.37 (1H, t, J=3.8 Hz), 7.19 (1H, t, J=7.7 Hz), 7.24–7.27 (2H, m), 7.34 (2H, d, J=7.3 Hz), 7.42 (2H, t, J=7.7 Hz), 7.56 (1H, t, J=7.3 Hz), 7.92 (2H, d, J=7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 47.4, 56.4, 69.6, 73.2, 73.7, 103.4, 127.6, 128.3, 128.7, 129.0, 129.3, 129.5, 133.1, 135.1, 165.2. IR (neat) 3470, 1719, 1453, 1316, 1269, 712 cm^{-1}. LRMS (EI) m/z: 389 (M^+(^{79}Br)–OCH_3), 267, 209. HRMS (EI) calcd for $C_{19}H_{18}{}^{79}BrO_4$; 389.0383. Found 389.0391. $[\alpha]_D^{21}$ −110.9 (c 1.1, $CHCl_3$).

12b and **12c** could be synthesized substantially as the same procedure.

4.1.2. Methyl 4-*O*-Benzoyl-3-*C*-benzyl-6-*C*-bromo-3,6-dideoxy-α-D-altropyranoside (12b). A colorless foam (85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.20 (1H, d, J=4.6 Hz), 2.49 (1H, dddd, J=4.6, 6.6, 7.7, 8.2 Hz), 2.78 (1H, dd, J=7.7, 13.7 Hz), 3.22 (1H, dd, J=8.2, 13.7 Hz), 3.53 (1H, dd, J=8.2, 11.1 Hz), 3.53 (3H, s), 3.57 (1H, dd, J=4.0, 11.1 Hz), 3.80 (1H, ddd, J=3.8, 4.1, 6.6 Hz), 4.25 (1H, ddd, J=4.0, 6.3, 8.2 Hz), 4.62 (1H, d, J=3.8 Hz), 5.14 (1H, dd, J=4.6, 6.3 Hz), 7.07–7.09 (2H, m), 7.12–7.15 (1H, m), 7.18–7.21 (2H, m), 7.44–7.47 (2H, m), 7.58–7.61 (1H, m), 8.04–8.06 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 31.8, 43.6, 56.2, 69.8, 70.4, 70.5, 102.1, 126.1, 128.3, 128.4, 128.9, 129.3, 129.6, 133.3, 138.9, 165.2. IR (neat) 3472, 3063, 3028, 2934, 1716, 1603, 1495, 1452, 1267 cm^{-1}. LRMS (EI) m/z: 434 (M^+(^{79}Br)). HRMS (EI) calcd for $C_{21}H_{23}{}^{79}BrO_5$; 434.0729. Found 434.0742. $[\alpha]_D^{25}$ +4.1 (c 1.1, $CHCl_3$).

4.1.3. Methyl 4-*O*-Benzoyl-6-*C*-bromo-3,6-dideoxy-3-*C*-(2-phenylethyl)-α-D-altropyranoside (12c). A colorless oil (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72–1.84 (1H, m), 2.09–2.25 (3H, m), 2.58–2.62 (2H, m), 3.52 (3H, s), 3.54–3.62 (2H, m), 3.83 (1H, m), 4.23 (1H, ddd, J=5.3, 5.3, 7.1 Hz), 4.54 (1H, d, J=4.4 Hz), 5.43 (1H, dd, J=4.4, 5.3 Hz), 7.09–7.19 (3H, m), 7.20–7.25 (2H, m), 7.44–7.49 (2H, m), 7.60 (1H, m), 8.02–8.07 (2H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.4, 31.3, 33.3, 40.2, 56.2, 70.2, 70.7, 71.8, 102.2, 126.0, 128.3, 128.4, 128.6, 129.4, 129.8, 133.5, 141.5, 165.7. IR (neat) 3443, 2930, 1719, 1453, 1269 cm^{-1}. LRMS (EI) m/z: 448 (M^+(^{79}Br)), 416 (M^+(^{79}Br)–CH_3OH), 294 (M^+(^{79}Br)–CH_3OH–PhCOOH). HRMS (EI) calcd for $C_{22}H_{25}{}^{79}BrO_5$; 448.0885. Found 448.0863. $[\alpha]^{22}{}_D$ +14.0 (c 0.6, $CHCl_3$).

4.1.4. (2*S*,3*R*,4*R*)-4-Benzoyloxy-3-phenylhex-5-ene-1,2-diol (9a). Under an Ar atmosphere, to a solution of bromide (**12a**, 50.8 mg, 0.121 mmol) in 1-propanol (1.2 mL) was added distilled water (120 μL) and the mixture was heated at 95 °C. To the mixture were added Zn dust (activated by washing with dil. HCl aq, then EtOH and Et_2O, and dried in vacuo, 239 mg, 3.63 mmol) and $NaBH_3CN$ (38 mg, 0.60 mmol) in one portion and stirred at the same temperature for 20 min. Zn dust (160 mg, 2.42 mmol) and $NaBH_3CN$ (23 mg, 0.36 mmol) were added and stirred further 30 min. The mixture was cooled to room temperature, and insoluble materials were filtered off through Celite. The filtrate was diluted with AcOEt (100 mL) and water (10 mL), and layers were separated. Organic layer was washed with water (10 mL), saturated aqueous NH_4Cl solution (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography (0.1% MeOH in $CHCl_3$) gave the product **9a** (29.1 mg, 62%) as white foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (1H, dd, J=3.7, 10.3 Hz), 3.21 (1H, dd, J=8.1, 11.2 Hz), 3.42 (1H, dd, J=3.7, 11.2 Hz), 4.08 (1H, dd, J=3.7, 8.1 Hz), 5.05 (1H, br d, J=10.6 Hz), 5.21 (1H, br d, J=17.0 Hz), 5.67 (1H, ddd, J=6.1, 10.6, 17.0 Hz), 6.03 (1H, dd, J=6.1, 10.3 Hz), 7.26–7.33 (5H, m), 7.45–7.49 (2H, m), 7.58–7.62 (1H, m), 8.09–8.12 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.9, 65.2, 70.4, 75.0, 117.9, 127.3, 128.3, 128.4, 129.6, 129.7, 129.7, 133.3, 134.5, 136.2, 166.5. IR (neat) 3389, 1721, 1601, 1493, 1453, 712 cm^{-1}. LRMS (EI) m/z: 312 (M^+), 295, 281, 159, 105, 77. HRMS (EI) calcd for $C_{19}H_{20}O_4$; 312.1362. Found 312.1361. $[\alpha]_D^{22}$ +66.6 (c 2.0, $CHCl_3$).

9b and **9c** were also synthesized substantially the same manner.

4.1.5. (2*S*,3*R*,4*R*)-4-Benzoyloxy-3-benzylhex-5-ene-1,2-diol (9b). A colorless oil (75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.21–2.24 (1H, m), 2.76 (1H, dd, J=7.2, 14.5 Hz), 2.92 (1H, dd, J=6.0, 14.5 Hz), 3.53 (1H, dd, J=3.8, 11.0 Hz), 3.63 (1H, dd, J=8.5, 11.0 Hz), 4.04–4.05 (1H, m), 5.28 (1H, d, J=10.7 Hz), 5.31 (1H, d, J=17.0 Hz), 5.59 (1H, apparent t, J=5.5 Hz), 5.91 (1H, ddd, J=6.0, 10.7, 17.0 Hz), 7.16–7.18 (3H, m), 7.25–7.26 (2H, m), 7.41–7.45 (2H, m), 7.56–7.58 (1H, m), 7.97–7.99 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 46.6, 65.1, 71.5, 76.0, 118.1, 126.2, 128.5, 128.6, 129.0, 129.6, 129.8, 133.3, 134.9, 140.4, 165.8. IR (neat) 3424, 3063, 3028, 2928, 1718, 1603, 1495, 1452, 1315, 1113, 700 cm^{-1}. LRMS (EI) m/z: 326 (M^+), 308 (M^+-H_2O). HRMS (EI) calcd for $C_{20}H_{22}O_4$; 326.1521. Found 326.1521. $[\alpha]_D^{25}$ +0.2 (c 0.5, $CHCl_3$).

4.1.6. (2*S*,3*R*,4*R*)-4-Benzoyloxy-3-(2-phenylethyl)hex-5-ene-1,2-diol (9c). A colorless oil (57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68–1.92 (3H, m), 2.62 (1H, ddd, J=6.1, 10.1, 13.5 Hz), 2.71 (1H, br s), 2.78 (1H, ddd, J=5.9, 9.9, 13.5 Hz), 3.03 (1H, br s), 3.53 (1H, dd, J=3.2, 10.9 Hz), 3.66 (1H, dd, J=8.6, 10.9 Hz), 3.93 (1H, m), 5.29 (1H, d, J=10.7 Hz), 5.29 (1H, d, J=17.1 Hz), 5.70 (1H, apparent t, J=6.1 Hz), 5.92 (1H, ddd, J=6.1, 10.7, 17.1 Hz), 7.10–7.19 (3H, m), 7.20–7.27 (2H, m), 7.38–7.44 (2H, m), 7.51–7.57 (1H, m), 7.99–8.06 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 34.4, 43.8, 65.0, 71.7, 76.0, 118.1, 125.8, 128.3, 128.3, 128.4, 129.5, 129.7, 133.1, 134.5, 141.8, 165.9. IR (neat) 3291, 2942, 1719, 1603, 1453, 1273, 1113, 1071, 1026, 940, 714 cm^{-1}. LRMS (EI) m/z: 340 (M^+), 322 (M^+-H_2O). HRMS (EI) calcd for $C_{21}H_{24}O_4$; 340.1675. Found 340.1670. $[\alpha]_D$ +26.3 (c 1.0, $CHCl_3$).

4.1.7. (3*R*,4*R*,5*S*)-3-Benzoyloxy-5,6-epoxy-4-phenylhex-1-ene (13a). *Synthesis of monotosylate*: Under an Ar atmosphere, to a solution of **9a** (475 mg, 1.52 mmol) in CH_2Cl_2 (15 mL) was added *p*-toluenesulfonyl chloride (406 mg, 2.13 mmol), triethylamine (316 μL, 2.28 mmol)

and 4-(*N*,*N*-dimethylamino)pyridine (1.14 mg, 9.3 μmol) and stirred at room temperature for 4 h. The mixture was diluted with AcOEt (100 mL) and washed with water (10 mL×2), saturated aqueous NH_4Cl (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography (hexane–AcOEt (9/1–6/1)) gave monotosylate (621 mg, 90%) as a colorless oil.

4.1.8. (2*S*,3*R*,4*R*)-4-Benzoyloxy-3-phenyl-1-(*p*-toluenesulfonyloxy)hex-5-en-2-ol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s), 3.04 (2H, br dd, J=3.7, 11.0 Hz), 3.70 (1H, d, J=6.6 Hz), 4.23–4.28 (1H, m), 5.03 (1H, d, J=10.6 Hz), 5.19 (1H, d, J=17.0 Hz), 5.63 (1H, ddd, J=6.4, 10.6, 17.0 Hz), 6.00 (1H, dd, J=6.4, 11.0 Hz), 7.24–7.26 (7H, m), 7.48–7.51 (2H, m), 7.60–7.68 (3H, m), 8.09–8.11 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 52.2, 67.5, 71.3, 74.7, 118.1, 127.5, 127.7, 128.3, 128.4, 129.4, 129.6, 129.7, 129.9, 132.4, 133.4, 134.3, 134.8, 144.7, 166.5. IR (neat) 3528, 3510, 1719, 1362, 1273, 1177 cm^{-1}. LRMS (EI) *m*/*z*: 466 (M^+), 344. HRMS (EI) calcd for $C_{26}H_{26}O_6S$; 466.1364. Found 466.1457. $[\alpha]_D^{17}$ +18.7 (*c* 1.0, $CHCl_3$).

Benzyl- and 2-phenylethyl substituted compounds could also be synthesized as substantially the same manner.

4.1.9. (2*S*,3*R*,4*R*)-4-Benzoyloxy-3-benzyl-1-(*p*-toluenesulfonyloxy)hex-5-en-2-ol. A colorless oil (82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.12–2.24 (1H, m), 2.42 (3H, s), 2.71 (1H, dd, J=7.1, 14.5 Hz), 2.81 (1H, dd, J=7.1, 14.5 Hz), 3.81–3.89 (2H, m), 4.20–4.22 (1H, m), 5.25 (1H, d, J=10.6 Hz), 5.27 (1H, d, J=16.7 Hz), 5.55 (1H, apparent t, J=5.5 Hz), 5.84 (1H, ddd, J=6.0, 10.6, 16.7 Hz), 7.06–7.09 (2H, m), 7.16–7.19 (1H, m), 7.21–7.22 (2H, m), 7.28–7.29 (2H, m), 7.43–7.46 (2H, m), 7.57–7.59 (1H, m), 7.67–7.68 (2H, m), 7.97–7.98 (2H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 31.4, 46.4, 68.7, 72.3, 75.6, 118.3, 126.4, 128.0, 128.6, 128.6, 129.1, 129.6, 129.7, 129.9, 132.5, 133.4, 134.7, 139.6, 145.0, 165.5. IR (neat) 3526, 3065, 3028, 2922, 1718, 1601, 1495, 1452, 1361, 1271, 1176, 1111, 1097, 970 cm^{-1}. LRMS (EI) *m*/*z*: 480 (M^+). HRMS (EI) calcd for $C_{27}H_{28}O_6S$; 480.1607. Found 480.1616. $[\alpha]_D^{25}$ +25.1 (*c* 0.3, $CHCl_3$).

4.1.10. (2*S*,3*R*,4*R*)-4-Benzoyloxy-3-(2-phenylethyl)-1-(*p*-toluenesulfonyloxy)hex-5-en-2-ol. A colorless oil (88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62–1.82 (2H, m), 1.89 (1H, dddd, J=2.8, 4.4, 6.2, 6.2 Hz), 2.42 (3H, s), 2.53 (1H, br d, J=3.6 Hz), 2.56 (1H, ddd, J=6.8, 10.0, 13.6 Hz), 2.75 (1H, ddd, J=6.0, 10.0, 13.6 Hz), 3.99 (1H, dd, J=4.8, 10.0 Hz), 4.05 (1H, dd, J=7.6, 10.0 Hz), 4.11–4.18 (1H, m), 5.29 (1H, ddd, J=1.2, 1.2, 10.5 Hz), 5.35 (1H, ddd, J=1.2, 1.2, 17.1 Hz), 5.69 (1H, dddd, J=1.2, 1.2, 6.2, 6.2 Hz), 5.88 (1H, ddd, J=6.2, 10.5, 17.1 Hz), 7.07–7.13 (2H, m), 7.14–7.20 (1H, m), 7.22–7.28 (2H, m), 7.28–7.34 (2H, m), 7.42–7.48 (2H, m), 7.58–7.62 (1H, m), 7.75–7.80 (2H, m), 7.99–8.03 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 27.1, 34.1, 43.4, 68.7, 71.8, 75.6, 118.4, 125.9, 127.9, 128.3, 128.3, 128.5, 129.5, 129.8, 132.5, 133.3, 134.5, 141.4, 145.0, 165.7. IR (neat) 3499, 3065, 3029, 2938, 1719, 1599, 1453, 1362, 1271, 1177, 1098, 972 cm^{-1}. LRMS (EI) *m*/*z*: 494 (M^+), 476 (M^+-H_2O). HRMS (EI) calcd for $C_{28}H_{30}O_6S$; 494.1763. Found 494.1759. $[\alpha]_D^{20}$ +23.4 (*c* 0.8, $CHCl_3$).

4.1.11. Base-promoted epoxide formation. Under an Ar atmosphere, to a cooled (−78 °C) solution of phenyl-substituted monotosylate (620 mg, 1.33 mmol) in THF (13 mL) was added LiHMDS (1 M in hexane, 1.6 mL, 1.60 mmol) and stirred at −78 °C for 20 min. and at room temperature for 45 min. The mixture was diluted with AcOEt (200 mL) and washed with water (10 mL×2), saturated aqueous NH_4Cl solution (10 mL), brine (10 mL) dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane–AcOEt (15/1)) gave the product **13a** (322.2 mg, 85%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (1H, dd, J=2.6, 5.0 Hz), 2.78 (1H, dd, J=3.9, 4.9 Hz), 2.84 (1H, dd, J=4.9, 7.6 Hz), 3.47 (1H, ddd, J=2.6, 3.9, 7.6 Hz), 5.13 (1H, ddd, J=1.1, 1.1, 10.6 Hz), 5.26 (1H, ddd, J=1.1, 1.1, 16.9 Hz), 5.76 (1H, ddd, J=6.2, 10.6, 16.9 Hz), 5.92–5.96 (1H, m), 7.24–7.35 (5H, m), 7.45–7.48 (2H, m), 7.57–7.60 (1H, m), 8.07–8.09 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.4, 52.8, 53.1, 75.8, 117.8, 127.3, 128.3, 128.4, 128.7, 129.4, 129.8, 133.0, 134.1, 136.8, 165.2. IR (neat) 1719, 1601, 1584, 1453 cm^{-1}. LRMS (EI) *m*/*z*: 294 (M^+), 172. HRMS (EI) calcd for $C_{19}H_{18}O_3$; 294.1256. Found 294.1257. $[\alpha]_D^{19}$ −23.3 (*c* 0.8, $CHCl_3$).

13b and **13c** could also be synthesized as substantially the same manner.

4.1.12. (3*R*,4*R*,5*S*)-3-Benzoyloxy-4-benzyl-5,6-epoxyhex-1-ene (13b). A colorless oil (86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.80 (1H, dddd, J=4.4, 5.4, 8.4, 8.4 Hz), 2.65 (1H, dd, J=2.8, 4.9 Hz), 2.84 (1H, dd, J=3.9, 4.9 Hz), 2.90 (1H, dd, J=8.4, 13.8 Hz), 3.00 (1H, dd, J=5.4, 13.8 Hz), 3.12 (1H, ddd, J=2.8, 3.9, 8.4 Hz), 5.26 (1H, ddd, J=1.4, 1.4, 10.4 Hz), 5.30 (1H, ddd, J=1.4, 1.4, 17.2 Hz), 5.83 (1H, dddd, J=1.4, 1.4, 4.4, 6.1 Hz), 5.89 (1H, ddd, J=6.1, 10.4, 17.2 Hz), 7.16–7.22 (3H, m), 7.25–7.29 (2H, m), 7.45–7.48 (2H, m), 7.57–7.61 (1H, m), 8.01–8.04 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.0, 47.9, 48.4, 52.5, 74.5, 117.7, 126.4, 128.5, 128.5, 129.3, 129.6, 130.0, 133.2, 134.5, 138.8, 165.3. IR (neat) 3065, 3030, 2928, 1718, 1603, 1495, 1452, 1273, 1133, 1070, 1026 cm^{-1}. LRMS (EI) *m*/*z*: 308 (M^+). HRMS (EI) calcd for $C_{20}H_{20}O_3$; 308.1412. Found 308.1410. $[\alpha]_D^{25}$ −3.3 (*c* 0.7, $CHCl_3$).

4.1.13. (3*R*,4*R*,5*S*)-3-Benzoyloxy-5,6-epoxy-4-(2-phenylethyl)hex-1-ene (13c). A colorless oil (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (1H, m) 1.89–2.00 (2H, m), 2.60 (1H, dd, J=2.6, 5.0 Hz), 2.80 (1H, ddd, J=7.2, 8.8, 14.2 Hz), 2.85 (2H, ddd, J=7.2, 9.2, 14.2 Hz), 2.79 (1H, dd, J=4.0, 5.0 Hz), 3.00 (1H, ddd, J=2.6, 4.0, 8.4 Hz), 5.28 (1H, ddd, J=1.2, 1.2, 10.8 Hz), 5.37 (1H, ddd, J=1.2, 1.2, 17.2 Hz), 5.68 (1H, dddd, J=1.2, 1.2, 5.3, 6.5 Hz), 5.90 (1H, ddd, J=6.5, 10.8, 17.2 Hz), 7.14–7.23 (3H, m), 7.25–7.29 (2H, m), 7.45–7.48 (2H, m), 7.57–7.61 (1H, m), 8.01–8.04 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 33.2, 45.8, 46.8, 53.2, 75.5, 117.9, 125.7, 128.2, 128.3, 128.3, 129.4, 129.9, 133.0, 134.2, 141.7, 165.2. IR (neat) 3063, 3029, 2994, 2926, 2867, 1721, 1603, 1495, 1453, 1271, 1111, 712 cm^{-1}. LRMS (EI) *m*/*z*: 322 (M^+), 218 (M^+−PhCO+H). HRMS (EI) calcd for $C_{21}H_{22}O_3$; 322.1569. Found 322.1572. $[\alpha]_D^{21}$ +22.2 (*c* 1.2, $CHCl_3$).

4.1.14. (3*R*,4*S*,5*R*)-3-Benzoyloxy-4-phenyl-8-(trimethylsilyl)oct-1-en-7-yn-5-ol (14a). Under an Ar atmosphere, to a cold (−78 °C) solution of ethynyltrimethylsilane (440 μL, 3.12 mmol) in THF (3 mL) was added *n*-BuLi (1.6 M in hexane, 1.6 mL, 2.5 mmol) and stirred at the same temperature for 10 min. To the mixture were added epoxide **13a** (369 mg, 1.25 mmol) in THF (2 mL) and $BF_3 \cdot OEt_2$ (174 μL, 1.37 mmol), and stirred at the same temperature for 2 h. The reaction was quenched by adding water (10 mL) and the mixture was extracted with AcOEt (150 mL). Organic layer was washed with water (10 mL), saturated aqueous NH_4Cl solution (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography (hexane–AcOEt (40/1–30/1)) gave the product **14a** (427 mg, 87%) as a colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (9H, s), 2.07 (1H, dd, J=7.2, 16.7 Hz), 2.24 (1H, dd, J=7.2, 16.7 Hz), 2.74 (1H, d, J=4.9 Hz), 3.16 (1H, dd, J=2.7, 10.5 Hz), 4.20 (1H, ddt, J=2.7, 4.9, 7.9 Hz), 5.05 (1H, ddd, J=1.2, 1.2, 11.2 Hz), 5.22 (1H, ddd, J=1.2, 1.2, 17.8 Hz), 5.68 (1H, ddd, J=6.3, 11.2, 17.8 Hz), 6.07 (1H, dddd, J=1.2, 1.2, 6.3, 10.5 Hz), 7.28–7.38 (5H, m), 7.48–7.52 (2H, m), 7.60–7.64 (1H, m), 8.13–8.16 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.2, 26.6, 54.0, 68.4, 75.1, 87.4, 103.4, 117.7, 127.3, 128.2, 128.4, 129.7, 129.8, 130.4, 133.2, 134.9, 135.6, 166.3. IR (neat) 2176, 1703 cm^{-1}. LRMS (EI) *m*/*z*: 392 (M^+), 377 ($M^+ - CH_3$). HRMS (EI) calcd for $C_{24}H_{28}O_3Si$; 392.1815. Found 392.1808. $[\alpha]_D^{18}$ −3.7 (*c* 1.0, $CHCl_3$).

14b and **14c** could also be prepared as substantially the same manner.

4.1.15. (3*R*,4*S*,5*R*)-3-Benzoyloxy-4-benzyl-8-(trimethylsilyl)oct-1-en-7-yn-5-ol (14b). A colorless oil (78%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.17 (9H, s), 2.36–2.39 (2H, m), 2.46 (1H, dd, J=7.7, 16.9 Hz), 2.55 (1H, dd, J=6.9, 16.9 Hz), 2.66 (1H, dd, J=9.0, 14.5 Hz), 2.98 (1H, dd, J=4.6, 14.5 Hz), 4.25 (1H, t, J=7.1 Hz), 5.22 (1H, ddd, J=1.2, 1.2, 5.0 Hz), 5.25 (1H, ddd, J=1.2, 1.2, 11.2 Hz), 5.64 (1H, dddd, J=1.2, 1.2, 4.2, 5.5 Hz), 5.86 (1H, ddd, J=5.5, 10.7, 16.2 Hz), 7.18–7.30 (5H, m), 7.31–7.49 (2H, m), 7.58–7.62 (1H, m), 7.96–8.07 (2H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 0.2, 26.7, 30.8, 47.6, 69.3, 75.9, 87.7, 103.0, 117.2, 126.0, 128.4, 128.5, 129.1, 129.4, 129.7, 133.1, 134.8, 140.2, 165.3. IR (neat) 3505, 2959, 2928, 2175, 1722, 1645, 1603, 1585, 1495, 1452, 1412, 1271, 1251, 1113, 1026 cm^{-1}. LRMS (EI) *m*/*z*: 406 (M^+), 388 ($M^+ - H_2O$). HRMS (EI) calcd for $C_{25}H_{30}O_3Si$; 406.1964. Found 406.1963. $[\alpha]_D^{25}$ −6.9 (*c* 0.6, $CHCl_3$).

4.1.16. (3*R*,4*S*,5*R*)-3-Benzoyloxy-4-(2-phenylethyl)-8-(trimethylsilyl)oct-1-en-7-yn-5-ol (14c). A colorless oil (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (9H, s), 1.74 (1H, dddd, J=5.6, 7.4, 9.9, 14.5 Hz) 1.91 (1H, dddd, J=4.0, 6.5, 10.3, 14.5 Hz), 2.01 (1H, dddd, J=2.7, 4.0, 5.3, 7.4 Hz), 2.36 (1H, br d, J=2.4 Hz), 2.43 (1H, dd, J=6.8, 16.8 Hz), 2.55 (1H, dd, J=7.2, 16.8 Hz), 2.68 (2H, ddd, J=6.5, 9.9, 13.7 Hz), 2.85 (1H, ddd, J=5.6, 10.3, 13.7 Hz), 4.07–4.13 (1H, m), 5.31 (1H, ddd, J=1.2, 1.2, 10.6 Hz), 5.38 (1H, ddd, J=1.2, 1.2, 16.8 Hz), 5.77 (1H, apparent ddt, J=1.2, 1.2, 6.0 Hz), 5.93 (1H, ddd, J=6.3, 10.6, 16.8 Hz), 7.15–7.20 (3H, m), 7.24–7.29 (2H, m), 7.44–7.50 (2H, m), 7.56–7.62 (1H, m), 8.03–8.07 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.2, 26.6, 34.5, 44.9, 69.5, 76.1, 87.5, 103.1, 117.8, 125.8, 128.2, 128.4, 129.5, 129.8, 133.1, 134.8, 141.7, 165.6. IR (neat) 3497, 3023, 2961, 2176, 1721, 1603, 1453, 1273, 1113, 1026, 845, 758, 712 cm^{-1}. LRMS (EI) *m*/*z*: 420 (M^+), 405 ($M^+ - CH_3$). HRMS (EI) calcd for $C_{26}H_{32}O_3Si$; 420.2121. Found 420.2117. $[\alpha]_D^{19}$ +19.7 (*c* 0.8, $CHCl_3$).

4.1.17. (3*R*,4*S*,5*R*)-3,5-Bis-(*tert*-butyldimethylsilyloxy)-4-phenyloct-1-en-7-yne (8a). *Deprotection*: To a solution of enyne **14a** (387 mg, 0.986 mmol) in MeOH (6.5 mL) was added K_2CO_3 (409 mg, 2.96 mmol) and stirred at room temperature for 4.5 h. The mixture was diluted with AcOEt (200 mL) and washed with water (20 mL×2), saturated aqueous NH_4Cl solution (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated. The residue was used for the next reaction without further purification, but, analytical sample could be obtained by purification by silica gel column chromatography (PhMe–AcOEt (9/1)) as a colorless foam.

4.1.18. (3*R*,4*S*,5*R*)-4-phenyloct-1-en-7-yne-3,5-diol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (1H, t, J=2.7 Hz), 2.11 (1H, ddd, J=2.7, 8.2, 16.5 Hz), 2.24 (1H, ddd, J=2.7, 7.4, 16.5 Hz), 2.43 (1H, br s), 2.70 (1H, br s), 2.88 (1H, dd, J=2.9, 7.4 Hz), 4.49 (1H, ddt, J=2.7, 7.4, 8.2 Hz), 4.67 (1H, dd, J=5.7, 7.6 Hz), 5.09 (1H, ddd, J=1.4, 1.4, 10.5 Hz), 5.25 (1H, ddd, J=1.4, 1.4, 17.0 Hz), 5.83 (1H, ddd, J=5.7, 10.5, 17.0 Hz), 7.26–7.36 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 54.4, 69.6, 70.6, 74.3, 81.1, 115.6, 127.1, 128.2, 129.9, 137.3, 139.3. IR (neat) 3443, 3283, 2119, 1239 704, 630 cm^{-1}. LRMS (EI) *m*/*z*: 216 (M^+), 198 ($M^+ - H_2O$). HRMS (EI) calcd for $C_{14}H_{16}O_2$; 216.1152. Found 216.1150. $[\alpha]_D^{18}$ −17.0 (*c* 1.0, $CHCl_3$).

Benzyl- and 2-phenylethyl substituted compounds could also be prepared as substantially the same manner.

4.1.19. (3*R*,4*S*,5*R*)-4-Benzyloct-1-en-7-yne-3,5-diol. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.02 (1H, dddd, J=1.7, 3.4, 4.9, 10.4 Hz), 2.07 (1H, t, J=2.7 Hz), 2.43 (1H, ddd, J=2.7, 7.1, 16.8 Hz), 2.52 (1H, d, J=3.3 Hz), 2.57 (1H, ddd, J=2.7, 7.4, 16.8 Hz), 2.83 (1H, dd, J=4.9, 14.3 Hz), 2.91 (1H, dd, J=10.4, 14.3 Hz), 3.14 (1H, br d, J=1.4 Hz), 4.21 (1H, br s), 4.26 (1H, apparent t, J=7.1 Hz), 5.22 (1H, ddd, J=1.7, 1.7, 10.7 Hz), 5.32 (1H, ddd, J=1.7, 1.7, 17.0 Hz), 5.84 (1H, ddd, J=4.4, 10.7, 17.0 Hz), 7.20–7.31 (5H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.6, 30.4, 46.9, 69.6, 70.6, 73.0, 80.9, 115.1, 126.0, 128.3, 129.2, 139.6, 140.1. IR (neat) 3302, 3026, 2922, 2120, 1495, 1454, 1321 cm^{-1}. LRMS (EI) *m*/*z*: 230 (M^+). HRMS (EI) calcd for $C_{15}H_{18}O_2$; 230.1307. Found 230.1296. $[\alpha]_D^{25}$ −18.2 (*c* 0.9, $CHCl_3$).

4.1.20. (3*R*,4*S*,5*R*)-4-(2-Phenylethyl)oct-1-en-7-yne-3,5-diol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (1H, dddd, J=2.6, 4.3, 4.3, 8.6 Hz) 1.75 (1H, dddd, J=4.3, 6.4, 9.4, 13.8 Hz), 1.89–2.00 (1H, m), 2.00 (1H, t, J=2.7 Hz), 2.29 (1H, ddd, J=2.7, 6.2, 16.7 Hz), 2.47 (1H, ddd, J=2.7, 7.9, 16.7 Hz), 2.63 (1H, ddd, J=6.4, 9.7, 14.0 Hz), 2.63 (1H, br s), 2.83 (1H, ddd, J=5.2, 9.4, 14.0 Hz), 2.93 (1H, br s), 4.20 (apparent t, J=7.2 Hz), 4.43 (1H, br s), 5.25 (1H, ddd, J=1.5, 1.5, 10.6 Hz), 5.36 (1H, ddd, J=1.5, 1.5, 17.4 Hz), 5.90

(1H, ddd, J=5.0, 10.6, 17.4 Hz), 7.16–7.22 (3H, m), 7.26–7.31 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 26.1, 33.9, 44.6, 70.2, 70.5, 74.0, 81.0, 115.5, 125.8, 128.3, 128.3, 139.8, 141.8. IR (neat) 3303, 2934, 2122, 1647, 1605, 1123, 1082, 1040, 924, 750, 700 cm^{-1}. LRMS (EI) *m/z*: 244 (M^+), 226 (M^+-H_2O). HRMS (EI) calcd for $C_{16}H_{20}O_2$; 244.1463. Found 244.1463. $[\alpha]_D^{16}$ −12.7 (*c* 0.8, $CHCl_3$).

4.1.21. Protection of hydroxy group. Under an Ar atmosphere, to a cooled (0 °C) solution of crude phenyl-substituted diol and 2,6-lutidine (459 μL, 3.94 mmol) in CH_2Cl_2 (14 mL) was added TBSOTf (1.5 mL, 6.41 mmol) and stirred at the same temperature for 40 min. The mixture was diluted with AcOEt (200 mL) and washed with water (20 mL×2), saturated aqueous NH_4Cl solution (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography (hexane–AcOEt (50/1)) gave the product **8a** (434 mg, 98% for 2 steps) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.05 (3H, s), 0.10 (3H, s), 0.10 (3H, s), 0.85 (9H, s), 0.91 (9H, s), 1.96 (1H, ddd, J=2.7, 9.8, 16.4 Hz), 2.06 (1H, t, J=2.7 Hz), 2.24 (1H, ddd, J=2.7, 4.4, 16.4 Hz), 3.04 (1H, dd, J=2.6, 9.2 Hz), 4.49–4.53 (2H, m), 4.86 (1H, dd, J=1.2, 9.7 Hz), 4.92 (1H, dd, J=1.2, 17.5 Hz), 5.54 (1H, ddd, J=8.1, 9.7, 17.5 Hz), 7.15–7.19 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.1, −4.0, −3.9, −2.4, 18.3, 18.4, 25.8, 26.0, 26.1, 26.2, 56.4, 69.6, 70.6, 75.2, 81.3, 116.9, 126.2, 127.1, 131.1, 137.4, 140.2. IR (neat) 3314, 2965, 2897, 2858, 2122, 1495, 1472, 1464, 1428, 1091, 700, 640 cm^{-1}. LRMS (EI) *m/z*: 444 (M^+), 312 (M^+−TBSOH). HRMS (EI) calcd for $C_{26}H_{44}O_2Si_2$; 444.2875. Found 444.2880. $[\alpha]_D^{18}$ −3.0 (*c* 2.5, $CHCl_3$).

8b and **8c** could also be prepared as substantially the same manner.

4.1.22. (3*R*,4*S*,5*R*)-4-Benzyl-3,5-bis-(*tert*-butyldimethylsilyloxy)oct-1-en-7-yne (8b). A colorless oil (88% for 2 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.02 (3H, s), 0.03 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 0.91 (9H, s), 1.94 (1H, t, J=2.7 Hz), 2.20 (1H, ddd, J=2.7, 7.1, 16.8 Hz), 2.26 (1H, dddd, J=2.7, 6.0, 6.0, 8.2 Hz), 2.30 (1H, ddd, J=2.7, 6.0, 14.3 Hz), 2.62 (1H, dd, J=6.0, 14.3 Hz), 2.70 (1H, dd, J=8.2, 14.3 Hz), 4.07 (1H, ddd, J=2.7, 6.0, 7.2 Hz), 4.18 (1H, dd, J=6.0, 7.3 Hz), 5.08 (1H, ddd, J=1.1, 1.1, 10.4 Hz), 5.17 (1H, ddd, J=1.1, 1.1, 17.3 Hz), 5.83 (1H, ddd, J=7.3, 10.4, 17.3 Hz), 7.14–7.26 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, −4.3, −3.9, −3.3, 18.3, 18.3, 25.9, 26.0, 26.1, 32.2, 51.4, 69.9, 70.9, 75.8, 82.2, 115.7, 125.4, 127.9, 129.2, 140.1, 142.0. IR (neat) 3314, 2955, 2930, 2858, 2122, 1471, 1361, 1253, 1084, 1064, 924, 837, 775 cm^{-1}. LRMS (EI) *m/z*: 458 (M^+). HRMS (EI) calcd for $C_{27}H_{46}O_2Si_2$; 458.3036. Found 458.3034. $[\alpha]_D^{25}$ +12.1 (*c* 0.9, $CHCl_3$).

