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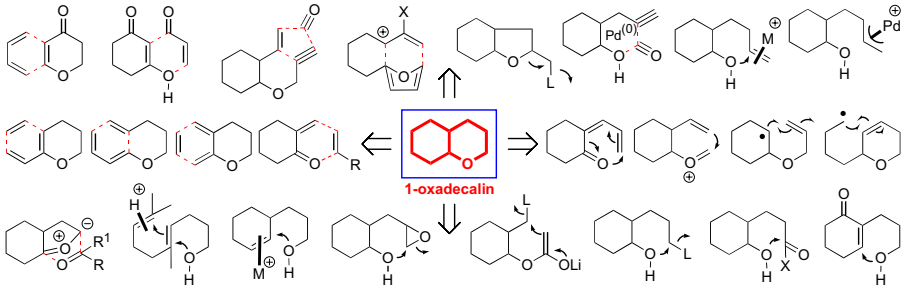
Contents

REPORT



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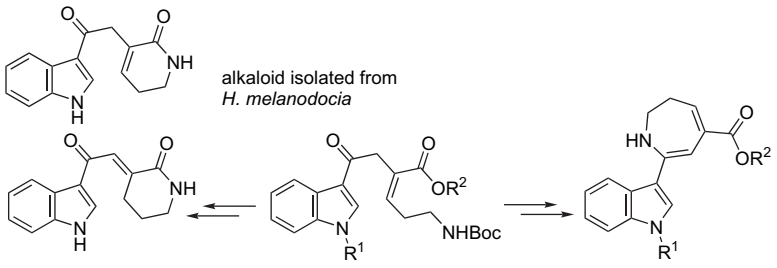
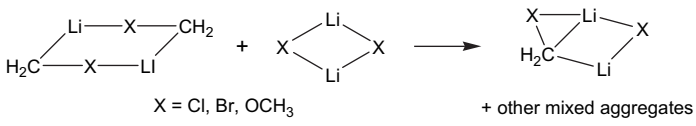
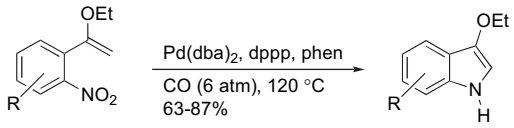
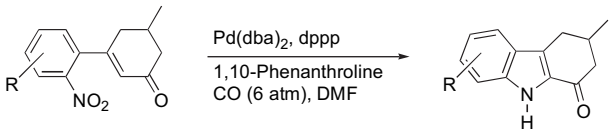
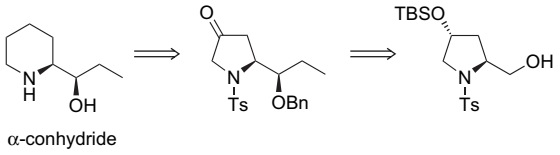
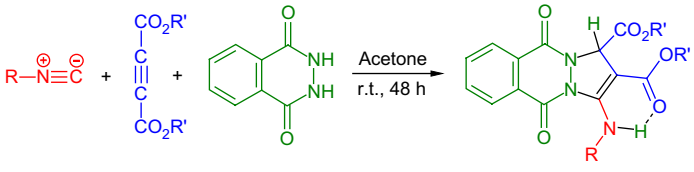


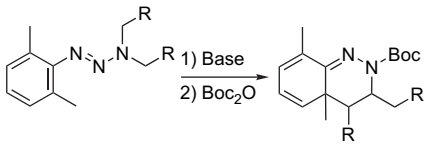


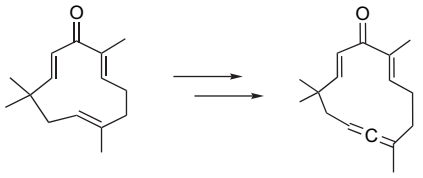


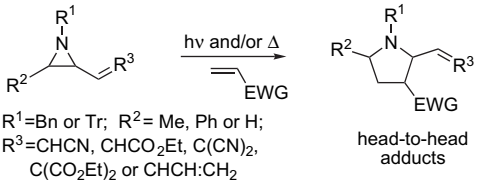




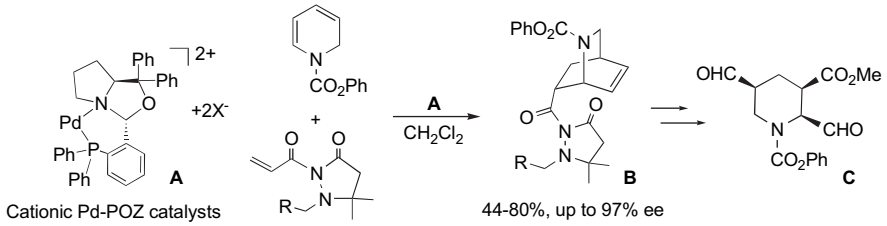




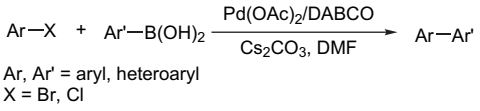


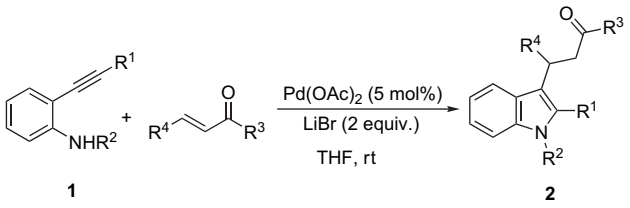


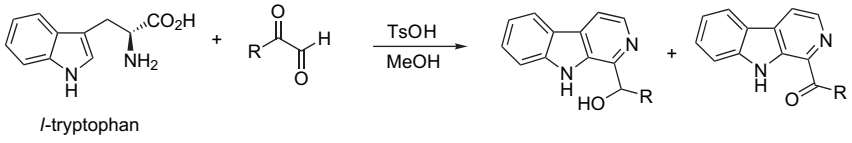
The photoreaction of tri- or disubstituted aziridines with electron-deficient alkenes afforded the novel head-to-head adducts selectivity and efficiently.

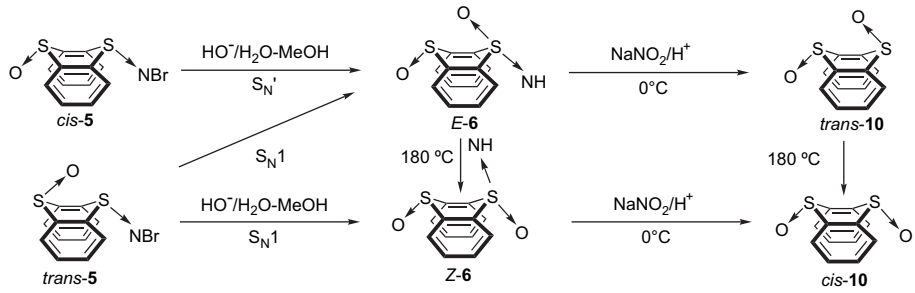


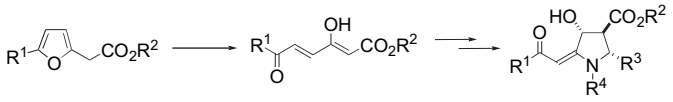
The DA reaction of 1-phenoxycarbonyl-1,2-dihydropyridine with 1-substituted 2-acryloylpyrazolidin-3-ones using cationic chiral Pd–phosphinooxazolidine catalyst **A** afforded chiral isoquinuclidines **B** with an excellent enantioselectivity (up to 97% ee). Furthermore, **B** was transformed to chiral piperidine **C** bearing three chiral carbon centers in the structure.

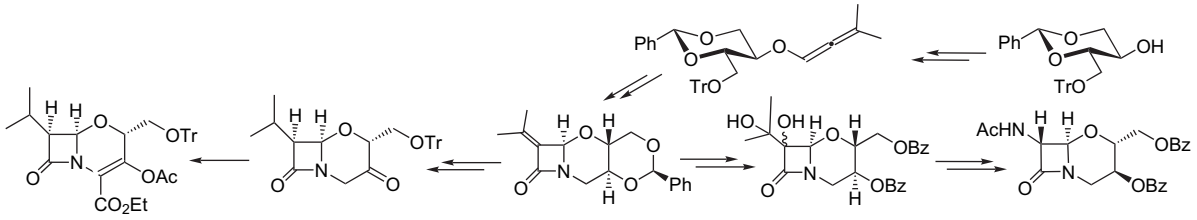


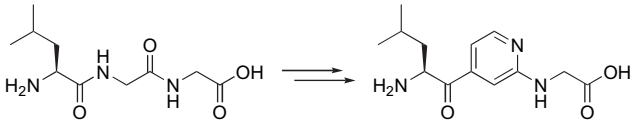


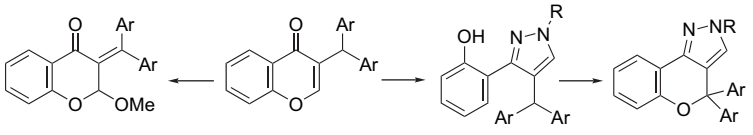


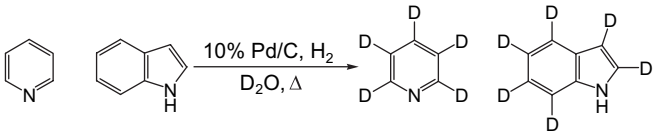


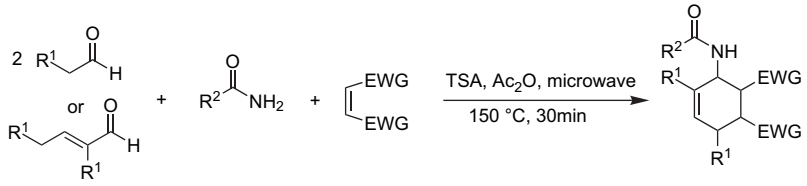




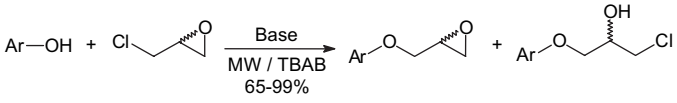


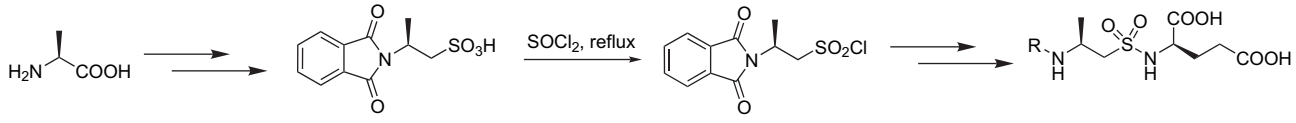


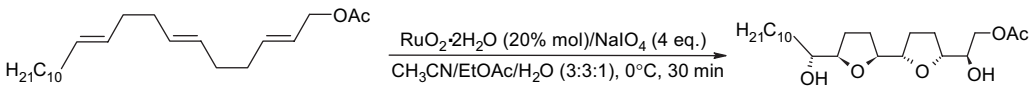


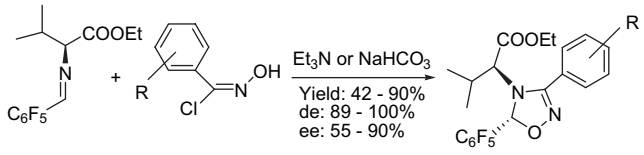


Microwave induced multicomponent reaction without solvent comprising of aldehydes, amides, and dienophiles.









Two methods for the stereospecific 1,3-dipolar cycloaddition reaction of chiral imines and nitrile oxides are described.

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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Strategies and approaches for constructing 1-oxadecalins

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1. Introduction

Tetrahydropyrans represent a fundamental structural motif ubiquitous in natural products and prevalent in organic transformations. In particular, 1-oxadecalins, in which the tetrahydropyranyl unit is fused to a six-membered ring, are commonly seen in biologically relevant natural products such as arisugacins,[1–4] cordypyridones,[5] hongoquercins,[6–8] penostatins,[9,10] rhododaurichromanic acids,[11,12] pyripyropenes,[13,14] phomactin A,[15–18] and forskolin [Fig. 1].[19,20] These are just a few representatives.

Given such prevalence, we decided to examine recent strategies and approaches employed in the constructions of 1-oxadecalins. In order to stay focussed on these strategies and approaches, we elected not to include strategies and approaches for constructing chromenes or chromanes related systems such as rhododaurichromanic acids, which have been summarized in other excellent recent reviews.[4a,c]

In this review, we have only selected work reported on 1-oxadecalins in the last 10 years. We intend to summarize these approaches based on their reaction types. As usual, we apologize in advance for any relevant work that is not cited and/or highlighted here, as it is not intended to be comprehensive but a sketch summary for efforts that have been exerted toward this fundamental structural motif.

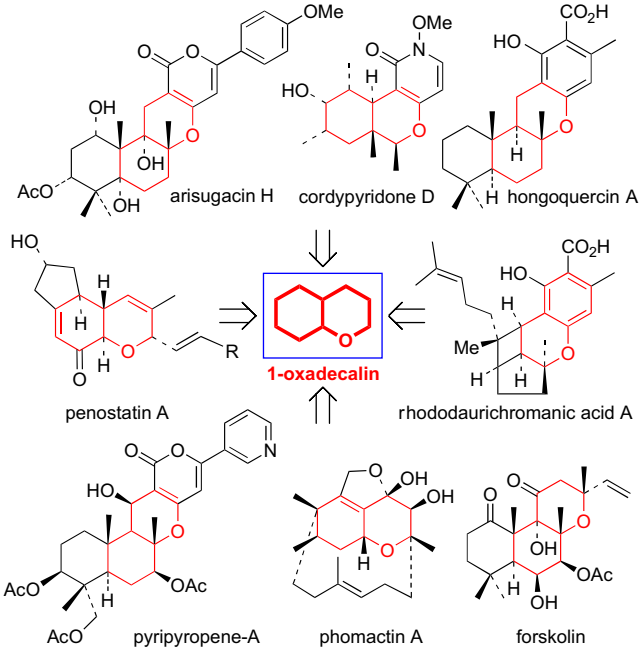
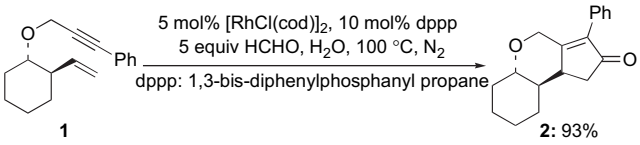


Figure 1.

2. Cycloaddition and annulation reactions

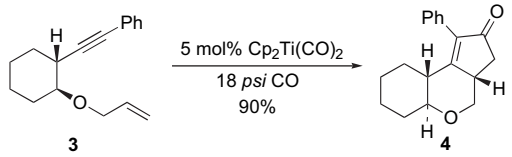
2.1. [2+2+1]

Given that [2+2+1] mathematically implies constructions of a five-membered ring, there are very few examples of [2+2+1] cycloadditions that actually led to 1-oxadecalins. Kakiuchi[21] reported the development of catalytic Pauson–Khand cycloadditions of enynes **1** in aqueous medium employing formaldehyde as a water-soluble source of CO [Scheme 1]. With the oxygen atom being the tether, the cycloaddition gave tricycle **2** that contains a 1-oxadecalin.



Scheme 1.

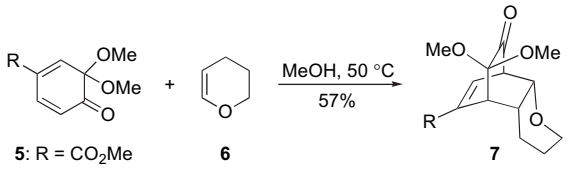
Buchwald[22] showed an interesting intramolecular titanocene-catalyzed Pauson–Khand cycloaddition reaction that led to 1-oxadecalin **4** when using enyne **3** also containing an oxygen atom tether [Scheme 2].



Scheme 2.

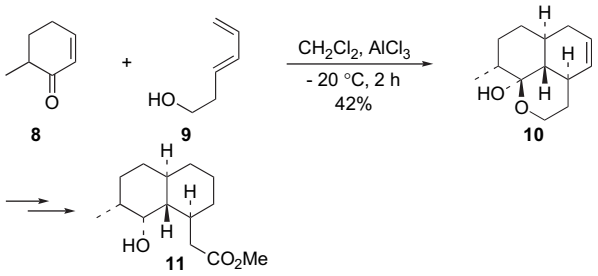
2.2. [4+2]

Including the next section on hetero [4+2] cycloadditions, its very nature implies that Diels–Alder type cycloadditions are quite prevalent as an approach in the synthesis of 1-oxadecalins. Plumet[23] reported that masked *o*-quinones **5** could serve as electron deficient dienes and react in an inverse-demand manner to give *endo*-cycloadduct **7** as a single diastereomer [Scheme 3].



Scheme 3.

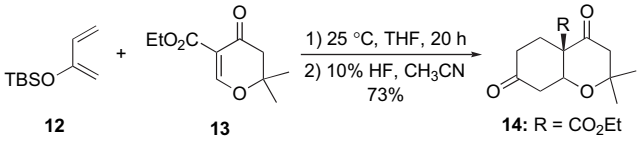
Haynes[24] uncovered a new variation of an $AlCl_3$-catalyzed [$Cu(OTf)_2$ in CH_3CN was also used] highly stereoselective ionic Diels–Alder reaction between enone **8** and diene **9**, which provided racemic hemiacetal **10** [Scheme 4].



Scheme 4.

Totah[25] developed an elegant method for preparations of 1-oxadecalinic frameworks through Diels–Alder reactions of Danishefsky's diene **12** with the 5-carbethoxy

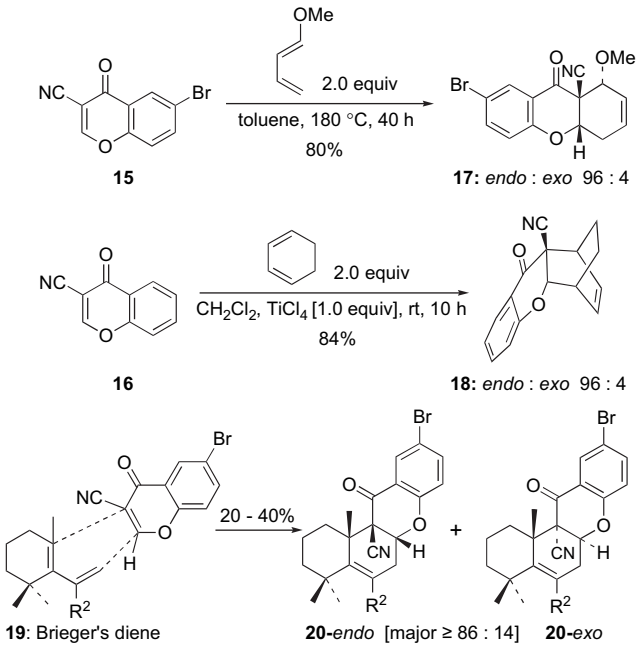
dihydro-γ-pyrone derivatives **13** [Scheme 5]. These cycloadditions can also be catalyzed by Lewis acid such as $ZnCl_2$. This work represents the best example in which γ-pyrones are being utilized as dienophiles and provides an excellent approach toward phomactin A.[15–18]



12 **13** **14:** R = CO_2Et

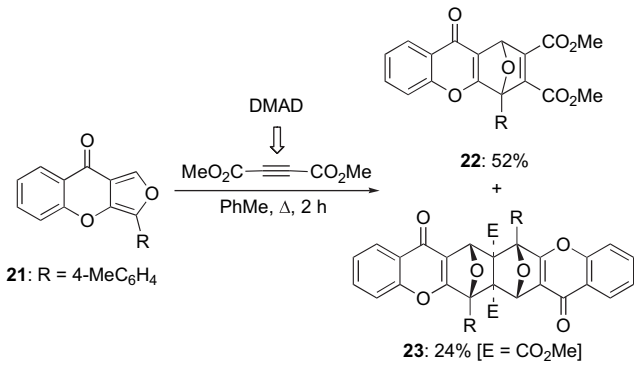
Scheme 5.

Hsung[26] also reported a related Diels–Alder cycloaddition but using 3-cyano-benzopyrones as dienophiles or surrogates of γ-pyrones, leading to the synthesis of xanthones **17** and **18** as well as more elaborate systems such as tetracycle **20** that could be useful for the synthesis of natural product such as hongoquercins[6–8] [Scheme 6].



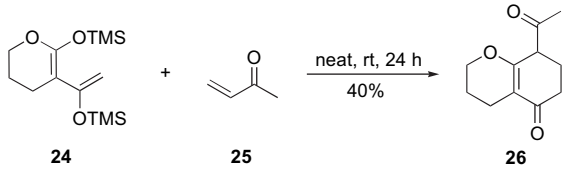
Scheme 6.

Gabbutt[27] found that the reaction of furan **21** with DMAD gave two compounds: cycloadduct **22** in 52% yield and a C_2 symmetric *anti exo–exo* bis-cycloadduct **23** in 24% yield [Scheme 7].



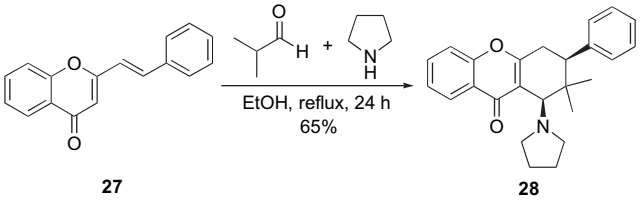
Scheme 7.

Diels–Alder reactions of a novel 'inner-outer-ring' 1,3-silyloxydiene with a variety of dienophiles were reported by Sarandeses [Scheme 8].[28] The reaction with methyl vinyl ketone gave 1-oxadecalin **26** in 40% yield.



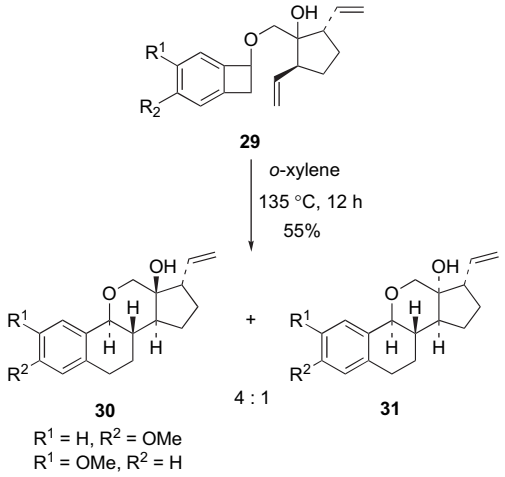
Scheme 8.

Kelkar[29] developed an interesting approach to the synthesis of C-ring substituted xanthones utilizing the [4+2] cycloaddition reactions of vinyl chromones **27** with enamines obtained in situ from the corresponding ketones or aldehydes [Scheme 9].



Scheme 9.

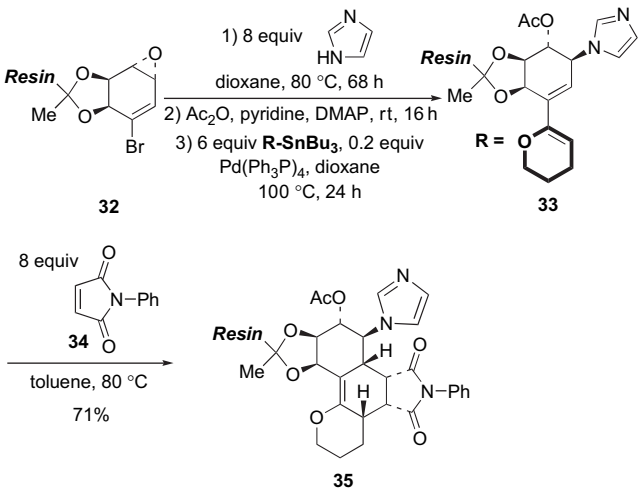
Santelli[30] reported a total synthesis of 11-*oxa*-steroids via an intramolecular Diels–Alder cycloaddition of *ortho*-quinonedimethane derived from ring-opening of benzocyclobutane **29** as the key-step [Scheme 10].



Scheme 10.

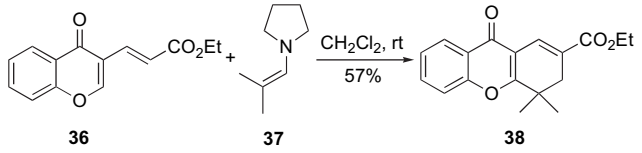
Wendeborn[31] demonstrated a highly efficient sequence of transformations including Stille coupling and *endo*-selective Diels–Alder reactions for the synthesis of highly functionalized polycycles **35** on solid phase [Scheme 11].[31]

In a related manner as Kelkar's work[29] shown in Scheme 9, Bodwell found that the reaction of vinyl chromone **36** with enamine **37** afforded **38** in 57% yield. Elimination of the pyrrolidine group in the initial cycloadduct and isomerizations



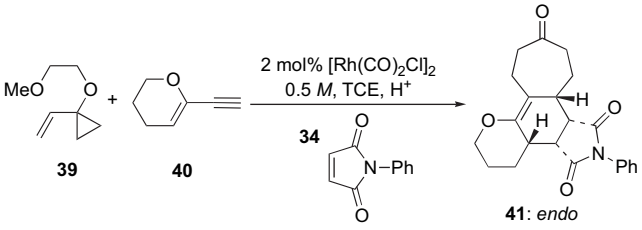
Scheme 11.

of the two olefins occurred to give the conjugation shown in **38** [Scheme 12].[32]



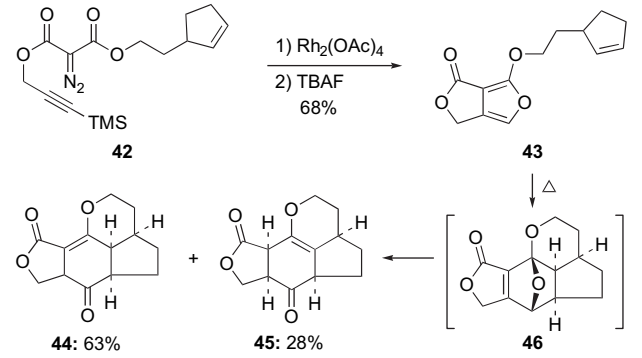
Scheme 12.

Wender[33] developed an impressive three-component tandem [5+2]/[4+2] cycloaddition process to synthesize polycyclic compounds such as **41** [Scheme 13].



Scheme 13.

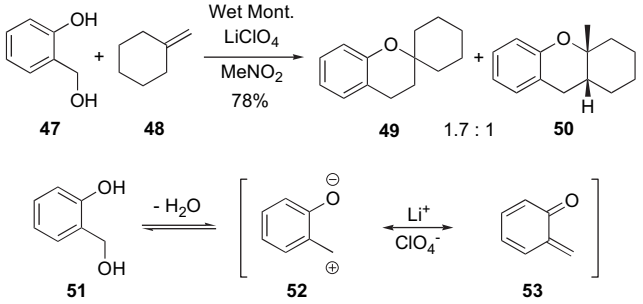
Padwa[34] reported an elegant tandem cyclization/cycloaddition sequence. As shown in Scheme 14, treatment of α-diazo ester **42** with Rh(II) catalyst gave the intramolecular Diels–Alder adduct **46** through furan intermediate **43**. Adduct **46** rearranged to a 2:1 mixture of **44** and **45** in 91% yield.



Scheme 14.

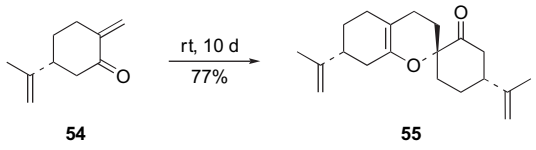
2.3. Hetero [4+2]

Chiba[35] found that intermolecular hetero-Diels–Alder reactions of in situ-generated *o*-quinomethanes **53** [from **47**] and unactivated dienophiles **48** could be accomplished through a wet Montmorillonite catalyst in an $LiClO_4/MeNO_2$ solution to give various chromane skeletons including 1-oxadecalin **50** [Scheme 15].



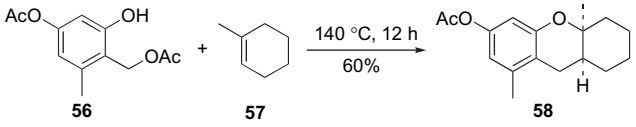
Scheme 15.

Kamat[36] found that the biogenesis of cymbodiacetal involved the key intermediate **55**, which could be prepared by self-dimerization of enone **54** [Scheme 16].



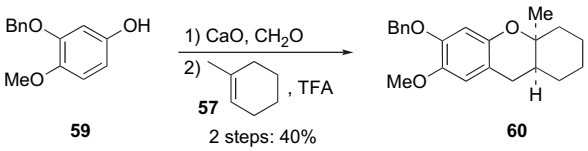
Scheme 16.

Baldwin[37] demonstrated that *o*-quinone methide generated thermally from *o*-methyleneacetoxy-phenol **56** could be employed in the preparation of benzopyrans such as **58** after hetero [4+2] cycloaddition with 1-methylcyclohexene **57** [Scheme 17].



Scheme 17.

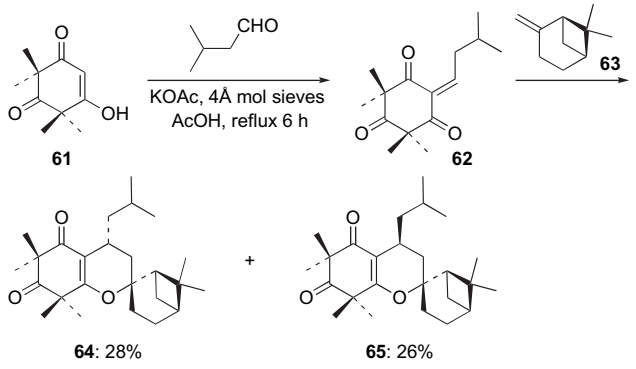
Kraus[38] uncovered a sequence of regioselective hydroxymethylation and hetero-Diels–Alder reaction that constitutes a convenient synthesis of tricyclic analogs of puupehenone [Scheme 18].



Scheme 18.

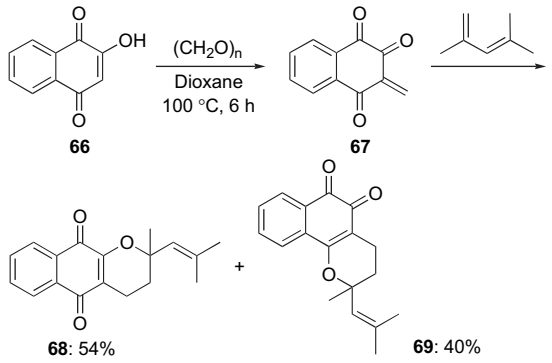
In the structural confirmation of ficifolidione, (1*S*)-β-pinene **63** was reacted with the Knoevenagel condensation product **62** derived in situ from syncarpic acid **61** and

iso-valeraldehyde, leading to the two diastereomers **64** and **65** with **64** being ficifolidione [Scheme 19].[39]



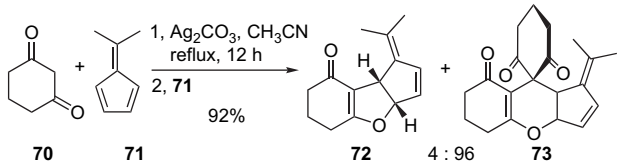
Scheme 19.

Nair[40] reported the generation of *o*-quinone methide **67** from 2-hydroxynaphthoquinone **66** and paraformaldehyde, and its hetero-Diels–Alder reaction as a one-pot synthesis of α- and β-lapachone derivatives [**68** and **69**] [Scheme 20].



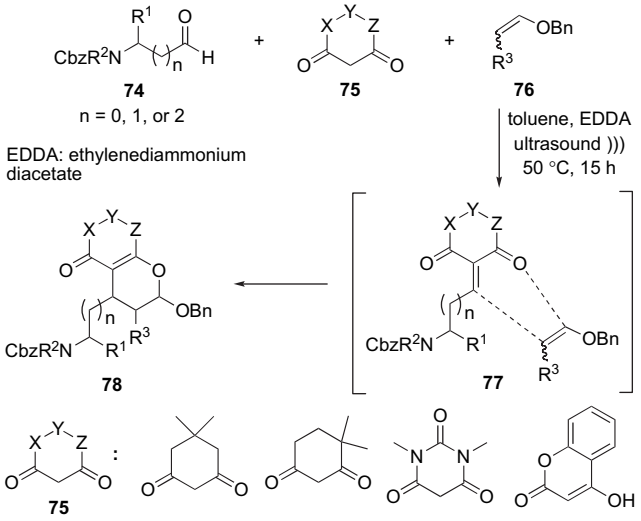
Scheme 20.

Hong[41] cleverly developed a novel sequence of oxidative dimerization/hetero-[3+2] or hetero-Diels–Alder cycloaddition of 1,3-diketones such as **70** with fulvene **71**. This sequence led to polycyclic products such as **72** and **73** [Scheme 21]. When diketone **70** was refluxed with Ag_2CO_3 prior to the addition of fulvene, **73** was almost the sole product [**72**:**73**=4:96]. The process is likely a radical-mediated dimerization.



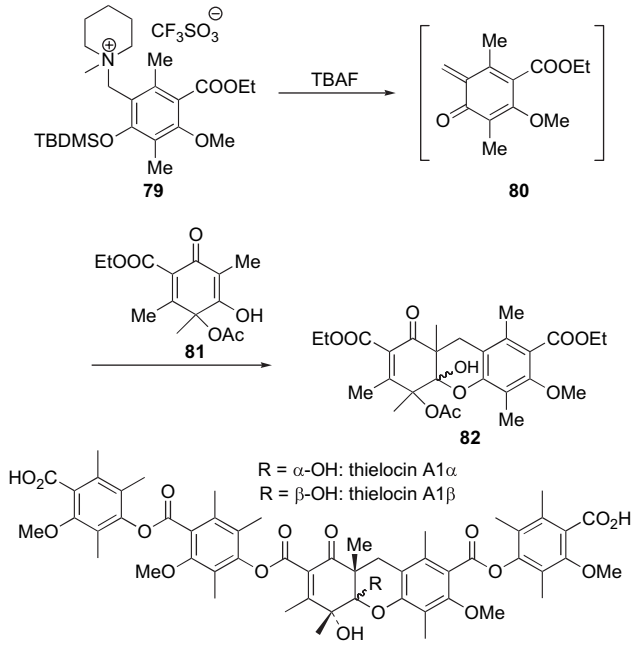
Scheme 21.

Over the last two decades, Tietze[42] has elegantly developed a range of different Knoevenagel condensation/hetero-DA cycloaddition tandem sequences. Specifically here, Knoevenagel condensations of amino aldehydes **74** with 1,3-dicarbonyl components **75** followed by Diels–Alder reactions with enol ethers afforded a range of 1-oxadecalins **78** [Scheme 22].



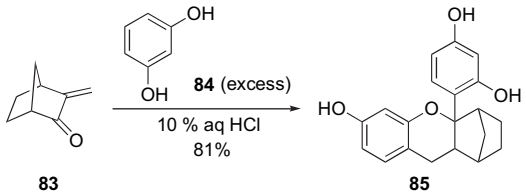
Scheme 22.

In their total synthesis of thielocin A1β, Young[43] used hetero [4+2] cycloaddition of an *o*-quinone methide intermediate **80** with vinylogous acid **81** to construct a 1-oxadecalin moiety **82** [Scheme 23].



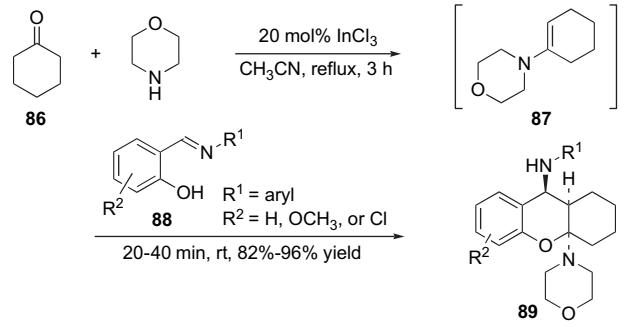
Scheme 23.

An acid-catalyzed reaction of resorcinol **84** with vinyl ketone **83**, which constitutes a formal [4+2] cycloaddition, led to **85** [no stereochemical assignment was given] [Scheme 24].[44]



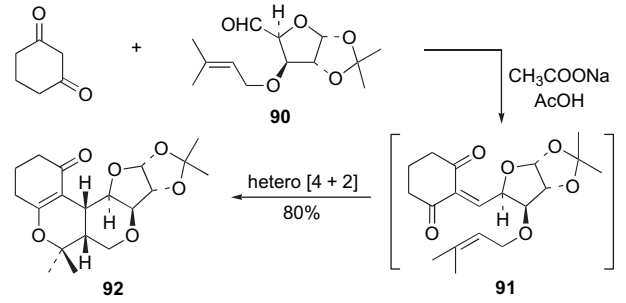
Scheme 24.

In the presence of $InCl_3$ as a catalyst, a one-pot reaction of cyclohexanone **86** and morpholine with salicylaldehyde imines **88** proceeded smoothly to give aminal **89** in good yields [Scheme 25].[45]



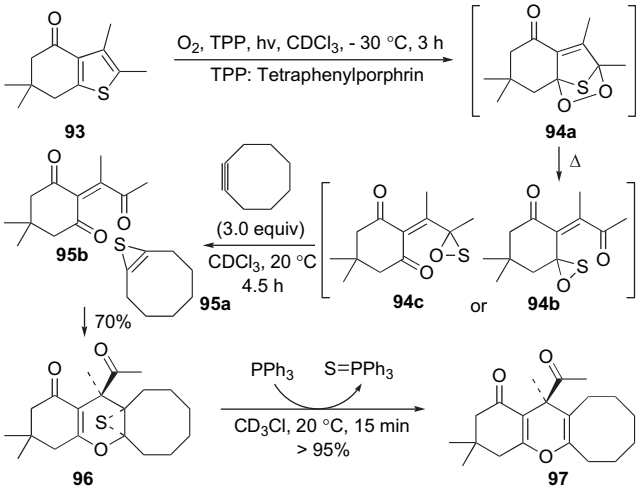
Scheme 25.

Yadav[46] illustrated that the *O*-prenylated sugar derivative **90** derived from D-glucose could undergo an intramolecular domino Knoevenagel condensation/hetero-Diels–Alder reaction with 1,3-cyclohexanediones to afford **92** in a good yield and high diastereoselectivity [Scheme 26].



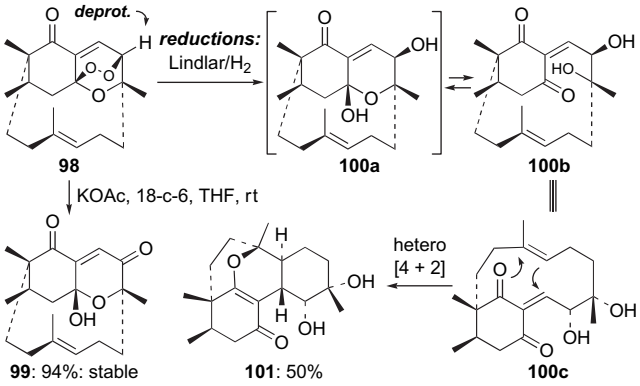
Scheme 26.

Adam[47] reported a very interesting sequence in which 1-oxadecalins **96** and **97** were obtained from thiophene **93** via: (a) a singlet-O_2 Diels–Alder cycloaddition, (b) thermal rearrangements of the resulting *endo*-peroxide **94a**, (c) a sulfur transfer from oxathiiranes **94c** or **94b**, and (d) a hetero [4+2] cycloaddition of the resulting thiirene **95a** with enedione **95b**. Compound **97** was a result of *epi*-sulfide contraction of **96** promoted by triphenylphosphine [Scheme 27].[47]



Scheme 27.

Hsung[48] reported another study also involving *endo*-peroxides [Scheme 28]. In this case, while under basic conditions, ring-opening of *endo*-peroxide **98** occurred to give hydroxy enone **99**, reductive conditions led to a new 1-oxadecalin **101** likely through ene-diol **100a** and an intramolecular hetero-Diels–Alder cycloaddition of **100c**.

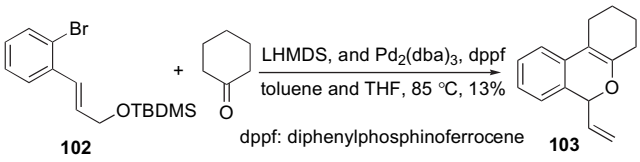


Scheme 28.

2.4. [3+3]

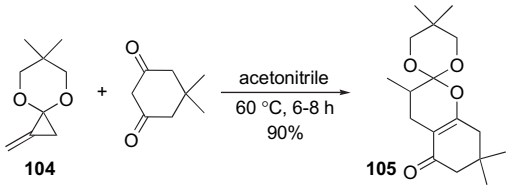
We note here that this section will only highlight some of the recent studies and try not to duplicate those [3+3] cycloaddition or annulations that are already reviewed in two excellent earlier reviews.

Wills[49] discovered a Pd(0)-catalyzed tandem sequence in a formal [3+3] cycloaddition or annulation manner to form 1-vinyl-1*H*-isochromene derivatives such as **103** from lithium enolate generated from cyclohexanone, albeit the yield is not high in this case [Scheme 29].



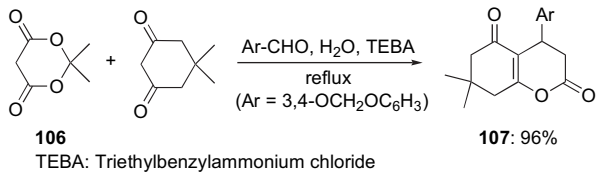
Scheme 29.

Nakamura[50] developed a well-designed [3+3] formal cycloaddition reaction employing ketal protected methylidene cyclopropanone **104** as a trimethylenemethane equivalent, leading to 1-oxadecalin **105** [Scheme 30].



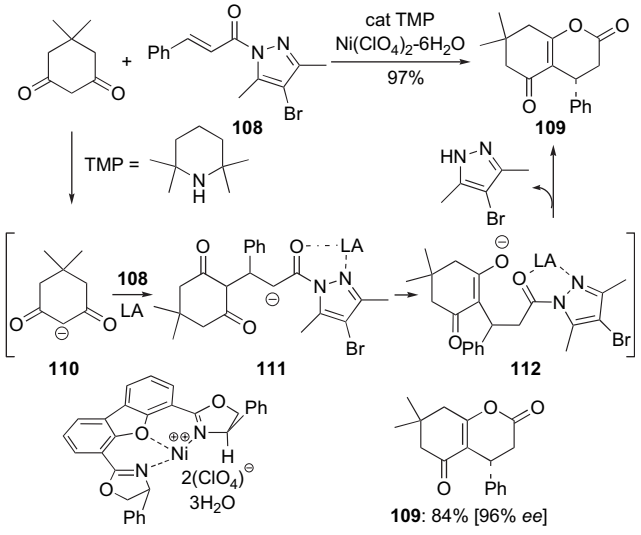
Scheme 30.

A three-component process involving aromatic aldehydes, Meldrum's acid **106**, and 5,5-dimethyl-1,3-cyclohexanedione led to the synthesis of **107** in 96% yield in aqueous media [Scheme 31].[51]



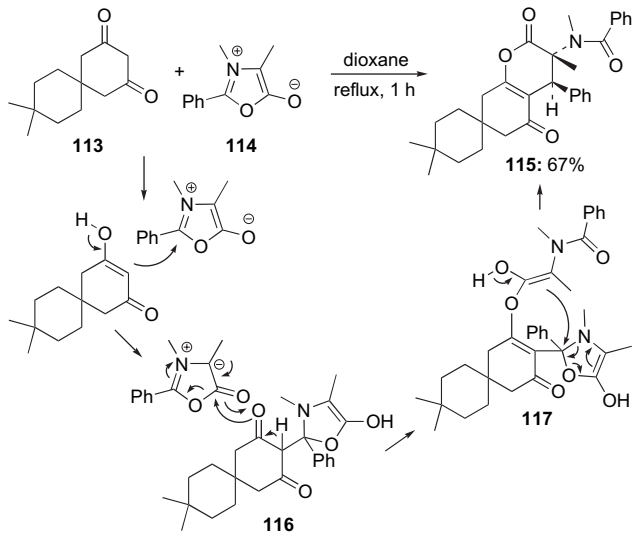
Scheme 31.

Kanemasa[52] reported an elegant series of studies on [3+3] annulations employing cyclic 1,3-dicarbonyl compound with acyl pyrrazole **108** under the double catalytic activation conditions consisting of Lewis acid [Ni(II)] and an amine catalyst [TMP] to provide a new synthetic route to enol lactone **109** by a Michael addition/cyclization sequence [Scheme 32]. Most impressively, they were able to render this reaction highly enantioselective [96% ee] using BOX-type ligand.



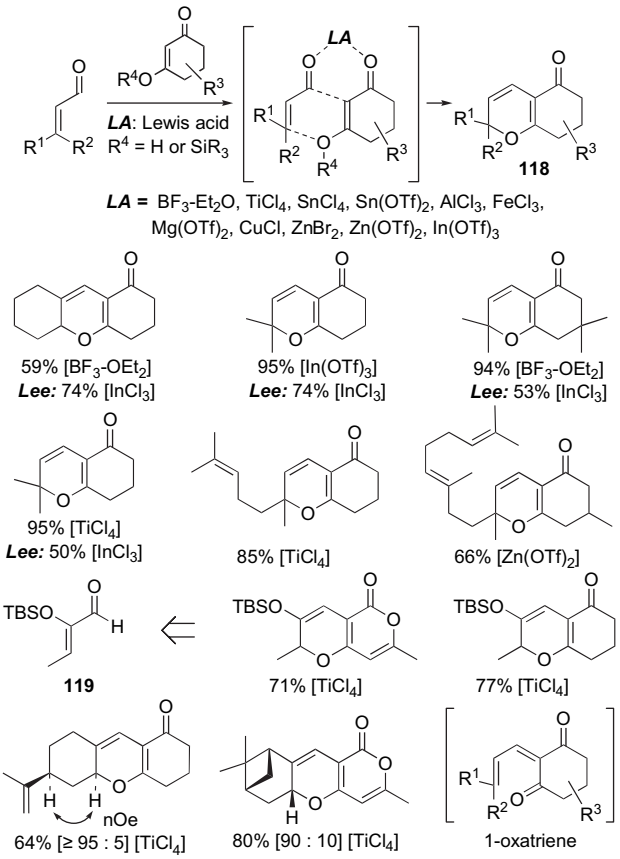
Scheme 32.

Another interesting [3+3] annulation is shown in Scheme 33. Enol lactone **115** was obtained through a one-pot reaction of diketone **113** and **114** [Scheme 33].[53]



Scheme 33.

Both Hsung[54] and Lee[55] [Scheme 34] reported Lewis acid promoted [3+3] annulations employing either diketones or vinylogous silyl esters. In Lee's work,[55] $InCl_3$ was the primary Lewis acid, while Hsung demonstrated that a range of different Lewis acids is feasible. These studies led to an array of 1-oxadecalins. Despite being different from earlier work using amine salts, the Lewis acid promoted version still involves an aldol condensation followed by a 6π-electron electrocyclic ring-closure of 1-oxatriene [see the bracket].



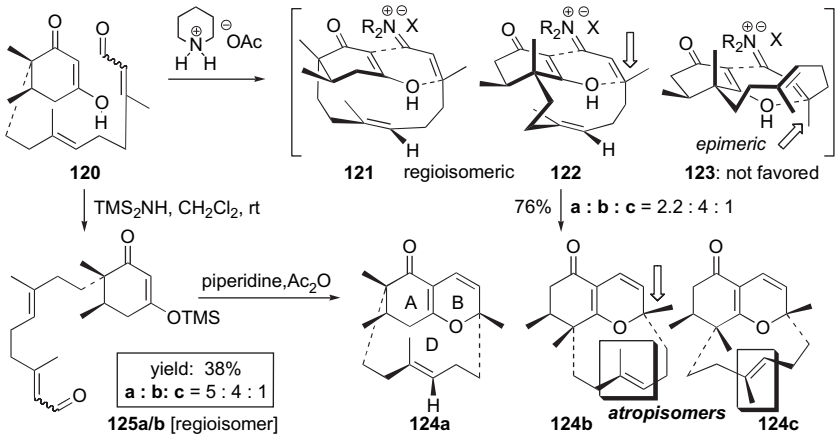
Scheme 34.

Hsung[48,56] reported the first example of an intramolecular *oxa*-[3+3] annulation employing 1,3-diketone **120** and isolated three products **124a–c**. The same three isomers were also found from the annulation of vinylogous TMS-ester **125a/b**, although in different ratios [Scheme 35].

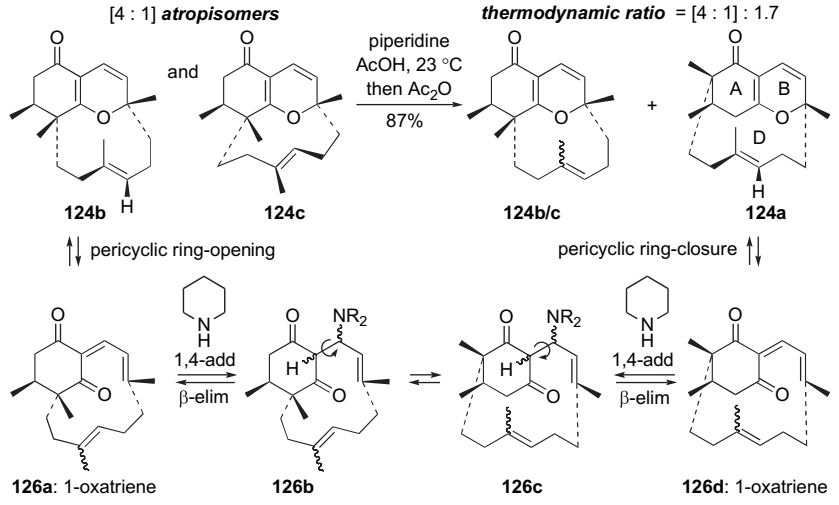
Interestingly, the two regioisomers **124b** and **124c** are actually atropisomers with respect to the orientations of their belt olefins, and thus, both are likely derived from TS-**122**. The respective annulation product derived from TS-**124** was not observed, as TS-**124** is highly strained for the annulation. In addition, the two regioisomers **124b** and **124c** could be equilibrated to give **124a** likely through a sequence of ring-opening and ring-closure sandwiching isomerizations [Scheme 36].

2.5. [3+2] Cycloadditions

Muthusamy[57a,b] discovered a tandem cyclization/hetero [3+2]-cycloaddition of Rh-carbenoids with various carbonyl

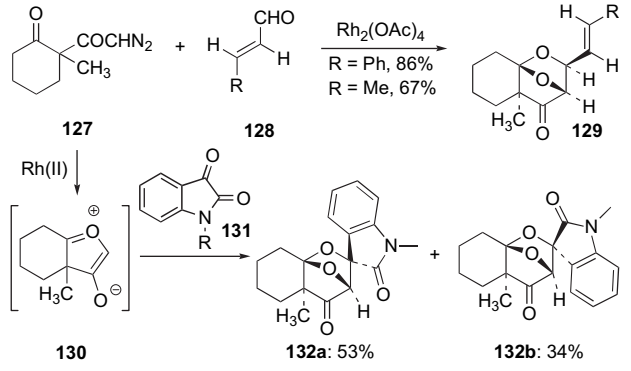


Scheme 35.



Scheme 36.

compounds to give 1-oxadecalins **129** and **132** with high regio- and/or diastereoselectivities [Scheme 37]. Muthusamy[57c,d] also recently used ionic liquids as a convenient and recyclable medium to promote these and related reactions.

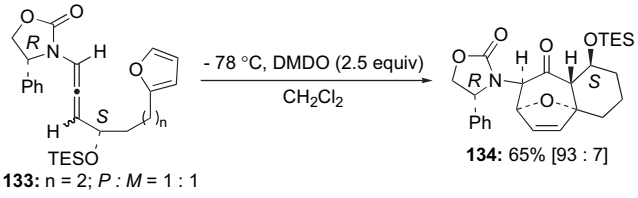


Scheme 37.

2.6. [4+3] Cycloadditions

There are only a few examples of approaches for constructing 1-oxadecalins in which a [4+3] cycloaddition is utilized.

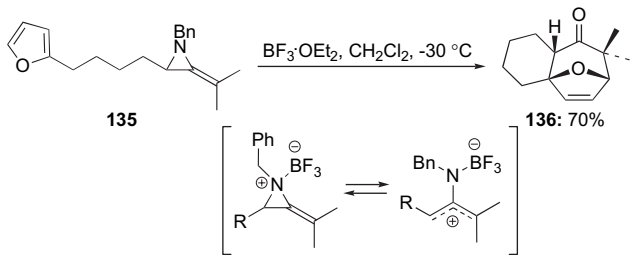
Hsung[58] reported a novel tandem DMDO epoxidation/stereoselective intramolecular [4+3] cycloaddition reaction involving nitrogen-stabilized oxyallyl cations derived from chiral allenamides **133** [Scheme 38].



Scheme 38.

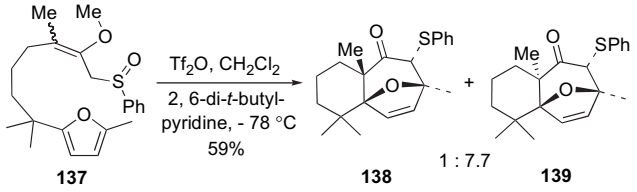
Shipman[59] developed an elegant Lewis acid [$BF_3 \cdot Et_2O$ or $Sc(OTf)_3$]-catalyzed intramolecular [4+3] cycloaddition employing vinyl aziridines such as **135** as a 1,3-dipole precursor [an aza-allyl cation equivalent see the bracket] en route to **136** in good yields [Scheme 39].

In their seminal work on [4+3] cycloadditions, Harmata[60] demonstrated that substituted alkoxyallylic sulfones **137**



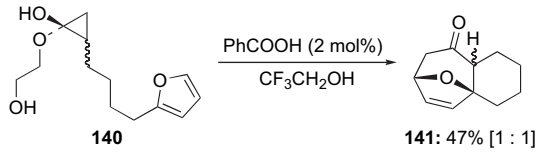
Scheme 39.

could produce vinylthionium ions that when treated with Lewis acids, can undergo intramolecular [4+3] cycloaddition reactions to give adducts **138** and **139** [Scheme 40].



Scheme 40.

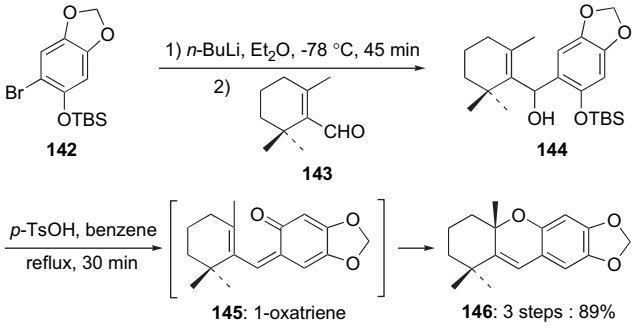
Cha[61] reported that a small amount of benzoic acid could promote intramolecular [4+3] cycloadditions of furan-tethered cyclopropanone hemiacetal **140** giving rise to **141** in 47% yield [Scheme 41].



Scheme 41.

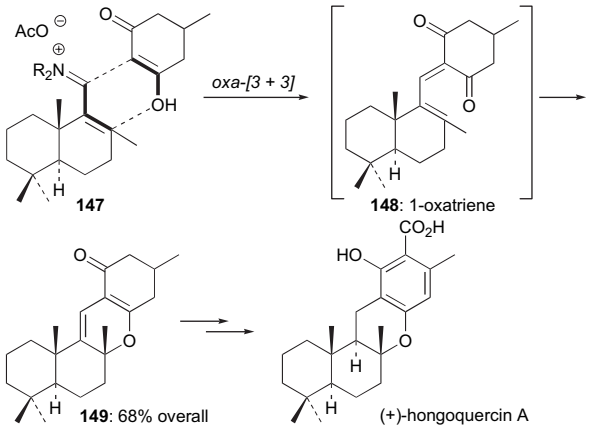
3. Pericyclic ring-closure

To study the structure–biological activity relationship for some activated compounds, Barrero[62] synthesized the cytotoxic benzopyran derivatives **146** from the aryl lithium derived from aryl bromide **142** and β-cyclocitral **143** through a ring-closure of 1-oxatriene **145** [Scheme 42].



Scheme 42.

In Hsung's recent total synthesis of (+)-hongoquercin A,[63] ring-closure of 1-oxatriene **148** occurred en route to the tetracycle **149** in 68% overall yield, thereby completing the oxa-[3+3] annulation sequence [Scheme 43].

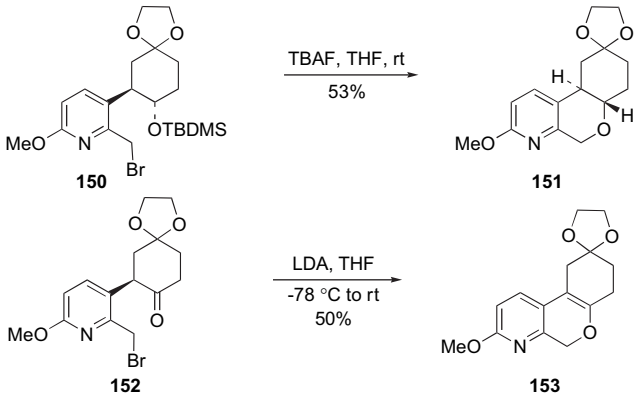


Scheme 43.

4. Cyclization reactions

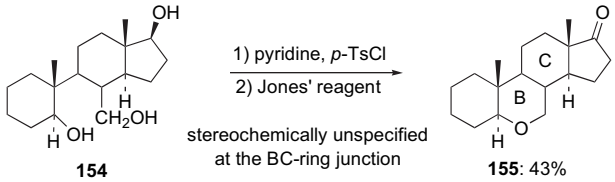
4.1. S_N2 additions

Mann[64] demonstrated that upon removal of the TBDMS group [*n*-Bu_4NF–THF] in compound **150**, a nucleophilic displacement of the bromide occurred concomitantly to produce **151** [Scheme 44]. In addition, lithium enolate derived from ketone **152** and LDA at −78 °C also gave **153** through an S_N2 addition.



Scheme 44.

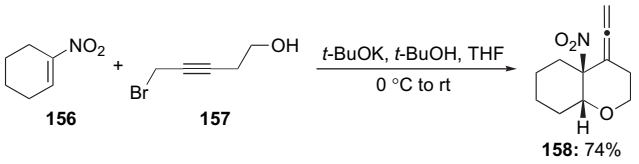
Hanson[65] found that the cyclization of triol **154** through a tosylate intermediate could take place to give tetracyclic ketone **155** after oxidation [Scheme 45].



Scheme 45.

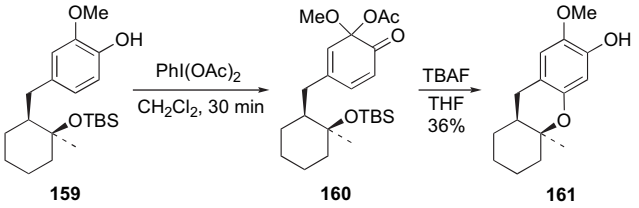
4.2. 1,4- or Oxa-1,4-addition

An oxa-1,4-addition/S_N2' substitution involving nitroalkene **156** and homo-propargyl alcohol derivatives **157** led to the synthesis of 1-oxadecalin **158** [Scheme 46].[66]



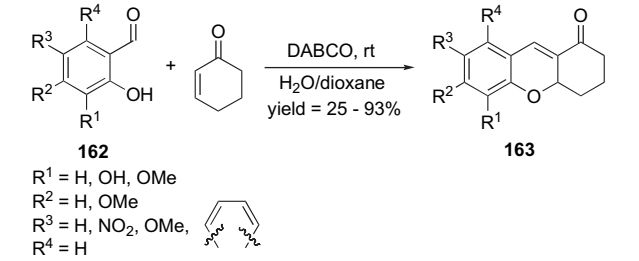
Scheme 46.

Quideau's[67] new preparation of orthoquinol acetates was applied in various O-1,4-addition reactions [Scheme 47]. Specifically, fluoride-mediated desilylation of **160** using TBAF occurred concomitantly with a 6-*exo-trig* cyclization to give **161** after aromatization via elimination of HOAc.



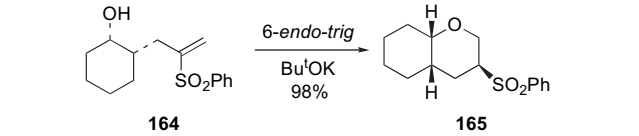
Scheme 47.

Bräse[68] described a domino oxa-1,4-addition and aldol condensation between salicylic aldehyde derivatives **162**s and 2-cyclohexenone that led to **163** [Scheme 48].



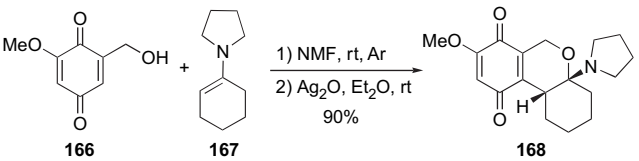
Scheme 48.

Khan[69] investigated the synthesis of *cis* and *trans* [not shown] 1-oxabicyclo[4,4,0]decanes through 6-*endo-trig* cyclization of hydroxy sulfone **164** [Scheme 49].



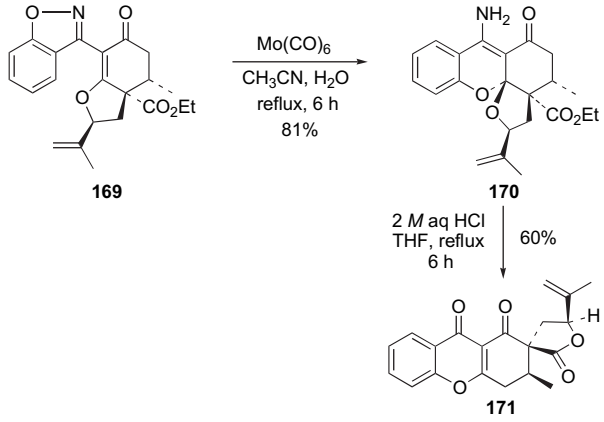
Scheme 49.

An efficient synthesis of the title benzo-pyranodione derivative **168** based on a stereoselective tandem 1,4-addition/cyclization sequence utilizing 2-(1-hydroxyalkyl)-1,4-benzoquinones and enamines was studied by Konishi[70] [Scheme 50].



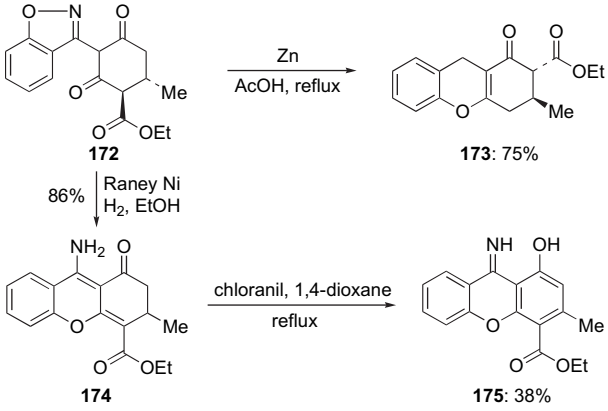
Scheme 50.

Bode and Suzuki[71] reported an interesting reduction of benzisoxazole **169** employing $Mo(CO)_6$ that led to tetracyclic vinylogous amide **170** in 81% yield. The subsequent acid hydrolysis resulted in the formation of **171** via a very unique structural rearrangement that can be an excellent cume question [Scheme 51].



Scheme 51.

Bode and Suzuki[72] also reported by other reductions of benzisoxazole **172** using Zn–AcOH or Raney-Ni led to the formation of 1-oxadecalins **173** or **175**, respectively [Scheme 52].

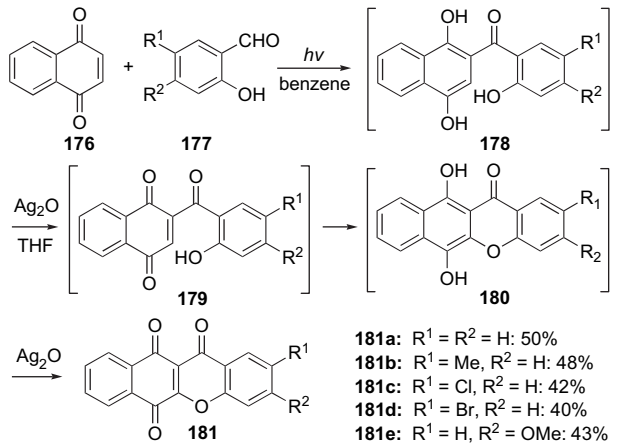


Scheme 52.

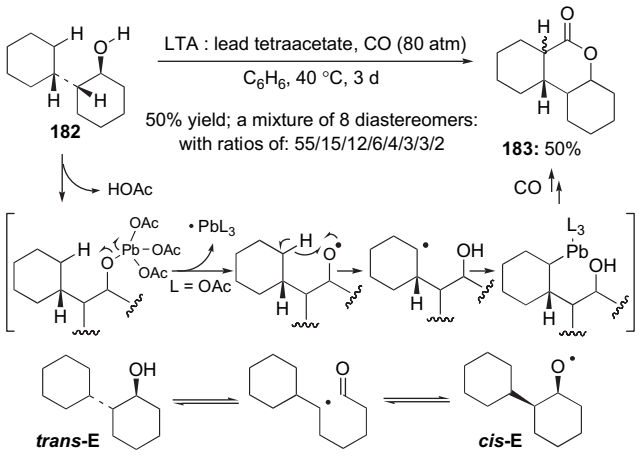
A two-step sequence, involving a photo-induced C-acylation of 1,4-naphthoquinone **176** with 2-hydroxybenzaldehyde **177** followed by O-1,4-addition and Ag_2O oxidations, for the synthesis of the xanthenequinone derivatives **181** was developed by Konishi[73] [Scheme 53].

4.3. Radical cyclizations

Ryu[74] observed an interesting formation of δ-lactones from saturated alcohol **182** in the presence of CO and lead tetraacetate [LTA] [Scheme 54]. The reaction likely proceeds through a 1,6-hydrogen abstraction [or 1,5-shift] by the alkoxyl radical intermediate [see in the bracket] presumably generated by LTA, serving as a one-electron oxidant, followed by carbonylation at the δ-carbon atom [assistance from Pb is a real possibility] and lactonization. Unfortunately, for



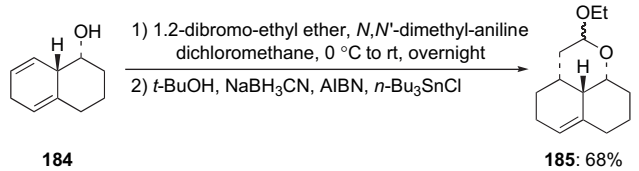
Scheme 53.



Scheme 54.

this specific example, β-bond cleavage occurred leading to scrambling of stereochemistry.

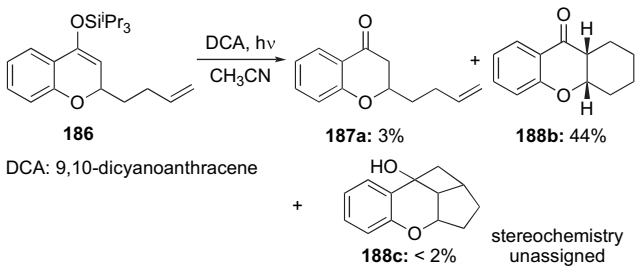
A Stork-type radical cyclization of the bromo-ketal intermediate derived from alcohol **184** and 1,2-dibromo-ethyl ether was revealed to give 1-oxadecalin **185** in a regio- and stereoselective manner [Scheme 55].[75]



Scheme 55.

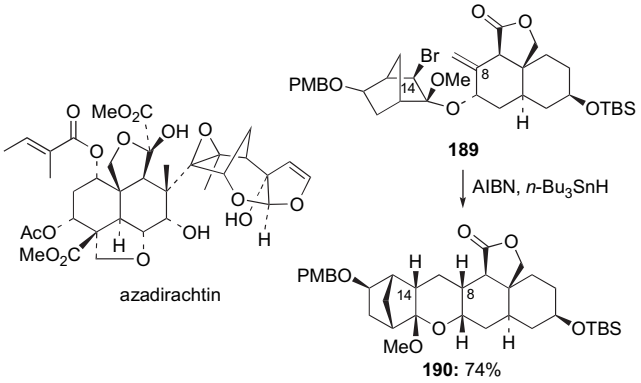
Oxidative photo-induced electron transfer (PET) reactions have been applied to the synthesis of a range of different oxygen heterocycles from silyl enol ethers such as **186** [Scheme 56].[76]

In their synthesis of azadirachtin, Nicolaou[77] attempted a radical-based approach for the construction of its crowded C8–C14 bond. Instead, treatment of the minor product bromo-ketal **189** with *n*-Bu_3SnH and AIBN [0.01 M in



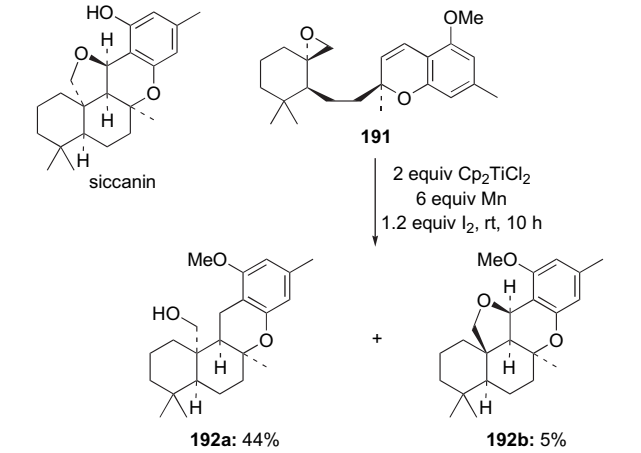
Scheme 56.

toluene, 110 °C] led to a 6-*endo-trig* radical cyclization product **190** in 74% yield [Scheme 57].



Scheme 57.

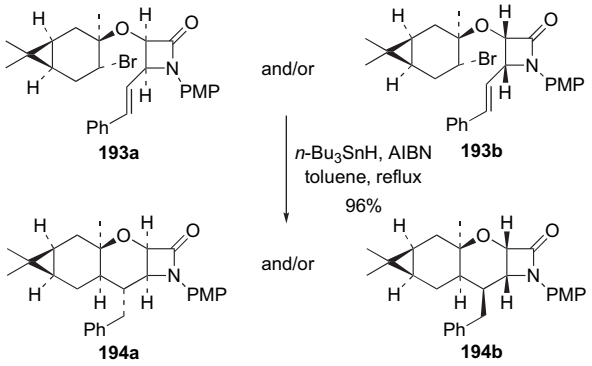
Trost[78] developed a nifty biomimetic enantioselective synthesis of (−)-siccanin that featured the Pd-catalyzed asymmetric allylic alkylation [AAA] and a Ti(III)-mediated 6-*exo-trig* radical cyclization of epoxyolefin **191** [Scheme 58].



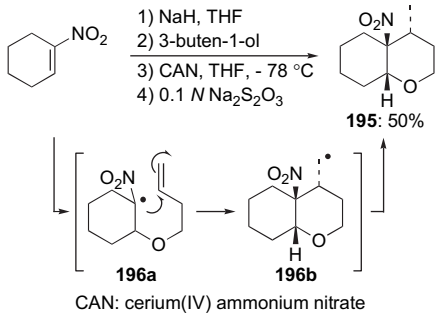
Scheme 58.

An efficient and diastereoselective synthesis of a β-lactam **194a** [or **194b**] has been achieved in high yield via a 6-*exo-trig* radical cyclization employing bromo alkene **193a** [or **193b**] [Scheme 59].[79]

Upon one-electron CAN-oxidation of the nitroanion resulting from an oxa-1,4-addition of homoallylic alcohol to nitroalkene, the radical intermediate **196a** underwent 6-*exo-trig* radical cyclization, leading to 2,3-dialkyl-4-methyl tetrahydropyran **195** stereoselectively [Scheme 60].[80]

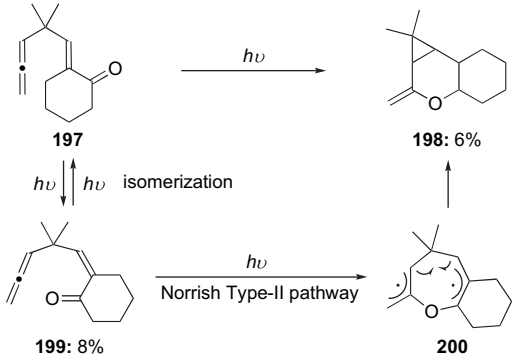


Scheme 59.



Scheme 60.

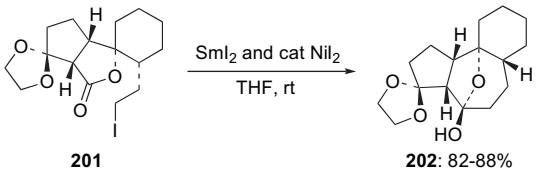
Tsuno[81] reported an interesting 1-oxadelic formation via photochemistry of γ-allenyl-substituted α,β-unsaturated enone derivative. As shown in Scheme 61, irradiation of **197** led to predominantly *E*–*Z* geometric isomerization, but the *Z*-isomer **199** apparently underwent radical cyclization in a Norrish Type-II manner to give **198** [stereochemistry unassigned] in 6% yield. The overall process represents an equivalent of photochemical hetero Diels–Alder reaction [Scheme 61].



Scheme 61.

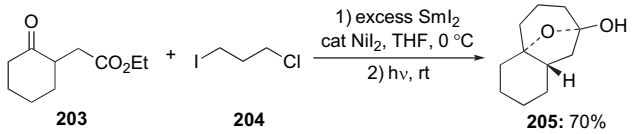
4.4. SmI_2-mediated cyclizations

In their synthetic efforts toward the phorbol ester, Little[82] used an intramolecular reductive cyclization of **201** using SmI_2 [Scheme 62]. The reaction was sluggish, but upon the addition of catalytic amount of NiI_2, the reaction reached completion within 1 h and yields were improved to 82–88%.



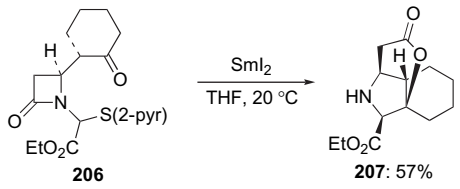
Scheme 62.

Molander[83] developed a beautiful tandem sequence of intermolecular carbonyl addition/intramolecular nucleophilic acyl substitution promoted by SmI_2 [Scheme 63]. They were able to construct bicyclic system **205** in good yields and high diastereoselectivities from simple and readily available ketoester **203** and dihalide **204**. The reducing power of SmI_2 with nickel(II) iodide serving as a catalyst is the key in the first step and irradiation with visible light was more useful in the second step.



Scheme 63.

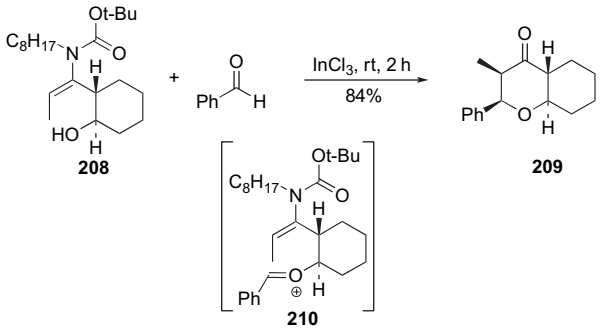
In attempts to promote a Reformasky-type cyclizations of **206** with SmI_2 to construct fused tricyclic β-lactams, Skrydstrup[84] found that the favored pathway is a cyclization pathway followed by a trans-acylation step involving the cleavage of the β-lactam ring to give bridged tricycle **207** [Scheme 64].



Scheme 64.

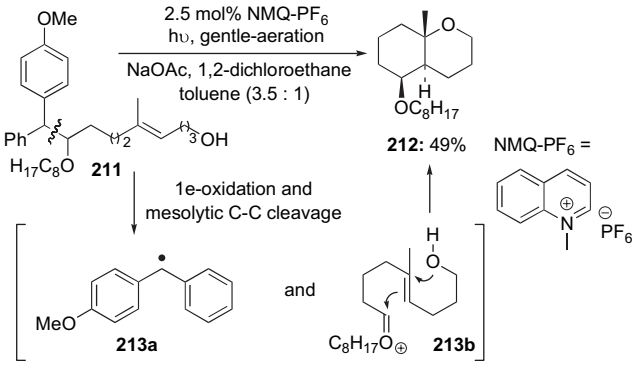
4.5. Prins-type cyclizations

Funk[85] reported an interesting approach to 1-oxadecalin through a diastereoselective Prins cyclization of enecarbamate **208** that was promoted by 0.5 equiv of $InCl_3$ [Scheme 65].



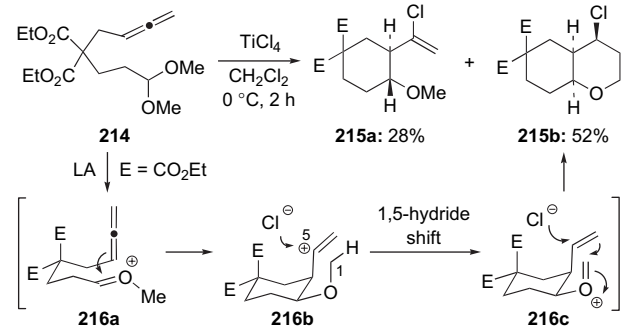
Scheme 65.

Floreancig[86] beautifully demonstrated that organic radical cations can be derived from single-electron oxidation under photochemical conditions and can further undergo the mesolytic C–C σ-bond cleavage to form benzyl radical **213a** and oxocarbenium ion **213b**, which can proceed through a Prins-type cyclization to give 1-oxadecalin **212** [Scheme 66].



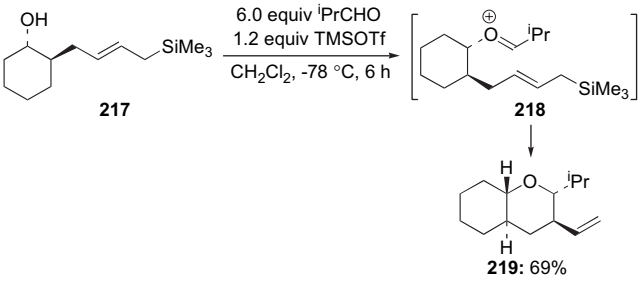
Scheme 66.

Treatment of allenyl-aldehyde dimethyl acetal **214** with $TiCl_4$ afforded the bicyclic pyran **215b** in 52% yield [Scheme 67].[87] The proposed reaction mechanism is a sequence [see the bracket] of an intramolecular allenyl-Prins-cyclization followed by 1,5-hydride shift of vinyl cation **216b**, which itself would lead to **215a** if trapped by the chloride anion. A second Prins cyclization from the resulting oxocarbenium ion **216c** should give **215b**.



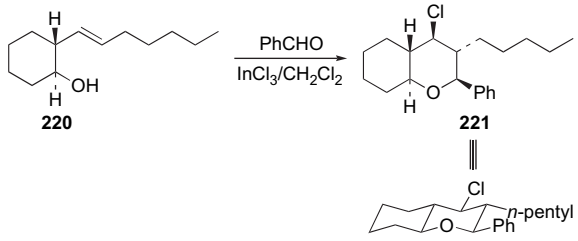
Scheme 67.

Another example of Prins cyclization would involve allyl silane **217** and *iso*-butyrlaldehyde in the presence of TMSOTf to afford 2,3-substituted octahydrochromanes **219** with excellent diastereoselectivity [Scheme 68].[88]



Scheme 68.

Li documented an elegant synthesis of poly-substituted tetrahydropyran **221** with excellent diastereoselectivity via an $InCl_3$-mediated Prins cyclization of alcohol **220** and benzaldehyde [Scheme 69].[89]

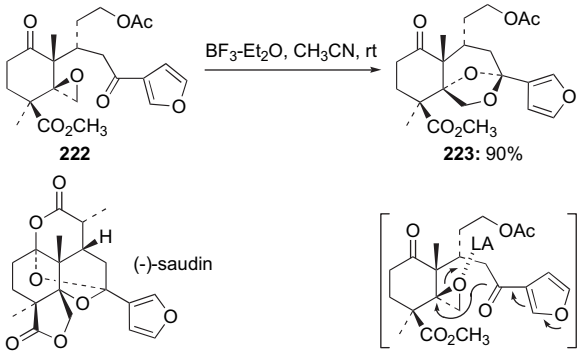


Scheme 69.

4.6. Acid-mediated cyclizations

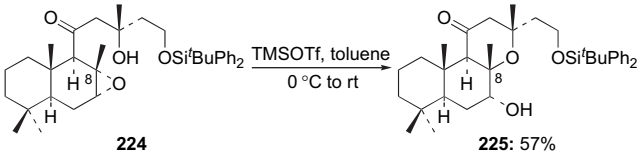
This is the most common approach for constructing 1-oxadecalins, and the section is further divided into four subsections: (1) those involving ring-opening of epoxides, (2) those involving additions onto an olefin, (3) those involving polyene-type cyclizations, and (4) other miscellaneous cyclizations.

4.6.1. Epoxide ring-opening. Boeckman[90] used a Lewis acid promoted ring-opening of epoxide **222** via nucleophilic participation of the side chain ketone carbonyl [see the bracket] followed by cyclization to bicyclic ketal **223** [Scheme 70]. The ring-opening of the epoxide occurred with complete inversion. This was a key-step toward their enantioselective total synthesis of (+)- and (−)-saudin.



Scheme 70.

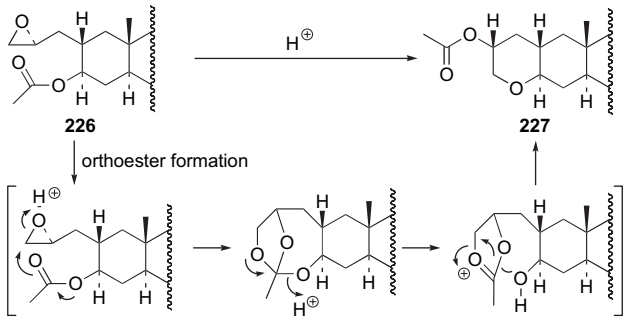
In a study aimed at the synthesis of forskolin [Fig. 1], Welzel[91] found that epoxide **224**, upon treatment with TMSOTf in toluene gave the cyclization product **225** in 57% yield with retention of configuration at C-8 [Scheme 71].



Scheme 71.

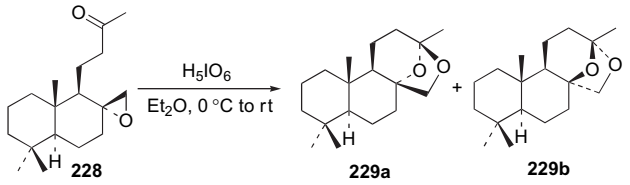
An acid-catalyzed epoxy-ester rearrangement of **226** was reported by Giner[92] to give **227** [Scheme 72]. This study

provides support for the hypothesis that epoxy-ester–orthoester–cyclic ether rearrangement could be involved in the biosynthesis of marine polyether toxins.



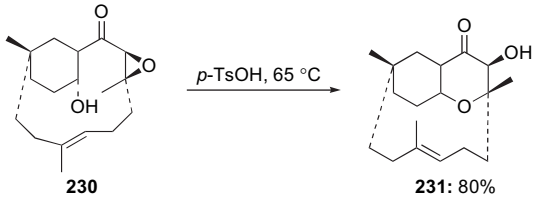
Scheme 72.

Davies-Coleman[93] concisely synthesized ambraketal [**229a**] and 8-*epi*-ambraketal [**229b**] that featured an acid-mediated cyclization of **228** [Scheme 73].



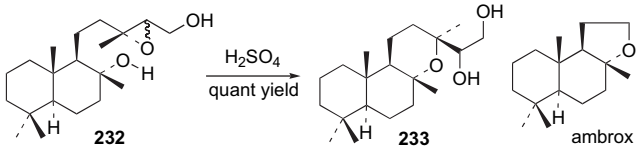
Scheme 73.

In their elegant approach toward phomactins [Fig. 1], Maleczka[94] used an intramolecular acid-mediated epoxide-ring-opening of **230** [Scheme 74].



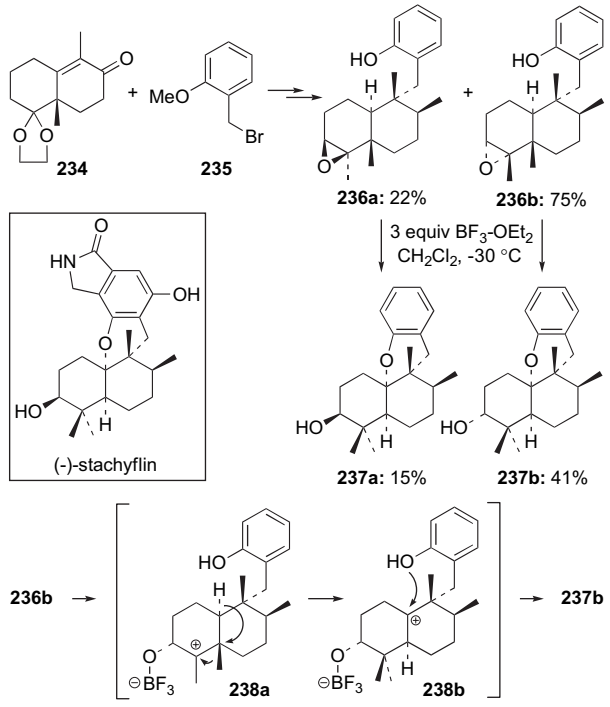
Scheme 74.

Moulines[95] used a key acid-mediated ring-opening of epoxide **232** to afford diol **233** in their synthesis of ambrox, an ambergris-type compound sought after by the perfume industries [Scheme 75].



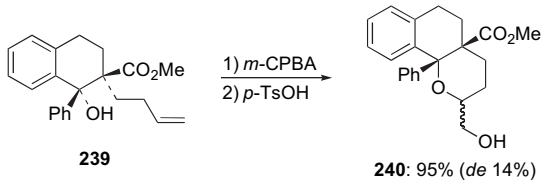
Scheme 75.

Katoh[96] reported in their elegant total synthesis of stachyflin a $BF_3 \cdot Et_2O$-induced domino sequence of epoxide-ring-opening, a double Meerwin rearrangement, and cyclization of **236a** and **236b**, thereby providing a concise route to the tetracyclic core of stachyflin [Scheme 76].



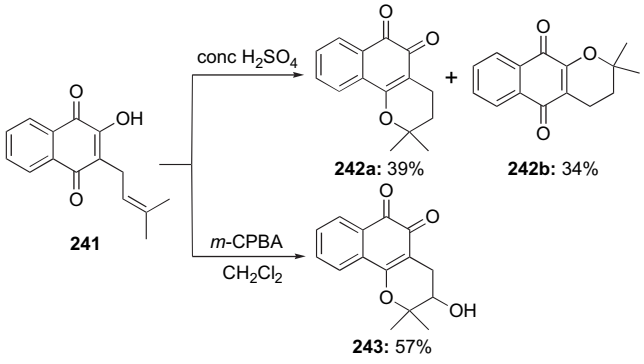
Scheme 76.

Compernolle[97] employed an acid promoted cyclization of alcohol **239** after an initial *m*-CPBA epoxidation [Scheme 77].

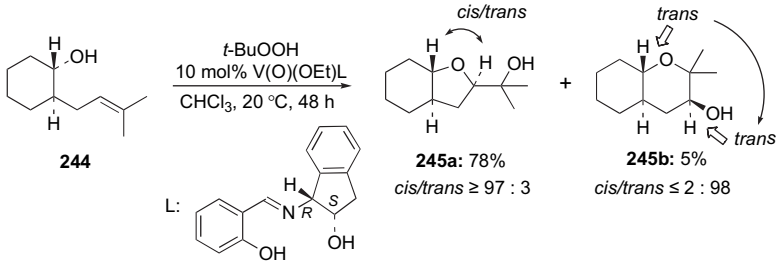


Scheme 77.

In an effort to study the inhibitory effect of lapachol derivatives on Epstein-Barr virus, Pérez Sacau[98] employed an acid-mediated cyclization of naphthoquinone lapachol **241** to obtain lapachol derivatives **242a** and **242b** and **243**, which involved an initial *m*-CPBA epoxidation [Scheme 78].



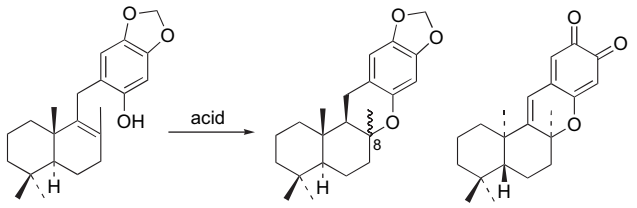
Scheme 78.



Scheme 79.

By using Schiff-based vanadium(V) complex, Hartung[99] efficiently synthesized the functionalized tetrahydrofuran **245a** and tetrahydropyran **245b** [Scheme 79].

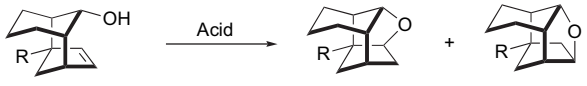
4.6.2. Additions to olefins. In their efforts toward the synthesis of puupehedione, Barrero[100] studied the acid-mediated cyclization of **246** under different conditions and the most significant results are depicted in Scheme 80.



acids	solvents	temp	time	ratios (yields%)
BF_3-Et_2O	CH_2Cl_2	0 °C	15 min	only **b** (85)
2-Naphthalenesulph	CH_2Cl_2	reflux	2 h	**a** : **b** (1 : 2.4) (76)
p-TsOH	benzene	reflux	50 h	**a** : **b** (1 : 4) (90)
conc H_2SO_4	nitropropane	0-10 °C	30 min	**a** : **b** (1 : 9) (93)

Scheme 80.

Ramos-Tombo and Ganter[101] used bridgehead-alkylated *endo*-cyclic olefin **248** to give a mixture of acid-mediated cyclized products **249a** and **249b** [Scheme 81].

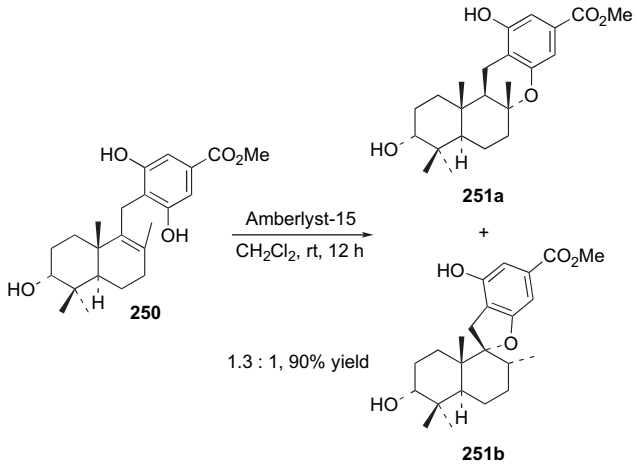


reactant	acid	temp	time (h)	ratio (**a** : **b**)	yield (%)
R = Me	HCl/$CHCl_3$	rt	24	65 : 35	quant
R = Et	HCl/Et_2O	rt	25	80 : 20	87
R = *i*-Pr	HCl/Et_2O	rt	16	95 : 5	90

Scheme 81.

Kende's[102] enantioselective total syntheses of various lactams containing natural products isolated from *Stachybotrys* sp. [not shown here] cleverly featured the Amberlyst-15-mediated cyclization of **250** to give a mixture of **251a** and **251b** in a 1.3:1 ratio [Scheme 82].

Katoh[103] reported an efficient synthesis of the tetracyclic ABCD ring system of the natural products kampanols [see A in Scheme 83], featuring an interesting cyclization of **252** to give both the trans-fused product **253a** using $BF_3 \cdot Et_2O$ and the cis-fused product **253b** using *N*-phenylseleno phthalimide in the presence of $SnCl_4$.



Scheme 82.

In an effort to study the mechanism of abietadiene synthase catalysis, Coates[104] synthesized **255** via an acid-catalyzed dehydrative cyclization of **254** [Scheme 84].

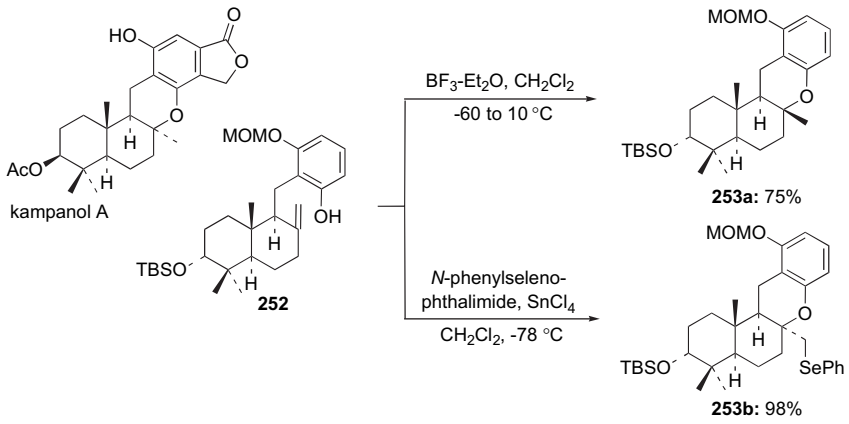
In the synthesis of 3-deoxyschweinfurthin B, Weimer[105] used an acid-catalyzed cationic cyclization of **256** to afford the advanced precursor **257** [Scheme 85].

In their synthesis of hongoquercin A [Fig. 1], Mori[106] cleverly employed an acid-mediated cyclization of **258** to form the ABCD ring system **259** [Scheme 86].

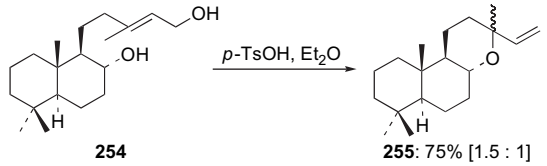
Starting from the appropriate *o*-quinones **260**, Nicolaides[107] used an acid-mediated cyclization to construct 3,4-dihydro-2*H*-benzo[*f*]pyrano[2,3-*h*]chromen-6-one derivatives **261** and **262** [Scheme 87].

Jansen and de Groot[108] were able to transform (+)-larixol to ambra oxides **264** featuring the acid-mediated cyclization of **263** [Scheme 88].

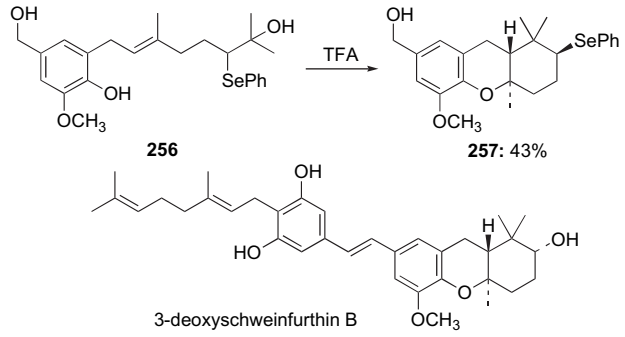
In their concise and elegant stereoselective synthesis of the AB-ring moiety of trichothecene sesquiterpene (+)-calonectrin, Tomioka[109] employed a Lewis acid-mediated cyclization of **265** to afford the cis-fused tetrahedrochromane **266** in good yields [Scheme 89].



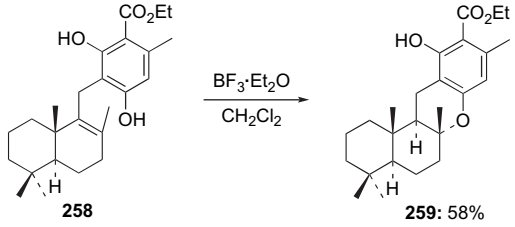
Scheme 83.



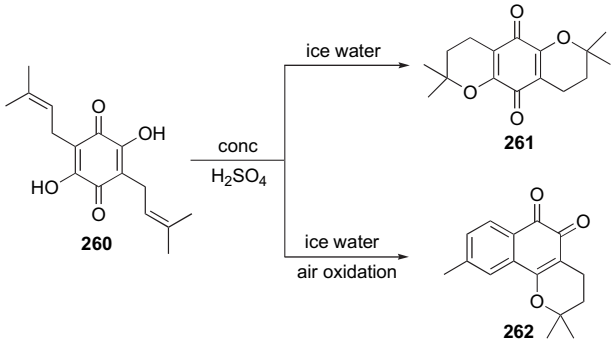
Scheme 84.



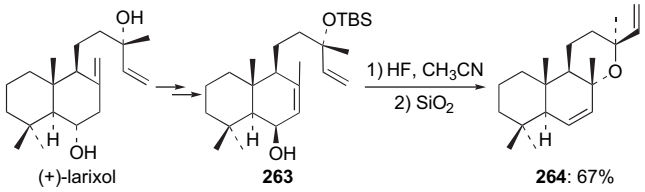
Scheme 85.



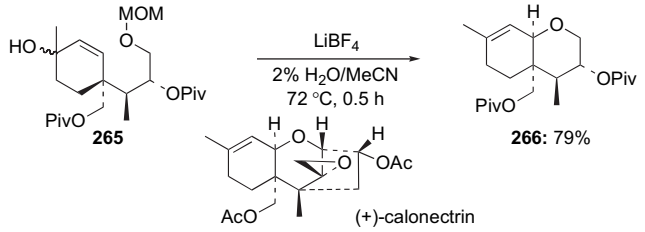
Scheme 86.



Scheme 87.

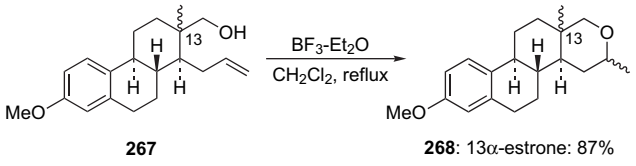


Scheme 88.



Scheme 89.

Schneider[110] reported a stereoselective approach to new oxa-D-homoestrone derivatives that showcased a key stereoselective Lewis acid-mediated cyclization of alkenol **267** to afford 13α-estrone **268** as the only product [Scheme 90].

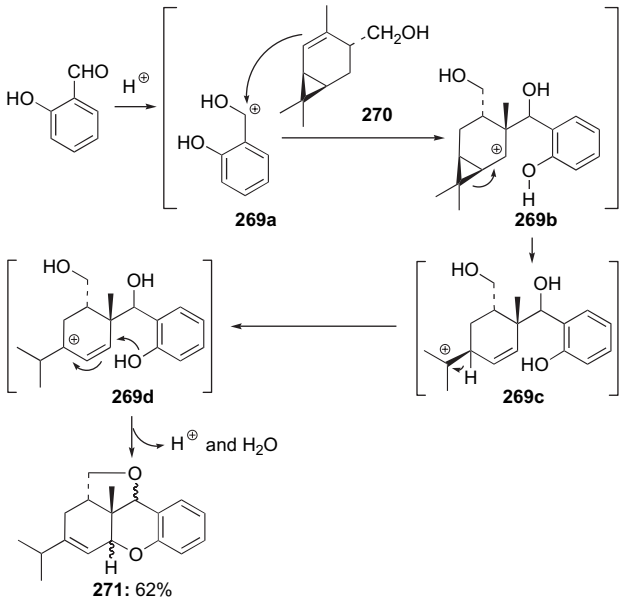


Scheme 90.

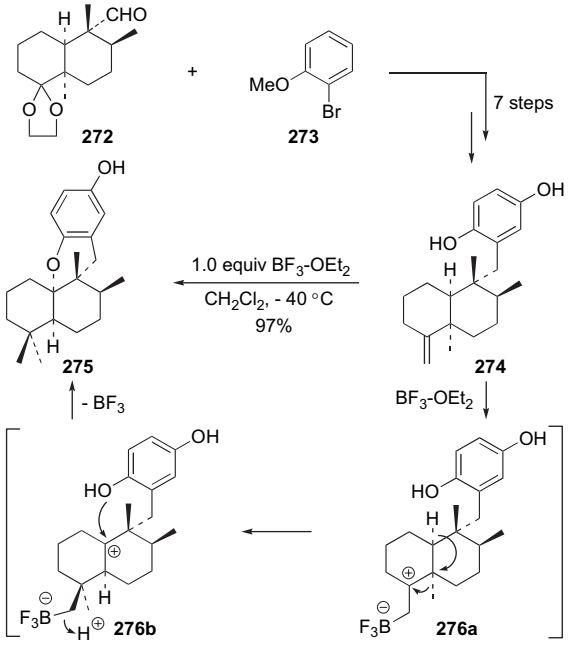
A xanthene skeleton bridged to a tetrahydrofuran ring as shown in **271** was synthesized in 62% yield when carene derivative **270** reacted with *o*-hydroxy aldehyde over the askanite–bentonite clay at room temperature [Scheme 91].[111]

Another interesting $BF_3 \cdot Et_2O$-promoted double Meerwin rearrangement/cyclization reaction employing (+)-arenarol **274** in an efficient synthesis of (+)-aureol **275** was reported by Katoh [Scheme 92].[112]

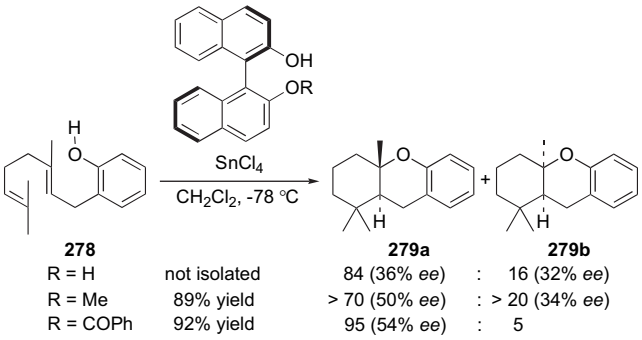
4.6.3. Polyene-type cyclizations. In their development of an enantioselective polyene cyclization, Ishihara and



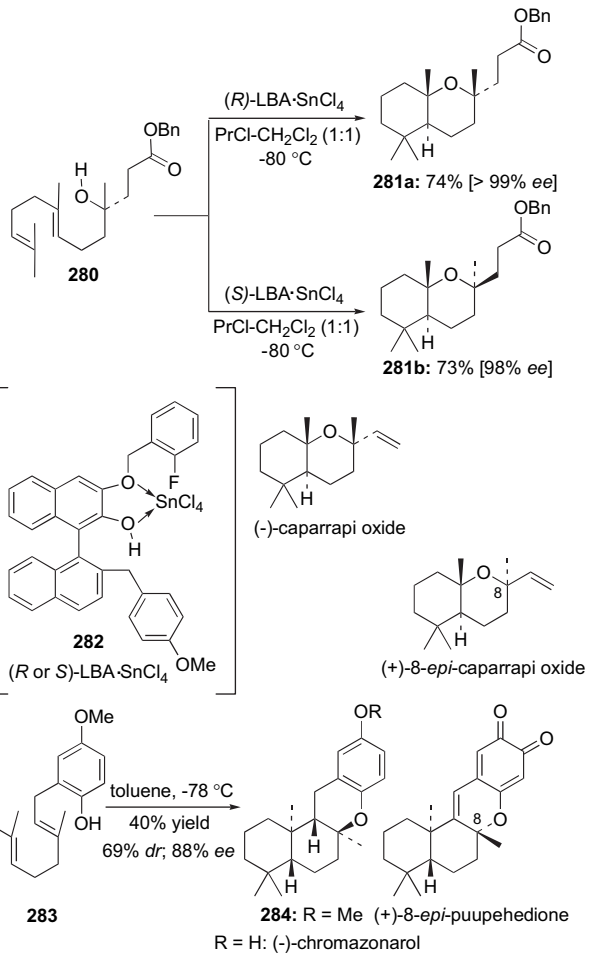
Scheme 91.



Scheme 92.



Scheme 93.



Scheme 94.

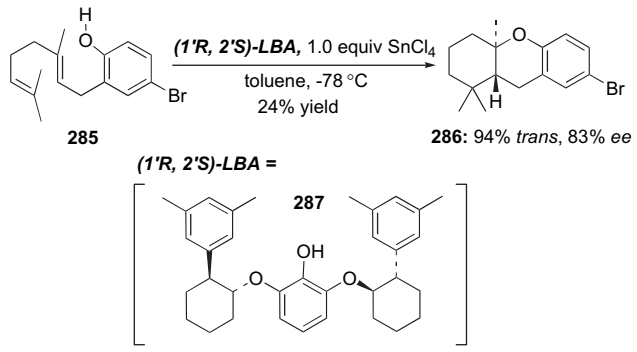
Yamamoto[113] employed Lewis acid-assisted chiral Brønsted acids [LBA] to cyclize various isoprenoids such as **278** into **279** in modest to excellent ees [Schemes 93 and 94].

In their recent asymmetric total synthesis of acid-sensitive (−)-caparrapi- and (+)-8-*epi*-caparrapi oxide, Ishihara[114] demonstrated an excellent application of their Lewis acid-assisted chiral Brønsted acid [LBA]-induced polyene cyclization of **280** [Scheme 94]. In addition, en route to elegant total syntheses of natural products such as (−)-chromazonarol and (+)-8-*epi*-puupehedione, polyene cyclization of **283**[115] employing LBA-**282** gave tetracycle **284** in good dr and ee.

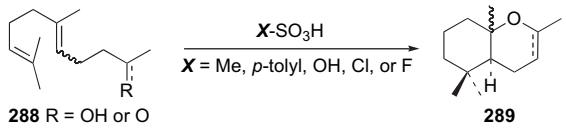
In addition, Ishihara[116] recently reported another novel Lewis acid-assisted chiral Brønsted that constitutes an artificial cyclase for biomimetic cyclization [Scheme 95].

Linares-Palomino[117] demonstrated that chlorosulfonic acid could also promote electrophilic olefin cyclization of substrates **288** to give cyclized products **289** [Scheme 96].

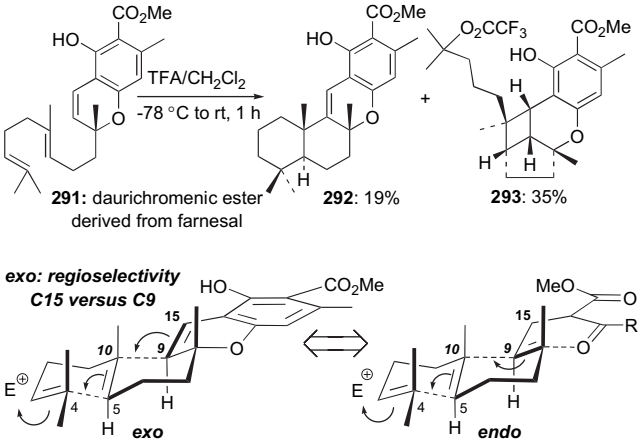
Hsung[63] reported an unusual polyene cyclization pathway that led to a divergent total synthesis of hongoquercin A and rhododaurichromanic acid A [Scheme 97]. This work uncovered a novel cationic cyclobutane formation that could be relevant to the biosynthetic pathway for the formation of



Scheme 95.



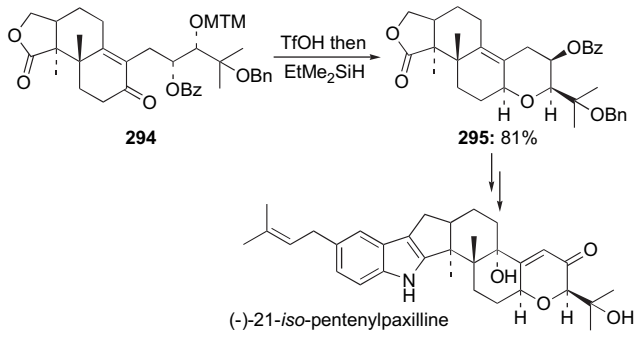
Scheme 96.



Scheme 97.

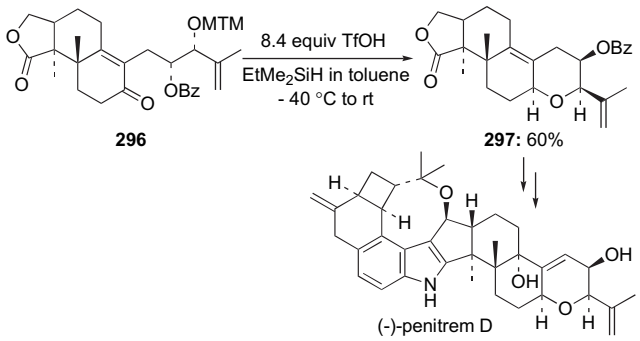
cyclobutane containing terpenoids in addition to rhododaurichromanic acids.

4.6.4. Miscellaneous acid promoted cyclizations. In their elegant total synthesis of (−)-21-isopentenylpaxilline, Smith[118] reported generation of the tetrahydropyran ring in **295** through a cascade process starting from the cleavage of the $MeSCH_2$ (MTM) protecting group to a $EtMe_2Si$-H reduction of the cyclized hemiacetal intermediate [Scheme 98].



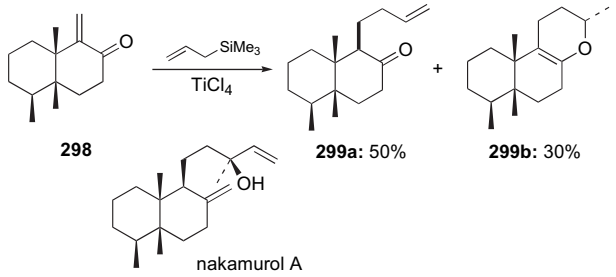
Scheme 98.

A similar strategy was also used in Smith's total synthesis of (−)-penitrem D [Scheme 99].[119]



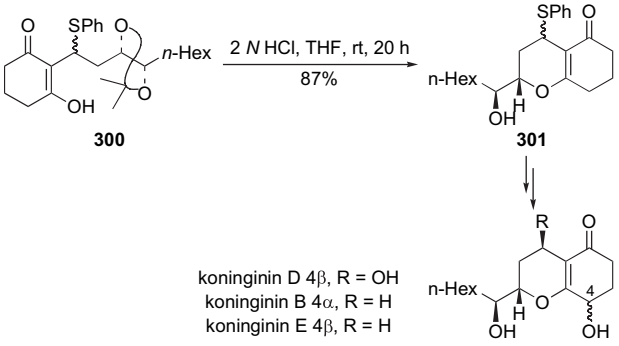
Scheme 99.

In their total synthesis of (±)-nakamurol-A, Bonjoch[120] found that when a slight excess of $TiCl_4$ was used, α-methylene ketone **298** could be transformed to the ketone **299b** via a desired Sakurai reaction, but another product **299b** was also found, which was likely derived from a hetero-Diels–Alder reaction or an acid-mediated cyclization from **299a** [Scheme 100].



Scheme 100.

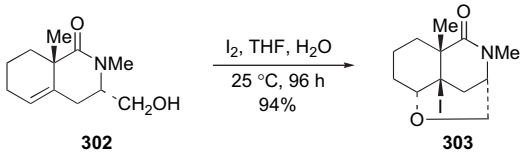
In the total synthesis of koninginins D, B, and E, the deprotection of ketal **300** by treatment with dilute HCl in acetone furnished 1-oxadecalin **301** [Scheme 101].[121]



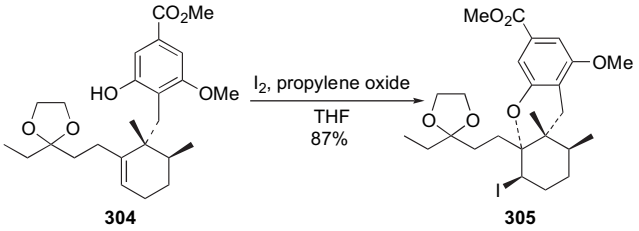
Scheme 101.

4.6.5. Electrophilic etherifications. Schultz[122] reported that treatment of olefinic alcohol **302** with I_2 in THF and H_2O under conditions of thermodynamic control gave iodopyran **303** in 94% yield [Scheme 102].

Mori's[123] total synthesis of (±)-stachyflin [see Scheme 76] showcased the construction of cis-fused 1-oxadecalin via an iodo-etherification [Scheme 103].

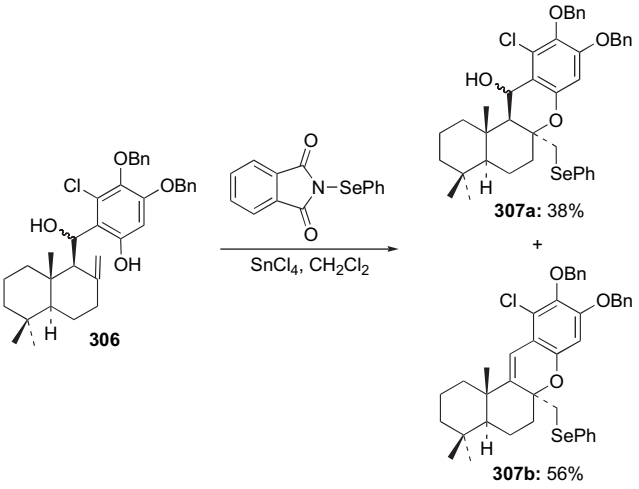


Scheme 102.



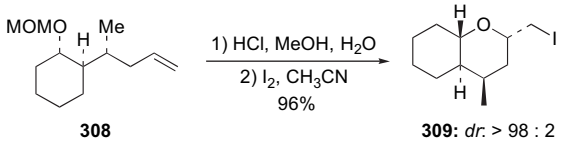
Scheme 103.

Hua[124a] and Katoh[124b] reported that oxy-selenylation of diol **306** with 1.1 equiv of *N*-phenylseleno phthalimide and 0.1 equiv of tin tetrachloride gave selenyl pyran **307a** in 38% yield and unsaturated pyran **307b** in 56% yield, which was formed from the dehydration of **307a** catalyzed by either $SnCl_4$ or HCl [Scheme 104].



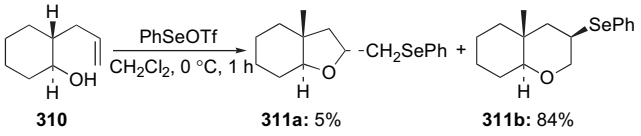
Scheme 104.

Chemla[125] reported the transformation of **308** into the substituted pyran **309** via hydrolysis of the MOM moiety followed by iodo-etherification of the resulting alcohol [Scheme 105].



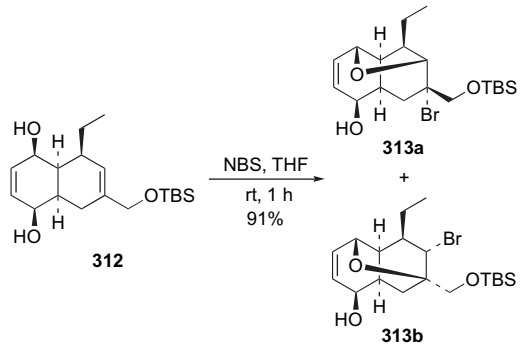
Scheme 105.

Murata[126] studied the selective intramolecular oxy-selennylation of olefinic alcohols and carboxylic acids by using organic cyano selenides in the presence of metal triflates to generate PhSeOTf. Depending on the conditions, reactions of *trans*-2-allylcyclohexanol **310** can selectively afford *exo*-cyclized tetrahydrofuran **311a** or *endo*-cyclized tetrahydropyran **311b** [Scheme 106].



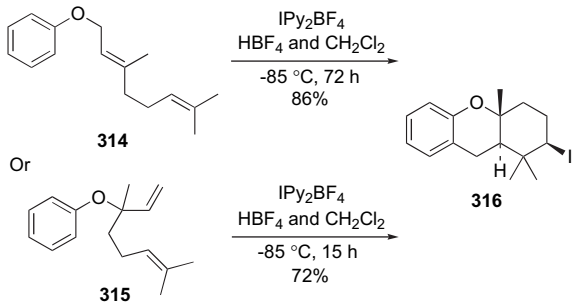
Scheme 106.

White[127] found that when *cis*-diol **312** was treated with *N*-bromosuccinimide [NBS], a mixture of inseparable bromoepoxy alcohols 5-*exo* product **313a** and 6-*endo* product **313b** were obtained [Scheme 107].



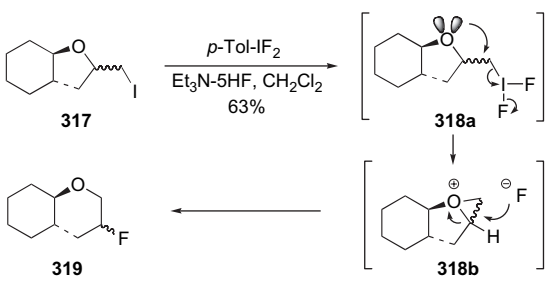
Scheme 107.