4.1.23. (3*R*,4*S*,5*R*)-3,5-Bis-(*tert*-butyldimethylsilyloxy)-4-(2-phenylethyl)oct-1-en-7-yne (8c). A colorless oil (74% for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.08 (3H, s), 0.05 (3H, s), 0.06 (3H, s), 0.09 (3H, s), 0.89 (18H, s), 1.59–1.73 (2H, m), 1.88 (1H, dddd, J=4.2, 5.6, 5.6, 5.6 Hz), 1.97 (1H, t, J=2.5 Hz), 2.41 (2H, dd, J=2.5, 6.3 Hz), 2.66 (1H, ddd, J=6.5, 10.3, 13.9 Hz), 2.73 (1H, ddd, J=6.5, 10.3, 13.9 Hz), 4.02 (1H, dt, J=4.2, 6.3 Hz), 4.19 (1H, dd, J=5.6, 7.2 Hz), 5.12 (1H, m), 5.19 (1H, m), 5.86 (1H, ddd, J=7.2, 10.0, 17.2 Hz), 7.17 (3H, m), 7.26 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.4, −4.2, −4.0, −3.5, 18.3, 18.3, 26.0, 26.1, 26.3, 28.0, 35.7, 49.2, 70.1, 71.5, 75.6, 81.9, 115.6, 125.4, 128.1, 128.2, 139.8, 143.0. IR (neat) 3314, 2955, 2930, 2859, 2122, 1472, 1462, 1254, 1076, 837, 776 cm^{-1}. LRMS (EI) *m/z*: 472 (M^+), 457 (M^+-CH_3), 415 (M^+−*t*-Bu), 340 (M^+−TBSOH). HRMS (EI) calcd for $C_{28}H_{48}O_2Si_2$; 472.3193. Found 472.3187. $[\alpha]_D^{23}$ +4.4 (*c* 0.7, $CHCl_3$).

4.1.24. 1α,25-Dihydroxy-2α-phenylvitamin D$_3$ (4). A solution of enyne **8a** (50 mg, 0.112 mmol), bromoolefin **7**[10] (66 mg, 0.185 mmol), $Pd(PPh_3)_4$ (64 mg, 0.056 mmol) in toluene (1 mL) and triethylamine (3 mL) was stirred under an Ar atmosphere at reflux for 2 h. After cooled to room temperature, the mixture was diluted with Et_2O and filtered. The filtrate was diluted with AcOEt (50 mL), washed with water (5 mL×2), brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was partially purified by passing through silica gel pad (elution; hexane–AcOEt (30/1)). The crude bisTBS ether was treated with TBAF (1 M in THF, 2.2 mL, 2.2 mmol) and stirred at room temperature for 48 h, and then 60 °C for 30 min. The mixture was diluted with AcOEt (50 mL), washed with water (5 mL×2), brine (5 mL) and concentrated. The residue was purified by silica gel column chromatography (hexane–AcOEt (2/1)) to give the product **4** (7 mg, 13% for 2 steps) as a white amorphous solid. This sample was further purified for biological studies by recycled reverse phase HPLC (YMC-Pack ODS column, 20×150 mm, 9.9 mL/min, CH_3CN–H_2O (9/1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54 (3H, s), 0.94 (3H, d, J=6.3 Hz), 1.21 (6H, s), 1.00–1.64 (16H, m), 1.64–1.78 (2H, m), 1.82–1.95 (1H, m), 1.98–2.03 (2H, m), 2.40 (1H, br t, J=11.9 Hz), 2.81–2.91 (3H, m), 4.31 (1H, br s), 4.50 (1H, dd, J=4.6, 10.2, 10.2 Hz), 5.07 (1H, d, J=1.8 Hz), 5.31 (1H, d, J=1.8 Hz), 6.04 (1H, d, J=11.2 Hz), 6.53 (1H, d, J=11.2 Hz), 7.29–7.32 (1H, m), 7.36–7.44 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 18.9, 21.0, 22.4, 23.6, 27.8, 29.2, 29.3, 29.4, 36.2, 36.5, 40.6, 44.3, 44.5, 46.0, 56.4, 56.6, 57.6, 68.3, 71.1, 115.1, 116.8, 125.4, 127.3, 128.7, 129.2, 132.0, 138.8, 143.5, 146.0. IR (film) 3405, 2944, 2870, 1647, 1603, 1495, 1377, 735 cm^{-1}. LRMS (EI) *m/z*: 492 (M^+), 456 ($M^+-2\times H_2O$). HRMS (EI) calcd for $C_{33}H_{48}O_3$; 492.3571. Found 492.3601. $[\alpha]_D^{17}$ +80.9 (*c* 0.05, $CHCl_3$).

5 and **6** were also synthesized as substantially the same manner.

4.1.25. 2α-Benzyl-1α,25-dihydroxyvitamin D$_3$ (5). A white amorphous solid (32% for 2 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.53 (3H, s), 0.93 (3H, d, J=6.6 Hz), 1.21 (9H, s), 1.00–1.72 (16H, m), 1.83–2.05 (6H, m), 2.27 (1H, dd, J=9.3, 12.6 Hz), 2.73 (1H, dd, J=4.4, 13.2 Hz), 2.82–2.86 (2H, m), 2.99 (1H, dd, J=5.5, 13.7 Hz), 3.93 (1H, ddd, J=4.4, 8.8, 8.8 Hz), 4.12 (1H, d, J=2.8 Hz), 4.94 (1H, d, J=2.0 Hz), 5.14 (1H, d, J=2.0 Hz), 5.97 (1H, d, J=11.0 Hz), 6.42 (1H, d, J=11.0 Hz), 7.21–7.31 (5H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 18.8, 20.8, 22.2, 23.5, 27.6, 29.1, 29.2, 29.3, 33.1, 36.1, 36.4, 40.5, 44.4, 44.6, 45.9, 51.6, 56.3, 56.5, 70.1, 71.1, 72.9, 113.9, 116.9, 124.9, 125.9, 128.4, 129.3, 132.7, 140.1, 143.4, 146.4. LRMS (EI) *m/z*: 506 (M^+). HRMS (EI) calcd for $C_{34}H_{50}O_3$; 506.3760. Found 506.3373. $[\alpha]_D^{25}$ +22.1 (*c* 0.07, $CHCl_3$).

4.1.26. 1α,25-Dihydroxy-2α-(2-phenylethyl)vitamin D_3 (6). A white amorphous solid (15% for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (3H, s), 0.93 (3H, d, J=6.4 Hz), 1.02–1.10 (2H, m), 1.22 (6H, s), 1.18–1.61 (13H, m), 1.62–1.78 (4H, m), 1.82–1.95 (3H, m), 1.95–2.04 (2H, m), 2.24 (1H, dd, J=8.5, 13.0 Hz), 2.62–2.72 (2H, m), 2.78–2.88 (2H, m), 3.92 (1H, ddd, J=4.3, 8.5, 8.5 Hz), 4.43 (1H, d, J=3.2 Hz), 4.99 (1H, d, J=1.6 Hz), 5.27 (1H, d, J=1.6 Hz), 6.00 (1H, d, J=11.2 Hz), 6.40 (1H, d, J=11.2 Hz), 7.15–7.31 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 18.8, 20.8, 22.2, 23.5, 27.6, 28.4, 29.0, 29.1, 29.3, 33.4, 36.0, 36.3, 40.4, 44.2, 44.3, 45.8, 48.9, 56.2, 56.4, 70.1, 70.9, 73.2, 113.2, 116.5, 124.5, 125.4, 128.0, 128.1, 132.3, 142.1, 143.0, 146.2. IR (film) 3357, 2934, 2870, 1456, 1377, 1063, 1040, 910, 733 cm^{-1}. HRMS (EI) calcd for $C_{35}H_{52}O_3$; 520.3916. Found 520.3920. $[\alpha]_D^{18}$ +53.0 (*c* 0.5, $CHCl_3$).

4.2. Vitamin D receptor binding assay

Bovine thymus VDR was obtained from Yamasa Biochemical (Chiba, Japan) and dissolved in 0.05 M phosphate buffer (pH 7.4) containing 0.3 M KCl and 5 mM dithiothreitol just before use. The receptor solution (500 μL) was pre-incubated with 50 μL of ethanol solution of 1α,25-dihydroxyvitamin D_3 or an analogue at various concentrations for 60 min at 25 °C. Then, the receptor mixture was left to stand overnight with 0.1 nM [^{3}H]-1α,25-dihydroxyvitamin D_3 at 4 °C. The bound and free [^{3}H]-1α,25-dihydroxyvitamin D_3 were separated by treatment with dextran-coated charcoal for 30 min at 4 °C and centrifuged at 3000 rpm for 10 min. The supernatant (500 μL) was mixed with ACS-II (9.5 mL) (Amersham, UK) and the radioactivity was counted. The relative potency of the analogues was calculated from their concentration needed to displace 50% of [^{3}H]-1α,25-dihydroxyvitamin D_3 from the receptor compared with the activity of 1α,25-dihydroxyvitamin D_3 (assigned a 100% value).

4.3. HL-60 cell differentiation assay

Activities of these analogues on differentiation of HL-60 cells were estimated by nitroblue tetrazolium (NBT) reduction assay[22] with some modifications. Human promyelocytic leukemia HL-60 cells were grown at 37 °C in RPMI 1640 medium (Asahi Technoglass Co., Chiba, Japan) supplemented with 10% heat-inactivated fetal bovine serum (Sigma, St. Louis, MO) in an atmosphere of 95% air and 5% CO_2. Cells were collected, suspended in 1.5 mL of the culture medium containing various concentrations (0, 10^{-10}–10^{-6} M) of the analogues at a density of ca. 5×10^5 cells/mL, and then cultivated for 5 days. After the treatment, cells were harvested and suspended in Tyrode's solution (140 mM NaCl, 2.7 mM KCl, 1.1 mM $MgCl_2$, 1 mM $CaCl_2$, 0.45 mM NaH_2PO_4, 5.6 mM D-glucose, pH 7.4) containing 25 mM HEPES and 0.05% NBT (Dojindo Laboratories, Kumamoto, Japan). After pre-incubation at 37 °C for 7 min, phorbol 12-myristate 13-acetate (4 μM, Sigma, St. Louis, MO) was added to the cell suspension and the suspension was incubated for 30 min at 37 °C. EDTA (10 mM) was added to stop the reaction, and then the percentage of positive cells (blue-stained cells) was determined using a hemocytometer. EC_{50} value was estimated from the obtained dose-response curve. Relative differentiation activity was calculated according to the following formula: Relative differentiation activity = EC_{50} of 1α,25-dihydroxyvitamin D_3/EC_{50} of the analogue × 100.

4.4. Transfections and transcriptional assays

CV-1 monkey kidney cells were plated in 35-mm dishes at a density of 10^5 cells/dish. Cells were transfected by the DEAE-dextran method with 2 μg/dish of WT or mutant VDR expression vectors and a reporter construct containing the human osteocalcin VDRE (ocVDRE) linked to the thymidine kinase promoter and the growth hormone reporter gene (*ocVDRE/TK-GH*).[15] The medium was collected 2days after transfection, and growth hormone was measured using a radioimmunoassay as described by the manufacturer (Nichols Institute, San Juan Capistrano, CA).

4.5. Protease sensitivity assays

WT and mutant VDRs were synthesized and labeled in vitro with [^{35}S]methionine (1000 Ci/mmol) using the TNT coupled transcription/translation system (*Promega*). The translated receptor preparations were incubated with 1α,25-dihydroxyvitamin D_3 or analogues for 10 min at ambient temperature. Next, trypsin was added to a concentration of 20 μg/mL, and the mixtures were incubated for 10 min. The digestion products were then separated by SDS polyacrylamide gel electrophoresis and detected by autoradiography.

Acknowledgements

We are grateful to Miss Junko Shimode, Miss Maroka Kitsukawa and Miss Akiko Tonoki (Teikyo University) for the spectroscopic measurements. This work has been supported by a Grant-in-Aid for Young Scientists (B) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, (No. 17799095 to S.H.) and in part by Grants-in-Aid for Scientific Research (C) from Japan Society for the Promotion of Science (No. 15590021 and 17590012 to A.K.) and an NIH grant DK-50583 (to S.P.). A.K. also thanks Uehara Memorial Foundation for financial support.

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Tetrahedron 61 (2005) 11264–11269
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Versatile acenaphtho[1,2-*b*]pyrrol-carbonitriles as a new family of heterocycles: diverse S_NAr^H reactions, cytotoxicity and spectral behavior

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Received 27 June 2005; revised 25 August 2005; accepted 25 August 2005

Available online 11 October 2005

Abstract—The diverse reactivity of highly electron-deficient 8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile **1** is attractive for the preparation of derivatives bearing different substituents via S_NAr^H reaction with N, O, S nucleophiles. These derivatives were versatile, possessing potential antitumor activities and displaying tunable fluorescence spectral behavior.

1. Introduction

Heterocycles are important constituents, which commonly exist in biologically active natural products and synthetic compounds of medicinal interest.[1] It is an efficient method to develop versatile heterocyclic precursors or leading compounds that can be diversely and conveniently functionalized to access large amounts of derivatives for pharmacological and cytotoxic investigations as well as for SAR (structure–activity relationship) establishment.[2] Thus, it is not surprising that novel heterocyclic families have been receiving special attention in drug discoveries.

On the other hand, many electron-deficient polycyclic chromophoric systems[3] have been demonstrated to play an important role in some valuable antitumor agents, such as the anthraquinone ring system in daunomycin, mitoxantron, and doxorubicin, naphthalimide in amonafide and acridine in DACA (Fig. 1).[3–6] Thus, in the current search for potential antitumor agents, a majority of attention has been devoted to the discovery of novel electron-deficient heterocycles, which can be easily derived or functionalized.

Among the multitude of reported organic heterocyclic compounds, acenaphtho-heterocycles have been once neglected. Less attention has been focused on the synthesis and functionalization of acenaphtho-heterocycles.[7] Recently, we have reported a new acenaphtho-heterocycle precursor **1**, 8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile, characteristic of a flat and highly electron-deficient heteroaromatic system. Some S_NAr^H reaction could easily occur between **1** and primary aliphatic amines in very mild conditions. Meanwhile, amino derivatives of **1** were typical intramolecular charge transfer (ICT) fluorophores.[8]

As a novel electron-deficient heterocycle, its derivation and potential is prospective. Thus, we further synthesized a variety of derivatives mainly with basic amino chains and expected that these compounds might possess promising bioactivities. Meanwhile, we also anticipated that the introduction of nitrogen, oxygen, sulfur nucleophiles with different electron-donating ability might give birth to a diversity of spectral behaviors.

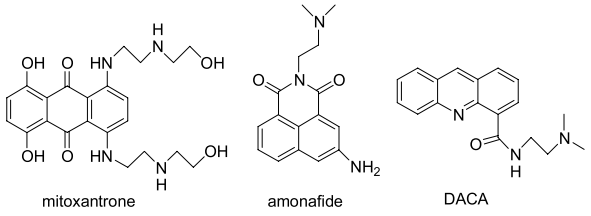

Figure 1. Structures of some available chromophores as antitumor agents.

Keywords: S_NAr^H reaction; Nucleophiles; Acenaphtho-heterocycles.
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0040–4020/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tet.2005.08.106

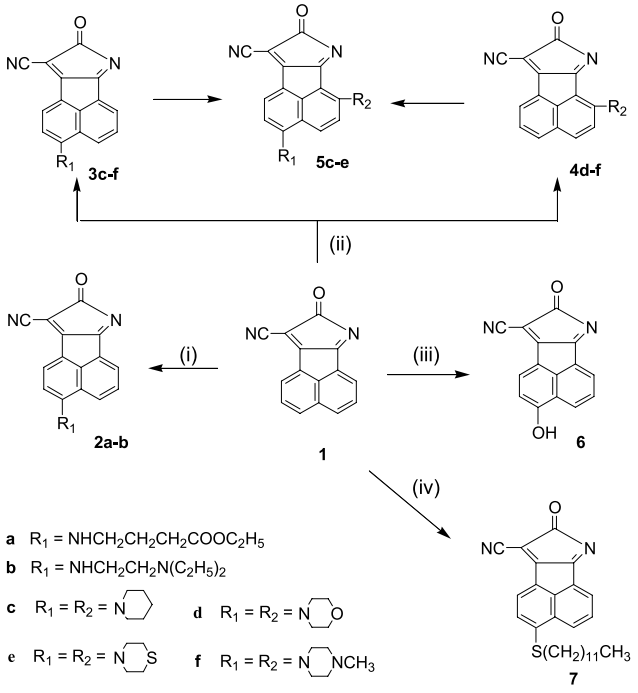
2. Results and discussion

2.1. Chemistry

Precursor **1** was prepared according to our previous publication.[8] Compounds **2–5** were synthesized according to Scheme 1. 3-Substituted products **2a–b** were formed as the sole product from the reaction of **1** with excess primary aliphatic amines at room temperature. Different results were observed in the reaction of **1** with alicyclic secondary amines under the same conditions. Besides 3-substituted products **3c–f**, 6-substituted products **4d–f** and 3,6-disubstituted products **5c–e** were also obtained. The formation of **4d–f** and **5c–e** is beyond what we had expected. Given adequate time, mono-substituted products **3c–f** and **4d–f** could be totally converted into 3,6-disubstituted products. Table 1 displays the ratio of 3-substituted to 6-substituted products.

The formation of 6-substituted isomer of **3c** was very slow and it was quickly converted into disubstituted product **5c**, thus the isomer could not be obtained. Disubstituted product of **3f** and **4f** was unstable and could not be obtained either.

The distinction between alicyclic secondary and primary amines is possibly attributed to steric hindrance from *peri*-hydrogen. Generally, nucleophilic amines preferentially attack the most electron-deficient carbon at 3-position, namely *peri*-position of naphthalene. Unlike primary aliphatic amine, when alicyclic secondary amine attacks the carbon at 3-position, it bears steric hindrance from another *peri*-hydrogen (namely 4-position). As a result, sub-electron-deficient carbon at 6-position becomes a competing



Scheme 1. Synthesis and yield: (i) 4 equiv corresponding primary amines, CH_3CN, rt, 1.0–2.0 h (**2a** 45%, **2b** 42% yield); (ii) 4–6 equiv corresponding secondary amines, CH_3CN, rt, 1.0–12 h (**3c** 49%, **3d** 30%, **3e** 35%, **3f** 30%, **4d** 18%, **4e** 12%, **4f** 16%, **5c** 48%, **5d** 45%, **5e** 45%, yield); (iii) 0.2 equiv K_2CO_3, H_2O, DMSO, rt, 1.0 h (**6** 38% yield); (iv) $CH_3(CH_2)_{11}SH$, reflux, 72 h (**7** 42% yield).

Table 1. Ratio of 3-substituted to 6-substituted products

Entry	Nucleophiles	Yields of **3** and **4** (%)	Ratio of **3** to **4**[a]
1	Morpholine	48 (**3d** and **4d**)	30:18
2	Thiomorpholine	47 (**3e** and **4e**)	35:12
3	4-Methyl-piperazine	46 (**3f** and **4f**)	30:16

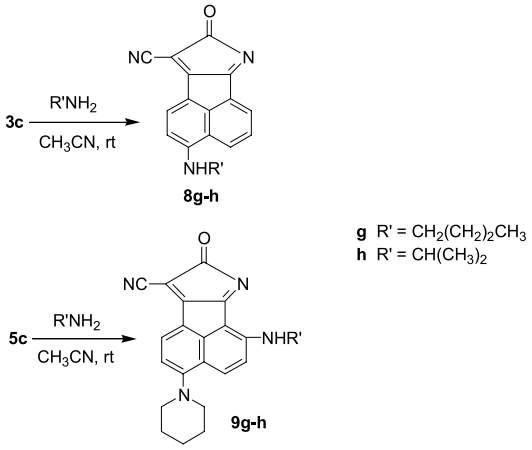
[a] The ratio was calculated according to isolated yields.

reactive site. Thus, for alicyclic secondary amine, 6-substituted and 3,6-disubstituted products are obtained. But for primary aliphatic amines, due to the absence of steric hindrance from *peri*-hydrogen, 3-carbon is the most preferential reactive site. Moreover, once the 3-substituted products of primary amines are formed, the hydrogen on nitrogen of amino substituents possibly departs under excess of amines in reaction system and a nitrogen anion forms. Such strong electron-donating ability of nitrogen anion greatly decreases the electron-deficient features of the system and thus 3-substituted products could not be attacked by the second nucleophiles.

Interestingly, we further found that alicyclic secondary amino substituents of 3-substituted and 3,6-disubstituted products could be easily replaced by aliphatic primary amines to give **8g–h**[8] or **9g–h** with different amino substituents, respectively (Scheme 2). Thus, some di-substituted products with different amino groups could be obtained.

Here, there are four unusual characteristics for the S_NAr^H reaction concluded in this case: (1) there are two active sites for S_NAr^H reaction in one molecule;[9] (2) regioselectivities for S_NAr^H reaction depend on the nature of nucleophiles; (3) two hydrogen atoms in one aromatic conjugation system is simultaneously replaced;[9a] (4) mono-substituted derivatives could be transformed to other derivatives by nucleophilic substitution or further S_NAr^H reaction. Since few phenomena alike for S_NAr^H were reported, such reactions possibly provided some particular and precious examples.

In order to further extend reaction prospect of precursor **1**, reactions of hydroxyl group and *n*-dodecyl thiol with **1** were successfully carried out (Scheme 1). Similar to



Scheme 2. Reaction of alicyclic amino derivatives with primary aliphatic amines. Synthesis and yield: 3 equiv RNH_2, CH_3CN, rt, 1–2 h (**8g** 75% yield; **8h** 78% yield; **9g** 70% yield; **9h** 72% yield).

the reaction of primary aliphatic amines, only 3-substituted products **6** and **7** were obtained. The formation of **7** was relatively slow and drastic reaction conditions were required (refluxed in the CH_3CN for 3 days and thiol was used in great excess). The reasons that the reaction of *n*-dodecyl thiol with **1** is less efficient are described as follows: S_NAr^H reaction proceeds via addition of nucleophiles to the most electrophilic carbon producing σ^H adduct, which are subsequently converted into final products by oxidation.[10–12] Besides the addition of external oxidants, σ^H adduct can also be oxidized by oxygen or electron-deficient reactant.[10d] In our case, the oxidation is presumably carried out by both the oxygen and reactant **1**.[8] The low yield of the reaction is attributed to the loss of **1** in oxidizing σ^H adduct. For sulfur-containing nucleophiles, which are strong reducing agents, they severely hamper the oxidation step, thus the reaction of thiol with **1** proceeds slowly. This explains why there are very few reports on direct replacement of hydrogen in aromatic heterocycles with sulfur nucleophiles.[10–12a] Whereas for nitrogen-containing and oxygen-containing nucleophiles, owing to the absence of reducing agents, the oxidation takes place rapidly and the reaction proceeds much quickly.

We found that the above observation on the reaction might be a unique example that S_NAr^H of **1** occurred through efficient remote activation, that is, electron-withdrawing substituents are located at the other terminal of the conjugated system, far from the hydrogen to be substituted. The reactivity of reported systems with S_NAr^H was usually acquired near-activation of electron-withdrawing groups or heteroatoms, that is, S_NAr^H generally occurs in arenes with strongly electron-withdrawing substituents (commonly nitro group) that exist in the same ring to the hydrogen substituted, or the nitrogen heterocycles such as 1,2,4-triazine, pyrimidine.[12–14] Furthermore, the systems that equally occur NASH reaction with different nucleophiles (nitrogen, hydroxy group, sulfur) are very few, and nitro-derivatives of several simple nitrogen heterocycles such as nitropyridine, nitroquinoline are reported to give birth to similar reaction.[10,12] The above characteristics of **1** are very attractive to us. We can further improve the structure of **1** to acquire new precursors with similar characteristics to **1** and utilize the diverse reactivity to prepare a variety of derivatives, which favors screenings of new compounds with potential biological activity.

2.2. Cytotoxicity results

Synthesized compounds were evaluated for growth inhibitory properties (measured as IC_{50} values) in human cervical carcinoma (HeLa) cell line (Table 2). 3-Subtituted compounds **2a–b**, **3c–f**, **4d–f** displayed higher activity than di-substituted compounds **5c–e**, **9g**. But **8g–h** with chain alkyl amino substituents exhibited weak activity, and **9h** with two various amino substituents exceptionally demonstrates higher activity. Furthermore, the compounds with sulfur-heterocycles showed higher bioactivity than those with oxo-heterocycles, for example, **3d** and **3e**, **4d** and **4e**, **5d** and **5e**. Among all the compounds, **3e** shows the highest activity (IC_{50}, 0.17 μM). Since most compounds show considerable activity and can be further improved in structure, they are potential leading compounds for the finding of valuable antitumor agents.

Table 2. Preliminary evaluation of synthesized compounds against human cervical carcinoma (HeLa) cell line in vitro (IC_{50}, μM)[a]

Entry	Compound	IC_{50} (μM)
1	**2a**	4.8
2	**2b**	6.8
3	**3c**	4.4
4	**3d**	12.6
5	**3e**	0.17
6	**3f**	2.8
7	**4d**	10.9
8	**4e**	2.1
9	**4f**	3.7
10	**5c**	nd[b]
11	**5d**	nd[b]
12	**5e**	34.1
13	**6**	nd[b]
14	**7**	nd[b]
15	**8g**	19.9
16	**8h**	50.5
17	**9g**	30.7
18	**9h**	7.5

[a] IC_{50}: concentration of drug (μM) to reduce cell number to 50% of control cultures. The value is the average of three independent determinations;
[b] nd = not determined.

2.3. Spectral behavior

Meanwhile, these versatile derivatives are also good fluorophores. As expected, the products with different nucleophiles as substituents show diversified spectral behavior. They emit strong fluorescence of modular color from yellow to reddish-orange.

Table 3 shows the spectral data of characteristic 3-substituted compounds **2a**, **3d**, **6** and **7** in chloroform at room temperature. The emission maxima of **6**, **7**, **2a** and **3d**, which varied form 548 to 607 nm, could be ascribed to their different intramolecular charge transfer (ICT) effects. The substantial spectral changes show that they might be used as tunable fluorophores.

Table 3. Spectrum data of **6**, **7**, **2a**, and **3d** in chloroform

Compound	λ_{abs} (nm)	λ_{em} (nm)	Φ_F[a]
6	504	548	0.87
7	531	567	0.43
2a	572	587	0.29
3d	545	607	0.18

[a] Quantum yield was determined using Rhodamine B in ethanol as a standard.

Furthermore, **3d** is environmentally sensitive fluorophore with long wavelength emission. Upon the increase of solvent polarity, a small red shift of the emission maxima of **3d** was observed, but accompanied with drastic decrease of the quantum yield. In toluene and chloroform, quantum yield is 0.25 and 0.18, respectively, and it is reduced to 0.042 and 0.023 in ethyl acetate and dichloromethane with moderate polarity. In the solvents with higher polarity, fluorescence is totally quenched. So it is attractive for developing fluorescent probe for polarity that can be used

for probing proteins, biological membrane, and micellar systems.[15]

3. Conclusion

In summary, with S_NAr^H reaction of **1**, a variety of acenaphtho-heterocyclic derivatives were readily obtained. Such reactions possibly provided particular and precious examples to lucubrate the mechanism and to develop simple synthetic method. The derivatives not only possess promising antitumor activities but also exhibit diversified spectral behaviors. The results suggest that the acenaphtho-heterocyclic derivatives might be used as screening candidates for antitumor agents as well as useful fluorophores. Further works on the reactivity, the structural refinement and application of the derivatives of **1** are in progress at our laboratory.

4. Experimental

4.1. General

All the solvents were of analytic grade. ^1H and ^{13}C NMR were obtained with Bruker AV-400 spectrometer with chemical shifts reported as ppm (in $CDCl_3$/DMSO-d_6, TMS as internal standard). IR were obtained using a Perkin-Elmer 2000 FTIR instrument. High-resolution mass spectra (HRMS) were obtained on HPLC-Q-Tof MS (Micro) spectrometer. Melting points were determined by an X-6 micro-melting point apparatus and are uncorrected. Column chromatography was performed using silica gel 200–300 mesh. Precursor **1** was prepared according to the procedure described earlier.[8]

4.2. General procedure for the preparation of 2a–b

8-Oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile **1** (0.5 mmol) and corresponding amines (2 mmol) in CH_3CN (20 mL) were stirred for 0.5–1 h at room temperature. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel. Products were separated with CH_2Cl_2/MeOH 20:1 (v/v) as a dark purple powder.

4.2.1. 3-[(4-Butyric acid ethyl ester butyl)amino]-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (2a). Yield 45%; mp 138.5–139.5 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.58 (br s, 1H, –N*H*), 8.90 (d, 1H, J=8.0 Hz), 8.55 (d, 1H, J=8.0 Hz), 7.93 (d, 1H, J=9.2 Hz), 7.87 (t, 1H, J=8.0 Hz), 7.02 (d, 1H, J=8.8 Hz), 4.05 (q, 2H, OCH_2CH$_3$, J=6.8 Hz), 3.61 (q, 2H, NHCH_2CH$_2$, J=7.2 Hz), 2.52–2.50 (m, 2H, CH_2COO), 1.99–1.96 (m, 2H, –NHCH$_2CH_2$), 1.68 ppm (t, 3H, OCH$_2CH_3$, J=6.8 Hz); IR (KBr) cm^{-1}: 3326, 2979, 2218, 1723, 1627, 1576, 1531. HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{21}H_{18}N_3O_3$ 360.1348, found 360.1349.

4.2.2. 3-(Diethylamino-ethylamino)-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (2b). Yield 42%; mp > 300 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 8.97 (d, 1H, J=7.6 Hz), 8.61 (d, 1H, J=7.6 Hz), 7.98 (d, 1H, J=9.2 Hz), 7.91 (t, 1H, J=8.0 Hz), 7.06 (1H, d, J=9.2 Hz), 3.79 (br s, 2H, –NHCH_2), 2.93 (br s, 2H, –NHCH$_2$CH_2), 2.38–2.41 (m, 4H, N(CH_2CH$_3$)$_2$), 1.12–1.15 ppm (m, 6H, N(CH$_2$CH_3)$_2$); IR (KBr) cm^{-1}: 3313, 2968, 2213, 1324, 1574, 1522. HRMS (ESI) m/z $(M-H)^+$ calcd for $C_{21}H_{21}N_4O$ 343.1559, found 343.1557.

4.3. General procedure for the preparation of 3c–f, 4d–f

8-Oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile **1** (0.5 mmol) and corresponding amines (2 mmol) in CH_3CN (20 mL) were stirred for 1–2 h at room temperature. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel. 3-Substituted and 6-substituted products **3c**, **3d** and **4d**, **3e**, and **4e**, **3f** and **4f** were separated with CH_2Cl_2/CH_3COCH_3 50:1 (v/v) as dark purple powders.

4.3.1. 3-Piperidin-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (3c). Yield 49%; mp 204–206 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, 1H, J=8.0 Hz), 8.46 (d, 1H, J=8.4 Hz), 8.10 (d, 1H, J=8.4 Hz), 7.80 (t, 1H, J=8.0 Hz), 7.11 (d, 1H, J=8.4 Hz), 3.60 (t, 4H, NH(CH_2-CH$_2$)$_2$, J=6.0 Hz), 1.94 ppm (br s, 6H, NH(CH$_2$CH_2)$_2$CH_2); IR (KBr) cm^{-1}: 2217, 1623, 1571, 1498. HRMS (ESI) m/z $(M+K)^+$ calcd for $C_{20}H_{15}N_3OK$ 352.0852, found 352.0861.

4.3.2. 3-Morpholin-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (3d). Yield 30%; mp > 300 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 8.66 (d, 1H, J=8.4 Hz), 8.64 (d, 1H, J=7.2 Hz), 8.14 (d, 1H, J=8.8 Hz), 7.94 (t, 1H, J=8.0 Hz), 7.40 (d, 1H, J=8.8 Hz), 3.90 (t, 4H, J=4.4 Hz, N(CH$_2$CH_2)$_2$O), 3.76 ppm (t, 4H, J=4.4 Hz, N(CH_2CH$_2$)$_2$O); IR (KBr) cm^{-1}: 2210, 1623, 1583, 1492. HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{19}H_{14}N_3O_2$ 316.1086, found 316.1080.

4.3.3. 6-Morpholin-8-oxo-8*H*-acen-aphtho[1,2-*b*]pyrrol-9-carbonitrile (4d). Yield 18%; mp 217 °C dec; ^1H NMR (400 MHz, DMSO-d_6): δ 8.35 (d, 1H, J=7.6 Hz), 8.30 (d, 1H, J=9.6 Hz), 8.24 (d, 1H, J=7.6 Hz), 7.82 (d, 1H, J=9.6 Hz), 7.72 (t, 1H, J=7.6 Hz), 3.83 (br s, 4H, N(CH$_2$CH_2)$_2$O), 3.61 ppm (br s, 4H, N(CH_2CH$_2$)$_2$O); IR (KBr) cm^{-1}: 2223, 1616, 1594, 1543. HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{19}H_{14}N_3O_2$ 316.1086, found 316.1080.

4.3.4. 3-Thiomorpholin-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (3e). Yield 35%; mp 232 °C dec; ^1H NMR (400 MHz, DMSO-d_6): δ 8.61 (d, 2H, J=8.0 Hz), 8.12 (d, 1H, J=8.4 Hz), 7.94 (t, 1H, J=8.0 Hz), 7.40 (d, 1H, J=8.8 Hz), 3.94 (t, 4H, J=4.8 Hz, N(CH_2CH$_2$)$_2$S), 2.97 ppm (t, 4H, J=4.8 Hz, N(CH$_2$CH_2)$_2$S); IR (KBr) cm^{-1}: 2219, 1624, 1572, 1499. HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{19}H_{14}N_3OS$ 332.0858, found 332.0861.

4.3.5. 6-Thiomorpholin-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (4e). Yield 12%; mp 247 °C dec; ^1H NMR (400 MHz, DMSO-d_6): δ 8.36 (d, 1H, J=8.8 Hz), 8.31 (d, 1H, J=9.6 Hz), 8.24 (d, 1H, J=7.6 Hz), 7.81 (d, 1H, J=9.6 Hz), 7.73 (t, 1H, J=7.6 Hz), 3.81 (br s, 4H, –N(CH_2CH$_2$)$_2$S), 2.88 ppm (br s, 4H, –N(CH_2CH$_2$)$_2$S); IR (KBr) cm^{-1}: 3431, 2924, 2852, 2224, 1618, 1600. HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{19}H_{14}N_3OS$ 332.0858, found 332.0851.