Barluenga[128] reported a flexible approach to chromane and tetrahydroquinoline derivatives by using intramolecular arylation reactions of alkenes employing IPy_2BF_4 as the source of iodonium ion [Scheme 108].



Scheme 108.

Interestingly, the fluorinated six-membered cyclic ether **319** was stereoselectively synthesized from furan **317** via a fluorinative ring-expansion reaction using *p*-iodo-toluene difluoride [Scheme 109].[129]

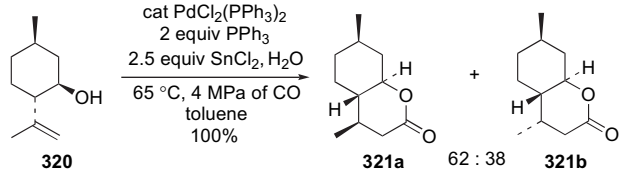


Scheme 109.

5. Transition metal-mediated cyclizations

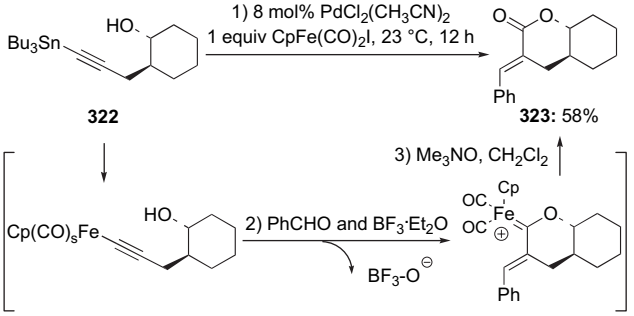
5.1. Palladium

Kalck[130] found that the cyclocarbonylation of isopulegol catalyzed by $PdCl_2(PPh_3)_2$ led to the desired lactone **321** in 60% de [Scheme 110]. A hydride intermediate [PdH–$SnCl_3L_2$] was proposed as the active species that hydro-palladated [likely directed by the hydroxy group] the terminal olefin in an anti-Markovnikov manner prior to carbonylation.



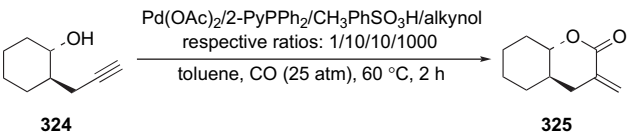
Scheme 110.

Liu[131] observed that in the presence of 1 equiv of $CpFe(CO)_2I$ and 8 mol % of $PdCl_2(CH_3CN)_2$, hydroxyalkynyl stannane **322** underwent Pd(0)-catalyzed transmetalation to give rise to a reactive iron–alkynyl complex, which was condensed in situ with $PhCHO/BF_3{\cdot}Et_2O$ to yield a cationic iron styryl carbene complex that underwent Me_3NO-oxidation to give lactone **323** [Scheme 111].



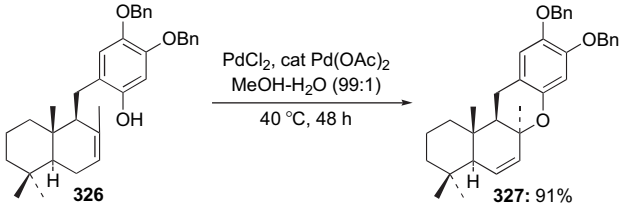
Scheme 111.

Dupont[132] reported that the cyclocarbonylation of alkynol **324** catalyzed by $Pd(OAc)_2$ in either organic solvents or ionic liquids led to *exo*-α-methylene δ-lactones **325** quantitatively in a highly regioselective manner [Scheme 112].



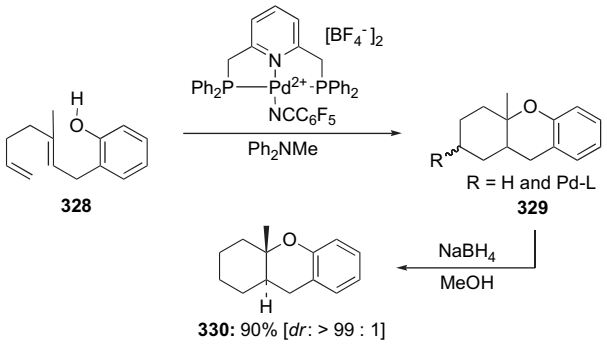
Scheme 112.

In an efficient enantioselective synthesis of the natural product (−)-15-oxopuupehenol [for a related structure see Scheme 80],[100] Alvarez-Manzaneda[133] found that Pd(II)-induced cyclization of **326** in a Wacker-type oxidative manner to give the desired tetracycle **327** as a single isomer [Scheme 113].



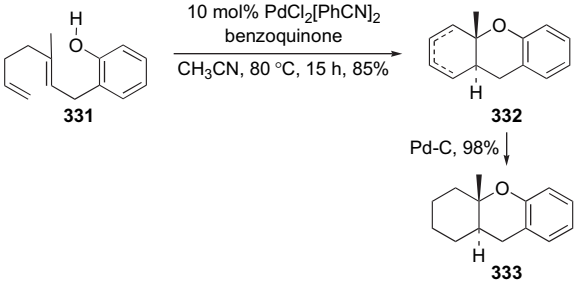
Scheme 113.

Gagne[134] reported an interesting Pd^{II}-mediated oxidative [Wacker-type] poly-cyclization reaction of 1,5-dienes **328** that led to tricycle **329** [Scheme 114].



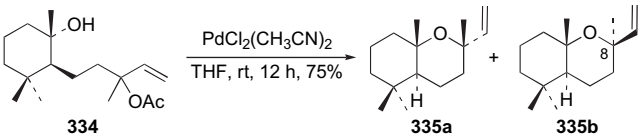
Scheme 114.

Gagne[135] also reported another related Pd^{II}-catalyzed oxidative polyoxa-ene cyclization reaction initiated by carbocyclization of 1,5-dienes **331**. These studies suggest the presence of carbocation-like intermediates that can ultimately be trapped by suitable nucleophiles such as phenols [Scheme 115].



Scheme 115.

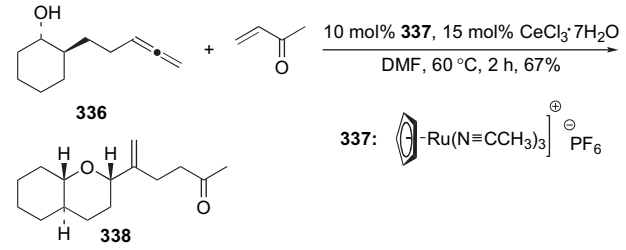
Barrero[136] illustrated that when treating allyl acetate **334** with $PdCl_2(CH_3CN)_2$, mono-carbocyclic terpenoids (−)-caparrapi **335a** and its C8-epimer **335b** [ratio 2:1] were isolated in 75% yield [Scheme 116].



Scheme 116.

5.2. Ruthenium

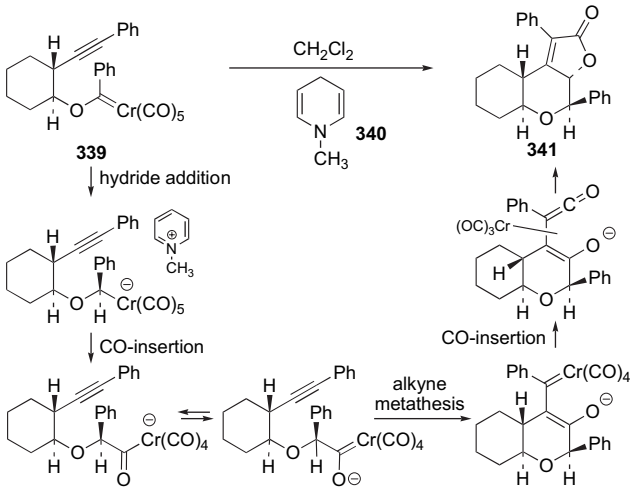
Trost[137] reported a ruthenium-catalyzed alkylative cycloetherification reaction that provided cyclic ethers such as **338** in 67% yield from alcohol **336** and methyl vinyl ketone [Scheme 117].



Scheme 117.

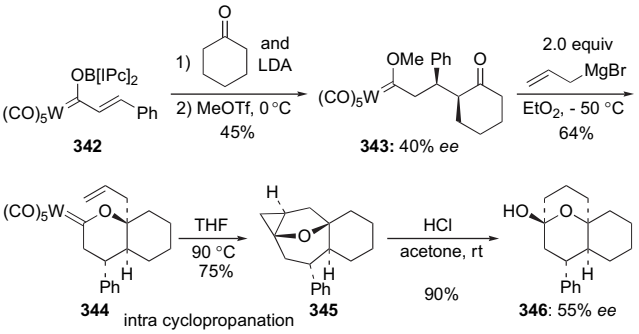
5.3. Chromium and tungsten

Rudler[138] reported a very interesting synthesis of tricyclic butenolide **341** from Fisher Cr(0)-carbene complex **339** through a unique sequence as shown in Scheme 118. The key steps are an initial reduction of the carbene carbon and the two CO insertions.



Scheme 118.

Barluenga[139] reported an interesting synthetic sequence leading to an enantioselective formation of bridged tricycle **346** from chiral alkenyl Fisher Cr(0)-carbene complex **342** and lithium enolate of cyclohexanone [Scheme 119].



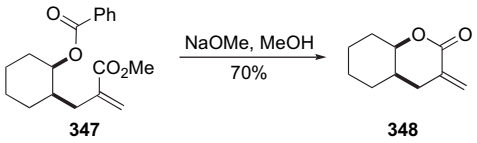
Scheme 119.

6. Simple lactone and lactol formations

This section presents another common and perhaps the most straightforward strategy for constructing 1-oxadecalins.

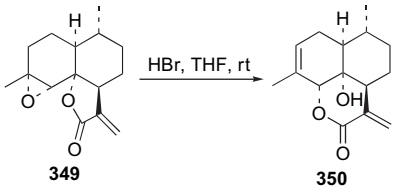
6.1. Lactones

A common way to form 1-oxadecalin containing compounds is esterification. Both Hon[140a] and Rigby[140b] reported that when benzoates such as **347** was subjected to basic condition, lactone **348** could be obtained in 70% yield [Scheme 120].



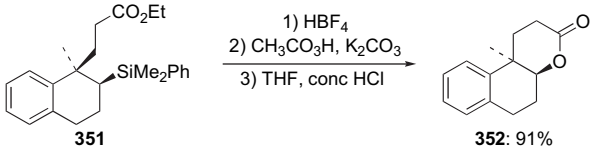
Scheme 120.

When epoxy lactone **349** was subjected to acidic condition, the resulting alcohol underwent trans-esterification in a ring-expansion manner to give the more stable lactone **350** [Scheme 121].[141]



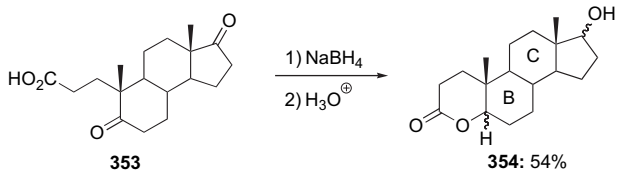
Scheme 121.

Meyers[142] showed an interesting example of employing the silyl substituent as an oxygen surrogate through Tamao–Fleming oxidation en route to lactone **352** [Scheme 122].



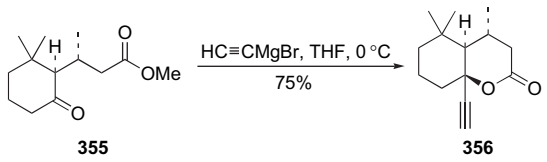
Scheme 122.

Fukazawa[143] illustrated that when diketone **353** was reduced to an alcohol intermediate, it cyclized under acidic condition to give lactone **354** [stereochemistry at its BC-ring junction was not defined] [Scheme 123].



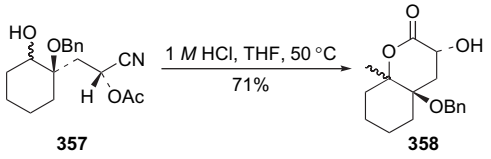
Scheme 123.

In Frater's work,[144] the addition of ethynyl magnesium bromide to ketoester **355** resulted in a tertiary alcohol intermediate that cyclized to give lactone **356** [Scheme 124].



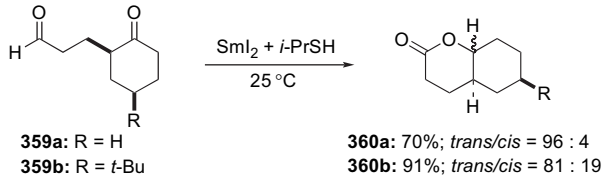
Scheme 124.

Cyanohydrin **357** was hydrolyzed under acidic conditions to give a carboxylic acid intermediate, which underwent lactone formation to give **358** in 71% yield [Scheme 125].[145]



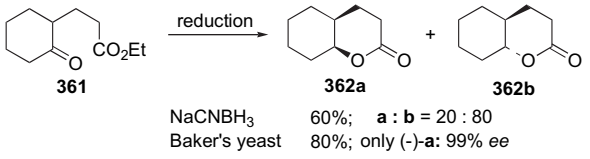
Scheme 125.

Fang[146] reported an interesting SmI_2/*i*-PrSH-mediated formation of 1-oxa-2-decalones **360a** and **360b** from ketone aldehydes **359a** and **359b**, respectively, through an Evans–Tischenko reductive pathway [Scheme 126].



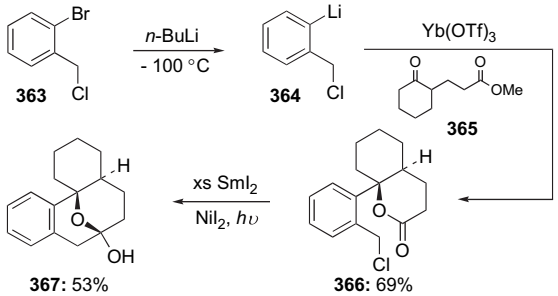
Scheme 126.

Valentin[147] cleverly obtained enantiomerically pure *cis* 1-oxa-2-decalone **362a** from reduction of δ-ketoester **361** using raw Baker's yeast. In comparison, using $NaCNBH_3$ as reducing agent provided a mixture of *trans* and *cis* decalones **362a** and **362b** [Scheme 127].



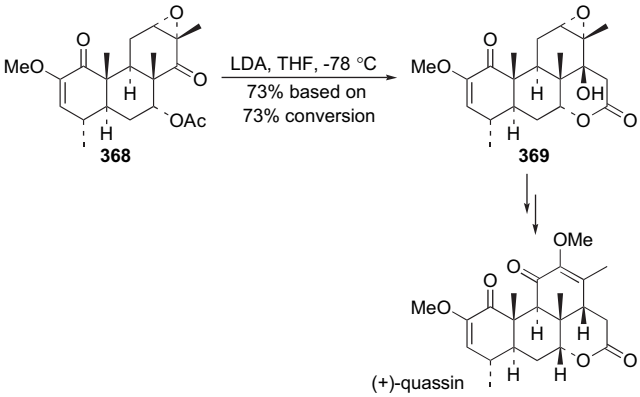
Scheme 127.

Molander[148] reported a sequence leading to lactone **366** via nucleophilic addition of the aryl lithium **364** to ketoester **365**. Subjecting the resulting chloro lactone **366** to intramolecular reductive coupling using SmI_2 and cat NiI_2 led to **367** [Scheme 128].



Scheme 128.

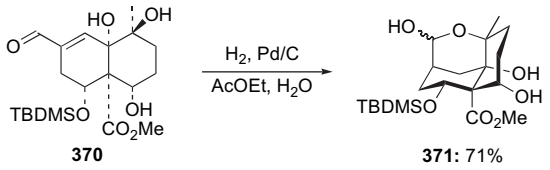
In their beautiful total synthesis of (+)-quassin, Shing[149] found that upon treating acetate **368** with LDA, intramolecular aldol occurred to give lactone **369** as a single diastereomer in good yield [Scheme 129].



Scheme 129.

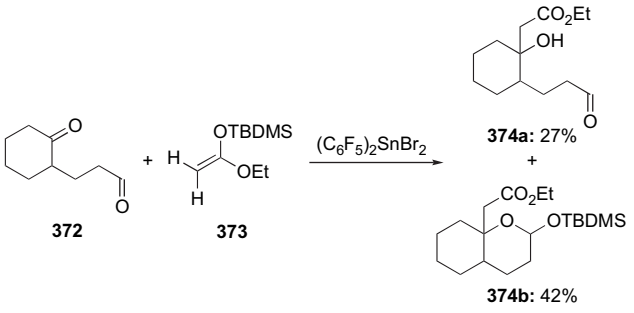
6.2. Lactols

Another commonly used way to form a 1-oxadecalins would involve an alcohol and an aldehyde moiety in the formation of acetal or hemiacetals. In the synthesis of agarofuran antifeedants, catalytic hydrogenation of the double bond of **370** occurred from α-face and resulted in the lactol formation to give hemiacetal **371** [Scheme 130].[150]



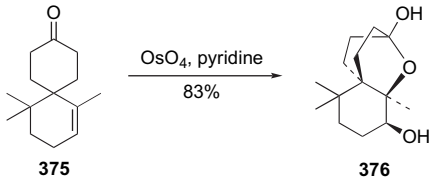
Scheme 130.

Otera[151] observed a very interesting reversal of chemoselectivity in $(C_6F_5)_2SnBr_2$-catalyzed aldol reaction of silyl ketene acetal **373** and ketoaldehyde **372**. The unusual preference for the ketone resulted in the formation of aldehyde **374a**, which was partially converted to 1-oxadecalin **374b** in the presence of Lewis acid [stereochemistry was unassigned] [Scheme 131].



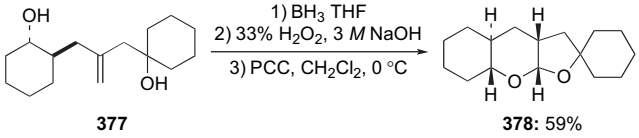
Scheme 131.

In Iwata's synthesis of laurencial [not shown],[152] dihydroxylation of the alkene moiety of enone **375** gave lactol **376** in 83% yield [Scheme 132].



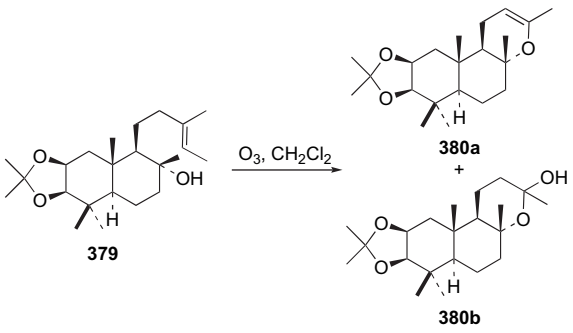
Scheme 132.

Pyran **378** containing 1-oxadecalin was synthesized from diol **377** through a sequence of hydroboration/oxidation developed by Yus[153] [Scheme 133].



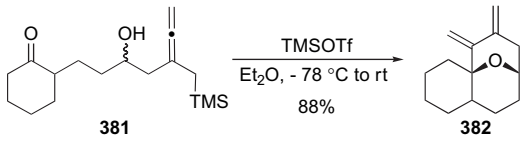
Scheme 133.

Ozonolysis of alkene **379** generated a ketone intermediate that subsequently reacted with the tertiary alcohol to give arise to a mixture of enol ether **380a** and hemiacetal **380b** [Scheme 134].[154]



Scheme 134.

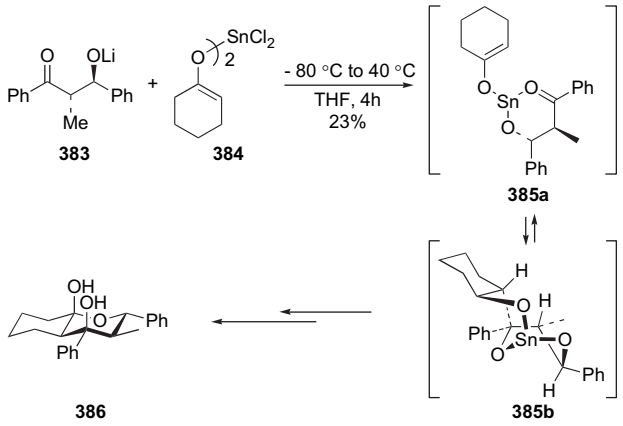
In the presence of TMSOTf, allenol **381** underwent lactol formation followed by addition of allyl silane to the oxocarbenium intermediate to give oxa-bicycle **382** [Scheme 135].[155]



Scheme 135.

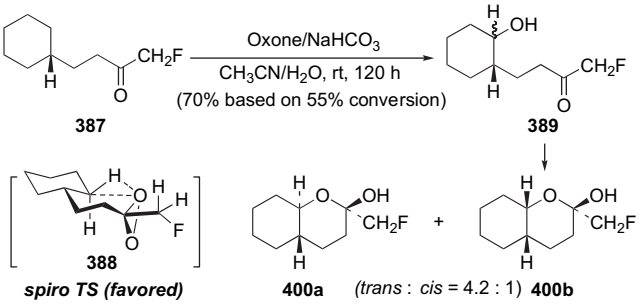
The addition of stannyl enolate **384** to ketone **383** was reported to give lactol **386** [Scheme 136].[156]

Last but not the least, Yang reported an elegant regioselective (δ-selective) intramolecular oxidation of unactivated C–H bonds by dioxiranes with a favored spiro-TS



Scheme 136.

[see **388** in bracket], in which oxidation of the equatorial δ C–H bond is strain-free, leading to the observed diastereoselectivity in 1-oxadecalins **400a** and **400b** after the lactol formation [Scheme 137].[157]



Scheme 137.

7. Conclusion

In conclusion, we have presented here a sample of various strategies and approaches that have been employed in constructing 1-oxadecalins for a diverse array of purposes. Given the prevalence of this structural motif among a diverse array of natural products, we hope this review could serve as a springboard that may help bringing forth future innovative approaches.

Acknowledgements

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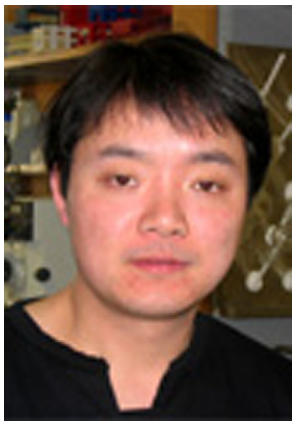
Biographical sketch



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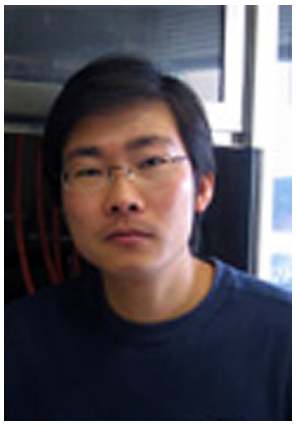

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Synthetic approaches towards an indole alkaloid isolated from the marine sponge *Halichondria melanodocia*

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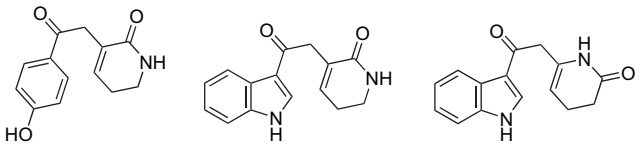
Abstract—The exocyclic analogue of the indole alkaloid isolated from the marine sponge *Halichondria melanodocia* has been prepared via olefination of a phosphonoester derived from 3-(2-bromoacyl)indole. The formation of an unexpected indolylazepine is also discussed.

1. Introduction

Marine organisms, such as sponges and tunicates, constitute a unique and vast resource for the discovery of bioactive molecules with novel structures. Many marine alkaloids have generated interest not only due to their various and often striking pharmacological activities but also as challenging problems for structure elucidation and synthesis.[1]

As far back as in 1979 two lactams were isolated from the isopropanol extracts of an algae-infested Caribbean sponge, *Halichondria melanodocia*.[2] The structures of the lactams were assigned as the related phenol and indole derivatives **1** and **2**, respectively (Fig. 1). Although structure **3** was discussed as an alternative for **2**, it was disregarded since it was incompatible with the chemical shift data.

To the best of our knowledge, the biological activity of the lactams isolated from *H. melanodocia* has not yet been evaluated, neither have their structures been confirmed via synthesis. It also seems to be uncertain whether the alkaloids are produced by the sponge itself or by the associated algae and bacteria.



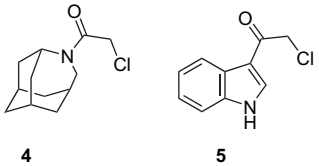
1 2 3

Figure 1.

2. Results and discussion

Our continuous interest in marine indole alkaloids[3] attracted our attention towards compound **2**. Since chloroacetylazahomoadamantane (**4**) (Fig. 2) has been reported to react with triethyl phosphonoacetate at the α-position,[4] we believed that 2-chloro-1-(1*H*-indol-3-yl)-ethanone (**5**)[5] could similarly afford the appropriate building block in our attempts to synthesise **2**. It was conceived that such a phosphonoester building block should provide a possibility to introduce the double bond in the correct position of the lactam.

Hence, triethyl phosphonoacetate was treated with a base (NaH) followed by the Boc-protected chloroacyl indole **6a**. The yields of **7a** were quite modest, under the conditions initially evaluated (NaH, THF), seldom over 30%, largely depending on the co-formation of product **8**[4] together with unreacted starting material (Scheme 1). Other bases were



4 5

Figure 2.

Keywords: *Halichondria melanodocia*; Indole alkaloids; Exocyclic; Lactams.
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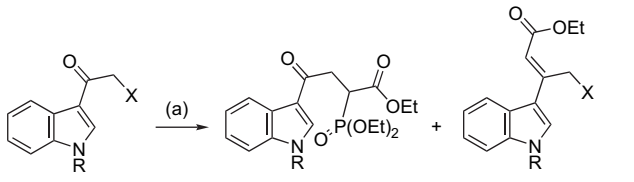
tried as well (BuLi, *t*-BuOK, LDA, DBU) with the result of either inferior yields or more by-product formation. Solvent and temperature changes did not improve the yield but, since we noticed that in the presence of a catalyst (NaI or Bu_4NI) the yields improved (less than 10% product without catalyst), we suspected that other 3-(2-haloacyl)indoles could give superior results. As expected, changing the chlorine atom to bromine or iodine (compounds **6b–d**) improved the yields significantly. As a consequence, the formation of **8** was minimised. Changing to a polar aprotic solvent improved the yields even further.



6a X = Cl, R = Boc
6b X = Br, R = Boc
6c X = I, R = Boc
6d X = Br, R = SO_2Ph

7a R = Boc
7b R = SO_2Ph

8 X = Cl, R = Boc

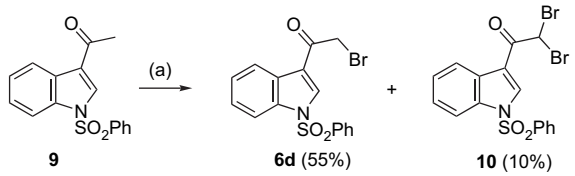
Scheme 1. (a) NaH; other reagents and conditions see Table 1.

Table 1

Indole derivative	Solvent	Other conditions	Yield **7a/7b** (%)	Yield **8** (%)
6a X=Cl, R=Boc	THF	Bu_4NI, rt, 18 h	27	14
6a X=Cl, R=Boc	THF	Bu_4NI, reflux, 4 h	42	n.i
6a X=Cl, R=Boc	THF	Bu_4NI, 0 °C to rt, 18 h	24	n.i
6a X=Cl, R=Boc	Toluene	Bu_4NI, reflux, 3 h	22	n.i
6a X=Cl, R=Boc	DMF	NaI, 60 °C, 36 h	—	—
6a X=Cl, R=Boc	THF	NaI, rt, 18 h	26	26
6d X=Br, R=SO_2Ph	THF	NaI, rt, 1.5 h	72	—
6a X=Cl, R=Boc	THF	rt, 18 h	8	n.i
6c X=I, R=Boc	THF	rt, 18 h	56	n.i
6b X=Br, R=Boc	THF	rt, 18 h	49	n.i
6c X=I, R=Boc	DMF	rt, 18 h	70	—
6d X=Br, R=SO_2Ph	DMF	NaI, rt, 18 h	56	—
6b X=Br, R=Boc	DMF	rt, 18 h	71	—
6d X=Br, R=SO_2Ph	DMF	rt, 18 h	64	—

rt=Room temperature, n.i.=not isolated.

Compound **6d**[6] was synthesised via bromination of 3-(1-benzenesulfonyl-1*H*-indolyl)-ethanone (**9**)[7] using pyridinium hydrobromide perbromide.[8] The minor co-product, the dibromo derivative **10**, could easily be separated from the main product by column chromatography (Scheme 2).



9 **6d** (55%) **10** (10%)

Scheme 2. (a) Py·HBr_3, $CHCl_3$, reflux 30 min.

The Horner–Wadsworth–Emmons olefination of **7a** and **7b** with *N*-Boc-3-aminopropionaldehyde[9] did however only proceed in a very modest yield. Using BuLi as the base afforded compound **11a** and **11b** in low yields, around 20%. Other bases tried (DBU, LDA, *t*-BuOK, $[(CH3)_3Si]_2NK$, NaH) failed to give the desired product (Scheme 3).

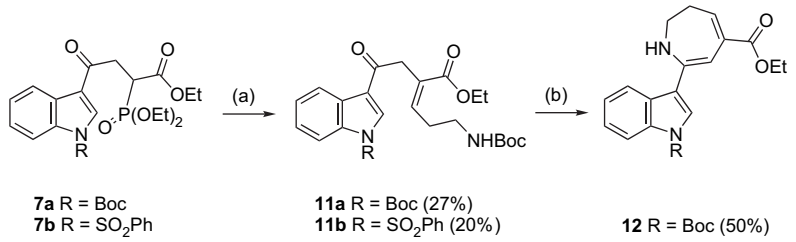
The plan was to remove the Boc-protecting groups and cyclise the amine to the desired lactam. However, treatment of **11a** with 20 equiv TFA and subsequent treatment with $NaHCO_3$ gave the seven-membered heterocycle **12** instead of the expected free amine or the six-membered heterocycle **2**. Also, quite surprisingly, the indole nitrogen remained Boc-protected despite the acid treatment. Due to the rather unstable enamine character of compound **12**, optimal conditions for preparation and isolation are still an issue, as is the deprotection of this compound.

It seems likely that the azepine formation could be induced by the electron withdrawing Boc-protecting group on the indole nitrogen, which would render the carbonyl at the 3-position of the indole more susceptible for attack than the ester functionality. Consequently, removal of the benzenesulfonyl group of **11b** under standard conditions afforded **13**, which was further reacted with *N*-hydroxysuccinimide (HOSu). Surprisingly, during hydrolysis of the ester of **11a** the acidic workup also removed the indole Boc-protecting group, affording compound **13**. This situation is in contrast with the treatment of **11a** with trifluoroacetic acid or formic acid where the amine group is more easily deprotected.

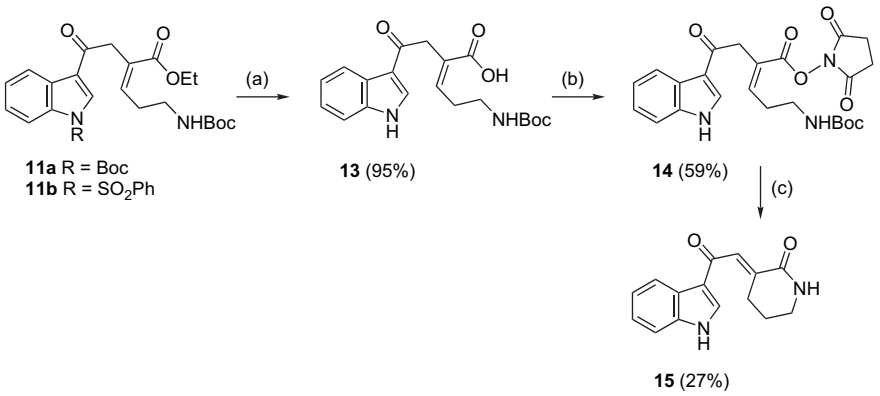
Attempts to accomplish the cyclisation to the lactam under basic conditions, prior to removal of the amine-protecting group were unsuccessful and did not afford the six-membered ring. Instead, treatment of **14** with DBU at −78 °C actually demonstrated the nucleophilic behaviour of DBU, resulting in an *N*-ε-caprolactam derivative.[10]

The *N*-succinimide ester **14** was treated with TFA, and thereafter with a biphasic mixture of aqueous $NaHCO_3$ solution and CH_2Cl_2. A six-membered lactam could thereafter be isolated from the mixture (Scheme 4). However, when comparing the data for this particular lactam with the data reported for the natural compound, it was realised that the exocyclic compound **15** was the product, rather than the endocyclic natural alkaloid. In the ^1H NMR spectrum of compound **15**, it was quite evident that the double bond had migrated, since all three methylenic groups are coupled and one proton *singlet* appears at δ 6.40. For the natural product, a one proton *triplet* appears at δ 6.64, which is coupled with one methylene group, also the methylene bridge appears as a broad singlet. Whether the exocyclic lactam **15** is the kinetic product in this reaction is uncertain, but there are indications from similar examples in the literature.[11]

The exocyclic analogue of the indole alkaloid isolated from the marine sponge *H. melanodocia* has thus been prepared in our laboratory. All attempts to produce the endocyclic lactam and thus to be able to confirm the structure assigned for the natural product to date have been unsuccessful.



Scheme 3. (a) BuLi, *N*-Boc-3-aminopropionaldehyde, THF, −78 °C to rt, 18 h; (b) (i) TFA, CH_2Cl_2, rt, 4 h, (ii) aq satd $NaHCO_3$; (c) TFA.



Scheme 4. (a) (i) 1 M KOH, EtOH, reflux, 1 h, (ii) 1 M HCl; (b) HOSu, EDCI, DMF, rt, 18 h; (c) (i) TFA, CH_2Cl_2, rt, 4 h, (ii) aq $NaHCO_3$, CH_2Cl_2.

3. Experimental

3.1. General

NMR spectra were recorded on a Bruker Avance 300 DPX at 300 MHz for ^{1}H and 75 MHz for ^{13}C. NMR spectra were recorded in DMSO-d_6 or $CDCl_3$, using the solvent signal as reference. δ Values are given in parts per million, coupling constants are given in hertz. The IR spectra were acquired using a ThermoNicolet Avatar 330 FT-IR instrument. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. High-resolution mass spectroscopic (HRMS) analyses were performed by E. Nilsson, University of Lund, Sweden. Melting points were determined on a Büchi B-545, using the capillary method and are uncorrected. All reagents used were purchased from Aldrich, Lancaster, Merck or Biosynth and were used as received. All solvents were purified by distillation or were of analytical grade. THF was distilled from sodium/benzophenone. Chromatographic separations were performed on silica gel 60 (230–400 mesh).

3.1.1. 3-(2-Chloro-acetyl)-indole-1-carboxylic acid *tert*-butyl ester (6a). To a stirred suspension of 2-chloro-1-(1*H*-indol-3-yl)-ethanone[5] (9.65 g, 50 mmol) in CH_3CN (120 mL) was added Boc_2O (12.0 g, 55 mmol), followed by DMAP (37 mg, 0.3 mmol) in small portions. The reaction mixture was stirred for 12 h and the solvent was thereafter evaporated under reduced pressure. The residue was crystallised from EtOH to give 3-(2-chloro-acetyl)-indole-1-carboxylic acid *tert*-butyl ester (**6a**) as a cream coloured amorphous solid (13.1 g, 89%).

Mp 156.0–157.0 °C; IR (neat): 2979, 1730, 1675, 1542, 1447, 1367, 1139, 1108, 836, 747 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.73 (s, 1H), 8.23–8.20 (m, 1H), 8.12–8.10 (m, 1H), 7.47–7.36 (m, 2H), 5.10 (s, 2H), 1.67 (s, 9H); ^{13}C NMR (DMSO-d_6): δ 187.6 (s), 148.4 (s), 134.8 (s), 134.0 (d), 126.8 (s), 125.7 (d), 124.5 (d), 121.7 (d), 116.6 (s), 115.0 (d), 85.7 (s), 47.1 (t), 27.6 (q); MS (ESI) *m*/*z* 294 (M+H)$^+$. Anal. Calcd for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.77. Found: C, 61.31; H, 5.55; N, 4.65.

3.1.2. 3-(2-Bromo-acetyl)-indole-1-carboxylic acid *tert*-butyl ester (6b). 3-(2-Bromo-acetyl)-indole-1-carboxylic acid *tert*-butyl ester (**6b**) was prepared from 2-bromo-1-(1*H*-indol-3-yl)-ethanone[12] as described above. Crystallisation from 2-propanol gave the title compound as a white amorphous solid. Yield: 76%.

Mp 149.0–150.5 °C; IR (neat): 2980, 1730, 1658, 1550, 1448, 1364, 1146, 1093, 837, 750 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.77 (s, 1H), 8.23–8.20 (m, 1H), 8.12–8.09 (m, 1H), 7.46–7.36 (m, 2H), 4.88 (s, 2H), 1.68 (s, 9H); ^{13}C NMR (DMSO-d_6): δ 187.7 (s), 148.4 (s), 134.9 (s), 134.5 (d), 126.9 (s), 125.7 (d), 124.5 (d), 121.7 (d), 116.5 (d), 114.9 (s), 85.7 (s), 34.1 (t), 27.6 (q). Anal. Calcd for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; N, 4.14. Found: C, 53.31; H, 4.68; N, 4.05.

3.1.3. 3-(2-Iodo-acetyl)-indole-1-carboxylic acid *tert*-butyl ester (6c). 3-(2-Iodo-acetyl)-indole-1-carboxylic acid *tert*-butyl ester (**6c**) was prepared from 2-iodo-1-(1*H*-indol-3-yl)-ethanone[12] as described above. Crystallisation from 2-propanol gave the title compound as a cream coloured amorphous solid. Yield: 79%.

Mp 142.0–144.0 °C; IR (neat): 2980, 1728, 1651, 1547, 1446, 1365, 1145, 1084, 836, 746 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.78 (s, 1H), 8.21–8.18 (m, 1H), 8.11–8.09

(m, 1H), 7.44–7.37 (m, 1H), 4.63 (s, 2H), 1.68 (s, 9H); ^{13}C NMR (DMSO-d_6): δ 189.8 (s), 148.5 (s), 135.0 (s), 134.4 (d), 127.0 (s), 125.6 (d), 124.4 (d), 121.9 (d), 116.0 (s), 114.9 (d), 85.7 (s), 27.6 (q), 6.3 (t). Anal. Calcd for $C_{15}H_{16}INO_3$: C, 46.77; H, 4.19; N, 3.64. Found: C, 46.87; H, 4.27; N, 3.57.

3.1.4. 3-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-bromo-ethanone (6d) and 3-(1-benzenesulfonyl-1*H*-indol-3-yl)-2,2-dibromo-ethanone (10). 3-(1-Benzenesulfonyl-1*H*-indol-3-yl)-ethanone[7] (**9**) (2.99 g, 10.0 mmol) and pyridinium hydrobromide perbromide (3.84 g, 12.0 mmol) were suspended in chloroform (50 mL) and heated at reflux for 30 min. The reaction mixture was allowed to cool and thereafter transferred to a separatory funnel, washed with H_2O (50 mL), dried over Na_2SO_4 and evaporated to dryness. The residue was subjected to column chromatography using CH_2Cl_2/hexane (80:20) as eluent to give **10** (0.44 g, 10%) followed by **6d** (2.07 g, 55%) as white solids.

3.1.4.1. 3-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-bromo-ethanone (6d). Mp 119.5–121.5 °C (lit.[6] 130.5–131.0 °C); IR (neat): 3137, 1669, 1536, 1373, 1176, 1134, 989, 749, 726, 589 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.36 (s, 1H), 8.31 (d, J=8.2, 1H), 7.98–7.93 (m, 3H), 7.63–7.58 (m, 1H), 7.52–7.47 (m, 2H), 7.42–7.33 (m, 2H), 4.37 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 187.1 (s), 137.4 (s), 135.0 (s), 134.9 (d), 133.0 (d), 129.9 (d), 127.7 (s), 127.3 (d), 126.3 (d), 125.4 (d), 123.2 (d), 118.4 (s), 113.3 (d), 31.6 (t). Anal. Calcd for $C_{16}H_{12}BrNO_3S$: C, 50.81; H, 3.20; N, 3.70. Found: C, 50.79; H, 3.30; N, 3.65.

3.1.4.2. 3-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2,2-dibromo-ethanone (10). Mp 144.0–145.0 °C; IR (neat): 3123, 1682, 1529, 1371, 1176, 1133, 985, 746, 725, 592 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.61 (s, 1H), 8.32–8.29 (m, 1H), 7.99–7.95 (m, 3H), 7.61–7.58 (m, 1H), 7.53–7.48 (m, 2H), 7.42–7.37 (m, 2H), 6.51 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 182.4 (s), 137.2 (s), 135.0 (d), 134.8 (s), 133.4 (d), 129.9 (d), 128.0 (s), 127.4 (d), 126.5 (d), 125.5 (d), 123.3 (d), 114.0 (s), 113.3 (d), 40.3 (d). Anal. Calcd for $C_{16}H_{11}Br_2NO_3S$: C, 42.04; H, 2.43; N, 3.06. Found: C, 41.95; H, 2.44; N, 2.89.

3.1.5. 3-[3-(Diethoxy-phosphoryl)-3-ethoxycarbonyl-propionyl]-indole-1-carboxylic acid *tert*-butyl ester (7a).

3.1.5.1. Representative procedure. To a suspension of NaH (88 mg, 2.2 mmol) in DMF (7 mL) at room temperature was added triethyl phosphonoacetate (0.4 mL, 2.0 mmol) in small portions. After 40 min at room temperature compound **6c** (770 mg, 2.0 mmol) dissolved in DMF (5 mL) was added in small portions. After 18 h the reaction mixture was poured into H_2O (15 mL) and extracted with EtOAc (3×10 mL). The combined organic phases were washed with H_2O (25 mL), brine (25 mL), dried over Na_2SO_4 and the solvents were evaporated. The residue was subjected to column chromatography using EtOAc/hexane (70:30) as eluent to give compound **7a** as pale yellow solid (674 mg, 70%).

Mp 119.5–121.0 °C; IR (neat): 2980, 1732, 1664, 1447, 1365, 1255, 1238, 1146, 1136, 1015, 764, 757 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.67 (s, 1H), 8.20 (d, J=7.9, 1H), 8.12 (d, J=7.9, 1H), 7.45–7.33 (m, 2H), 4.16–4.08 (m, 6H), 3.70–3.36 (m, 3H), 1.68 (s, 9H), 1.30–1.17 (m, 9H). Anal. Calcd for $C_{23}H_{32}NO_8P$: C, 57.37; H, 6.70; N, 2.91. Found: C, 57.57; H, 6.81; N, 2.84.

3.1.6. 4-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-(diethoxy-phosphoryl)-4-oxo-butyric acid ethyl ester (7b). Compound **7b** was prepared from 3-(1-benzenesulfonyl-1*H*-indol-3-yl)-2-bromo-ethanone (**6d**) using the procedure described above. Silica gel column chromatography using hexane/EtOAc (60:40) with increasing amounts of EtOAc as eluent afforded compound **7b** as pale yellow oil. Yield: 64%.

IR (neat): 2982, 1731, 1669, 1538, 1446, 1384, 1250, 1164, 1135, 1018, 750, 727 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.00 (s, 1H), 8.23–8.13 (m, 3H), 7.98 (d, J=8.2, 1H), 7.76–7.63 (m, 3H), 7.43–7.36 (m, 2H), 4.17–4.07 (m, 6H), 3.75–3.46 (m, 3H), 1.30 (dt, J=1.9, 7.0, 6H), 1.20 (t, J=7.1, 3H); HRMS (FAB$^+$) m/z calcd for $C_{24}H_{29}NO_8PS$ $(M+H)^+$ 522.1351, found 522.1350.

3.1.7. 3-(1-Chloromethyl-2-ethoxycarbonyl-vinyl)-indole-1-carboxylic acid *tert*-butyl ester (8). To a suspension of NaH (220 mg, 5.5 mmol) in THF (15 mL) at room temperature was added triethyl phosphonoacetate (0.4 mL, 5.0 mmol) in small portions. After 40 min at room temperature compound **6a** (1.47 g, 5.0 mmol) was added as a solid in small portions together with NaI (75 mg, 0.5 mmol). After 18 h, H_2O (5 mL) was added to the reaction mixture and THF was evaporated. The residue was redissolved in EtOAc (20 mL) and washed with H_2O (2×10 mL), brine (15 mL), dried over Na_2SO_4 and evaporated. The residue was subjected to column chromatography using hexane/EtOAc (90:10) with increasing amounts of EtOAc as eluent to give compound **8** (472 mg, 26%) followed by compound **7a** (637 mg, 26%) as pale yellow solids.

Mp 114–116 °C; IR (neat): 2978, 1735, 1709, 1621, 1450, 1367, 1240, 1146, 1106, 1052, 1035, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.23 (d, J=7.9, 1H), 7.96 (s, 1H), 7.84–7.81 (m, 1H), 7.40–7.32 (m, 2H), 6.48 (s, 1H), 5.10 (s, 2H), 4.33 (q, J=7.1, 14.3, 2H), 1.70 (s, 9H), 1.39 (t, J=7.1, 3H); ^{13}C NMR ($CDCl_3$): δ 165.9 (s), 149.4 (s), 146.9 (s), 136.2 (s), 127.8 (s), 126.7 (d), 125.3 (d), 123.7 (d), 120.5 (d), 119.4 (d), 119.3 (s), 115.8 (d), 84.9 (s), 60.7 (t), 40.0 (t), 28.3 (q), 14.5 (q); HRMS (FAB$^+$) m/z calcd for $C_{19}H_{22}ClNO_4$ $(M)^+$ 363.1237, found 363.1253.

3.1.8. 3-(6-*tert*-Butoxycarbonylamino-3-ethoxycarbonyl-hex-3-enoyl)-indole-1-carboxylic acid *tert*-butyl ester (11a). Compound **7a** (2.20 g, 4.57 mmol) was dissolved in THF (20 mL) and cooled to −78 °C under a nitrogen atmosphere. To the solution was added *n*-BuLi (3.14 mL, 5.03 mmol) in a dropwise manner. After the addition the solution was warmed up to 0 °C for 30 min, then again cooled down to −78 °C. A solution of *N*-Boc-3-aminopropionaldehyde[9] (791 mg, 4.57 mmol) in THF (10 mL) was added in small portions and the reaction mixture was thereafter allowed to reach room temperature over night. After 18 h H_2O (2 mL) was added and the solvent was evaporated. The residue was redissolved in EtOAc (20 mL) and washed

with H_2O (20 mL). The aqueous phase was extracted with an additional portion of EtOAc (20 mL) and the combined organic phases were washed with brine (20 mL) and dried over Na_2SO_4. After evaporation the oily residue was purified by silica gel column chromatography using hexane/EtOAc (80:20 to 60:40) to give compound **11a** as a yellow oil. Yield: 610 mg (27%).

IR (neat): 3365, 2978, 1742, 1701, 1449, 1364, 1236, 1136, 1100, 749 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.67 (s, 1H), 8.21 (d, J=7.7, 1H), 8.12 (d, J=8.0, 1H), 7.44–7.32 (m, 2H), 6.94–6.89 (m, 2H), 4.11–4.04 (m, 4H), 3.07–3.01 (m, 2H), 2.36–2.29 (m, 2H), 1.67 (s, 9H), 1.35 (s, 9H), 1.14 (t, J=7.1, 3H); ^{13}C NMR (DMSO-d_6): δ 192.7 (s), 166.4 (s), 155.6 (s), 148.5 (s), 142.2 (d), 134.9 (s), 133.3 (d), 127.7 (s), 127.0 (s), 125.4 (d), 124.2 (d), 121.9 (d), 118.9 (s), 114.8 (d), 85.4 (s), 77.5 (s), 60.1 (t), 38.8 (t), 37.6 (t), 29.0 (t), 28.1 (q), 27.5 (q), 14.0 (q); HRMS (FAB$^+$) m/z calcd for $C_{27}H_{37}N_2O_7$ (M+H)$^+$ 501.2601, found 501.2598.

3.1.9. 2-[2-(1-Benzenesulfonyl-1*H*-indol-3-yl)-5-*tert*-butoxycarbonylamino]-pent-2-enoic acid ethyl ester (11b). Compound **11b** was prepared from 4-(1-benzenesulfonyl-1*H*-indol-3-yl)-2-(diethoxy-phosphoryl)-4-oxo-butyric acid ethyl ester (**7b**) using the procedure described above. Column chromatography using hexane/EtOAc (60:40) eluent afforded compound **11b** as pale yellow oil. Yield: 23%.

IR (neat): 2978, 1701, 1536, 1376, 1166, 1135, 748, 727, 592, 571 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.42 (s, 1H), 8.32–8.27 (m, 1H), 7.99–7.92 (m, 4H), 7.63–7.58 (m, 1H), 7.53–7.48 (m, 3H), 7.39–7.29 (m, 2H), 7.08 (t, J=7.8, 1H), 5.11 (br, 1H), 4.20–4.08 (m, 2H), 3.95 (s, 2H), 3.31–3.29 (m, 2H), 2.50–2.42 (m, 2H), 1.39 (s, 9H), 1.31–1.18 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 192.7 (s), 166.9 (s), 156.2 (s), 143.0 (d), 137.8 (s), 135.1 (s), 134.8 (d), 132.6 (d), 129.8 (d), 128.1 (s), 127.9 (s), 127.4 (d), 126.1 (d), 125.1 (d), 123.4 (d), 121.1 (s), 113.2 (d), 77.4 (s), 61.2 (t), 39.6 (t), 38.0 (t), 29.9 (t), 28.5 (q), 14.4 (q); HRMS (FAB$^+$) m/z calcd for $C_{28}H_{33}N_2O_7S$ (M+H)$^+$ 541.2008, found 541.2010.

3.1.10. 5-*tert*-Butoxycarbonylamino-2-[2-(1*H*-indol-3-yl)-2-oxo-ethyl]-pent-2-enoic acid (13). To compound **11a** (429 mg, 0.86 mmol) dissolved in EtOH (10 mL) was added 1 M KOH (5 mL). The reaction mixture was heated to reflux for 1 h and was then allowed to cool. EtOH was evaporated and the residue diluted with H_2O (5 mL). The resulting mixture was cooled on ice and acidified with 1 M HCl until a precipitate appeared. The solid was collected by filtration, washed with water and dried to give **13** as a yellowish solid (302 mg, 95%).

Mp 168–170 °C; IR (neat): 3267, 2978, 1693, 1638, 1515, 1428, 1244, 1154, 1135, 746 cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.18 (s, 1H), 11.94 (s, 1H), 8.40 (d, J=3.1, 1H), 8.15–8.12 (m, 1H), 7.49–7.46 (m, 1H), 7.21–7.16 (m, 2H), 6.91–6.84 (m, 2H), 3.91 (s, 2H), 3.07–3.00 (m, 2H), 2.33–2.26 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (DMSO-d_6): δ 191.6 (s), 168.3 (s), 155.6 (s), 141.2 (d), 136.5 (s), 133.9 (d), 128.8 (s), 125.4 (s), 122.7 (d), 121.6 (d), 121.3 (d), 115.9 (s), 112.1 (d), 77.5 (s), 39.0 (t), 37.0 (t), 29.0 (t), 28.2 (q). Anal. Calcd for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.37; H, 6.70; N, 7.39.

3.1.11. 5-*tert*-Butoxycarbonylamino-2-[2-(1*H*-indol-3-yl)-2-oxo-ethyl]-pent-2-enoic acid 2,5-dioxo-pyrrolidin-1-yl ester (14). Compound **13** (474 mg, 1.27 mmol) was dissolved in DMF (4 mL). EDCI (269 mg, 1.40 mmol) and HOSu (161 mg, 1.40 mmol) were added and the resulting reaction mixture was kept at room temperature for 18 h. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (3×10 mL). The combined organic phases were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4 and evaporated. The oily residue was purified on column chromatography using EtOAc/hexane (50:50 to 70:30) as eluent to give compound **14** as a light brown oil. Yield: 354 mg (59%).

IR (neat): 3230, 2932, 1733, 1700, 1646, 1521, 1204, 1163, 1067, 749 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.25 (s, 1H), 8.35–8.32 (m, 1H), 7.95 (d, J=3.1, 1H), 7.40–7.37 (m, 1H), 7.30–7.21 (m, 4H), 3.87 (s, 2H), 3.30–3.26 (m, 2H), 2.77 (s, 4H), 2.54–2.47 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (acetone-d_6): δ 190.8 (s), 170.5 (s), 163.2 (s), 148.6 (d), 137.8 (s), 134.0 (d), 126.9 (s), 125.5 (s), 123.6 (d), 122.9 (d), 122.8 (d), 117.6 (s), 112.7 (d), 78.7 (s), 39.8 (t), 38.0 (t), 30.7 (t), 28.6 (q), 26.3 (t), 26.11 (t); HRMS (FAB$^+$) m/z calcd for $C_{24}H_{28}N_3O_7$ (M+H)$^+$ 470.1927, found 470.1927.

3.1.12. 3-(4-Ethoxycarbonyl-6,7-dihydro-1*H*-azepin-2-yl)-indole-1-carboxylic acid *tert*-butyl ester (12). Compound **11a** (378 mg, 0.76 mmol) dissolved in formic acid (15 mL) was stirred at room temperature for 4 h. The acid was evaporated and the residue was dissolved in EtOAc (20 mL) and washed with satd aq $NaHCO_3$ (3×15 mL). The organic phase was washed with H_2O (15 mL) and brine (15 mL), dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography using hexane/EtOAc (60:40) with increasing amounts of EtOAc as eluent to afford the title compound as a yellow oil (144 mg, 50%).

^1H NMR ($CDCl_3$): δ 8.20 (d, J=7.9, 1H), 7.91 (d, J=7.7, 1H), 7.72 (s, 1H), 7.38–7.26 (m, 2H), 6.87 (t, J=6.15, 1H), 5.80 (s, 1H), 4.36 (br s, 1H), 4.29 (q, J=7.1, 14.2, 2H), 3.52–3.51 (m, 2H), 2.75–2.70 (m, 2H), 1.69 (s, 9H), 1.34 (t, J=7.1, 3H); ^{13}C NMR ($CDCl_3$): δ 168.4 (s), 149.4 (s), 140.8 (s), 135.6 (s), 133.5 (d), 130.4 (s), 128.5 (s), 124.6 (d), 123.4 (d), 122.9 (d), 121.6 (s), 120.5 (d), 115.2 (d), 94.5 (d), 83.9 (s), 60.7 (t), 45.2 (t), 35.0 (t), 28.1 (q), 14.2 (q); MS (ESI) m/z 383 (M+H)$^+$; HRMS (EI) m/z calcd for $C_{22}H_{27}N_2O_4$ (M+H)$^+$ 383.1971, found 383.1948; HRMS (EI) m/z calcd for $C_{22}H_{25}N_2O_4$ (M−H)$^-$ 381.1814, found 381.1841.

3.1.13. 3-[2-(1*H*-Indol-3-yl)-2-oxo-ethylidene]-piperidin-2-one (15). To a solution of compound **14** (500 mg, 1.07 mmol) in CH_2Cl_2 (20 mL) was added TFA (1.64 mL, 21.3 mmol) and the resulting solution was stirred at room temperature for 7 h. The solvent was evaporated and the residue was parted between CH_2Cl_2 (25 mL) and H_2O (20 mL), adding $NaHCO_3$ (540 mg, 6.43 mmol) to reach pH ~7–8. After 12 h at room temperature a beige solid was collected by filtration from the biphasic mixture, washed with water and dried to give the title compound. Yield: 72 mg (27%).

Mp 200.0–201.5 °C; IR (neat): 3232, 2938, 1746, 1683, 1642, 1587, 1575, 1523, 1426, 1132, 795, 738 cm^{-1}; ^1H

NMR (DMSO-d_6): δ 11.74 (s, 1H), 8.16–8.13 (m, 1H), 7.84 (d, J=2.7, 1H), 7.56 (br s, 1H), 7.47–7.44 (m, 1H), 7.22–7.14 (m, 2H), 6.40 (s, 1H), 3.24–3.19 (m, 2H), 2.62–2.58 (m, 2H), 1.90–1.84 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 189.8 (s), 163.1 (s), 136.7 (s), 134.8 (d), 133.8 (d), 133.7 (s), 125.3 (s), 122.5 (d), 121.3 (d), 121.2 (d), 116.5 (s), 112.0 (d), 41.41 (t), 30.0 (t), 22.8 (t). HRMS (FAB$^+$) *m/z* calcd for $C_{15}H_{15}N_2O_2$ $(M+H)^+$ 255.1134, found 255.1141.

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A computational study of halomethyllithium carbenoid mixed aggregates with lithium halides and lithium methoxide

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Abstract—Density functional theory calculations were used to examine the formation of lithium halide and lithium alkoxide mixed aggregates with halomethyllithium carbenoids. These mixed aggregates may be the important intermediates in carbenoid reactions where lithium halides are formed as byproducts, or when the mixture has been exposed to small amounts of air. The calculations showed that in the gas phase and in THF solution, mixed dimers, trimers, and tetramers may coexist with free lithium carbenoids, depending on the lithium salt. The calculations also indicated that mixed aggregates may influence the activation free energies of cyclopropanation reactions of lithium carbenoids.

1. Introduction

Lithium carbenoids are used extensively in organic synthesis. In addition to cyclopropanation reactions with alkenes, carbenoids undergo a variety of single bond insertion reactions, including both C–H and C–heteroatom insertions. The instability and reactivity of lithium carbenoids makes them difficult to study by conventional experimental methods, although low temperature ^{13}C NMR spectroscopy has been used for structure determination of a few of the more stable haloalkyllithium carbenoids.[1,2] Those investigations proved the carbene-like character of the halomethyllithium species from the lithium–carbon spin coupling constants, but provided no information on the aggregation behavior of lithium carbenoids. To date little is known about the detailed reaction mechanisms of these compounds, and several research groups have turned to computational studies to investigate the structure and reactions of these species in more detail. Cyclopropanation reactions have been the subject of several theoretical investigations of monomeric lithium and zinc carbenoids in the gas phase.[3–5]

Nearly all organolithium compounds can exist as aggregates, and lithium carbenoids are no exception. A previous computational study showed that halomethyllithium carbenoids dimerize in the gas phase and sometimes in ethereal solvents.[6] Small changes in the structure of lithium compounds or in solvation can cause significant changes in the aggregation behavior. Mixed aggregates between two different lithium compounds are also quite common and can have significant effects on the product distribution. This was illustrated by several studies on lithium dialkylamide mixed aggregates and their effect on the stereochemistry of ketone enolization.[7–12]

A clear picture of the reactions of lithium carbenoids is beginning to emerge, and will almost certainly include homo- and mixed aggregates. Nakamura and co-workers showed that monomeric lithium and zinc carbenoids can react with alkenes either in a concerted or stepwise manner.[3] Our own work, currently in progress, suggests that the concerted mechanism is also operative in the lithium carbenoid dimer. The monomer and homo-dimer are likely reactive species at the beginning of lithium carbenoid reactions before much lithium halide byproduct has been formed. We hypothesize that the lithium halide byproduct will form mixed aggregates with the halomethyllithium carbenoids, similar to those that have recently been reported with lithium dialkylamides.[13] Likewise, exposure of the reaction mixture, or the alkyllithium used to generate the carbenoid, to small amounts of air will result in the formation of lithium alkoxides. Of course, either of those compounds can be intentionally added to the reaction mixture to take advantage of any favorable reactions of mixed aggregates, and addition of LiCl to reaction mixtures of lithium compounds is quite common. In this paper we use computational methods to elucidate the structures and solvation states of lithium carbenoid mixed aggregates with lithium halides and lithium methoxide. In addition, we investigate whether mixed aggregates significantly alter the activation free energy of cyclopropane formation between chloromethyllithium and ethylene. The

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significance of this is that lithium carbenoids may undergo several types of insertion reactions, or non-insertion reactions like the FBW rearrangement of 1-halovinyllithium carbenoids. The competition between the different types of reactions is likely influenced by mixed aggregates.

2. Computational methods

All calculations were performed using the *Gaussian 98* or *Gaussian 03* programs.[14] The reported gas phase and solution energies include the electronic and nuclear repulsion energy (E_{en}), thermal corrections to the free energy (including ZPE) at 200 and 298 K, and where applicable, solvation terms. Due to the possibility of several possible conformations of similar energy, it was sometimes necessary to optimize two or more conformations of the same structure and the lowest energy conformer was used in subsequent calculations.

The solvation free energy change of the gas phase organolithium molecule $(RLi)_n$ due to microsolvation by m explicit ethereal solvent ligands E (in this case, THF) is calculated by considering the process

$$(RLi)_n + mE \rightarrow (RLi)_n \cdot mE. \quad (1)$$

The microsolvation model assumes that the free energy change accompanying this reaction adequately represents the solvation free energy ΔG^{o}_{solv}, of the solute $(RLi)_n$ in the solvent E, so that

$$G^{o}_{T}(\text{solute}) = G^{o}_{T}(\text{gas}) + \Delta G^{o}_{solv} \quad (2)$$

In other words, the free energy of a 'supermolecule' $(RLi)_n \cdot mE$ relative to that of m solvent molecules is assumed to yield a good approximation to the free energy of the solvated molecule $(RLi)_n$ in the condensed phase. The gas phase free energies at temperature T of the relevant species are obtained computationally as

$$G^{o}_{T}(\text{gas}) = E_{en} + \Delta G^{o}_{T}, \quad (3)$$

where the terms on the right hand side as well as the procedure used for calculating them are described below. The geometry of each molecule or transition structure was first optimized using the B3LYP hybrid density functional method[15,16] with the MIDIX basis set,[17] and that basis set was also used for frequency calculations and to determine the ZPE's and thermal corrections to the free energies. A further refinement of the geometry and electronic energy was done at the B3LYP/6-31+G(d)[18,19] level of theory, as diffuse functions are needed for molecules that have substantial carbanion character. Basis set superposition errors (BSSE) were corrected by counterpoise corrections for all homo- and mixed aggregates, defining the fragments in each aggregate as the lithium carbenoid or lithium halide monomer units. When calculating the energies of mixed aggregate formation, each aggregated species was counterpoise corrected at the B3LYP/6-31+G(d) level, including the lithium carbenoid and lithium halide dimers. Thus we have:

E_{en}=the electronic plus nuclear repulsion energy of the equilibrium geometry, using B3LYP/6-31+G(d).

E^{vib}_{0}=unscaled B3LYP/MIDIX vibrational zero point energy.

ΔG^{o}_{T}=B3LYP/MIDIX thermal corrections to the free energy for a standard state of 1 atm and specified temperature from the masses. This includes contributions from translational, rotational, and vibrational degrees of freedom, as well as the zero point energy.

Calculations of the free energy changes for the 'reactions' (dimerizations, tetramerizations, etc.) are straightforward using the G^{o}_{T}(gas) terms defined in Eq. 3.

Density functional theory is not always reliable for transition structure calculations, so a slightly different approach was used to determine activation free energies. The geometry was optimized and the thermal corrections to the free energies were obtained at the Hartree–Fock/6-31+G(d) level. The geometries were then re-optimized at the B3LYP and MP2 levels with the same basis set, and the Hartree–Fock thermal corrections were added to the E_{en} at each level of theory to obtain approximate activation free energies.

The standard state of a solution is taken as 1 mol/L at 298.15 K, and an additional correction to the free energy terms is needed to convert the standard state of an ideal gas (1 atm) to the standard state of the solution. This was incorporated by simply adding the term $RT\ln(RT)$ to each free energy term, where the numerical value of the argument of the logarithm was obtained using the pressure–volume (0.082057 L atm/K/mol) value for the gas constant. This replaces the logarithm argument term PV (24.47 L atm) with RT, corresponding to a concentration of approximately 0.0409 mol/L, and this correction corresponds to the free energy of compressing the gas to a concentration of 1 mol/L. These corrections amount to 1.1120 kcal/mol at 200 K and 1.8943 kcal/mol at 298 K. These correction terms were included in all solution phase reactions below, i.e., calculations where the microsolvation model was used.

Yet another correction is required for proper treatment of the explicit solvent molecules used in microsolvation. The traditional approach is to set the standard state of a pure liquid to be the concentration of the pure liquid itself, which then allows one to drop the concentration of the pure liquid from equilibrium expressions (consider the ionic product of water, for example). However, since we have decided to adopt the standard state of 1 mol/L for all species, the free energy change for the process

$$2RLi \cdot 2THF \rightarrow (RLi \cdot THF)_2 + 2THF \quad (4)$$

is given by Ref. 20

$$\Delta G^{o} = -RT\ln\left\{\left[(RLi \cdot THF)_2\right]/[RLi \cdot 2THF]^2\right\} - 2RT\ln[THF] \quad (5)$$

The molarity of the THF solvent was calculated to be 13.26 at 200 K, and 12.33 at 298 K, from its tabulated density.[21] These corrections amount to −1.0273 and −1.4883 kcal/mol per THF at 200 and 298 K, respectively. Thus, the $-2RT\ln[THF]$ term in Eq. 5 will favor the disolvated monomer by 2.0546 kcal/mol at 200 K.

3. Results and discussion

Because frequency calculations on large systems are often prohibitively expensive, the smaller MIDIX basis set was used to calculate the thermal corrections to the free energies. To be sure that those corrections were reasonable, the geometries of gas phase carbenoid monomers and dimers were optimized with both the MIDIX and 6-31+G(d) basis sets and the thermal corrections calculated, as shown in Table 1. The total thermal correction for the dimerization of the halomethyllithiums is the correction to the dimer free energy minus twice the correction to the monomer, shown in the last column of Table 1. The differences between the MIDIX and 6-31+G(d) results were 0.8 and 0.5 kcal/mol, respectively, for the dimerization of chloro- and bromomethyllithium. We therefore concluded that the use of the smaller basis set for the frequencies is a reasonable approximation for this system.

Table 1. Calculated thermal corrections to the free energy (Hartree) for the dimerization of lithium carbenoids

Carbenoid	Basis set	Monomer	Dimer	$D-2M$
$LiCH_2Cl$	MIDIX	0.000844	0.022119	0.020431
$LiCH_2Cl$	6-31+G(d)	0.000762	0.020666	0.019142
$LiCH_2Br$	MIDIX	−0.000875	0.017992	0.019742
$LiCH_2Br$	6-31+G(d)	−0.000838	0.017277	0.018953

The free energies of mixed aggregate formation were calculated from the free energies of the lithium carbenoid and lithium halide dimers. The lithium halide dimers were used in these calculations based on the experimental result that LiBr is mostly dimeric in THF solution.[22] Lithium methoxide could potentially exist as a dimer or tetramer, and the energy of gas phase and THF solvated tetramer formation was calculated according to Eqs. 6 and 7, respectively. The calculated energies at the counterpoise corrected B3LYP/6-31+G(d) level are shown in Table 2. In both the gas phase and in solution, the tetramer was energetically favored, and that the species was used in the calculation of mixed aggregate energies of formation.

$$2(LiOCH_3)_2 \rightarrow (LiOCH_3)_4 \quad (6)$$

$$2(LiOCH_3)_2 \cdot 2THF \rightarrow (LiOCH_3)_4 \cdot 4THF \quad (7)$$

The mixed aggregates that were investigated include a mixed dimer, two mixed trimers, and four mixed tetramers. The mixed aggregate structures and free energies of formation were first calculated in the gas phase to determine the aggregation behavior in the absence of solvent effects, and then using the microsolvation model with THF ligands. Because basis set superposition errors (BSSE) can be substantial with lithium halides (particularly bromides), all reported free energies were counterpoise corrected, as described in the Section 2. The gas phase free energies of lithium halide mixed aggregate formation were calculated according to Eqs. 8–13, and the corresponding lithium methoxide mixed aggregates by Eqs. 14–19. The optimized gas phase geometries of the chloromethyllithium carbenoids and their mixed aggregates (structures **1**–**9**) are shown in Figure 1, and the analogous lithium methoxide tetramer and mixed aggregates (structures **10**–**17**) are shown in Figure 2. The lithium

Table 2. Calculated free energies of lithium methoxide tetramer formation (kcal/mol)

Phase	Temp (K)	ΔG tetramer formation
Gas	200	−35.8
Gas	298.15	−31.6
THF solution	200	−13.4
THF solution	298.15	−8.11

chloro- and bromocarbenoid mixed aggregates optimized to similar geometries.

$$1/2(LiCH_2X)_2\ (\mathbf{1}) + 1/2(LiX)_2\ (\mathbf{2}) \rightarrow (LiCH_2X)(LiX)\ (\mathbf{3}) \quad (8)$$

$$1/2(LiCH_2X)_2 + (LiX)_2 \rightarrow (LiCH_2X)(LiX)_2\ (\mathbf{4}) \quad (9)$$

$$(LiCH_2X)_2 + 1/2(LiX)_2 \rightarrow (LiCH_2X)_2(LiX)\ (\mathbf{5}) \quad (10)$$

$$(LiCH_2X)_2 + (LiX)_2 \rightarrow (LiCH_2X)_2(LiX)_2 \text{ (two isomers, } \mathbf{6} \text{ and } \mathbf{7}) \quad (11)$$

$$1/2(LiCH_2X)_2 + 3/2(LiX)_2 \rightarrow (LiCH_2X)(LiX)_3\ (\mathbf{8}) \quad (12)$$

$$3/2(LiCH_2X)_2 + 1/2(LiX)_2 \rightarrow (LiCH_2X)_3(LiX)\ (\mathbf{9}) \quad (13)$$

$$1/2(LiCH_2X)_2\ (\mathbf{1}) + 1/4(LiOMe)_4\ (\mathbf{10}) \rightarrow (LiCH_2X)(LiOMe)\ (\mathbf{11}) \quad (14)$$

$$1/2(LiCH_2X)_2\ (\mathbf{1}) + 1/2(LiOMe)_4\ (\mathbf{10}) \rightarrow (LiCH_2X)(LiOMe)_2\ (\mathbf{12}) \quad (15)$$

$$(LiCH_2X)_2\ (\mathbf{1}) + 1/4(LiOMe)_4\ (\mathbf{10}) \rightarrow (LiCH_2X)_2(LiOMe)\ (\mathbf{13}) \quad (16)$$

$$(LiCH_2X)_2 + 1/2(LiOMe)_4 \rightarrow (LiCH_2X)_2(LiOMe)_2 \text{ (two isomers, } \mathbf{14} \text{ and } \mathbf{15}) \quad (17)$$

$$1/2(LiCH_2X)_2 + 3/4(LiOMe)_4 \rightarrow (LiCH_2X)(LiOMe)_3\ (\mathbf{16}) \quad (18)$$

$$3/2(LiCH_2X)_2 + 1/4(LiOMe)_2 \rightarrow (LiCH_2X)_3(LiOMe)\ (\mathbf{17}) \quad (19)$$

The calculated free energies of gas phase mixed dimer and trimer formation are shown in Table 3. For each system, mixed trimer formation is favored over mixed dimer formation, and the formation of both mixed aggregates is weakly temperature dependent, with the higher temperature disfavoring lithium halide mixed aggregate formation. Formation of lithium halide mixed dimers and trimers is more energetically favored than those of lithium methoxide. In the gas phase, steric effects on the chloromethyllithium dimer are negligible, and the driving force toward mixed aggregate formation is likely to be primarily the difference in base strengths of the carbenoid and the lithium salt.

Table 4 shows the calculated free energies for mixed tetramer formation. Two isomeric $(LiCH_2X)_2(LiX)_2$ mixed tetramers optimized to planar ladder (**6**) and distorted tetrahedral (**7**) geometries, with the ladder structure being favored by about 0.5–1 kcal/mol per lithium atom. The analogous lithium methoxide symmetrically mixed tetramers optimized to a ladder (**14**) or bent (**15**) geometry, with the ladder structure

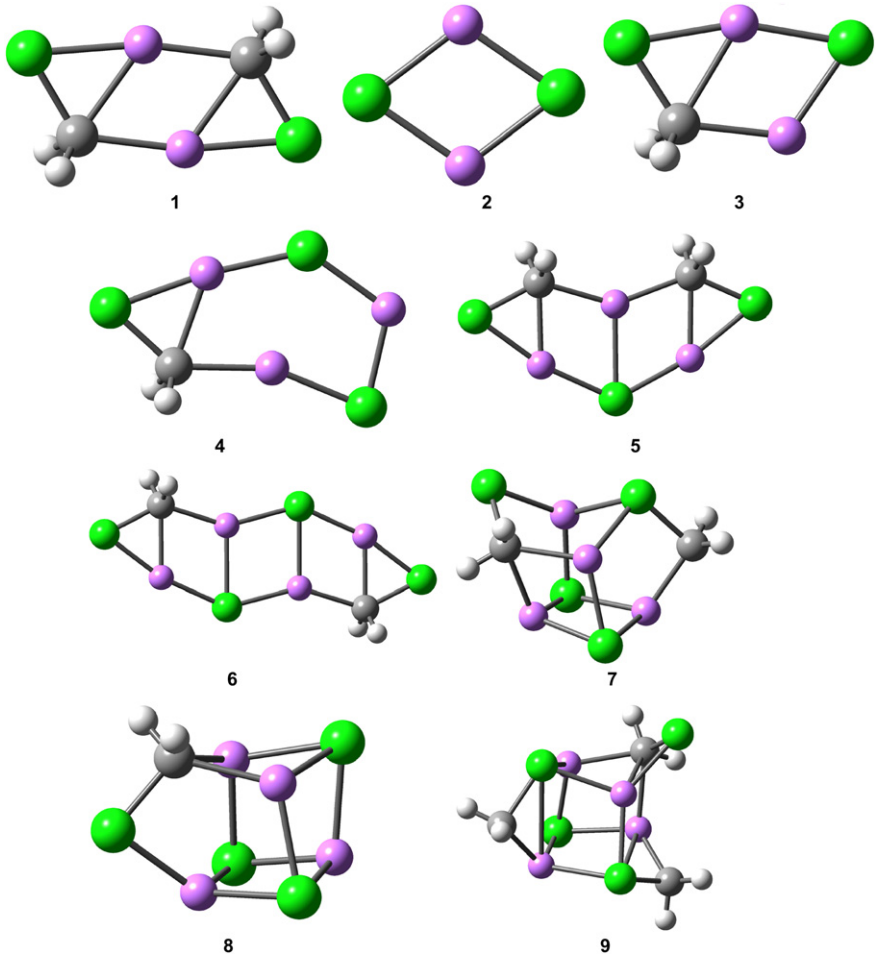

Figure 1. Optimized geometries of gas phase chloromethyllithium, LiCl, and mixed aggregates **1–9**. Gray: carbon; white: hydrogen; violet: lithium; green: chlorine; red: oxygen.

being highly favored over the bent one. The two unsymmetrically mixed tetramers also optimized to distorted tetrahedral structures (**8**, **16** and **9**, **17**). For the lithium halide mixed aggregates, the unsymmetrically mixed tetramer **8** was favored over **9**. The analogous lithium methoxide **16** optimized to a weakly bound complex of the mixed dimer **11** and $(LiOMe)_2$. Of all the lithium methoxide mixed tetramers with $LiCH_2X$, structure **17** was the most energetically favorable. As with the mixed dimer and mixed trimers, the higher temperature disfavored the formation of mixed tetramers. Comparison of the data in Tables 3 and 4 indicates that several lithium halide mixed trimers and tetramers will be present in the gas phase, while the lithium methoxide mixed aggregates will exist almost exclusively as the mixed tetramers **14** and **17**.

Solvation is expected to have a significant effect on the formation of mixed aggregates due to both dipole and steric effects. For the lithium carbenoid (**1**) and lithium halide (**2**) dimers, and for the mixed dimer (**3** or **11**), a question arose as to the number of solvent ligands associated with each lithium atom. Therefore, calculations were performed on the disolvated and tetrasolvated homo- and mixed dimers (Eqs. 20–22), and the results are shown in Table 5.

$$(LiCH_2X)_2\cdot 2THF\ (\mathbf{1}) + 2THF \rightarrow (LiCH_2X)_2\cdot 4THF \quad (20)$$

$$(LiX)_2\cdot 2THF\ (\mathbf{2}) \rightarrow (LiX)_2\cdot 4THF \quad (21)$$

$$(LiCH_2X)(LiX)\cdot 2THF\ (\mathbf{3}\text{ or }\mathbf{11}) + 2THF \rightarrow (LiCH_2X)(LiX)\cdot 4THF \quad (22)$$

The solvation state of the homo- and mixed dimers shows significant temperature dependence, with higher temperatures favoring the disolvated form. Because of the extreme instability of haloalkyllithium carbenoids, reactions are normally performed in a dry ice bath (about 195–200 K) or at even lower temperatures. At 200 K a 1 M solution of the carbenoid would contain the disolvated and tetrasolvated $LiCH_2Cl$ dimers in nearly equal concentrations, and the bromo analog is predominantly the tetrasolvate. The LiX (**2**) and mixed dimer (**3**) are all tetrasolvated at that temperature, and at lower temperatures sometimes required, the $LiCH_2Cl$ dimer will also exist mostly as the tetrasolvate. Therefore, tetrasolvated (**1**), (**2**), and (**3**) were used in the subsequent calculations. The situation is different for the $LiCH_2X$–LiOMe mixed dimers, which the data in Table 5 show to be mostly disolvated by THF, and the disolvated form was used in subsequent calculations.

The formation of THF solvated lithium halide mixed aggregates are described by Eqs. 23–28, and the corresponding lithium methoxide mixed aggregates by Eqs. 29–34. The

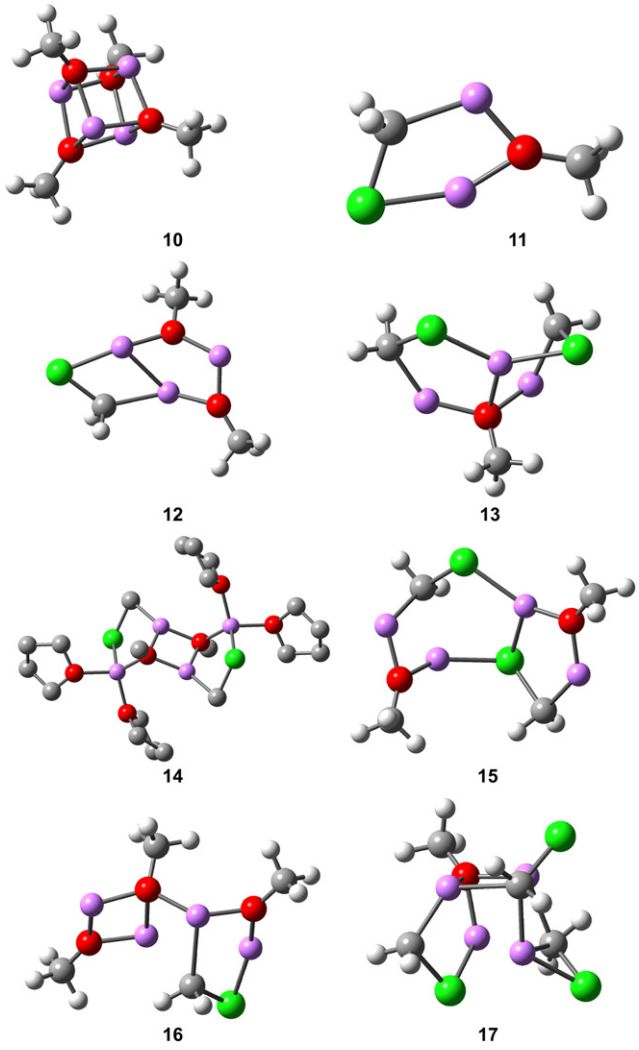

Figure 2. Optimized geometries of lithium carbenoid mixed aggregates with lithium methoxide **10**–**17**.

optimized geometries of the solvated chloromethyllithium–lithium chloride aggregates are shown in Figure 3, and those of the chloromethyllithium–lithium methoxide mixed aggregates in Figure 4.

$$1/2(LiCH_2X)_2\cdot 4THF\ (\mathbf{1}) + 1/2(LiX)_2\cdot 4THF\ (\mathbf{2}) \rightarrow (LiCH_2X)(LiX)\cdot 4THF\ (\mathbf{3}) \quad (23)$$

$$1/2(LiCH_2X)_2\cdot 4THF + (LiX)_2\cdot 4THF \rightarrow (LiCH_2X)(LiX)_2\cdot 3THF\ (\mathbf{4}) + 3THF \quad (24)$$

Table 3. Gas phase free energies of $LiCH_2X$ mixed dimer and mixed trimer formation (kcal/mol per Li) at 200 K (298.15 K)

Mixed aggregates	Temp (K)	Dimer (**3** or **11**)	Trimer (**4** or **12**)	Trimer (**5** or **13**)
$LiCH_2Cl$ LiCl	200	0.164	−3.31	−3.23
$LiCH_2Cl$ LiCl	298.15	0.0650	−2.90	−2.76
$LiCH_2Cl$ LiOMe	200	3.76	2.22	0.556
$LiCH_2Cl$ LiOMe	298.15	3.16	2.12	0.833
$LiCH_2Br$ LiBr	200	0.160	−2.82	−2.60
$LiCH_2Br$ LiBr	298.15	0.0631	−2.43	−2.05
$LiCH_2Br$ LiOMe	200	3.79	2.40	1.43
$LiCH_2Br$ LiOMe	298.15	3.24	2.33	1.78

Table 4. Gas phase free energies of $LiCH_2X$ mixed tetramer formation (kcal/mol per Li) at 200 K (298.15 K)

Mixed aggregates	Temp (K)	Ladder (**6** or **14**)	Tetrahedral or bent (**7** or **15**)	Tetramer (**8** or **16**)	Tetramer (**9** or **17**)
$LiCH_2Cl$ LiCl	200	−5.20	−4.58	−6.57	−2.36
$LiCH_2Cl$ LiCl	298.15	−4.52	−3.52	−5.54	−1.22
$LiCH_2Cl$ LiOMe	200	−1.18	2.95	3.32	−1.93
$LiCH_2Cl$ LiOMe	298.15	−0.747	3.47	3.52	−0.977
$LiCH_2Br$ LiBr	200	−3.69	−2.81	−5.03	−1.13
$LiCH_2Br$ LiBr	298.15	−2.95	−1.72	−4.01	0.00533
$LiCH_2Br$ LiOMe	200	−0.860	3.92	3.60	−1.43
$LiCH_2Br$ LiOMe	298.15	−0.390	4.45	3.82	−0.455

$$(LiCH_2X)_2\cdot 4THF + 1/2(LiX)_2\cdot 4THF \rightarrow (LiCH_2X)_2(LiX)\cdot 3THF\ (\mathbf{5}) + 3THF \quad (25)$$

$$(LiCH_2X)_2\cdot 4THF + (LiX)_2\cdot 4THF \rightarrow (LiCH_2X)_2(LiX)_2\cdot 4THF + 4THF\ (\mathbf{6}\text{ and }\mathbf{7}) \quad (26)$$

$$1/2(LiCH_2X)_2\cdot 4THF + 3/2(LiX)_2\cdot 4THF \rightarrow (LiCH_2X)(LiX)_3\cdot 4THF\ (\mathbf{8}) + 4THF \quad (27)$$

$$3/2(LiCH_2X)_2\cdot 4THF + 1/2(LiX)_2\cdot 4THF \rightarrow (LiCH_2X)_3(LiX)\cdot 4THF\ (\mathbf{9}) + 4THF \quad (28)$$

$$1/2(LiCH_2X)_2\cdot 4THF + 1/4(LiOCH_3)_4\cdot 4THF \rightarrow (LiCH_2X)(LiOCH_3)\cdot 2THF + THF \quad (29)$$

$$1/2(LiCH_2X)_2\cdot 4THF + 1/2(LiOCH_3)_4\cdot 4THF \rightarrow (LiCH_2X)(LiOCH_3)_2\cdot 3THF + THF \quad (30)$$

$$(LiCH_2X)_2\cdot 4THF + 1/4(LiOCH_3)_4\cdot 4THF \rightarrow (LiCH_2X)_2(LiOCH_3)\cdot 3THF + 2THF \quad (31)$$

$$(LiCH_2X)_2\cdot 4THF + 1/2(LiX)_4\cdot 4THF \rightarrow (LiCH_2X)_2(LiX)_2\cdot 4THF + 2THF\ (\mathbf{14}\text{ and }\mathbf{15}) \quad (32)$$

$$1/2(LiCH_2X)_2\cdot 4THF + 3/4(LiOCH_3)_4\cdot 4THF \rightarrow (LiCH_2X)(LiOCH_3)_3\cdot 4THF + THF \quad (33)$$

$$3/2(LiCH_2X)_2\cdot 4THF + 1/4(LiOCH_3)_4\cdot 4THF \rightarrow (LiCH_2X)_3(LiOCH_3)\cdot 4THF + 3THF \quad (34)$$

Table 5. Calculated free energies of tetrasolvated dimer formation (Eqs. 20–22, kcal/mol per Li) at 200 K (298.15 K)

Mixed aggregates	Temp (K)	$(LiCH_2X)_2$ (**1**)	$(LiX)_2$ (**2**)	Mixed dimer (**3**)
$LiCH_2Cl$ LiCl	200	0.0984	−9.31	−6.89
$LiCH_2Cl$ LiCl	298.15	5.93	−3.02	−0.825
$LiCH_2Cl$ LiOMe	200	0.0984	N/A	0.690
$LiCH_2Cl$ LiOMe	298.15	5.93	N/A	7.56
$LiCH_2Br$ LiBr	200	−1.55	−15.7	−9.96
$LiCH_2Br$ LiBr	298.15	3.24	−10.1	−3.93
$LiCH_2Br$ LiOMe	200	−1.55	N/A	1.10
$LiCH_2Br$ LiOMe	298.15	3.24	N/A	8.15

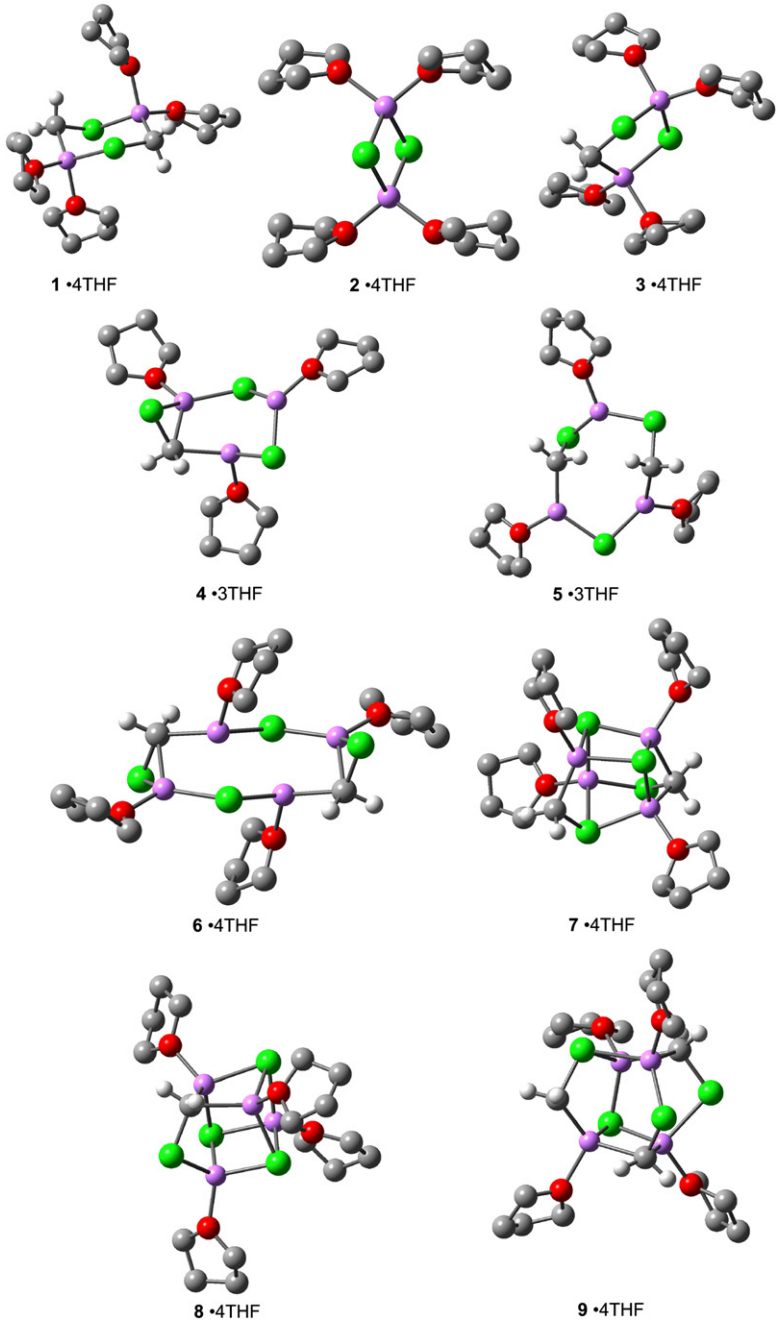

Figure 3. Optimized geometries of THF solvated chloromethyllithium, LiCl, and mixed aggregates **1**–**9**.

Comparison of the data in Tables 3 and 6 shows quite different behavior for the lithium halide and lithium methoxide mixed aggregates. With the lithium halide mixed aggregates, THF solvation has only a small effect on the free energy of mixed dimer formation. At 200 K, the equilibrium constant for LiCl mixed dimer formation will be close to unity, and increase slightly with increasing temperature. The significance of this result is that the mixed dimer cannot be ignored when elucidating reaction mechanisms of chloroalkyllithium carbenoids under conditions where significant amounts of LiCl are present, e.g., late in the reaction. Intentional addition of LiCl to the reaction mixture will also favor formation of the mixed dimer. Formation of the mixed trimers (**4**)·3THF and (**5**)·3THF is energetically unfavorable with respect to the mixed dimer, and showed a similar temperature dependence. Compared to lithium halides, lithium methoxide mixed aggregate formation has a larger temperature dependence, with mixed dimer **11** being favored at room temperature, together with a small amount of mixed trimer **12**. At lower temperatures there is little tendency for lithium methoxide to form mixed dimers or trimers.

Table 7 shows the calculated free energy of formation of the symmetric (**6**, **14** and **7**, **15**) and unsymmetric (**8**, **16** and **9**, **17**) mixed tetramers. In general, mixed tetramer formation with lithium halides is energetically unfavorable at 200 K, but in the case of the lithium chlorocarbenoids, some mixed tetramers may be formed at higher temperatures. The most

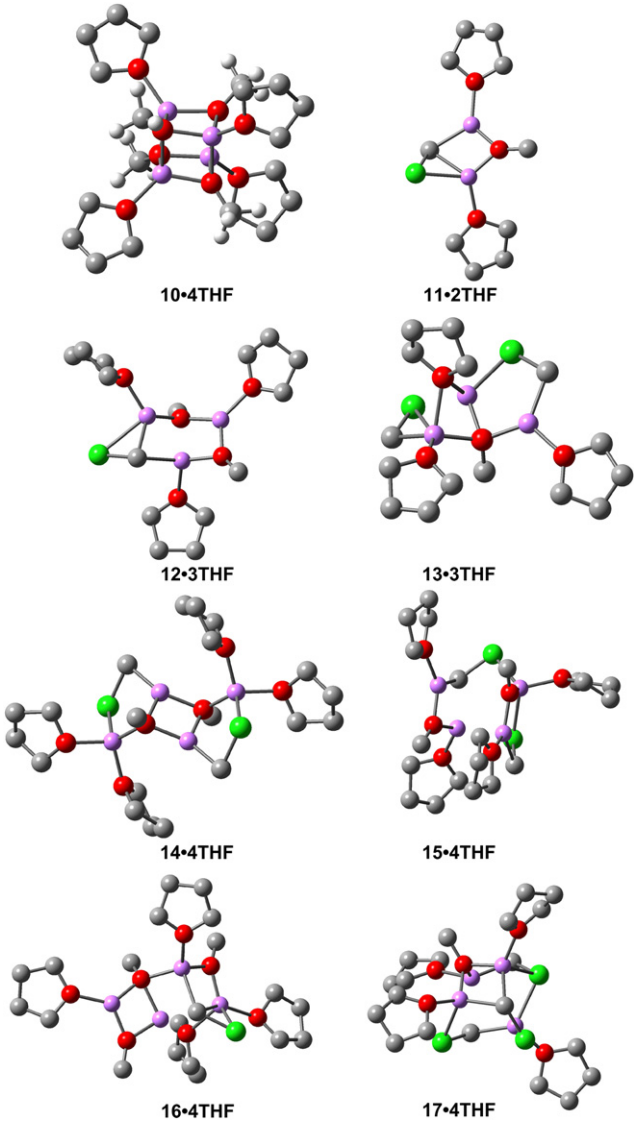

Figure 4. Optimized geometries of THF solvated lithium carbenoid mixed aggregates with lithium methoxide **10**–**17**.

favorable lithium halide mixed tetramer is the $(LiCH_2Cl)$-$(LiCl)_3$ (**8**), which may be present in significant amounts if the reaction mixture contains an excess of lithium chloride. The most favorable solvated $LiCH_2Cl$–lithium methoxide mixed tetramer was **14**, which is favored over the mixed dimers and trimers even at 200 K, and is the only lithium methoxide mixed aggregate that will be formed in appreciable amounts at that temperature.

Table 6. Calculated free energies of THF solvated $LiCH_2X$ mixed dimer and mixed trimer formation (kcal/mol per Li) at 200 K (298.15 K)

Mixed aggregates	Temp (K)	(**3** or **11**)·*n*THF	(**4** or **12**)·3THF	(**5** or **13**)·3THF
$LiCH_2Cl$ LiCl	200	0.0427	3.15	5.66
$LiCH_2Cl$ LiCl	298.15	0.0157	0.790	3.51
$LiCH_2Cl$ LiOMe	200	1.05	1.06	2.07
$LiCH_2Cl$ LiOMe	298.15	−1.17	−0.113	0.590
$LiCH_2Br$ LiBr	200	0.453	5.71	5.61
$LiCH_2Br$ LiBr	298.15	0.778	3.56	3.58
$LiCH_2Br$ LiOMe	200	1.20	0.837	3.25
$LiCH_2Br$ LiOMe	298.15	−0.900	−0.305	2.01

Table 7. Calculated free energies of THF solvated $LiCH_2X$ mixed tetramer formation (kcal/mol per Li) at 200 K (298.15 K)

Mixed Aggregates	Temp (K)	(**6** or **14**)·4THF	(**7** or **15**)·4THF	(**8** or **16**)·4THF	(**9** or **17**)·4THF
$LiCH_2Cl$ LiCl	200	2.68	1.57	0.787	2.29
$LiCH_2Cl$ LiCl	298.15	1.06	−0.351	−1.209	0.464
$LiCH_2Cl$ LiOMe	200	−0.340	2.80	2.87	1.00
$LiCH_2Cl$ LiOMe	298.15	−1.73	1.76	2.36	−0.377
$LiCH_2Br$ LiBr	200	5.27	5.25	4.48	5.27
$LiCH_2Br$ LiBr	298.15	3.69	3.59	2.48	3.56
$LiCH_2Br$ LiOMe	200	1.11	4.18	3.02	2.47
$LiCH_2Br$ LiOMe	298.15	0.0229	3.25	2.57	1.25

Halomethyllithium carbenoids could potentially undergo cyclopropanation reactions via a monomer, homo-dimer, or mixed dimer. To test the hypothesis concerning changes in lithium carbenoid reaction pathways caused by mixed aggregates, the gas phase activation barrier for the cyclopropanation reaction of chloromethyllithium with ethylene was calculated. Although DFT methods generally generate good geometries and energies for ground state species, they are less reliable for transition structure and activation barrier calculations.[23] The activation free energies were calculated at the Hartree–Fock, B3LYP, and MP2 levels, each with the 6-31+G(d) basis set, and the results are shown in Table 8. At the MP2 level, the calculated activation barrier for the mixed dimer (**3**) was lower than that of the chloromethyllithium homo-dimer by 1.0 kcal/mol and lower than that of the monomer by 0.5 kcal/mol. A comprehensive study on the role of mixed aggregates in carbenoid reactions is beyond the scope of this paper and will be the subject of a study in the near future. However, these preliminary calculations show that mixed aggregate formation in these reactions cannot be ignored under conditions where lithium halides are present in significant amounts, such as near the end of the reaction. Even with such a relatively small change in activation energies, the mechanism is subjected to change as new potentially reactive species are formed. After a few half lives the reaction mechanism may change at least once and perhaps twice if significant amounts of tetramer are present after several half lives.

Table 8. Calculated gas phase activation free energies of cyclopropanation reactions of $LiCH_2Cl$ aggregates with ethylene (kcal/mol)

Aggregate	Hartree–Fock	B3LYP	MP2
Monomer	14.2	14.2	17.1
Dimer (**1**)	11.1	15.4	17.6
Mixed dimer (**3**)	9.45	14.2	16.6

4. Conclusions

Lithium halomethyllithium carbenoids can form mixed aggregates with lithium halides. In the gas phase, mixed trimers and tetramers are formed preferentially over mixed dimers. THF solvation disfavors the formation of the mixed trimers and tetramers, but has only a small effect on the free energy of mixed dimer formation. At temperatures below 200 K, chloromethyllithium, and to a lesser extent, bromomethyllithium mixed dimers will coexist with the free carbenoids. Mixed aggregate formation can affect the activation

barriers of carbenoid reactions and may cause a change in the mechanism during the course of a reaction.

In the gas phase, chloro- and bromomethyllithium can form two different mixed tetramers with lithium methoxide. Formation of mixed dimers and trimers is energetically unfavorable. Solvation with THF reduces the tendency of these carbenoids to form mixed aggregates, although there appears to be a modest tendency toward mixed tetramer formation.

The major significance of this work is that the mixed aggregate formation can affect the activation barriers of carbenoid reactions and may cause a change in the mechanism during the course of the reaction. Similar mixed aggregates have been exploited to alter the reactivity and stereoselectivity of other organolithium reagents. The mixed aggregates described in this paper have potential for use in synthetic reactions of lithium carbenoids.

Acknowledgements

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Supplementary data

Tables of optimized geometries and energies of all reactants, and a derivation of the standard state equations. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.104.

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Palladium-catalyzed synthesis of 3-alkoxysubstituted indoles

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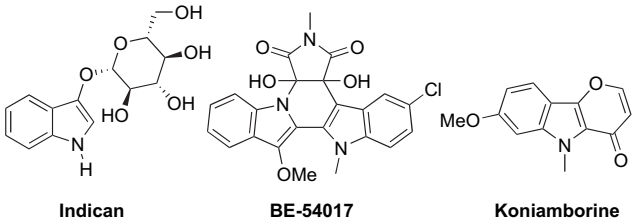
Abstract—Indoles having an electron-donating alkoxy-group in the 3-position were prepared from 1-(2-nitrophenyl)-1-alkoxyalkene derivatives via a palladium-catalyzed reductive N-heteroannulation using carbon monoxide as the ultimate reducing agent. The required starting materials were prepared by a Stille coupling of 2-halonitroarenes with tributyl(1-ethoxyethenyl)stannane or tributyl(3,4-dihydro-2*H*-pyran-6-yl)stannane.

1. Introduction

Indoles oxygenated in the 3-position are relatively rare in nature but a few have been isolated, for example, indican the precursor to indigo,[1] the anti-tumor compound BE-54017,[2] and koniamborine (Fig. 1).[3] In addition, a variety of synthetic 3-alkoxyindoles have been prepared as potential 5-HT1A receptor antagonism with SSRI activities,[4] reversible inhibitors of aminopeptidase N/CD13,[5] tubulin polymerization inhibitors,[6] and selective serotonin 5-HT2 receptor ligands.[7]

3-Alkoxyindole-2-carboxylic acid derivatives are readily prepared by direct O-alkylation of the corresponding anion using alkyl halides, diazomethane[8] or dialkylsulfates.[9] In contrast, 2-unsubstituted or 2-alkylated 3-alkoxyindoles cannot be selectively prepared in this manner due to competing C-2-alkylation. Thus, 3-alkoxyindole derivatives of this type are usually prepared by decarboxylation of 3-alkoxyindole carboxylic acids at elevated temperatures.[10,11] More recently developed methodologies include palladium-catalyzed cyclization of *N*-alkyl-2-siloxyallylanilines,[12] rhodium-catalyzed oxygen–hydrogen bond insertion using 3-diazoindole,[13] and benzoylperoxide oxidation of *N*-alkylindoles.[14]



Indican BE-54017 Koniamborine

Figure 1.

Palladium-catalyzed reductive N-heteroannulation of 1-(2-nitroaryl)-1-alkenes is emerging as a versatile methodology for the preparation of a variety of functionalized indoles.[15–19] Synthetic application of this reaction include tjipanazoles,[20] 1*H*-indole-2-yl-1*H*-quinolin-2-ones,[21] murrayaquinone,[22] bauerine A,[23] and mushroom metabolites.[24] The 1-(2-nitrophenyl)-1-alkenes used to date has been limited to substrates with alkyl-, aryl-, or electron-withdrawing groups on the alkene moiety. In an attempt to extend the palladium-catalyzed heteroannulation reaction to substrates having an electron-rich alkene and to develop a short methodology for the synthesis of 3-alkoxysubstituted indoles, 1-(2-nitrophenyl)-1-alkoxyethene (**3**) was prepared via a Stille coupling of 2-iodo-1-nitrobenzene (**1**) and tributyl(1-ethoxyethenyl)stannane (**2**). Submitting **3** to the annulation conditions previously used to prepare tetrahydrocarbazolones, bis(dibenzylideneacetone)palladium (6 mol %), 1,3-bis(diphenylphosphino)propane (6 mol %), and 1,10-phenanthroline (6 mol %) in the presence of carbon monoxide, gave the expected 3-ethoxyindole (**4**) in good yield. With this initial result in hand, a number of additional examples were examined and herein is presented the formation of 3-alkoxysubstituted indoles via palladium-catalyzed reductive N-heteroannulation of 1-(2-nitrophenyl)-1-alkoxyalkenes (Scheme 1).

2. Results and discussion

Seven additional nitroaryl-substituted alkenes (**12–18**) were prepared using a Stille coupling of 2-nitroarylbromides or iodides (**5–11**) employing either stannane **2** or tributyl(3,4-dihydro-2*H*-pyran-6-yl)stannane. The results of the cross-coupling reactions are summarized in Table 1. A 52–82%

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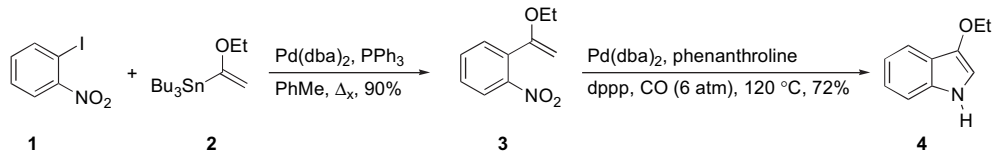


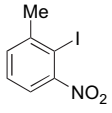
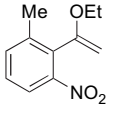
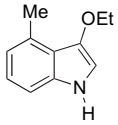
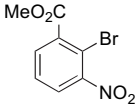
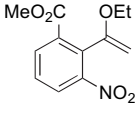
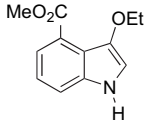
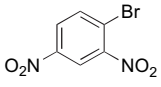
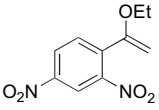
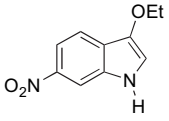
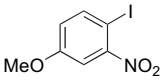
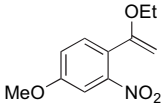
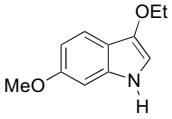
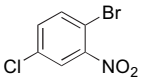
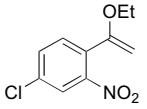
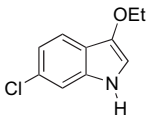
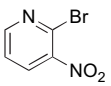
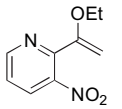
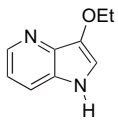
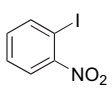
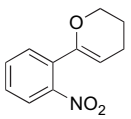
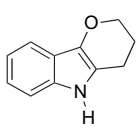
1 2 3 4

Scheme 1.

yield was obtained after chromatography in the cases examined. The compounds were selected to have either electron-donating or electron-withdrawing substituents on the benzene ring, to be sterically congested around the alkene (entries 1 and 2), one heterocyclic substrate (entry 6), and one substrate having a substituent adjacent to the alkoxy-group on the alkene (entry 7).

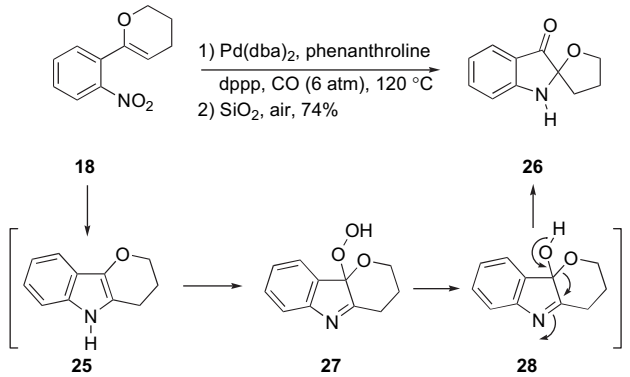
Subjecting the nitro alkenyl ethers to the reaction conditions described above for compound **3**, produced the anticipated 3-alkoxysubstituted indole in 63–87% isolated yield after column chromatography on silica gel. As was earlier observed, the substituents on the aromatic ring had little or no effect on the annulation reaction.[17] It should be noted that all compounds prepared (**12**–**25**) were relatively unstable and slowly decomposed upon standing. The alkoxyalkenes decomposed to the corresponding ketones and the indoles to deep blue or purple colored products of unknown identity. The pyranoindole **25** was particularly problematic and the compound could not be isolated without significant or complete oxidation. The oxidation product was identified as the spiroindolone **26** (Scheme 2) and its structure was determined by ^{1}H, ^{13}C, HETCOR, long-range HETCOR, and DPFGSENoE NMR experiments. Compound **26** is probably formed via the peroxide **27** and the alcohol **28**. Related oxidative-rearrangements in air have been reported in a number of cases.[25–30]

Table 1. Stille coupling and reductive N-heteroannulation

Entry	Nitroarene	Stille product[a,b]	3-Alkoxyindole[a,b]
1	 **5**	 **12** (81%)	 **19** (84%)
2	 **6**	 **13** (66%)	 **20** (87%)
3	 **7**	 **14** (52%)	 **21** (85%)
4	 **8**	 **15** (68%)	 **22** (79%)
5	 **9**	 **16** (56%)	 **23** (63%)
6	 **10**	 **17** (67%)	 **24** (85%)
7	 **11**	 **18** (81%)	 **25** (decomposed)

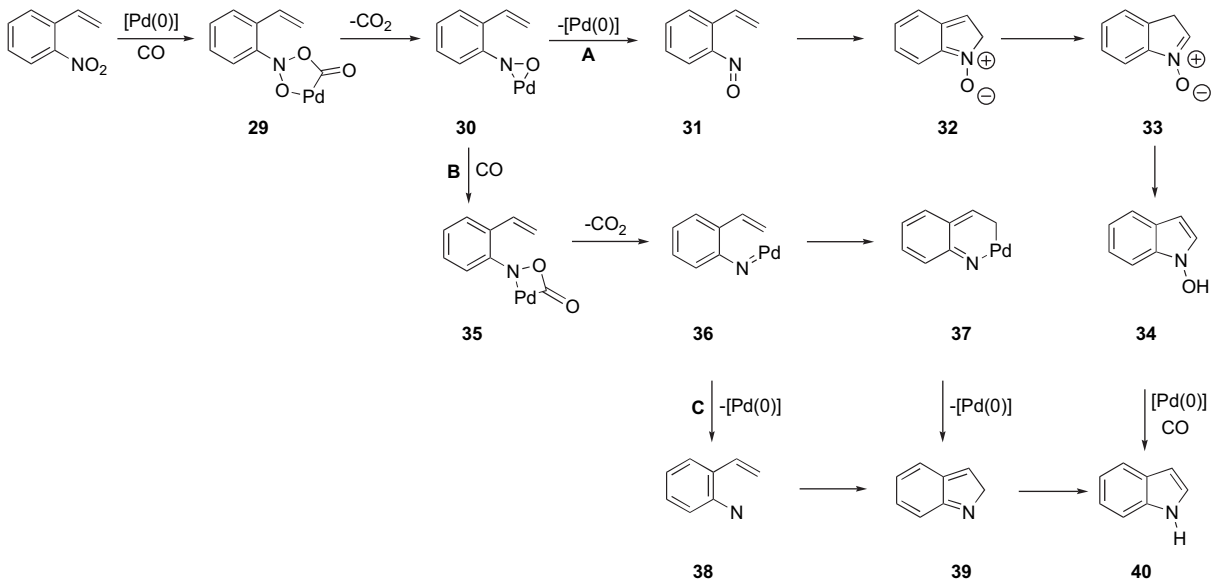
[a] For experimental details and analytical data, see Section 2.
[b] Isolated yields in parentheses.

The mechanism of the palladium-catalyzed reductive N-heteroannulation of 1-(2-nitroaryl)-1-alkenes to give indoles has previously been examined in some detail and a few different reaction paths have been proposed (**A**–**C**, Scheme 3). It is generally accepted that the initial transformation involves a reduction (deoxygenation) of the nitro to a nitroso group via the metallacycle **29**. The nitroso group may either be metal bound (**30**) or free (**31**). In path **A**, the nitrosoarene **31** undergoes an intramolecular electrocyclic reaction to give nitronate **32** followed by a 1,5-hydrogen shift and tautomerization (**32**→**33**→**34**) to give an *N*-hydroxyindole (**34**). Reduction of **34** using palladium and a second molecule of carbon monoxide would give the product (**40**).[31] Path **A** has been demonstrated to be viable using computational methods.[32] *N*-Hydroxyindoles have been isolated in a few cases from 1-(2-nitroaryl)-1-alkenes via palladium-catalyzed annulations using carbon monoxide[33,31] or tin dichloride[34] as the reducing agent. In addition, in situ formation of nitrosoarenes by oxidation of 1-(2-hydroxylaminoaryl)-1-alkenes also furnished *N*-hydroxyindoles.[35–37] However, *N*-hydroxyindoles are not isolated



18 26 25 27 28

Scheme 2.



Scheme 3.

in an overwhelming majority of palladium-catalyzed reductive N-heteroannulations. This may be due to a very rapid reduction of the intermediately formed *N*-hydroxyindole or a different mechanism. Path **B** involves a second deoxygenation prior to cyclization, most likely via the metallacyclobutane **35**. Loss of carbon dioxide from **35** would furnish a palladium-bound nitrene **36** that via a 6π-electron electrocyclic reaction affords a six-membered heterocycle **37**. A related rhodium-bound nitrene has been isolated and characterized by X-ray diffraction.[38] Reductive elimination regenerating the palladium(0) catalyst followed by a 1,5-hydrogen-shift (**37**→**39**→**40**) affords the observed product. An alternative path **C** can also be envisioned involving a free nitrene (**38**) followed by an electrocyclization to give **39** and 1,5-hydrogen shift to give **40**.

In summary, we have developed a rapid and expedient synthesis of 3-alkoxysubstituted indoles based on two palladium-catalyzed reactions. The indoles were prepared in good yield from readily available starting materials in a few synthetic steps.

3. Experimental

3.1. General procedures

NMR spectra were determined in $CDCl_3$ at 270 MHz (^{1}H NMR) and 67.5 MHz (^{13}C NMR) and for compound **26** at 600 and 150 MHz. The chemical shifts are expressed in δ values relative to Me_4Si (0.0 ppm, ^{1}H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) used as internal standards. ^{1}H–^{1}H coupling constants are reported as calculated from spectra; thus a slight difference between $J_{a,b}$ and $J_{b,a}$ is usually obtained. Results of APT (attached proton test)—^{13}C NMR experiments are shown in parentheses where, relative to $CDCl_3$, (−) denotes CH_3 or CH and (+) denotes CH_2 or C.

Tetrahydrofuran (THF), 1,4-dioxane, and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Benzene and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Hexanes, dichloromethane, and ethyl acetate were distilled from calcium hydride. Toluene was dried by filtration through activated alumina prior to use. Chemicals prepared according to literature procedures have been footnoted; all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in an oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure. Chromatography was performed on silica gel 60 (35–75 μm, VWR). Melting points were determined on a MelTemp and are uncorrected. Elemental analyses were performed in the Department of Chemical Engineering, College of Engineering and Mineral Resources, West Virginia University.

3.1.1. 1-Ethoxy-1-(2-nitrophenyl)ethene (3). A solution of 2-iodonitrobenzene (**1**) (236 mg, 0.948 mmol), bis(dibenzylideneacetone)palladium Pd(dba$_2$) (27.4 mg, 0.0476 mmol), and triphenylphosphine (PPh_3) (50 mg, 0.19 mmol) in toluene (55 mL) was stirred (5 min) under a positive flow of nitrogen. To the yellow solution was added tributyl(1-ethoxy-1-ethenyl)stannane (**2**)[39] (391 mg, 1.08 mmol) dissolved in toluene (10 mL). The yellow solution was heated at reflux (36 h) whereupon a dark brown solution was formed. The progress of the reaction was monitored to completion using TLC (hexanes). The reaction mixture was cooled to ambient temperature, washed with NH_4OH (10% aqueous, 50 mL), and dried over anhydrous $MgSO_4$. Filtration and removal of solvent gave a black viscous oil that was purified by chromatography (hexanes/EtOAc, 7:3) to give **3** (166 mg, 0.859 mmol, 90%) as a pale yellow oil. ^{1}H NMR δ 7.75 (d, J=7.9 Hz, 1H), 7.65–7.38 (m, 3H), 4.48 (d, J=2.8 Hz, 1H), 4.37 (d, J=2.8 Hz, 1H), 3.86 (q, J=6.9 Hz, 3H), 1.29 (t, J=7.1 Hz, 2H); ^{13}C NMR δ 158.4 (+), 149.4 (+), 132.3 (+), 132.1 (−), 130.4 (−), 129.2 (−), 123.8 (−), 86.5 (+), 64.4 (+), 13.9 (−); IR (neat) 2983, 1533 cm^{-1}; MS (EI) *m*/*z* 193 (M$^+$), 135, 79 (100%); Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.84; H, 6.04; N, 7.08.

3.1.2. 1-Ethoxy-1-(6-methyl-2-nitrophenyl)ethene (12). Reaction of 2-iodo-3-nitrotoluene (**5**)[40] (270 mg, 1.03 mmol) with **2** (447 mg, 1.24 mmol) in the presence of $Pd(dba)_2$ (30 mg, 0.051 mmol) and PPh_3 (54 mg, 0.21 mmol) in toluene (65 mL), as described for **3** (76 h), gave, after extraction and chromatography (hexanes/EtOAc, 95:5), **12** (172 mg, 0.830 mmol, 81%) as a pale yellow oil. ^{1}H NMR δ 7.63 (d, J=7.9 Hz, 1H), 7.43 (d, J=7.5 Hz, 1H), 7.33 (t, J=7.9 Hz, 1H), 4.41 (d, J=2.8 Hz, 1H), 4.13 (d, J=2.8 Hz, 1H), 3.93 (q, J=6.9 Hz, 2H), 2.44 (s, 3H), 1.37 (t, J=7.1 Hz, 3H); ^{13}C NMR δ 155.6 (+), 150.0 (+), 139.4 (−), 134.1 (−), 131.5 (+), 128.5 (−), 121.0 (−), 87.0 (+), 63.8 (+), 19.6 (−), 14.3 (−); IR (neat) 2983, 1531 cm^{-1}; MS (EI) m/z 207 (M^+), 149, 120 (100%); Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 64.09; H, 6.42; N, 6.87.