4.3.6. 3-(4-Methyl-piperazin)-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (3f). Yield 30%; mp 201–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, 1H, J=7.6 Hz), 8.50 (d, 1H, J=8.4 Hz), 8.12 (d, 1H, J=8.4 Hz), 7.82 (t, 1H, J=8.4, 7.6 Hz), 7.06 (d, 1H, J=8.4 Hz), 3.67 (t, 4H, J=4.6 Hz, N(CH_2CH_2)$_2$NCH$_3$), 2.77 (t, 4H, J=4.6 Hz, N(CH$_2$$CH_2$)$_2NCH_3$), 2.45 ppm (s, 3H, N$CH_3$); IR (KBr) cm^{-1}: 3423, 2941, 2214, 1623, 1572. HRMS (ESI) m/z (M+H)$^+$ calcd for $C_{20}H_{17}N_4O$ 329.1402, found 329.1415.

4.3.7. 6-(4-Methyl-piperazin)-8-oxo-8*H*acenaphtho-[1,2-*b*]pyrrol-9-carbonitrile (4f). Yield 16%; mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 (d, 1H, J=7.6 Hz), 8.27 (d, 1H, J=9.6 Hz), 8.23 (d, 1H, J=8.0 Hz), 7.84 (d, 1H, J=9.6 Hz), 7.71 (t, 1H, J=7.6 Hz), 3.61 (br s, 4H, N(CH_2CH_2)$_2$NCH$_3$), 2.58 (br s, 4H, N(CH$_2$$CH_2$)$_2NCH_3$), 2.29 ppm (s, 3H, N$CH_3$); IR (KBr) cm^{-1}: 3439, 2942, 2794, 2227, 1618, 1597, 1544. HRMS (ESI) m/z (M+H)$^+$ calcd for $C_{20}H_{17}N_4OS$ 329.1402, found 329.1415.

4.4. General procedure for the preparation of 5c–e

8-Oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile **1** (0.5 mmol) and corresponding amines (3 mmol) in CH_3CN (20 mL) were stirred for 24 h at room temperature. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel. 3,6-Disubstituted products **5c–e** were separated with CH_2Cl_2/CH_3COCH_3 20:1 (v/v) as dark purple powder.

4.4.1. 3,6-Di-piperidin-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (5c). Yield 48%; mp 155 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, 1H, J=10 Hz), 7.92 (d, 1H, J=8.8 Hz), 7.28 (d, 1H, J=10 Hz), 7.01 (d, 1H, J=8.8 Hz), 3.54 (br s, 4H, N(CH_2CH_2)$_2$$CH_2$), 3.42 (br s, 4H, N($CH_2CH_2$)$_2$$CH_2$), 1.87 (br s, 4H), 1.78 ppm (br s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 159.2, 156.8, 133.4, 133.1, 132.9, 124.9, 117.3, 117.0, 115.9, 115.6, 114.4, 114.0, 113.9, 55.0, 53.4, 26.6, 26.4, 24.4, 24.0 ppm; IR (KBr) cm^{-1}: 2215, 1598, 1542, 1506. HRMS (ESI) m/z (M+H)$^+$ calcd for $C_{25}H_{25}N_4O$ 397.2028, found 397.2036.

4.4.2. 3,6-Di-morpholin-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (5d). Yield 45%; mp 180 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (d, 1H, J=10 Hz), 8.05 (d, 1H, J=8.4 Hz), 7.59 (d, 1H, J=10 Hz), 7.31 (d, 1H, J=8.8 Hz), 3.88 (br s, 4H, N(CH$_2$$CH_2$)$_2$O), 3.82 (br s, 4H, –N(CH$_2$$CH_2$)$_2$O), 3.54 (br s, 4H, N($CH_2CH_2$)$_2$O), 3.46 ppm (br s, 4H, N(CH_2CH_2)$_2$O); IR (KBr) cm^{-1}: 2219, 1610, 1546, 1502. HRMS (ESI) m/z (M+H)$^+$ calcd for $C_{23}H_{21}N_4O_3$ 401.1614, found 401.1606.

4.4.3. 3,6-Di-thiomorpholin-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (5e). Yield 45%; mp 182 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, 1H, J=9.6 Hz), 8.06 (d, 1H, J=8.8 Hz), 7.61 (d, 1H, J=9.6 Hz), 7.33 (d, 1H, J=8.8 Hz), 3.76 (br s, 4H, N(CH_2CH_2)$_2$S), 3.69 (br s, 4H, N(CH_2CH$_2$)$_2$S), 2.92 (br s, 4H, N(CH$_2$CH_2)$_2$S), 2.86 ppm (br s, 4H, N(CH$_2$CH_2)$_2$S); IR (KBr) cm^{-1}: 3441, 2908, 2834, 2219, 1607, 1543. HRMS (ESI) m/z (M+H)$^+$ calcd for $C_{23}H_{21}N_4OS_2$ 433.1157, found 433.1150.

4.4.4. 3-Hydroxyl-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (6). 8-Oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile **1** (0.5 mmol), K_2CO_3 20 mg and 0.2 mL H_2O in 6 mL DMSO were stirred for 15 min at room temperature. The reaction mixture was poured into 40 mL H_2O, and acetic acid was added to make pH=5–6. The resulting solid was filtered off and washed with H_2O. Filtrate was extracted three times with CH_2Cl_2. The organic layer was collected and dried over anhydrous $MgSO_4$. After evaporation to dryness, the residue and filter cake were combined to give crude product. Compound **6** was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 5:1, v/v) to give dark red solid. Yield 38%; mp 162–164 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.51 (d, 1H, J=7.2 Hz), 8.44 (d, 1H, J=7.6 Hz), 7.69–7.74 (m, 2H, J=8.8 Hz), 6.40 ppm (d, 1H, J=9.6 Hz); IR (KBr) cm^{-1}: 3434, 2206, 1627, 1567, 1508. HRMS (ESI) m/z (M+H)$^+$ calcd for $C_{15}H_7N_2O_2$ 247.0508, found 247.0506.

4.4.5. 3-Dodecylsulfanyl-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (7). 8-Oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile **1** (0.5 mmol) and dodecyl mercaptan (7.5 mmol) in CH_3CN (20 mL) were refluxed for 72 h. Ether (10 mL) was added to reaction mixture and the dark red precipitation was filtered off. The precipitation was purified by column chromatography on silica gel (CH_2Cl_2) to give red solid. Yield 42%; mp 191.6–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, 2H, J=8.4 Hz), 8.17 (d, 1H, J=8.0 Hz), 7.90 (t, 1H, J=8.0 Hz), 7.50 (d, 1H, J=8.0 Hz), 3.24 (t, 2H, SCH_2CH$_2$–, J=7.2 Hz), 1.86–1.89 (m, 2H, SCH$_2$CH_2CH$_2$), 1.26 (br s, 18H), 0.88 ppm (t, 3H, J=6.4 Hz); IR (KBr) cm^{-1}: 3049, 2964, 2917, 2851, 2229, 1629, 1588, 1576. HRMS (EI) m/z (M$^{\cdot}$) calcd for $C_{27}H_{30}N_2OS$ 430.2079, found 430.2092.

4.5. General procedure for the preparation of 8g–h

3-Piperidin-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile **3c** (0.2 mmol) and corresponding primary amines in CH_3CN (10 mL) were stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel. The products were separated with CH_2Cl_2/MeOH 20:1 (v/v) as a dark purple powder.

4.5.1. 3-Butylamino-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (8g). Yield 75%; mp>300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (br s, –N*H*–, 1H), 8.94 (d, 1H, J=7.6 Hz), 8.59 (d, 1H, J=7.2 Hz), 7.97 (d, 1H, J=8.8 Hz), 7.90 (t, 1H, J=7.8 Hz), 7.03 (d, 1H, J=9.2 Hz), 3.60–3.59 (br s, NHCH_2CH$_2$–, 2H), 1.75–1.71 (m, NHCH$_2$-CH_2CH$_2$, 2H), 1.47–1.43 (m, 2H, CH$_2$CH_2CH$_3$), 0.96 ppm (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.4, 155.8, 138.7, 132.4, 131.0, 129.6, 128.0, 127.0, 125.5, 122.0, 116.1, 114.3, 111.3, 108.1, 104.0, 43.4, 30.05, 19.7, 13.7 ppm; IR (KBr) cm^{-1}: 3284, 2217, 1619, 1562, 1529; ESI-MS: m/z=300, (M−H)$^-$. HRMS (EI) m/z calcd for $C_{19}H_{15}N_3O$ 301.1215, found 301.1223.

4.5.2. 3-*iso*-Propylamino-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (8h). Yield 78%; mp>300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (d, 1H, N*H*–, J=8.0 Hz), 9.04 (d, 1H, J=8.0 Hz), 8.56 (d, 1H, J=7.2 Hz),

7.94 (d, 1H, J=9.2 Hz), 7.88 (t, 1H, J=8.0 Hz), 7.05 (d, 1H, J=9.2 Hz), 4.28 (m, NHCH(CH_3)$_2$, 1H), 1.40–1.39 ppm (m, NHCH(CH_3)$_2$, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.3, 154.8, 138.6, 132.3, 131.3, 129.5, 128.0, 126.7, 125.4, 121.9, 115.9, 114.2, 111.1, 108.2, 103.9, 45.9, 21.3 ppm; IR (KBr) cm^{-1}: 3328, 2214, 1627, 1575, 1546. HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{18}H_{14}N_3O$ 288.1137, found 288.1139.

4.6. General procedure for the preparation of 9g–h

3,6-Di-piperidin-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile **5c** (0.2 mmol) and corresponding primary amines in CH_3CN (10 mL) were stirred for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel. The products were separated with CH_2Cl_2/CH_3COCH_3 60:1 (v/v) as a red powder.

4.6.1. 3-Piperidino-6-butylamino-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (9g). Yield 70%; mp 266.7–267.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.42 (br s, –N*H*–, 1H), 8.25 (d, 1H, J=9.6 Hz), 8.05 (d, 1H, J=8.8 Hz), 7.16 (d, 1H, J=8.8 Hz), 7.11 (d, 1H, J=9.6 Hz), 3.60–3.55 (m, NHCH_2, 2H), 3.48 (br s, 4H, NH(CH_2CH$_2$)$_2$-CH$_2$), 1.92 (br s, 4H, NH(CH$_2$CH_2)$_2$CH$_2$), 1.84–1.82 (m, 2H, NH(CH$_2$CH$_2$)$_2$CH_2), 1.79–1.76 (m, 2H, CH_2CH$_2$CH$_3$), 1.58–1.53 (m, 2H, CH_2CH$_3$), 1.01 ppm (t, 3H, CH_3, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 159.2, 157.2, 136.6, 133.1, 131.0, 123.6, 115.7, 115.3, 115.1, 114.3, 112.5, 112.0, 111.5, 110.7, 55.3, 43.3, 31.2, 26.3, 24.3, 20.5, 14.0 ppm; IR (KBr) cm^{-1}: 3441, 2934, 2857, 2217, 1617. HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{24}H_{25}N_4O$ 385.2028, found 385.2036.

4.6.2. 3-Piperidino-6-*iso*-propylamino-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile (9h). Yield 72%; mp 255 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.50 (d, –N*H*–, 1H, J=5.6 Hz), 8.19 (d, 1H, J=9.6 Hz), 8.02 (d, 1H, J=8.8 Hz), 7.13 (d, 1H, J=8.8 Hz), 7.11 (d, 1H, J=9.6 Hz), 4.13–4.14 (m, –NHCH(CH_3)$_2$, 1H), 3.46 (t, 4H, NH(CH_2CH$_2$)$_2$CH$_2$, J=4.2 Hz), 1.89 (br s, 4H, NH(CH$_2$-CH_2)$_2$CH$_2$), 1.77–1.78 (m, 2H, NH(CH$_2$CH$_2$)$_2$CH_2), 1.47 ppm (d, 6H, J=6.4 Hz); IR (KBr) cm^{-1}: 3390, 2934, 2857, 2217.91, 1617. HRMS (ESI) m/z $(M-H)^+$ calcd for $C_{23}H_{21}N_4O$ 369.1715, found 369.1722.

4.7. In vitro growth delay assays

Into 96-well microculture plates 100 μL of cell suspension was seeded and allowed to adhere for 24 h before compounds were added. Cells were exposed to compounds at concentrations from 100 to 1 μM for 72 h. The experiments were performed in triplicates. At the end of the exposure time, the medium was removed and 100 μL of MTT solution (0.4 mg MTT/mL in serum free medium) was added to each well. The plates were incubated at 37 °C for 4 h. Then the solution was removed and 150 μL DMSO was added to each well. After shaking for 4 min, the optical value was read by means of a GENios microplate reader (TECAN, Germany) at a wavelength of 550 nm.

Acknowledgements

This work was supported by the National Key Project for Basic Research (2003CB114400) and under the auspices of National Natural Science Fundation of China.

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Tetrahedron 61 (2005) 11270–11278

5-Hydroxy-3-phenyl-5-vinyl-2-isoxazoline and 3-phenyl-5-vinylisoxazole: synthesis and reactivity

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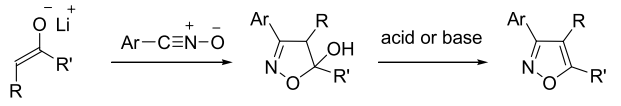
Received 30 May 2005; revised 4 August 2005; accepted 18 August 2005

Available online 29 September 2005

Abstract—5-Hydroxy-3-phenyl-5-vinyl-2-isoxazoline has been synthesized by reacting benzonitrile oxide with the enolate ion of methyl vinyl ketone. From 5-hydroxy-5-vinyl-2-isoxazoline, 5-vinylisoxazole was then quantitatively obtained by dehydration–aromatization under acidic conditions. Similar results, though not quantitative, were also found by treatment in 2-propanol under basic conditions (*i*-PrOH/H_2O, Na_2CO_3, reflux). In contrast to 2-propanol, reactions performed in methanol (and, in part, those carried out in ethanol) revealed a more complex behaviour, the nucleophilic addition of ROH onto the vinyl group being mainly observed. Nucleophilic addition was also found with alkyllithiums. The mechanism of the nucleophilic addition is discussed. Epoxidation and further reaction with benzonitrile oxide of both 3-hydroxy-5-phenyl-5-vinyl-2-isoxazoline and 3-phenyl-5-vinylisoxazole are also described.

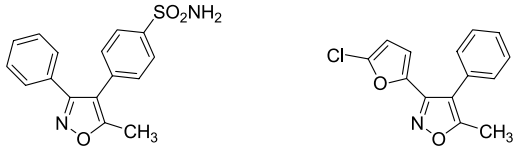
It is well-known that isoxazolines and isoxazoles are interesting heterocycles from both a synthetic and biological point of view.[1–3] As for the synthetic utility, they are masked forms of iminoalcohols and iminocarbonyls. The latter compounds, in fact, can readily and selectively be obtained by reductive cleavage of the N–O bond using various methods.[4]

The synthesis of both isoxazolines and isoxazoles by new and more efficient procedures has been the goal of a number of our previous investigations. Concerning the synthesis of 5-hydroxy-2-isoxazolines, we developed a new efficient methodology consisting in the cycloaddition of various enolate ions (including the enolate ion of acetaldehyde) with arylnitrile oxides.[5–7] From these, the corresponding isoxazoles were then obtained in high yields by simple dehydration–aromatization under acidic or basic conditions (Scheme 1). By this procedure various 3-aryl-(or 3,4-diaryl)-5-alkyl (or 5-unsubstituted) isoxazoles (**2a–c**) have been synthesized.



Scheme 1.

We found[8,9] that some of the above compounds (**2c**), as analogues of Valdecoxib (**3**, Fig. 1),[10] were endowed with cyclooxygenase inhibitory activity and that 3-(5-chloro-2-furyl)-5-methyl-4-phenylisoxazole (**4**, Fig. 1) tested in human whole blood (HWB) assay[11] was a selective and highly potent COX-1 inhibitor, which could represent an interesting tool in order to study the involvement of COX-1 in atherosclerosis,[12,13] pain[14] and cancer development.[15]



3 (valdecoxib) **4**

Figure 1.

Furthermore, concerning 3-aryl-5-alkylisoxazoles, the possibility of side-chain elongation by α-metallation followed by reaction with electrophiles (CH_3I, $PhCH_2Br$) has also been ascertained. Thus, by this procedure, a number of other isoxazole derivatives can be obtained.[6]

On the other hand, concerning the elongation (and/or

Keywords: Vinylisoxazolines; Vinylisoxazoles; Nucleophilic additions.
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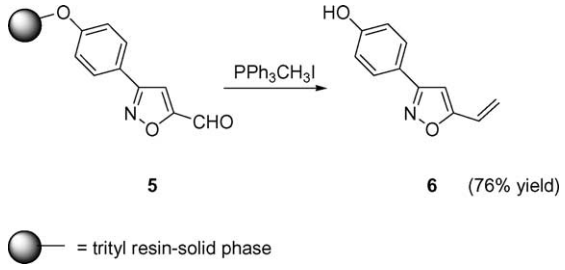
doi:10.1016/j.tet.2005.08.077

elaboration) of the C_5 side-chain in order to obtain more complex isoxazole derivatives, wider possibilities could in principle be expected starting from 5-vinyl- instead of 5-alkyl-derivatives. The vinyl group can be extended (or elaborated) at both the vinyl carbons, including the possibility of a further cyclization allowing the construction of an additional homo- or heterocyclic moiety.

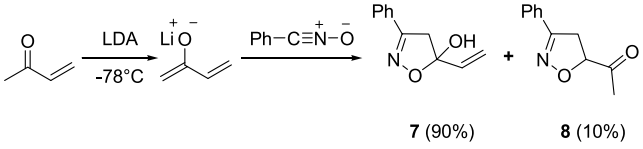
As for the synthesis of some 3-substituted-5-vinylisoxazoles, some procedures have so far been reported.[16,17] In particular, concerning a 3-aryl-derivative, namely 3-(4-hydroxyphenyl)-5-vinylisoxazole (**6**), the synthesis was accomplished by C_5 side-chain elaboration of 5-formyl isoxazole (Scheme 2). In this way **6** was obtained in 76% yield.[17]



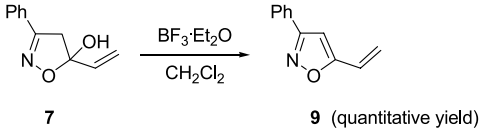
Scheme 2.

We explored, instead, the possibility of extending the same procedure successfully developed by us for 3-aryl-5-alkylisoxazoles to the synthesis of 5-vinyl-derivatives.

Thus, we reacted benzonitrile oxide with the enolate ion from methyl vinylketone and LDA (−78 °C), obtaining the expected 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (**7**) in high yield (90%) together with a little amount (10%) of 5-acetyl-3-phenyl-2-isoxazoline (**8**) deriving from the cycloaddition to the vinyl C=C bond (Scheme 3). In contrast, it is known that the latter is the only product if the same reaction is performed at room temperature and in the absence of LDA.[18] Subsequent dehydration of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (**7**) under acidic conditions ($BF_3 \cdot Et_2O$) gave quantitatively 3-phenyl-5-vinylisoxazole (**9**) (Scheme 4).



Scheme 3.



Scheme 4.

Dehydration of **7** in methanol under basic conditions (Na_2CO_3, $MeOH/H_2O$, reflux), previously successfully used for obtaining 3-aryl-5-alkylisoxazoles (**2b**) from 5-alkyl-3-aryl-5-hydroxy-2-isoxazolines (**1b**),[6] showed instead a more complex behaviour. Together with the expected 3-phenyl-5-vinylisoxazole (**9**), large amounts of the products of nucleophilic addition of MeOH to the vinyl group of both 5-hydroxy-5-vinyl-2-isoxazoline and 5-vinyl-isoxazole (**10a** and **11a**, respectively) were isolated (Scheme 5 and Table 1).

Table 1. Products of reaction of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (**7**) with ROH/Na_2CO_3 (Scheme 5)

ROH	Time (h)	**9** (%)[a]	**10** (%)[a]	**11** (%)[a]
MeOH	1	19	38 (**10a**)	43 (**11a**)
EtOH	2	65	—	24 (**11b**)
i-PrOH	2	48	—	—

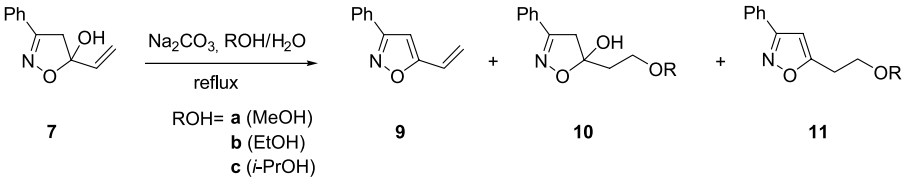
[a] Yields refer to the products actually isolated by chromatography.

A relative decrease of nucleophilic addition compared to dehydration was observed in ethanol. Only the dehydrated product of the nucleophilic addition (**11b**) was isolated in this case. No alcohol addition but only dehydration to vinylisoxazole **9** was finally observed using isopropanol as solvent.

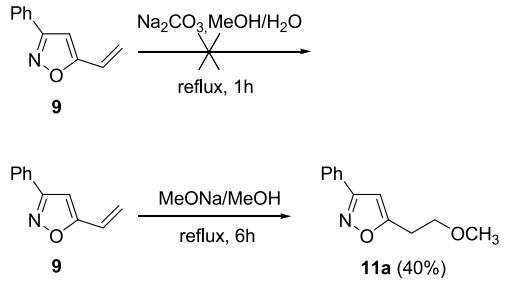
On the other hand, concerning the products of nucleophilic addition of MeOH, while compound **10a** should actually be formed from 5-hydroxy-5-vinyl-2-isoxazoline **7**, we could instead demonstrate that **11a** is not correspondingly formed from vinylisoxazole **9**. By directly reacting the latter with $MeOH/Na_2CO_3$ under the same conditions, no reaction at all is in fact observed. Partial addition of MeOH to 3-phenyl-5-vinylisoxazole **9** could be obtained only by using sodium methoxide in methanol and more prolonged times of reaction (Scheme 6).

Thus, by excluding the direct involvement of 3-phenyl-5-vinylisoxazole (**9**), the alternative possibility is that **11a** is formed by partial dehydration–aromatization of **10a**, so that the alcohol addition should only concern hydroxyisoxazoline **7** in all cases (Scheme 7).

On the other hand, concerning the mechanism of the alcohol addition to 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline, the possible pathways are depicted in Scheme 8.



Scheme 5.



Scheme 6.

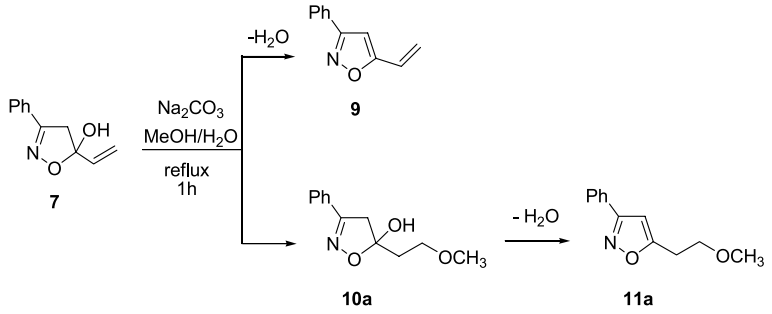
Path 1, i.e., direct nucleophilic addition to hydroxyisoxazoline anion **12** (or to alcohol **7**) should involve ring-opening in order to satisfactorily delocalize the negative charge introduced by the nucleophile.

On the other hand, ring-opening of hydroxyisoxazoline can also occur spontaneously and rapidly (ring-chain tautomerism),[19] in hydroxylic solvents. This also means, in our case, fast equilibration with little amounts of α,β-unsaturated ketone **13**. So, taking into account the well-known ability of conjugated enones to undergo nucleophilic additions by alcohols,[20] Path 2 is also possible. According to this hypothesis, the products of sole conjugate addition B (in part or completely converted into the corresponding isoxazoles by subsequent dehydration–aromatization) are, as expected for alcohol additions, the only isolated adducts.

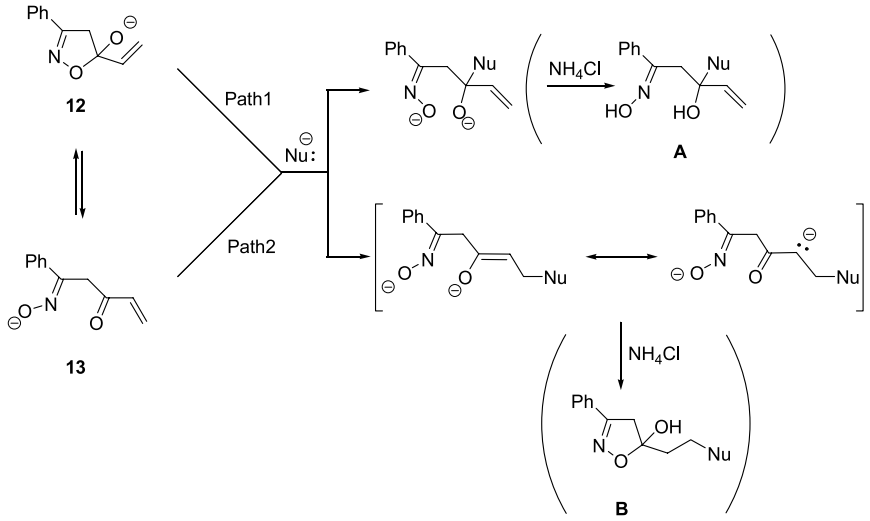
As for the apparent order of reactivity of alcohols (MeOH > EtOH; no addition but only dehydration–aromatization to vinylisoxazole in the case of *i*-PrOH), which is opposite compared to the known reactivity sequence of alcoholates with enones (i-$PrO^- > MeO^-$),[19] it should not be in contrast with the above hypothesis. Taking into account the used conditions (ROH/Na_2CO_3), and as also previously reported for alcohol addition to enones under competitive conditions,[20] the order of reactivity could in fact just be determined in our case by the alcohol acidity instead of the alcoholate nucleophilicity.

On the other hand, unlike reactions with alcohols, Path 1 seems instead more reasonable in reactions of the hydroxyvinylisoxazoline with alkyllithiums (MeLi, *n*-BuLi).

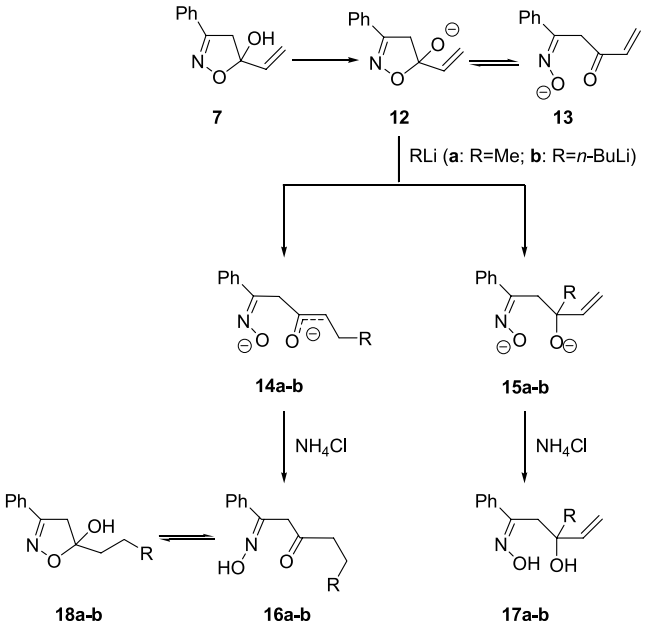
In this case, due to the used aprotic solvents, the rate of ring-chain equilibration should in fact be low compared to reactions with ROH, thus making more difficult the alternative Path 2. Further, both products A and B (**17** and **18**, respectively, the latter no further converted into the corresponding isoxazole, as the dehydration–aromatization of hydroxyisoxazolines is made difficult in the presence of strong bases),[5] are isolated (Scheme 9), B being also the major product in the case of *n*-BuLi (Table 2). And this could in fact just be consistent with Path 1, while should be a rather unusual result if Path 2 was involved, as it is known



Scheme 7.



Scheme 8.



Scheme 9.

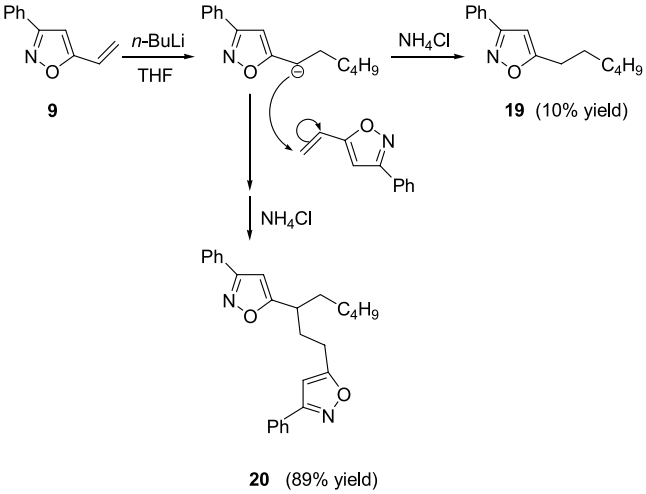
that alkyllithiums generally add to conjugated enones directly[21] (addition to the carbonyl carbon with formation of product A).

On the other hand, at variance with Na_2CO_3/MeOH (or even MeO^-/MeOH), alkyllithiums are able to completely react also with 5-vinylisoxazole **9**. The main isolated product under these conditions (reaction with *n*-BuLi) is not, however, **19**, corresponding to the 'simple' nucleophilic addition to the vinyl group, but **20**, involving also a second molecule of vinylisoxazole (Scheme 10). Further investigations are in progress on this point.

Table 2. Products of reaction of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (**7**) with RLi (Scheme 9)

RLi	**17a–b** (%)[a]	**18a–b** (%)[a]
MeLi	75	23
n-BuLi	29	65

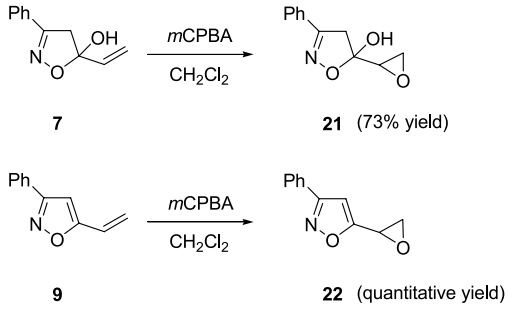
[a] Yields refer to the products actually isolated by chromatography.



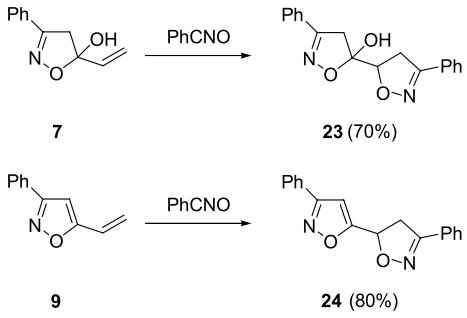
Scheme 10.

Finally, unlike the reactions with nucleophiles, a more similar behaviour could instead be expected by subjecting both vinylhydroxyisoxazoline **7** and vinylisoxazole **9** to reactions at the vinyl group not directly involving the adjacent ring.

Accordingly, not very different results were observed both in the epoxidation reaction with *m*-CPBA (Scheme 11) and in the reaction with benzonitrile oxide generating an additional isoxazoline ring (Scheme 12).



Scheme 11.



Scheme 12.

For either epoxidation by *m*-CPBA[22] or cycloaddition of nitrile oxides[2] a concerted mechanism should in fact operate (concerning the latter reaction a stepwise mechanism has only been hypothesized in the case of species like enolate ions),[5] so that both reactions, just as expected, seem to proceed similarly for hydroxyvinylisoxazoline **7** as well as for isoxazole **9**.

Further investigations aimed to the synthetic exploitation of compounds **21**–**24** (Schemes 11 and 12) are in progress.

2. Experimental

2.1. General methods

Melting points taken on Electrothermal apparatus were uncorrected. ^{1}H NMR spectra were recorded on a Varian-Mercury 300 MHz spectrometer and chemical shifts are reported in parts per million (δ). Absolute values of the coupling constant are reported. FT-IR spectra were recorded on a Perkin–Elmer 681 spectrometer. GC analyses were

performed by using a HP1 column (methyl siloxane; 30 m × 0.32 mm × 0.25 μm film thickness) on a HP 6890 model, Series II. Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator, the spots on the TLC were observed under ultraviolet light or were visualized by I_2 vapour. Chromatography was conducted by using silica gel 60 with a particle size distribution 40–63 μm and 230–400 ASTM. GC–MS analyses were performed on an HP 5995C model and microanalyses on an Elemental Analyzer 1106-Carlo Erba-instrument. MS-ESI analyses were performed on an Agilent 1100 LC/MSD trap system VL.

2.2. Materials

Commercially available tetrahydrofuran (THF) was distilled (twice) from sodium wire under nitrogen. Standardized 1.6 M methyllithium in diethyl ether and 2.5 M *n*-butyllithium in hexane was purchased from Aldrich Chemical Co. Titration of *n*-butyllithium was performed by using *N*-pivaloyl-*o*-toluidine.[23] Methyl vinyl ketone was dried over molecular sieves (4 Å) just prior to use. Benzonitrile oxide was prepared by treatment of benzohydroximinoyl chloride with Et_3N.[5] All other chemicals and solvents were commercial grade further purified prior to use.

2.3. Synthesis of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (7)

A 2.25 M solution of *n*-butyllithium in hexane (15.8 mL, 35.48 mmol) was dropwise added to diisopropylamine (5 mL, 35.48 mmol) in THF (30 mL) at 0 °C under nitrogen atmosphere, using a nitrogen-flushed three necked flask equipped with a magnetic stirrer, nitrogen inlet and two dropping funnels. The mixture was stirred for 15 min at 0 °C and then cooled to −78 °C. To LDA so formed, the methyl vinyl ketone (2.95 mL, 35.48 mmol) in THF (80 mL) was dropwise added. The reaction mixture was stirred at −78 °C for 1 h and then the benzonitrile oxide (32.25 mmol) in THF (80 mL) was added. The reaction mixture was stirred at −78 °C for 1 h and then quenched by adding aqueous NH_4Cl solution. The reaction products were extracted three times with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. ^1H NMR of the crude mixture contained the products **7** and **8** in the ratio 90:10. Column chromatography (silica gel, petroleum ether/ethyl acetate = 8:2) of the residue affords the 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (**7**) in 74% yield (Table 1), and 10% of 5-acetyl-3-phenyl-2-isoxazoline (**8**).[18]

2.3.1. 5-Hydroxy-3-phenyl-5-vinyl-2-isoxazoline (7). Yield 74% (4.5 g). Mp 88–89 °C (ethyl ether/hexane), white crystals. FT-IR (KBr): 3600–3200, 3060, 2955, 2918, 2849, 1560, 1446, 1359, 1235, 1104, 919, 761, 691 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 3.33 (d, 1H, J = 17.3 Hz); 3.40 (d, 1H, J = 17.3 Hz); 3.50–3.60 (br s, 1H, OH: exchanges with D_2O); 5.37 (dd, 1H, J = 0.8, 10.7 Hz); 5.67 (dd, 1H, J = 0.8, 17.3 Hz); 6.16 (dd, 1H, J = 17.3, 10.7 Hz); 7.35–7.44 (m, 3H, aromatic protons); 7.61–7.69 (m, 2H, aromatic protons). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 46.5, 106.5, 117.9, 127.0, 129.0, 129.4, 130.6, 136.5, 157.7. GC–MS (70 eV) *m*/*z* (rel int.): 189 (M^+, 24), 188 (23), 172 (39), 171 (33), 144 (44), 143 (12), 117 (49), 116 (11), 103 (23), 77 (62), 55 (100), 51 (22). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.80; H, 5.84; N, 7.42.