3.1.3. 1-Ethoxy-1-(6-methoxycarbonyl-2-nitrophenyl)-ethene (13). Reaction of methyl 2-bromo-3-nitrobenzoate (**6**)[22] (120 mg, 0.46 mmol) and **2** (220 mg, 0.55 mmol) in the presence of $Pd(dba)_2$ (13 mg, 0.023 mmol) and PPh_3 (24 mg, 0.092 mmol) in toluene (70 mL), as described for **3** (52 h), gave, after extraction and chromatography (hexanes/EtOAc, 9:1), **13** (76 mg, 0.30 mmol, 66%) as a dark yellow oil. ^{1}H NMR δ 7.90–7.83 (m, 2H), 7.52 (t, J=7.9 Hz, 1H), 4.36 (d, J=3.0 Hz, 1H), 4.27 (d, J=3.0 Hz, 1H), 3.97 (s, 3H), 3.88 (q, J=7.1 Hz, 2H), 1.33 (t, J=7.1 Hz, 3H); ^{13}C NMR δ 168.4 (+), 154.9 (+), 151.8 (+), 151.2 (+), 150.0 (+), 133.0 (+), 132.6 (−), 125.9 (−), 87.4 (+), 64.5 (+), 52.7 (−), 14.2 (−); IR (neat) 2942, 1774, 1542 cm^{-1}; MS (EI) m/z 251 (M^+), 193, 161 (100%); Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.33; H, 5.63; N, 5.49.

3.1.4. 1-Ethoxy-1-(2,4-dinitrophenyl)ethene (14). Reaction of 1-bromo-2,4-dinitrobenzene (**7**) (140 mg, 0.57 mmol) with **2** (246 mg, 0.681 mmol) in the presence of $Pd(dba)_2$ (16 mg, 0.028 mmol) and PPh_3 (30 mg, 0.11 mmol) in toluene (75 mL), as described for **3** (64 h), gave, after extraction and chromatography (hexanes/EtOAc, 95:5), **14** (70 mg, 0.29 mmol, 52%) as a yellow oil. ^{1}H NMR δ 8.59 (d, J=2.2 Hz, 1H), 8.40 (dd, J=8.5, 2.2 Hz, 1H), 7.77 (d, J=8.5 Hz, 1H), 4.62 (d, J=3.2 Hz, 1H), 4.53 (d, J=3.1 Hz, 1H), 3.88 (q, J=7.1 Hz, 2H), 1.30 (t, J=7.1 Hz, 3H); ^{13}C NMR δ 156.5 (+), 148.8 (+), 147.5 (−), 137.8 (−), 131.5 (−), 126.5 (−), 119.5 (+), 89.1 (+), 64.9 (+), 13.8 (−); IR (neat) 2984, 1545 cm^{-1}; MS (EI) m/z 238 (M^+), 180 (100%), 134; Anal. Calcd for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.42; H, 4.63; N, 11.19.

3.1.5. 1-Ethoxy-1-(4-methoxy-2-nitrophenyl)ethene (15). Reaction of 4-iodo-3-nitro-1-methoxybenzene (**8**) (279 mg, 1.00 mmol) with **2** (412 mg, 1.14 mmol) in the presence of $Pd(dba)_2$ (28.9 mg, 0.0503 mmol) and PPh_3 (53 mg, 0.20 mmol) in toluene (75 mL), as described for **3** (56 h), gave, after extraction and chromatography (hexanes/EtOAc, 8:2), **15** (151 mg, 0.676 mmol, 68%) as a dark yellow oil. ^{1}H NMR δ 7.44 (d, J=8.5 Hz, 1H), 7.26 (d, J=2.6 Hz, 1H), 7.04 (dd, J=8.5, 2.6 Hz, 1H), 4.40 (d, J=2.8 Hz, 1H), 4.30 (d, J=2.8 Hz, 1H), 3.91–3.80 (m, 5H), 1.28 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 159.9 (+), 158.3 (+), 149.5 (+), 131.5 (−), 124.7 (+), 118.0 (−), 109.1 (−), 85.7 (+), 64.3 (+), 55.9 (−), 14.0 (−); IR (neat) 2359, 1537 cm^{-1}; MS (EI) m/z 223 (M^+), 165, 109 (100%); Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.17; H, 6.22; N, 6.43.

3.1.6. 1-Ethoxy-1-(4-chloro-2-nitrophenyl)ethene (16). Reaction of 1-bromo-4-chloro-2-nitrobenzene (**9**) (118 mg, 0.499 mmol) with **2** (206 mg, 0.570 mmol) in the presence of $Pd(dba)_2$ (15 mg, 0.025 mmol) and PPh_3 (26 mg, 0.10 mmol) in toluene (70 mL), as described for **3** (72 h), gave, after extraction and chromatography (hexanes/EtOAc, 95:5), **16** (65 mg, 0.27 mmol, 56%) as a pale yellow oil. ^{1}H NMR δ 7.73 (d, J=1.6 Hz, 1H), 7.51–7.43 (m, 2H), 4.45 (d, J=3.0 Hz, 1H), 4.36 (d, J=3.0 Hz, 1H), 3.82 (q, J=6.9 Hz, 2H), 1.26 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 159.9 (+), 158.3 (+), 149.5 (−), 131.5 (+), 124.7 (+), 118.0 (−), 109.1 (−), 85.7 (+), 64.3 (+), 14.0 (−); IR (neat) 2349, 1531 cm^{-1}; MS (EI) m/z 229 (M^++2), 227 (M^+), 171, 169 (100%), 113; Anal. Calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.87; H, 4.51; N, 6.23.

3.1.7. 1-Ethoxy-1-(3-nitro-2-pyridyl)ethene (17). Reaction of 2-bromo-3-nitropyridine (**10**) (176 mg, 0.867 mmol) with **2** (376 mg, 1.04 mmol) in the presence of $Pd(dba)_2$ (25 mg, 0.044 mmol) and PPh_3 (45 mg, 0.17 mmol) in toluene (55 mL), as described for **3** (42 h), gave, after extraction and chromatography (hexanes/EtOAc, 95:5), **17** (113 mg, 0.582 mmol, 67%) as a pale yellow oil. ^{1}H NMR δ 8.73 (dd, J=4.7, 1.8 Hz, 1H), 7.98 (dd, J=8.1, 1.4 Hz, 1H), 7.42 (dd, J=8.1, 4.8 Hz, 1H), 5.10 (d, J=2.6 Hz, 1H), 4.56 (d, J=2.6 Hz, 1H), 3.91 (q, J=6.9 Hz, 2H), 1.31 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 157.2 (+), 151.2 (−), 148.1 (+), 146.2 (+), 131.6 (−), 123.4 (−), 89.2 (+), 64.6 (+), 13.9 (−); IR (neat) 2984, 1537 cm^{-1}; MS (EI) m/z 194 (M^+), 136, 78 (100%); Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.88; H, 5.50; N, 14.06.

3.1.8. 3,4-Dihydro-6-(2-nitrophenyl)-2*H*-pyran (18).[41,42] Reaction of **1** (180 mg, 0.72 mmol), $Pd(dba)_2$ (21 mg, 0.036 mmol), and PPh_3 (38 mg, 0.14 mmol) with tributyl(3,4-dihydro-2*H*-pyran-6-yl)stannane[43] (324 mg, 0.868 mmol) in toluene (75 mL total), as described above for **3** (48 h), gave, after extraction and chromatography (hexanes), **18** as a yellow oil (120 mg, 0.58 mmol, 81%). Spectral data (^{1}H NMR) in complete accordance with literature values.[41]

3.1.9. 3-Ethoxyindole (4). 1-Ethoxy-1-(2-nitrophenyl)-ethene (**3**) (47 mg, 0.24 mmol), $Pd(dba)_2$ (9 mg, 0.02 mmol), 1,3-bis-(diphenylphosphino)propane (dppp) (6 mg, 0.01 mmol), and 1,10-phenanthroline (phen) (6 mg, 0.03 mmol) were dissolved in anhydrous DMF (2 mL) in a threaded ACE glass pressure tube. The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (four cycles of 6 atm of CO). The reaction mixture was heated at 120 °C (oil bath temperature) under CO (6 atm) until all starting material was consumed (96 h), as judged by TLC. Water (10 mL) was added and the brown solution was extracted with ethyl acetate (3×20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The resulting crude product was purified by chromatography (hexanes/EtOAc, 7:3) to afford **4** (28 mg, 0.17 mmol, 72%) as a purple oil. ^{1}H NMR δ 7.68 (d, J=7.9 Hz, 1H), 7.45 (br s, 1H), 7.25

(dd, J=8.0, 1.0 Hz, 1H), 7.18 (dt, J=8.1, 1.2 Hz, 1H), 7.07 (dt, J=7.4, 1.2 Hz, 1H), 6.67 (d, J=2.6 Hz, 1H), 4.07 (q, J=6.9 Hz, 2H), 1.46 (t, J=7.1 Hz, 3H); ^{13}C NMR δ 140.8 (+), 134.3 (+), 122.7 (−), 120.0 (+), 118.9 (−), 118.0 (−), 111.1 (−), 105.2 (−), 66.7 (+), 15.1 (−); IR (neat) 3478, 909, 731 cm^{-1}; MS (EI) m/z 161 (M$^+$), 132 (100%); Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.79; H, 6.95; N, 8.75.

3.1.10. 3-Ethoxy-4-methylindole (19). Reaction of **12** (37 mg, 0.18 mmol) in the presence of Pd(dba)$_2$ (6 mg, 0.01 mmol), dppp (6 mg, 0.01 mmol), phen (4 mg, 0.02 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (48 h), gave, after chromatography (hexanes/EtOAc, 9:1), **19** (27 mg, 0.15 mmol, 84%) as a dark green oil. ^{1}H NMR δ 7.76–7.01 (m, 3H), 6.83–6.78 (m, 1H), 6.64 (d, J=2.6 Hz, 1H), 3.99 (q, J=6.9 Hz, 2H), 2.70 (s, 3H), 1.45 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 142.6 (+), 134.5 (+), 130.4 (+), 122.7 (−), 120.0 (−), 118.9 (+), 108.5 (−), 104.4 (−), 66.8 (+), 18.9 (−), 15.1 (−); IR (neat) 3470, 908, 734 cm^{-1}; MS (EI) m/z 175 (M$^+$), 147 (100%); Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.41; H, 7.58; N, 8.00.

3.1.11. Methyl 3-ethoxyindole-4-carboxylate (20). Reaction of **13** (21 mg, 0.084 mmol) in the presence of Pd(dba)$_2$ (3 mg, 0.005 mmol), dppp (2 mg, 0.005 mmol), phen (2 mg, 0.01 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (72 h), gave, after chromatography (hexanes/EtOAc, 95:5) **20** (16 mg, 0.078 mmol, 87%) as a yellow oil. ^{1}H NMR δ 7.78 (br s, 1H), 7.53 (dd, J=7.2, 0.7 Hz, 1H), 7.43 (dd, J=8.2, 0.8 Hz, 1H), 7.18 (t, J=7.7 Hz, 1H), 6.85 (d, J=2.5 Hz, 1H), 4.00 (q, J=6.9 Hz, 2H), 3.97 (s, 3H), 1.46 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 169.1 (+), 140.6 (+), 134.9 (+), 124.0 (+), 121.7 (−), 121.5 (−), 115.8 (+), 114.8 (−), 108.0 (−), 67.2 (+), 51.9 (−), 15.1 (−); IR (neat) 3251, 1742, 908, 734 cm^{-1}; MS (EI) m/z 219 (M$^+$), 190, 159 (100%); Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.59; H, 6.12; N, 6.38.

3.1.12. 3-Ethoxy-6-nitroindole (21). Reaction of **14** (48 mg, 0.20 mmol) in the presence of Pd(dba)$_2$ (7 mg, 0.01 mmol), dppp (5 mg, 0.01 mmol), phen (5 mg, 0.03 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (72 h), gave, after chromatography (hexanes/EtOAc, 95:5), **21** (36 mg, 0.17 mmol, 85%) as a dark yellow oil.[44] ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 7.92 (d, J=1.0 Hz, 1H), 7.69 (dd, J=8.7, 1.6 Hz, 1H), 7.66 (d, J=8.5 Hz, 1H), 7.10 (d, J=2.4 Hz, 1H), 6.88 (d, J=2.8 Hz, 1H), 4.11 (q, J=7.1 Hz, 2H), 1.49 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 149.9 (+), 141.6 (+), 135.4 (+), 132.7 (+), 118.6 (−), 112.9 (−), 109.7 (−), 109.5 (−), 66.9 (+), 15.4 (−); IR (neat) 3422, 1545, 1348, 908, 734 cm^{-1}.

3.1.13. 3-Ethoxy-6-methoxyindole (22). Reaction of **15** (28 mg, 0.13 mmol) in the presence of Pd(dba)$_2$ (5 mg, 0.008 mmol), dppp (3 mg, 0.008 mmol), phen (3 mg, 0.02 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (96 h), gave, after chromatography (hexanes/EtOAc, 95:5) **22** (19 mg, 0.10 mmol, 79%) as a yellow solid.[44] Mp 62–63 °C; ^{1}H NMR δ 7.52 (d, J=9.3 Hz, 1H), 7.29 (br s, 1H), 6.76 (d, J=2.2 Hz, 1H), 6.74 (dd, J=6.1, 2.1 Hz, 1H), 6.56 (d, J=2.4 Hz, 1H), 4.05 (q, J=6.9 Hz, 2H), 3.83 (s, 3H), 1.45 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 140.8 (+), 134.5 (+), 122.3 (+), 118.8 (−), 109.1 (−), 94.5 (−), 66.6 (+), 60.6 (+), 55.7 (−), 15.2 (−), 14.3 (−); IR (neat) 3422, 908, 741 cm^{-1}; MS (EI) m/z 191 (M$^+$), 162 (100%).

3.1.14. 6-Chloro-3-ethoxyindole (23). Reaction of **16** (126 mg, 0.553 mmol) in the presence of Pd(dba)$_2$ (19 mg, 0.033 mmol), dppp (14 mg, 0.033 mmol), phen (13 mg, 0.066 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (72 h), gave, after chromatography (hexanes/EtOAc, 7:3) **23** (62 mg, 0.32 mmol, 63%) as a yellow solid.[44] Mp 85.5–86.5 °C; ^{1}H NMR δ 7.57 (d, J=8.5 Hz, 1H), 7.45 (br s, 1H), 7.22 (d, J=1.2 Hz, 1H), 7.05 (dd, J=8.3, 1.8 Hz, 1H), 6.63 (d, J=2.4 Hz, 1H), 4.03 (q, J=6.9 Hz, 2H), 1.42 (t, J=7.1 Hz, 3H); ^{13}C NMR δ 140.9 (+), 134.6 (+), 128.8 (−), 119.7 (−), 119.1 (+), 118.6 (−), 111.1 (+), 105.5 (−), 66.8 (+), 15.1 (−); IR (neat) 3478, 908, 731 cm^{-1}; MS (EI) m/z 197 (M$^+$+2), 195 (M$^+$), 168, 166 (100%).

3.1.15. 3-Ethoxy-1*H*-pyrrolo[3,2-*b*]pyridine (24). Reaction of **17** (31 mg, 0.16 mmol) in the presence of Pd(dba)$_2$ (6 mg, 0.01 mmol), dppp (4 mg, 0.01 mmol), phen (4 mg, 0.02 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (72 h), gave, after chromatography (hexanes/EtOAc, 8:2), **24** (22 mg, 0.14 mmol, 85%) as a yellow solid.[44] Mp 84–85 °C; ^{1}H NMR δ 8.44 (dd, J=4.7, 1.5 Hz, 1H), 7.83 (br s, 1H), 7.58 (dd, J=8.2, 1.2 Hz, 1H), 7.11 (dd, J=8.4, 4.7 Hz, 1H), 6.96 (d, J=2.7 Hz, 1H), 4.19 (q, J=6.9 Hz, 2H), 1.49 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 142.7 (−), 127.5 (+), 118.5 (+), 118.4 (−), 117.6 (+), 114.9 (−), 109.4 (−), 66.9 (+), 15.1 (−); IR (neat) 3418, 909, 734 cm^{-1}; MS (EI) m/z 162 (M$^+$), 147, 79 (100%).

3.1.16. 2,3,4,5-Tetrahydropyrano[3,2-*b*]indole (25)[45] and 4,5-dihydrospiro[furan-2(3*H*),2′-[2*H*]indol]-3′-(1′*H*)-one (26). Reaction of **18** (193 mg, 0.941 mmol), Pd(dba)$_2$ (32 mg, 0.056 mmol), dppp (22 mg, 0.11 mmol), phen (23 mg, 0.056 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (80 h), gave, after chromatography (hexanes/EtOAc/acetone, 95:4:1), a 3.5:1 mixture of **25** and **26** as a yellow oil (152 mg). Spectral data of **25** from the mixture: ^{1}H NMR δ 7.50 (d, J=7.5 Hz, 1H), 7.39 (br s, 1H), 7.20 (d, J=7.1 Hz, 1H), 7.11 (dt, J=7.1, 1.4 Hz), 7.04 (dt, J=6.9, 1.2 Hz, 1H), 4.23 (t, J=4.9 Hz, 2H), 2.77 (t, J=6.3 Hz, 2H), 2.10 (pent, J=5.1 Hz, 2H); ^{13}C NMR δ 133.1 (+), 132.2 (+), 122.4 (+), 121.5 (−), 119.2 (+), 118.9 (−), 116.4 (−), 110.7 (−), 67.2 (+), 22.6 (+), 20.1 (+). (Lit.[31] ^{1}H NMR δ 7.60–6.85 (m, 5H), 4.18 (t, J=5.0 Hz, 2H), 2.78 (t, J=6.2 Hz, 2H), 2.30–1.86 (m, 2H).

Complete oxidative-rearrangement of **25** to **26** was accomplished using the following procedure. Silica gel (approx. 500 mg) was added to a solution of the mixture of **25** and **26** in acetone (10 mL). The solvent was removed and the residual solid was allowed to stand open to the air overnight (14 h). Purification by chromatography (hexanes/EtOAc/acetone, 95:4:1) afforded **26** as a bright yellow oil (131 mg, 0.692 mmol, 74% from **18**). ^{1}H NMR (600 MHz) δ 7.55 (d, J=7.8 Hz, 1H), 7.42 (dt, J=7.8, 1.2 Hz, 1H), 6.81 (t, J=7.8 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 4.77 (br s, 1H), 4.13 (m, 2H), 2.28 (m, 2H), 2.07 (m, 1H), 1.99 (m, 1H); ^{13}C NMR δ (150 MHz) 200.9 (+), 159.6 (+), 137.8 (−), 125.1 (−), 119.7 (−), 119.2 (+), 112.2 (−), 95.0 (+),

69.3 (+), 34.0 (+), 25.8 (+); IR (neat) 3250, 1702, 1007 cm^{-1}; HRMS calcd for $C_{11}H_{12}NO_2$ (M^++H) 190.0868, found 190.0862.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.101.

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Palladium-catalyzed syntheses of tetrahydrocarbazolones as advanced intermediates to carbazole alkaloids

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Abstract—Two sequential palladium-catalyzed reactions, an intermolecular Stille cross-coupling followed by a recently developed palladium-catalyzed reductive N-heteroannulation, have been employed as the key synthetic steps toward six tetrahydrocarbazolones. The products are advanced intermediates toward a number of naturally occurring carbazole alkaloids.

1. Introduction

Carbazole alkaloids are of significant synthetic interest due to their range of biological activities. For example, these natural products show antitumor, antibiotic, antimalarial, and antifungal properties.[1] Several carbazole alkaloids have been isolated from plants belonging to the Rutaceae family.[2] Many of these compounds have a one-carbon substituent in the 3-position and an oxygenated functionality in the 1- or 2-position. Dimeric- and quinoid-structures are also known in this group.[2] We have been interested in a number of these natural products, many of which are from plants of the genus *Murraya*. These plants consist of small trees and shrubs endemic to Southern Asia that have been used for years in folk medicine for analgesics and treatment of ailments such as eczema and rheumatism.[3]

Tetrahydrocarbazolones have been used extensively as advanced intermediates in synthetic efforts toward a number of naturally occurring carbazole alkaloids including, murrayaquinone A,[4–6] murrayanine,[7] koenigine-quinones A and B,[8] clausenalene,[9] glycoborine,[10] (+)-aspidospermidine,[11] clausenamine,[12] clausenol and clausenine,[13] clausenal,[14] dimeric murrayafoline A,[15] pyrrayaquinones A and B,[6] murrayafoline B and murrayaquinone B,[16] hepazolidine,[17] glycozolinol,[18] (−)-gilbertine,[19] and glycozoline.[20] The tetrahydrocarbazolones are usually prepared by a Japp–Klingemann condensation of diazonium salts with 2-(hydroxymethylene)-1-cyclohexanones followed by a Fischer indole synthesis of the formed hydrazones. The Fischer indole synthesis works reasonably well for 2- and 4-substituted arylhydrazones. However, the reaction usually affords regioisomeric cyclization products from the 3-substituted analogs,[21,22] and the reaction fails completely in some more substituted cases.[12] Herein is reported a new synthesis of tetrahydrocarbazolone compounds used as advanced intermediates in the synthesis of a significant number of functionalized oxygenated carbazoles.

2. Result and discussion

We have recently described a novel route to tetrahydrocarbazolones using two consecutive palladium-catalyzed reactions, a Stille-type cross-coupling and a reductive N-heteroannulation.[23] This sequence was used in a formal synthesis of murrayaquinone A as outlined in Scheme 1.

While working on the synthesis of murrayaquinone A, we initialized an alternative route to this compound via carbazolone **4** (Scheme 2). The conditions developed by Piers and Nagakura[24] to prepare 3-iodo-α,β-unsaturated ketones were used to synthesize 3-iodo-5-methyl-2-cyclohexen-1-one (**1**) from 5-methyl-1,3-cyclohexanedione. Stille-type cross-coupling of 3-iodocyclohexenone **1** and 2-nitrophenyl tributylstannane (**2**) using bis(benzonitrile)palladium dichloride, triphenylarsine, and copper iodide in *N*-methylpyrrolidinone, produced the expected product **3** in excellent yield. Palladium-catalyzed reductive N-heteroannulation of **3** gave uneventfully the expected carbazolone **4**. Carbazolone **4** is an advanced intermediate in reported syntheses of four different carbazole alkaloids, murrayaquinone A,[6] murrayafoline A,[6,7] murrayanine,[7,25] and dimeric *O*-demethylmurrayafoline A.[26]

Keywords: Carbazoles; Palladium-catalyzed; Alkaloids.
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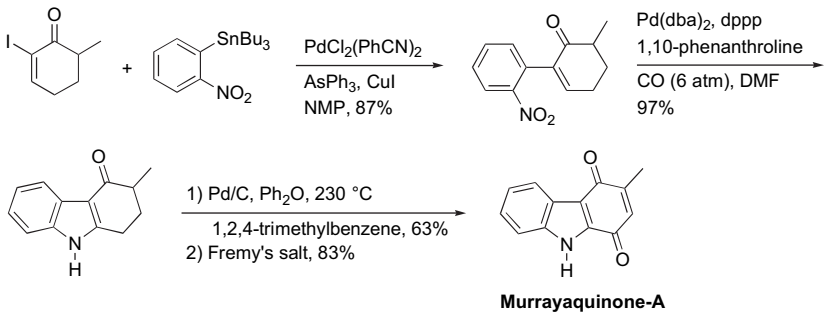
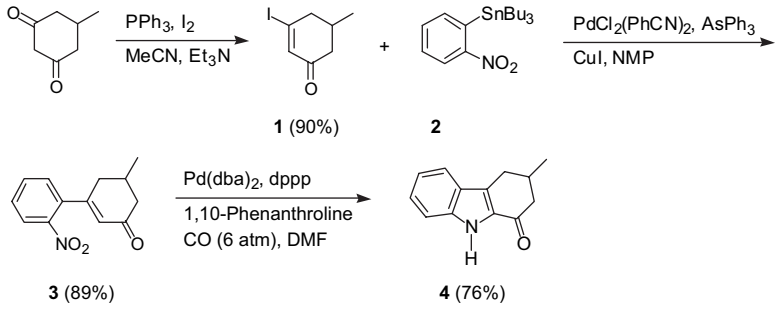


Scheme 1.

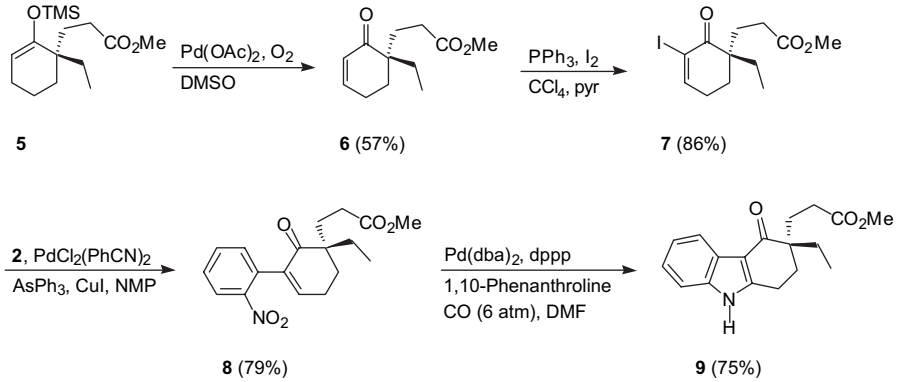


Scheme 2.

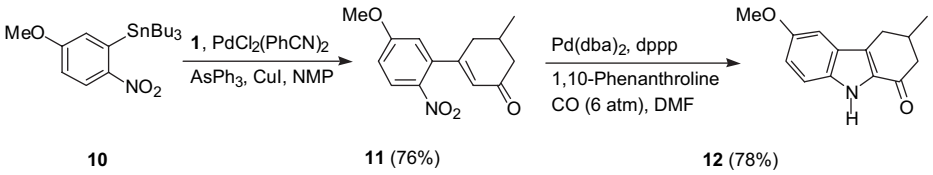
Carbazolone **9** is a key intermediate in Desmaele and d'Angelo's synthesis of (+)-aspidospermidine (Scheme 3).[11] The synthesis of this intermediate was realized in 35% overall yield starting from cyclohexenone **6**. It was anticipated that we could improve upon the synthesis of carbazolone **9** using our methodology. Cyclohexenone **6** was prepared by Desmaele and d'Angelo by a DDQ oxidation of the trimethylsilylenol ether **5**. In our hands, despite several attempts, the procedure reported in the literature completely failed to produce **6**. However, a palladium-catalyzed Saegusa oxidation[27] of **5** furnished **6** in 57% yield. Iodide **7**, prepared by treatment of **6** with iodine and pyridine in tetrachloromethane,[28] was coupled with **2** to afford **8** in good yield. The palladium-catalyzed N-heteroannulation of **8** proceeded smoothly to give carbazolone **9** in 75% yield. In comparison with the previous route to this intermediate, carbazolone **9** was obtained in a 52% overall yield starting from **6**.

The third example, 6-methoxy-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**12**), has been used as an advanced intermediate toward the naturally occurring alkaloids clausenol and clausenine,[13] clausenamine A,[12] and glycozoline.[29] In the event, Stille-type cross-coupling of tributyl(5-methoxy-2-nitrophenyl)stannane **10** with vinyl iodide **1** gave the expected product **11** (Scheme 4). Palladium-catalyzed annulation of **11** furnished the expected carbazolone **12**.

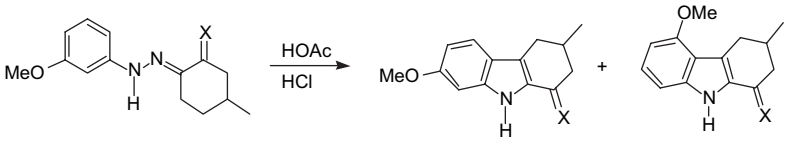
For the carbazolones **4** and **12** discussed above, the regioselectivity of the reported Fischer indole syntheses leading to the carbazolones does not pose a problem since only one isomer can be formed. In contrast, reactions of 3-substituted arylhydrazones frequently afford two regioisomeric products. For example, reaction of **13** has been described three times in the literature by the same authors. In each case, **13** was treated with a mixture of acetic and hydrochloric acid (at reflux) to afford **14** and **15** (Scheme 5). A detailed experimental procedure was not found in either of the papers. The yield of the isomers was not reported in the first paper,[30] and in the second paper the yield of **15** was reported to be 50%.[21] In the third paper, compound **14** was isolated in 65.5% yield



Scheme 3.



Scheme 4.



Scheme 5.

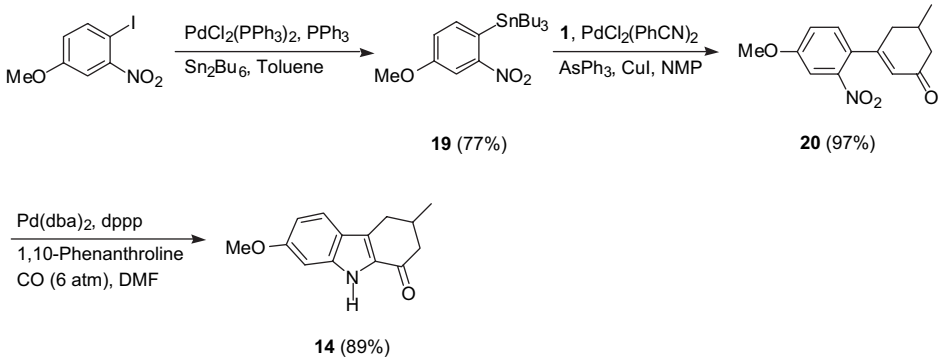
using identical reaction conditions and times with no mentioning of **15**.[8] We decided to repeat the reaction but were unable to obtain **15** as the major product using the reaction conditions described. In our hands an approximately 7:1 mixture of **14** and **15** was obtained in 57% yield. A similar result was reported by Chakravarty et al. from a Fischer indole synthesis of the corresponding 4-methylcyclohexane hydrazone derivative **16** in place of **13**.[10] In this case, a 9:1 mixture (60% yield) of the 3-methyl-7-methoxy- and 3-methyl-5-methoxy-tetrahydrocarbazoles **17** and **18** was obtained, respectively. Wolff–Kishner–Huang–Minlon reduction[21] of **14** gave the expected compound **17**, having identical ^{1}H NMR chemical shifts compared to reported data.[10]

In contrast to the Fischer indole synthesis, the palladium-catalyzed N-heteroannulation is inherently regiospecific and both **14** and **15** can be obtained in good overall yield. 7-Methoxy-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**14**), has been used as an advanced intermediate toward the naturally occurring alkaloids koenigenine-quinone A,[8] murrayafoline B and murrayaquinone B,[16] and pyrrayaquinones A and B.[6] The formal synthesis of these compounds using the palladium-catalyzed methodology was carried out in the same manner as described above for murrayaquinone A. Organostannane **19**[31] was first prepared starting from commercially available 1-iodo-4-methoxy-2-nitrobenzene and hexabutylditin using Kosugi's procedure (Scheme 6).[32]

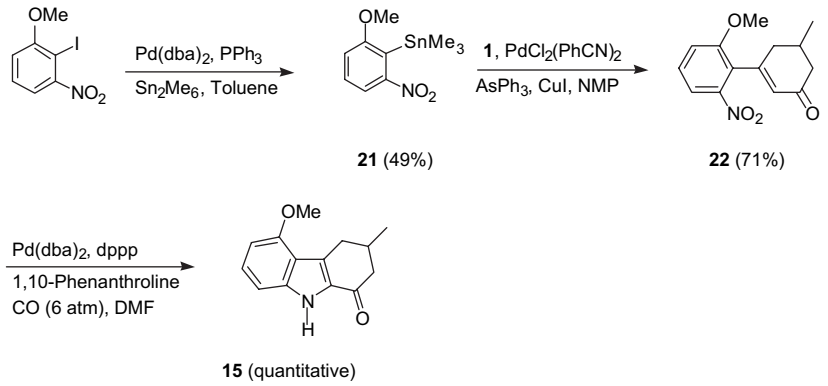
Stille-type cross-coupling of **19** with **1** under standard reaction conditions produced **20** in excellent yield. The reductive cyclization of **20** also proceeded smoothly affording the carbazolone **14**.

5-Methoxy-3-methyl-3,4-dihydrocarbazol-1(2*H*)-one (**15**) has previously been used as an intermediate in a synthesis of 5-methoxy-3-methylcarbazole; a structure initially named glycozolicine.[21] However, the structure of glycozolicine was later shown not to be 5-methoxy-3-methylcarbazole based on extensive NMR data and synthesis.[10] A second compound, glycoborine was identified as 5-methoxy-3-methylcarbazole. It should be noted that the true structure of the glycozolicine is still unknown.

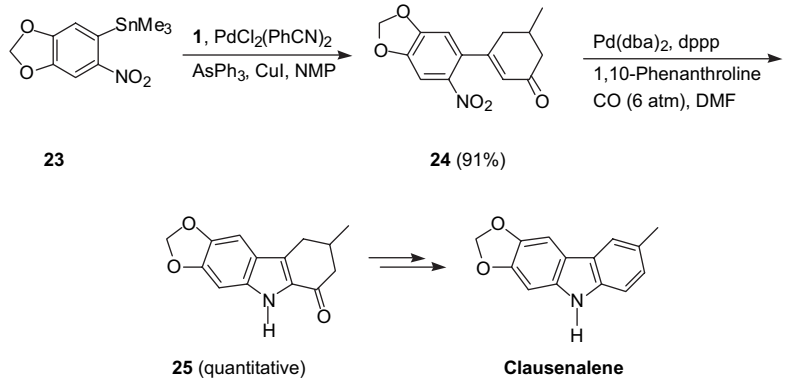
For the synthesis of **15**, a novel tin coupling partner was required. Initially, hexabutylditin was used to prepare 6-methoxy-2-nitrophenyl tributylstannane from 1-iodo-2-methoxy-6-nitrobenzene. However, the reaction was sluggish and a complex mixture of products was obtained. Turning to hexamethylditin solved this problem and **21** was obtained in 49% yield. The ensuing Stille coupling, affording **22**, and annulation proceeded uneventfully to give carbazolone **15**. The significant lower yield of products **21** and **22** compared to the previous examples is probably a reflection of the hindered nature of the substrates. The annulation, in contrast, gave a quantitative yield of product (Scheme 7).



Scheme 6.



Scheme 7.



Scheme 8.

As a final example, a synthesis of the antibacterial carbazole clausenalene, isolated from the stem bark of *Clausena heptaphylla* was pursued.[9] Clausenalene is the first reported methylenedioxy carbazole alkaloid isolated from a plant source. The known arylstannane **23** was coupled with **1** to give **24** (Scheme 8). Reductive N-heteroannulation of **24** gave tetrahydrocarbazolone **25**, which has been previously used to prepare clausenalene via a Wolff–Kishner reduction and aromatization.

3. Conclusion

In conclusion, we have successfully applied a sequential Stille-type cross-coupling reaction followed by a palladium-catalyzed reductive N-heteroannulation to the synthesis of six tetrahydrocarbazolones. The products are late intermediates in the synthesis of a number of naturally occurring carbazole alkaloids.

4. Experimental

4.1. General procedures

NMR spectra were determined in $CDCl_3$ at 270 MHz or 600 MHz (^{1}H NMR) and 67.5 MHz or 150 MHz (^{13}C NMR). The chemical shifts are expressed in δ values relative to Me_4Si (0.0 ppm, ^{1}H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) internal standards. ^{1}H–^{1}H coupling constants are reported as calculated from spectra; thus a slight difference between $J_{a,b}$ and $J_{b,a}$ is usually obtained. Results of APT (attached proton test)—^{13}C NMR experiments are shown in parentheses where, relative to $CDCl_3$, (−) denotes CH_3 or CH and (+) denotes CH_2 or C.

Toluene, pyridine, hexanes, acetonitrile, and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under an argon or nitrogen atmosphere in oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure or by bulb-to-bulb distillation under reduced pressure. Chromatography was performed on silica gel 60 (35–75 μm, VWR). Melting points were determined on a MelTemp and are uncorrected. High resolution mass spectra (HRMS) were performed at University of California, Riverside Mass Spectrometry Center. Elemental analyses were performed in the Department of Chemical Engineering, College of Engineering and Mineral Resources, West Virginia University.

4.1.1. 3-Iodo-5-methyl-2-cyclohexen-1-one (1). To a solution of triphenylphosphine (4.75 g, 18.1 mmol) in acetonitrile (80 mL) was added iodine (4.53 g, 17.8 mmol). The reaction mixture was stirred for 2 h. Triethylamine (2.60 mL,

18.5 mmol) was added slowly, followed by 5-methyl-1,3-cyclohexanedione (2.04 g, 16.2 mmol). The reaction mixture was stirred for 14 d at ambient temperature. The solvent was evaporated and the crude product was purified by chromatography (hexanes/EtOAc, 95:5) to give **1** (3.44 g, 14.6 mmol, 90%) as a faint yellow oil. IR (neat): 2956, 1676, 1592 cm^{-1}; ^1H NMR (270 MHz): δ 1.07 (dd, J=6.5, 1.8 Hz, 3H), 2.10 (ddd, J=12.1, 11.7, 3.6 Hz, 1H), 2.24–2.40 (m, 1H), 2.46–2.65 (m, 2H), 2.95–3.06 (m, 1H), 6.77–6.82 (m, 1H); ^{13}C NMR (67.5 MHz): δ 19.9 (−), 30.9 (+), 44.0 (−), 47.6 (−), 125.7 (+), 139.4 (−), 194.3 (+); HRMS (EI) calcd for C_7H_9IO (M^+): 235.9698, found: 235.9696; Anal. Calcd for C_7H_9IO: C, 35.62; H, 3.84. Found: C, 35.65; H, 4.01.

4.1.2. 3-(2-Nitrophenyl)-5-methyl-2-cyclohexen-1-one (3). A solution of **1** (1.00 g, 4.24 mmol), tributyl(2-nitrophenyl)stannane (**2**)[32] (2.10 g, 5.10 mmol), $PdCl_2(PhCN)_2$ (81 mg, 0.21 mmol), $AsPh_3$ (130 mg, 0.42 mmol), and CuI (81 mg, 0.42 mmol) in *N*-methylpyrrolidinone (NMP) (8.4 mL) was heated at 80 °C for 48 h. The reaction was diluted with benzene (100 mL) and washed with NH_4OH (10%, aq, 3×30 mL) and H_2O (2×30 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvents were removed by bulb-to-bulb distillation under reduced pressure. The crude product was purified by chromatography (hexanes) to give **3** (873 mg, 3.78 mmol, 89%) as a pale yellow solid. Mp 62–64.5 °C; IR (neat): 2956, 1669, 1525, 1346 cm^{-1}; ^1H NMR (600 MHz): δ 1.13 (d, J=6.6 Hz, 3H), 2.20 (dd, J=16.2, 12.6 Hz, 1H), 2.34 (ddd, J=18.6, 11.4, 2.4 Hz, 1H), 2.44–2.54 (overlapping s and m, 2H), 2.59 (dd, J=16.8, 4.2 Hz, 1H), 5.98 (d, J=2.4 Hz, 1H), 7.30 (dd, J=7.8, 1.2 Hz, 1H), 7.55 (dt, J=8.4, 1.8 Hz, 1H), 7.67 (dt, J=7.2, 1.2 Hz, 1H), 8.10 (dd, J=8.1, 1.2 Hz, 1H); ^{13}C NMR (150 MHz): δ 21.0 (+), 30.8 (+), 38.8 (−), 45.5 (−), 124.9 (+), 127.2 (+), 129.5 (+), 129.7 (+), 133.8 (+), 136.5 (−), 146.6 (-), 159.8 (−), 199.1 (−); HRMS (DEI) calcd for $C_{13}H_{13}NO_3$ (MH^+): 232.0974, found: 232.0974; Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 68.13; H, 6.01; N, 5.79.

4.1.3. 2,3,4,9-Tetrahydro-3-methyl-1*H*-carbazol-1-one (4).[15] 5-Methyl-3-(2-nitrophenyl)-2-cyclohexenone (**3**) (133 mg, 0.575 mmol), $Pd(dba)_2$ (19.9 mg, 0.0346 mmol), dppp (14.3 mg, 0.0347 mmol), 1,10-phenanthroline monohydrate (13.7 mg, 0.0691 mmol), and DMF (6 mL) were placed into a pressure tube fitted with a pressure head. The tube was flushed three times with CO and the reaction was heated and stirred at 80 °C under CO (6 atm, 72 h). The reaction mixture was filtered through Celite and the solvent was removed by bulb-to-bulb distillation under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 7:3) to give **4** (88 mg, 0.44 mmol, 77%) as a white powder. Mp 193–195 °C (lit.[32] 197 °C).

4.1.4. Methyl (*S*)-1-ethyl-2-oxo-3-cyclohexene-1-propanoate (6).[11] To a solution of methyl (*S*)-1-ethyl-2-oxo-cyclohexane-1-propanoate (**5**) (3.25 g, 15.3 mmol) in DMF (23 mL) was added triethylamine (11.3 mL, 80.4 mmol). Chlorotrimethylsilane (5.93 mL, 46.4 mmol) was added dropwise and the reaction mixture was heated (100 °C, 3 d). The reaction was allowed to cool to ambient temperature, diluted with hexanes (50 mL), and poured into cold water (50 mL). The layers were separated and the aqueous portion was extracted with hexanes (3×50 mL). The organic phases were combined, dried ($MgSO_4$), filtered, and the solvents were removed by bulb-to-bulb distillation under reduced pressure. To a portion of the crude silylenol ether **5** (1.94 g, 6.82 mmol) in DMSO (50 mL) was added $Pd(OAc)_2$ (159 mg, 0.708 mmol). The flask containing the reaction mixture was flushed with oxygen and was kept under oxygen (1 atm, balloon) while being heated at 40 °C (72 h). Additional $Pd(OAc)_2$ (95.6 mg, 0.426 mmol) was added to the reaction mixture and the reaction was heated at 60 °C (24 h). The reaction mixture was cooled and diluted with ethyl acetate (200 mL). The mixture was washed with water (3×50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 7:3) to give **6** (820 mg, 3.90 mmol, 57%) as a colorless oil. Spectral data (^1H NMR) are in complete accordance with the literature values.[11]

4.1.5. Methyl (*S*)-1-ethyl-2-oxo-3-iodo-3-cyclohexenone-1-propanoate (7). To a solution of **6** (508 mg, 2.42 mmol) in 10 mL of 1:1 CCl_4/pyridine cooled to 0 °C was added drop wise a solution of iodine (1.26 g, 4.96 mmol) dissolved in 10 mL of 1:1 CCl_4/pyridine with stirring. The reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was diluted with ether (100 mL) and washed successively with water (40 mL), HCl (5%, aq, 2×40 mL), water (40 mL), and $Na_2S_2O_3$ (20%, aq, 40 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 8:2) to give **7** (698 mg, 2.08 mmol, 86%) as a pale yellow oil. IR (neat): 3450, 2944, 1732, 1679 cm^{-1}; ^1H NMR (270 MHz): δ 0.83 (t, J=7.5 Hz, 3H), 1.49–1.71 (m, 2H), 1.80–2.01 (m, 4H), 2.11–2.36 (m, 2H), 2.43–2.50 (m, 2H), 7.64 (t, J=4.1 Hz, 1H); ^{13}C NMR (67.5 MHz): δ 7.9 (−), 26.8 (+), 28.5 (+), 28.5 (+), 30.0 (+), 47.7 (+), 51.4 (−), 103.4 (+), 157.3 (−), 173.5 (+), 195.3 (+); HRMS (DEI) calcd for $C_{12}H_{17}IO_3$ (MH^+): 336.0222, found: 336.0210; Anal. Calcd for $C_{13}H_{13}NO_3$: C, 42.87; H, 5.10. Found: C, 42.87; H, 5.38.

4.1.6. Methyl (*S*)-1-ethyl-2-oxo-3-(2-nitrophenyl)-3-cyclohexenone-1-propanoate (8). Reaction of **7** (250 mg, 0.744 mmol), tributyl(2-nitrophenyl)stannane (**2**) (369 mg, 0.895 mmol), $PdCl_2(PhCN)_2$ (14.9 mg, 0.0388 mmol), $AsPh_3$ (23.1 mg, 0.0754 mmol), CuI (14.5 mg, 0.0761 mmol), and NMP (1.4 mL), as described for **3** (80 °C, 40 h), gave after workup and chromatography (hexanes/EtOAc, in sequence 9:1 and 8:2) **8** (196 mg, 0.591 mmol, 79%) as a yellow oil. IR (neat): 3446, 2939, 1736, 1669, 1526, 1353 cm^{-1}; ^1H NMR (600 MHz): δ 0.87 (t, J=7.2 Hz, 3H), 1.54–1.66 (m, 1H), 1.68–1.80 (m, 1H), 1.86–2.08 (m, 4H), 2.29 (t, J=8.4 Hz, 2H), 2.59 (q, J=4.2 Hz, 2H), 3.64 (s, 3H), 6.93 (t, J=4.2 Hz, 1H), 7.23 (dd, J=7.8, 1.2 Hz, 1H), 7.46 (dt, J=7.8, 1.2 Hz, 1H), 7.58 (dt, J=7.2, 1.2 Hz, 1H), 7.98 (dd, J=7.8, 1.2 Hz, 1H); ^{13}C NMR (150 MHz): δ 7.9 (+), 22.8 (−), 26.3 (−), 28.5 (−), 28.6 (−), 30.2 (−), 46.9 (−), 51.5 (+), 123.9 (+), 128.6 (+), 131.9 (+), 132.3 (+), 133.0 (−), 138.2 (−), 145.3 (+), 148.8 (−), 174.2 (−), 199.5 (−); HRMS (DEI) calcd for $C_{18}H_{21}NO_5$ (MH^+): 332.1498, found: 332.1512; Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.32; H, 7.05; N, 3.86.

4.1.7. Methyl (*S*)-[3-ethyl-4-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl]propanoate (9).[11] Reaction of **8** (184 mg, 0.555 mmol), $Pd(dba)_2$ (19.5 mg, 0.0339 mmol), dppp (14.0 mg, 0.0339 mmol), and 1,10-phenanthroline monohydrate (13.5 mg, 0.0681 mmol) in DMF (5 mL), as described for **4** (80 °C, 6 atm CO, 20 h), gave after workup and chromatography (hexanes/EtOAc, in sequence 8:2 and 1:1) and recrystallization (hexanes/EtOAc, 2:1) **9** (126 mg, 0.421 mmol, 75%) as a white solid. Mp 126–126.5 °C (lit.[11] 125–126 °C).

4.1.8. 3-(5-Methoxy-2-nitrophenyl)-5-methyl-2-cyclohexen-1-one (11). Reaction of **1** (619 mg, 2.62 mmol), tributyl(5-methoxy-2-nitrophenyl)stannane (**10**)[33] (1.29 g, 2.92 mmol), $PdCl_2(PhCN)_2$ (50.2 mg, 0.131 mmol), $AsPh_3$ (80.2 mg, 0.262 mmol), and CuI (50.0 mg, 0.262 mmol) in NMP (2 mL), as described for **3** (80 °C, 6 atm CO, 20 h), gave after workup and chromatography (hexanes/EtOAc, 8:2) **11** (577 mg, 2.21 mmol, 76%) as a yellow solid. Mp 124–126 °C; IR (neat): 3462, 2959, 2252, 1663, 912 cm^{-1}; ^1H NMR (600 MHz): δ 1.13 (d, J=6.6 Hz, 3H), 2.20 (dd, J=16.2, 12.0 Hz, 1H), 2.31 (ddd, J=18.0, 10.8, 3.0 Hz, 1H), 2.44–2.55 (overlapping dd and m, 2H), 2.58 (ddd, J=16.2, 4.2, 1.8 Hz, 1H), 3.92 (s, 3H), 5.96 (d, J=2.4 Hz, 1H), 6.71 (d, J=2.4 Hz, 1H), 6.97 (dd, J=9.0, 3.0 Hz, 1H), 8.18 (dd, J=9.0, 1.2 Hz, 1H); ^{13}C NMR (150 MHz): δ 21.1 (+), 30.8 (+), 38.9 (−), 45.5 (−), 56.1 (+), 114.0 (+), 114.6 (+), 126.6 (+), 127.7 (+), 139.2 (+), 139.3 (+), 160.8 (−), 163.7 (−), 199.3 (−); Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79. Found: C, 64.56; H, 6.27.

4.1.9. 6-Methoxy-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (12).[12] Reaction of **11** (220 mg, 0.842 mmol), $Pd(dba)_2$ (29 mg, 0.055 mmol), dppp (21 mg, 0.051 mmol), and 1,10-phenanthroline monohydrate (18 mg, 0.091 mmol) in DMF (5 mL), as described for **4** (80–90 °C, 6 atm, 36 h), gave after workup and chromatography (hexanes/EtOAc, 8:2) **12** (151 mg, 0.659 mmol, 78%) as a faint yellow solid. Mp 206–209 °C (lit.[12] mp 200–203 °C).

4.1.10. Tributyl(4-methoxy-2-nitrophenyl)stannane (19). To a solution of 1-iodo-4-methoxy-2-nitrobenzene (923 mg, 3.31 mmol) in toluene (6 mL) were added hexabutylditin (2.50 mL, 4.95 mmol), $PdCl_2(PPh_3)_2$ (23.6 mg, 0.0336 mmol), and PPh_3 (17.6 mg, 0.0671 mmol). The reaction was heated at 80 °C for 4 d. The reaction was diluted with benzene (100 mL) and washed with NH_4OH (10%, aq, 3×30 mL) and H_2O (2×30 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (hexanes) to give **19** (1.13 g, 2.56 mmol, 77%) as a yellow oil. IR (neat): 2956, 1528, 1344 cm^{-1}; ^1H NMR (270 MHz): δ 0.87 (t, J=7.3 Hz, 3H), 1.10 (t, J=7.7 Hz, 2H), 1.30 (sextet, J=4.0 Hz, 2H), 1.42–1.54 (m, 2H), 3.89 (s, 3H), 7.19 (dd, J=8.1, 2.6 Hz, 1H), 7.54 (d, J=8.1 Hz, 1H), 7.85 (d, J=4.3 Hz, 1H); ^{13}C NMR (67.5 MHz): δ 10.8 (+), 13.6 (−), 27.3 (+), 29.0 (+), 55.5 (−), 108.8 (−), 120.6 (−), 130.0 (+), 138.0 (−), 154.5 (+), 160.5 (+); HRMS (FAB) calcd for $C_{19}H_{33}NO_3Sn$ (M^-): 443.1482, found: 443.1491; Anal. Calcd for $C_{19}H_{33}NO_3Sn$: C, 51.71; H, 7.52; N, 3.17. Found: C, 50.31; H, 7.67; N, 3.02.

4.1.11. 3-(4-Methoxy-2-nitrophenyl)-5-methyl-2-cyclohexen-1-one (20). Reaction of **1** (208 mg, 0.881 mmol), **19** (445 mg, 1.01 mmol), $PdCl_2(PhCN)_2$ (17.2 mg, 0.0448 mmol), $AsPh_3$ (27.1 mg, 0.0885 mmol), CuI (17.8 mg, 0.0935 mmol), and NMP (2 mL), as described for **3** (80 °C, 2 d), gave after workup and chromatography (hexanes/EtOAc, in sequence 9:1 and 8:2) **20** (222 mg, 0.850 mmol, 97%) as a yellow solid. Mp 45–47 °C; IR (neat): 2953, 1666, 1531, 1350 cm^{-1}; ^1H NMR (600 MHz): δ 1.12 (d, J=6.6 Hz, 3H), 2.18 (dd, J=16.2, 12.0 Hz, 1H), 2.30 (ddd, J=18.0, 10.8, 2.4 Hz, 1H), 2.38–2.50 (m, 2H), 2.56 (dd, J=17.4, 4.8 Hz, 1H), 3.91 (s, 3H), 5.95 (d, J=2.4 Hz, 1H), 7.19 (dd, J=8.4, 2.4 Hz, 1H), 7.22 (d, J=9.0 Hz, 1H), 7.58 (d, J=3.0 Hz, 1H); ^{13}C NMR (150 MHz): δ 20.9 (+), 30.6 (+), 38.8 (−), 45.4 (−), 55.9 (+), 109.7 (+), 119.8 (+), 127.2 (+), 128.5 (+), 130.6 (−), 147.3 (−), 159.8 (−), 160.0 (−), 199.2 (−); HRMS (DEI) calcd for $C_{14}H_{15}NO_4$ (MH^+): 262.1080, found: 262.1078; Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79. Found: C, 64.08; H, 6.04.

4.1.12. 2,3,4,9-Tetrahydro-7-methoxy-3-methyl-1*H*-carbazol-1-one (14).[8] Reaction of **20** (73.6 mg, 0.282 mmol), $Pd(dba)_2$ (9.7 mg, 0.017 mmol), dppp (6.9 mg, 0.017 mmol), 1,10-phenanthroline monohydrate (6.7 mg, 0.034 mmol), and DMF (5 mL), as described for **4** (80–90 °C, 6 atm CO, 3 d), gave after workup and chromatography (hexanes/EtOAc, 7:3) **14** (57.7 mg, 0.252 mmol, 89%) as a white solid. Mp 206–209 °C (lit.[12] 200–203 °C).

4.1.13. Trimethyl(2-methoxy-6-nitrophenyl)stannane (21). To a solution of 1-iodo-2-methoxy-6-nitrobenzene[34,35] (1.83 g, 6.56 mmol) in toluene (25 mL) was added hexamethylditin (2.36 g, 7.20 mmol), $PdCl_2(PPh_3)_2$ (25 mg, 0.036 mmol), and PPh_3 (34 mg, 0.13 mmol). The reaction was heated at 80 °C (2 d). The reaction mixture was diluted with EtOAc (100 mL) and washed with NH_4OH (10%, aq, 3×30 mL) and H_2O (2×30 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The crude product was purified by chromatography (hexanes) to give **21** (1.02 g, 3.23 mmol, 49%) as a yellow solid. Mp 49–52 °C; IR (neat): 2956, 1528, 1344 cm^{-1}; ^1H NMR (270 MHz): δ 0.87 (t, J=7.3 Hz, 3H), 1.10 (t, J=7.7 Hz, 2H), 1.30 (sextet, J=4.0 Hz, 2H), 1.42–1.54 (m, 2H), 3.89 (s, 3H), 7.19 (dd, J=8.1, 2.6 Hz, 1H), 7.54 (d, J=8.1 Hz, 1H), 7.85 (d, J=4.3 Hz, 1H); ^{13}C NMR (67.5 MHz): δ −5.7 (+), −4.33 (d, $J_{C,Sn}$=189.4 Hz), 55.8 (+), 114.1 (+), 116.2 (+), 127.6 (−), 130.5 (+), 155.6 (−), 164.9 (−); Anal. Calcd for $C_{10}H_{15}NO_3Sn$: C, 38.02; H, 4.79. Found: C, 38.37; H, 5.14.

4.1.14. 3-(2-Methoxy-6-nitrophenyl)-5-methyl-2-cyclohexen-1-one (22). Reaction of **1** (557 mg, 2.36 mmol), **21** (820 mg, 2.60 mmol), $PdCl_2(PhCN)_2$ (45 mg, 0.12 mmol), $AsPh_3$ (72.3 mg, 0.236 mmol), and CuI (50 mg, 0.26 mmol) in NMP (2 mL), as described for **3** (80 °C, 48 h), gave after workup and chromatography (hexanes/EtOAc, 8:2) **22** (437 mg, 1.67 mmol, 71%) as a yellow oil. IR (neat): 3456, 2957, 2250, 1668, 911, 726 cm^{-1}; ^1H NMR (600 MHz): δ 1.15 (d, J=3.6 Hz, 3H), 2.15–2.30 (m, 1H), 2.40–2.65 (m, 4H), 3.89 (d, J=3.0 Hz, 3H), 5.78 (s, 1H), 7.55 (d, J=7.8 Hz, 1H), 7.21 (dd, J=8.4, 1.2 Hz, 1H), 7.46 (dt, J=8.4, 2.4 Hz, 1H); ^{13}C NMR (150 MHz): δ 20.8 (+), 30.1 (+), 37.9 (−), 45.4 (−), 56.3 (+), 115.3 (+), 124.7 (−), 127.2 (+), 129.4 (+), 147.9 (−), 156.4 (−), 156.8 (−),

198.9 (−); Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79. Found: C, 64.44; H, 5.27.

4.1.15. 5-Methoxy-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (15).[21] Reaction of **22** (57 mg, 0.22 mmol), $Pd(dba)_2$ (7.5 mg, 0.014 mmol), dppp (5.4 mg, 0.013 mmol), and 1,10-phenanthroline monohydrate (4.7 mg, 0.024 mmol) in DMF (4 mL), as described for **4** (80–90 °C, 6 atm CO, 2 d), gave after workup and chromatography (hexanes/EtOAc, 19:1), **15** (50 mg, 0.22 mmol, 100%) as a white solid. Mp 240–242 °C (lit.[21] mp 201 °C); IR (neat): 3460, 2253, 1646, 1471, 1381, 1264, 1108 cm^{-1}; ^1H NMR (270 MHz): δ 1.14 (d, J=6.2 Hz, 3H), 2.29 (ddd, J=15.3, 11.4, 0.98 Hz, 1H), 2.45 (m, 1H), 2.56 (ddd, J=15.6, 3.2, 1.2 Hz, 1H), 2.75 (dd, J=17.1, 10.9 Hz, 1H), 3.38 (dd, J=17.1, 3.8 Hz, 1H), 3.86 (s, 3H), 6.38 (d, J=7.7 Hz, 1H), 6.91 (d, J=8.2 Hz, 1H), 7.17 (t, J=8.2 Hz, 1H), 8.98 (br s, 1H); ^{13}C NMR (67.5 MHz): δ 21.4 (−), 31.7 (+), 33.1 (−), 46.1 (+), 55.2 (−), 99.5 (−), 105.2 (−), 116.8 (+), 128.0 (−), 129.6 (+), 130.0 (+), 139.4 (+), 156.5 (+), 190.7 (+).

4.1.16. 5-Methyl-3-(6-nitro-1,3-benzodioxol-5-yl)-2-cyclohexen-1-one (24). Reaction of **1** (104 mg, 0.441 mmol), trimethyl(6-nitro-1,3-benzodioxol-5-yl)stannane (**23**)[31] (160 mg, 0.485 mmol), $PdCl_2(PhCN)_2$ (8.5 mg, 0.022 mmol), $AsPh_3$ (13.5 mg, 0.0441 mmol), and CuI (8.4 mg, 0.044 mmol) in NMP (2 mL), as described for **3** (80 °C, 48 h), gave after workup and chromatography (hexanes then hexanes/EtOAc, in sequence 19:1, 9:1, and 8:2), **24** (110 mg, 0.400 mmol, 91%) as a yellow solid. Mp 124–126 °C; IR (neat): 3619, 2254, 1711, 911, 735 cm^{-1}; ^1H NMR (600 MHz): δ 1.12 (d, J=6.0 Hz, 3H), 2.18 (dd, J=16.8, 12.6 Hz, 1H), 2.28 (ddd, J=17.4, 9.6, 2.4 Hz, 1H), 2.40–2.54 (overlapping dd and m, 2H), 2.57 (dd, J=16.2, 3.0 Hz, 1H), 5.92 (d, J=1.8 Hz, 1H), 6.17 (s, 2H), 6.65 (s, 1H), 7.61 (s 1H); ^{13}C NMR (150 MHz): δ 21.0 (+), 30.8 (+), 39.0 (−), 45.5 (−), 103.4 (−), 105.7 (+), 108.6 (+), 126.9 (+), 133.4 (−), 140.5 (−), 148.1 (−), 152.2 (−), 160.6 (−), 199.2 (−). For unknown reasons, the compound did not give satisfactory combustion analysis even after extensive purification.

4.1.17. 8-Methyl-5,7,8,9-tetrahydro-6*H*-1,3-dioxolo[4,5-*b*]carbazol-6-one (25).[9] Reaction of **24** (50 mg, 0.18 mmol), $Pd(dba)_2$ (6.5 mg, 0.012 mmol), dppp (3.9 mg, 0.095 mmol), and 1,10-phenanthroline monohydrate (4.5 mg, 0.011 mmol) in DMF (2 mL), as described for **4** (80–90 °C, 6 atm CO, 24 h), gave after workup and chromatography (hexanes then hexanes/EtOAc, in sequence 9:1 and 8:2) **25** (44 mg, 0.18 mmol, 100%) as a white solid. Mp 271–273 °C (lit.[9] mp 270 °C (dec)).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.100.

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Synthesis of α-conhydrine

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Abstract—A synthesis of α-conhydrine has been achieved from *trans*-(2*S*,4*R*)-4-hydroxyproline via diastereoselective Grignard addition, regioselective Baeyer–Villiger reaction, and ring-closing metathesis as the key steps.

1. Introduction

Based on the structural framework of *trans*-(2*S*,4*R*)-4-hydroxyproline, it possesses three functional groups that can be easily modified, and these are 1-amino, 2-carboxylate, and 4-hydroxy groups.[1] The skeleton represents the significant feature for producing a series of different carbon frameworks using an efficient modification technique.[2] Recently we have introduced a straightforward approach toward anisomycin,[2h] epibatidine,[2i] pancracine,[2j] and streptorubin B core[2k] employing *trans*-(2*S*,4*R*)-4-hydroxyproline as the starting material. To explore a new application, synthetic studies toward α-conhydrine were further investigated.

These alkaloids containing a 2-(1-hydroxyalkyl)piperidine unit with biological activities are abundant in nature.[3] Conhydrine is one of the alkaloids of the hemlock, isolated from the seeds and leaves of the poisonous alkaloids plant *Conium maculatum*, whose extracts were used in the ancient Greece for execution of criminals (Fig. 1).[4] Various methods for the asymmetric synthesis of α-conhydrine (**1a**) and β-conhydrine (**1b**) and mainly based on auxiliary-supported or chiral pool approaches have been documented in the literature.[5] In connection with our studies on the *trans*-(2*S*,4*R*)-4-hydroxyproline (**2**) as the chiral material, we are interested in developing a feasible and straightforward approach to α-conhydrine (**1a**) via diastereoselective Grignard addition, regioselective Baeyer–Villiger reaction, and ring-closing metathesis.

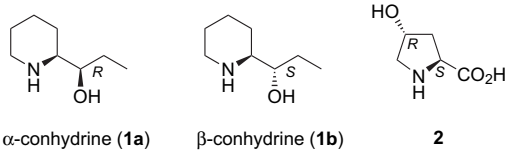
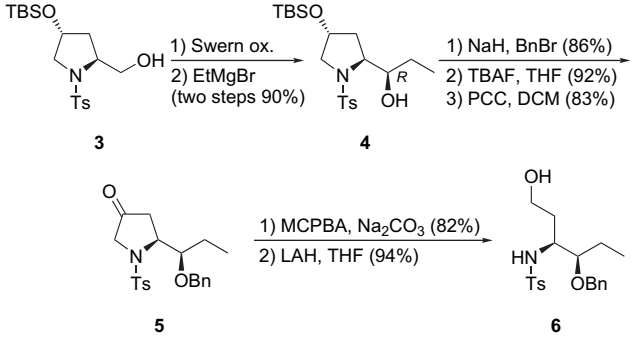


Figure 1.

2. Results and discussion

The synthesis of α-conhydrine (**1a**) began from prolinol **3** as illustrated in Scheme 1. The four-step preparation of compound **3** with 90% overall yield was reported from *trans*-(2*S*,4*R*)-4-hydroxyproline (**2**).[2i–k] First, prolinol **3** was treated with Swern oxidation and followed by Grignard addition to give compound **4** as a single isomer at −78 °C.[6] The diastereoselective addition occurred in favor of the *anti* isomer through a chelated intermediate.[5a,6] Subsequently, alcohol **4** was treated with O-benzylation, desilylation, and oxidation to afford ketone **5**. The relative *anti* configurations of compound **5** were based upon the single-crystal X-ray analysis (Fig. 2).[7]



Scheme 1.

Keywords: *trans*-(2*S*,4*R*)-4-Hydroxyproline; α-Conhydrine; Grignard addition; Regioselective Baeyer–Villiger reaction; Ring-closing metathesis.
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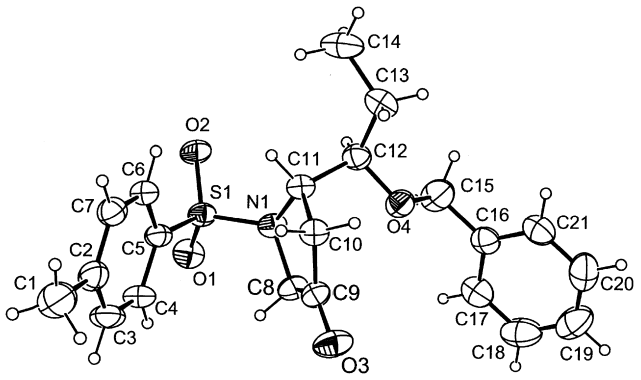
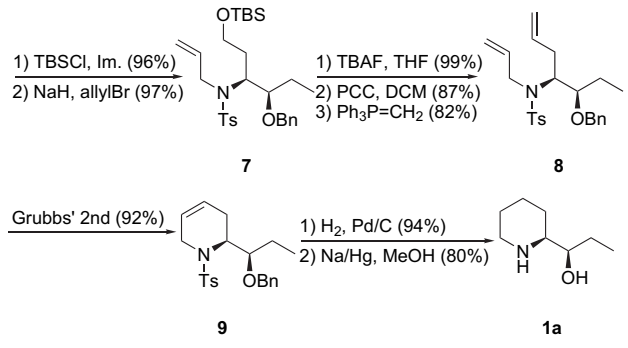


Figure 2. X-ray crystallography of compound **5**.

With the result in hand, regioselective Baeyer–Villiger reaction of ketone **5** was next examined. While poring over the related literature, we found that Young's group had developed the copper(II) acetate-mediated expansion of 4-ketoprolines with *m*-chloroperoxybenzoic acid.[8] We believe that the nitrogen atom can play an important factor to initiate the regiospecific ring expansion.[8c] According to the reports, compound **5** was first treated with the combination of copper(II) acetate and *m*-chloroperoxybenzoic acid. The resulting tetrahydro-1,3-oxazin-6-one skeleton was provided in moderate (42%) yield. In order to increase higher yields, other commercial available reagents and reaction conditions were tested. When the reaction was treated with the combination of sodium carbonate and *m*-chloroperoxybenzoic acid, the yield was increased to 82% yield without other regioisomers. For the synthetic efficiency, sodium carbonate is better than copper(II) acetate in our cases during the regiospecific ring expansion. The difference between sodium carbonate and copper(II) acetate was not clear. Next, reduction of the corresponding regioisomer provided aminoalcohol **6**.

As shown in Scheme 2, compound **7** was synthesized via silylation of compound **6** and N-allylation of the resultant product. Further, in order to achieve the synthesis of target compound **1a**, we required a reasonable intermediate **8** for the synthetic manipulation. To this end, compound **7** was treated with desilylation, oxidation, and Wittig olefination to afford diene **8**. To build up the piperidine skeleton, diene **8** was subjected to a ring-closing metathesis employing Grubbs' second catalyst, the expected piperidine ring **9** was generated.[9] Finally, synthesis of α-conhydrine (**1a**) was accomplished via hydrogenation and desulfonation.



Scheme 2.

3. Conclusion

In summary, we succeeded in accomplishing the synthesis of α-conhydrine (**1a**) from *trans*-(2*S*,4*R*)-4-hydroxyproline (**2**) in moderate yields (ca. 18%) via diastereoselective Grignard addition, regioselective Baeyer–Villiger reaction, and ring-closing metathesis as the key steps. Currently studies are in progress in this direction.

4. Experimental

4.1. General

Dichloromethane (DCM) and tetrahydrofuran (THF) were distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo.

4.1.1. 2-(1-Hydroxypropyl)-4-(*tert*-butyldimethylsilanyloxy)-1-(4-methylphenylsulfonyl)pyrrolidine (4). A stirred solution of oxalyl chloride (400 mg, 3.15 mmol) in dichloromethane (20 mL) was mixed with dimethyl sulfoxide (400 mg, 5.1 mmol) at −78 °C. The solution was warmed to −40 °C for 15 min and recooled to −78 °C, and then a solution of prolinol **3** (385 mg, 1.0 mmol) in dichloromethane (10 mL) was added dropwise for 90 min followed by excess triethylamine (4 mL, 28.5 mmol) for 30 min. The reaction mixture was warmed to rt and poured into aqueous ammonium chloride solution (15%, 2 mL), and concentrated under reduced pressure. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine and water, dried, filtered, and concentrated under reduced pressure to produce crude aldehyde. Without further purification, a solution of ethylmagnesium bromide (1.0 M in tetrahydrofuran, 1.5 mL, 1.5 mmol) was added to a stirred solution of resulting aldehyde in tetrahydrofuran (20 mL) at −78 °C. The reaction mixture was stirred at rt for 2 h. Saturated sodium bicarbonate solution (1 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. Water (3 mL) and ethyl acetate (10 mL) was added to the residue and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=4/1) afforded alcohol **4** (372 mg, 90% of two steps). $[\alpha]_D^{29}$ −46.54 (*c* 0.104, $CHCl_3$); IR ($CHCl_3$) 3503, 2955, 1598, 1343, 1090, 836 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{36}NO_4SSi$ (M^++1) 414.2134, found 414.2133; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.0 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 4.28–4.25 (m, 1H), 4.14–4.11 (m, 1H), 3.60 (dd, *J*=4.0, 11.5 Hz, 1H), 3.60–3.57 (m, 1H), 3.27 (ddd, *J*=2.0, 4.0, 11.5 Hz, 1H), 2.46 (d, *J*=4.0 Hz, 1H), 2.42 (s, 3H), 2.07–2.01 (m, 1H), 1.61–1.57 (m, 1H), 1.47–1.40 (m, 1H), 1.38–1.30 (m, 1H), 1.02 (t, *J*=7.0 Hz, 3H), 0.71 (s, 9H), −0.08 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.54, 133.84, 129.66 (2×), 127.83

(2×), 72.92, 69.80, 63.62, 58.62, 35.08, 25.76, 25.65 (3×), 21.49, 17.94, 10.79, −4.93, −5.05; Anal. Calcd for $C_{20}H_{35}NO_4SSi$: C, 58.07; H, 8.53; N, 3.39. Found: C, 58.39; H, 8.21; N, 3.58.

4.1.2. 2-(1-Benzyloxypropyl)-1-(4-methylphenylsulfonyl) pyrrolidin-4-one (5). A solution of compound **4** (415 mg, 1.0 mmol) in tetrahydrofuran (5 mL) was added to a rapidly stirred suspension of sodium hydride (60%, 100 mg, 2.5 mmol) in tetrahydrofuran (10 mL). After the reaction mixture was stirred at rt for 10 min, a solution of benzyl bromide (200 mg, 1.16 mmol) in tetrahydrofuran (2 mL) was added. The reaction mixture was stirred at rt for 20 h, and poured into aqueous ammonium chloride solution (15%, 2 mL), and concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=10/1) afforded benzyl product (432 mg, 86%). $[\alpha]_D^{28}$ −18.89 (*c* 0.01, $CHCl_3$); IR ($CHCl_3$) 2927, 1342, 1090, 755 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{42}NO_4SSi$ (M^++1) 504.2604, found 504.2608; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J*=8.0 Hz, 2H), 7.38–7.26 (m, 7H), 4.81 (d, *J*=11.5 Hz, 1H), 4.72 (d, *J*=11.5 Hz, 1H), 4.39–4.35 (td, *J*=4.5, 10.0 Hz, 1H), 4.08 (t, *J*=7.0 Hz, 1H), 3.69 (t, *J*=7.0 Hz, 1H), 3.56 (dd, *J*=4.5, 10.0 Hz, 1H), 3.07 (dd, *J*=4.5, 10.0 Hz, 1H), 2.43 (s, 3H), 2.21–2.16 (m, 1H), 1.51–1.45 (m, 2H), 1.40–1.33 (m, 1H), 0.99 (t, *J*=7.5 Hz, 3H), 0.72 (s, 9H), −0.12 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.25, 139.21, 134.33, 129.60 (2×), 128.23 (2×), 127.82 (2×), 127.78 (2×), 127.36, 82.48, 74.38, 70.39, 62.62, 56.69, 34.74, 26.06, 25.72 (3×), 21.49, 18.03, 10.68, −5.01, −5.10; Anal. Calcd for $C_{27}H_{41}NO_4SSi$: C, 64.37; H, 8.20; N, 2.78. Found: C, 64.66; H, 8.08; N, 2.98. A solution of tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 1.2 mL, 1.2 mmol) in tetrahydrofuran (2 mL) was added to a solution of benzyl compound (400 mg, 0.8 mmol) in tetrahydrofuran (5 mL) at rt. The reaction mixture was stirred at rt for 2 h, and poured into aqueous ammonium chloride solution (15%, 2 mL), and concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=2/1) afforded alcohol product (285 mg, 92%). $[\alpha]_D^{29}$ −32.35 (*c* 0.011, $CHCl_3$); IR ($CHCl_3$) 3501, 2933, 1338, 1156, 1090 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{28}NO_4S$ (M^++1) 390.1739, found 390.1741; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.5 Hz, 2H), 7.35–7.26 (m, 7H), 4.79 (d, *J*=11.5 Hz, 1H), 4.71 (d, *J*=11.5 Hz, 1H), 4.33 (br s, 1H), 4.03 (ddd, *J*=2.0, 5.5, 8.0 Hz, 1H), 3.85 (td, *J*=2.0, 8.0 Hz, 1H), 3.48 (dd, *J*=4.0, 12.0 Hz, 1H), 3.36 (dt, *J*=2.0, 12.0 Hz, 1H), 2.43 (s, 3H), 2.25 (ddd, *J*=4.5, 7.0, 12.5 Hz, 1H), 1.69–1.64 (m, 1H), 1.51–1.32 (m, 2H), 1.13–1.11 (m, 1H), 0.96 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.65, 139.07, 134.69, 129.64 (2×), 128.29 (2×), 127.83 (2×), 127.75 (2×), 127.45, 82.35, 74.35, 70.61, 62.43, 56.95, 34.08, 25.82, 21.55, 10.61; Anal. Calcd for $C_{21}H_{27}NO_4S$: C, 64.75; H, 6.99; N, 3.60. Found: C, 64.58; H, 7.20; N, 3.88. A solution of alcohol product (390 mg, 1.0 mmol) in dichloromethane (5 mL) was added to a mixture of pyridinium chlorochromate (431 mg, 2.0 mmol) and Celite (1.0 g) in dichloromethane (20 mL). After being stirred at rt for 20 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered, and evaporated to yield crude compound. Purification on silica gel (hexane/ethyl acetate=5/1) afforded ketone **5** (320 mg, 83%). $[\alpha]_D^{29}$ +32.47 (*c* 0.023, $CHCl_3$); IR ($CHCl_3$) 2955, 1763, 1307, 1158, 1063, 697 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{26}NO_4S$ (M^++1) 388.1583, found 388.1586; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.5 Hz, 2H), 7.34–7.25 (m, 5H), 7.18 (d, *J*=7.0 Hz, 2H), 4.60 (d, *J*=12.0 Hz, 1H), 4.44 (d, *J*=12.0 Hz, 1H), 4.29 (dt, *J*=2.0, 9.5 Hz, 1H), 3.81 (td, *J*=2.0, 7.0 Hz, 1H), 3.69 (d, *J*=17.5 Hz, 1H), 3.64 (d, *J*=17.5 Hz, 1H), 2.50 (d, *J*=17.5 Hz, 1H), 2.44 (s, 3H), 2.10 (dd, *J*=9.5, 17.0 Hz, 1H), 1.65–1.58 (m, 1H), 1.42–1.33 (m, 1H), 0.98 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.13, 144.16, 138.05, 135.31, 130.12 (2×), 128.38 (2×), 127.59, 127.13 (2×), 127.09 (2×), 84.11, 72.89, 59.87, 53.37, 37.10, 24.60, 21.55, 10.06; Anal. Calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 65.48; H, 6.78; N, 3.32. Single-crystal X-ray diagram: crystal of ketone **5** was grown by slow diffusion of ethyl acetate into a solution of ketone **5** in dichloromethane to yield colorless prism. The compound crystallizes in the monoclinic crystal system. space group *P*21(#4), *a*=7.9147(16) Å, *b*=6.1920(12) Å, *c*=21.110(4) Å, *V*=1033.5(4) $Å^3$, *Z*=2, d_{calcd}=1.245 mg/m^3, absorption coefficient=0.182 mm^{-1}, *F*(000)=412, 2θ range (1.93–26.00°).

4.1.3. 4-Benzyloxy-3-(4-methylphenylsulfonylamino) hexan-1-ol (6). A solution of *m*-chloroperoxybenzoic acid (75%, 600 mg, 2.6 mmol) in dichloromethane (10 mL) was added to a solution of ketone **5** (390 mg, 1.0 mmol) and sodium carbonate (420 mg, 4.0 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at rt for 20 h. Saturated sodium carbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=4/1 to 2/1) afforded lactone product (330 mg, 82%). $[\alpha]_D^{29}$ −102.74 (*c* 0.008, $CHCl_3$); IR ($CHCl_3$) 2923, 1764, 1352, 1156, 998 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{21}H_{26}NO_5S$ 404.1532, found 404.1538; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J*=8.5 Hz, 2H), 7.39–7.31 (m, 7H), 5.79 (d, *J*=11.5 Hz, 1H), 5.17 (d, *J*=11.5 Hz, 1H), 4.76 (d, *J*=11.0 Hz, 1H), 4.67 (d, *J*=11.0 Hz, 1H), 3.97 (td, *J*=2.0, 7.0 Hz, 1H), 3.73 (ddd, *J*=2.0, 7.0, 10.0 Hz, 1H), 2.96 (dd, *J*=11.0, 16.0 Hz, 1H), 2.43 (s, 3H), 2.42 (dd, *J*=7.0, 16.0 Hz, 1H), 1.64–1.55 (m, 1H), 1.39–1.30 (m, 1H), 0.98 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.11, 144.94, 138.05, 134.53, 130.14 (2×), 128.55 (2×), 127.96, 127.93 (2×), 127.86 (2×), 83.47, 75.76, 74.32, 53.95, 28.19, 24.08, 21.64, 10.13; Anal. Calcd for $C_{21}H_{25}NO_5S$: C, 62.51; H, 6.25; N, 3.47. Found: C, 62.83; H, 6.58; N, 3.60. A solution of the resulting product (310 mg, 0.77 mmol) in tetrahydrofuran (10 mL) was added to a rapidly stirred suspension of lithium aluminum hydride (76 mg, 2.0 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h. Aqueous ammonium chloride solution (15%, 2 mL) was added to the reaction mixture

and filtered through a short silica gel column. The filtrate was dried, filtered, and evaporated to yield crude compound. Purification on silica gel (hexane/ethyl acetate=5/1) afforded aminoalcohol **6** (273 mg, 94%). $[\alpha]_D^{29}$ −46.75 (*c* 0.015, $CHCl_3$); IR ($CHCl_3$) 3290, 2962, 1598, 1325, 1160, 815 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{20}H_{28}NO_4S$ 378.1739, found 378.1742; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J*=8.0 Hz, 2H), 7.41–7.34 (m, 4H), 7.25–7.22 (m, 3H), 4.89 (d, *J*=9.5 Hz, 1H), 4.55 (d, *J*=12.0 Hz, 1H), 4.18 (d, *J*=12.0 Hz, 1H), 3.88–3.82 (m, 1H), 3.69–3.64 (m, 1H), 3.49–3.43 (m, 1H), 2.89–2.86 (m, 1H), 2.64 (dd, *J*=6.0, 7.0 Hz, 1H), 2.42 (s, 3H), 1.74–1.67 (m, 1H), 1.65–1.55 (m, 2H), 1.38–1.29 (m, 1H), 0.70 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.39, 138.08, 137.38, 129.62 (2×), 128.70 (2×), 128.03, 127.76 (2×), 126.97 (2×), 81.57, 71.36, 58.18, 51.67, 30.38, 22.56, 21.51, 9.58; Anal. Calcd for $C_{20}H_{27}NO_4S$: C, 63.63; H, 7.21; N, 3.71. Found: C, 63.28; H, 7.56; N, 3.46.

4.1.4. *N*-Allyl-*N*-{2-benzyloxy-1-[2-(*tert*-butyldimethylsilanyloxy)ethyl]butyl}-4-methylbenzenesulfonamide (7). *tert*-Butyldimethylsilyl chloride (150 mg, 1.0 mmol) and imidazole (136 mg, 2.0 mmol) were added to a stirred solution of compound **6** (300 mg, 0.8 mmol) in dimethylforamide (5 mL) at rt. The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with saturated sodium bicarbonate solution and brine, dried, filtered, and evaporated under reduced pressure to yield crude product. Purification on silica gel (hexane/ethyl acetate=5/1) afforded silyl product (375 mg, 96%). HRMS (ESI) *m/z* calcd for $C_{26}H_{42}NO_4SSi$ (M^++1) 492.2604, found 492.2606; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J*=8.0 Hz, 2H), 7.37–7.24 (m, 7H), 5.31 (d, *J*=7.5 Hz, 1H), 4.54 (d, *J*=11.5 Hz, 1H), 4.35 (d, *J*=11.5 Hz, 1H), 3.62–3.57 (m, 1H), 3.53–3.48 (m, 1H), 3.46–3.41 (m, 1H), 3.36–3.33 (m, 1H), 2.42 (s, 3H), 1.69–1.54 (m, 3H), 1.49–1.40 (m, 1H), 0.89 (s, 9H), 0.85 (t, *J*=7.5 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.06, 138.54, 137.93, 129.52 (2×), 128.42 (2×), 127.65 (3×), 127.16 (2×), 81.88, 72.02, 60.21, 53.68, 31.03, 25.86 (3×), 23.08, 21.51, 18.11, 9.63, −5.49, −5.53; Anal. Calcd for $C_{26}H_{41}NO_4SSi$: C, 63.50; H, 8.40; N, 2.85. Found: C, 63.77; H, 8.22; N, 2.70. A solution of silyl compound (350 mg, 0.71 mmol) in dimethylforamide (2 mL) was added to a rapidly stirred suspension of sodium hydride (60%, 100 mg, 2.5 mmol) in dimethylforamide (3 mL). After the reaction mixture was stirred at ice bath for 5 min, allyl bromide (250 mg, 2.1 mmol) was added at ice bath. The resulting mixture was stirred at rt for 3 h. The reaction was quenched with 15% ammonium chloride solution (1 mL) and the mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with saturated sodium bicarbonate solution and brine, dried, filtered, and evaporated under reduced pressure to yield crude product. Purification on silica gel (hexane/ethyl acetate=10/1) afforded compound **7** (367 mg, 97%) as viscous oil. $[\alpha]_D^{29}$ −27.78 (*c* 0.011, $CHCl_3$); IR ($CHCl_3$) 2928, 1462, 1340, 1255, 1162, 1027, 835 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{46}NO_4SSi$ (M^++1) 532.2917, found 532.2920; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.0 Hz, 2H), 7.34–7.25 (m, 7H), 5.81–5.73 (m, 1H), 5.10 (d, *J*=17.0 Hz, 1H), 5.02 (d, *J*=10.0 Hz, 1H), 4.55 (d, *J*=11.5 Hz, 1H), 4.36 (d, *J*=11.5 Hz, 1H), 4.02 (dd, *J*=6.5, 16.0 Hz, 1H), 3.97 (dt, *J*=4.0, 9.5 Hz, 1H), 3.89 (dd, *J*=6.5, 16.0 Hz, 1H), 3.49–3.46 (m, 1H), 3.44–3.40 (m, 1H), 3.36–3.31 (m, 1H), 2.42 (s, 3H), 1.88–1.82 (m, 1H), 1.80–1.73 (m, 1H), 1.70–1.63 (m, 1H), 1.60–1.52 (m, 1H), 0.94 (t, *J*=7.5 Hz, 3H), 0.87 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.94, 138.44, 138.33, 136.06, 129.41 (2×), 128.29 (2×), 127.50 (2×), 127.48, 127.45 (2×), 117.01, 84.10, 71.48, 60.50, 56.50, 47.32, 30.75, 25.88 (3×), 24.01, 21.49, 18.20, 9.78, −5.38, −5.42; Anal. Calcd for $C_{29}H_{45}NO_4SSi$: C, 65.49; H, 8.53; N, 2.63. Found: C, 65.83; H, 8.62; N, 2.44.

4.1.5. *N*-Allyl-*N*-[1-(1-benzyloxypropyl)but-3-enyl]-4-methylbenzenesulfonamide (8). A solution of tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 1.2 mL, 1.2 mmol) in tetrahydrofuran (2 mL) was added to a solution of compound **7** (530 mg, 1.0 mmol) in tetrahydrofuran (20 mL) at rt. The reaction mixture was stirred at rt for 2 h, and poured into aqueous ammonium chloride solution (15%, 2 mL), and concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=4/1) afforded alcohol product (410 mg, 99%). HRMS (ESI) *m/z* calcd for $C_{23}H_{32}NO_4S$ (M^++1) 418.2052, found 418.2055; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J*=8.5 Hz, 2H), 7.34–7.24 (m, 7H), 5.88–5.80 (m, 1H), 5.09 (dd, *J*=1.5, 17.5 Hz, 1H), 5.05 (dd, *J*=1.0, 10.0 Hz, 1H), 4.54 (d, *J*=11.5 Hz, 1H), 4.27 (d, *J*=11.5 Hz, 1H), 4.06 (dd, *J*=7.5, 16.0 Hz, 1H), 3.96 (dt, *J*=3.5, 10.0 Hz, 1H), 3.92 (dd, *J*=10.0, 16.0 Hz, 1H), 3.71–3.65 (m, 1H), 3.64–3.58 (m, 1H), 3.19 (dt, *J*=4.5, 8.5 Hz, 1H), 2.56 (dd, *J*=5.0, 7.5 Hz, 1H), 2.44 (s, 3H), 1.89–1.77 (m, 2H), 1.61–1.53 (m, 1H), 1.16–1.37 (m, 1H), 0.48 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.37, 138.02, 137.97, 136.02, 129.60 (2×), 128.37 (2×), 127.66, 127.51 (2×), 127.29 (2×), 117.43, 82.91, 71.00, 58.59, 55.95, 47.29, 29.58, 23.56, 21.53, 9.80; Anal. Calcd for $C_{23}H_{31}NO_4S$: C, 66.16; H, 7.48; N, 3.35. Found: C, 66.39; H, 7.62; N, 3.71. A solution of alcohol product (420 mg, 1.0 mmol) in dichloromethane (5 mL) was added to a mixture of pyridinium chlorochromate (431 mg, 2.0 mmol) and Celite (1.0 g) in dichloromethane (20 mL). After being stirred at rt for 20 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered, and evaporated to yield crude compound. Purification on silica gel (hexane/ethyl acetate=5/1) afforded aldehyde product (364 mg, 87%). $[\alpha]_D^{28}$ −35.20 (*c* 0.013, $CHCl_3$); IR ($CHCl_3$) 3029, 2927, 2733, 1722, 1598, 1398, 1089 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{30}NO_4S$ (M^++1) 416.1896, found 416.1899; ^1H NMR (500 MHz, $CDCl_3$) δ 9.45 (dd, *J*=1.0, 2.5 Hz, 1H), 7.71 (d, *J*=8.0 Hz, 2H), 7.33–7.24 (m, 7H), 5.79–5.71 (m, 1H), 5.10 (d, *J*=9.0 Hz, 1H), 5.09 (d, *J*=18.0 Hz, 1H), 4.53 (d, *J*=11.5 Hz, 1H), 4.42 (dt, *J*=5.0, 8.0 Hz, 1H), 4.33 (d, *J*=11.5 Hz, 1H), 3.94 (dd, *J*=6.0, 16.5 Hz, 1H), 3.65 (dd, *J*=7.0, 16.5 Hz, 1H), 3.55 (dt, *J*=5.0, 7.5 Hz, 1H), 2.61 (dd, *J*=3.0, 8.5, 16.5 Hz, 1H), 2.42 (s, 3H), 2.23 (dd,

J=5.0, 16.5 Hz, 1H), 1.73–1.62 (m, 2H), 0.95 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.68, 143.67, 137.58, 137.21, 135.18, 129.77 (2×), 128.39 (2×), 127.92 (2×), 127.79, 127.32 (2×), 118.01, 80.92, 71.66, 55.12, 48.26, 43.94, 22.70, 21.51, 8.36; Anal. Calcd for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.03; N, 3.37. Found: C, 66.69; H, 7.09; N, 3.49. *n*-Butyllithium (1.6 M in hexane, 1.0 mL, 1.6 mmol) was added to a stirred solution of methyl triphenylphosphonium iodide (808 mg, 2.0 mmol) in tetrahydrofuran (20 mL) at −78 °C. The orange red colored mixture was stirred at −78 °C for 1 h. A solution of aldehyde product (290 mg, 0.7 mmol) in tetrahydrofuran (5 mL) was added to the reaction mixture at −78 °C via a syringe and further stirred at −78 °C for 2 h. The reaction was quenched with aqueous saturated ammonium chloride (10 mL) and the mixture was extracted with diethyl ether (3×20 mL) and the combined organic layers were washed with brine, dried, filtered, and evaporated. Purification on silica gel (hexane/ethyl acetate=2/1) afforded compound **8** (237 mg, 82%). $[\alpha]_D^{28}$ +3.33 (*c* 0.009, $CHCl_3$); IR ($CHCl_3$) 2925, 1455, 1337, 1090, 662 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{32}NO_3S$ (M^++1) 414.2103, found 414.2104; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J=8.5 Hz, 2H), 7.33–7.26 (m, 7H), 5.95–5.77 (m, 1H), 5.52–5.44 (m, 1H), 5.10 (dd, J=1.5, 17.5 Hz, 1H), 5.04 (dd, J=1.5, 10.0 Hz, 1H), 4.92 (dd, J=1.5, 17.5 Hz, 1H), 4.81 (d, J=10.0 Hz, 1H), 4.56 (d, J=11.0 Hz, 1H), 4.38 (d, J=11.0 Hz, 1H), 3.99 (dd, J=6.0, 16.5 Hz, 1H), 3.92 (td, J=5.0, 10.0 Hz, 1H), 3.80 (dd, J=6.5, 16.5 Hz, 1H), 3.47 (dd, J=5.5, 11.5 Hz, 1H), 2.49–2.42 (m, 1H), 2.43 (s, 3H), 2.35–2.28 (m, 1H), 1.71–1.59 (m, 2H), 0.96 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.03, 138.35, 138.16, 136.15, 135.69, 129.32 (2×), 128.33 (2×), 127.60 (2×), 127.55, 127.54 (2×), 116.98, 116.78, 83.20, 71.62, 60.12, 47.39, 32.39, 23.90, 21.49, 9.65; Anal. Calcd for $C_{24}H_{31}NO_3S$: C, 69.70; H, 7.56; N, 3.39. Found: C, 66.91; H, 7.82; N, 3.58.

4.1.6. 2-(1-Benzyloxypropyl)-1-(4-methylphenylsulfonyl)-1,2,3,6-tetrahydropyridine (9). Grubbs' second generation catalyst (30 mg) was added to a solution of compound **8** (210 mg, 0.51 mmol) in dichloromethane (50 mL) at rt. The reaction mixture was refluxed under nitrogen atmosphere for 2 h. The mixture was concentrated and purified by flash column chromatography (hexane/ethyl acetate=4/1) to yield compound **9** (180 mg, 92%). $[\alpha]_D^{28}$ −56.00 (*c* 0.005, $CHCl_3$); IR ($CHCl_3$) 2924, 1598, 1342, 1091, 754 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{28}NO_3S$ (M^++1) 386.1790, found 386.1795; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J=9.0 Hz, 2H), 7.34–7.24 (m, 7H), 5.55–5.52 (m, 2H), 4.59 (d, J=11.5 Hz, 1H), 4.35 (d, J=11.5 Hz, 1H), 4.17 (19.0 Hz, 1H), 4.05 (dd, J=6.5, 9.5 Hz, 1H), 3.60 (dt, J=3.0, 19.0 Hz, 1H), 3.52–3.48 (m, 1H), 2.41 (s, 3H), 2.25 (d, J=18.0 Hz, 1H), 1.89–1.82 (m, 1H), 1.80–1.75 (m, 1H), 1.72–1.63 (m, 1H), 1.04 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.08, 138.26, 137.86, 129.54 (2×), 128.36 (2×), 127.66 (2×), 127.62, 126.93 (2×), 124.22, 122.38, 77.66, 72.21, 51.96, 41.31, 23.01, 22.99, 21.50, 8.26; Anal. Calcd for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.63. Found: C, 68.78; H, 6.91; N, 3.44.

4.1.7. 1-Piperidin-2-yl-propan-1-ol (α-conhydrine, 1a). Compound **9** (80 mg, 0.21 mmol) was dissolved in ethanol (20 mL) and 10% palladium on activated carbon (10 mg) as catalyst was added. Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at rt for 10 h. The mixture was filtered through a short silica gel column. The filtrate was dried, filtered, and evaporated to yield crude compound. Purification on silica gel (hexane/ethyl acetate=5/1) afforded alcohol product (58 mg, 94%). $[\alpha]_D^{28}$ −33.21 (*c* 0.026, $CHCl_3$); IR ($CHCl_3$) 3516, 2935, 1455, 1332, 1092, 933, 658 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{23}NO_3S$ (M^++1) 298.1477, found 298.1481; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J=8.5 Hz, 2H), 7.30 (d, J=8.5 Hz, 2H), 3.85–3.74 (m, 3H), 3.03 (ddd, J=3.0, 13.0, 14.5 Hz, 1H), 2.43 (s, 3H), 1.94–1.91 (m, 1H), 1.82–1.79 (m, 1H), 1.59–1.50 (m, 1H), 1.46–1.37 (m, 3H), 1.26–1.16 (m, 1H), 1.14–1.05 (m, 1H), 1.01 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.97, 138.75, 129.69 (2×), 126.99 (2×), 71.12, 57.14, 42.34, 27.04, 23.42, 23.03, 21.51, 18.84, 10.85; Anal. Calcd for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.79; N, 4.71. Found: C, 60.68; H, 7.94; N, 4.69. Sodium amalgam (Na/Hg, 0.5 g, 6%) and sodium phosphate (71 mg, 0.5 mmol) were added to a stirred solution of *N*-tosylconhydrine (30 mg, 0.1 mmol) in methanol (10 mL), and vigorously stirred for 5 h at rt. The residue was filtered and washed with methanol (2×10 mL) and the combined organic layers were evaporated to afford the crude products. Purification on silica gel (hexane/ethyl acetate=1/1 to 1/2) afforded α-conhydrine (**1a**) (12 mg, 80%). The NMR spectral data of α-conhydrine (**1a**) were in accordance with those reported in the literature.[5g]

Acknowledgements

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Supplementary data

Photocopies of NMR (^{1}H and ^{13}C) spectral data for new compounds were supported. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.004.

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7. CCDC 619412 (compound **5**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
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One-pot three-component reaction of isocyanides, dialkyl acetylenedicarboxylates and phthalhydrazide: synthesis of highly functionalized 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones

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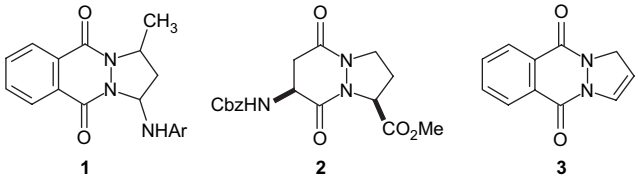
Abstract—Protonation of the highly reactive 1:1 intermediate produced in the reaction between alkyl isocyanides and electron-deficient acetylenic esters with phthalhydrazide, leads to a vinylisonitrilium cation, which undergoes an addition reaction with the conjugate base of the phthalhydrazide to produce dialkyl 3-(alkylamino)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylates in fairly good yields at room temperature.

1. Introduction

Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications to biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more and more important.[1] The development of new efficient methods to synthesize *N*-heterocycles with structural diversity is one major interest of modern synthetic organic chemists.[2] Among a large variety of nitrogen-containing heterocyclic compounds, heterocycles containing bridgehead hydrazine have received considerable attention because of their pharmacological properties and clinical applications.[3] For example, 1-arylamino-2,3-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives **1** were reported to possess antiinflammatory, analgesic, antihypoxic, and antipyretic properties.[4] Furthermore, pyrazolidine compounds have been converted into azaproline amino acids, which have been studied upon incorporation into traditional peptides as well as small molecule peptidomimetics **2**.[5]

So far, only a few procedures have been described in the literature for the preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione skeleton **3**. In 1937, Drew and Hatt reported the first synthesis of this triheterocyclic structure via the reaction between phthalhydrazide and cinnamaldehyde.[6] Recently, Sinkkonen and co-workers reexamined the cycloaddition reactions of cyclic hydrazides of dicarboxylic acids (such as maleic and phthalic acids) and α,β-unsaturated carbonyl compounds leading to the formation of 1-amino-2,3-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones. They also studied their structures by NMR and mass spectrometric methods and theoretical calculations.[7] Moreover, the oxidation of phthalhydrazide with lead tetraacetate in the presence of furfural derivatives in methylene chloride afforded 5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]-phthalazine-1-carboxylic acids in moderate yields (Scheme 1).[8]



1 **2** **3**

Scheme 1.

The nucleophilic addition of alkyl or aryl isocyanides to electron-deficient acetylenic esters such as dimethyl acetylenedicarboxylate (DMAD) is well documented.[9] It has been shown that alkyl or aryl isocyanides add to dialkyl acetylenedicarboxylates to generate zwitterionic species, which serve as intermediates in many different reactions.[10–13] Recently, these highly reactive zwitterionic intermediates have been captured by suitable CH–,[11] NH–,[12] and OH-acids[13] substrates such as (ethoxycarbonylmethyl)triphenylphosphonium bromide,[11j] 1,2-diacylhydrazines,[12f] and benzoic acids,[13d] which produced *N*-alkyl-2-triphenylphosphoranylidene glutarimides, 1*H*-pyrazoles and butenedioate derivatives, respectively.

Keywords: Dialkyl acetylenedicarboxylate; Isocyanide; Multicomponent reaction; Phthalhydrazide; 1*H*-Pyrazolo[1,2-*b*]phthalazine.
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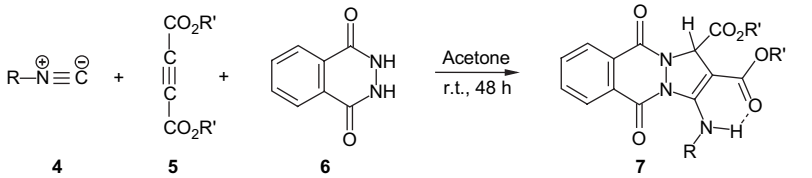
In an extension of our continuing efforts[11i,12a,b,14] on the application of isocyanide-based multicomponent reactions in heterocyclic synthesis, starting with the compounds containing –CH, –NH or –OH acidic group, herein the synthesis of some fused pyrazolophthalazine heterocycles, is reported.

Phthalhydrazide (2,3-dihydro-1,4-phthalazinedione) is a very interesting fused heterobicyclic compound, which has two rather NH-acidic protons.[15] In the present study, this was taken advantage in the formation of the polyfunctional pyrazolophthalazine derivatives incorporating 1*H*-pyrazolo-[1,2-*b*]phthalazine-5,10-dione substructure via a three-component condensation reaction of isocyanides.

2. Results and discussion

The one-pot three-component condensation reactions of alkyl isocyanides **4** with dialkyl acetylenedicarboxylates **5** in the presence of phthalhydrazide **6** proceeded at room temperature in dry acetone and were complete after 48 h to afford corresponding dialkyl 3-(alkylamino)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylates **7**, in moderate to good yields (51–77%). ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of fused pyrazolophthalazine **7**. Any other products could not be detected by NMR spectroscopy. The structures of the products **7a**–**h** were deduced from their elemental analyses and IR, ^{1}H NMR, and ^{13}C NMR spectra (Scheme 2).

The mechanism of this reaction has not been established experimentally, a likely mechanism for the formation of these heterocycles **7** is shown in Scheme 3. In a first step, nucleophilic attack of the isocyanide to the acetylenic ester and subsequent protonation of the highly reactive 1:1 zwitterionic intermediate by NH-acid (phthalhydrazide) affords the vinylisonitrilium cation **8**. Then, vinylisonitrilium cation

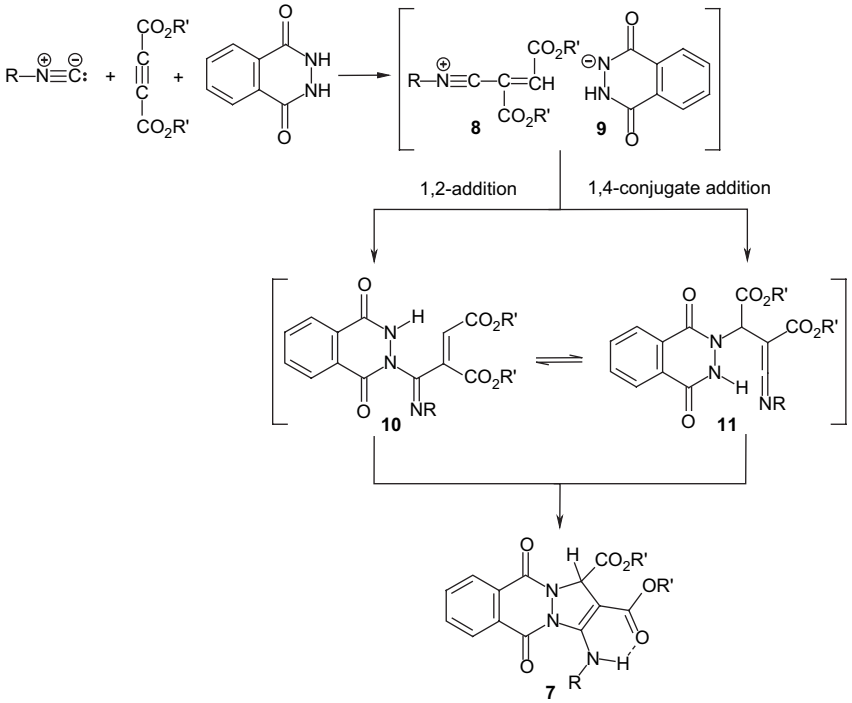


4 **5** **6** **7**

	R	R'
4a	*tert*-Octyl	**5a** Methyl
4b	*tert*-Butyl	**5b** Ethyl
4c	Cyclohexyl	**5c** *tert*-Butyl

	R	R'	Yield (%)
7a	*tert*-Octyl	Methyl	61
7b	*tert*-Butyl	Methyl	57
7c	Cyclohexyl	Methyl	77
7d	*tert*-Octyl	Ethyl	55
7e	*tert*-Butyl	Ethyl	63
7f	Cyclohexyl	Ethyl	69
7g	*tert*-Butyl	*tert*-Butyl	51
7h	Cyclohexyl	*tert*-Butyl	60

Scheme 2.



8 **9** **10** **11** **7**

Scheme 3.

8 could undergo addition reactions with the nitrogen atom of the conjugate base of the NH-acid **9** on the two possible electrophilic sites (1,2-addition and 1,4-conjugate addition) to produce two possible intermediates **10** and **11** in equilibrium with each other. These intermediates can then cyclize under the reaction conditions employed to produce the dialkyl 3-(alkylamino)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylates **7** (Scheme 3).

In summary, the one-pot three-component condensation reaction of alkyl isocyanides with dialkyl acetylenedicarboxylates in presence of phthalhydrazide can be successfully applied to the synthesis of dialkyl 3-(alkylamino)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylate derivatives. To the best of our knowledge, this new procedure provides the first example of the efficient synthetic method for 5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylate ring systems by formation of three bonds.

3. Experimental

3.1. General

Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN–O-Rapid analyzer. FT-IR Spectra were recorded on a Bruker Equinox-55 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer at 400.13 and 100.77 MHz, respectively, with $CDCl_3$ as solvent. The solvents, dimethyl and diethyl acetylenedicarboxylates, cyclohexyl and 1,1,3,3-tetramethylbutyl (*tert*-octyl) isocyanides used in this work were purchased from Merck and the *tert*-butyl isocyanide, and di-*tert*-butylacetylenedicarboxylate were obtained from Fluka (Buchs, Switzerland). The benzyl isocyanide and phthalhydrazide were obtained from Aldrich chemical company. All reagents were used without further purification.

3.2. Typical procedure for preparation of dimethyl 3-[(1,1,3,3-tetramethylbutyl)amino]-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylate (7a)

To a magnetically stirred solution of phthalhydrazide (0.081 g, 0.5 mmol) and *tert*-octyl isocyanide (0.070 g, 0.5 mmol) in dry acetone (40 mL) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.071 g, 0.5 mmol) in acetone (2 mL) at room temperature over 10 min via a syringe. The reaction mixture was stirred at room temperature for 48 h. The solvent was removed under reduced pressure and the solid residue was washed with diethyl ether and crystallized from CH_2Cl_2/*n*-hexane (1:3) to give **7a** as yellow crystals (0.136 g, 61%).

Mp 239–242°C (dec); IR (KBr) (ν_{max}, cm^{-1}): 3180 (N–H), 1740, 1662 and 1635 (C=O), 1576 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 1.06 (9H, s, $C(CH_3)_3$), 1.49 and 1.54 (6H, 2s, $C(CH_3)_2$), 1.76 and 2.14 (2H, AB system, $^2J_{HH}$=14.9 Hz, CH_2), 3.74 and 3.79 (6H, 2s, $2OCH_3$), 5.76 (1H, s, NCH), 7.86 and 8.32 (4H, 2m, C_6H_4), 9.04 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 29.01 (C*Me*$_2$), 30.74 (2*C*Me$_3$), 31.65 (C*Me*$_3$), 51.20 (CH_2), 52.94 and 52.96 ($2OCH_3$), 61.23 (*C*Me$_2$), 62.40 (N–CH), 81.00 (*C*=C–N), 127.43, 127.82, 128.22, 129.39, 133.75 and 134.53 (C_6H_4), 149.39 (=*C*–N), 154.21, 158.09, 163.68, 169.77 (4C=O). Anal. Calcd for $C_{23}H_{29}N_3O_6$ (443.49): C, 62.29; H, 6.59; N, 9.47%. Found: C, 62.35; H, 6.65; N, 9.44%.

3.2.1. Dimethyl 3-(*tert*-butylamino)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylate (7b). Yellow prisms (0.111 g, 57%); mp 181–183°C (dec); IR (KBr) (ν_{max}, cm^{-1}): 3178 (N–H), 1736, 1711 and 1657 (C=O), 1594 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 1.52 (9H, s, $C(CH_3)_3$), 3.71 and 3.77 (6H, 2s, $2OCH_3$), 5.69 (1H, s, NCH), 7.84 and 8.32 (4H, 2m, C_6H_4), 8.97 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 29.95 (C*Me*$_3$), 51.42 and 52.96 ($2OCH_3$), 57.54 (*C*Me$_3$), 62.64 (N–CH), 81.87 (*C*=C–N), 127.37, 127.80, 128.25, 129.40, 133.73 and 134.47 (C_6H_4), 149.64 (=*C*–N), 154.50, 157.91, 163.33, 169.14 (4C=O). Anal. Calcd for $C_{19}H_{21}N_3O_6$ (387.38): C, 58.91; H, 5.46; N, 10.85%. Found: C, 59.01; H, 5.44; N, 10.80%.

3.2.2. Dimethyl 3-(cyclohexylamino)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylate (7c). Yellow prisms (0.160 g, 77%); mp 171–173°C (dec); IR (KBr) (ν_{max}, cm^{-1}): 3176 (N–H), 1748, 1710 and 1660 (C=O), 1599 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 1.26–2.06 (10H, m, $5CH_2$), 3.69 and 3.76 (6H, 2s, $2OCH_3$), 4.38 (NHC*H*), 5.66 (1H, s, NCH), 7.83 and 8.27 (4H, 2m, C_6H_4), 8.98 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 24.08, 24.28, 25.49, 33.13 and 33.67 ($5CH_2$), 51.17 and 52.90 ($2OCH_3$), 53.94 (NH–CH), 62.29 (N–CH), 77.92 (*C*=C–N), 127.45, 127.76, 128.20, 129.09, 133.78 and 134.61 (C_6H_4), 149.83 (=*C*–N), 154.09, 157.84, 162.99, 169.93 (4C=O). Anal. Calcd for $C_{21}H_{23}N_3O_6$ (413.42): C, 61.01; H, 5.61; N, 10.16%. Found: C, 59.92; H, 5.60; N, 10.11%.

3.2.3. Diethyl 3-[(1,1,3,3-tetramethylbutyl)amino]-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylate (7d). Yellow prisms (0.130 g, 55%); mp 223–225°C (dec); IR (KBr) (ν_{max}, cm^{-1}): 3189 (N–H), 1744, 1668 and 1609 (C=O), 1588 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 1.08 (9H, s, $C(CH_3)_3$), 1.26 and 1.31 (6H, 2t, $^3J_{HH}$=7.0 Hz, $2OCH_2CH_3$), 1.50 and 1.54 (6H, 2s, $C(CH_3)_2$), 1.77 and 2.12 (2H, AB system, $^2J_{HH}$=15.0 Hz, CH_2), 4.18–4.24 (4H, m, $2ABX_3$ overlapping systems, $2OCH_2CH_3$), 5.86 (1H, s, NCH), 7.88 and 8.32 (4H, 2m, C_6H_4), 8.98 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 14.10 and 14.44 ($2OCH_2CH_3$), 28.97 (C*Me*$_2$), 30.81 (2*C*Me$_3$), 31.70 (C*Me*$_3$), 50.11 (CH_2), 60.02 and 62.21 ($2OCH_2$), 62.23 (*C*Me$_2$), 62.48 (N–CH), 82.23 (*C*=C–N), 127.44, 127.85, 128.41, 129.35, 133.81 and 134.52 (C_6H_4), 149.47 (=*C*–N), 154.90, 159.02, 164.31, 169.80 (4C=O). Anal. Calcd for $C_{25}H_{33}N_3O_6$ (471.55): C, 63.68; H, 7.05; N, 8.91%. Found: C, 63.74; H, 6.99; N, 8.90%.

3.2.4. Diethyl 3-(*tert*-butylamino)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylate (7e). Yellow prisms (0.131 g, 63%); mp 232–234°C (dec); IR (KBr) (ν_{max}, cm^{-1}): 3185 (N–H), 1744, 1712 and 1661 (C=O), 1604 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 1.28 and 1.29 (6H, 2t, $^3J_{HH}$=7.0 Hz, $2OCH_2CH_3$), 1.50 (9H, s,

$C(CH_3)_3$), 4.18–4.24 (4H, m, $2ABX_3$ overlapping systems, $2OCH_2CH_3$), 5.74 (1H, s, NCH), 7.84 and 8.31 (4H, 2m, C_6H_4), 8.77 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 14.12 and 14.43 ($2OCH_2CH_3$), 29.95 (CMe_3), 57.50 (CMe_3), 59.98 and 61.93 ($2OCH_2$), 62.53 (N–CH), 82.27 (C=C–N), 127.42, 127.78, 128.26, 129.40, 133.71 and 134.45 (C_6H_4), 149.74 (=C–N), 154.33, 157.93, 163.29, 169.23 (4C=O). Anal. Calcd for $C_{21}H_{25}N_3O_6$ (415.44): C, 60.71; H, 6.07; N, 10.11%. Found: C, 60.74; H, 6.02; N, 10.08%.

3.2.5. Diethyl 3-(cyclohexylamino)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylate (7f). Yellow prisms (0.153 g, 69%); mp 208–210°C (dec); IR (KBr) (ν_{max}, cm^{-1}): 3204 (N–H), 1740, 1708 and 1656 (C=O), 1574 (C=C). ^1H NMR ($CDCl_3$): δ_H 1.26 and 1.31 (6H, 2t, $^3J_{HH}$=7.0 Hz, $2OCH_2CH_3$), 1.28–2.05 (10H, m, $5CH_2$), 4.11–4.25 (4H, m, $2ABX_3$ overlapping systems, $2OCH_2CH_3$), 4.43 (NH–CH), 5.70 (1H, s, NCH), 7.80 and 8.28 (4H, 2m, C_6H_4), 9.01 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 14.14 and 14.42 ($2OCH_2CH_3$), 24.10, 24.28, 25.47, 33.16 and 33.59 ($5CH_2$), 60.18 and 61.90 ($2OCH_2$), 54.01 (NH–CH), 62.40 (N–CH), 79.23 (C=C–N), 127.44, 127.81, 128.23, 128.98, 133.80 and 134.56 (C_6H_4), 149.88 (=C–N), 155.11, 157.81, 163.06, 170.02 (4C=O). Anal. Calcd for $C_{23}H_{27}N_3O_6$ (441.48): C, 62.57; H, 6.16; N, 9.52%. Found: C, 62.60; H, 6.10; N, 9.50%.

3.2.6. Di(*tert*-butyl) 3-(*tert*-butylamino)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylate (7g). Yellow prisms (0.121 g, 51%); mp 163–165°C (dec); IR (KBr) (ν_{max}, cm^{-1}): 3171 (N–H), 1743, 1710 and 1651 (C=O), 1589 (C=C). ^1H NMR ($CDCl_3$): δ_H 1.18, 1.25, 1.50 (27H, s, $3C(CH_3)_3$), 5.61 (1H, s, NCH), 7.82 and 8.30 (4H, 2m, C_6H_4), 8.80 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 27.87, 28.11 and 29.86 ($3CMe_3$), 57.56 ($NCMe_3$), 62.60 (N–CH), 79.25 (C=C–N), 127.38, 127.79, 128.31, 129.39, 133.70 and 134.48 (C_6H_4), 148.53 (=C–N), 154.21, 157.84, 164.09, 169.30 (4C=O). Anal. Calcd for $C_{25}H_{33}N_3O_6$ (471.55): C, 63.68; H, 7.05; N, 8.91%. Found: C, 63.74; H, 7.04; N, 8.87%.

3.2.7. Di(*tert*-butyl) 3-(cyclohexylamino)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-1,2-dicarboxylate (7h). Yellow prisms (0.150 g, 60%); mp 199–201°C (dec); IR (KBr) (ν_{max}, cm^{-1}): 3188 (N–H), 1735, 1709 and 1648 (C=O), 1587 (C=C). ^1H NMR ($CDCl_3$): δ_H 1.18–2.04 (10H, m, $5CH_2$), 1.23 and 1.47 (18H, 2s, $2C(CH_3)_3$), 4.40 (NHCH), 5.59 (1H, s, NCH), 7.81 and 8.28 (4H, 2m, C_6H_4), 8.81 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 24.08, 24.28, 25.49, 33.13 and 33.67 ($5CH_2$), 27.15 and 27.26 (CMe_3), 54.12 (NH–CH), 62.36 (N–CH), 81.49 (C=C–N), 81.79 and 84.80 (CMe_3), 127.44, 127.78, 128.23, 129.09, 133.79 and 134.62 (C_6H_4), 149.91 (=C–N), 155.04, 157.88, 162.90, 169.86 (4C=O). Anal. Calcd for $C_{27}H_{35}N_3O_6$ (497.58): C, 65.17; H, 7.09; N, 8.44%. Found: C, 65.23; H, 7.06; N, 8.43%.

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A new method of constructing dearomatized compounds using triazene

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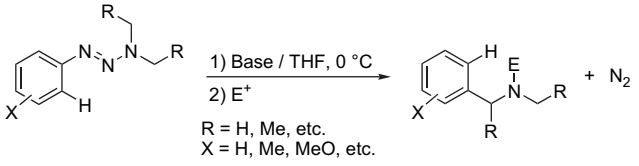
Abstract—We are reporting on a new method of constructing dearomatized compounds from α-substituted aryltriazenes. Deprotonation occurs at C atom α to N3. Nucleophilic attack of generated anion at the *ortho*-position of aryl group forms a new carbon–carbon bond. A stereoselective reaction was observed when the substituents on the C α to N3 are tied together in either a pyrrolidine or a piperidine. The product of this reaction possessed an interesting dearomatized tetrahydrobenzotriazine framework.

1. Introduction

Destroying the aromaticity of a benzene ring is a powerful strategy for the synthesis of cyclohexane derivatives. The Birch reduction,[1] Reimer–Tiemann,[2] and Alder reactions[3] are well-known methods of constructing dearomatized compounds. Recently some new methods have been reported: oxidation with *Pseudomonas putida*;[4] electrophilic addition of an osmium–arene complex;[5] nucleophilic addition to a chromium–arene complex;[6] an aluminum tris(2,6-diphenylphenoxide) (ATPH)-promoted nucleophilic addition to aromatic aldehydes and ketones;[7] radical cyclization;[8] the thia-Sommelet reaction;[9] anion cyclization of *N*-benzylbenzamides;[10] and phosphoramides.[11] 3,3-Dialkyl-1-aryltriazenes are also used in many ways in organic syntheses.[12] We previously reported on the transformation of aryltriazene compounds to benzylamine derivatives including an intramolecular C–C bond formation with N_2 releasing and discussed the preliminary results of the dearomatization reaction of aryltriazenes (Scheme 1).[13]

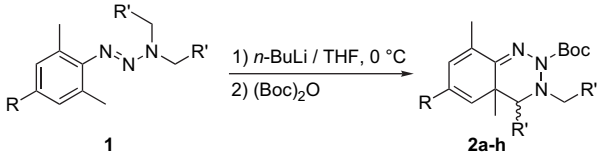


Scheme 1. Formation of benzylamine.