2.4. Synthesis of 3-phenyl-5-vinylisoxazole (9)

To a solution of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (**7**) (3.86 g, 20.43 mmol) in freshly distilled CH_2Cl_2 (100 mL) kept at room temperature, $BF_3 \cdot Et_2O$ (2.6 mL, 20.43 mmol) was added. The reaction mixture was stirred for 1 h and then quenched by adding water. The reaction product was extracted three times with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure.

2.4.1. 3-Phenyl-5-vinylisoxazole (9). The title compound was obtained in quantitative yield (3.5 g) by crystallization (hexane). Mp 39–40 °C (hexane, lit.[13] 37–38 °C), white crystals. FT-IR (KBr): 3029, 2917, 2849, 1560, 1466, 1443, 1404, 1278, 926, 767, 692 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 5.59 (dd, 1H, J = 0.8, 11.4 Hz); 6.06 (dd, 1H, J = 0.8, 17.7 Hz); 6.51 (s, 1H); 6.66 (dd, 1H, J = 17.7, 11.4 Hz); 7.43–7.48 (m, 3H, aromatic protons); 7.79–7.85 (m, 2H, aromatic protons). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 99.7, 120.9, 122.6, 127.0, 129.1, 130.2, 162.9, 169.0. GC–MS (70 eV) *m*/*z* (rel int.): 171 (M^+, 95), 145 (10), 144 (100), 143 (35), 117 (29), 116 (22), 115 (11), 89 (14), 77 (47), 63 (11), 55 (34), 51 (22). Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.20; H, 5.29; N, 8.20.

2.5. Reaction of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (7) with Na_2CO_3 in MeOH/H_2O

A solution of Na_2CO_3 (155 mg, 1.46 mmol) in water (10 mL) was added to 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline **7** (138 mg, 0.73 mmol) in MeOH (10 mL) contained in a round bottom flask equipped with magnetic stirrer. The reaction mixture was then refluxed for 1 h. The MeOH was evaporated under reduced pressure and aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate = 8:2) of the residue affords 5-(2-methoxyethyl)-3-phenylisoxazole (**11a**) in 43% yield (Scheme 3), 5-hydroxy-5-(2-methoxyethyl)-3-phenyl-2-isoxazoline (**10a**) in 38% yield and 3-phenyl-5-vinylisoxazole (**9**) in 19% yield.

2.5.1. 5-Hydroxy-5-(2-methoxyethyl)-3-phenyl-2-isoxazoline (10a). Yield 38% (61 mg). Oil. FT-IR (KBr): 3600–3150, 3030, 2924, 2853, 1620, 1447, 1361, 1208, 1114, 916, 853, 761, 693 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.02–2.09 (m, 1H); 2.40–2.50 (m, 1H); 3.23 (d, 1H, J = 17.3 Hz, isoxazoline ring proton); 3.34 (d, 1H, J = 17.3 Hz, isoxazoline ring proton); 3.43 (s, 3H); 3.65–3.70 (m, 1H); 3.99–4.06 (m, 1H); 5.35 (s, 1H, OH: exchanges with D_2O); 7.35–7.50 (m, 3H, aromatic protons); 7.63–7.68 (m, 2H, aromatic protons). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 37.6, 46.3, 59.4, 69.6, 108.5, 126.8, 128.9, 129.9, 130.3, 157.6. GC–MS (70 eV) *m*/*z* (rel int.): 221 (M^+, 5), 204 (17), 203 (65), 189 (4), 173 (9), 162 (13), 144 (12), 135 (17), 134 (13), 117 (38), 103 (28), 87 (20), 77 (40), 51 (14), 45 (100). Anal. Calcd for

$C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.15; H, 6.83; N, 6.32.

2.5.2. 5-(2-Methoxyethyl)-3-phenylisoxazole (11a). Yield 43% (63 mg). Oil. FT-IR (KBr): 3127, 3053, 2927, 1603, 1580, 1471, 1443, 1408, 1117, 914, 769, 694 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 3.07 (t, 2H, $J=6.4$ Hz); 3.39 (s, 3H); 3.73 (t, 2H, $J=6.4$ Hz); 6.40 (s, 1H); 7.40–7.48 (m, 3H, aromatic protons); 7.76–7.84 (m, 2H, aromatic protons). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 27.9, 59.0, 69.8, 100.2, 127.0, 129.1, 129.5, 130.1, 162.7, 171.3. GC–MS (70 eV) *m/z* (rel int.): 203 (M^+, 100), 173 (21), 144 (24), 130 (7), 118 (9), 116 (9), 103 (5), 89 (10), 77 (30), 63 (5), 51 (12), 45 (92). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.92; H, 6.44; N, 6.90.

2.6. Reaction of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (7) with Na_2CO_3 in EtOH/H_2O

A solution of Na_2CO_3 (861 mg, 8.12 mmol) in water (80 mL) was added to 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline **7** (769 mg, 4.06 mmol) in EtOH (80 mL) contained in a round bottom flask equipped with a magnetic stirrer. The reaction mixture was then refluxed for 2 h. The EtOH was evaporated under reduced pressure and aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate = 7:3) of the residue affords 3-phenyl-5-vinylisoxazole **9** in 65% yield and 5-(2-ethoxyethyl)-3-phenylisoxazole **11b** in 24% yield (Table 1).

2.6.1. 5-(2-Ethoxyethyl)-3-phenylisoxazole (11b). Yield 24% (211 mg). Oil. FT-IR (KBr): 3029, 2925, 1603, 1580, 1481, 1443, 1407, 1113, 770, 694 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, δ): 1.20 (t, 3H, $J=7.0$ Hz); 3.07 (t, 2H, $J=6.5$ Hz); 3.53 (q, 2H, $J=7.0$ Hz); 3.77 (t, 2H, $J=6.5$ Hz); 6.39 (s, 1H); 7.41–7.46 (m, 3H, aromatic protons); 7.76–7.81 (m, 2H, aromatic protons). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 15.3, 28.0, 66.7, 67.7, 100.1, 127.0, 129.1, 130.0, 162.7, 171.5. GC–MS (70 eV) *m/z* (rel int.): 217 (M^+, 66), 187 (15), 159 (11), 144 (21), 130 (18), 117 (11), 116 (10), 104 (15), 103 (12), 89 (10), 77 (35), 59 (100), 51 (14). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.85; H, 6.95; N, 6.42.

2.7. Reaction of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline with Na_2CO_3 in *i*-PrOH/H_2O

A solution of Na_2CO_3 (482 mg, 4.55 mmol) in water (20 mL) was added to 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (**7**) (430 mg, 2.27 mmol) in *i*-PrOH (20 mL) contained in a round bottom flask equipped with a magnetic stirrer. The reaction mixture was then refluxed for 2 h. The *i*-PrOH was evaporated under reduced pressure and aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate = 7:3) of the residue afforded 3-phenyl-5-vinylisoxazole (**9**) in 48% yield (Table 1).

2.8. Reaction of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (7) with MeLi

A 1.6 M solution of MeLi in ethyl ether (5.786 mL, 9.26 mmol) was added to a solution of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (**7**) (350 mg, 1.852 mmol) in THF (18 mL) kept at 0 °C under nitrogen, using a nitrogen-flushed two necked flask equipped with a magnetic stirrer and a nitrogen inlet. The obtained red reaction mixture was stirred for 3 h at 0 °C before to add aq NH_4Cl. The two phases were separated and aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate = 7:3) of the residue afforded 5-hydroxy-3-phenyl-5-propyl-2-isoxazoline (**18a**)[6] in 23% yield and 3-hydroxy-3-methyl-1-phenylpent-4-en-1-one oxime (**17a**) in 75% yield (Scheme 6 and Table 1).

2.8.1. 3-Hydroxy-3-methyl-1-phenylpent-4-en-1-one oxime (17a). Yield 75% (284 mg). Yellow oil. FT-IR ($CHCl_3$, 0.09 M): 3693, 3579, 3500–3100, 3028, 2969, 2932, 2876, 1602, 1448, 1361, 1111, 994, 944, 910 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 1.27 (s, 3H); 3.00–3.20 (br s, 1H, OH: exchanges with D_2O); 3.17 (s, 2H); 4.95 (dd, 1H, $J=10.6$, 1.2 Hz); 5.25 (dd, 1H, $J=17.2$, 1.2 Hz); 5.87 (dd, 1H, $J=10.6$, 17.2 Hz); 7.30–7.60 (br s, 1H, OH: exchanges with D_2O); 7.35–7.41 (m, 3H, aromatic protons); 7.54–7.59 (m, 2H, aromatic protons). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 28.1, 39.0, 73.9, 112.1, 127.0, 128.8, 129.7, 136.9, 144.6, 157.9. GC–MS (70 eV) *m/z* (rel int.): 205 (M^+, 4), 189 (16), 188 (100), 171 (20), 170 (16), 169 (10), 160 (20), 148 (39), 146 (20), 144 (25), 135 (15), 134 (25), 130 (57), 129 (17), 117 (23), 115 (14), 106 (19), 104 (38), 103 (38), 91 (20), 78 (10), 77 (60), 51 (17), 43 (48). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.21; H, 7.35; N, 6.80.

2.9. Reaction of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline with *n*-BuLi

A 2.1 M solution of *n*-BuLi in hexane (3.16 mL, 6.613 mmol) was added to a solution of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (**7**) (500 mg, 2.645 mmol) in THF (26 mL) kept at 0 °C under nitrogen, using a nitrogen-flushed two necked flask equipped with a magnetic stirrer and a nitrogen inlet. The obtained red reaction mixture was stirred for 1 h at 0 °C before to add aq NH_4Cl. The two phases were separated and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and then the solvent was evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate = 7:3) of the residue afforded 5-hexyl-5-hydroxy-3-phenylisoxazoline (**18b**) in 64% yield and 3-hydroxy-1-phenyl-3-vinylheptan-1-one oxime (**17b**) in 29% yield (Scheme 6 and Table 1).

2.9.1. 5-Hexyl-5-hydroxy-3-phenylisoxazoline (18b). Yield 64% (418 mg). Colourless oil. FT-IR (neat): 3600–3200, 3061, 2955, 2928, 2859, 1599, 1568, 1498, 1466, 1447, 1361, 1234, 1075, 919, 759, 692 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.89 (t, 3H, $J=6.4$ Hz); 1.30–1.59 (m, 8H);

1.90–2.03 (m, 2H); 2.85–3.00 (br s, 1H, OH: exchanges with D_2O); 3.27 (s, 2H); 7.36–7.45 (m, 3H, aromatic protons); 7.62–7.68 (m, 2H, aromatic protons). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.3, 22.7, 24.9, 29.5, 31.9, 38.6, 44.7, 109.1, 126.9, 128.9, 129.8, 130.5, 157.6. GC–MS (70 eV) *m/z* (rel int.): 247 (M^+, 14), 231 (11), 230 (56), 229 (29), 186 (10), 172 (23), 162 (10), 159 (21), 146 (15), 144 (39), 135 (68), 134 (22), 118 (18), 117 (100), 113 (46), 104 (12), 103 (25), 85 (24), 77 (55), 57 (14), 55 (14), 51 (13), 43 (63), 41 (20). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.85; H, 8.55; N, 5.62.

2.9.2. 3-Hydroxy-1-phenyl-3-vinylheptan-1-one oxime (17b). It was not isolated as a pure compound, but mixed with 5-hexyl-5-hydroxy-3-phenylisoxazoline (**18b**) in the ratio 65:35. 29% yield (189 mg). Yellow oil. ^1H NMR ($CDCl_3$, δ): 0.81 (t, 3H, $J=6.5$ Hz); 1.10–1.63 (m, 6H); 3.00–3.30 (br s, 1H, OH: exchanges with D_2O); 3.08 (d, 1H, $J=13.4$ Hz); 3.22 (d, 1H, $J=13.4$ Hz); 4.96 (dd, 1H, $J=10.7$, 1.5 Hz); 5.22 (dd, 1H, $J=17.1$, 1.5 Hz); 5.71 (dd, 1H, $J=10.7$, 17.1 Hz); 7.30–7.45 (m, 3H, aromatic protons); 7.48–7.60 (m, 2H, aromatic protons); 8.60–9.30 (br s, 1H, OH: exchanges with D_2O). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.3, 23.2, 25.9, 38.3, 41.9, 76.3, 113.0, 127.1, 128.7, 129.0, 129.6, 137.0, 143.1, 158.4. LC–MS (ESI^+) *m/z*: 270.1 (45) $[M+Na]^+$.

2.10. Reaction of 3-phenyl-5-vinylisoxazole with *n*-BuLi

A 2.10 M solution of *n*-butyllithium in hexane (1.873 mL, 3.933 mmol) was added to 3-phenyl-5-vinylisoxazole (0.269 g, 1.573 mmol) in THF (13 mL) kept at −78 °C under nitrogen, using a nitrogen-flushed two necked flask equipped with a magnetic stirrer and a nitrogen inlet. The obtained red reaction mixture was stirred for 2 h at −78 °C before to add aq NH_4Cl. The two phases were separated and aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and then the solvent was evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate = 8:2) of the residue afforded 3-phenyl-5-(3-(3-phenylisoxazol-5-yl)octyl)isoxazole (**20**) in 89% yield and 5-hexyl-3-phenylisoxazole (**19**) in 10% yield.

2.10.1. 5-Hexyl-3-phenylisoxazole (19). Yield 10% (36 mg). Oil. FT-IR (neat): 3127, 3053, 2930, 2859, 1602, 1580, 1471, 1443, 1408, 1378, 1079, 950, 916, 767, 693 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.90 (t, 3H, $J=7.0$ Hz); 1.24–1.45 (m, 6H); 1.74 (quintet, 2H, $J=7.3$ Hz); 2.79 (t, 2H, $J=7.3$ Hz); 6.28 (s, 1H); 7.40–7.47 (m, 3H, aromatic protons); 7.76–7.82 (m, 2H, aromatic protons). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.3, 22.7, 27.0, 27.7, 29.0, 31.6, 99.0, 127.0, 129.1, 129.7, 130.0, 162.5, 174.5. GC–MS (70 eV) *m/z* (rel int.): 229 (M^+, 62), 200 (6), 186 (23), 173 (10), 172 (48), 159 (42), 158 (13), 145 (13), 144 (74), 130 (9), 118 (14), 117 (100), 116 (16), 104 (10), 89 (12), 77 (39), 68 (9), 55 (9), 51 (10), 43 (11), 41 (12). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.55; H, 8.32; N, 6.09.

2.10.2. 3-Phenyl-5-(3-(3-phenylisoxazol-5-yl)octyl)isoxazole (20). Yield 89% (280 mg). Oil. FT-IR (KBr): 3113, 3030, 2925, 2856, 1599, 1577, 1470, 1443, 1409, 1380, 1081, 951, 907, 771, 692 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.86 (t, 3H, $J=6.2$ Hz); 1.23–1.38 (m, 6H); 1.67–1.79 (m, 2H); 2.13–2.21 (m, 2H); 2.70–2.85 (m, 2H); 2.94–3.04 (m, 1H); 6.28 (s, 1H); 6.34 (s, 1H); 7.40–7.48 (m, 6H, aromatic protons); 7.73–7.81 (m, 4H, aromatic protons). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.2, 22.7, 24.9, 27.0, 31.8, 32.1, 34.2, 38.0, 99.4, 99.5, 127.0, 129.1, 129.4, 130.1, 162.6, 173.1, 176.1. GC–MS (70 eV) *m/z* (rel int.): 400 (M^+, 14), 330 (4), 243 (18), 242 (100), 240 (12), 229 (15), 200 (6), 186 (8), 173 (9), 172 (49), 159 (30), 144 (34), 130 (6), 117 (32), 116 (11), 104 (8), 89 (7), 77 (27), 55 (12). Anal. Calcd for $C_{26}H_{28}N_2O_2$: C, 77.97; H, 7.05; N, 6.99. Found: C, 78.00; H, 7.02; N, 7.01.

2.11. Reaction of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline with *m*-CPBA

m-CPBA (70%, 1.546 g, 6.275 mmol) was added to a solution of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (**7**) (475 mg, 2.51 mmol) in anhydrous CH_2Cl_2 (24 mL) contained in a round bottom flask equipped with a magnetic stirrer. The mixture was stirred for 24 h at room temperature before to add 10% aq K_2CO_3. The two phases were separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and then, the solvent was evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate = 8:2) of the yellow solid crude afforded 73% yield of 5-hydroxy-5-(oxiran-2-yl)-3-phenyl-2-isoxazoline (**21**), 10% yield of 3-phenyl-5-vinylisoxazole (**9**) and 10% yield of 5-(oxiran-2-yl)-3-phenyl-isoxazole (**22**).

2.11.1. 5-Hydroxy-5-(oxiran-2-yl)-3-phenyl-2-isoxazoline (21). Diastereoisomeric ratio = 64:36 (determined by ^1H NMR). 73% yield (375 mg). Mp 58–61 °C, white solid. FT-IR (KBr): 3600–3200, 3062, 2925, 2852, 1601, 1569, 1527, 1498, 1447, 1417, 1362, 1264, 1218, 1093, 906, 858, 761, 691 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.83 (dd, 1H, $J=2.7$, 5.1 Hz, oxiranyl proton of the major diastereoisomer); 2.88 (dd, 1H, $J=4.0$, 5.1 Hz, oxiranyl proton of the major diastereoisomer); 2.90–2.95 (m, 2H, oxiranyl protons of the minor diastereoisomer); 3.22–3.48 (m, 6H, isoxazoline ring CH_2 and oxiranyl CH of both diastereoisomers); 3.56–3.74 (br s, 2H, OH: exchange with D_2O, 1H for each diastereoisomer); 7.35–7.44 (m, 6H, aromatic protons of both diastereoisomers), 7.62–7.68 (m, 4H, aromatic protons of both diastereoisomers). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 43.0 (minor diastereoisomer), 43.8 (major diastereoisomer), 44.3 (major diastereoisomer), 45.2 (minor diastereoisomer), 53.0 (major diastereoisomer), 53.1 (minor diastereoisomer), 104.9 (major diastereoisomer), 106.7 (minor diastereoisomer), 127.0, 129.0, 129.1, 130.7, 157.1 (major diastereoisomer), 157.7 (minor diastereoisomer). GC–MS (70 eV) *m/z* (rel int.): 205 (M^+, 46), 188 (11), 162 (49), 144 (14), 134 (12), 120 (29), 118 (13), 117 (70), 104 (27), 103 (66), 91 (20), 78 (11), 77 (100), 76 (13), 63 (8), 51 (25), 43 (16). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.40; H, 5.44; N, 6.82.

2.12. Reaction of 3-phenyl-5-vinylisoxazole (9) with *m*-CPBA

m-CPBA (70%, 0.995 g, 4.035 mmol) was added to a solution of 3-phenyl-5-vinylisoxazole **9** (276 mg,

1.614 mmol) in anhydrous CH_2Cl_2 (20 mL) contained in a round bottom flask equipped with a magnetic stirrer. The reaction mixture was stirred for 24 h at room temperature before to add 10% aq K_2CO_3. The two phases were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and then the solvent was evaporated under reduced pressure. The reaction was quantitative. The 5-(oxiran-2-yl)-3-phenylisoxazole (**22**) was obtained in 80% yield after crystallization (hexane).

2.12.1. 5-(Oxiran-2-yl)-3-phenyl-isoxazole (22). Yield 80% (241 mg). Mp 64–65 °C (hexane), white crystals. FT-IR (KBr): 3114, 2918, 2850, 1616, 1582, 1475, 1446, 1408, 1361, 1293, 1242, 1186, 1140, 1003, 952, 923, 864, 834, 822, 767, 694 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, δ): 3.20 (dd, 1H, $J=2.6$, 5.5 Hz); 3.25 (dd, 1H, $J=3.8$, 5.5 Hz); 4.05 (ddd, 1H, $J=0.3$, 2.6, 3.8 Hz); 6.57 (d, 1H, $J=0.3$ Hz); 7.41–7.49 (m, 3H, aromatic protons); 7.74–7.85 (m, 2H, aromatic protons). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 45.1, 49.2, 100.8, 127.0, 128.8, 129.2, 130.4, 162.8, 169.3. GC–MS (70 eV) *m/z* (rel int.): 187 (M^+, 62), 171 (5), 158 (14), 145 (11), 144 (100), 130 (14), 128 (12), 127 (26), 126 (8), 116 (26), 103 (36), 89 (11), 77 (61), 63 (8), 51 (22). Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.60; H, 4.84; N, 7.46.

2.13. Reaction of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline with benzonitrile oxide

A solution of benzonitrile oxide (0.634 mmol) in anhydrous THF (5 mL) was dropwise added to a solution of 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (**7**) (100 mg, 0.529 mmol) in anhydrous THF (24 mL) contained in a round bottom flask equipped with a magnetic stirrer. The reaction mixture was stirred for 3 h at room temperature before to add satd aq NH_4Cl. The two phases were separated and the aqueous layer was extracted three times with AcOEt. The combined organic extracts were dried over anhydrous Na_2SO_4 and then the solvent was evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate = 8:2) of the residue afforded 5-hydroxy-3-phenyl-5-(3-phenyl-2-isoxazolin-5-yl)-2-isoxazoline (**23**) in 70% yield.

2.13.1. 5-Hydroxy-3-phenyl-5-(3-phenyl-2-isoxazolin-5-yl)-2-isoxazoline (23). Yield 70% (114 mg, mixture of the two diastereoisomers, dr = 1:1). Mp 194–197 °C (EtOH), white crystals. FT-IR (KBr): 3574, 3426 (strong broad band), 3050, 2987, 2925, 2853, 1598, 1569, 1497, 1447, 1360, 1253, 1219, 1103, 891, 811, 755, 688 cm^{-1}. ^1H NMR (acetone-d_6, δ): 2.92 (s, 1H, OH: exchanges with D_2O, one diastereoisomer); 3.35 (dd, 1H, $J=6.7$, 17.8 Hz, one diastereoisomer); 3.50–3.73 (m, 7H, three protons of one diastereoisomer and four of the other diastereoisomer); 5.02–5.09 (m, 2H, one proton for each diastereoisomer); 6.30 (d, 1H, $J=8.8$ Hz, OH: exchanges with D_2O, the other diastereoisomer); 7.40–7.48 (m, 12H, aromatic protons, both diastereoisomers); 7.68–7.77 (m, 8H, aromatic protons, both diastereoisomers). ^{13}C NMR (75 MHz, CD_3OD, δ): 36.1 (one diastereoisomer), 36.9 (the other diastereoisomer), 41.3 (one diastereoisomer), 42.4 (the other diastereoisomer), 82.07 (one diastereoisomer), 82.13 (the other diastereoisomer), 107.9 (one diastereoisomer), 108.3 (the other diastereoisomer), 126.5, 126.68, 126.73, 128.7, 129.2, 129.3, 129.6, 130.3, 157.4 (one diastereoisomer), 157.5 (the other diastereoisomer), 157.6, 157.7. LC–MS (ESI^+) *m/z*: 331.2 (100) $[M+Na]^+$. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.15; H, 5.24; N, 9.01.

2.14. Reaction of 3-phenyl-5-vinylisoxazole with benzonitrile oxide

A solution of benzonitrile oxide (1.683 mmol) in anhydrous THF (10 mL) was dropwise added to a solution of 3-phenyl-5-vinylisoxazole **9** (240 mg, 1.403 mmol) in anhydrous THF (10 mL) contained in a round bottom flask equipped with a magnetic stirrer. The reaction mixture was stirred for 3 h at room temperature before a satd aq NH_4Cl was added. The two phases were separated and the aqueous layer was extracted three times with AcOEt. The combined organic extracts were dried over anhydrous Na_2SO_4 and then the solvent was evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate = 8:2) of the residue afforded 3-phenyl-5-(3-phenyl-2-isoxazolin-5-yl)isoxazole (**24**) in 80% yield after crystallization (EtOH).

2.14.1. 3-Phenyl-5-(3-phenyl-2-isoxazolin-5-yl)isoxazole (24). Yield 80% (325 mg). Mp 110–112 °C (lit.[24] 108–109 °C), white crystals. FT-IR (KBr): 3122, 3049, 2979, 2915, 2894, 1614, 1473, 1446, 1406, 1362, 1164, 1084, 1007, 921, 887, 757, 691 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, δ): 3.67 (dd, 1H, $J=7.0$, 16.7 Hz); 3.80 (dd, 1H, $J=10.8$, 16.7 Hz); 5.88 (ddd, 1H, $J=0.6$, 7.0, 10.8 Hz); 6.68 (d, 1H, $J=0.6$ Hz); 7.40–7.48 (m, 6H, aromatic protons); 7.66–7.72 (m, 2H, aromatic protons); 7.75–7.81 (m, 2H, aromatic protons). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 40.4, 74.5, 100.7, 127.1, 127.2, 128.8, 129.1, 129.2, 130.4, 130.9, 156.6, 162.8, 170.9. GC–MS (70 eV) *m/z* (rel int.): 290 (M^+, 100), 260 (17), 171 (25), 145 (10), 144 (78), 143 (20), 117 (12), 116 (12), 103 (7), 89 (9), 77 (44), 63 (5), 51 (14). Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.50; H, 4.85; N, 9.62.

Acknowledgements

Work carried out under the framework of the National Projects 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni' supported by the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, Rome), 'Progetto Strategico BS2—PREVENZIONE, DIAGNOSTICA PRECOCE E CONTROLLO DELLA MALATTIA NEOPLASTICA' supported by the Ministero della Salute (MinSan, Rome), and by the University of Bari and Istituto di Chimica dei Composti OrganoMetallici (ICCOM-CNR, Bari).

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Synthesis and gelation properties of a new class of α-amino acid-based sector block dendrons

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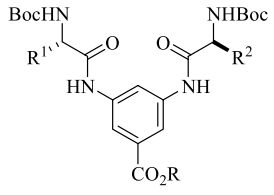
Received 7 June 2005; revised 1 August 2005; accepted 2 August 2005

Available online 10 October 2005

Abstract—A new series of α-amino acid-based sector block dendrons containing alanine, phenylalanine, and valine dendritic sectors was prepared by a solution phase peptide coupling methodology. The structures of the dendrons were fully characterized by nuclear magnetic resonance and mass spectroscopy and by optical polarimetry, and their purities were determined by size exclusion chromatography. Some of the dendrons, especially those containing phenylalanine residues, were found to form strong physical gels with aromatic solvents. The gelation mechanism was further investigated by infra-red and circular dichroism spectroscopy. It was found that both inter-molecular hydrogen bonding and aromatic π–π stacking interactions were the main driving forces for gelation.

1. Introduction

The use of α-amino acids as ingredients for the construction of dendrimers has become a topic of current interest. Such compounds can be used as biomimetic models toward the property studies of artificial proteins and enzymes.[1] Furthermore, such materials are also envisaged to possess better bio-compatibility[2] because of their compositions are consisted of naturally occurring amino acids. Depending on how the amino acids are linked together, such dendrimers can be classified as peptide-based or amino acid-based dendrimers. In the former category the amino acid units are directly connected to each other, while in the latter they are linked to each other through non-amino acid spacers. Typical peptide-based dendrimers are the poly(lysine) dendrimers,[3] poly(ornithine) dendrimers,[4] and poly(glutamate) dendrimers,[5] and some of their derivatives have shown very interesting biological and gelation properties.[3b–3e] Interest in amino acid-based dendrimers and dendrons has also appeared recently.[6] However, most of the peptide-based and amino acid-based dendrimers reported to date are synthesized from only one type of amino acid. Hence, if more than one kind of amino acids are used in their constructions, such as those encountered in natural proteins and peptides, dendrimers with diverse structural variety can then be resulted. In this context Reymond recently reported a combinatorial approach to the synthesis of a library of catalytically active layer block peptide-based dendrimers.[7] One of the most intriguing findings was that the catalytic reactivity was shown to be dependent on the nature of the amino acid in the different concentric layers. This suggested that the amino acid arrangement within the dendrimers, similar to the amino acid sequence of enzymes, has a profound effect on their properties. Our group recently reported the synthesis of a combinatorial series of amino acid-based layer block dendrons using alanine, phenylalanine, and valine as the ingredients.[8] We also found that gelation properties of these dendrons were strongly influenced by their layer block amino acid sequence. Herein, we wish to describe the synthesis of a new series of G1-G2 amino acid-based sector block dendrons **1**–**4**. In addition, we also show that such amino acid-based dendrimers possess rich structural diversities and exhibit amino acid dependent gelation properties.



1 R = Et, [G1-(aa^1)(aa^2)-CO_2Et]
2 R = H, [G1-(aa^1)(aa^2)-CO_2H]
aa^{1}aa^2 = AF, AV and FV

Keywords: Dendrimers; Amino acid-based dendrimers; Organogelators.
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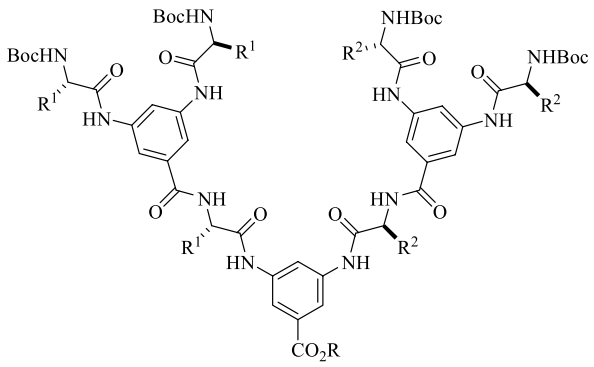
doi:10.1016/j.tet.2005.08.006



3 R = Et, [G2-(aa^1)$_3$(aa^2)$_3$-CO_2Et]
4 R = H, [G2-(aa^1)$_3$(aa^2)$_3$-CO_2H]
(aa^1)$_3$(aa^2)$_3$ = A_3F_3, A_3V_3 and F_3V_3

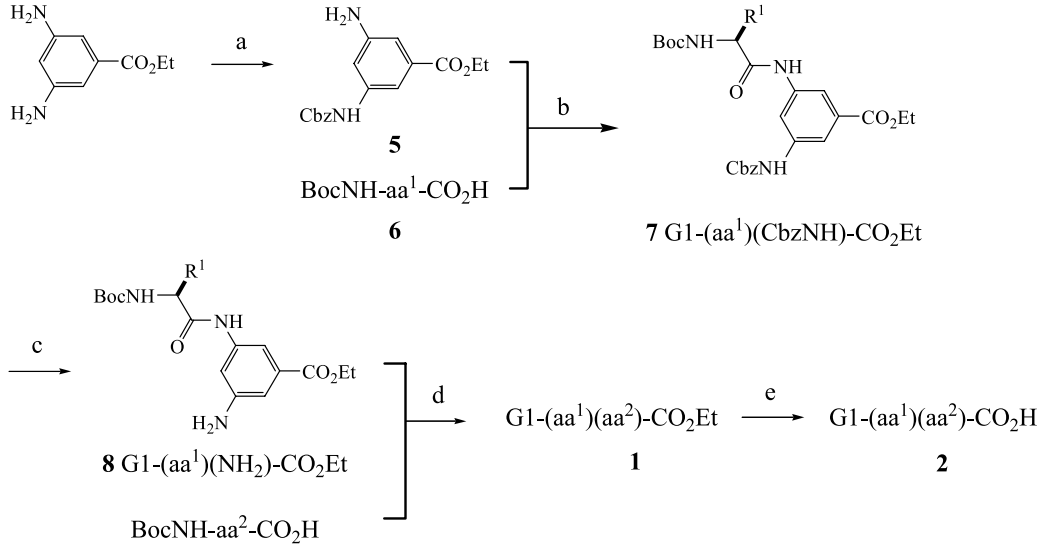
R^1 = Me, Bn or *i*-Pr
R^2 = Me, Bn or *i*-Pr
and $R^1 \neq R^2$

2. Results and discussion

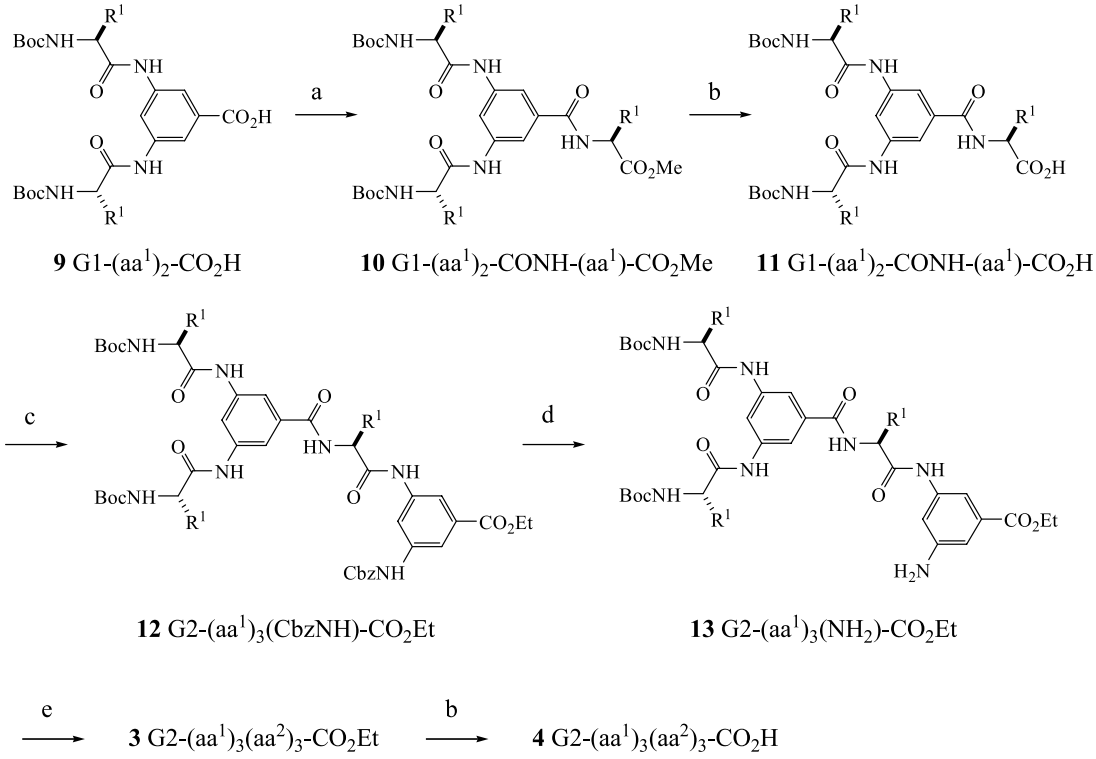
2.1. Synthesis

We employed 3,5-diaminobenzoic acid as the branching agent in this class of sector block dendrimers. In contrast to the synthesis of layer block dendrimers, the synthesis of sector block dendrimers or dendrons requires a high degree of control over the number and placement of functional groups within the same dendritic layer. Therefore, one needs to differentiate the two amino groups in our branching agent. Hence, one of the amino groups was selectively protected as the Cbz derivative **5** in 71% yield by reacting ethyl 3,5-diaminobenzoate with 1 equiv of benzyl chloroformate (Scheme 1). The other amino group was subsequently coupled to either BocNH-L-alanine **6** (aa^1=A) or BocNH-L-valine **6** (aa^1=V) in the presence of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) to furnish G1-A(CbzNH)-CO_2Et **7** (aa^1=A) or G1-V(CbzNH)-CO_2Et **7** (aa^1=V), respectively, in excellent yields. The Cbz protective group in compounds **7** was then removed by catalytic hydrogenation to afford G1-(aa^1)(NH_2)-CO_2Et **8** in about 95% yields. The different products **8** were then coupled to a second amino acid BocNH-aa^2-CO_2H in the presence of EEDQ to give the three sector block dendrons G1-(aa^1)(aa^2)-CO_2Et **1** (aa^{1}aa^2=AF, AV, and VF) in 87–98% yield as white solids. Alkaline hydrolysis of the ethyl ester group then gave the corresponding carboxylic acid dendrons G1-(aa^1)(aa^2)-CO_2H **2** (aa^{1}aa^2=AF, AV, and VF) in nearly quantitative yields.

The starting materials for the preparation of the three different G2 sector block dendrons **3** were the known layer block dendrons G1-(aa^1)$_2$-CO_2H **9** reported earlier by us.[8] Hence, coupling of compounds **9** (aa^1=A, F, or V) with H_3N^+-(aa^1)-CO_2Me Cl^- bearing the same aa^1 amino acid residue in the presence of dicyclohexylcarbodiimide (DCC), 4-methylmorpholine, and 1-hydroxybenzotriazole (HOBt) afforded the three G1-(aa^1)$_2$-CONH-(aa^1)-CO_2Me (aa^1=A, F, or V) esters **10** in 62–80% yields (Scheme 2). The methyl ester functionality was then removed by alkaline hydrolysis to produce the corresponding acid dendrons G1-(aa^1)$_2$-CONH-(aa^1)-CO_2H (aa^1=A, F, or V) **11** in nearly quantitative yields. The acid dendrons **11** were then anchored to the mono-protected branching unit **5** using either DCC or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (EDCI) as the coupling agent and HOBt to give the hemi-substituted G2-(aa^1)$_3$(CbzNH)-CO_2Et dendrons **12** containing the aa^1 amino acid dendritic sector. The Cbz protecting group was then dismantled by catalytic hydrogenolysis (10% Pd on C, MeOH) to release the free amino group. The product **13** was then subsequently coupled (DCC or EDCI, HOBt, THF) to an aa^2 containing acid dendron G1-(aa^2)$_2$-CONH-(aa^2)-CO_2H **12** to give the target sector block dendrons G2-(aa^1)$_3$(aa^2)$_3$-CO_2Et **3** (aa^{1}aa^2=AF, AV, FV) in 35–46% yield as white solids. Finally, base hydrolysis (1.0 M aqueous KOH in MeOH) of the ethyl ester group produced the sector block acid dendrons G2-(aa^1)$_3$(aa^2)$_3$-CO_2H **4** (aa^{1}aa^2=AF, AV, FV) in 94–99% yields.



Scheme 1. Reagents and conditions: (a) BnOCOCl, NaOH (1 M), THF, 5–25 °C, 3 h; (b) EEDQ, CH_2Cl_2, 0–25 °C, 12 h; (c) H_2, 10% Pd on C, MeOH, 25 °C, 1 h; (d) EEDQ, THF/CH_2Cl_2, 0–25 °C, 12 h; (e) KOH (1.0 M), MeOH/H_2O, 25 °C.



Scheme 2. Reagents and conditions: (a) $Cl^{-}\ H_3N^{+}$-(aa^1)-CO_2Me, DCC, HOBt, 4-methylmorpholine, THF, −10–25 °C, 22 h; (b) KOH (1.0 M), MeOH/H_2O, 25 °C; (c) **5**, DCC or EDCI, HOBt, THF, −10–25 °C, 22 h; (d) H_2, 10% Pd on C, MeOH, 25 °C, 1 h; (e) G1-(aa^2)$_2$-CONH-(aa^2)-CO_2H, DCC or EDCI, HOBt, THF, −10–25 °C, 50 h.

2.2. Characterization

2.2.1. NMR spectroscopy. The structural identities of all the intermediates and target compounds were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. In contrast to the layer block dendrons reported earlier,[8] the sector block dendrons **1**–**4** are devoid of a *pseudo*-C_2 axis and their ^{1}H NMR spectra are slightly more complex. Nonetheless, the characteristics of the 'finger print' peaks due to the protons on the amino acid side chains were readily diagnosed. For example, the ^{1}H NMR spectrum of G1-AF-CO_2Et showed the presence of the alanine methyl side chain as a doublet at δ 1.26 and the diastereotopic benzylic protons of the phenylalanine side chain as a multiplet at δ 2.72–3.05 (Fig. 1). The two anilide protons were chemically non-equivalent and appeared as two separate singlets at δ 10.18 and 10.29. The two Boc groups were also different and showed up as two singlets at δ 1.32 and 1.38. On the other hand, the isopropyl side chain of the valine residue in the dendron G1-AV-CO_2Et appeared as a doublet at δ 0.89 and a multiplet at δ 1.85–2.08. The chemical shift values of the amino acid side chain protons remained essentially the same on going from the G1 to the G2 dendrons when they were located on the surface layer. Hence, in the ^{1}H NMR spectrum of G2-A_3F_3-CO_2Et, the surface alanine methyl groups appeared as a doublet at δ 1.26 and the surface

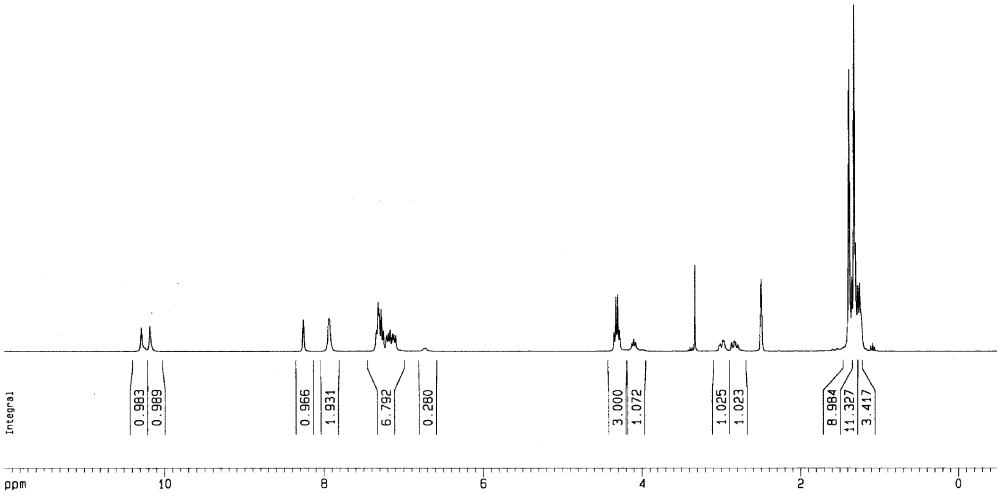


Figure 1. ^{1}H NMR spectrum of G1-AF-CO_2Et in d_6-DMSO.

benzylic protons of the phenylalanine side chains appeared as a multiplet at δ 2.70–3.08. On the other hand, the chemical shift values of the interior amino acid side chain protons were slightly downfield shifted due to a change of the *N*-linking group from the Boc to the benzamide functionality.

The ^{13}C NMR spectra of the target sector block dendrons share a common spectral feature; the chemical shift values of the carbon nuclei due to the dendritic backbone and the aromatic 3,5-diaminobenzamide branching unit are nearly the same for the different dendrons of the same generation. Hence, the primary and tertiary carbons of the Boc groups resonated at δ 29 and 79, respectively, while the peaks for the ethyl ester focal point group were located at δ 15 and 61. Due to a broken down of the C_2 symmetry, up to six aromatic carbon signals originated from the interior branching unit could be identified (δ 115–140). Likewise, the carbon signals due to the surface aromatic branching units were also found to scatter between the same spectral regions. The carbonyl ^{13}C signals appeared at the most downfield region of the spectra. The ^{13}C signal(s) at $\sim\delta$ 156 corresponded to the Boc carbamate group(s) while the one(s) at $\sim\delta$ 167 could be attributed to the focal point carbonyl ester/acid or to the benzamide carbonyl moieties. On the other hand, the signal(s) located at $\sim\delta$ 172 corresponded to the anilide C=O(s). The chemical identities of the amino acid side chains could be similarly assigned by their respective 'fingerprint' signals as in the case of ^{1}H NMR spectroscopic analysis.

2.2.2. Mass spectroscopic analysis. The structures of all the G1 and G2 sector block dendrons were also characterized by FAB or ESI mass spectrometry. For both the G1 and G2 series of compounds, molecular ions appeared in forms of M^+, $(M+H)^+$, and/or $(M+Na)^+$ could be identified. It was found that ESI was a superior ionization technique than FAB in order to obtain the molecular mass data for the higher molecular weight G2 series. The exact masses of the molecular ion peak were measured and the results also matched well with the theoretical values.

2.2.3. Size exclusion chromatography. Due to the presence of a large number of amide and carbamate functional groups, the amino acid-based dendrons prepared here were found to form hydrates.[8,9] As a result, elemental analysis data could not be used to assess their structural purity. Furthermore, it has been noted that elemental analysis data are not reliable in assessing dendrimer purities due to the extremely small variation of the analysis data across a series of dendrimers bearing the same architectural elements. Most often their homogeneities were assessed by size exclusion chromatography (SEC). Hence, all the dendrons as well as the intermediates were subjected to SEC analysis and they were found to produce a symmetrical peak with a narrow polydispersity (PDI$\leq$1.03) in their SEC chromatogram (Table 1 and Fig. 2). Therefore, all the dendrons were determined to be >95% pure by SEC analysis. More interestingly, the G2 acid and ester dendrons all have nearly the same retention volume ($\sim$16.1 min), suggesting that they possess similar hydrodynamic radius, irrespective of the amino acid composition and the focal point functionality.

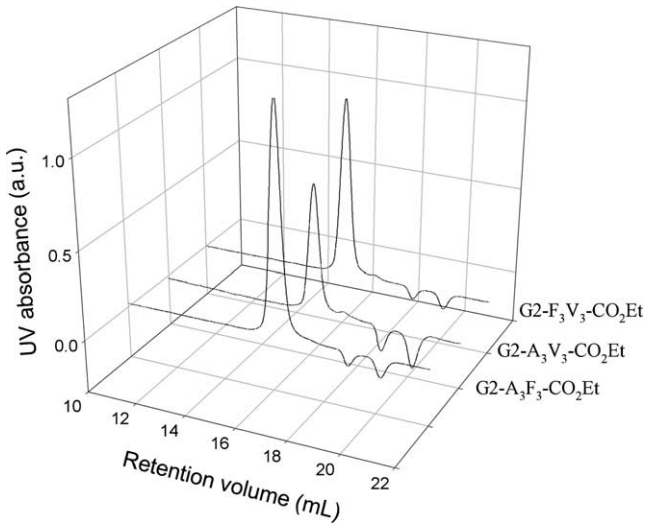


Figure 2. SEC chromatograms of G2 ester dendrons (flow rate: 1 mL min^{-1}; temperature = 40 °C; solvent = 5% HOAc/DMF). The negative absorption peaks are due to signals of water and acetic acid.

2.3. Properties

2.3.1. Chiroptical properties. The chiroptical properties of the sector block dendrons were measured and tabulated (Table 2). To avoid complications due to self aggregation,[8,9] the data were acquired in 5% HOAc in 1,2-dichloroethane. Previously, it was found that the sign of the specific rotations of the layer block dendrons generally did not change from the dendritic esters to their corresponding carboxylic acids and that the molar rotation of the resulting dendron was the simple sum of the molar rotations of all the constituted amino acid chiral units resided within the dendron.[8] Such observations were consistent with the notion that the focal point functionality had little effect on the chiral conformation of the layer block dendrons and that they adopted an open and conformationally flexible

Table 1. SEC data of sector block dendrons

Dendron	Retention time (min)	PDI	Dendron	Retention time (min)	PDI
G1-AF-CO_2Et	17.92	1.02	G1-A_2-CONH-A-CO_2H	16.81	1.02
G1-AV-CO_2Et	18.00	1.02	G1-F_2-CONH-F-CO_2H	16.79	1.01
G1-FV-CO_2Et	17.61	1.01	G1-V_2-CONH-V-CO_2H	16.98	1.02
G1-AF-CO_2H	17.36	1.01	G2-A_3F_3-CO_2Et	16.10	1.01
G1-AV-CO_2H	17.42	1.01	G2-A_3V_3-CO_2Et	16.18	1.01
G1-FV-CO_2H	17.52	1.02	G2-F_3V_3-CO_2Et	16.09	1.02
G1-A_2-CONH-A-CO_2Me	17.01	1.02	G2-A_3F_3-CO_2H	15.92	1.02
G1-F_2-CONH-F-CO_2Me	17.23	1.03	G2-A_3V_3-CO_2H	15.98	1.02
G1-V_2-CONH-V-CO_2Me	17.40	1.02	G2-F_3V_3-CO_2H	16.03	1.02

Table 2. Chiroptical data of sector block dendrons

Dendrons	$[\alpha]_D$[a]	$[\Phi]_D$[b]	Dendrons	$[\alpha]_D$[a]	$[\Phi]_D$[b]
G1-AF-CO_2Et	−12.1	−72	G1-A_2-CONH-A-CO_2H	−43.9	−248
G1-AV-CO_2Et	−50.8	−279	G1-F_2-CONH-F-CO_2H	+42.0	+333
G1-FV-CO_2Et	+8.6	+54	G1-V_2-CONH-V-CO_2H	−8.9	−58
G1-AF-CO_2H	−14.1	−80	G2-A_3F_3-CO_2Et	+25.8	+388
G1-AV-CO_2H	−57.7	−301	G2-A_3V_3-CO_2Et	+38.5	+523
G1-FV-CO_2H	−7.3	−44	G2-F_3V_3-CO_2Et	+78.3	+1242
G1-A_2-CONH-A-CO_2Me	−50.8	−294	G2-A_3F_3-CO_2H	+22.9	+338
G1-F_2-CONH-F-CO_2Me	+46.6	+376	G2-A_3V_3-CO_2H	+27.9	+371
G1-V_2-CONH-V-CO_2Me	−15.3	−101	G2-F_3V_3-CO_2H	+63.8	+995

[a] Specific rotation (10^{-1} degrees cm^2 g^{-1}).
[b] Molar rotation (10 degrees cm^2 mol^{-1}).

architecture in such a solvent system. However, for the sector block dendrons reported here, some anomalies to these trends were found. Hence, the absolute signs of G1-FV-CO_2H and G1-FV-CO_2Et were different. In addition, while the specific rotations of G1-A_2-CONH-A-CO_2R (R=H or Me) and G2-V_2-CONH-V-CO_2R (R=H or Me) are negative, the values of G2-A_3V_3-CO_2R (R=H or Et) are positive. We speculated that these abnormalities were probably due to a change of the chiral conformations on going from G1 to G2 dendrons, but were unable to offer an explanation at the present moment.

2.3.2. Gelation properties. Similar to the strong gelation property of the layer block dendrons[8] reported by us, the sector block dendrons described here also exhibited very excellent gelation behavior in aromatic solvents (Fig. 3).

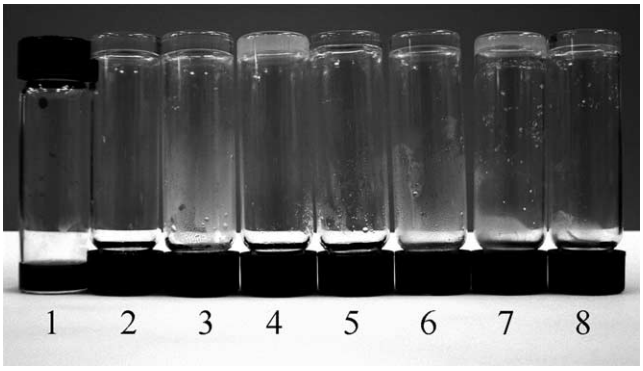


Figure 3. Gels (concentration = 10 mg mL^{-1}) formed from G1-AF-CO_2H in (2) toluene, (3) nitrobenzene, (4) *o*-xylene, (5) anisole, (6) G1-FV-CO_2H in nitrobenzene, G2-A_3V_3-CO_2Et in (7) *o*-xylene and (8) toluene. The first one on the left is $KMnO_4$ solution.

The gel was prepared by heating a weighted amount of an organogelator in a specified solvent inside a septum-capped vial until dissolution, and the sample was allowed to stand at room temperature for 1 day and the state of the sample was then examined. A stable gel was formed when a homogeneous phase exhibited no gravitation flow by inverting the sample. The gel state could be further classified as transparent gel (CG) or opaque gel (OG) according to its transparency. If part of the sample formed a gel and part of it remained in solution, it was considered as a partial gel (PG). The sample was regarded as soluble (S) when the solution remained clear and no gelation occurred. For the transparent gels described here, they were stable up to several months when stored in screw-capped vials.

Generally, the G1 acid dendrons are better organogelators than the G1 ester dendrons. This observation was similar to that observed with the G1 layer block dendrons.[8] It was also noted that the phenylalanine containing dendron G1-AF-CO_2H was the best organogelator with minimum gelation concentration (mgc) below 10 mg mL^{-1} in nearly all aromatic solvent tested (Table 3). The other phenylalanine containing dendron, G1-FV-CO_2H, was also a good organogelator with slightly inferior mgc values (<100 mg mL^{-1}). Again, these observations were in line with the fact that G1-F_2-CO_2H was found to be the best gelating agent among the layer block dendrons.[8] All these findings strongly suggested that the aromatic phenylalanine side chain was responsible for stabilizing the gel via π–π stacking interaction with the aromatic solvents.

Similar to the G2 layer block dendrons, the G2 sector block dendrons generally possess weaker gelation ability. Another

Table 3. Gelation behavior of sector block dendrons in aromatic solvents[a]

Dendrons	Toluene	*o*-Xylene	Anisole	Nitrobenzene	*o*-Dichlorobenzene
G1-AF-CO_2Et	S	S	S	S	S
G1-AV-CO_2Et	PG	PG	PG	PG	PG
G1-FV-CO_2Et	S	S	S	S	S
G1-AF-CO_2H	CG (3)	OG (4)	CG (10)	CG (4)	CG (40)
G1-AV-CO_2H	OG (40)	OG (50)	OG (50)	CG (100)	PG
G1-FV-CO_2H	OG (100)	OG (100)	OG (100)	CG (5)	OG (100)
G2-A_3F_3-CO_2Et	OG (50)	OG (50)	S	S	PG
G2-A_3V_3-CO_2Et	CG (30)	OG (40)	PG	PG	CG (100)
G2-F_3V_3-CO_2Et	PG	PG	PG	PG	PG
G2-A_3F_3-CO_2H	OG (50)	OG (50)	S	S	PG
G2-A_3V_3-CO_2H	PG	PG	CG (100)	PG	OG (100)
G2-F_3V_3-CO_2H	OG (50)	OG (50)	PG	PG	CG (100)

[a] CG, transparent gel; OG, opaque gel; PG, partial gel; S, soluble (>100 mg mL^{-1}). The values given in parentheses are the minimum concentration (mg mL^{-1}) to achieve gelation at 25 °C.

interesting observation was that none of the phenylalanine containing G2 dendrons showed strong gelating ability. In fact, the most efficient organogelator among the G2 dendrons was G2-A_3V_3-CO_2Et, highlighting the intriguing influence of the amino acid side chain on the gelation ability. Hence, the amino acid side chains have a subtle yet determining role on the gelation property, and only those possessing favorable hydrophobic and steric parameters can stabilize the physical gel.

2.4. Gelation mechanism

The gelation mechanism of the organogelators was investigated by infra-red (IR) spectroscopy. The FT-IR spectra of a 10 mg mL^{-1} $CHCl_3$ solution of G1-AF-CO_2H and a 10 mg mL^{-1} clear transparent gel in *o*-xylene were recorded and the data were tabulated (Table 4). The IR spectrum in $CHCl_3$ exhibited two peaks at 3439 and 3329 cm^{-1} in the ν_{N-H} region, which could be attributed to the stretching bands of the carbamate and anilide N–H, respectively. In addition, one broad peak at 1691 cm^{-1}, assignable to C=O stretching frequency was noted. On the other hand, the IR spectrum of the *o*-xylene gel showed a broad N–H absorption peak at 3313 cm^{-1} and another broad C=O absorption at peak 1668 cm^{-1}, both of which were significantly red-shifted. Hence, in addition to aromatic π–π stacking, intermolecular hydrogen bonding is also an important driving force for gelation.

Table 4. FT-IR data of G1-AF-CO_2H (concentration = 10 mg mL^{-1}) in the solution and gel states[a]

Conditions	Absorption frequency (cm^{-1})	
	ν (carbamate/anilide N–H)	ν (acid/anilide/carbamate C=O)
$CHCl_3$ solution	3429, 3329	1691
o-Xylene gel	3313	1668

[a] All spectra were recorded at 25 °C.

To further investigate the chirality of the gel aggregates, circular dichroism (CD) spectra of G1-AF-CO_2H in *o*-xylene (10 mg mL^{-1}) were recorded at different temperatures (Fig. 4). At a temperature above the melting temperature, the solution sample exhibited a positive Cotton effect at 338 nm. As the temperature decreases below the melting temperature, the molar ellicipity of the gel sample increases, indicating the emergence of secondary chiral architecture in the gel state. Furthermore, a gradual shift (~2 nm) of the λ_{max} to the blue region was also noted on cooling of the sample, suggesting the gradual transition from an isotropic solution to an anisotropic environment in the gel state.

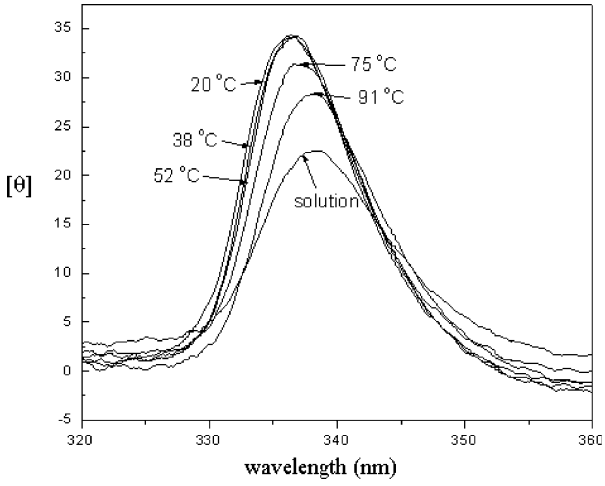


Figure 4. Temperature dependent CD spectra of G1-AF-CO_2H in *o*-xylene (10 mg mL^{-1}).

3. Conclusions

A new series of G1 and G2 α-amino acid-based sector block dendrons based on alanine, phenylalanine, and valine was synthesized by a convergent synthesis strategy involving selective functionalization and protection of a branching agent. Such dendrons were found to exhibit very strong gelation property (mgc down to 3 mg mL^{-1}) with aromatic solvents through aromatic π–π stacking, intermolecular hydrogen bonding, and more interestingly, hydrophobic interactions among the amino acid side chains. As a result, only those dendrons with the optimal amino acid constitution and focal point functionality can form strong physical gels. This new library of sector block dendrons, together with the layer block dendrons reported earlier, provide a new repertoire of biomimetic dendrimers with rich structural diversity and interesting physico–chemical properties that can be used as new bio-compatible materials.

4. Experimental

4.1. General

THF was distilled from sodium benzophenone ketyl and CH_2Cl_2 from P_2O_5 prior to use. Silica gel for flash chromatography is Macherey Nagel 60 M (230–400 mesh) silica gel. *N*-Boc-protected L-amino acids [BocNH-(aa^1)-CO_2H], L-amino acid methyl ester hydrochlorides [H_3N^+-(aa^1)-CO_2Me Cl^-] and other reagents were used as supplied from Aldrich or Sigma. All reactions were conducted under dry N_2 unless otherwise stated. All NMR spectra were recorded in d_6-DMSO (dried over molecular sieve 4 Å) on a Brüker DPX spectrometer at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus at 25 °C. The residual proton or carbon signals of d_6-DMSO (δ_H=2.50; δ_C=40.5) were used as internal references. All chemical shifts are reported in ppm (δ) and coupling constants in Hz. Positive ion ESI and FAB spectra were carried out on a Thermo Finnigan MAT 95XL mass spectrometer. Melting points were measured on an Electrothermal IA9100 Digital Melting Point Apparatus and were uncorrected. Melting temperatures (T_m) were recorded on a Perkin-Elmer DCS6 differential scanning meter and are referred to the onset of the transition. IR spectra were recorded on a Nicolet 420 FT-IR spectrophotometer. Optical rotations were taken on a Perkin Elmer 341 Polarimeter at 589 nm and at 20 °C, in a solvent mixture of 1,2-dichloroethane/HOAc (*v*/*v* 95:5). CD spectra were recorded on a JASCO J-715 spectropolarimeter connected to a NESLAB RTE-211 temperature controller. Size exclusion chromatography (SEC) analyses were performed on Waters® Styragel columns (HR 1 and HR 3 in serial) at

40 °C in 5% HOAc/DMF as eluent (flow rate = 1.0 mL min^{-1}) on a Waters HPLC 515 pump equipped with a Waters 486 tunable UV absorbance detector. Molecular weights obtained from SEC measurements were based on a calibration curve derived from polystyrene standards. Elemental analyses were performed at MEDAC LTD, Brunel Science Centre, Cooper's Hill Lane, Englefield Green, Egham, Surrey TW20 0JZ, UK.

4.1.1. Ethyl 3-amino-5-(*N*-benzyloxycarbonylamino) benzoate 5. A mixture of benzyl chloroformate (14.4 mL, 100 mmol) and aqueous NaOH (100 mL, 1.0 M) in THF (200 mL) was added dropwise to a stirred solution of ethyl 3,5-diaminobenzoate[9] (18.0 g, 100 mmol) in THF (500 mL) at 5 °C. After the mixture had been kept at 25 °C for 3 h, the solvent was evaporated in vacuo. The residue was dissolved in $CHCl_3$ (300 mL) and washed with water (2×75 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was chromatographed on silica gel (eluent: EtOAc/hexane 1:2) to afford the title compound as a white solid (22.3 g, 71%). R_f 0.53 (EtOAc/hexane 2:3). Mp 160–161 °C. ^{1}H NMR: 1.28 (3H, t, J=7.1 Hz, CH_2CH_3), 4.24 (2H, q, J=7.1 Hz, CH_2Me), 5.13 (2H, s, $PhCH_2$), 5.39 (2H, s, NH_2), 6.85 (1H, s, ArH), 6.98 (1H, s, ArH), 7.26 (1H, s, ArH), 7.28–7.49 (5H, m, PhH), 9.67 (1H, s, CONHAr). ^{13}C NMR: 15.2, 61.3, 66.6, 107.8, 108.6, 110.0, 129.0, 129.2, 129.4, 131.7, 137.7, 140.9, 150.3, 154.2, 167.1. MS (FAB): 315 [$(M+H)^+$, 58%]. HRMS (FAB): calcd for $C_{17}H_{18}N_2O_4+H^+$, 315.1339; found, 315.1340. Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91; found: C, 65.20; H, 5.88; N, 8.89.

4.2. General procedure for the preparation of G1-(aa^1)(CbzNH)-CO_2Et 7

EEDQ (1.0 equiv) was added to a stirred mixture of BocNH-(aa^1)-CO_2H **6** (1 equiv) and ethyl 3-amino-5-(*N*-benzyloxycarbonylamino)benzoate **5** (1 equiv) in dry CH_2Cl_2 at 0 °C. The mixture was kept at 25 °C for 12 h after which the solvent was evaporated in vacuo. The residue was redissolved in EtOAc (200 mL), and washed successively with saturated $NaHCO_3$ solution (50 mL), 10% citric acid solution (2×50 mL), saturated $NaHCO_3$ solution (2×50 mL), and water (2×50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to give the target compound, which was further purified by flash chromatography on silica gel.

4.2.1. G1-A(CbzNH)-CO_2Et (7, aa^1=A). Starting from BocNH-A-CO_2H (1.02 g, 5.4 mmol), ethyl 3-amino-5-(*N*-benzyloxycarbonylamino)benzoate **5** (1.70 g, 5.4 mmol) and EEDQ (1.34 g, 5.4 mmol), the titled compound was obtained as a white solid (2.37 g, 90%) after flash chromatography (eluent: EtOAc/hexane 2:3). R_f 0.29 (EtOAc/hexane 2:3). Mp 153–155 °C. $[\alpha]_D^{20}$ −42.5 (*c* 1.16). ^{1}H NMR: 1.25 (3H, d, J=7.1 Hz, $CHCH_3$), 1.31 (3H, t, J=7.1 Hz, CH_2CH_3), 1.38 (9H, s, $C(CH_3)_3$), 4.02–4.18 (1H, m, NCHMe), 4.30 (2H, q, J=7.1 Hz, CH_2Me), 5.17 (2H, s, $PhCH_2$), 7.10 (1H, d, J=7.1 Hz, NHCHMe), 7.28–7.49 (5H, m, PhH), 7.81 (1H, s, ArH), 7.95 (1H, s, ArH), 8.05 (1H, s, ArH), 10.03 (1H, s, CONHAr), 10.15 (1H, s, CONHAr). ^{13}C NMR: 15.1, 18.8, 29.2, 51.4, 61.8, 66.8, 79.0, 114.1, 114.6, 115.0, 129.0, 129.4, 131.6, 137.5, 140.7, 154.3, 156.1, 166.4, 173.1. MS (FAB): 486 [$(M+H)^+$, 21%]. HRMS (FAB): calcd for $C_{25}H_{31}N_3O_7+H^+$, 486.2235; found, 486.2234.

4.2.2. G1-V(CbzNH)-CO_2Et (7, aa^1=V). Starting from BocNH-V-CO_2H (1.46 g, 6.7 mmol), ethyl 3-amino-5-(*N*-benzyloxycarbonylamino)benzoate **5** (2.10 g, 6.7 mmol) and EEDQ (1.66 g, 6.7 mmol), the target compound was obtained as a white solid (2.90 g, 85%) after flash chromatography (eluent: EtOAc/hexane 1:4 gradient to 1:3). R_f 0.20 (EtOAc/hexane 1:4). Mp 154–156 °C. $[\alpha]_D^{20}$ −29.4 (*c* 0.97). ^{1}H NMR: 0.89 (6H, d, J=6.5 Hz, $CH(CH_3)_2$), 1.31 (3H, t, J=7.1 Hz, CH_2CH_3), 1.39 (9H, s, $C(CH_3)_3$), 1.85–2.08 (1H, m, $CHMe_2$), 3.91 (1H, t, J=7.7 Hz, NCH), 4.30 (2H, q, J=7.1 Hz, CH_2Me), 5.17 (2H, s, $PhCH_2$), 6.92 (1H, d, J=8.5 Hz, NHCH), 7.28–7.49 (5H, m, PhH), 7.81 (1H, s, ArH), 7.97 (1H, s, ArH), 8.06 (1H, s, ArH), 10.02 (1H, s, CONHAr), 10.20 (1H, s, CONHAr). ^{13}C NMR: 15.1, 19.4, 20.1, 29.1, 31.2, 61.6, 61.8, 66.8, 79.0, 114.1, 114.7, 114.9, 129.0, 129.4, 131.6, 137.5, 140.5, 140.8, 154.3, 156.5, 166.4, 172.0. MS (FAB): 514 [$(M+H)^+$, 25%]. HRMS (FAB): calcd for $C_{27}H_{35}N_3O_7+H^+$, 514.2548; found, 514.2557.

4.3. General procedure for the preparation of G1-(aa^1)(NH_2)-CO_2Et 8

A suspension of G1-(aa^1)(CbzNH)-CO_2Et **7** and 10% palladium on charcoal in MeOH was stirred under H_2 for 1 h. The catalyst was removed by filtration and the solvent evaporated in vacuo to give the target compound G1-(aa^1)(NH_2)-CO_2Et **8**.

4.3.1. G1-A(NH_2)-CO_2Et (8, aa^1=A). Starting from G1-A(CbzNH)-CO_2Et (2.00 g, 4.1 mmol), the target compound was obtained as a white solid (1.38 g, 95%). Mp 142–144 °C. $[\alpha]_D^{20}$ −49.5 (*c*=0.77). ^{1}H NMR: 1.22 (3H, d, J=7.1 Hz, $CHCH_3$), 1.29 (3H, t, J=7.0 Hz, CH_2CH_3), 1.38 (9H, s, $C(CH_3)_3$), 3.90–4.12 (1H, m, NCHMe), 4.25 (2H, q, J=7.1 Hz, CH_2Me), 5.42 (2H, s, NH_2), 6.89 (1H, s, ArH), 7.03 (1H, d, J=7.1 Hz, OCONH), 7.18 (1H, s, ArH), 7.31 (1H, s, ArH), 9.80 (1H, s, CONHAr). ^{13}C NMR: 15.2, 18.9, 29.1, 51.4, 61.3, 78.9, 108.7, 109.6, 110.5, 131.6, 140.8, 150.3, 156.1, 167.1, 172.8. MS (FAB): 351 (M^+, 26%). HRMS (FAB): calcd for $C_{17}H_{25}N_3O_5^+$, 351.1789; found, 351.1795.

4.3.2. G1-V(NH_2)-CO_2Et (8, aa^1=V). Starting from G1-V(CbzNH)-CO_2Et (1.62 g, 3.2 mmol), the titled product was obtained as a white solid (1.13 g, 94%). Mp 88–90 °C. $[\alpha]_D^{20}$ −34.1 (*c* 0.63). ^{1}H NMR: 0.88 (6H, d, J=6.3 Hz, $CH(CH_3)_2$), 1.28 (3H, t, J=7.3 Hz, CH_2CH_3), 1.38 (9H, s, $C(CH_3)_3$), 1.85–2.08 (1H, m, $CHMe_2$), 3.88 (1H, t, J=7.8 Hz, NCH), 4.25 (2H, q, J=6.9 Hz, CH_2Me), 5.42 (2H, s, NH_2), 6.84 (1H, d, J=8.1 Hz, OCONH), 6.89 (1H, s, ArH), 7.19 (1H, s, ArH), 7.32 (1H, s, ArH), 9.85 (1H, s, CONHAr). ^{13}C NMR: 15.2, 19.4, 20.1, 29.1, 31.3, 61.3, 61.6, 79.0, 108.7, 109.7, 110.6, 131.6, 140.6, 150.3, 156.5, 167.0, 171.6. MS (FAB): 379 (M^+, 100%). HRMS (FAB): calcd for $C_{19}H_{29}N_3O_5^+$, 379.2102; found, 379.2112.

4.4. General procedure for the preparation of G1-(aa^1)(aa^2)-CO_2Et 1

EEDQ (1 equiv) was added to a stirred mixture of BocNH-(aa^2)-CO_2H (1 equiv) and G1-(aa^1)(NH_2)-CO_2Et (1 equiv) in dry THF/CH_2Cl_2 (*v*/*v* 1:1) at 0 °C. The mixture was kept at 25 °C overnight and the solvent was evaporated in vacuo. The residue was redissolved in EtOAc (200 mL), and washed successively with saturated $NaHCO_3$ solution (50 mL), 10% citric acid solution (2×50 mL), saturated $NaHCO_3$ solution (2×50 mL), and water (2×50 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo to give the target compound that was purified by flash chromatography on silica gel.