We obtained additional significant results through further investigation into the course of these reactions. When we treated 3,3-dialkyl-1-aryltriazenes possessing substituents at both the second and sixth positions on the aryl group with *n*-BuLi, we obtained new dearomatized heterocyclic compounds in good to moderate yields.

2. Results and discussion

The results are summarized in Scheme 2 and Table 1. In the case of R′=Me, we obtained two diastereomers (entries 2 and 6). In each case the minor product was unstable and decomposed slowly. On the other hand, triazenes derived from pyrrolidine (entries 3 and 7) and piperidine (entries 4 and 8) provided a single diastereomer in both cases.



Scheme 2. Formation of dearomatized compounds.

We determined the molecular structures of the products (**2a**–**h**) by their spectral data. The aromatic protons and carbons were disappeared and the newly appeared olefin protons and carbons were observed by NMR spectra. Fortunately the single crystal of **2d** was obtained, and the structure was confirmed by X-ray crystallography (Fig. 1).[14] The planar-like three rings system was constructed and the relative

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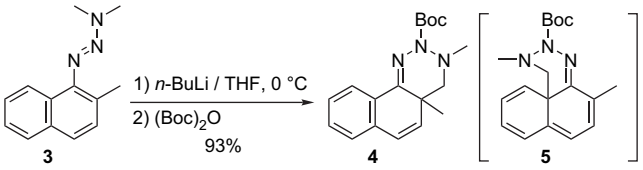
Table 1. Results of dearomatization reactions

Entry	Triazene **1**		Product	Yield (%)
	R	R′		
1	H	H	**2a**	73
2	H	Me	**2b**	64 (1:2.9)
3	H	$-(CH_2)_2-$	**2c**	75
4	H	$-(CH_2)_3-$	**2d**	58
5	Me	H	**2e**	65
6	Me	Me	**2f**	52 (1:5)
7	Me	$-(CH_2)_2-$	**2g**	85
8	Me	$-(CH_2)_3-$	**2h**	63

configuration of the substituents on C2 and C9 was *syn*. The bond length of N1–N2 was 1.391 Å and that of N2–N3 was 1.453 Å. It is known that the N–N bond length of hydrazine is 1.453 Å. The newly generated bond of C2–C9 was 1.554 Å.

In the case of 3,3-dimethyl-1-(2-methylnaphthyl)triazene (**3**), the C–C bond formation occurred selectively at the second position to form **4** in 93% yield, and we did not observe **5** (Scheme 3). Since one aromatic ring remained in product **4**, we presumed that **4** was more stable than **5**.

No dearomatized heterocyclic compounds of these types have ever been reported. The dearomatized heterocyclic



Scheme 3. Regioselectivity of reaction of **3** with base.

compounds possess interesting structures, specifically one quaternary or vicinal quaternary and tertiary carbons conjugated with a hydrazone group. Therefore, these compounds may play a part as valuable synthons in organic syntheses.

As mentioned above, we observed stereoselectivities in the newly formed vicinal quaternary and tertiary carbons. To investigate this stereoselectivity in the formation of **2d**, we examined the course of the reaction of **6** by semiempirical molecular orbital calculations (PM3 method) (Scheme 4).[15] The heat of the formation energy of the *anti* isomer **10** was 0.8 kcal/mol lower than that of *syn* isomer **8**, which was the precursor of **2d**. In transition states, however, the energy of **7** was lower than that of **9** by 1.3 kcal/mol. This evidence suggests that the reaction proceeded under kinetic control.

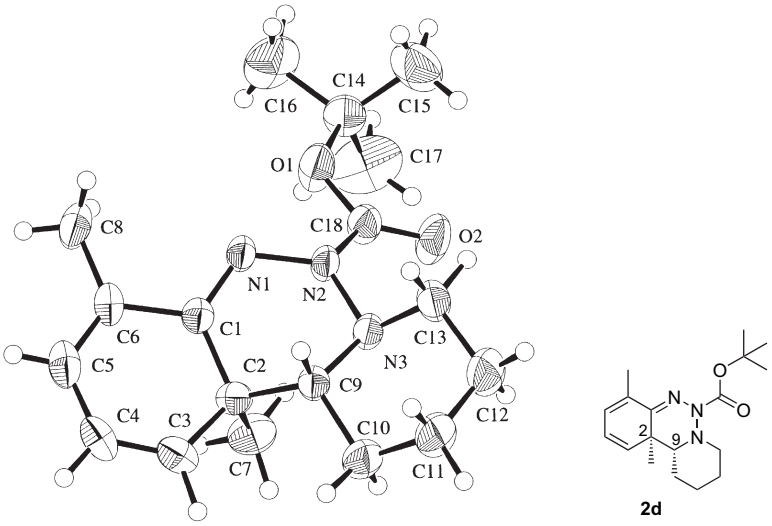
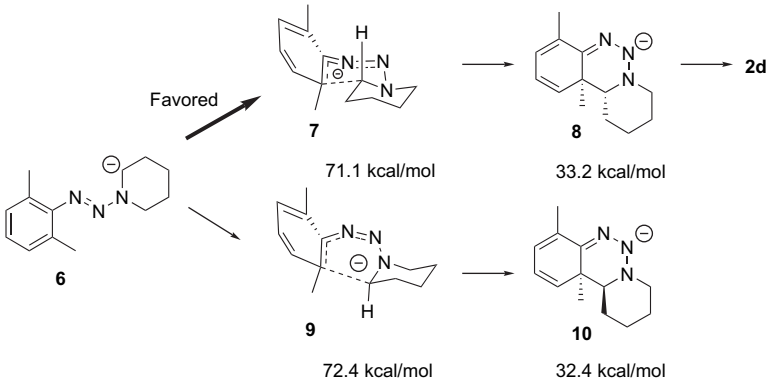


Figure 1. Perspective view of compound **2d**.



Scheme 4. Theoretical analysis of stereoselectivity of **2d**.

3. Conclusion

We have revealed new dearomatized reactions including an intramolecular C–C bond formation from 3,3-dialkyl-1-aryltriazenyl compounds. This reaction provides a new synthetic route for six-membered ring compounds from benzene derivatives. These products possess an interesting structure, one quaternary or vicinal quaternary and tertiary carbons conjugated with a hydrazone group. In addition, the configuration of the substituents of the newly formed C–C bond formation was exclusively *syn* when the anion formed triazene was bound as part of either a pyrrolidine or a piperidine. This stereoselectivity depended on the energy difference of the intermediate in the carbon–carbon bond forming stage. Since these new dearomatized compounds have a brand-new and interesting framework, we expect that these compounds will play the important role in the synthesis of drugs and functional compounds as new potential synthons.

4. Experimental

4.1. General methods

NMR spectra were recorded on JEOL GSX-270 (^{1}H 270 MHz, ^{13}C 67.5 MHz) spectrometer in $CDCl_3$ or CD_3OD with TMS as an internal standard. Mass spectra (EI) were recorded on a JMS-HX100 spectrometer. Infrared spectra were recorded on a Shimadzu IR-435 spectrophotometer. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was freshly distilled under nitrogen from sodium benzophenone ketyl prior to use.

4.2. General procedure for the transformation of triazenes into tetrahydrobenzotriazine derivatives

To a solution (0.5–1 M) of triazene (**1**) in dry THF (2 mL) was added dropwise a solution of *n*-BuLi/hexane (1 equiv) at 0 °C. After stirring for 1 h, the reaction mixture was quenched with Boc_2O (1.5 equiv). Extractive work-up and the subsequent purification afforded tetrahydrobenzotriazine derivatives (**2**).

4.2.1. *tert*-Butyl 3,4a,8-trimethyl-4,4a-dihydrobenzo[*d*][1,2,3]triazine-2(3*H*)-carboxylate (2a). Oil, 73%; ^{1}H NMR ($CDCl_3$) δ: 6.15 (dsep, J=6.0, 2.0 Hz, 1H), 5.93 (dd, J=9.0, 6.0 Hz, 1H), 5.79 (dt, J=9.0, 0.7 Hz, 1H), 3.60 (d, J=13.0 Hz, 2H), 3.28 (d, J=13.0 Hz, 2H), 2.51 (s, 3H), 2.08 (t, J=0.7 Hz, 3H), 1.56 (s, 9H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 160.96, 152.45, 137.78, 131.17, 125.95, 121.20, 81.67, 63.97, 40.11, 33.68, 28.23, 26.94, 16.54; IR (neat) cm^{-1}: 2950 (m), 1720 (s), 1560 (w), 1450 (m), 1400 (m), 1360 (m), 1320 (s), 1250 (m), 1140 (s), 870 (w), 720 (m); MS (EI) (*m*/*z*, %): 277 (M$^+$, 2.5), 177 (16), 162 (28), 133 (13), 119 (21), 105 (58), 91 (10), 77 (10), 57 (100), 41 (19); HRMS: 277.1805 (Calcd for $C_{15}H_{23}N_3O_2$, 277.1790).

4.2.2. *tert*-Butyl 3-ethyl-4,4a,8-trimethyl-4,4a-dihydrobenzo[*d*][1,2,3]triazine-2(3*H*)-carboxylate (2b). Brown oil, 48% as a major product; ^{1}H NMR ($CDCl_3$) δ: 6.26 (dt, J=6.0, 1.5 Hz, 1H), 5.97 (dd, J=9.0, 2.0 Hz, 1H), 5.87 (d, J=9.0 Hz, 1H), 3.17 (q, J=7.0 Hz, 1H), 2.54 (m, 2H), 2.10 (s, 3H), 1.53 (s, 9H), 1.29 (d, J=7.0 Hz, 3H), 0.97 (t, J=7.0 Hz, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 167.52, 153.59, 138.32, 130.91, 127.57, 119.68, 80.57, 66.78, 48.20, 38.74, 28.20, 20.00, 16.69, 16.01, 11.93; IR (neat) cm^{-1}: 2950 (m), 1700 (s), 1540 (w), 1450 (m), 1400 (s), 1330 (s), 1250 (m), 1140 (s), 900 (m), 720 (s); MS (EI) (*m*/*z*, %): 305 (M$^+$, 15), 204 (9), 105 (100), 72 (36), 57 (66); HRMS: 305.2122 (Calcd for $C_{17}H_{27}N_3O_2$, 305.2103).

4.2.3. *tert*-Butyl 7,10a-dimethyl-1,2,3,10b-tetrahydrobenzo[*e*]pyrrolo[1,2-*c*][1,2,3]triazine-5(10a*H*)-carboxylate (2c). Brown oil, 75%; ^{1}H NMR ($CDCl_3$) δ: 5.97 (dt, J=6.0, 1.5 Hz, 1H), 5.93 (dd, J=9.0, 6.0 Hz, 1H), 5.74 (d, J=9.0 Hz, 1H), 3.87 (dt, J=9.0, 4.0 Hz, 1H), 3.26 (dd, J=7.5, 2.5 Hz, 1H), 3.10 (dt, J=9.0, 7.5 Hz, 1H), 2.18 (m, 2H), 2.05 (s, 3H), 1.85 (m, 2H), 1.57 (s, 9H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 152.15, 149.94, 132.33, 131.93, 123.61, 121.89, 81.97, 55.10, 53.63, 37.48, 28.16, 23.31, 19.75, 16.79; IR (neat) cm^{-1}: 2900 (m), 1720 (s), 1540 (w), 1450 (m), 1400 (m), 1360 (s), 1310 (s), 1250 (s), 1140 (s), 720 (m); MS (EI) (*m*/*z*, %): 303 (M+, 9), 105 (73), 70 (29), 57 (100); HRMS: 303.1916 (Calcd for $C_{17}H_{25}N_3O_2$, 303.1947).

4.2.4. *tert*-Butyl 4,11b-dimethyl-8,9,10,11,11a,11b-hexahydro-6*H*-benzo[*e*]pyrido[1,2-*c*][1,2,3]triazine-6-carboxylate (2d). Yellow crystal, 58%; mp 85.5–86.0 °C (recryst. from hexane); ^{1}H NMR ($CDCl_3$) δ: 6.07 (dt, J=6.5, 1.5 Hz, 1H), 5.98 (dd, J=9.5, 6.0 Hz, 1H), 5.81 (d, J=6.0 Hz, 1H), 3.85 (m, 1H), 2.74 (dd, J=10.0, 2.5 Hz, 1H), 2.50 (dt, J=10.0, 3.0 Hz, 1H), 1.97 (s, 3H), 1.75 (m, 4H), 1.54 (s, 9H), 1.30 (m, 2H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 158.80, 150.56, 132.59, 130.65, 126.00, 122.33, 81.19, 65.29, 56.34, 40.07, 28.29, 25.54, 25.28, 23.74, 16.97, 16.47; IR (KBr) cm^{-1}: 2900 (m), 1700 (s), 1560 (w), 1440 (m), 1400 (m), 1360 (m), 1320 (s), 1230 (m), 1150 (s), 1090 (s), 730 (w); MS (EI) (*m*/*z*, %): 317 (M$^+$, 16), 217 (8), 105 (100), 84 (45), 57 (66); HRMS: 317.2123 (Calcd for $C_{18}H_{27}N_3O_2$, 317.2103); Anal. Calcd for $C_{18}H_{27}N_3O_2$: C, 68.11; H, 8.57; N, 13.24. Found: C, 68.35; H, 8.44; N, 13.42.

4.2.5. *tert*-Butyl 3,4a,6,8-tetramethyl-4,4a-dihydrobenzo-[*d*][1,2,3]triazine-2(3*H*)-carboxylate (2e). Brown oil, 65%; ^{1}H NMR ($CDCl_3$) δ: 6.03 (t, J=1.5 Hz, 1H), 5.45 (br s, 1H), 3.55 (d, J=13.0 Hz, 1H), 3.22 (d, J=13.0 Hz, 1H), 2.51 (s, 3H), 2.07 (d, J=1.0 Hz, 3H), 1.79 (d, J=1.5 Hz, 3H), 1.56 (s, 9H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 161.19, 152.49, 132.26, 130.68, 130.19, 128.66, 81.62, 63.88, 40.47, 33.39, 28.25, 27.15, 20.99, 16.47; IR (neat) cm^{-1}: 2980 (s), 2910 (s), 1730 (s), 1715 (s), 1570 (w), 1455 (m), 1410 (m), 1390 (m), 1370 (m), 1350 (m), 1320 (s), 1250 (m), 1140 (m), 1080 (m), 1030 (w), 980 (w), 910 (w), 860 (w), 800 (w), 750 (w); MS (EI) (*m*/*z*, %): 291 (M$^+$, 22), 191 (19), 176 (43), 147 (17), 133 (58), 119 (19), 91 (18), 77 (9), 57 (100), 41 (16); HRMS: 291.1940 (Calcd for $C_{16}H_{25}N_3O_2$, 291.1947).

4.2.6. *tert*-Butyl 3-ethyl-4,4a,6,8-tetramethyl-4,4a-dihydrobenzo[*d*][1,2,3]triazine-2(3*H*)-carboxylate (2f). Brown oil, 43% as a major product; ^{1}H NMR ($CDCl_3$)

δ: 6.14 (t, J=1.5 Hz, 1H), 5.55 (br s, 1H), 3.12 (d, J=7.0 Hz, 1H), 2.54 (m, 2H), 2.09 (br s, 3H), 1.82 (d, J=1.5 Hz, 3H), 1.53 (s, 9H), 1.27 (d, J=1.5 Hz, 3H), 0.98 (t, J=7.5 Hz, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 167.83, 153.70, 133.10, 131.99, 130.55, 127.16, 80.63, 48.53, 38.59, 28.32, 21.16, 20.20, 16.71, 16.15, 12.11; IR (neat) cm^{-1}: 2950 (m), 2200 (w), 1710 (s), 1540 (w), 1450 (m), 1360 (s), 1320 (s), 1250 (m), 1140 (s), 910 (w), 720 (m); MS (EI) (*m*/*z*, %): 319 (M^+, 10), 218 (6), 147 (29), 119 (100), 72 (29),57 (59); HRMS: 319.2233 (Calcd for $C_{18}H_{29}N_3O_2$, 319.2260).

4.2.7. *tert*-Butyl 7,9,10a-trimethyl-1,2,3,10b-tetrahydrobenzo[*e*]pyrrolo[1,2-*c*][1,2,3]triazine-5(10a*H*)-carboxylate (2g). Brown oil, 85%; ^{1}H NMR ($CDCl_3$) δ: 5.85 (t, J=1.5 Hz, 1H), 5.43 (br s, 1H), 3.86 (dt, J=8.8, 2.5 Hz, 1H), 3.23 (dd, J=9.5, 7.5 Hz, 1H), 3.08 (m, 1H), 2.16 (m, 2H), 2.05 (d, J=1.0 Hz, 3H), 1.88 (m, 2H), 1.76 (d, J= 1.5 Hz, 3H), 1.58 (s, 9H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 152.01, 150.01, 131.40, 129.22, 127.65, 126.91, 81.72, 55.43, 53.47, 37.00, 28.05, 23.21, 21.18, 19.67, 16.56; IR (neat) cm^{-1}: 2900 (s), 2200 (w), 1700 (s), 1560 (m), 1440 (s), 1320 (br s), 1140 (br s), 940 (w), 910 (m), 850 (w), 800 (w), 720 (s); MS (EI) (*m*/*z*, %): 317 (M^+, 14), 216 (3), 119 (100), 70 (30), 57 (83); HRMS: 317.2123 (Calcd for $C_{18}H_{27}N_3O_2$, 317.2103).

4.2.8. *tert*-Butyl 2,4,11b-trimethyl-8,9,10,11,11a,11b-hexahydro-6*H*-benzo[*e*]pyrido[1,2-*c*][1,2,3]triazine-6-carboxylate (2h). Brown oil, 63%; ^{1}H NMR ($CDCl_3$) δ: 5.95 (t, J=1.5 Hz, 1H), 5.50 (br s, 1H), 3.85 (m, 1H), 2.69 (dd, J=10.0, 2.5 Hz, 1H), 2.48 (dt, J=10.5, 3.0 Hz, 1H), 1.97 (s, 3H), 1.80 (d, J=1.5 Hz, 3H), 1.75 (m, 4H), 1.54 (4s, 9H), 1.31 (m, 2H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 158.98, 150.59, 130.28, 129.76, 127.18, 81.11, 65.67, 56.40, 39.71, 28.31, 25.59, 25.33, 23.81, 21.58, 17.08, 16.83; IR (neat) cm^{-1}: 2900 (m), 1700 (s), 1560 (w), 1440 (m), 1400 (m), 1360 (m), 1310 (s), 1260 (m), 1160 (m), 1100 (m), 740 (m); MS (EI) (*m*/*z*, %): 331 (M^+, 20), 230 (8), 119 (100), 84 (41), 57 (51); HRMS: 331.2270 (Calcd for $C_{19}H_{29}N_3O_2$, 331.2260).

4.2.9. *tert*-Butyl 3,4a-dimethyl-4,4a-dihydronaphtho[1,2-*d*][1,2,3]triazine-2(3*H*)-carboxylate (4). Yellow oil, 93%; ^{1}H NMR ($CDCl_3$) δ: 7.98 (m, 1H), 7.32 (m, 2H), 7.10 (m, 1H), 6.42 (d, J=10.0 Hz, 1H), 5.89 (d, J=10.0 Hz, 1H), 3.56 (d, J=14.0 Hz, 1H), 3.41 (d, J=14.0 Hz, 1H), 2.69 (s, 3H), 1.59 (s, 9H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 155.15, 152.04, 136.94, 133.40, 129.89, 129.74, 128.22, 126.49, 125.28, 124.76, 82.01, 61.85, 40.31, 31.86, 28.25, 26.45; IR (neat) cm^{-1}: 3000 (s), 1700 (s), 1610 (s), 1580 (w), 1480 (m), 1370 (s), 1310 (s), 1250 (m), 1170 (m), 1140 (s), 1100 (s), 910 (w); MS (EI) (*m*/*z*, %): 313 (M^+, 3.8), 212 (35), 198 (16), 182 (10), 168 (16), 155 (100), 141 (85), 128 (6.3), 115 (27), 115 (28), 89 (3.1), 63 (3.1), 57 (59), 51 (2.5), 41 (2.4); HRMS: 313.1759 (Calcd for $C_{18}H_{23}N_3O_2$, 313.1790).

4.3. X-ray crystallographic analysis

Data of compound **2d** was taken on a RigakuAFC5R diffractometer with graphite-monochromated Mo Kα radiation (k=0.71069 Å). The structure of **2d** was solved by direct methods with SAPI91.[16] Full-matrix least-squares refinement was employed with anisotropic thermal parameters for all non-hydrogen atoms. All calculations were performed using the teXsan[17] crystallographic software package of Molecular Structure Corporation. An ORTEP drawing of compound **2d** is shown in Figure 1.

4.3.1. Crystal data for 2d. Monoclinic, space group $P2_1/n$, a=9.988(5), b=9.321(4), c=19.961(3) Å, V=1850(1) Å^3, Z=4, μ(Mo Kα)=0.75 cm^{-1}, F(000)=688, D_{calcd}=1.139 g/cm^3, crystal dimensions: 0.30×0.30×0.40 mm. A total of 4761 reflections (4511 unique) were collected using the $\omega-2\theta$ scan technique to a maximum 2θ value of 55°, and 1291 reflections with $I>3\sigma(I)$ were used in the structural determination. Final R and wR values were 0.045 and 0.042, respectively. The maximum and minimum peaks in the difference map were 0.14 e$^-$ Å^{-3}.

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Remarkable synthesis and structure of allene type zerumbone

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Abstract—The ring expansion of zerumbone to a 12-membered ring was studied via a ring opening system or a ring closure system of zerumbone. We succeeded in the synthesis of a zerumbone derivative with 12-membered ring, an allene type zerumbone. For the first time, a Doering–LaFlamme allene synthesis method was adopted and the structure was confirmed by monocrystal X-ray diffraction. It was obtained in total 27.7% yield from zerumbone. We believe that this compound is not only an important building block in synthesizing the BC ring of paclitaxel, but also plays an important role in a novel structure formation and a reactive discovery.

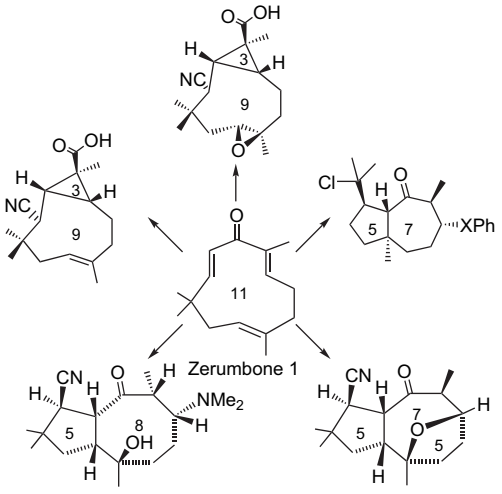
1. Introduction

Zerumbone **1**[1] having potent ability in natural materials-related diversity-oriented synthesis '*NMRDOS*'. The representative concept of diversity-oriented synthesis was established by Schreiber in 2000.[2] However, the choice of substrate is important and moreover, if the substrate is a natural material, much chemical development may be needed. Zerumbone **1**, having powerful latent reactivity and containing three double bonds, two conjugated and one isolated, and a double conjugated carbonyl group in an 11-membered ring structure, is a monocyclic sesquiterpene found as the major component of the essential oil of wild ginger, *Zingiber zerumbet* Smith. It is anticipated to be a powerful tool in the implementation of green chemistry with respect to the provision of materials followed on from the cultivation of ginger.

Also, zerumbone as a natural resource showed attractive reactivity and could be converted into various structures (e.g., transannular and ring contracting skeletons).[3–7] Crystallized zerumbone is obtained quite simply by direct steam distillation from the rhizome of *Z. zerumbet* Smith in more than 3% yield per dry rhizome.[8] In addition, the growth of the plant is very fast. From the viewpoint of purification and reactivity, zerumbone is a powerful resource that exceeds the camphor obtained from camphor trees and menthol obtained from peppermint trees. These have been chemically applied in the chemical industry as typical natural products.

We built the foundation for the industrial use of zerumbone by establishing novel methods such as asymmetric induction, ring scission, and transannular reactions. Since many quite useful polycyclic compounds exist in nature, the development of the transannular reaction and the construction of various transannular products are very important in organic and material chemistry.

As shown in Scheme 1, we examined the transannular reaction of zerumbone in detail and succeeded in the development of many useful transannular products. Thus, since it leads to synthetically difficult products using reactive diversity from the 11-membered structure of zerumbone and the range of the application such as synthesizing the various analogues is very wide, it will be necessary to continue further development of zerumbone chemistry in the future.



Scheme 1.

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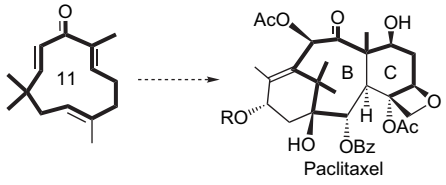
With respect to an opposite aspect, however, it is analogized that the skeleton formation of non-natural system is very difficult since in the structure of the zerumbone derivatives formed using the character and the skeleton of zerumbone as a natural resource, it is very difficult to get rid of the category of the structure that exists naturally and to form a novel skeleton. If the ring structure can be increased and decreased maintaining the double conjugated system of zerumbone, various wide-ranging transannular compounds can be constructed. It is also expected to have great industrial development, and moreover, the versatile compound that is normally quite difficult to obtain might be synthesized easily from the zerumbone structure. We have insisted and imagined zerumbone as a starting material of the paclitaxel formation. If ring expansion of the 12-membered system is established maintaining double conjugate system, then the synthesis of paclitaxel approaches reality as shown in Scheme 2, namely, the BC ring of paclitaxel is corresponding to the outer carbon numbers of zerumbone with the 12-membered ring. Moreover, each position such as the carbonyl carbon, the adjacent methyl group, and *gem*-methyl group against paclitaxel and zerumbone analogue with 12-membered ring is also corresponded mutually.



Scheme 2.

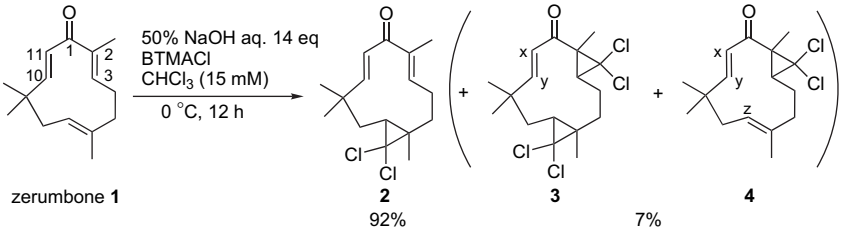
In our current research, however, we comprehended that the conservation of the double conjugated system was extremely difficult since the reactivity of double conjugated system of zerumbone was quite high. We report here that in an attempt with many reaction conditions, finally, the effective synthesis of the allene-zerumbone was accomplished. This beautiful and attractive 12-membered cyclic structure, retaining the double conjugated system, which is a non-natural system, was accomplished when Doering–LaFlamme synthesis[9] was applied.

2. Results and discussion

Sodium hydroxide (50% aq) was added to zerumbone and benzyltrimethylammonium chloride (BTMACl) as a phase transfer catalyst in chloroform at −1 to 0 °C near the coagulation temperature of the solvent. The mixture was then reacted for 12 h to afford 12,12-dichloro-1,5,9,9-tetramethylbicyclo[9.1.0]dodeca-4,7-dien-6-one **2** in 92% yield with the regioselectivity as shown in Scheme 3.

The synthetic development of **2** was very important in that it is possible to produce novel derivatives while maintaining the double conjugated system of zerumbone. Dichloro carbene, produced by chloroform, reacted with the isolated olefin regioselectively since there is a stable SOMO energy on the isolated olefin though stable LUMO energy contributed to the double conjugated system of zerumbone. Thus, orbital energy calculations will show important information in the forecast of the reactivity of zerumbone. Orbital energy of zerumbone was calculated in detail, and it will be reported in the near future. Controlling the reaction temperature and the concentration of the solution were the major factors in preparing **2** as shown in Table 1.

Compound **2** was obtained in 92% yield when the reaction temperature was precisely controlled at −1 to 0 °C and the concentration of zerumbone was 15 mM (run 6). However, 5,5,13,13-tetrachloro-1,6,10,10-tetramethyltricyclo[10.1.0.0^{4,6}]tridec-8-en-7-one **3** and 12,12-dichloro-1,5,5,8-tetramethylbicyclo[9.1.0]dodeca-3,7-dien-2-one **4** as by-products, whose ratio was approximately 1:1 analyzed



Scheme 3.

Table 1. Preparation of **2**

Run	Solvent	Concn (mM)	Base	Equiv	Temp (°C)	Time (h)	Yield (%), **2**	Yield (%), **3**+**4**
1	$CHCl_3$	150	NaOH (solid)	3.3	rt	12	Trace	
2	$CHCl_3$	150	50% NaOH aq	14	rt	12	66	
3	$CHCl_3$	15	50% NaOH aq	14	4	12	82	
4	$CHCl_3$	150	50% NaOH aq	14	0	12	67	
5	$CHCl_3$	40	50% NaOH aq	14	0	12	73	
6	$CHCl_3$	15	50% NaOH aq	14	0	12	92	7
7	$CHCl_3$	15	50% NaOH aq	17	0	2	86	13
8	THF	150	50% NaOH aq	3.3	rt	12	Trace	
9	$CHBr_3$	150	50% NaOH aq	14	rt	12	6[a]	

[a] Dibromo substitution.

Table 2. ^{1}H NMR spectrum of olefinic parts of **3** and **4**

Position	3		4	
	ppm	Coupling constant	ppm	Coupling constant
x	5.82	17.3 (doublet)	6.10	16.2 (doublet)
y	6.55	17.3 (doublet)	6.45	16.2 (doublet)
z	—	—	5.83–5.84	Broad

by ^{1}H NMR, were obtained if the reaction conditions were not followed precisely. They were isolated using silica gel chromatography or re-crystallization as mixtures and mainly confirmed by GC–MS (column: DB-1: 30 m, carrier gas: He, injection, and detector: 200 °C, column: 180 °C, t_R **3**: 58.6 min, **4**: 17.1 min). Moreover, ^{1}H NMR spectrum of each olefinic part (positions x, y, and z) in the mixture of **3** and **4** appeared very clear as shown in Table 2. With increasing amount of the NaOH concentration, reaction time has been greatly improved but the amount of by-products increased (run 7). It is necessary to do a complete reactive control, since it is very difficult to separate these compounds with chromatography in case of large-scale system. One explanation might be that since the differentiation of activated energy between **2** and by-products **3** or **4** is very small, it is very easy to spoil the regioselectivity even if the reaction temperature and the concentration of **1** are raised only slightly.

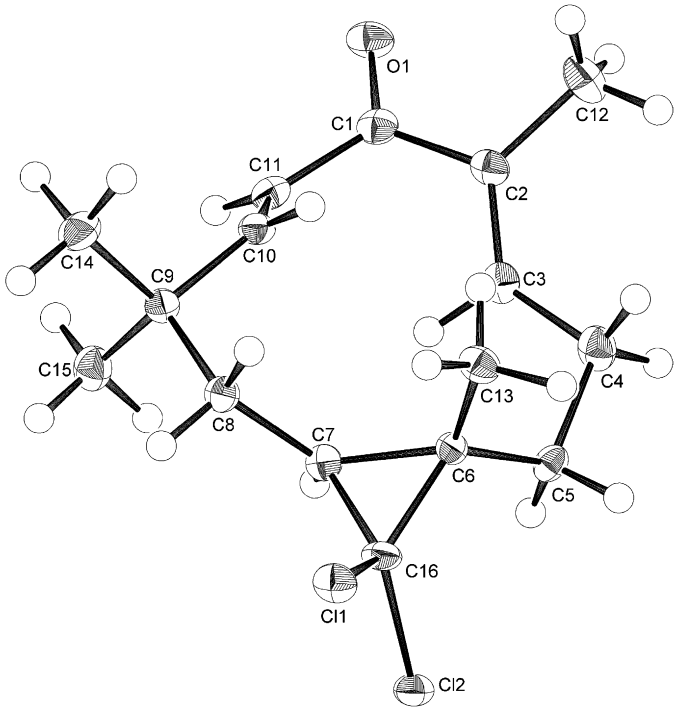
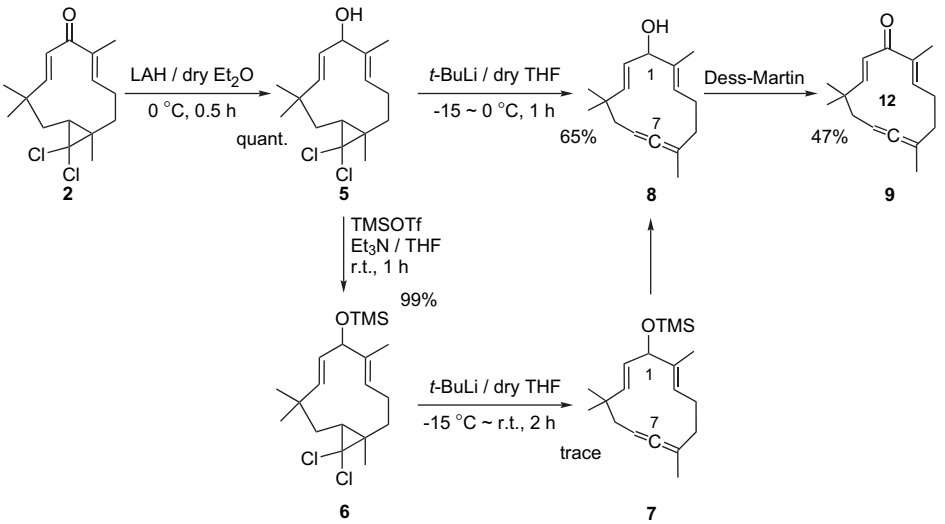


Figure 1. ORTEP drawing of the crystal structure of **2**.

Monoclinic white crystalline **2** could be prepared in a mixture of ethyl acetate and hexane to get ORTEP figure from single crystal X-ray diffraction as shown in Figure 1.

The torsion angle of olefins with double conjugated system of **2** was smaller than that of zerumbone and the structural distortion was dissolved a little since the center of gravity of the ring balance of **2** moved near 6,7-position. Concretely, though the torsion angles between C10–C11 and C1–O1 were 43.2° and 43.5°, respectively, the angles between C2–C3 and C1–O1 were 34.9° and 28.8°, respectively. When the torsion angle shows small value, structural distortion is small.

As shown in Scheme 4, **2** was reacted with $LiAlH_4$ (LAH) in anhydrous ether at 0 °C for 0.5 h to afford 6,7-dichlorocyclopropylzerumbol **5** quantitatively as a diastereomeric mixture. Compound **5** was protected by TMSOTf using Et_3N as a catalyst in THF at room temperature for 1 h to afford **6** quantitatively. Treatment of **6** with *t*-BuLi in THF at −15 °C to room temperature for 2 h gave allene type zerumbol **7** with the 12-membered system in low yield with one carbon enhancement over zerumbone. Deprotection of **7** with TsOH might give allene type zerumbol **8** quantitatively. The development of this formation is the first successful experiment, however, the yield was not high, so direct ring expansion of **5** was examined without protection. Under the same condition as the above-mentioned, **8** was obtained directly from **5** in 65% yield.



Scheme 4.

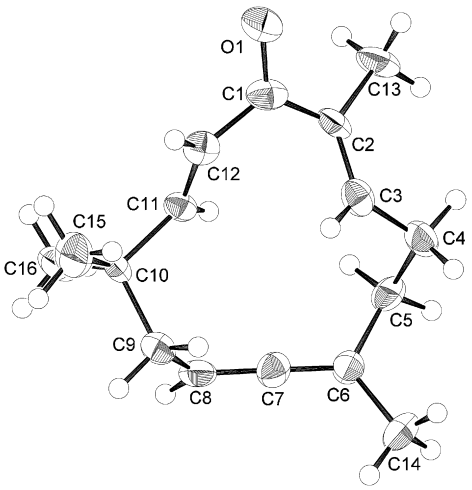
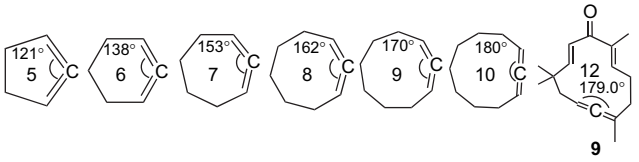


Figure 2. ORTEP drawing of the crystal structure of **9**.

Finally, Dess–Martin oxidation of **8** gave **9** with 12-membered allene system in 47% yield. Since all of the compounds **5**–**8** were diastereomers, separation and purification was quite difficult. Therefore, complete structural data were not obtained except for high-resolution mass spectroscopy. Racemic compound **9** was used to determine the structure, and spectroscopic results could be obtained completely. Moreover, monoclinic crystals of **9** could be prepared from a mixture of diethyl ether and dichloromethane to analyze the single crystal X-ray diffraction and get the preliminary structure as shown in Figure 2. This result will rapidly deepen the role of zerumbone showing potent ability in NMRDOS, and become a trigger to lead to a novel creation. It is expected that examining the reactivity of **9** might give attractive results synthetically.

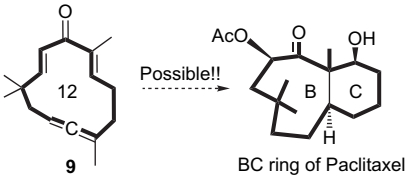
When **1** was compared to the X-ray of the structure of **9**, an interesting result was obtained. The angle of the allene part tends to be smaller than 180° when the number of the ring system is smaller than the 10-membered cyclic system as shown in Scheme 5.[10] It has been found that in spite of the structural distortion of **9** due to the double conjugated system, the angle of C6–C7–C8 in **9** was 179° and there is hardly any distortion of the allene part. This result proved that **9** was the reasonable structure to be produced easily. This might be a reason why **9** shows the beautiful structure without distortion on the allene site.



Scheme 5.

3. Conclusion

We believe that the development of the allene type zerumbone can be contributed to a novel skeleton formation. Especially the transannular reaction of **9** gives quite a different type of novel cyclic structure, e.g., paclitaxel, compared with the reaction from zerumbone **1** as shown in Scheme 6.



Scheme 6.

4. Experimental

4.1. General methods

NMR spectra were obtained at 270 MHz for protons, and 68 MHz for ^{13}C in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard unless otherwise noted. Chemical shifts δ were reported in parts per million from TMS. Mass spectra were recorded at 70 eV, and high-resolution mass spectra (HRMS) were almost obtained by direct injection. The X-ray diffraction and CCDC numbers appear in Section 4.1.2. Chemicals were commercially available, were of reagent grade, and used without further purification.

4.1.1. 12,12-Dichloro-1,5,9,9-tetramethylbicyclo[9.1.0]-dodeca-4,7-dien-6-one 2. BTMACl (10 mg) and 50% NaOH aq (2.5 mL) were added into a solution of zerumbone (1.0 g, 4.6 mmol) and chloroform (300 mL) and stirred vigorously at 0 °C for 12 h. The progress of the reaction was monitored by TLC. The mixture was washed with H_2O (3×300 mL) and brine (3×100 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was subjected to silica gel column chromatography using hexane and AcOEt (15/1) as an eluent to afford 12,12-dichloro-1,5,9,9-tetramethylbicyclo[9.1.0]dodeca-4,7-dien-6-one **2** as a colorless solid in 92% yield and the mixture of **3** and **4** in 7% yield. Monoclinic colorless crystalline **2** was prepared in the mixture of ethyl acetate and hexane to analyze the single crystal X-ray diffraction. Mp: 112.0–113.0 °C; IR (KBr): 2957, 1651 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.09 (s, 3H, CH_3 at C9), 1.12 (s, 3H, CH_3 at C9), 1.24 (m, 5H, CH_3 at C1, CH at C11, and CH at C10), 1.59 (m, 1H, CH_2 at C2), 1.85 (m, 4H, CH_3 at C5 and CH at C10), 2.26–2.32 (m, 1H, CH at C2), 2.43–2.47 (m, 2H, CH_2 at C3), 6.09 (s, 2H, CH at C8 and C7), 6.15–6.20 (m, 1H, CH at C4); ^{13}C NMR: δ 11.9 (CH_3 at C5), 13.3 (CH_3 at C9), 23.7 (CH_3 at C1), 25.1 (CH_2 at C10), 29.1 (CH_3 at C9), 30.8 (C9), 35.9 (C1), 36.3 (CH at C11), 37.1 (CH_2 at C2), 41.1 (CH_2 at C10), 71.3 (Cl2), 127.7 (CH at C4), 139.3 (C at C5), 147.9 (CH at C8), 160.4 (CH at C7), 202.6 (C═O); HRMS (EI-DI): *m/z* calcd mass for $C_{16}H_{22}Cl_2O$: 300.1048, found: 300.1048.

4.1.2. Crystallographic study of 2. A colorless prism crystal, crystal size 0.20×0.30×0.02 mm^3, monoclinic, space group $P2_1/a$ (no. 14), a=8.889(9), b=18.15(2), c=9.772(10) Å, β=101.929(12)°, V=1542.5(27) $Å^3$, Z=4, D_{calcd}=1.297 g/cm^3, μ(Mo Kα)=4.11 cm^{-1}, was used for data collection. The intensity data were measured on a

Rigaku Mercury CCD detector using Mo Kα radiation at a temperature of −180±1 °C. The structure was solved by direct methods (SIR97)[11] and expanded using Fourier techniques (DIRDIF99).[12] All calculations were performed using the crystal structure crystallographic software package. The final cycle of full-matrix least-squares refinement on F^2 was based on 3533 reflections (all data) and 261 variable parameters and gave $R1=0.063$ ($I>2.0\ \sigma\ (I)$) and $wR2=0.192$ (all data). The value of the goodness of fit indicator was 1.08 (Summary of Data CCDC 608648).

4.1.3. 5,5,13,13-Tetrachloro-1,6,10,10-tetramethyltricyclo[10.1.0.0^{4,6}]tridec-8-en-7-one 3. HRMS (EI–GC): *m/z* calcd mass for $C_{16}H_{22}Cl_4O$: 382.0425, found: 382.0417.

4.1.4. 12,12-Dichloro-1,5,5,8-tetramethylbicyclo[9.1.0]-dodeca-3,7-dien-2-one 4. HRMS (EI–GC): *m/z* calcd mass for $C_{16}H_{22}Cl_2O$: 300.1048, found: 300.1046.

4.1.5. 12,12-Dichloro-1,5,9,9-tetramethylbicyclo[9.1.0]-dodeca-4,7-dien-6-ol 5. Under N_2 atmosphere, a solution of **2** (500 mg, 1.66 mmol) in dry Et_2O (5 mL) was added into a suspension of LAH (70 mg, 1.83 mmol) in dry Et_2O (10 mL) at 0 °C and stirred at the same temperature for 1 h. The progress of the reaction was monitored by TLC (hexane/AcOEt=4/1). H_2O (50 mL) was added to the mixture carefully at 0 °C and the aqueous solution was extracted with Et_2O (3×30 mL). The combined organic extracts were washed with brine (3×30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was subjected to silica gel column chromatography using hexane and AcOEt (15/1) as an eluent to afford diastereomeric mixture of 12,12-dichloro-1,5,9,9-tetramethylbicyclo[9.1.0]dodeca-4,7-dien-6-ol **5** as a white solid quantitatively. Mp: 95.5–96.5 °C; IR (KBr): 3320, 2962 cm^{-1}; HRMS (EI-DI): *m/z* calcd mass for $C_{16}H_{24}Cl_2O$: 302.1204, found: 302.1142.

4.1.6. 2,6,10,10-Tetramethylcyclododeca-2,6,7,11-tetraen-1-ol 8. Under N_2 atmosphere, *t*-BuLi (23 mL, 26.8 mmol, 1.48 M in pentane) was dropped into a solution of **5** (810 mg, 2.68 mmol) in dry THF (48 mL) at −15 °C and then the temperature was raised to 0 °C gradually. The mixture was stirred at 0 °C for 1 h. The progress of the reaction was monitored by TLC (hexane/AcOEt=4/1). H_2O (50 mL) was added to the mixture carefully at 0 °C and the aqueous solution was extracted with Et_2O (3×30 mL). The combined organic extracts were washed with brine (3×30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was subjected to aluminum column chromatography using hexane and AcOEt (15/1) as an eluent to afford diastereomeric mixture of 2,6,10,10-tetramethylcyclododeca-2,6,7,11-tetraen-1-ol **8** as a colorless oil in 65% yield. IR (NaCl): 3329, 2957, 1956 cm^{-1}; HRMS (EI-DI): *m/z* calcd mass for $C_{16}H_{24}O$: 232.1827, found: 232.1830.

4.1.7. 2,6,10,10-Tetramethylcyclododeca-2,6,7,11-tetraen-1-one 9. Under N_2 atmosphere, Dess–Martin periodinane (460.8 mg, 1.09 mmol) was added into CH_2Cl_2 (6 mL) at room temperature and stirred until the mixture dissolved completely. Compound **8** (202 mg, 0.87 mmol) in CH_2Cl_2 (6 mL) was dropped into the Dess–Martin solution and then stirred at the same temperature for 1 h. The progress of the reaction was monitored by TLC (hexane/AcOEt=4/1). Et_2O (30 mL) and 1 M NaOH aq (30 mL) were added into the solution and then the aqueous solution was extracted with Et_2O (3×30 mL). The combined organic extracts were washed with brine (3×30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was subjected to silica gel column chromatography using hexane and AcOEt (30/1) as an eluent to afford 2,6,10,10-tetramethylcyclododeca-2,6,7,11-tetraen-1-one **9** as a colorless solid in 47% yield. Monoclinic single crystal of **9** was prepared from the mixture of diethyl ether and dichloromethane to analyze the single crystal X-ray diffraction. Mp: 46.0–47.0 °C; IR (KBr): 2961, 1639 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.97 (s, 3H, CH_3 at C10), 1.07 (s, 3H, CH_3 at C10), 1.66 (s, 3H, CH_3 at C6), 1.78 (s, 3H, CH_3 at C2), 1.96 (m, 2H, CH_2 at C9), 2.08–2.26 (m, 2H, CH_2 at C5 and CH at C4), 2.28–2.52 (m, 1H, CH_2 at C4), 4.90–5.07 (br, 1H, CH at C8), 5.87 (d, 1H, J=16.33 Hz, CH at C12), 6.50 (br, 1H, CH at C3), 6.65 (d, 1H, J=16.33 Hz, CH at C11); ^{13}C NMR: δ 12.2 (CH_3 at C2), 18.3 (CH_3 at C6), 24.4 (CH_3 at C10), 26.1 (CH_2 at C4), 27.1 (CH_3 at C10), 36.1 (CH_2 at C5), 37.7 (C at C10), 45.0 (CH_2 at C9), 84.3 (CH at C8), 95.5 (C at C6), 124.6 (CH at C12), 134.8 (C at C2), 145.7 (CH at C3), 159.9 (CH at C11), 201.3 (C=O at C1), 204.5 (=C= at C7); HRMS (EI-DI): *m/z* calcd mass for $C_{16}H_{22}O$: 230.1671, found: 230.1682.

Acknowledgements

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Photoreactions of β-aziridinylacrylonitriles and acrylates with alkenes: the substituent effects on the formation of [3+2] cycloadducts

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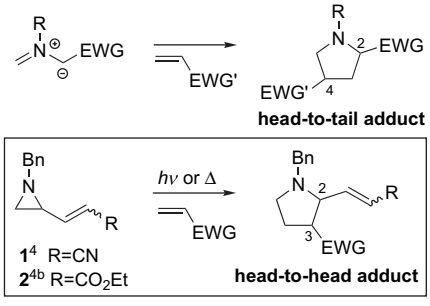
Abstract—The photochemical C,C-bond cleavage of trisubstituted aziridines **3**–**6** and consequent [3+2] cycloaddition with electron-deficient alkenes afforded the novel head-to-head adducts (1,2,3,5-tetrasubstituted pyrrolidines) selectively and efficiently. The aziridines **3** and **5** reacted with molecular oxygen, affording dioxazolidine **26** and cleaved products, respectively. The results may suggest that the C,C-bond of aziridine cleaves biradically. The photoreactions of *N*-tritylaziridines **7**–**9** possessing diester, dinitrile, and butadiene groups in the side chain with electron-deficient alkenes yielded 2,3-*cis*-pyrrolidine derivatives **29**, **30**, and **33** exclusively. In particular, the dinitrile **8** also reacted with non-electron-deficient alkenes. The formal synthesis of the indolizidine fragment **10** of stellettamides starting from the pyrrolidine (*E*)-**33** was achieved in a convenient manner.

1. Introduction

The 1,3-dipolar cycloaddition of azomethine ylides with alkenes is an important and useful strategy for the construction of pyrrolidines.[1] On irradiation or under thermal conditions the aziridine ring is cleaved to give the corresponding azomethine ylide.[2] In general, the 1,3-dipolar cycloaddition of the azomethine ylide possessing one electron withdrawing group (EWG) at the ylide carbon and electron-deficient alkenes affords head-to-tail adducts (1,2,4-trisubstituted pyrrolidines; Scheme 1). The regiochemistries of the adducts have been explained by the frontier MO interaction of azomethine ylides and alkenes.[2b,3]



Scheme 1.

We have reported previously that direct irradiation (via singlet state) or heating of β-aziridinylacrylonitrile **1** or acrylate **2** with electron-deficient alkenes undergoes ring opening and subsequent [3+2] cycloaddition leading to head-to-head adducts (1,2,3-trisubstituted pyrrolidines; Scheme 1) selectively and efficiently (Scheme 1).[4] The regiochemistry of the head-to-head adducts could not be clearly rationalized by the interaction between HOMO of azomethine ylide generated from **1** or **2** and LUMO of electron-deficient alkenes. Therefore, in order to study the scope and limitations of the cycloaddition, the reactions of various aziridines (di- and trisubstituted aziridines and aziridines bearing diester, dinitrile, and butadiene groups in the side chain) **1**–**9** and alkenes were performed. Furthermore, we describe a convenient synthetic application of **9** to indolizidine part **10** of stellettamides A–C[5] (Fig. 1).

2. Results and discussion

2.1. Preparations of aziridines

The δ-methyl γ,δ-epimino α,β-unsaturated nitriles **3a** and (*E*)-**3b** were synthesized by the Horner–Emmons reaction of aldehydes **12a**[8,9] and **12b**[9] obtained by Swern oxidation of the *cis*-alcohol **11a**[6,7] and *trans*-alcohol **11b**[6,7] with diethyl cyanomethylphosphonate in 87% yield (*E*:*Z*=51:36) and 34% yield from **11a** and **11b**, respectively. Similarly, the aldehydes **12a** and **12b** were treated with (carbethoxymethylene)triphenylphosphorane and triethyl phosphonoacetate affording the ester **4a** in 67% yield (*E*:*Z*=46:21) and (*E*)-**4b** in 52% yield from **11a** and **11b**, respectively.

Keywords: Aziridine; Photolysis; [3+2] Cycloaddition; Pyrrolidine; Indolizidine.
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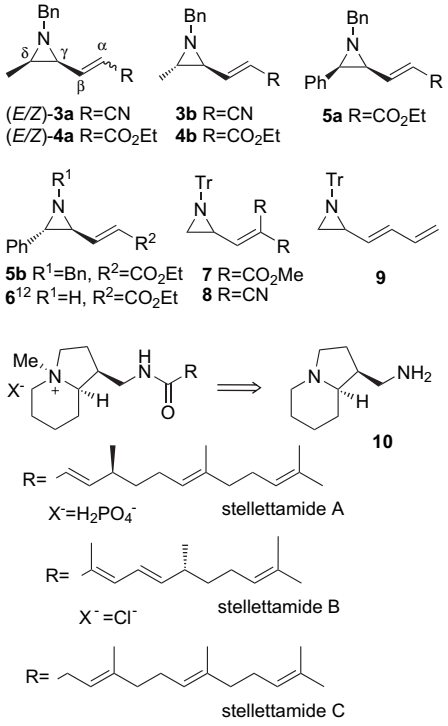
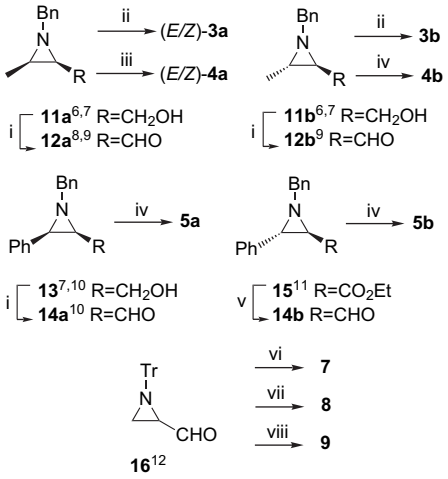


Figure 1.

Each 2,3-*trans* aziridine, **3b** and **4b**, was obtained as a 1:0.7 mixture of two invertomers at nitrogen in the aziridine (Scheme 2).[7]



Scheme 2. Reagents and conditions: (i) $(COCl)_2$, Me_2SO, NEt_3, CH_2Cl_2, −70 °C; (ii) $(EtO)_2P(O)CH_2CN$, NaH, THF, 0 °C; (iii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, −40 °C; (iv) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF or CH_2Cl_2, 0 °C; (v) DIBAL-H, CH_2Cl_2, −70 °C; (vi) $CH_2(CO_2Me)_2$, pyrrolidine, CH_2Cl_2; (vii) $CH_2(CN)_2$, toluene, 110 °C; (viii) $Ph_2(PO)CH_2CH{=}CH_2$, *n*BuLi, THF, −70 °C.

In a similar manner, the δ-phenyl γ,δ-epimino α,β-unsaturated esters **5a** and **5b** were obtained by the Horner–Emmons reaction of the aldehyde **14a**[10] with triethyl phosphonoacetate in 26% yield and in 53% yield from *cis*-alcohol **13**[7,10] and ester **15**,[11] respectively. The compound **6** was prepared according to the literature procedure.[12] The *N*-trityl diester **7**, dinitrile **8**, and butadiene **9** were synthesized from *N*-trityl aldehyde **16**[13] as shown in Scheme 2 (see Section 4).

2.2. Reactions of aziridine (*Z*)-1 with disubstituted alkenes

The disubstituted aziridine (*Z*)-**1** reacts with cyclic alkenes (e.g., 2-cyclopentenone and *N*-phenylmaleimide), affording the adducts in moderate yields.[4] The stereochemistries at 2-, 3-, and 4-position of these pyrrolidines were all cis. Therefore, we investigated the cycloaddition of acyclic 1,2-disubstituted alkenes and (*Z*)-**1**. Direct irradiation of a solution of (*Z*)-**1** with 10 equiv of (*Z*)-2-pentenenitrile in acetonitrile with a low-pressure mercury lamp in a quartz test tube at room temperature (conversion 78%) afforded adduct **17** (56%)[14] (Fig. 2). Ethyl crotonate reacted also with (*Z*)-**1** (conversion 56%), yielding a 1:2 mixture of adducts **18a** and **18b** (50%).[14] The structures of adducts **17**, **18a**, and **18b** were deduced on the basis of their spectral data. Especially, the stereochemistries of **17**, **18a**, and **18b** were determined by the phase-sensitive NOESY spectra (see Supplementary data). The stereochemistries of the 3,4-positions in adducts **17**, **18a**, and **18b** conserve the stereochemistries of the corresponding alkenes.

2.3. Reactions of 3-substituted aziridines 3–6 with alkenes

The effects of the substituent at the 3-position in the aziridine ring on the [3+2] cycloaddition with alkenes were studied. Irradiation and heating of 3-methylaziridine (*E*)-**3a** with acyclic 1,2-disubstituted alkenes [e.g., (*Z*)-2-pentenenitrile] afforded no pentasubstituted pyrrolidines owing to the steric hindrance between five substituents in the aziridine and the alkene. The photochemical and thermal reactions of 3-methyl and 3-phenylaziridines **3**–**6** with *tert*-butyl acrylate were performed, and the results are summarized in Tables 1 and 2 and Schemes 3 and 4. The cycloaddition of *cis*-methylaziridine **3a** gave *a mixture of* 2,5-*cis*- and -*trans*-pyrrolidines **19a** and **19b** photochemically and thermally, and *trans*-aziridine **3b** afforded the same products without (*E*/*Z*)-isomerization at the side chain (entries 1–6 in Table 1). The results show that stereochemistries of aziridines **3a** and **3b** were not reflected in stereochemistries at 2- and 5-positions in the cycloadducts. The same tendency was also observed on the photocycloaddition of the esters **4a** (2,3-*cis*) and **4b** (2,3-*trans*) (entries 7 and 9 in Table 1). In the thermal reactions of aziridines, the *cis*-aziridines (*E*)- and (*Z*)-**3a** gave the adducts (entries 2 and 6 in Table 1). However, the *trans*-aziridines **3b** and *cis*- and *trans*-aziridines **4a** and **4b** yielded no adducts (entries 4, 8, and 10 in Table 1). In particular, **4b** underwent homosigmatropic rearrangement of vinyl aziridine moiety[15] to afford imine **21** (Scheme 3).

The photoreactions of *trans*-phenylaziridines **6** with methyl acrylate yielded the 2,5-*trans*-pyrrolidines (*E*)-**24b** (entry 5

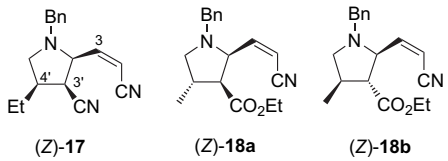


Figure 2.