4.4.1. G1-AF-CO_2Et (1, aa^1aa^2=AF). Starting from BocNH-F-CO_2H (0.75 g, 2.9 mmol), G1-A(NH_2)-CO_2Et (1.00 g, 2.9 mmol) and EEDQ (0.70 g, 2.9 mmol), the target compound was obtained as a white solid (1.48 g, 87%) after flash chromatography (eluent: EtOAc/hexane 1:2). R_f 0.23 (EtOAc/hexane 1:2). Mp 167–169 °C. $[\alpha]_D^{20}$ −12.1 (*c* 1.04). ^{1}H NMR: 1.26 (3H, d, *J*=7.1 Hz, CHC*H*$_3$), 1.25–1.32 (12H, m, CH_2CH_3 and C(C*H*$_3$)$_3$), 1.38 (9H, s, C(C*H*$_3$)$_3$), 2.72–2.91 (1H, m, C*H*HPh), 2.91–3.05 (1H, m, CH*H*Ph), 4.00–4.15 (1H, m, NC*H*Me), 4.26–4.37 (3H, m, C*H*$_2$Me and NC*H*Bn), 7.03–7.39 (7H, m, Ar*H* and OCON*H*), 7.93 (2H, s, Ar*H*), 8.26 (1H, s, Ar*H*), 10.18 (1H, s, CON*H*Ar), 10.29 (1H, s, CON*H*Ar). ^{13}C NMR: 15.1, 18.8, 29.1, 29.2, 38.2, 51.4, 57.6, 61.8, 79.0, 79.1, 115.1, 115.6, 127.3, 129.0, 130.2, 131.5, 138.9, 140.5, 140.6, 156.1, 156.3, 166.4, 172.1, 173.2. MS (FAB): 599 [(M+H)$^+$, 31%]. HRMS (FAB): calcd for $C_{31}H_{42}N_4O_8+H^+$, 599.3075; found, 599.3067.

4.4.2. G1-AV-CO_2Et (1, aa^1aa^2=AV). Starting from BocNH-V-CO_2H (0.41 g, 1.9 mmol), G1-A(NH_2)-CO_2Et (0.67 g, 1.9 mmol) and EEDQ (0.47 g, 1.9 mmol), the target compound was obtained as a white solid (1.0 g, 98%) after flash chromatography (eluent: EtOAc/hexane 1:2). R_f 0.17 (EtOAc/hexane 1:2). Mp 150–151 °C. $[\alpha]_D^{20}$ −50.8 (*c* 1.05). ^{1}H NMR: 0.89 (6H, d, *J*=6.5 Hz, CH(C*H*$_3$)$_2$), 1.25 (3H, d, *J*=7.1 Hz, CHC*H*$_3$), 1.32 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.38 (18H, s, C(C*H*$_3$)$_3$), 1.85–2.08 (1H, m, C*H*Me$_2$), 3.90 (1H, t, *J*=7.8 Hz, NC*H*CH), 4.05–4.16 (1H, m, NC*H*Me), 4.31 (2H, q, *J*=7.0 Hz, C*H*$_2$Me), 6.93 (1H, d, *J*=8.3 Hz, OCON*H*), 7.11 (1H, d, *J*=7.0 Hz, OCON*H*), 7.94 (2H, s, Ar*H*), 8.25 (1H, s, Ar*H*), 10.17 (1H, s, CON*H*Ar), 10.21 (1H, s, CON*H*Ar). ^{13}C NMR: 15.1, 18.8, 19.4, 20.1, 29.2, 31.2, 51.4, 61.6, 61.8, 79.0, 115.1, 115.5, 115.6, 131.5, 140.4, 140.7, 156.1, 156.5, 166.4, 172.0, 173.2. MS (FAB): 551 [(M+H)$^+$, 30%]. HRMS (FAB): calcd for $C_{27}H_{42}N_4O_8+H^+$, 551.3075; found, 551.3073.

4.4.3. G1-FV-CO_2Et (1, aa^1aa^2=FV). Starting from BocNH-F-CO_2H (0.70 g, 2.6 mmol), G1-V(NH_2)-CO_2Et (1.00 g, 2.6 mmol) and EEDQ (0.65 g, 2.6 mmol), the product was obtained as a white solid (1.43 g, 87%) after flash chromatography (eluent: EtOAc/hexane 1:3). R_f 0.27 (EtOAc/hexane 1:2). Mp 114–116 °C. $[\alpha]_D^{20}$ +8.6 (*c* 1.09). ^{1}H NMR: 0.90 (6H, d, *J*=6.6 Hz, CH(C*H*$_3$)$_2$), 1.17–1.35 (12H, m, CH_2CH_3 and C(C*H*$_3$)$_3$), 1.39 (9H, s, C(C*H*$_3$)$_3$), 1.85–2.08 (1H, m, C*H*Me$_2$), 2.72–2.91 (1H, m, C*H*HPh), 2.91–3.05 (1H, m, CH*H*Ph), 3.91 (1H, t, *J*=7.9 Hz, NC*H*), 4.26–4.37 (3H, m, NC*H*Bn and C*H*$_2$Me), 6.94 (1H, d, *J*=8.4 Hz, OCON*H*), 7.09–7.43 (6H, m, Ar*H* and OCON*H*), 7.93 (1H, s, Ar*H*), 7.96 (1H, s, Ar*H*), 8.26 (1H, s, Ar*H*), 10.23 (1H, s, CON*H*Ar), 10.30 (1H, s, CON*H*Ar). ^{13}C NMR: 15.1, 19.5, 20.1, 29.1, 31.2, 38.2, 57.6, 61.7, 61.9, 79.1, 115.1, 115.7, 127.3, 129.0, 130.2, 131.5, 138.9, 140.4, 140.5, 156.4, 156.5, 166.4, 172.1. MS (FAB): 626 (M$^+$, 26%). HRMS (FAB): calcd for $C_{33}H_{46}N_4O_8^+$, 626.3310; found, 626.3302.

4.5. General procedure for the preparation of G1-(aa^1)(aa^2)-CO_2H 2

An aqueous KOH solution (1.0 M) was added to a solution of G1-(aa^1)(aa^2)-CO_2Et **1** in MeOH. The reaction mixture was stirred at 25 °C until completion of the reaction as monitored by TLC analysis. The solvent was evaporated in vacuo and the residue was poured into large amount of water. The precipitate formed was collected by filtration, washed with water and dried in vacuo.

4.5.1. G1-AF-CO_2H (2, aa^1aa^2=AF). Starting from G1-AF-CO_2Et (0.50 g, 0.84 mmol) in MeOH (10 mL) and aqueous KOH solution (2 mL, 1.0 M), the target compound was obtained as a white solid (0.47 g, 98%). T_m 160 °C. $[\alpha]_D^{20}$ −14.1 (*c* 1.07). ^{1}H NMR: 1.26 (3H, d, *J*=7.2 Hz, CHC*H*$_3$), 1.32 (9H, s, C(C*H*$_3$)$_3$), 1.38 (9H, s, C(C*H*$_3$)$_3$), 2.72–2.91 (1H, m, C*H*HPh), 2.91–3.05 (1H, m, CH*H*Ph), 3.90–4.15 (1H, m, NC*H*Me), 4.22–4.36 (1H, m, NC*H*Bn), 7.03–7.39 (7H, m, Ar*H* and OCON*H*), 7.92 (2H, s, Ar*H*), 8.20 (1H, s, Ar*H*), 10.13 (1H, s, CON*H*Ar), 10.24 (1H, s, CON*H*Ar), 12.95 (1H, br s, COO*H*). ^{13}C NMR: 18.8, 29.1, 29.2, 38.3, 51.5, 57.7, 79.0, 79.1, 114.8, 116.0, 127.3, 129.0, 130.2, 132.6, 138.9, 140.3, 140.5, 156.1, 156.4, 168.0, 172.0, 173.1. MS (FAB): 571 [(M+H)$^+$, 100%]. HRMS (FAB): calcd for $C_{29}H_{38}N_4O_8+H^+$, 571.2762; found, 571.2770.

4.5.2. G1-AV-CO_2H (2, aa^1aa^2=AV). Starting from G1-AV-CO_2Et (0.79 g, 1.4 mmol) in MeOH (10 mL) and aqueous KOH solution (3.0 mL, 1.0 M), the titled compound was obtained as a white solid (0.72 g, 96%). T_m 202 °C. $[\alpha]_D^{20}$ −57.7 (*c* 0.22). ^{1}H NMR: 0.89 (6H, d, *J*=6.6 Hz, CH(C*H*$_3$)$_2$), 1.25 (3H, d, *J*=7.1 Hz, CHC*H*$_3$), 1.38 (18H, s, C(C*H*$_3$)$_3$), 1.85–2.08 (1H, m, C*H*Me$_2$), 3.91 (1H, t, *J*=7.7 Hz, NC*H*CH), 4.00–4.19 (1H, m, NC*H*Me), 6.91 (1H, d, *J*=8.4 Hz, OCON*H*), 7.10 (1H, d, *J*=7.1 Hz, OCON*H*), 7.92 (2H, s, Ar*H*), 8.19 (1H, s, Ar*H*), 10.12 (1H, s, CON*H*Ar), 10.16 (1H, s, CON*H*Ar), 12.98 (1H, br s COO*H*). ^{13}C NMR: 18.8, 19.5, 20.1, 29.2, 31.2, 51.4, 61.6, 78.98, 79.02, 114.9, 115.9, 116.0, 132.5, 140.2, 140.5, 156.1, 156.5, 167.9, 172.0, 173.1. MS (FAB): 523 [(M+H)$^+$, 7%]. HRMS (FAB): calcd for $C_{25}H_{38}N_4O_8+H^+$, 523.2762; found, 523.2752.

4.5.3. G1-FV-CO_2H (2, aa^1aa^2=FV). Starting from G1-FV-CO_2Et (0.66 g, 1.1 mmol) in MeOH (10 mL) and aqueous KOH solution (2.1 mL, 1.0 M), the target product was obtained as a white solid (0.63 g, 100%). T_m 167 °C. $[\alpha]_D^{20}$ −7.3 (*c* 0.39). ^{1}H NMR: 0.90 (6H, d, *J*=6.5 Hz, CH(C*H*$_3$)$_2$), 1.32 (9H, s, C(C*H*$_3$)$_3$), 1.39 (9H, s, C(C*H*$_3$)$_3$), 1.85–2.08 (1H, m, C*H*Me$_2$), 2.72–2.91 (1H, m, C*H*HPh), 2.91–3.05 (1H, m, CH*H*Ph), 3.91 (1H, t, *J*=7.8 Hz, NC*H*CH), 4.23–4.36 (1H, m, NC*H*Bn), 6.92 (1H, d, *J*=

8.3 Hz, OCONH), 7.09–7.43 (6H, m, ArH and OCONH), 7.93 (2H, s, ArH), 8.20 (1H, s, ArH), 10.18 (1H, s, CONHAr), 10.25 (1H, s, CONHAr), 12.98 (1H, br s, COOH). ^{13}C NMR: 19.5, 20.1, 29.1, 31.2, 38.3, 57.7, 61.7, 79.1, 114.9, 116.1, 127.3, 129.0, 130.2, 132.6, 138.9, 140.2, 140.4, 156.4, 156.5, 168.0, 172.0. MS (FAB): 599 [$(M+H)^+$, 100%]. HRMS (FAB): calcd for $C_{31}H_{42}N_4O_8+H^+$, 599.3075; found, 599.3079.

4.6. General procedure for the synthesis of G1-(aa^1)$_2$-CONH-(aa^1)-CO_2Me 10

DCC (1 equiv) was added to a stirred mixture of $Cl^-H_3N^+$-(aa^1)-CO_2Me (1 equiv), G1-(aa^1)$_2$-CO_2H[8] **9** (1 equiv), 4-methylmorpholine (1 equiv) and HOBt (1 equiv) in dry THF at −10 °C. After stirring at −10 °C for 2 h and then at 25 °C for 20 h, the insoluble DCU was removed by filtration and the solvent evaporated in vacuo. The residue was dissolved in EtOAc, and washed successively with saturated $NaHCO_3$ solution, 10% citric acid solution, saturated $NaHCO_3$ solution, and water. The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to give the target compound **10** that was purified by flash chromatography on silica gel.

4.6.1. G1-A_2-CONH-A-CO_2Me (10, aa^1=A). Starting from L-alanine methyl ester hydrochloride (1.40 g, 10.0 mmol), G1-A_2-CO_2H[8] (4.94 g, 10.0 mmol), 4-methylmorpholine (1.01 g, 10.0 mmol), DCC (2.06 g, 10.0 mmol) and HOBt (1.35 g, 10.0 mmol), the target compound was obtained as a white solid (3.60 g, 62%) after flash chromatography (eluent: EtOAc/hexane 1:1 gradient to 2:1). R_f 0.20 (EtOAc/hexane 2:1). T_m 182 °C. $[\alpha]_D^{20}$ −50.8 (*c* 1.10). ^{1}H NMR: 1.25 (6H, d, *J*=7.1 Hz, CH_3CH), 1.33–1.40 (21H, m, C(CH_3)$_3$ and CH_3CH), 3.64 (3H, s, CO_2CH_3), 3.92–4.21 (2H, m, NCHCON), 4.35–4.51 (1H, m, NCHCO_2Me), 7.09 (2H, d, *J*=7.1 Hz, OCONH), 7.68 (2H, s, ArH), 8.13 (1H, s, ArH), 8.81 (1H, d, *J*=6.8 Hz, ArCONH), 10.07 (2H, s, CONHAr). ^{13}C NMR: 17.7, 18.9, 29.2, 49.2, 51.4, 52.8, 79.0, 113.9, 114.4, 136.3, 140.2, 156.1, 167.7, 173.0, 174.0. MS (FAB): 579 (M^+, 27%). HRMS (FAB): calcd for $C_{27}H_{41}N_5O_9^+$, 579.2899; found, 579.2890.

4.6.2. G1-F_2-CONH-F-CO_2Me (10, aa^1=F). Starting from L-phenylalanine methyl ester hydrochloride (2.16 g, 10.0 mmol), G1-F_2-CO_2H[8] (6.46 g, 10.0 mmol), 4-methylmorpholine (1.01 g, 10.0 mmol), DCC (2.06 g, 10.0 mmol) and HOBt (1.35 g, 10.0 mmol), the product was obtained as a white solid (5.12 g, 63%) after flash chromatography (eluent: EtOAc/hexane 2:3). R_f 0.46 (EtOAc/hexane 1:1). T_m 195 °C. $[\alpha]_D^{20}$ +46.6 (*c* 0.85). ^{1}H NMR: 1.33 (18H, s, C(CH_3)$_3$), 2.72–2.91 (2H, m, PhCHH), 2.91–3.08 (2H, m, PhCHH), 3.08–3.25 (2H, m, PhCH_2CHCO_2Me), 3.65 (3H, s, CO_2CH_3), 4.18–4.42 (2H, m, NCHCON), 4.58–4.72 (1H, m, NCHCO_2Me), 7.06–7.42 (17H, m, ArH and OCONH), 7.68 (2H, s, ArH), 8.13 (1H, s, ArH), 8.90 (1H, d, *J*=7.2 Hz, ArCONH), 10.23 (2H, s, CONHAr). ^{13}C NMR: 29.1, 37.1, 38.3, 52.9, 55.1, 57.6, 79.1, 114.1, 114.5, 127.3, 127.4, 129.0, 129.2, 130.0, 130.2, 136.2, 138.6, 138.9, 140.1, 156.4, 167.7, 172.0, 173.0. MS (FAB): 808 [$(M+H)^+$, 7%]. HRMS (FAB): calcd for $C_{45}H_{53}N_5O_9+H^+$, 808.3916; found, 808.3940.

4.6.3. G1-V_2-CONH-V-CO_2Me (10, aa^1=V). Starting from L-valine methyl ester hydrochloride (1.68 g, 10.0 mmol), G1-V_2-CO_2H[8] (5.50 g, 10.0 mmol), 4-methylmorpholine (1.01 g, 10.0 mmol), DCC (2.06 g, 10.0 mmol) and HOBt (1.35 g, 10.0 mmol), the titled compound was obtained as a white solid (5.34 g, 80%) after flash chromatography (eluent: EtOAc/hexane 3:8 gradient to 2:5). R_f 0.46 (EtOAc/hexane 1:1). T_m 196 °C. $[\alpha]_D^{20}$ −15.3 (*c* 0.79). ^{1}H NMR: 0.87–0.99 (18H, m, (CH_3)$_2$CH), 1.38 (18H, s, C(CH_3)$_3$), 1.85–2.08 (2H, m, CHMe$_2$), 2.08–2.28 (1H, m, CHMe$_2$), 3.65 (3H, s, CO_2CH_3), 3.93 (2H, t, *J*=7.9 Hz, NCHCON), 4.26 (1H, t, *J*=7.5 Hz, NCHCO_2Me), 6.91 (2H, d, *J*=8.5 Hz, OCONH), 7.66 (2H, s, ArH), 8.19 (1H, s, ArH), 8.63 (1H, d, *J*=7.5 Hz, ArCONH), 10.12 (2H, s, CONHAr). ^{13}C NMR: 19.5, 19.9, 20.1, 20.2, 29.2, 30.4, 31.2, 52.6, 59.5, 61.6, 79.0, 113.7, 114.6, 136.6, 139.9, 156.5, 168.4, 171.9, 173.1. MS (FAB): 663 (M^+, 11%). HRMS (FAB): calcd for $C_{33}H_{53}N_5O_9^+$, 663.3838; found, 663.3832.

4.7. General procedure for the synthesis of G1-(aa^1)$_2$-CONH-(aa^1)-CO_2H 11

A mixture of aqueous KOH solution (1.0 M) and G1-(aa^1)$_2$-CONH-(aa^1)-CO_2Me **10** in MeOH was stirred at 25 °C until completion of the reaction as monitored by TLC analysis. The solvent was evaporated in vacuo and the residue poured into large amount of water. The precipitate formed was collected by filtration, washed with water and dried in vacuo.

4.7.1. G1-A_2-CONH-A-CO_2H (11, aa^1=A). Starting from G1-A_2-CONH-A-CO_2Me (1.30 g, 2.3 mmol) in MeOH (20 mL) and aqueous KOH solution (5.0 mL, 1.0 M), the titled compound was obtained as a white solid (1.16 g, 91%). T_m 182 °C. $[\alpha]_D^{20}$ −43.9 (*c* 0.12). ^{1}H NMR: 1.26 (6H, d, *J*=7.0 Hz, CH_3CHCON), 1.29–1.49 (21H, m, C(CH_3)$_3$ and CH_3CHCO_2H), 3.92–4.21 (2H, m, NCHCON), 4.30–4.45 (1H, m, NCHCO_2H), 7.09 (2H, d, *J*=7.1 Hz, OCONH), 7.67 (2H, s, ArH), 8.14 (1H, s, ArH), 8.64 (1H, d, *J*=6.8 Hz, ArCONH), 10.07 (2H, s, CONHAr), 12.52 (1H, br s, CO_2H). ^{13}C NMR: 17.8, 18.9, 29.2, 49.1, 51.4, 79.0, 113.8, 114.4, 136.5, 140.1, 156.1, 167.5, 173.0, 175.0. MS (FAB): 565 (M^+, 8%). HRMS (FAB): calcd for $C_{26}H_{39}N_5O_9+H^+$, 566.2821; found, 566.2809.

4.7.2. G1-F_2-CONH-F-CO_2H (11, aa^1=F). Starting from G1-F_2-CONH-F-CO_2Me (2.05 g, 2.5 mmol) in MeOH (40 mL) and aqueous KOH solution (6.0 mL, 1.0 M), the target compound was obtained as a white solid (1.95 g, 97%). T_m 159 °C. $[\alpha]_D^{20}$ +42.0 (*c* 1.30). ^{1}H NMR: 1.32 (18H, m, C(CH_3)$_3$), 2.72–2.91 (2H, m, PhCHH), 2.91–3.08 (2H, m, PhCHH), 3.08–3.25 (2H, m, PhCH_2CHCO_2H), 4.18–4.42 (2H, m, NCHCON), 4.52–4.65 (1H, m, NCHCO_2H), 7.06–7.42 (17H, m, ArH and OCONH), 7.65 (2H, s, ArH), 8.13 (1H, s, ArH), 8.65 (1H, d, *J*=7.4 Hz, ArCONH), 10.21 (2H, s, CONHAr), 12.80 (1H, br s, CO_2H). ^{13}C NMR: 29.1, 37.2, 38.3, 39.6, 55.0, 57.6, 79.0, 114.0, 114.5, 127.3, 129.0, 129.1, 130.0, 130.2, 136.5, 138.9, 139.1, 140.0, 156.3, 167.4, 172.0, 174.0. MS (FAB): 794 [$(M+H)^+$, 7%]. HRMS (FAB): calcd for $C_{44}H_{51}N_5O_9+H^+$, 794.3760; found, 794.3772.

4.7.3. G1-V_2-CONH-V-CO_2H (11, aa^1=V). Starting from G1-V_2-CONH-V-CO_2Me (0.39 g, 0.6 mmol) in MeOH (10 mL) and aqueous KOH solution (1.2 mL, 1.0 M), the titled compound was obtained as a white solid (0.36 g, 94%). T_m 194 °C. $[\alpha]_D^{20}$ −8.9 (*c* 0.61). ^{1}H NMR: 0.90 (12H, d, *J*=6.0 Hz, $(CH_3)_2CH$), 0.96 (6H, d, *J*=4.7 Hz, $(CH_3)_2CH$), 1.38 (18H, s, $C(CH_3)_3$), 1.85–2.08 (2H, m, $Me_2CHCHCONH$), 2.08–2.28 (1H, m, $Me_2CHCHCO_2H$), 3.93 (2H, t, *J*=7.5 Hz, NC*H*CONH), 4.25 (1H, t, *J*=7.1 Hz, NC*H*CO_2H), 6.90 (2H, d, *J*=8.2 Hz, OCON*H*), 7.66 (2H, s, Ar*H*), 8.20 (1H, s, Ar*H*), 8.38 (1H, d, *J*=7.3 Hz, ArCON*H*), 10.12 (2H, s, CON*H*Ar), 12.64 (1H, br s, CO_2H). ^{13}C NMR: 19.4, 19.6, 20.17, 20.20, 29.1, 30.4, 31.2, 59.2, 61.6, 79.0, 113.6, 114.5, 136.8, 139.9, 156.5, 168.2, 171.9, 173.9. MS (ESI): 672 [(M+ Na)$^+$, 100%]. HRMS (ESI): calcd for $C_{32}H_{51}N_5O_9$+ Na^+, 672.3579; found, 672.3579.

4.8. General procedure for the synthesis of G2-(aa^1)$_3$(CbzNH)-CO_2Et 12

DCC or EDCI (1 equiv) was added to a stirred mixture of G1-(aa^1)$_2$-CONH-(aa^1)-CO_2H (1 equiv), ethyl 3-amino-5-(*N*-benzyloxycarbonylamino)benzoate **5** (1 equiv) and HOBt (1 equiv) in dry THF at −10 °C. The mixture was kept at −10 °C for 2 h and then at 25 °C for 20 h. When DCC was used as coupling reagent, the insoluble DCU produced was first removed by filtration. The filtrate or the reaction solvent (in the case of EDCI as the coupling agent) was then evaporated in vacuo. The residue was redissolved in EtOAc, and washed successively with saturated $NaHCO_3$ solution, 10% citric acid solution, saturated $NaHCO_3$ solution, and water. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo to give the target compound that was purified by precipitation or flash chromatography on silica gel.

4.8.1. G2-A_3(CbzNH)-CO_2Et (12, aa^1=A). Starting from G1-A_2-CONH-A-CO_2H (1.57 g, 2.8 mmol), ethyl 3-amino-5-(*N*-benzyloxycarbonylamino)benzoate (0.87 g, 2.8 mmol), EDCI (0.85 g, 2.8 mmol) and HOBt (0.38 g, 2.8 mmol), the desired compound was obtained as a white solid (1.66 g, 69%) after flash chromatography (eluent: EtOAc/hexane 2:1). R_f 0.24 (EtOAc/hexane 2:1). T_m 202 °C. $[\alpha]_D^{20}$ −21.3 (*c* 1.01). ^{1}H NMR: 1.26 (6H, d, *J*=7.1 Hz, surface CHCH_3), 1.30 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.32–1.48 (21H, m, $C(CH_3)_3$ and interior CHCH_3), 4.02–4.18 (2H, m, surface NC*H*), 4.30 (2H, q, *J*=7.1 Hz, CH_2Me), 4.48–4.64 (1H, m, interior NC*H*), 5.17 (2H, s, PhCH_2), 7.09 (2H, d, *J*=7.1 Hz, OCON*H*CH), 7.28–7.49 (5H, m, Ar*H*), 7.70 (2H, s, surface Ar*H*), 7.81 (1H, interior Ar*H*), 7.97 (1H, s, interior Ar*H*), 8.08 (1H, s, interior Ar*H*), 8.16 (1H, s, surface Ar*H*), 8.58 (1H, br s, ArCON*H*), 10.02 (1H, s, CON*H*Ar), 10.07 (2H, s, CON*H*Ar) 10.29 (1H, s, CON*H*Ar). ^{13}C NMR: 15.1, 18.7, 18.9, 29.2, 50.8, 51.4, 61.8, 66.8, 79.0, 113.8, 114.1, 114.5, 114.7, 115.0, 129.0, 129.4, 131.6, 136.4, 137.5, 140.1, 140.7, 154.3, 156.1, 166.4, 167.6, 172.5, 173.0. MS (FAB): 862 [(M+H)$^+$, 100%]. HRMS (FAB): calcd for $C_{43}H_{55}N_7O_{12}$+H$^+$, 862.3981; found, 862.3991.

4.8.2. G2-F_3(CbzNH)-CO_2Et (12, aa^1=F). Starting from G1-F_2-CONH-F-CO_2H (1.40 g, 1.8 mmol), ethyl 3-amino-5-(*N*-benzyloxycarbonylamino)benzoate (0.55 g, 1.8 mmol), DCC (0.36 g, 1.8 mmol), and HOBt (0.24 g, 1.8 mmol), the target product was obtained as a white solid (1.23 g, 64%) after precipitation from H_2O/MeOH. T_m 195 °C. $[\alpha]_D^{20}$+ 54.9 (*c* 1.01). ^{1}H NMR: 1.18–1.42 (21H, m, CH_2CH_3 and $C(CH_3)_3$), 2.72–2.91 (2H, m, PhC*H*H), 2.91–3.08 (2H, m, PhC*H*H), 3.08–3.25 (2H, m, interior PhCH_2C), 4.20–4.42 (4H, m, surface NC*H* and CH_2Me), 4.78–4.92 (1H, m, interior NC*H*), 5.18 (2H, s, PhCH_2O), 7.06–7.42 (22H, m, Ar*H* and OCON*H*CH), 7.69 (2H, s, surface Ar*H*), 7.84 (1H, s, interior Ar*H*), 7.98 (1H, s, interior Ar*H*), 8.11 (1H, s, interior Ar*H*), 8.14 (1H, s, surface ArH), 8.71 (1H, br s, ArCON*H*), 10.05 (1H, s, CON*H*Ar), 10.22 (2H, s, surface CON*H*Ar), 10.43 (1H, s, interior CON*H*Ar). ^{13}C NMR: 15.1, 29.1, 38.1, 38.3, 56.7, 57.6, 61.8, 66.8, 79.0, 114.0, 114.2, 114.6, 114.8, 115.1, 127.3, 129.0, 129.1, 129.4, 130.2, 131.6, 136.5, 137.5, 138.9, 140.0, 140.6, 140.8, 154.3, 156.4, 166.4, 167.7, 171.4, 172.0. MS (FAB): 1090 [(M+H)$^+$, 100%]. HRMS (FAB): calcd for $C_{61}H_{67}N_7O_{12}$+H$^+$, 1090.4920; found, 1090.4942.

4.9. General procedure for the synthesis of G2-(aa^1)$_3$(NH_2)-CO_2Et 13

A suspension of G2-(aa^1)$_3$(CbzNH)-CO_2Et **12** and 10% palladium on charcoal in MeOH was stirred under H_2 for 1 h. After the reaction, the catalyst was removed by filtration and the solvent evaporated in vacuo to give the target compound.

4.9.1. G2-A_3(NH_2)-CO_2Et (13, aa^1=A). Starting from G2-A_3(CbzNH)-CO_2Et (1.30 g, 1.5 mmol), the titled compound was obtained as a white solid (1.08 g, 98%). T_m 189 °C. $[\alpha]_D^{20}$ −27.9 (*c* 0.69). ^{1}H NMR: 1.26 (6H, d, *J*=6.2 Hz, surface NCHCH_3), 1.29 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.32–1.42 (21H, m, $C(CH_3)_3$ and interior NCHCH_3), 4.02–4.18 (2H, m, surface NC*H*), 4.25 (2H, q, *J*=7.1 Hz, CH_2Me), 4.42–4.60 (1H, m, interior NC*H*), 5.42 (2H, s, NH_2), 6.90 (1H, s, interior Ar*H*), 7.09 (2H, d, *J*=7.2 Hz, OCON*H*), 7.20 (1H, s, interior Ar*H*), 7.35 (1H, s, interior Ar*H*), 7.70 (2H, s, surface Ar*H*), 8.15 (1H, s, surface Ar*H*), 8.52 (1H, br s, ArCON*H*), 9.95 (1H, s, CON*H*Ar), 10.07 (2H, s, CON*H*Ar). ^{13}C NMR: 15.2, 18.8, 18.9, 29.2, 50.8, 51.4, 61.3, 79.0, 108.7, 109.7, 110.6, 113.8, 114.4, 131.6, 136.5, 140.2, 140.8, 150.3, 156.1, 167.1, 167.5, 172.2, 173.0. MS (FAB): 727 (M^+, 100%). HRMS (FAB): calcd for $C_{35}H_{49}N_7O_{10}^+$, 727.3535; found, 727.3542.

4.9.2. G2-F_3(NH_2)-CO_2Et (13, aa^1=F). Starting from G2-F_3(CbzNH)-CO_2Et (1.22 g, 1.1 mmol), the titled compound was obtained as a white solid (1.02 g, 95%). T_m 191 °C. $[\alpha]_D^{20}$+53.0 (*c* 0.70). ^{1}H NMR: 1.18–1.42 (21H, m, CH_2CH_3 and $C(CH_3)_3$), 2.72–2.91 (2H, m, PhC*H*H), 2.91–3.08 (2H, m, PhC*H*H), 3.08–3.25 (2H, m, PhCH_2), 4.26 (2H, q, *J*=7.1 Hz, CH_2Me), 4.20–4.42 (2H, m, surface NC*H*), 4.78–4.92 (1H, m, interior NC*H*), 5.45 (2H, s, NH_2), 6.92 (s, 1H, interior Ar*H*), 7.06–7.42 (19H, m, Ar*H*, OCON*H* and interior Ar*H*), 7.69 (2H, s, surface Ar*H*), 8.13 (1H, s, surface Ar*H*), 8.67 (1H, br s, ArCON*H*), 10.10 (1H, s, interior CON*H*Ar), 10.23 (2H, s, surface CON*H*Ar). ^{13}C NMR: 15.2, 29.1, 38.2, 38.3, 56.8, 57.6, 61.4, 79.0, 108.8, 109.8, 110.7, 113.9, 114.6, 127.3, 129.0, 129.1, 130.2, 131.6, 136.5, 138.9, 140.0, 140.6, 150.3, 156.4, 167.1, 167.6,

171.1, 172.0. MS (FAB): 955 (M^+, 100%). HRMS (FAB): calcd for $C_{53}H_{61}N_7O_{10}^+$, 955.4474; found, 955.4492.

4.10. General procedure for the preparation of G2-(aa^1)$_3$(aa^2)$_3$-CO$_2$Et 3

DCC or EDCI (1 equiv) was added to a stirred mixture of G2-(aa^1)$_3$(NH$_2$)-CO$_2$Et **13** (1 equiv), G1-(aa^2)$_2$-CONH-(aa^2)-CO$_2$H (1 equiv) and HOBt (1 equiv) in dry THF at −10 °C. The mixture was kept at −10 °C for 2 h and then at 25 °C for 48 h. When DCC was used as the coupling agent, the insoluble DCU produced was removed by filtration. The filtrate or the reaction solvent (in the case of EDCI as the coupling agent) was evaporated in vacuo. The residue was redissolved in $CHCl_3$, and washed successively with saturated $NaHCO_3$ solution, 10% citric acid solution, saturated $NaHCO_3$ solution and water. The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to give the target compound that was purified by flash chromatography on silica gel.

4.10.1. G2-A$_3$F$_3$-CO$_2$Et (3, aa^{1}aa^2=AF). Starting from G2-F$_3$(NH$_2$)-CO$_2$Et (0.75 g, 0.78 mmol), G1-A$_2$-CONH-A-CO$_2$H (0.44 g, 0.78 mmol), DCC (0.16 g, 0.78 mmol) and HOBt (0.11 g, 0.81 mmol), the target compound was obtained as a white solid (0.51 g, 43%) after flash chromatography (eluent: $CHCl_3$/MeOH 60:1). R_f 0.14 ($CHCl_3$/MeOH 50:1). T_m 191 °C. $[\alpha]_D^{20}$ +25.8 (*c* 0.89). ^{1}H NMR: 1.26 (6H, d, *J*=7.1 Hz, surface CHC*H*$_3$), 1.27–1.51 (42H, m, C(C*H*$_3$)$_3$, interior CHC*H*$_3$ and CH$_2$C*H*$_3$), 2.70–2.91 (2H, m, surface PhC*H*H), 2.91–3.08 (2H, m, surface PhC*H*H), 3.08–3.25 (2H, m, interior PhC*H*$_2$), 3.98–4.19 (2H, m, surface NC*H*Me), 4.19–4.44 (4H, m, surface NC*H*Bn and C*H*$_2$Me), 4.48–4.64 (1H, m, interior NC*H*Me), 4.75–4.92 (1H, m, interior NC*H*Bn), 7.08 (2H, d, *J*=7.1 Hz, OCON*H*Me), 7.11–7.45 (17H, m, Ph*H* and OCON*H*Bn), 7.69 (2H, s, surface Ar*H*), 7.71 (2H, s, surface Ar*H*), 7.99 (2H, s, interior Ar*H*), 8.14 (1H, s, surface Ar*H*), 8.16 (1H, s, surface Ar*H*), 8.31 (1H, s, interior Ar*H*), 8.60 (1H, br s, ArCON*H*CHMe), 8.73 (1H, br s, ArCON*H*CHBn), 10.08 (2H, s, surface CON*H*Ar), 10.22 (2H, s, surface CON*H*Ar), 10.34 (1H, s, interior CON*H*Ar), 10.44 (1H, s, interior CON*H*Ar). ^{13}C NMR: 15.1, 18.6, 18.9, 29.1, 38.1, 38.3, 50.9, 51.4, 56.8, 57.6, 61.8, 78.96, 79.04, 113.8, 114.5, 114.6, 115.3, 115.8, 127.3, 129.0, 129.1, 130.2, 131.5, 136.5, 138.9, 140.0, 140.1, 140.5, 140.6, 156.1, 156.4, 166.4, 167.7, 171.4, 172.0, 172.6, 173.0. MS (FAB): 1526 [(M+ Na)$^+$, 100%]. HRMS (ESI): calcd for $C_{79}H_{98}N_{12}O_{18}$+ Na$^+$, 1525.7014; found, 1525.7036.

4.10.2. G2-A$_3$V$_3$-CO$_2$Et (3, aa^{1}aa^2=AV). Starting from G2-A$_3$(NH$_2$)-CO$_2$Et (0.42 g, 0.58 mmol), G1-V$_2$-CONH-V-CO$_2$H (0.37 g, 0.58 mmol), DCC (0.12 g, 0.58 mmol) and HOBt (0.08 g, 0.58 mmol), the target product was obtained as a white solid (0.27 g, 35%) after flash chromatography (eluent: $CHCl_3$/MeOH 70:1 gradient to 30:1). R_f 0.55 ($CHCl_3$/MeOH 50:1). T_m 194 °C. $[\alpha]_D^{20}$ +38.5 (*c* 0.86). ^{1}H NMR: 0.90 (12H, d, *J*=6.5 Hz, surface CH(C*H*$_3$)$_2$), 0.97 (3H, d, *J*=6.9 Hz, interior CH(C*H*$_3$)$_2$), 1.00 (3H, d, *J*=6.9 Hz, interior CH(C*H*$_3$)$_2$), 1.26 (6H, d, *J*=7.1 Hz, surface CHC*H*$_3$), 1.32–1.55 (42H, m, C(C*H*$_3$)$_3$, CH$_2$C*H*$_3$ and interior CHC*H*$_3$), 1.85–2.08 (2H, m, surface C*H*Me$_2$), 2.10–2.29 (1H, m, interior C*H*Me$_2$), 3.92 (2H, t, *J*=7.9 Hz, surface NC*H*CHMe$_2$), 4.05–4.19 (2H, m, surface NC*H*Me), 4.31 (2H, q, *J*=7.1 Hz, C*H*$_2$Me), 4.35 (1H, t, *J*=7.0 Hz, interior NC*H*CHMe$_2$), 4.48–4.64 (1H, m, interior NC*H*Me), 6.90 (2H, d, *J*=8.4 Hz, OCON*H*), 7.08 (2H, d, *J*=7.1 Hz, OCON*H*), 7.70 (4H, s, surface Ar*H*), 7.98 (1H, s, Ar*H*), 8.00 (1H, s, Ar*H*), 8.16 (1H, s, Ar*H*), 8.20 (1H, s, Ar*H*), 8.31 (1H, s, Ar*H*), 8.43 (1H, br s, ArCON*H*), 8.59 (1H, br s, ArCON*H*), 10.07 (2H, s, surface CON*H*Ar), 10.13 (2H, s, surface CON*H*Ar), 10.32 (1H, s, CON*H*Ar), 10.41 (1H, s, CON*H*Ar). ^{13}C NMR: 15.1, 18.6, 18.9, 19.4, 20.0, 20.2, 29.1, 31.1, 31.2, 50.9, 51.4, 61.0, 61.6, 61.8, 79.0, 113.7, 114.5, 115.2, 115.7, 115.8, 131.5, 136.4, 136.7, 139.9, 140.1, 140.3, 140.6, 156.1, 156.5, 166.4, 167.6, 168.1, 171.6, 171.9, 172.6, 173.0. MS (FAB): 1382 [(M+ Na)$^+$, 12%]. HRMS (FAB): calcd for $C_{67}H_{98}N_{12}O_{18}$+ Na$^+$, 1381.7014; found, 1381.7036.

4.10.3. G2-F$_3$V$_3$-CO$_2$Et (3, aa^{1}aa^2=FV). Starting from G2-F$_3$(NH$_2$)-CO$_2$Et (0.41 g, 0.43 mmol), G1-V$_2$-CONH-V-CO$_2$H (0.28 g, 0.43 mmol), EDCI (0.13 g, 0.43 mmol) and HOBt (0.06 g, 0.43 mmol), the target compound was obtained as a white solid (0.31 g, 46%) after flash chromatography (eluent: $CHCl_3$/MeOH 80:1 gradient to 60:1). R_f 0.18 ($CHCl_3$/MeOH 50:1). T_m 192 °C. $[\alpha]_D^{20}$ +78.3 (*c* 0.79). ^{1}H NMR: 0.90 (12H, d, *J*=6.5 Hz, surface CH(C*H*$_3$)$_2$), 0.99 (3H, d, *J*=6.8 Hz, interior CH(C*H*$_3$)$_2$), 1.01 (3H, d, *J*=6.8 Hz, interior CH(C*H*$_3$)$_2$), 1.14–1.35 (21H, m, CH$_2$C*H*$_3$ and C(C*H*$_3$)$_3$), 1.38 (18H, s, C(C*H*$_3$)$_3$), 1.85–2.08 (2H, m, surface C*H*Me$_2$), 2.10–2.29 (1H, m, interior C*H*Me$_2$), 2.70–2.91 (2H, m, surface PhC*H*H), 2.91–3.08 (2H, m, surface PhC*H*H), 3.08–3.25 (2H, m, interior PhC*H*$_2$), 3.93 (2H, t, *J*=8.0 Hz, surface NC*H*CHMe$_2$), 4.17–4.49 (5H, C*H*$_2$Me, interior NC*H*CHMe$_2$ and surface C*H*Bn), 4.70–4.92 (1H, m, interior C*H*Bn), 6.90 (2H, d, *J*=8.6 Hz, OCON*H*), 7.03–7.45 (17H, m, Ar*H* and OCON*H*), 7.69 (2H, s, surface Ar*H*), 7.71 (2H, s, surface Ar*H*), 8.00 (2H, s, Ar*H*), 8.13 (1H, s, Ar*H*), 8.19 (1H, s, Ar*H*), 8.31 (1H, s, Ar*H*), 8.42 (1H, br s, ArCON*H*), 8.73 (1H, br s, ArCON*H*), 10.13 (2H, s, surface CON*H*Ar), 10.21 (2H, s, surface CON*H*Ar), 10.43 (1H, s, interior CON*H*Ar), 10.44 (1H, s, interior CON*H*Ar). ^{13}C NMR: 15.2, 19.5, 20.0, 20.2, 29.1, 31.1, 31.2, 38.0, 38.3, 56.9, 57.6, 61.1, 61.6, 61.9, 79.0, 113.7, 114.0, 114.6, 115.3, 116.0, 127.3, 129.0, 129.1, 130.2, 131.6, 136.5, 136.7, 138.9, 140.0, 140.3, 140.5, 156.4, 156.5, 166.4, 167.8, 168.1, 171.5, 171.6, 171.9, 172.0. MS (ESI): 1610 [(M+Na)$^+$, 100%]. HRMS (ESI): calcd for $C_{85}H_{110}N_{12}O_{18}$+ Na$^+$, 1609.7953; found, 1609.7946.

4.11. General procedure for the synthesis of G2-(aa^1)$_3$(aa^2)$_3$-CO$_2$H 4

A mixture of aqueous KOH solution (1.0 M) and G2-(aa^1)$_3$(aa^2)$_3$-CO$_2$Et **3** in MeOH was stirred at 25 °C until completion of the reaction as monitored by TLC. The solvent was evaporated in vacuo and the residue was poured into large amount of water. The precipitate formed was collected by filtration, washed with water, and dried in vacuo.

4.11.1. G2-A$_3$F$_3$-CO$_2$H (4, aa^{1}aa^2=AF). Starting from G2-A$_3$F$_3$-CO$_2$Et (0.32 g, 0.21 mmol) in MeOH (10 mL) and aqueous KOH solution (0.5 mL, 1.0 M), the target

compound was obtained as a white solid (0.30 g, 95%). T_m 169 °C. $[\alpha]_D^{20}+22.9$ (*c* 0.52). ^{1}H NMR: 1.26 (6H, d, $J=$ 7.2 Hz, surface CHCH_3), 1.27–1.51 (39H, m, C(CH_3)$_3$, interior CHCH_3), 2.70–2.91 (2H, m, surface PhC*H*H), 2.91–3.08 (2H, m, surface PhC*H*H), 3.08–3.25 (2H, m, interior PhCH_2), 3.98–4.19 (2H, m, surface NC*H*Me), 4.19–4.44 (2H, m, surface NC*H*Bn), 4.48–4.64 (1H, m, interior NC*H*Me), 4.75–4.92 (1H, m, interior NC*H*Bn), 7.08 (2H, d, $J=7.1$ Hz, OCON*H*), 7.11–7.45 (17H, m, Ar*H* and OCON*H*), 7.69 (2H, s, surface Ar*H*), 7.71 (2H, s, surface Ar*H*), 7.96 (1H, s, Ar*H*), 7.98 (1H, s, Ar*H*), 8.14 (1H, s, Ar*H*), 8.16 (1H, s, Ar*H*), 8.26 (1H, s, Ar*H*), 8.60 (1H, br s, ArCON*H*), 8.72 (1H, br s, ArCON*H*), 10.08 (2H, s, surface CON*H*Ar), 10.22 (2H, s, surface CON*H*Ar), 10.29 (1H, s, interior CON*H*Ar), 10.40 (1H, s, interior CON*H*Ar), 12.93 (1H, br s, COO*H*). ^{13}C NMR: 18.7, 18.9, 29.2, 38.1, 38.3, 50.9, 51.4, 56.8, 57.6, 79.0, 79.1, 113.8, 114.5, 114.6, 115.1, 116.1, 127.3, 129.0, 129.1, 130.2, 132.5, 136.5, 138.9, 140.0, 140.2, 140.3, 140.5, 156.1, 156.4, 167.7, 168.0, 171.4, 172.0, 172.6, 173.0. MS (FAB): 1476 [$(M+H)^+$, 10%]. HRMS (FAB): calcd for $C_{77}H_{94}N_{12}O_{18}+H^+$, 1475.6882; found, 1475.6873.

4.11.2. G2-A$_3$V$_3$-CO$_2$H (4, aa^{1}aa^2=AV). Starting from G2-A$_3$V$_3$-CO$_2$Et (0.34 g, 0.25 mmol) in MeOH (7.0 mL) and aqueous KOH solution (1.0 mL, 1.0 M), the titled compound was obtained as a white solid (0.33 g, 99%). T_m 181 °C. $[\alpha]_D^{20}+27.9$ (*c* 0.89). ^{1}H NMR: 0.90 (12H, d, $J=$ 6.4 Hz, surface CH(CH_3)$_2$), 0.97 (3H, d, $J=7.0$ Hz, interior CH(CH_3)$_2$), 1.00 (3H, d, $J=7.0$ Hz, interior CH(CH_3)$_2$), 1.26 (6H, d, $J=6.9$ Hz, surface CHCH_3), 1.31–1.55 (39H, m, C(CH_3)$_3$ and interior CHCH_3), 1.95–2.10 (2H, m, surface C*H*Me$_2$), 2.10–2.29 (1H, m, interior C*H*Me$_2$), 3.93 (2H, t, $J=7.7$ Hz, surface NC*H*CMe$_2$), 4.07–4.21 (2H, m, surface NC*H*Me), 4.39 (1H, t, $J=7.0$ Hz, interior NC*H*CMe$_2$), 4.48–4.64 (1H, m, interior NC*H*Me), 6.90 (2H, d, $J=7.5$ Hz, OCON*H*), 7.08 (2H, d, $J=7.1$ Hz, OCON*H*), 7.70 (4H, s, surface Ar*H*), 7.96 (2H, s, Ar*H*), 8.17 (1H, s, Ar*H*), 8.20 (2H, s, Ar*H*), 8.25 (1H, s, Ar*H*), 8.41 (1H, br s, ArCON*H*), 8.59 (1H, br s, ArCON*H*), 10.07 (2H, s, surface CON*H*Ar), 10.13 (2H, s, surface CON*H*Ar), 10.27 (1H, s, interior CON*H*Ar), 10.36 (1H, s, interior CON*H*Ar). ^{13}C NMR: 18.7, 18.9, 19.5, 20.0, 20.2, 29.2, 31.3, 50.9, 51.4, 61.0, 61.6, 78.97, 79.01, 113.7, 113.8, 114.5, 115.0, 116.1, 116.2, 132.7, 136.4, 136.7, 140.0, 140.1, 140.5, 156.1, 156.5, 167.7, 168.0, 168.1, 171.5, 171.9, 172.5, 173.0. MS (FAB): 1353 [$(M+Na)^+$, 15%]. HRMS (FAB): calcd for $C_{65}H_{94}N_{12}O_{18}+Na^+$, 1353.6701; found, 1353.6727.

4.11.3. G2-F$_3$V$_3$-CO$_2$H (4, aa^{1}aa^2=FV). Starting from G2-F$_3$V$_3$-CO$_2$Et (0.26 g, 0.16 mmol) in MeOH (7 mL) and aqueous KOH solution (0.6 mL, 1.0 M), the titled compound was obtained as a white solid (0.24 g, 94%). T_m 175 °C. $[\alpha]_D^{20}+63.8$ (*c* 0.90). ^{1}H NMR: 0.90 (12H, d, $J=$ 6.5 Hz, surface CH(CH_3)$_2$), 0.98 (3H, d, $J=6.8$ Hz, interior CH(CH_3)$_2$), 1.00 (3H, d, $J=6.8$ Hz, interior CH(CH_3)$_2$), 1.32 (18H, s, C(CH_3)$_3$), 1.38 (18H, s, C(CH_3)$_3$), 1.85–2.08 (2H, m, surface C*H*Me$_2$), 2.10–2.29 (1H, m, interior C*H*Me$_2$), 2.70–2.91 (2H, m, surface PhC*H*H), 2.91–3.08 (2H, m, surface PhC*H*H), 3.08–3.25 (2H, m, interior PhCH_2), 3.93 (2H, t, $J=8.0$ Hz, surface NC*H*CHMe$_2$), 4.17–4.49 (3H, interior NC*H*CHMe$_2$ and surface NC*H*Bn), 4.70–4.92 (1H, m, interior NC*H*Bn), 6.90 (2H, d, $J=8.3$ Hz, OCON*H*), 7.03–7.45 (17H, m, Ar*H* and OCON*H*), 7.68 (2H, s, surface Ar*H*), 7.71 (2H, s, surface Ar*H*), 7.98 (2H, s, Ar*H*), 8.14 (1H, s, Ar*H*), 8.20 (1H, s, Ar*H*), 8.25 (1H, s, Ar*H*), 8.42 (1H, br s, ArCON*H*), 8.73 (1H, br s, ArCON*H*), 10.13 (2H, s, surface CON*H*Ar), 10.22 (2H, s, surface CON*H*Ar), 10.39 (1H, s, interior CON*H*Ar), 10.40 (1H, s, interior CON*H*Ar), 12.91 (1H, br s, COO*H*). ^{13}C NMR: 19.5, 20.0, 20.2, 29.1, 31.2, 38.0, 38.3, 56.9, 57.6, 61.0, 61.6, 78.99, 79.04, 113.6, 113.9, 114.5, 115.1, 116.2, 127.3, 129.0, 129.1, 130.2, 132.5, 136.5, 136.7, 138.9, 139.96, 140.01, 140.2, 140.3, 156.4, 156.5, 167.8, 168.0, 168.1, 171.4, 171.5, 171.9, 172.0, 172.2. MS (FAB): 1582 [$(M+Na)^+$, 100%]. HRMS (ESI): calcd for $C_{83}H_{106}N_{12}O_{18}+Na^+$, 1581.7640; found, 1581.7656.

Acknowledgements

The work described in this paper was fully supported by a grant from the Research Grants Council, HKSAR (Project no. CUHK4273/00P).

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Tetrahedron 61 (2005) 11291–11298
Tetrahedron

A convergent and stereoselective synthesis of a *seco*-precursor of macrolactin A

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Received 24 May 2005; revised 11 July 2005; accepted 12 July 2005

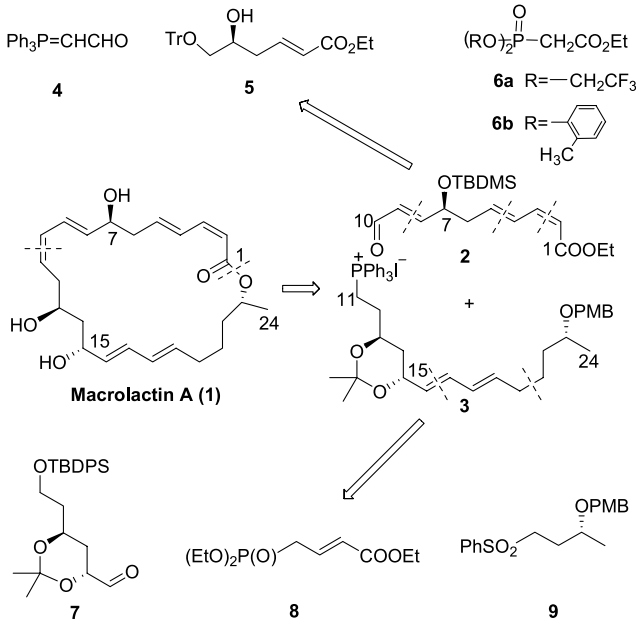
Available online 30 September 2005

Abstract—A *seco*-precursor of macrolactin A was synthesized by coupling two advanced segments. Wittig reaction and Horner–Emmons reaction were utilized to construct the three characteristic *E*,*Z* and *E*,*E* dienes. The C_1–C_{10} segment was synthesized through Horner–Emmons reaction with phosphonate reagent. The α-alkylation of sulfone stabilized anion with allyl bromide followed by desulfonation gave the C_{11}–C_{24} segment.

1. Introduction

Macrolactin A (**1**) is the parent aglycone of a novel family of polyene 24-membered macrolides isolated from a taxonomically unidentified deep-sea bacterium.[1] In preliminary biological evaluation, it was showed to inhibit B_{16}–F_{10} murine melanoma cancer cells and mammalian HSV-I and HSV-II. More significantly, it was found to inhibit the HIV replication in T-lymphoblasts[1] and to be a neuronal cell protecting substance against the glutamate toxicity.[2] However, macrolactin A is no longer readily available from the bacterial sources due to the unavailability of this deep-sea bacterium, and thus further biological studies were retarded. The significant biological activities combined with the scarcity of the natural resource of macrolactin A prompted many synthetic organic chemists to investigate its total synthesis.[3,4] Three total syntheses by Smith, Carreira, and Marino groups have been reported independently.[5] However, they addressed the problem of the *E*,*Z*-dienes stereochemistry when they utilized palladium-catalyzed sp^2–sp^2 Stille coupling to install three conjugated dienes. We have also involved in the synthesis of this molecule with a totally different approach.[4] Herein, we report our stereoselective synthesis of the *seco*-precursor **28** of macrolactin A, which features the judicious use of Wittig and Horner–Emmons reactions to elaborate all three stereofined 1,3-diene units in the target molecule.

Our strategy for the asymmetric synthesis of **1** is based on the coupling of the advanced segments **2** and **3**. To assemble the complex polyene macrolide,[6] we envisioned that a Wittig coupling between C_1–C_{10} segment **2** and C_{11}–C_{24} segment **3** would provide much better stereoselectivity of C_{10}–C_{11} double bond than palladium-catalyzed sp^2–sp^2 coupling (Scheme 1). Further bond-disconnections revealed that building blocks **4**–**9** were required.



Scheme 1. Retrosynthesis of macrolactin A.

Keywords: Horner–Emmons reaction; *seco*-Precursor; Macrolactin A.
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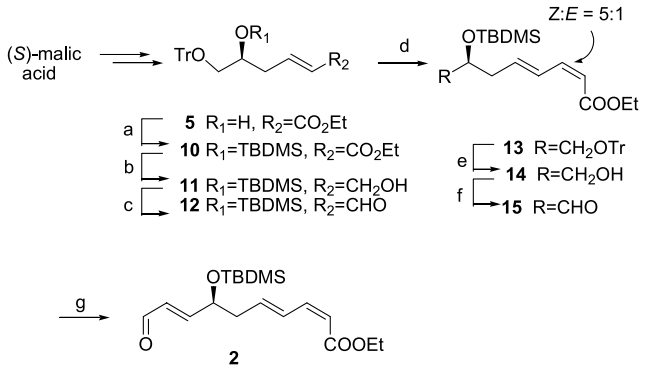
doi:10.1016/j.tet.2005.07.106

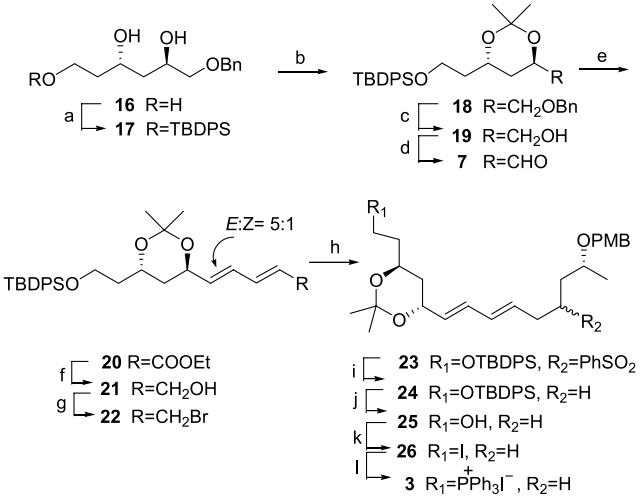
2. Results and discussion

The synthesis of C_1–C_{10} segment **2** (Scheme 2) started with the known compound **5**,[4] which was derived from *S*-malic acid. Protection of the secondary alcohol in **5** as TBDMS ether furnished ester **10**, which was then reduced with DIBAL-H to allyl alcohol **11** in 91% yield for two steps. Swern oxidation of **11** gave aldehyde **12**, which afforded the requisite dienoate **13** via Horner–Emmons reaction with phosphonate **6**.[7] At first, phosphonate **6a** was adopted and delivered **13** in 44% yield as a chromatographically separable mixture of isomers (*Z*,*E*/*E*,*E*=12.5:1). Nevertheless, phosphonate **6b** provided **13** as a mixture of isomers (*Z*,*E*/*E*,*E*=5:1) in 60% yield for two steps. A Wittig reaction involving the use of formylmethylene triphenylphosphorane[8] for a two-carbon chain elongation was utilized to accomplish the synthesis of C_1–C_{10} segment **2**. To this end, selective hydrolysis of trityl group in **13** with formic acid in ether[9] followed by Swern oxidation and subsequent Wittig reaction furnished **2** in 60% overall yield for three steps.



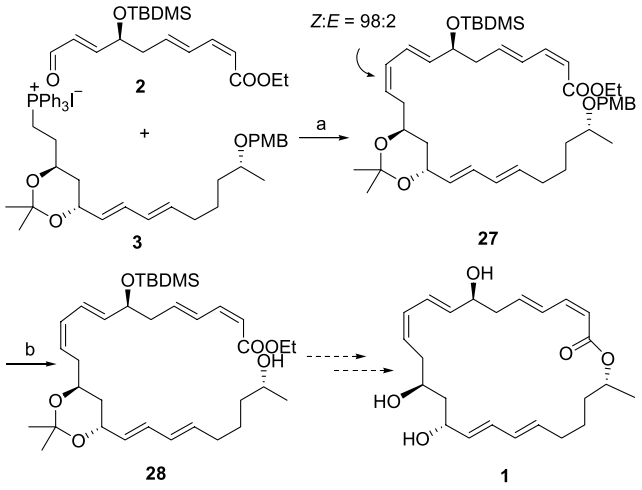
Scheme 2. Reagents and conditions: (a) TBDMSOTf, Et_3N, CH_2Cl_2, 0 °C, 40 min, 95%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 96.5%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78–0 °C; (d) $(o\text{-}CH_3\text{–}C_6H_4O)_2P(O)CH_2COOEt$ (**6b**), NaH, and then **12**, THF, 60% for two steps; (e) HCOOH, Et_2O, 75%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78–0 °C; (g) $Ph_3P{=}CHCHO$ (**5**), $CHCl_3$, 80% for two steps.

The preparation of C_{11}–C_{24} phosphonium salt **3** (Scheme 3) was accomplished by Horner–Emmons reaction as well. Conversion of triol **16**[10] to monoprotected silyl compound **17** (84%) followed by protection of the 1,3-*anti* diol using 2,2-dimethoxypropane in the presence of CSA furnished the acetonide **18** in 97% yield. Reductive removal of benzyl group in compound **18** by Raney nickel (98%) followed by oxidation of the resulting alcohol **19** under Swern conditions provided the corresponding aldehyde **7**, which was unstable on column chromatography and used directly to the next step without purification. Referring to our previous work,[4] the crude aldehyde **7** underwent Horner–Emmons reaction with triethyl phosphonocrotonate **8** in the presence of LDA. But the conjugated dienoate **20** was obtained in low yield (30%). LiHMDS and *n*-BuLi were also used instead of LDA, the yields of dienoate **20** were not improved. To our delight, the Takacs modified procedure[11] led to the conjugated dienoate **20** as a mixture of *E*,*E*- and *Z*,*E*-diene isomers in a ratio of 5:1 in 62% yield for two steps. Selective reduction of the ester group in **20** by DIBAL-H (92%) followed by bromination of the corresponding alcohol **21** at −78 °C by Ph_3P/NBS[12] yielded allyl bromide **22**, which was unstable, and decomposed on a silica gel column. It is worthy to be pointed out that temperature is critical to the successful bromination. At temperature over −20 °C, no desired product could be yielded. With allyl bromide **22** and sulfone **9** in hand, we embarked on the coupling of the two subunits on the basis of the previous research.[4] Gratifyingly, sulfone **9** and allyl bromide **22** could be efficiently coupled by treatment with *n*-BuLi, giving **23** in 93% yield as a mixture of two diastereomers. The phenylsulfonyl group was then removed by 6% Na–Hg in methanol giving **24** as a single isomer in 66% yield. Fluoride ion catalyzed hydrolysis of TBDPS group in **24** with TBAF (89%) and iodination of the corresponding alcohol **25** (92%) followed by phosphonium salt formation of **26** delivered the requisite C_{11}–C_{24} segment **3**.



Scheme 3. Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, 84%; (b) $Me_2C(OMe)_2$, CSA, 97%; (c) Raney Ni, EtOH, 98%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78–0 °C; (e) triethyl phosphonocrotonate (**8**), LiOH, 4 Å MS, THF, reflux, 10 h, 62% for two steps; (f) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 92%; (g) NBS, PPh_3, CH_2Cl_2, −78 °C, 30 min, 95%; (h) **9**, *n*-BuLi, and then **22**, THF, −78 °C; 93%; (i) 6% Na–Hg, Na_2HPO_4, MeOH, 0 °C, 66%; (j) TBAF, THF, 89%; (k) Ph_3P, imidazole, I_2, benzene, 0 °C, 92%; (l) Ph_3P, CH_3CN, reflux, 48 h, 97%.

The coupling of two advanced segments **2** and **3** in the presence of NaHMDS smoothly provided macrocyclization precursor **27** in 79% yield. The *Z*:*E* ratio of the newly formed double bond is 98:2. Subsequent removal of the PMB group in **27** proved problematic. Treatment of **27** with a slight excess of DDQ in wet CH_2Cl_2[13] gave the *seco*-precursor **28** in low yield accompanying by decomposition. Similar results were encountered in the co-solvent of $CHCl_3$–H_2O, CH_2Cl_2–*t*-BuOH-buffer (pH=6.5) and C_6H_6–H_2O. All attempted PMB group removal with other reagents, such as $MgBr_2{\cdot}Et_2O$–Me_2S,[14] $SnCl_4$–PhSH,[15] CAN–CH_3CN–H_2O,[16] TMSCl–$SnCl_2$–anisole,[17] $SnCl_2$–EtSH[18] failed to generate the desired product. Failure of deprotection of PMB ether **27** was attributed to 1,3-diene and the conjugated allylic alkoxy in the molecule. The same problem was also reported in literature.[14,19] Unfortunately, dearth of material did not permit us to fully study the macrocyclization (Scheme 4).



Scheme 4. Reagents and conditions: (a) **2** and **3**, NaHMDS, THF, −78 °C, 79%; (b) DDQ, CH_2Cl_2–H_2O (17/1), 14.4%.

3. Conclusion

In summary, a synthesis of the *seco*-precursor of macrolactin A was achieved through a highly convergent and efficient route. In the synthesis, Wittig reaction and Horner–Emmons reaction with phosphonate reagents **6** were utilized to construct the three characteristic *E*,*Z*- and *E*,*E*-dienes. An α-alkylation of sulfone stabilized anion with allyl bromide was used for the elongation of C_{11}–C_{20} segment. Although the removal of PMB protecting group gave troubles to the completion of the target molecule, this strategy should still be applicable to a range of similar polyene compounds.

4. Experimental

4.1. General

Unless otherwise noted, materials were obtained from commercial sources and used without further purification. All solvents were purified and dried by the standard procedures before use. Organic solutions of the products were dried over anhydrous sodium sulfate. All reactions involving organometallic reagents were conducted under a nitrogen or argon atmosphere. Silica gel (200–300 mesh) from Qingdao Marine Chemical Corporation was used for column chromatography unless otherwise noted. Solvents were removed by rotary evaporation under reduced pressure. Infrared spectra were obtained on a Nicoler Magna 750. NMR spectra were measured on 400 or 300 MHz spectrometers for ^{1}H and 100 or 75 MHz spectrometers for ^{13}C, respectively, with tetramethylsilane as internal standard. *J* values were given in Hz. Optical rotations were measured on a Perkin-Elmer 241 MC. Mass spectra and high-resolution mass spectra were measured on a Varian MAT-711 and MAT-95, respectively.

4.2. Synthesis of segment C_1–C_{10}

4.2.1. Ethyl (5*S*,2*E*)-5-*tert*-butyldimethylsilyloxy-6-trityloxy-2-hexenoate (10). To a stirred solution of alcohol **5** (9.8 g, 23.57 mmol) in CH_2Cl_2 (60 mL) were added Et_3N (13.0 mL, 94.28 mmol) and TBDMSOTf (8.1 mL, 35.35 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 40 min. Then a saturated aqueous solution of NH_4Cl (40 mL) was added followed by the addition of Et_2O (400 mL). The organic layer was separated and washed with saturated aqueous solution of $NaHCO_3$ (40 mL), water (40 mL×2) and brine (40 mL×2). The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo, yielding an oily residue, which was purified by flash chromatography (*n*-hexane/EtOAc, 20:1) to give **10** (11.8 g, 95%) as a colorless oil; $[\alpha]_D^{20}$ −2.6 (*c* 0.8, $CHCl_3$); IR (film): 3059, 2950, 2936, 1720, 1658, 1491, 1448, 1259, 1087, 837, 706, 632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (ddd, 6H, *J*=7.7, 7.5, 1.5 Hz), 7.27 (dd, 6H, *J*=7.5, 1.5 Hz), 7.20 (t, 3H, *J*=7.7 Hz), 6.89 (dt, 1H, *J*=15.6, 1.5 Hz), 5.80 (d, 1H, *J*=15.6 Hz), 4.18 (q, 2H, *J*=7.0 Hz), 3.87–3.80 (m, 1H), 3.18–2.92 (m, 2H), 2.62–2.54 (m, 1H), 2.44–2.36 (m, 1H), 1.29 (t, 3H, *J*=7.0 Hz), 0.86 (s, 9H), −0.02 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 146.0, 144.2×3, 134.5, 128.5×6, 127.8×3, 127.7×3, 127.0×3, 86.6, 70.7, 66.9, 60.5, 38.0, 25.7×3, 18.2, 14.3, −4.6, −4.9; MS (ESI): *m*/*z* (%)=553 (100) [M+Na$^+$].

4.2.2. (5*S*,2*E*)-5-*tert*-Butyldimethylsilyloxy-6-trityloxy-2-hexenol (11). To a stirred solution of ester **10** (13.1 g, 24.7 mmol) in CH_2Cl_2 (100 mL) was added DIBAL-H (74.2 mL, 1.0 M in cyclohexane, 74.2 mmol) slowly at −78 °C. The resulting solution was stirred at −78 °C for 1 h. Then MeOH (1 mL) was added followed by the addition of Et_2O (500 mL). The mixture was shaked vigorously with saturated aqueous solution of Rochelle's salt (200 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (100 mL×2) and EtOAc (100 mL). The combined organic layers were further washed with water (100 mL×2), brine (100 mL×2), and dried over Na_2SO_4. Concentration and flash chromatography (*n*-hexane/EtOAc, 5:1) provided **11** (11.7 g, 96.5%) as a colorless oil; $[\alpha]_D^{20}$ −2.6 (*c* 4.1, $CHCl_3$); IR (film): 3446, 2928, 2856, 1597, 1448, 1256, 1078, 775, 706 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (ddd, 6H, *J*=7.7, 7.5, 1.3 Hz), 7.27 (dd, 6H, *J*=7.5, 1.3 Hz), 7.20 (t, 3H, *J*=7.7 Hz), 5.62–5.59 (m, 2H), 4.08 (br s, 2H), 3.85–3.81 (m, 1H), 3.10–2.98 (m, 2H), 2.48–2.40 (m, 1H), 2.34–2.22 (m, 1H), 0.90 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.1×3, 131.5, 128.9, 128.7×6, 127.7×6, 126.9×3, 86.4, 71.4, 66.8, 63.6, 37.8, 25.8×3, 18.1, −4.6, −4.8; MS (EI, 70 eV): *m*/*z* (%)=488 (5) [M$^+$], 487 (6), 470 (40), 243 (100).

4.2.3. (5*S*,2*E*)-5-*tert*-Butyldimethylsilyloxy-6-trityloxy-2-hexenal (12). To a stirred solution of oxalyl chloride (4.0 mL, 45.94 mmol) in CH_2Cl_2 (100 mL) was added a solution of DMSO (6.6 mL, 91.88 mmol) in CH_2Cl_2 (20 mL) at −78 °C over 40 min. Upon completion of the addition, a solution of alcohol **11** (11.2 g, 22.97 mmol) in CH_2Cl_2 (15 mL) was added to the mixture over 30 min at −78 °C. The stirring was continued for 1.5 h, and then Et_3N (19.0 mL, 137.82 mmol) was added slowly at −78 °C. The reaction mixture was allowed to warm to 0 °C and stirred at this temperature for an additional 1.5 h. A saturated aqueous solution of NH_4Cl (50 mL) was added followed by the addition of Et_2O (500 mL). The organic layer was separated, washed with water (50 mL×2) and brine (50 mL×2), dried

over Na_2SO_4. Concentration of the organic layer gave the crude aldehyde **12**, which was used directly in the next reaction without further purification; $[\alpha]_D^{20}$ +1.1 (*c* 1.6, $CHCl_3$); IR (film): 3060, 2927, 2854, 1691, 1491, 1448, 1257, 995, 833, 777, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.44 (d, 1H, *J*=7.9 Hz), 7.45 (ddd, 6H, *J*=7.7, 7.5, 1.3 Hz), 7.27 (dd, 6H, *J*=7.5, 1.3 Hz), 7.20 (t, 3H, *J*=7.7 Hz), 6.82 (dt, 1H, *J*=15.4, 8.0 Hz), 6.15 (dd, 1H, *J*=15.4, 7.9 Hz), 4.01–3.97 (m, 1H), 3.12–3.08 (m, 1H), 3.06–3.02 (m, 1H), 2.81–2.72 (m, 1H), 2.67–2.58 (m, 1H), 0.90 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.6, 154.8, 143.8×3, 134.9, 128.5×6, 127.9×3, 127.7×3, 127.0×3, 86.6, 70.3, 66.6, 38.3, 25.7×3, 17.9, −4.6, −4.9; MS (EI, 70 eV): *m/z* (%)=485 (1) [M^+-1], 243 (100), 183 (37), 105 (28), 77 (13).

4.2.4. Ethyl (7*S*,2*Z*,4*E*)-7-*tert*-butyldimethylsilyloxy-8-trityloxy-2,4-octadienoate (13). To a stirred solution of ethyl bis(*o*-methylphenyl)phosphonoacetate (9.07 g, 26 mmol) in THF (30 mL) was added NaH (1.46 g, 60% in mineral oil, 36.4 mmol) at 0 °C. The resulting solution was stirred at this temperature for 15 min. Then the mixture was cooled to −78 °C, and a solution of the above crude aldehyde **12** (11.9 g, 24.5 mmol) in THF (30 mL) was added slowly. The mixture was allowed to stir at −78 °C for 2.5 h. A saturated aqueous solution of NH_4Cl (80 mL) was added to the reaction mixture. Et_2O (500 mL) was added to the reaction mixture, which was washed with H_2O (80 mL×2) and brine (80 mL×2). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash chromatography (*n*-hexane/ether, 10:1), providing **13** (8.18 g, 60%) as a colorless oil; $[\alpha]_D^{20}$ +5.7 (*c* 2.0, $CHCl_3$); IR (film): 3059, 2928, 2856, 1716, 1639, 1598, 1178, 835, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (ddd, 6H, *J*=7.7, 7.5, 1.4 Hz), 7.27–7.20 (m, 10H), 6.48 (t, 1H, *J*=11.3 Hz), 5.99 (dt, 1H, *J*=15.3, 7.3 Hz), 5.57 (d, 1H, *J*=11.3 Hz), 4.20 (q, 2H, *J*=7.2 Hz), 3.84 (q, 1H, *J*=5.8 Hz), 3.12–3.00 (m, 2H), 2.62–2.55 (m, 1H), 2.46–2.39 (m, 1H), 1.23 (t, 3H, *J*=7.2 Hz), 0.9 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 144.8×3, 144.1, 141.3, 129.0, 128.7×6, 128.2×3, 127.7×3, 126.7×3, 115.9, 86.5, 71.3, 67.2, 59.8, 38.7, 25.8×3, 18.1, 14.3, −4.5, −4.8; MS (ESI): *m/z* (%)=579 (19) [$M+Na^+$].

4.2.5. Ethyl (7*S*,2*Z*,4*E*)-7-*tert*-butyldimethylsilyloxy-8-hydroxy-2,4-octadienoate (14). To a vigorously stirred solution of trityl ether **13** (5.82 g, 10.47 mmol) in Et_2O (130 mL) was added freshly distilled formic acid (80 mL) at room temperature. The reaction mixture was stirred for 1 h, which was then slowly poured down to a saturated aqueous solution of $NaHCO_3$ (300 mL) at 0 °C. The mixture was extracted with Et_2O (200 mL×3), and combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (50 mL×2) and brine (50 mL×2). The organic layer was dried over Na_2SO_4, filtered, concentrated, and the residue was subjected to flash chromatography (*n*-hexane/ethyl acetate, 4:1), providing **14** (2.47 g, 75%) as a colorless oil; $[\alpha]_D^{20}$ +27.3 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (dd, 1H, *J*=15.2, 11.5 Hz), 6.54 (t, 1H, *J*=11.5 Hz), 6.04 (dt, 1H, *J*=15.2, 7.7 Hz), 5.60 (d, 1H, *J*=11.5 Hz), 4.20 (q, 2H, *J*=7.0 Hz), 3.84 (q, 1H, *J*=3.9 Hz), 3.62–3.56 (m, 1H), 3.51–3.44 (m, 1H), 2.46–2.41 (m, 2H), 1.35 (t, 3H, *J*=7.0 Hz), 0.90 (s, 9H), 0.1 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 144.5, 140.2, 129.2, 116.3, 72.3, 66.1, 59.8, 37.6, 25.8×3, 18.0, 14.2, −4.5, −4.6; MS (EI, 70 eV): *m/z* (%)=314 (16) [M^+], 257 (22), 117 (56), 73 (100); HRMS-EI: *m/z* (%) [M^+] calcd for $C_{16}H_{30}SiO_4$: 314.1913; found 314.1919.

4.2.6. Ethyl (7*S*,2*Z*,4*E*)-7-*tert*-butyldimethylsilyloxy-8-oxo-2,4-octadienoate (15). To a stirred solution of oxaly chloride (1.1 mL, 13.00 mmol) in CH_2Cl_2 (20 mL) was added a solution of DMSO (1.9 mL, 25.98 mmol) in CH_2Cl_2 (15 mL) at −78 °C over 40 min. Upon completion of the addition, a solution of alcohol **14** (2.04 g, 6.49 mmol) in CH_2Cl_2 (10 mL) was added to the mixture over 30 min at −78 °C. The reaction mixture was further stirred at −78 °C for 1.5 h, and then Et_3N (5.4 mL, 38.96 mmol) was added to slowly at −78 °C. The reaction mixture was then allowed to warm to 0 °C, and stirred at this temperature for 1.5 h. A saturated aqueous solution of NH_4Cl (30 mL) was added followed by the addition of Et_2O (300 mL). The organic layer was separated, which was washed with water (30 mL×2), brine (30 mL×2), and dried over Na_2SO_4. Concentration gave the crude aldehyde **15** (2.14 g), which was used directly in the next reaction without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ 9.58 (d, 1H, *J*=7.4 Hz), 7.42 (dd, 1H, *J*=15.2, 11.5 Hz), 6.50 (t, 1H, *J*=11.3 Hz), 5.99 (dt, 1H, *J*=15.2, 7.4 Hz), 5.60 (d, 1H, *J*=11.3 Hz), 4.20 (q, 2H, *J*=7.0 Hz), 4.06–4.02 (m, 1H), 2.61–2.46 (m, 2H), 1.30 (t, 3H, *J*=7.0 Hz), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

4.2.7. C_1-C_{10} segment (2). To a stirred solution of formylmethylenetriphenylphosphorane (2.17 g, 7.14 mmol) in $CHCl_3$ (30 mL) was added slowly a solution of the crude aldehyde **15** (2.14 g) in $CHCl_3$ (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then at room temperature overnight. The solvent was removed in vacuo and the residue was subjected to flash chromatography (*n*-hexane/ethyl acetate, 20:1), yielding **2** (1.75 g, 80% over two steps) as a colorless oil; $[\alpha]_D^{20}$ +75.5 (*c* 0.4, $CHCl_3$); IR (film): 3411, 2958, 2856, 1712, 1693, 1639, 1600, 1259, 1178, 1095, 835, 781 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.59 (d, 1H, *J*=7.9 Hz), 7.43 (ddd, 1H, *J*=15.1, 11.3, 1.1 Hz), 6.78 (dd, 1H, *J*=15.3, 7.9 Hz), 6.53 (t, 1H, *J*=11.2 Hz), 6.28 (ddd, 1H, *J*=15.3, 8.0, 1.4 Hz), 6.00 (dt, 1H, *J*=15.2, 7.5 Hz), 5.62 (d, 1H, *J*=11.6 Hz), 4.55–4.51 (m, 1H), 4.20 (q, 2H, *J*=7.1 Hz), 2.53–2.49 (m, 2H), 1.30 (t, 3H, *J*=7.1 Hz), 0.90 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 166.2, 158.5, 144.1, 138.4, 131.0, 129.9, 116.9, 71.1, 59.9, 40.7, 25.7×3, 18.1, 14.2, −4.7, −4.9; MS (EI, 70 eV): *m/z* (%)=338 (3) [M^+], 281 (53), 199 (100), 73 (90); HRMS-EI: *m/z* (%) [M^+] calcd for $C_{18}H_{30}SiO_4$: 338.1913; found: 338.1907.

4.3. Synthesis of segment C_{11}–C_{24}

4.3.1. (2*R*,4*S*)-1-Benzyloxy-6-*tert*-butyldiphenylsilyloxy-2,4-hexandiol (17). To a stirred solution of triol **16** (6.38 g, 26.58 mmol), imidazole (3.00 g, 44.12 mmol) in dry DMF (50 mL) was added *t*-butyldiphenylchlorosilane (7.76 mL, 29.94 mmol). The mixture was stirred for 15 h at room temperature. Then ether (400 mL) was added to the mixture. The organic layer was separated and washed with water

(50 mL) and brine (50 mL), dried and concentrated. Purification of the residue by a column chromatography on silica gel (ethyl acetate/petroleum ether, 1:2) gave **17** (10.65 g, 84%) as a colorless oil; $[\alpha]_D^{22}$ +8.7 (*c* 1.3, $CHCl_3$); IR (film) 3419, 2951, 2858, 1738, 1454, 1427, 1244, 1113, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66–7.63 (m, 4H), 7.44–7.36 (m, 6H), 7.33–7.27 (m, 5H), 4.55 (s, 2H), 4.24–4.18 (m, 1H), 4.17–4.11 (m, 1H), 3.87–3.84 (m, 2H), 3.50 (dd, 1H, J=4.1, 9.5 Hz), 3.41 (dd, 1H, J=7.4, 9.4 Hz), 1.87–1.76 (m, 1H), 1.68–1.57 (m, 3H), 1.03 (s, 9H); MS (EI, 70 eV): *m*/*z* (%)=421 (19.5) [$M^+ - {}^t$Bu], 403 (25.8), 313 (6.1), 199 (31.7), 91 (100).

4.3.2. Benzyl (2*R*,4*S*)-6-*tert*-butyldiphenylsilyloxy-2,4-di-*O*-isopropylidene hexyl ether (18). The diol **17** (10.20 g, 21.34 mmol) and CSA (106 mg, 0.46 mmol) were dissolved in 2, 2-dimethoxypropane (71 mL). The mixture was stirred for 2 h at room temperature, then neutralized with $NaHCO_3$, filtered and concentrated. The residue was extracted with ether (400 mL), and the organic layer was washed with aqueous solution of $NaHCO_3$ (50 mL), water (50 mL) and brine (50 mL) successively, then dried and concentrated. The residue was purified by column chromatography on silica gel (ether/petroleum ether, 1:8) to afford **18** (10.15 g, 97% based on partially recovered starting material) as a colorless oil; $[\alpha]_D^{22}$ +20.3 (*c* 0.9, $CHCl_3$); IR (film): 3070, 2933, 2858, 1473, 1427, 1379, 1225, 1113, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65–7.62 (m, 4H), 7.42–7.32 (m, 6H), 7.35–7.25 (m. 5H), 4.61 (d, 1H, J=12.3 Hz), 4.54 (d, 1H, J=12.2 Hz), 4.13–4.00 (m, 2H), 3.80–3.74 (m, 1H), 3.69–3.64 (m, 1H), 3.49 (dd, 1H, J=6.8, 10.5 Hz), 3.41 (dd, 1H, J=4.2, 10.5 Hz), 1.73–1.48 (m, 4H), 1.35 (s, 6H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 135.5×4, 133.9, 133.9, 129.5×3, 128.3×3, 127.7×2, 127.6×3, 100.3, 73.3, 72.8, 66.3, 63.3, 60.0, 38.8, 34.8, 26.8×3, 24.9×2, 19.2; MS (EI, 70 eV): *m*/*z* (%)=503 (0.4) [$M^+ - CH_3$], 397 (0.4), 255 (2), 235 (6), 199 (100), 181 (6), 121 (3).

4.3.3. (2*R*,4*S*)-6-*tert*-Butyldiphenylsilyloxy-2,4-di-*O*-isopropylidene hexanol (19). To a stirred solution of benzyl ether **18** (6.34 g, 12.24 mmol) in ethanol (200 mL) was added the freshly prepared W_2 Raney Ni. The mixture was stirred for 6 h at 60 °C. Then the mixture was cooled to room temperature and filtered. Concentration of the filtrate and purification of the residue by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:8) gave **19** (5.19 g, 98%) as a colorless oil; $[\alpha]_D^{22}$ +9.0 (*c* 1.1, $CHCl_3$); IR (film): 3454, 2933, 1473, 1427, 1381, 1225, 1113, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66–7.63 (m, 4H), 7.43–7.34 (m, 6H), 4.10–4.02 (m, 1H), 3.96–3.90 (m, 1H), 3.80–3.75 (m, 1H), 3.70–3.65 (m, 1H), 3.61–3.55 (m, 1H), 3.54–3.48 (m, 1H), 1.78–1.59 (m, 3H), 1.52–1.44 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.4×4, 133.7×2, 129.5×2, 127.5×4, 100.4, 67.5, 65.3, 63.3, 59.9, 38.7, 33.7, 26.8×3, 24.9, 24.8, 19.1; MS (EI, 70 eV): *m*/*z* (%)=413 (2.6) [$M^+ - CH_3$], 313 (40), 255 (20.2), 235 (26.8), 199 (100), 183 (19.1). Anal. Calcd for $C_{25}H_{36}O_4Si$: C, 70.04; H, 8.46. Found: C, 69.68; H, 8.39.

4.3.4. (2*R*,4*S*)-6-*tert*-Butyldiphenylsilyloxy-2,4-di-*O*-isopropylidene hexanal (7). To a stirred solution of oxalyl chloride (2.12 mL, 24.28 mmol) in dry CH_2Cl_2 (90 mL) at −78 °C was added DMSO (3.43 mL, 48.41 mmol) in CH_2Cl_2 (10 mL) dropwise over 5 min. The resulting mixture was stirred for 15 min, then the alcohol **19** (5.18 g, 12.10 mmol) in CH_2Cl_2 (10 mL) was added. After stirring for 40 min, triethylamine (8.5 mL, 61.09 mmol) was added dropwise while the reaction temperature was maintained at −78 °C. The stirring was continued for 5 min, then the mixture was warmed slowly to room temperature over 1.5 h. Water (10 mL) was added to the mixture. The organic layer was separated and washed with water (10 mL). The aqueous layer was extracted with ether (100 mL×2). The combined organic layers were washed with brine (30 mL), dried and concentrated. The residual oil was dissolved in ether (50 mL). The solution was filtered and concentrated to give crude aldehyde **7** as a yellow oil, which was directly used in the next step without further purification.

4.3.5. (*E*,*E*)-Conjugated diene ester (20). Triethyl 4-phosphonocrotonate (6.06 g, 24.38 mmol), $LiOH \cdot H_2O$ (1.02 g, 24.28 mmol), 4 Å molecular sieves (18 g) and crude aldehyde **19** were mixed in THF (121 mL). The mixture was refluxed for 10 h, then filtered with a short silica gel column. The filtrate was concentrated, and the residue was purified by column chromatography (ethyl acetate/petroleum ether, 1:20) to give **20** (3.85 g, 62% for two steps) as a colorless oil. The stereoselectivity (*E*,*E*/*Z*,*E*=5:1) was determined by ^1H NMR; IR (film): 2931, 2858, 1716, 1647, 1620, 1473, 1429, 1379, 1227, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65–7.62 (m, 4H), 7.42–7.34 (m, 6H), 7.25 (dd, 1H, J=11.0, 15.2 Hz), 6.31 (dd, 1H, J=11.2, 15.2 Hz), 6.10 (dd, 1H, J=5.4, 15.4 Hz), 5.86 (d, 1H, J=15.4 Hz), 4.46–4.41 (m, 1H), 4.19 (q, 2H, J=7.1 Hz), 4.15–4.06 (m, 1H), 3.81–3.73 (m, 1H), 3.71–3.65 (m, 1H), 1.81–1.65 (m, 4H), 1.37 (s, 3H), 1.35 (s, 3H), 1.30 (t, 3H, J=7.1 Hz), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 143.9, 142.4, 135.5×4, 133.8×2, 129.6×2, 127.6×4, 121.5, 120.0, 100.5, 66.7, 63.1, 60.3, 59.9, 38.8, 37.6, 26.8×3, 25.5, 24.7, 19.7, 14.2; MS (EI, 70 eV): *m*/*z* (%)=507 (0.1) [$M^+ - CH_3$], 407 (6), 255 (84), 225 (27), 199 (100), 183 (20), 117 (18).

4.3.6. (*E*,*E*)-Conjugated diene alcohol (21). To a stirred solution of ester **20** (1.07 g, 2.05 mmol) in CH_2Cl_2 (70 mL) at −78 °C was added DIBAL-H (6.20 mL, 1 M in hexane, 6.20 mmol). After stirring for 30 min, methanol (3 mL) was added. The mixture was warmed slowly to 0 °C and a saturated aqueous solution of sodium potassium tartrate (10 mL) was added. After stirring for 1 h at 0 °C, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with water (15 mL) and brine (20 mL), dried and concentrated. The residue was purified by column chromatography (ethyl acetate/petroleum ether, 1:6) to give **21** (0.90 g, 91%) as a colorless oil; $[\alpha]_D^{24}$ +15.5 (*c* 1.1, $CHCl_3$); IR (film): 3419, 3070, 2996, 2931, 2858, 1473, 1427, 1379, 1223, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66–7.62 (m, 4H), 7.42–7.34 (m, 6H), 6.28–6.14 (m, 2H), 5.87–5.78 (m, 1H), 5.72 (dd, 1H, J=6.1, 14.5 Hz), 4.40–4.34 (m, 1H), 4.21–4.12 (m, 3H), 3.82–3.75 (m, 1H), 3.71–3.65 (m, 1H), 1.80–1.64 (m, 4H), 1.36 (s, 3H), 1.35 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.4×4, 133.8×3,

132.5, 130.5, 129.7, 129.5×2, 127.6×4, 100.3, 67.2, 63.1, 63.0, 59.9, 38.8, 37.8, 26.8×3, 25.5, 24.7, 19.1; MS (EI, 70 eV): *m/z* (%)=465 (0.1) [M^+-CH_3], 347 (3), 255 (100), 225 (30), 199 (26), 183 (20).

4.3.7. (*E*,*E*)-Conjugated diene bromide (22). To a stirred solution of alcohol **21** (2.70 g, 5.62 mmol) in CH_2Cl_2 (30 mL) was added triphenylphosphine (1.70 g, 6.49 mmol). The solution was cooled to −78 °C, and NBS (1.17 g, 6.57 mmol) was added in portions. After stirring for 30 min at −78 °C, methanol (0.58 mL) was added followed by the addition of ether (50 mL). The mixture was washed with water (10 mL), saturated aqueous solution of sodium carbonate (10 mL) and brine (15 mL) successively. The organic layer was dried and concentrated. The residue was dissolved in hexane (60 mL) and allowed to stand in a freezer overnight. The solution was filtered and the filtrate was concentrated. The residue was treated with hexane three times as described above to afford bromide **22** (2.95 g, 95%); $[\alpha]_D^{24}$ +2.8 (*c* 1.9, $CHCl_3$); IR (film): 3070, 2931, 2858, 1471, 1427, 1379, 1200, 987 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66–7.64 (m, 4H), 7.43–7.34 (m, 6H), 6.28–6.17 (m, 2H), 5.91–5.82 (m, 1H), 5.80–5.67 (m, 1H), 4.42–4.36 (m, 1H), 4.18–4.08 (m, 1H), 4.01 (d, 2H, *J*= 7.8 Hz), 3.85–3.76 (m, 1H), 3.68 (dd, 1H, *J*=5.3, 10.5 Hz), 1.79–1.62 (m, 4H), 1.36 (s, 3H), 1.35 (s, 3H), 1.03 (s, 9H); MS (EI, 70 eV): *m/z* (%)=527/529 (3.3/3.2) [M^+-CH_3], 463 (21.5), 311 (19.6), 255 (100), 199 (36.0); HRMS-EI: *m/z* [M^+−Bu–Me_2CO] calcd for $C_{22}H_{24}^{79}BrO_2Si$: 427.0729; found: 427.0707; calcd for $C_{22}H_{24}^{81}BrO_2Si$: 429.0709; found: 429.0683.

4.3.8. (*E*,*E*)-Conjugated diene phenylsulfone (23). To a solution of **9** (1.00 g, 2.99 mmol) in THF (20 mL) was added dropwise *n*-BuLi (1.77 mL, 3.54 mmol, 2 M solution in hexane) under stirring at −78 °C. After 30 min, the bromide **22** (1.68 g, 3.09 mmol) in THF (10 mL) was added rapidly. The reaction mixture was stirred at −78 °C for 1 h, then warmed up to −40 °C. A saturated aqueous solution of NH_4Cl (5 mL) was added followed by the addition of ether (100 mL). The organic layer was washed with water (10 mL) and brine (15 mL), dried and concentrated. Purification of the residue by column chromatography on silica gel (petroleum ether/ethyl acetate, 8:1) afforded **23** (2.2 g, 93%) as a mixture of diastereomers. IR (film): 3070, 2931, 2856, 1612, 1514, 1379, 1304, 1248, 1146, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, 2H, *J*=7.6 Hz), 7.64–7.60 (m, 5H), 7.53–7.50 (m, 2H), 7.40–7.34 (m, 6H), 7.22 (d, 2H, *J*=7.3 Hz), 6.87 (d, 2H, *J*=7.4 Hz), 6.13–6.04 (m, 1H), 6.00–5.91 (m, 1H), 5.57–5.47 (m, 2H), 4.47 (d, 1H, *J*=11.2 Hz), 4.36–4.27 (m, 1H), 4.22 (d, 1H, *J*=11.3 Hz), 4.17–4.05 (m, 1H), 3.80 (s, 3H), 3.85–3.75 (m, 1H), 3.75–3.65 (m, 2H), 3.29–3.21 (m, 1H), 2.54–2.46 (m, 1H), 2.29–2.20 (m, 1H), 2.02–1.92 (m, 1H), 1.78–1.68 (m, 4H), 1.67–1.57 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 1.11 (d, 3H, *J*= 5.9 Hz), 1.02 (s, 9H); MS (EI, 70 eV): *m/z* (%)=796 (4.7) [M^+], 781 (4.2), 681 (18.8), 539 (11.6), 397 (16.6), 323 (18.8), 255 (100); HRMS-EI: *m/z* [M^+−Bu–Me_2CO] calcd for $C_{40}H_{45}O_6SSi$: 681.2707; found: 681.2711.

4.3.9. (*E*,*E*)-Conjugated diene *tert*-butyldiphenylsilyl ether (24). To a solution of the mixture **23** (1.99 g, 2.5 mmol) in dry methanol (100 mL) were added Na_2HPO_4 (7.14 g, 50.3 mmol) and Na/Hg (17.22 g, 6%, 44.9 mmol) at 0 °C. The mixture was stirred for 5 h at room temperature, filtered through a short silica gel column. The filtrate was concentrated and purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) to afford **24** (1.08 g, 66%) as a colorless oil; $[\alpha]_D^{22}$ −2.2 (*c* 1.2, $CHCl_3$); IR (film): 3070, 2933, 1612, 1514, 1464, 1427, 1379, 1248, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66–7.62 (m, 4H), 7.40–7.34 (m, 6H), 7.24 (d, 2H, *J*= 8.2 Hz), 6.85 (d, 2H, *J*=8.5 Hz), 6.18–6.11 (m, 1H), 6.02–5.94 (m, 1H), 5.70–5.64 (m, 1H), 5.60–5.53 (m, 1H), 4.47 (d, 1H, *J*=11.5 Hz), 4.35 (d, 1H, *J*=11.3 Hz), 4.38–4.30 (m, 1H), 4.17–4.07 (m, 1H), 3.78 (s, 3H), 3.85–3.74 (m, 1H), 3.70–3.65 (m, 1H), 3.49–3.43 (m, 1H), 2.08–2.03 (m, 2H), 1.74–1.62 (m, 4H), 1.61–1.18 (m, 4H), 1.36 (s, 3H), 1.35 (s, 3H), 1.15 (d, 3H, *J*=6.1 Hz), 1.02 (s, 9H); MS (EI, 70 eV): *m/z* (%)=656 (13.4) [M^+], 641 (7.7), 541 (12.8), 339 (18.0), 269 (32.5), 255 (100), 225 (99.8); HRMS-EI: *m/z* calcd for $C_{41}H_{56}SiO_5$: 656.3897; found: 656.3911.

4.3.10. (*E*,*E*)-Conjugated diene alcohol (25). To a solution of **24** (1.05 g, 1.60 mmol) in THF (40 mL) at 0 °C was added TBAF (20 mL, 0.1 M solution in THF, 2 mmol). The mixture was warmed to room temperature and stirred for 10 h. Ether (100 mL) was added to the mixture. The organic layer was washed with water (10 mL) and brine (15 mL), dried and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 4:1) to give **25** (0.60 g, 89%) as a colorless oil; $[\alpha]_D^{22}$ +9.2 (*c* 0.6, $CHCl_3$); IR (film): 3440, 1612, 1514, 1379, 1248, 1171, 991, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, 2H, *J*=8.4 Hz), 6.85 (d, 2H, *J*=8.5 Hz), 6.15 (dd, 1H, *J*=15.3, 10.5 Hz), 5.98 (dd, 1H, *J*=15.0, 10.5 Hz), 5.67 (dt, 1H, *J*=6.9, 14.3 Hz), 5.55 (dd, 1H, *J*=15.3, 6.6 Hz), 4.47 (d, 1H, *J*=11.3 Hz), 4.38–4.34 (m, 1H), 4.34 (d, 1H, *J*= 11.2 Hz), 4.12–4.06 (m, 1H), 3.78 (s, 3H), 3.80–3.72 (m, 2H), 3.47–3.43 (m, 1H), 2.49 (br s, 1H), 2.06–2.02 (m, 2H), 1.78–1.66 (m, 4H), 1.55–1.32 (m, 4H), 1.39 (s, 3H), 1.37 (s, 3H), 1.14 (d, 3H, *J*=6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 135.5, 131.3, 131.2, 130.6, 129.6, 129.1×2, 113.7×2, 100.4, 74.3, 69.9, 67.5, 66.6, 61.0, 55.2, 37.7× 2, 36.1, 32.6, 25.4, 25.1, 24.8, 19.6; MS (EI, 70 eV): *m/z* (%)=418 (2.65) [M^+], 3.60 (11.2), 342 (8.55), 286 (9.23), 260 (6.32), 121 (100); HRMS-EI: *m/z* calcd for $C_{25}H_{38}O_5$: 418.2719; found: 418.2709.

4.3.11. (*E*,*E*)-Conjugated diene iodide (26). To a stirred solution of **25** (103 mg, 0.25 mmol) in benzene (51 mL) at 0 °C were added iodine (94 mg, 0.37 mmol), triphenyl phosphine (98 mg, 0.37 mmol) and imidazole (51 mg, 0.75 mmol) successively. The mixture was stirred at 0 °C for 1 h. A saturated aqueous solution of $NaHCO_3$ (50 mL) was added. Stirring was continued for an additional 30 min. The organic layer was washed with saturated aqueous solution of $Na_2S_2O_3$ (50 mL), water (20 mL), and brine (50 mL) successively, dried and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 15:1) to afford **26** (0.12 g, 92%) as a colorless oil; $[\alpha]_D^{22}$ −12.8 (*c* 1.2, $CHCl_3$); IR (film): 2935, 1612, 1514, 1379, 1248, 1173, 1038, 989, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, 2H, *J*= 8.5 Hz), 6.85 (d, 2H, *J*=8.5 Hz), 6.22–6.12 (m, 1H), 6.02–5.94 (m, 1H), 5.70–5.63 (m, 1H), 5.59–5.47 (m, 1H), 4.47

(d, 1H, J=11.2 Hz), 4.42–4.32 (m, 1H), 4.35 (d, 1H, J=11.2 Hz), 3.99–3.92 (m, 1H), 3.78 (s, 3H), 3.48–3.43 (m, 1H), 3.30–3.22 (m, 2H), 2.07–2.03 (m, 2H), 1.96–1.91 (m, 4H), 1.57–1.31 (m, 4H), 1.39 (s, 3H), 1.36 (s, 3H), 1.15 (d, 3H, J=5.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 135.4, 131.3, 131.1, 130.5, 129.6, 129.1×2, 113.7×2, 100.4, 74.2, 69.8, 67.4, 66.1, 55.2, 39.2, 37.3, 36.1, 32.5, 25.2, 25.1, 24.9, 19.6, 2.2; MS (EI, 70 eV): m/z (%)=528 (10.26) [M^+], 513 (6.5), 470 (9.83), 349 (32.56), 269 (16.24), 121 (100); HRMS-EI: m/z calcd for $C_{25}H_{37}IO_4$: 528.1737; found: 528.1731.

4.3.12. C_{11}–C_{24} segment (3). To a solution of **26** (279 mg, 0.53 mmol) in CH_3CN (2 mL) was added Ph_3P (277 mg, 1.06 mmol). The resulting mixture was refluxed for 48 h under N_2. Then the mixture was cooled to room temperature, and washed with petroleum ether. Concentration of the mixture gave **3** (412 mg, 97%) as a white foam solid; $[\alpha]_D^{24}$ +6.7 (c 0.8, $CHCl_3$); IR (film): 1587, 1512, 1437, 1379, 1248, 1173, 1113, 1032, 997 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.67 (m, 15H), 7.22 (d, 2H, J=8.4 Hz), 6.83 (d, 2H, J=8.3 Hz), 6.14–6.08 (m, 1H), 6.00–5.91 (m, 1H), 5.67–5.59 (m, 1H), 5.54 (dd, 1H, J=6.6, 15.5 Hz), 4.45 (d, 1H, J=11.2 Hz), 4.33 (d, 1H, J=11.4 Hz), 4.32–4.27 (m, 1H), 4.21–4.12 (m, 1H), 4.11–4.07 (m, 1H), 3.76 (s, 3H), 3.50–3.40 (m, 2H), 2.03–1.98 (m, 2H), 1.91–1.55 (m, 4H), 1.54–1.34 (m, 4H), 1.40 (s, 3H), 1.38 (s, 3H), 1.13 (d, 3H, J=6.0 Hz); MS (EI, 70 eV): m/z (%)=715 (0.4) [$M^+-C_3H_7O_2$], 664 (0.6), 578 (15.5), 319 (69.2), 262 (100), 121 (93.1).

4.4. Synthesis of *seco*-precursor

4.4.1. PMB ether of *seco*-precursor (27). To a solution of **2** (31 mg, 0.913 mmol) and 3 (86.6 mg, 0.110 mmol) in THF (3 mL) was added dropwise NaHMDS (55 μL, 0.110 mmol, 2 M solution in THF) under stirring at −78 °C. The reaction mixture was stirred at −78 °C for 2 h. A saturated aqueous solution of $NaHCO_3$ (3 mL) was added followed by the addition of ether (50 mL). The organic layer was washed with water (10 mL) and brine (15 mL), dried and concentrated. Purification of the residue by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) afforded **27** (52 mg, 79%) as a colorless oil, (Z/E= 98:2 by HPLC, Waters Spherisorb 4.6×150 mm column with cyclohexane/isopropanol, 97.5:2.5 as eluents); $[\alpha]_D^{20}$ +9.2 (c 0.6, $CHCl_3$); IR (film): 2928, 2854, 1716, 1514, 1464, 1377, 1248, 1178, 1070, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, 1H, J=15.4, 11.5 Hz), 7.24 (d, 2H, J=8.4 Hz), 6.85 (d, 2H, J=8.4 Hz), 6.51 (dd, 1H, J=11.3, 11.1 Hz), 6.42 (dd, 1H, J=14.8, 11.2 Hz), 6.15 (dd, 1H, J=15.0, 10.2 Hz), 6.06—5.95 (m, 3H), 5.64 (dd, 2H, J=14.9, 6.2 Hz), 5.56 (d, 1H, J=11.8 Hz), 5.57–5.53 (m, 1H), 5.45–5.38 (m, 1H), 4.47 (d, 1H, J=11.2 Hz), 4.35 (d, 1H, J=11.3 Hz), 4.36–4.31 (m, 1H), 4.27–4.21 (m, 1H), 4.16 (q, 2H, J=7.1 Hz), 3.91–3.83 (m, 1H), 3.78 (s, 3H), 3.49–3.43 (m, 1H), 2.47–2.31 (m, 4H), 2.10–1.98 (m, 2H), 1.80–1.60 (m, 6H), 1.37 (s, 3H), 1.36 (s, 3H), 1.28 (t, 3H, J=7.1 Hz), 1.15 (d, 3H, J=5.9 Hz), 0.87 (s, 9H), 0.02 (s, 3H), 0.006 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 159.0, 144.9×2, 141.0, 136.5, 135.3, 131.2, 130.9, 129.8, 129.1, 129.0×2, 126.9, 124.9, 116.1×2, 113.7×2, 100.3, 74.3, 72.7, 69.9, 67.5, 66.3, 59.8, 55.3, 42.0, 37.4, 36.2, 32.6, 29.7, 25.8×3, 25.5, 25.2, 24.9, 19.6, 18.2, 14.3, −4.4, −4.8; MS (EI, 70 eV): m/z (%)=722 (0.3) [M^+], 707 (2.4), 583 (10.1), 525 (68.8), 121 (100); HRMS-EI: m/z calcd for $C_{43}H_{66}O_7Si$: 722.4578; found: 722.4538.

4.4.2. *seco*-Precursor alcohol (28). To a solution of **27** (25.0 mg, 34.6 μmol) in CH_2Cl_2/H_2O (2.8/0.16 mL) was added DDQ (11.8 mg, 52.0 μmol) at room temperature in portions. The mixture was stirred for 2 h at room temperature and filtered. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1–4:1) to afford **28** (3.0 mg, 14.4%) as a colorless oil; $[\alpha]_D^{20}$ +5.4 (c 0.5, $CHCl_3$); IR (film): 3419, 2955, 1714, 1639, 1462, 1377, 1252, 1176, 1067, 837, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (dd, 1H, J=15.4, 11.3 Hz), 6.83 (dd, 1H, J=15.0, 11.0 Hz), 6.55 (dd, 1H, J=11.3, 11.0 Hz), 6.42 (dd, 1H, J=15.4, 11.0 Hz), 6.06 (dd, 1H, J=15.4, 10.9 Hz), 6.02 (dd, 1H, J=11.3, 11.0 Hz), 5.68 (dt, 1H, J=15.4, 7.2 Hz), 5.62 (dd, 1H, J=15.0, 5.8 Hz), 5.59 (d, 1H, J=11.4 Hz), 5.42–5.41 (m, 3H), 4.26–4.21 (m, 1H), 4.18 (q, 2H, J=7.0 Hz), 4.12–4.06 (m, 1H), 3.92–3.82 (m, 1H), 3.50–3.43 (m, 1H), 2.44–2.38 (m, 4H), 2.10–1.99 (m, 2H), 1.62–1.58 (m, 2H), 1.50–1.41 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H), 1.36–1.32 (m, 2H), 1.30 (t, 3H, J=7.0 Hz), 1.19 (d, 3H, J=6.2 Hz), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H), (hydroxy hydrogen was not observed); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 144.8, 141.0, 136.5, 132.0, 131.7, 130.0, 129.8, 129.0, 126.9, 124.9, 124.6, 116.2, 100.8, 72.8, 68.9, 68.5, 59.8, 55.3, 42.0, 39.8, 36.1, 34.7, 30.2, 29.7, 27.2, 25.8×3, 23.2, 19.8, 18.2, 14.3, −4.3, −4.8; MS (EI, 70 eV): m/z (%)=602 (3) [M^+], 587 (15), 545 (3), 527 (6), 463 (23), 405 (26), 273 (24), 171 (28), 75 (100); HRMS-EI: m/z calcd for $C_{35}H_{58}O_6Si$: 602.4003; found: 602.3966.

Acknowledgements

This work was supported by a grant from the National Natural Science Foundation of China and a grant from the State Key Laboratory of Bio-organic and Natural Products Chemistry.

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