Table 1. Photochemical and thermal reactions of aziridines **3** and **4** with *tert*-butyl acrylate

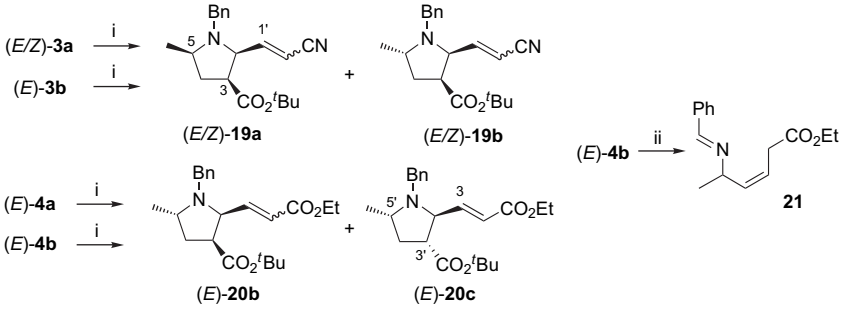
Entry	Aziridine	Reaction conditions	Reaction time (h)	Conversion (%)	Products and yields (%)[14,a]
1	(*E*)-**3a**	hν[b]	2.5	88	(*E*)-**19a** (14) and (*E*)-**19b** (27)
2	(*E*)-**3a**	Δ[c]	3	81	(*E*)-**19a** (35) and (*E*)-**19b** (12)
3	(*E*)-**3b**	hν	0.75	78	(*E*)-**19a** (21) and (*E*)-**19b** (21)
4	(*E*)-**3b**	Δ	0.5	100	Complex mixture
5	(*Z*)-**3a**	hν	2	93	(*Z*)-**19a** (12) and (*Z*)-**19b** (59)
6	(*Z*)-**3a**	Δ	3	83	(*Z*)-**19a** (26) and (*Z*)-**19b** (17)
7	(*E*)-**4a**	hν	2.5	91	(*Z*)-**20b** (26) and (*Z*)-**20c** (26)
8	(*E*)-**4a**	Δ	2	0	No reaction
9	(*E*)-**4b**	hν	1.5	69	(*Z*)-**20b** (17) and (*Z*)-**20c** (17)
10	(*E*)-**4b**	Δ	0.5	100	**21** (33)

[a] Isolated yield.
[b] A 0.060 mol L^{-1} solution of aziridine in acetonitrile with 10 equiv of *tert*-butyl acrylate was irradiated at rt.
[c] A 0.060 mol L^{-1} solution of aziridine in xylene with 10 equiv of *tert*-butyl acrylate was heated under reflux.

Table 2. Photochemical and thermal reactions of aziridines **5** and **6** with alkyl acrylate

Entry	Aziridine	Reaction conditions	Reaction time (h)	Conversion (%)	Products and yields (%)[14,a]
1	(*E*)-**5a**	hν[b,c]	2	58	(*E*)-**22b** (18) and (*E*)-**22d** (9)
2	(*E*)-**5a**	Δ[c,d]	1.5	100	(*E*)-**22d** (21) and (*E*)-**23b** (11)
3	(*E*)-**5b**	hν	0.5	100	(*E*)-**22b** (20) and (*E*)-**22d** (7)
4	(*E*)-**5b**	Δ	0.75	100	(*E*)-**22a** (14), (*E*)-**22c** (19), and (*E*)-**23a** (5)
5	**6**	hν[b,e]	1	92	(*E*)-**24b** (26)
6[f]	**6**	Δ	—	—	(*E*)-**24a** (28) and (*E*)-**25** (16)

[a] Isolated yield.
[b] A 0.060 mol L^{-1} solution of aziridine in acetonitrile with 10 equiv of *tert*-butyl acrylate was irradiated at rt.
[c] *tert*-Butyl acrylate (3 equiv) was used.
[d] A 0.060 mol L^{-1} solution of aziridine in xylene with 10 equiv of *tert*-butyl acrylate was heated under reflux.
[e] Methyl acrylate (10 equiv) was used.
[f] See Ref. 12.

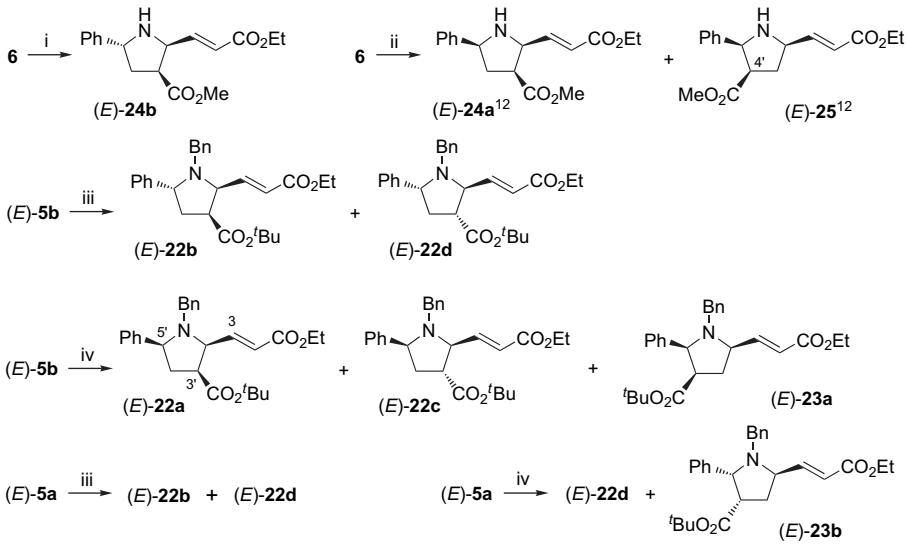


Scheme 3. Reagents and conditions: (i) λ=254 nm, CH_2=$CHCO_2{}^tBu$, MeCN, rt; (ii) CH_2=$CHCO_2{}^tBu$, xylene, 145 °C.

in Table 2) and those thermal reactions afforded the 2,5-*cis*-pyrrolidines (*E*)-**24a** and (*E*)-**25**[12] exclusively (entry 6 in Table 2). The photochemical cycloaddition of *trans*-aziridine **5b** with *tert*-butyl acrylate similarly afforded the 2,5-*trans*-pyrrolidines (*E*)-**22b** and (*E*)-**22d** (entry 3 in Table 2) and the thermal reactions gave the 2,5-*cis*-pyrrolidines (*E*)-**22a**, (*E*)-**22c**, and (*E*)-**23a** exclusively (entry 4 in Table 2). From the results, the ring opening of 3-phenylaziridine **6** and **5b** and cycloaddition with alkenes seems to proceed based on the Woodward–Hoffmann prediction.[2a] On the other hand, both photochemical and thermal reactions of *cis*-phenylaziridine **5a** afforded only the 2,5-*trans*-pyrrolidines [(*E*)-**22b**, (*E*)-**22d**, and (*E*)-**23b**] (entries 1 and 2 in Table 2; Scheme 4). Therefore, in the reactions of 3-phenylaziridines **5** and **6** with alkenes, the stereochemistries of aziridines were not strictly reflected in stereochemistries of the cycloadducts.

Especially, the 3-phenylaziridines **5** and **6** react with *tert*-butyl acrylate thermally, also affording head-to-tail adducts (*E*)-**23a**, (*E*)-**23b**, and (*E*)-**25**, whose formation is discussed later in this paper.

The structures of adducts **19**, **20**, and **22**–**24** were deduced on the basis of their spectral data. Especially, the stereochemistries of (*E*)-**19a**,**b**, (*E*)-**20b**,**c**, (*E*)-**22a**,**d**, (*E*)-**23a**,**b**, and (*E*)-**24b** were determined by the phase-sensitive NOESY spectra (see Supplementary data). The regio- and stereochemistries of (*Z*)-**19a** and (*Z*)-**19b** were determined from the H–H and C–H COSY spectra and from a comparison of the spectral data with those of (*E*)-**19a** and (*E*)-**19b**. In particular, the configuration in the pyrrolidine ring was deduced from the comparison of the ^{1}H NMR chemical shifts at the 3-position of (*Z*)-**19a** (δ 2.64–2.71) and (*Z*)-**19b** (δ 3.28–3.36) with those of (*E*)-**19a** (δ 2.64) and (*E*)-**19b** (δ 3.20–3.28).



Scheme 4. Reagents and conditions: (i) λ=254 nm, CH_2=$CHCO_2Me$, MeCN, rt; (ii) Ref. 12; (iii) λ=254 nm, CH_2=$CHCO_2{}^tBu$, MeCN, rt; (iv) CH_2=$CHCO_2{}^tBu$, xylene, 145 °C.

2.4. Reactions of aziridines 3 and 5 with molecular oxygen

The reactions of aziridines **1**–**6** and electron-deficient alkenes mainly gave head-to-head adducts. The regiochemistries for the adducts could not be clearly rationalized by the interaction between HOMO of the azomethine ylide **A** generated from **1**–**6** and LUMO of the electron-deficient alkenes. Therefore, we assumed that the intermediates for the reaction possess a biradical character (e.g., **B**; Fig. 3) and attempted to trap the chemical species with molecular oxygen.[16] Direct irradiation of a solution of (*Z*)-**3a** in acetonitrile under bubbling oxygen with a low-pressure mercury lamp in a quartz test tube at room temperature (conversion 83%) afforded dioxazolidine **26** (56%). By analogy with the photoreactions of (*Z*)-**3a**, the ester (*E*)-**5b** gave (conversion 100%) benzaldehyde (30%), *N*-benzylbenzamide (28%), and crotonate **27** (20%), which would be afforded by decomposition of dioxazolidine **28** (Scheme 5). Reactions of disubstituted aziridines **1** and **2** under oxygen were also performed, and the corresponding dioxazolidines could not be observed.

The aziridines **1**–**6** underwent photochemical and thermal C,C-bond cleavage giving mainly the biradical intermediate **B** (Fig. 3), followed by [3+2] cycloaddition to alkene to afford the head-to-head adducts presumably. The azomethine ylide intermediate **A** (Fig. 3) generated from 3-phenylaziridines **5** and **6** simultaneously was especially stabilized by the phenyl substituent, and then cyclized with alkenes yielding the head-to-tail adducts (*E*)-**23a**, (*E*)-**23b**, and (*E*)-**25** by heating. The formation of the head-to-tail adducts occurred only in the thermal conditions. The results may show the

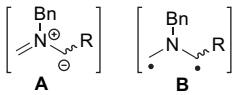
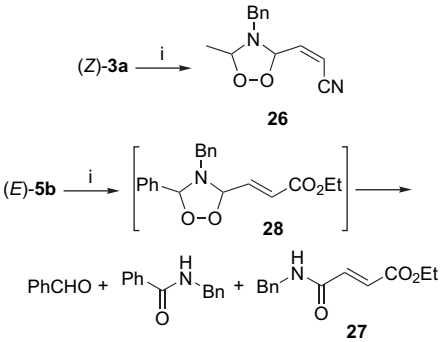


Figure 3.



Scheme 5. Reagents and conditions: (i) λ=254 nm, O_2, MeCN, rt.

transition state for the cyclization step lies much higher than those of the head-to-head adducts.

The structures of benzaldehyde and *N*-benzylbenzamide were identified by a comparison of their ^1H and ^{13}C NMR spectra with those of commercial products. The structures of **26** and **27** were deduced on the basis of their spectral data. The molecular ion peak in the mass spectrum (MS) of **26** indicates the 1:1 adducts of intermediate **B** and oxygen. The ^{13}C NMR spectrum of **26** shows characteristic signals at δ_C 93.8 and 95.3 due to the dioxazolidine moiety. The compound **26** was obtained as a single stereoisomer, and the stereochemistry could not be determined due to the instability. The molecular ion peak in MS of **27** shows 233 [M^+ of **28** (339) minus M^+ of benzaldehyde (106)], and the IR bands at 3430, 1720, and 1670 cm^{-1} reveal amine, ester, and amide moieties, respectively.

2.5. Reactions of aziridines 7–9 possessing diester, dinitrile, and butadiene functional groups at the 2-position with various alkenes

The aziridines **1**–**6** bearing one electron-withdrawing group (e.g., ester or nitrile) underwent [3+2] cycloaddition with only electron-deficient alkenes to give adducts.

Table 3. Photochemical reactions of aziridines **7–9** with various alkenes[a]

Entry	Aziridine	Alkene	Reaction time (h)	Conversion (%)	Products and yields (%)[14,b]
1	**7**	Acrylonitrile	1	56	**29** (18)
2	**7**	Vinyl acetate	3.5	—	—[c]
3	**8**	Acrylonitrile	2	49	**30** (31)
4	**8**	Vinyl acetate	3	100	**31** (7)
5	**8**	Isoprene[d]	3.5	37	**32** (19)
6	**9**	Acrylonitrile	1	72	(*E*)-**33** (54) and (*Z*)-**33** (12)

[a] A 0.060 mol L^{-1} solution of aziridine in acetonitrile with 10 equiv of alkene was irradiated at rt.
[b] Isolated yield.
[c] The reaction gave complex mixture.
[d] Isoprene (3 equiv) was used.

The electron-withdrawing inductive effects at the 2-position in the aziridine ring on the [3+2] cycloaddition with alkenes were studied. In earlier studies of the 1,3-dipolar cycloaddition of carbonyl ylide and alkenes, the carbonyl ylides possessing stronger electron-withdrawing substituents (e.g., dinitrile) reacted with electron-rich alkenes better than the ylides possessing weaker ones (e.g., diester and mononitrile).[17] Therefore, we became interested in the reactivity of the [3+2] cycloaddition of aziridines **7–9** with various alkenes. The results are summarized in Table 3 and Fig. 4. The reactions of aziridines **7–9** and acrylonitrile afforded adducts **29**, **30**, and (*E*/*Z*)-**33** in moderate yields (entries 1, 3, and 6). With the decreasing electron-withdrawing inductive effects of the substituent, the reaction proceeded more efficiently. Only the most electron-deficient aziridine **8** reacted with non-electron-deficient alkenes (vinyl acetate and isoprene) to give the adducts (entries 4 and 5).

The stereo- and regiochemistries of **29–33** were determined by the mean of the ^{1}H and ^{13}C NMR spectra and/or H–H COSY and phase-sensitive NOESY spectra. In particular, the phase-sensitive NOESY spectra of **30–32** and (*Z*)-**33** show the cis-orientation at C-2 and C-3 in the pyrrolidine ring (see Supplementary data).

The photoreactions of *N*-tritylaziridines **7–9** and alkenes exclusively gave the cis-adducts **29–33** owing to the steric hindrance of the trityl group.[4b]

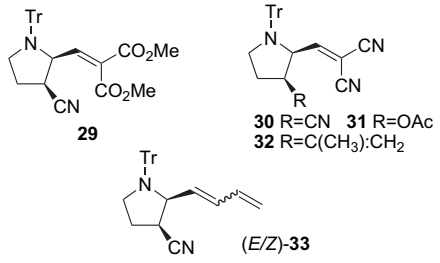


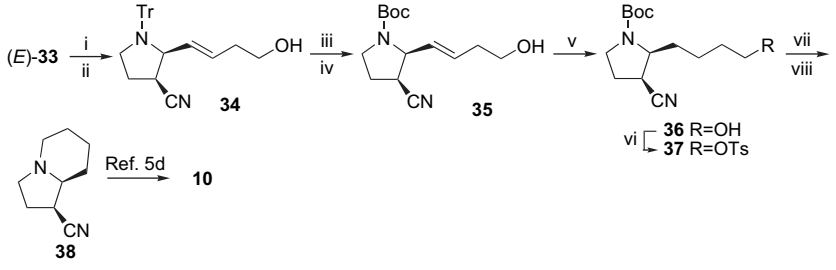
Figure 4.

2.6. Application to the synthesis of indolizidine fragment of stellettamides 10

Since the photoreaction of *N*-tritylaziridine **9** and acrylonitrile gave 2,3-*cis*-pyrrolidine **33** in a moderate yield, we focused on preparing the indolizidine core **10**[5] of stellettamides, using the substituents and the stereochemistry of **33**. Hydroboration of the side chain in (*E*)-**33** with 9-BBN and H_2O_2 gave alcohol **34** in 25% yield. Detritylation of **34**, *N*-Boc protection (79%), and reduction of the double bond in **35** proceeded successfully, yielding butanol **36** (95%). After tosylation of **36** (76%), deprotection of *N*-Boc for **37** occurred in HCl–dioxane and cyclization by treatment of NaOH afforded indolizidine **38**,[5d,18] which had been transformed by authentic methods[5d] into **10**, in 89% yield (Scheme 6).

3. Conclusions

The reactions of β-aziridinylacrylonitrile **1** with disubstituted electron-deficient alkene and photoreactions of 3-substituted aziridines **3–6** with electron-deficient alkenes afforded the novel head-to-head adducts (1,2,3,5-tetrasubstituted pyrrolidines) selectively and efficiently. However, the thermal reactions of 3-phenylaziridines **5** and **6** with electron-deficient alkenes gave head-to-tail adducts **23** and **25** in addition to head-to-head adducts. The trisubstituted aziridines **3** and **5** reacted with molecular oxygen, affording dioxazolidine **26** and cleaved products, respectively. From the result, the [3+2] cycloaddition of aziridines and alkenes may occur via an intermediate **B** with a biradical character. The photoreaction of *N*-tritylaziridines **7–9** bearing diester, dinitrile, and butadiene groups in the side chain with electron-deficient alkenes yielded 2,3-*cis*-pyrrolidine derivatives **29**, **30**, and **33** exclusively. In particular, the dinitrile **8** reacted also with non-electron-deficient alkenes. The formal synthesis of the indolizidine fragment of stellettamides **10** starting from the pyrrolidine (*E*)-**33** was achieved in a convenient manner.



Scheme 6. Reagents and conditions: (i) 9-BBN, THF, rt; (ii) H_2O_2, THF, rt; (iii) TFA, $CHCl_3$, MeOH, 0 °C; (iv) Boc_2O, NaOH, THF–H_2O, 0 °C; (v) H_2, Pd/C, EtOH, rt; (vi) TsCl, pyridine, −20 °C; (vii) HCl, dioxane, rt; (viii) NaOH aq, rt.

4. Experimental

4.1. General

Mps are uncorrected. Mps were measured with a Yanaco MP-3 apparatus. IR spectra were recorded on a Hitachi 215 spectrometer. ^{1}H NMR spectra were obtained with a JEOL JNM-AL300 (300 MHz), a JEOL JNM-AL400 (400 MHz) or a JEOL JNM-LA500 (500 MHz) spectrometer. ^{13}C NMR spectra were recorded on a JEOL JNM-AL300 (75 MHz), a JEOL JNM-AL400 (100 MHz) or a JEOL JNM-LA500 (125 MHz) spectrometer. Unless otherwise noted, NMR spectra were measured in $CDCl_3$ using tetramethylsilane as an internal standard at room temperature. Mass spectra (MS) and high-resolution MS (HRMS) were taken on a JEOL JMS-700 spectrometer. Column chromatography was performed with Merck silica gel 60 (230–400 mesh) and preparative TLC with Wakogel B-5F.

An Eikosha 60 W low-pressure mercury lamp was used for irradiation. The photolysis solutions were purged with argon before and during irradiation.

4.2. Preparations of aziridines

4.2.1. (*E*,2′*RS*,3′*SR*)-3-(1′-Benzyl-3′-methylaziridin-2′-yl)acrylonitrile [(*E*)-3a] and (*Z*,2′*RS*,3′*SR*)-3-(1′-benzyl-3′-methylaziridin-2′-yl)acrylonitrile [(*Z*)-3a]. To a solution of oxalyl chloride (1.80 g, 14.2 mmol) in dry methylene chloride (33 mL) was added dropwise a solution of DMSO (2.00 g, 25.6 mmol) in dry methylene chloride (26 mL) at −70 °C. After the mixture had been stirred for 20 min at −70 °C, a solution of alcohol **11a**[6,7] (2.28 g, 12.9 mmol) in dry methylene chloride (13 mL) was added dropwise, and stirring was continued for 15 min at −70 °C. Triethylamine (9.0 mL, 65 mmol) was added slowly to the reaction mixture, which was stirred for 10 min at −70 °C, warmed to 0 °C and further stirred for 2 h. Water was added to the mixture and the organic phase was extracted with methylene chloride. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo, giving aldehyde **12a**[8,9] that was used for the next step without further purification. To a suspension of NaH [680 mg, 17.0 mmol; prepared from an NaH dispersion (60%, 1.13 g) by washing it twice with hexane (12 mL)] in dry THF (10 mL) was added dropwise a solution of diethyl cyanomethylphosphonate (3.01 g, 17.0 mmol) in dry THF (15 mL) at 0 °C. After the mixture had been stirred for 10 min at 0 °C, a solution of aldehyde **12a** (12.9 mmol) in dry THF (15 mL) was added dropwise, and stirring was continued for 1.5 h at 0 °C. Ice/water was added to the mixture, and the organic phase was extracted with diethyl ether. The ethereal extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo, giving a residue that was subjected to flash column chromatography [hexane–ethyl acetate (7:3)] to afford (*E*)-**3a** (1.29 g, 51%) and (*Z*)-**3a** (914 mg, 36%).

Compound (*E*)-**3a**, an oil; IR (film): 2200 cm^{-1} (C≡N); ^{1}H NMR (400 MHz): δ 1.14 (d, 3H, J=5.9 Hz, CH_3), 1.98–2.04 (m with quintet character, 1H, J=6 Hz, H-3′), 2.13–2.17 (m with t-character, 1H, J=6 Hz, H-2′), 3.49, 3.62 (each d, 2H, J=13.7 Hz, CH_2Ph), 5.58 (dd, 1H, J=16.1, 0.8 Hz, H-2), 6.60 (dd, 1H, J=16.1, 6.4 Hz, H-3), 7.25–7.36 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 13.3 (q, CH_3), 43.5, 43.8 (2d, C-2′, C-3′), 63.8 (t, *C*H$_2$Ph), 101.2 (d, C-2), 117.1 (s, C-1), 126.9, 127.4, 128.1 (3d, 5C in Ph), 138.1 (s, C in Ph), 151.4 (d, C-3); EI-MS *m*/*z* 198 (M$^+$, 5%), 107 (100), 91 (51), 80 (12); HRMS calcd for $C_{13}H_{14}N_2$: 198.1157, found: 198.1157.

Compound (*Z*)-**3a**, an oil; IR (film): 2200 cm^{-1} (C≡N); ^{1}H NMR (400 MHz): δ 1.21 (d, 3H, J=5.9 Hz, CH_3), 2.05–2.11 (m with quintet character, 1H, J=6 Hz, H-3′), 2.55 (dd, 1H, J=9, 7 Hz, H-2′), 3.53, 3.66 (each d, 2H, J=13.7 Hz, CH_2Ph), 5.45 (dd, 1H, J=11.2, 1 Hz, H-2), 6.28 (dd, 1H, J=11.2, 9 Hz, H-3), 7.26–7.36 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 14.6 (q, CH_3), 43.2, 43.5 (2d, C-2′, C-3′), 64.0 (t, *C*H$_2$Ph), 100.7 (d, C-2), 115.8 (s, C-1), 127.1, 127.6, 128.3 (3d, 5C in Ph), 138.1 (s, C in Ph), 152.3 (d, C-3); EI-MS *m*/*z* 198 (M$^+$, 7%), 107 (100), 91 (53), 80 (15); HRMS calcd for $C_{13}H_{14}N_2$: 198.1157, found: 198.1165.

4.2.2. Ethyl (*E*,2′*RS*,3′*SR*)-3-(1′-benzyl-3′-methylaziridin-2′-yl)acrylate [(*E*)-4a] and ethyl (*Z*,2′*RS*,3′*SR*)-3-(1′-benzyl-3′-methylaziridin-2′-yl)acrylate [(*Z*)-4a]. To a solution of oxalyl chloride (584 mg, 4.6 mmol) in dry methylene chloride (9.1 mL) was added dropwise a solution of DMSO (440 mg, 7.6 mmol) in dry methylene chloride (7.6 mL) at −70 °C. After the mixture had been stirred for 20 min at −70 °C, a solution of alcohol **11a**[6,7] (675 mg, 3.81 mmol) in dry methylene chloride (3.8 mL) was added dropwise, and stirring was continued for 25 min at −70 °C. Triethylamine (2.7 mL, 19 mmol) was added slowly to the reaction mixture, which was stirred for 10 min at −70 °C, warmed to −40 °C and further stirred for 40 min. To the mixture was added dropwise a solution of (carbethoxymethylene)triphenylphosphorane (3.3 g, 9.48 mmol) in methylene chloride (4.6 mL) at −40 °C. After the mixture had been stirred for 1.5 h at −40 °C, ice/water (30 mL) was added to the mixture, and the organic phase was extracted with methylene chloride. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo, giving a residue that was subjected to flash column chromatography [hexane–ethyl acetate (2:3)] to afford (*E*)-**4a** (443 mg, 46%) and (*Z*)-**4a** (191 mg, 21%).

Compound (*E*)-**4a**, an oil; IR (film): 1710 cm^{-1} (C=O); ^{1}H NMR (400 MHz): δ 1.19 (d, 3H, J=5.6 Hz, 3′-CH_3), 1.28 (t, 3H, J=7.2 Hz, OCH$_2$CH_3), 1.92–1.98 (m with quintet character, 1H, J=6 Hz, H-3′), 2.13–2.17 (m with t-character, 1H, J=7 Hz, H-2′), 3.53, 3.60 (each d, 2H, J=13.6 Hz, CH_2Ph), 4.18 (q, 2H, J=7.2 Hz, OCH$_2$), 6.05 (dd, 1H, J=15.8, 0.7 Hz, H-2), 6.81 (dd, 1H, J=15.6, 7.3 Hz, H-3), 7.24–7.32 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 14.0, 14.5 (2q, 2CH_3), 43.2, 44.3 (2d, C-2′, C-3′), 60.6, 64.5 (2t, OCH$_2$, *C*H$_2$Ph), 124.0 (d, C-2), 127.5, 128.1, 129.0 (3d, 5C in Ph), 139.3 (s, C in Ph), 146.1 (d, C-3), 166.7 (s, C-1); EI-MS *m*/*z* 245 (M$^+$, 7%), 200 (11), 172 (88), 154 (100), 126 (9), 108 (10), 91 (61), 80 (16); HRMS calcd for $C_{15}H_{19}NO_2$: 245.1416, found: 245.1418.

Compound (*Z*)-**4a**, an oil; IR (film): 1715 cm^{-1} (C=O); ^{1}H NMR (400 MHz): δ 1.21 (d, 3H, J=5.6 Hz, 3′-CH_3), 1.30 (t, 3H, J=7.2 Hz, OCH$_2$CH_3), 2.00–2.07 (m, 1H, H-3′),

3.31–3.35 (m with t-character, 1H, J=8 Hz, H-2′), 3.53, 3.67 (each d, 2H, J=13.7 Hz, CH_2Ph), 4.20 (q, 2H, J=7.2 Hz, OCH_2), 5.93 (dd, 1H, J=11.5, 0.8 Hz, H-2), 6.04 (dd, 1H, J=11.5, 8.5 Hz, H-3), 7.23–7.34 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 14.3, 14.6 (2q, $2CH_3$), 42.3, 43.0 (2d, C-2′, C-3′), 60.2, 64.3 (2t, OCH_2, CH_2Ph), 122.4 (d, C-2), 127.3, 128.1, 128.7 (3d, 5C in Ph), 139.4 (s, C in Ph), 148.2 (d, C-3), 166.8 (s, C-1); EI-MS m/z 245 (M^+, 1%), 200 (2), 172 (18), 154 (22), 133 (13), 112 (20), 91 (100); HRMS calcd for $C_{15}H_{19}NO_2$: 245.1416, found: 245.1413.

4.2.3. (*E*,2′*RS*,3′*RS*)-3-(1′-Benzyl-3′-methylaziridin-2′-yl)acrylonitrile (3b). By analogy with the synthesis of **3a**, oxidation of alcohol **11b**[6,7] (180 mg, 1.02 mmol) with oxalyl chloride and DMSO gave aldehyde **12b**,[9] which was consequently treated with NaH (60%, 48 mg, 1.2 mmol) and diethyl cyanomethylphosphonate (213 mg, 1.2 mmol) in dry THF at 0 °C, and the resulting mixture was stirred for 1 h at 0 °C. Flash column chromatography [hexane–ethyl acetate (2:1)] of the reaction mixture afforded esters **3b** (68.7 mg, 34%) as a 1:0.7 mixture of invertomers at nitrogen; an oil; IR (film): 2210 cm^{-1} (C≡N); ^{1}H NMR (400 MHz): δ 1.14 (d, 3H, J=6.0 Hz, CH_3), 1.29 (d, 2.1H, J=5.2 Hz, CH_3), 1.90–1.94 (m, 1H, H-2′), 1.97–2.03 (m, 0.7H, H-3′), 2.18–2.23 (m, 1H, H-3′), 2.41–2.46 (m with d-character, 0.7H, J=10.0 Hz, H-2′), 3.62, 3.83 (each d, 2H, J=14.0 Hz, CH_2Ph), 3.70, 3.81 (each d, 1.4H, J=14.0 Hz, CH_2Ph), 5.54 (d, 1H, J=16.0 Hz, H-2), 5.58 (d, 0.7H, J=16.0 Hz, H-2), 6.57–6.66 (m, 1+0.7H, H-3), 7.25–7.36 (m, 5+3.5H, Ph); ^{13}C NMR (100 MHz): δ major invertomer 11.3 (q, CH_3), 43.8, 45.8 (2d, C-2′, C-3′), 54.8 (t, CH_2Ph), 98.9 (d, C-2), 117.4 (s, C-1), 126.9, 127.5, 128.3 (3d, 5C in Ph), 138.9 (s, C in Ph), 154.3 (d, C–3); EI-MS m/z 198 (M^+, 10%), 107 (100), 91 (40), 80 (8); HRMS calcd for $C_{13}H_{14}N_2$: 198.1157, found: 198.1156.

4.2.4. Ethyl (*E*,2′*RS*,3′*RS*)-3-(1′-benzyl-3′-methylaziridin-2′-yl)acrylate (4b). By analogy with the synthesis of **3a**, oxidation of alcohol **11b**[6,7] (335 mg, 1.89 mmol) with oxalyl chloride and DMSO gave aldehyde **12b**,[9] which was consequently treated with NaH (60%, 90.8 mg, 2.3 mmol) and triethyl phosphonoacetate (515 mg, 2.3 mmol) in dry THF at 0 °C, and the resulting mixture was stirred for 1 h at 0 °C. Flash column chromatography [hexane–ethyl acetate (4:1)] of the reaction mixture afforded esters **4b** (241 g, 52%) as a 1:0.7 mixture of invertomers at nitrogen; an oil; IR (film): 1710 cm^{-1} (C═O); ^{1}H NMR (400 MHz): δ 1.24–1.32 (m, 6+2.1H, 3′-CH_3 and OCH_2CH_3), 1.38 (d, 2.1H, J=5.9 Hz, CH_3), 1.92–2.01 (m, 1+0.7H, H-3′), 2.26–2.29 (m, 0.7H, H-2′), 2.49 (dd, 1H, J=10.3, 2.7 Hz, H-2′), 3.66, 3.83 (each d, 1.4H, J=14.2 Hz, CH_2Ph), 3.68, 3.90 (each d, 2H, J=13.8 Hz, CH_2Ph), 4.11–4.23 (m, 2+1.4H, OCH_2), 6.01 (d, 0.7H, J=15.6 Hz, H-2), 6.13 (d, 1H, J=15.4 Hz, H-2), 6.75 (dd, 0.7H, J=15.6, 7.6 Hz, H-3), 6.89 (dd, 1H, J=15.4, 10.3 Hz, H-3), 7.24–7.34 (m, 5+3.5H, Ph); ^{13}C NMR (100 MHz): δ major invertomer 14.2, 18.1 (2q, $2CH_3$), 44.5, 44.8 (2d, C-2′, C-3′), 57.2, 60.3 (2t, OCH_2, CH_2Ph), 124.2 (d, C-2), 126.7, 127.4, 128.1 (3d, 5C in Ph), 138.9 (s, C in Ph), 144.1 (d, C-3), 165.4 (s, C-1); minor invertomer 11.1, 14.2 (2q, $2CH_3$), 42.1, 46.1 (2d, C-2′, C-3′), 54.8, 60.1 (2t, OCH_2, CH_2Ph), 121.0 (d, C-2), 126.5, 127.3, 128.1 (3d, 5C in Ph), 139.1 (s, C in Ph), 148.3 (d, C-3), 165.9 (s, C-1); EI-MS m/z 245 (M^+, 5%), 200 (14), 172 (85), 154 (100), 126 (10), 108 (12), 91 (63), 80 (20); HRMS calcd for $C_{15}H_{19}NO_2$: 245.1416, found: 245.1421.

4.2.5. Ethyl (*E*,2′*RS*,3′*SR*)-3-(1′-benzyl-3′-phenylaziridin-2′-yl)acrylate (5a). By analogy with the synthesis of **3a**, oxidation of alcohol **13**[7,10] (1.07 mg, 4.48 mmol) with oxalyl chloride and DMSO gave aldehyde **14a**,[10] which was consequently treated with NaH (60%, 215 mg, 5.4 mmol) and triethyl phosphonoacetate (1.20 g, 5.4 mmol) in dry methylene chloride at 0 °C, and the resulting mixture was stirred for 12 h at room temperature. Flash column chromatography [hexane–ethyl acetate (4:1)] of the reaction mixture afforded esters **5a** (361 mg, 26%); an oil; IR (film): 1720 cm^{-1} (C═O); ^{1}H NMR (300 MHz): δ 1.20 (t, 3H, J=7.2 Hz, CH_3), 2.51 (dd, 1H, J=7.9, 6.5 Hz, H-2′), 3.06 (d, 1H, J=6.5 Hz, H-3′), 3.72, 3.80 (each d, 2H, J=13.6 Hz, CH_2Ph), 4.08 (q, 2H, J=7.2 Hz, OCH_2), 6.01 (d, 1H, J=15.8 Hz, H-2), 6.49 (dd, 1H, J=15.8, 7.9 Hz, H-3), 7.20–7.39 (m, 10H, 2Ph); ^{13}C NMR (100 MHz): δ 14.3 (q, CH_3), 47.3, 49.5 (2d, C-2′, d C-3′), 60.2, 64.2 (2t, OCH_2, CH_2Ph), 123.7 (d, C-2), 127.0, 127.5, 127.7, 128.0, 128.3 (5d, 10C in 2Ph), 135.8, 138.2 (2s, 2C in 2Ph), 144.4 (d, C-3), 165.5 (s, C-1); EI-MS m/z 307 (M^+, 18%), 234 (100), 216 (20), 91 (63); HRMS calcd for $C_{20}H_{21}NO_2$: 307.1572, found: 307.1576.

4.2.6. Ethyl (*E*,2′*RS*,3′*RS*)-3-(1′-benzyl-3′-phenylaziridin-2′-yl)acrylate (5b). To a solution of the ester **15**[11] (480 mg, 1.71 mmol) in dry methylene chloride (8.5 mL) was added dropwise a 0.97 M solution of DBAL-H (3.5 mL, 3.4 mmol) in hexane at −70 °C. After the mixture had been stirred for 15 min at −70 °C, sodium fluoride (1.43 g, 34 mmol) was added to the mixture. The reaction was quenched by the addition of water (1.0 mL), and the reaction mixture was allowed to reach room temperature. The white precipitate was filtered off and washed with diethyl ether. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo giving an aldehyde **14b** that was used for the next step without further purification. To a suspension of NaH [41 mg, 1.71 mmol; prepared from an NaH dispersion (60%, 68 mg) by washing it twice with hexane (0.5 mL)] in dry methylene chloride (2 mL) was added dropwise a solution of triethyl phosphonoacetate (383 mg, 1.71 mmol) dry methylene chloride (2 mL) at 0 °C. After the mixture had been stirred for 10 min at 0 °C, a solution of aldehyde **14b** in dry methylene chloride (4 mL) was added dropwise, and stirring was continued for 0.5 h at 0 °C. Ice/water (20 mL) was added slowly to the mixture, and the organic phase was extracted with methylene chloride. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo, giving a residue that was subjected to flash column chromatography [hexane–ethyl acetate (2:1)] to afford **5b** (277 mg, 53% from **15**); an oil; IR (film): 1720 cm^{-1} (C═O); ^{1}H NMR (400 MHz): δ 1.30 (t, 3H, J=7.2 Hz, CH_3), 2.78 (dd, 1H, J=10, 2.8 Hz, H-2′), 2.94 (br s, 1H, H-3′), 3.91, 4.07 (each br d, 2H, J=14.0 Hz, CH_2Ph), 4.21 (q, 2H, J=7.2 Hz, OCH_2), 6.13 (d, 1H, J=15.6 Hz, H-2), 7.02 (dd, 1H, J=15.6, 10 Hz, H-3), 7.22–7.52 (m, 10H, 2Ph); ^{13}C NMR (100 MHz): δ 14.3 (q, CH_3), 48.6 (d, C-2′), 51.0 (d, C-3′), 57.4 (t, OCH_2), 60.5 (t, CH_2Ph), 124.9 (d, C-2), 125.9, 126.9, 127.2, 127.6, 128.3, 128.4 (6d, 10C in 2Ph), 138.5, 138.7 (2s, 2C in

2Ph), 142.9 (d, C-3), 165.5 (s, C-1); EI-MS *m/z* 307 (M^+, 12%), 262 (10), 234 (58), 216 (100), 142 (10), 129 (10), 105 (18), 91 (42); HRMS calcd for $C_{20}H_{21}NO_2$: 307.1572, found: 307.1573.

4.2.7. Dimethyl 1-tritylaziridin-2-ylmethlylenemalonate (7). To a solution of the aldehyde **16**[13] (932 mg, 3.0 mmol) in dry methylene chloride (18 mL) was added dimethyl malonate (367 mg, 2.8 mmol). Pyrrolidine (five drops) was added to the mixture at −70 °C, which stirred for 5 h at −70 °C and was warmed to room temperature and further stirred for 30 h. The reaction was quenched with 5% citric acid and the organic phase was extracted with methylene chloride. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo, giving a residue that was subjected to flash column chromatography [hexane–ethyl acetate (3:1)] to afford **7** (596 mg, 47%) as colorless needles; mp 165–168 °C (hexane–ethyl acetate); IR ($CHCl_3$): 1720 cm^{-1} (C=O); ^1H NMR (400 MHz): δ 1.58 (d, 1H, *J*=6.1 Hz, H-3′), 2.07 (d, 1H, *J*=2.7 Hz, H-3′), 2.20 (ddd, 1H, *J*=9.5, 6.1 Hz, 2.7, H-2′), 3.62, 3.81 (2s, 6H, 2Me), 7.00 (d, 1H, *J*=9.5 Hz, H-3), 7.19–7.30 (m, 9H, 3Ph), 7.42–7.45 (m, 6H, 3Ph); ^{13}C NMR (100 MHz): δ 30.7 (t, C-3′), 31.8 (d, C-2′), 52.1, 52.5 (2q, 2OMe), 74.4 (s, *C*Ph_3), 126.8, 127.4, 129.2 (3d, 15C in 3Ph), 128.4 (s, C-2), 143.6 (s, 3C in 3Ph), 151.4 (d, C-3), 163.9, 164.9 (2s, $2CO_2$); EI-MS *m/z* 427 (M^+, 1%), 257 (1), 243 (100), 228 (3), 165 (22); Anal. Calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28%. Found: C, 75.99; H, 5.98; N, 3.24%.

4.2.8. 1-Tritylaziridin-2-ylmethlylenemalononitrile (8). To a solution of the malononitrile (793 mg, 11.9 mmol) in dry toluene (15 mL) was added aldehyde **16**[13] (3.1 g, 9.9 mmol). The reaction mixture was stirred for 10 min at 110 °C and concentrated in vacuo, giving a residue that was subjected to flash column chromatography [hexane–ethyl acetate (5:1)] to afford **8** (1.72 g, 56%) as colorless prisms; mp 85–87 °C (hexane–chloroform); IR ($CHCl_3$): 2210 cm^{-1} (C≡N); ^1H NMR (400 MHz): δ 1.80 (d, 1H, *J*=6.0 Hz, H-3′), 2.28 (br s, 1H, H-3′), 2.28–2.33 (m, 1H, H-2′), 7.21–7.47 (m, 16H, H-3, 3Ph); ^{13}C NMR (100 MHz): δ 32.6 (t, C-3′), 33.8 (d, C-2′), 74.7 (s, *C*Ph_3), 89.4 (s, C-2), 110.3, 111.8 (2s, 2CN), 127.2, 127.8, 128.9 (3d, 15C in 3Ph), 142.7 (s, 3C in 3Ph), 169.4 (d, C-3); EI-MS *m/z* 361 (M^+, 1%), 260 (3), 245 (100), 183 (5), 165 (25), 105 (4), 77 (4); HRMS calcd for $C_{25}H_{19}N_3$: 361.1578, found: 361.1570.

4.2.9. 2-[(*E*)-1,3-Butadien-1-yl]-1-tritylaziridine (9). To a solution of allyldiphenylphosphine oxide (1.0 g, 4.2 mmol) and HMPA (1.5 g, 8.4 mmol) in dry THF (15 mL) was added dropwise butyl lithium (2.6 mL, 1.6 M in hexane) at −70 °C. After the mixture had been stirred for 10 min at −70 °C, a solution of aldehyde **16**[13] (1.1 g, 3.5 mmol) in dry THF (5 mL) was added dropwise at −70 °C. The mixture was stirred for 1 h, warmed to room temperature, and further stirred for 3 h. Ice/water (20 mL) was added slowly to the mixture, the organic phase was extracted with ether. The organic extract was washed with satd aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo, giving a residue that was subjected to flash column chromatography [hexane–ethyl acetate (10:1)] to afford **9** (666 mg, 56%) as colorless oil; IR ($CHCl_3$): 1590 cm^{-1} (C=C); ^1H NMR (400 MHz): δ 1.38 (d, 1H, *J*=6.1 Hz, H-3), 1.68–1.73 (m, 1H, H-2), 1.82 (d, 1H, *J*=2.7 Hz, H-3), 5.03 (d, 1H, *J*=10.0 Hz, H-4′), 5.13 (d, 1H, *J*=6.8 Hz, H-4′), 5.71 (dd, 1H, *J*=15.1, 7.8 Hz, H-1′), 6.24 (dd, 1H, *J*=15.1, 10.5 Hz, H-2′), 6.34–6.44 (m with dt-character, 1H, *J*=16.8 Hz, 10, H-3′), 7.15–7.29, 7.46–7.48 (2m, 15H, 3Ph); ^{13}C NMR (100 MHz): δ 29.6 (t, C-3), 34.3 (d, C-2), 74.4 (s, *C*Ph_3), 115.9 (t, C-4′), 126.5, 127.3, 129.4 (3d, 15C in 3Ph), 132.2, 134.8, 136.5 (3d, C-1′, C-2′, C-3′), 144.2 (s, 3C in 3Ph); EI-MS *m/z* 337 (M^+, 2%), 257 (1), 243 (100), 228 (3), 165 (23), 94 (2), 77 (2); HRMS calcd for $C_{25}H_{23}N$: 337.1831, found: 337.1834.

4.3. Reactions of aziridines (*Z*)-1 with disubstituted alkenes

4.3.1. (*Z*)-1 and (*Z*)-2-Pentenenitrile. A solution of aziridine (*Z*)-**1** (510 mg, 2.77 mmol) in dry acetonitrile (45 mL) with (*Z*)-2-pentenenitrile (2.19 g, 27.7 mmol) was irradiated with a low-pressure mercury lamp (conversion 78%) in a quartz test tube for 1.5 h at room temperature. After removal of the solvent, flash column chromatography [hexane–ethyl acetate (4:1)] of the residue afforded (*Z*)-**17** (320 mg, 56%[14]).

(2*Z*,2′*RS*,3′*RS*,4′*SR*)-3-(1-Benzyl-3-cyano-4-ethylpyrrolidin-2-yl)acrylonitrile [(*Z*)-**17**], an oil; IR (film): 2210 cm^{-1} (C≡N); ^1H NMR (500 MHz): δ 0.93 (t, 3H, *J*=7.3 Hz, 4′-CH_2CH_3), 1.55–1.73 (m, 2H, *J*=7.3 Hz, 4′-CH_2), 2.30–2.37 (m, 1H, H-4′), 2.64 (t, 1H, *J*=9.8 Hz, H-5′), 2.87 (dd, 1H, *J*=9.8, 7.0 Hz, H-5′), 3.29 (dd, 1H, *J*=7.3, 5.5 Hz, H-3′), 3.48, 3.83 (each d, 2H, *J*=13.7 Hz, CH_2Ph), 3.87 (dd, 1H, *J*=9.2, 5.5 Hz, H-2′), 5.55 (d, 1H, *J*=11.0 Hz, H-2), 6.63 (dd, 1H, *J*=11.0, 9.2 Hz, H-3), 7.24–7.32 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 12.4 (q, 4′-CH_2CH_3), 24.8 (t, 4′-CH_2), 39.9 (d, C-3′), 41.1 (d, C-4′), 56.3 (t, C-5′), 57.5 (t, *C*H_2Ph), 65.4 (d, C-2′), 103.4 (d, C-2), 114.9, 114.9 (2s, 2CN), 127.3, 128.3, 128.4 (3d, 5C in Ph), 137.9 (s, C in Ph), 152.7 (d, C-3); EI-MS *m/z* 265 (M^+, 26%), 225 (5), 184 (37), 174 (9), 91 (100), 65 (10); HRMS calcd for $C_{17}H_{19}N_3$: 265.1579, found: 265.1575.

4.3.2. (*Z*)-1 and (*E*)-Ethyl crotonate. A solution of aziridine (*Z*)-**1** (44.7 mg, 0.24 mmol) in dry acetonitrile (4.0 mL) with (*E*)-ethyl crotonate (275 mg, 2.4 mmol) was irradiated with a low-pressure mercury lamp (conversion 56%) in a quartz test tube for 1.5 h at room temperature. After removal of the solvent, flash column chromatography [hexane–ethyl acetate (2:1)] of the residue afforded a 1:2 mixture of **18a** and **18b** (20.1 mg, 50%[14]).

Ethyl (2*RS*,3*RS*,4*RS*)-1-benzyl-2-[(*Z*)-2-cyanovinyl]-4-methylpyrrolidine-3-carboxylate [(*Z*)-**18a**]; ^1H NMR (500 MHz): δ 1.04 (d, 3H, *J*=6.4 Hz, 4-Me), 1.24 (t, 3H, *J*=7 Hz, OCH_2CH_3), 2.12 (t, 1H, *J*=9.5 Hz, H-5), 2.62–2.70 (m, 1H, H-4), 2.87 (t, 1H, *J*=9.8 Hz, H-3), 3.11 (dd, 1H, *J*=9, 6.7 Hz, H-5), 3.53, 3.75 (each d, 2H, *J*=13.1 Hz, CH_2Ph), 3.96 (t, 1H, *J*=9.8 Hz, H-2), 4.11 (q, 2H, *J*=7 Hz, OCH_2), 5.27 (d, 1H, *J*=11.0 Hz, H-2′), 6.41–6.46 (m with t-character, 1H, *J*=10 Hz, H-1′), 7.22–7.31 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 14.4 (q, 4-Me), 17.2 (q, OCH_2CH_3), 36.0 (d, C-4), 55.6 (d, C-3), 58.1 (t, C-5), 60.5 (t, *C*H_2Ph), 60.8 (t, OCH_2), 65.4 (d, C-2), 100.2 (d, C-2′), 115.4 (s,

CN), 127.0, 128.1, 128.7 (3d, 5C in Ph), 138.1 (s, C in Ph), 153.7 (d, C-1′), 171.4 (s. CO_2).

Ethyl (2*RS*,3*SR*,4*SR*)-1-benzyl-2-[(*Z*)-2-cyanovinyl]-4-methylpyrrolidine-3-carboxylate [(*Z*)-**18b**]; ^{1}H NMR (500 MHz): δ 1.13 (d, 3H, *J*=6.7 Hz, 4-Me), 1.29 (t, 3H, *J*=7 Hz, OCH_2CH_3), 2.40 (dd, 1H, *J*=9, 7 Hz, H-3), 2.52–2.61 (m, 1H, H-4), 2.62–2.70 (m, 2H, 2H-5), 3.40, 3.81 (each d, 2H, *J*=13.1 Hz, CH_2Ph), 3.79 (t, 1H, *J*=9 Hz, H-2), 4.19 (q, 2H, *J*=7 Hz, OCH_2), 5.39 (d, 1H, *J*=11.0 Hz, H-2′), 6.37 (dd, 1H, *J*=11.0, 9.8 Hz, H-1′), 7.22–7.31 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 14.3 (q, 4-Me), 20.8 (q, OCH_2CH_3), 35.5 (d, C-4), 57.7 (d, C-3), 58.2 (t, C-5), 60.2 (t, CH_2Ph), 61.2 (t, OCH_2), 68.6 (d, C-2), 101.7 (d, C-2′), 115.2 (s, CN), 127.0, 128.1, 128.4 (3d, 5C in Ph), 138.5 (s, C in Ph), 154.7 (d, C-1′), 172.0 (s, CO_2).

4.4. Reactions of 3-methyl aziridines 3 and 4 with alkenes

4.4.1. (*E*)-3a and (*Z*)-2-pentenenitrile. A solution of aziridine (*E*)-**3a** (220 mg, 1.10 mmol) in dry acetonitrile (18.3 mL) with 10 equiv of (*Z*)-2-pentenenitrile was irradiated with a low-pressure mercury lamp in a quartz test tube for 1.5 h at room temperature. The reactant was recovered quantitatively.

A solution of aziridine (*E*)-**3a** (54 mg, 0.27 mmol) in xylene (4.5 mL) with 10 equiv of (*Z*)-2-pentenenitrile was heated under reflux for 4 h affording a complex mixture.

4.4.2. Aziridines 3 and 4 with *tert*-butyl acrylate. A 0.060 mol L^{-1} solution of aziridines **3** and **4** in dry acetonitrile with 10 equiv of *tert*-butyl acrylate was irradiated with a low-pressure mercury lamp in a quartz test tube at room temperature. After removal of the solvent, flash column chromatography afforded the adducts. A 0.060 mol L^{-1} solution of aziridines **3** and **4** in xylene with 10 equiv of *tert*-butyl acrylate was heated under reflux. The results are summarized in Table 1.

4.4.3. *tert*-Butyl (2*RS*,3*RS*,5*SR*)-1-benzyl-2-[(*E*)-2-cyanovinyl]-5-methylpyrrolidine-3-carboxylate [(*E*)-19a]. An oil; IR ($CHCl_3$): 2220 (C≡N), 1720 cm^{-1} (C=O); ^{1}H NMR (300 MHz): δ 1.03 (d, 3H, *J*=6.4 Hz, 5′-Me), 1.45 (s, 9H, CMe_3), 1.86 (ddd, 1H, *J*=13.0, 5.0, 4.4 Hz, H-4), 2.29 (ddd, 1H, *J*=13.0, 10.3, 7.4 Hz, H-4), 2.64 (m with quintet character, 1H, *J*=5 Hz, H-3), 3.15–3.28 (m, 1H, H-5), 3.51, 3.76 (each d, 2H, *J*=13.9 Hz, CH_2Ph), 3.73 (dd, 1H, *J*=8.4, 5.5 Hz, H-2), 5.42 (dd, 1H, *J*=16.2, 0.7 Hz, H-2′), 6.64 (dd, 1H, *J*=16.2, 8.4 Hz, H-1′), 7.21–7.33 (m, 5H, Ph); ^{13}C NMR (125 MHz): δ 16.3 (q, 5-Me), 28.0 (q, CMe_3), 34.7 (t, C-4), 48.9 (d, C-3), 51.4 (t, CH_2Ph), 54.9 (d, C-5), 65.6 (d, C-2), 81.1 (s, CMe_3), 101.2 (d, C-2′), 117.0 (s, CN), 127.0, 128.2, 128.3 (3d, 5C in Ph), 138.8 (s, C in Ph), 155.5 (d, C-1′), 172.5 (s, CO_2); EI-MS *m*/*z* 326 (M^+, 7%), 269 (32), 253 (11), 179 (33), 91 (100); HRMS calcd for $C_{20}H_{26}N_2O_2$: 326.1994, found: 326.1999.

4.4.4. *tert*-Butyl (2*RS*,3*RS*,5*RS*)-1-benzyl-2-[(*E*)-2-cyanovinyl]-5-methylpyrrolidine-3-carboxylate [(*E*)-19b]. Colorless crystals; mp 115–116 °C (hexane–ethyl acetate); IR ($CHCl_3$): 2220 (C≡N), 1720 cm^{-1} (C=O); ^{1}H NMR (300 MHz): δ 1.10 (d, 3H, *J*=6.1 Hz, 5-Me), 1.39 (s, 9H, CMe_3), 1.70 (ddd, 1H, *J*=13.2, 9.2, 4.2 Hz, H-4), 2.48 (ddd, 1H, *J*=13.2, 9.9, 8.6 Hz, H-4), 3.15–3.25 (m, 1H, H-5), 3.20–3.28 (m, 1H, H-3), 3.46, 3.83 (each d, 2H, *J*=13.9 Hz, CH_2Ph), 3.66 (dd, 1H, *J*=9.7, 7.9 Hz, H-2), 5.25 (d, 1H, *J*=16.2 Hz, H-2′), 6.66 (dd, 1H, *J*=16.2, 9.7 Hz, H-1′), 7.21–7.34 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 19.2 (q, 5-Me), 28.2 (q, CMe_3), 33.7 (t, C-4), 46.8. (d, C-3), 52.0 (t, CH_2Ph), 55.3 (d, C-5), 64.7 (d, C-2), 81.2 (s, CMe_3), 102.6 (d, C-2′), 116.5 (s, CN), 126.9, 128.1, 128.2 (3d, 5C in Ph), 138.6 (s, C in Ph), 151.9 (d, C-1′), 170.5 (s, CO_2); EI-MS *m*/*z* 326 (M^+, 7%), 269 (19), 253 (31), 179 (41), 91 (100); Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58%. Found: C, 73.66; H, 7.99; N, 8.61%.

4.4.5. *tert*-Butyl (2*RS*,3*RS*,5*SR*)-1-benzyl-2-[(*Z*)-2-cyanovinyl]-5-methylpyrrolidine-3-carboxylate [(*Z*)-19a]. Colorless crystals; mp 77–78 °C (hexane–ethyl acetate); IR ($CHCl_3$): 2220 (C≡N), 1720 cm^{-1} (C=O); ^{1}H NMR (400 MHz): δ 1.05 (d, 3H, *J*=6.6 Hz, 5-Me), 1.48 (s, 9H, CMe_3), 1.92 (ddd, 1H, *J*=12.9, 5.1, 3.7 Hz, H-4), 2.28 (ddd, 1H, *J*=12.9, 10.5, 7.5 Hz, H-4), 2.64–2.71 (m, 1H, H-3), 3.24–3.32 (m, 1H, H-5), 3.61, 3.73 (each d, 2H, *J*=13.9 Hz, CH_2Ph), 4.07 (dd, 1H, *J*=10, 6.6 Hz, H-2), 5.37 (d, 1H, *J*=10.7 Hz, H-2′), 6.36 (dd, 1H, *J*=10.7, 10 Hz, H-1′), 7.22–7.33 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 15.8 (q, 5-Me), 28.0 (q, CMe_3), 34.6 (t, C-4), 49.5 (d, C-3), 51.7 (t, CH_2Ph), 55.3 (d, C-5), 64.6 (d, C-2), 81.3 (s, CMe_3), 101.3 (d, C-2′), 115.2 (s, CN), 126.8, 128.1, 128.2 (3d, 5C in Ph), 138.9 (s, C in Ph), 154.9 (d, C-1′), 172.0 (s, CO_2); EI-MS *m*/*z* 326 (M^+, 3%), 269 (29), 253 (11), 179 (41), 91 (100); HRMS calcd for $C_{20}H_{26}N_2O_2$: 326.1994, found: 326.1988.

4.4.6. *tert*-Butyl (2*RS*,3*RS*,5*RS*)-1-benzyl-2-[(*Z*)-2-cyanovinyl]-5-methylpyrrolidine-3-carboxylate [(*Z*)-19b]. Colorless crystals; mp 104–106 °C (hexane–ethyl acetate); IR ($CHCl_3$): 2220 (C≡N), 1720 cm^{-1} (C=O); ^{1}H NMR (400 MHz): δ 1.09 (d, 3H, *J*=6.3 Hz, 5-Me), 1.40 (s, 9H, CMe_3), 1.70 (ddd, 1H, *J*=13, 9.0, 3.9 Hz, H-4), 2.49 (ddd, 1H, *J*=13, 10, 8.5 Hz, H-4), 3.19–3.27 (m, 1H, H-5), 3.28–3.36 (m, 1H, H-3), 3.54, 3.78 (each d, 2H, *J*=13.9 Hz, CH_2Ph), 4.18 (dd, 1H, *J*=10.7, 8.1 Hz, H-2), 5.41 (dd, 1H, *J*=11.0, 0.7 Hz, H-2′), 6.46 (dd, 1H, *J*=11.0, 10.7 Hz, H-1′), 7.22–7.34 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 19.1 (q, 5-Me), 28.2 (q, CMe_3), 33.9 (t, C-4), 46.7 (d, C-3), 52.5 (t, CH_2Ph), 55.7 (d, C-5), 63.2 (d, C-2), 81.2 (s, CMe_3), 102.0 (d, C-2′), 114.9 (s, CN), 126.9, 128.2, 128.3 (3d, 5C in Ph), 138.7 (s, C in Ph), 151.7 (d, C-1′), 170.9 (s, CO_2); EI-MS *m*/*z* 326 (M^+, 3%), 269 (17), 255 (28), 235 (28), 179 (30), 107 (23) and 91 (100); Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58%. Found: C, 73.57; H, 7.98; N, 8.48%.

4.4.7. Ethyl (*E*,2′*RS*,3′*RS*,5′*RS*)-3-(1-benzyl-3-*tert*-butyloxycarbonyl-5-methylpyrrolidin-2-yl)acrylate [(*E*)-20b] and ethyl (*E*,2′*RS*,3′*SR*,5′*RS*)-3-(1-benzyl-3-*tert*-butyloxycarbonyl-5-methylpyrrolidin-2-yl)acrylate [(*E*)-20c]. An oily 5:4 mixture; ^{1}H NMR (400 MHz): δ 1.03 (d, 3H, *J*=6.4 Hz, 5′-Me for **c**), 1.09 (d, 3H, *J*=6.4 Hz, 5′-Me for **b**), 1.27 (t, 3H, *J*=7.3 Hz, OCH_2CH_3 for **b**), 1.29 (t, 3H,

J=7.4 Hz, OCH_2CH_3 for **c**), 1.34 (s, 9H, CMe_3 for **b**), 1.44 (s, 9H, CMe_3 for **c**), 1.65 (ddd, 1H, J=13.1, 4.3, 4.0 Hz, H-4′ for **b**), 1.83–1.88 (m with dt-character, 1H, J=12.8, 5 Hz, H-4′ for **c**), 2.30 (ddd, 1H, J=12.8, 10.4, 7.6 Hz, H-4′ for **c**), 2.53 (td, 1H, J=13.1, 9.2 Hz, H-4′ for **b**), 2.64–2.69 (m with quintet character, 1H, J=5 Hz, H-3′ for **c**), 3.19–3.25 (m, 3H, H-3′ for **b** and H-5′ for **b** and **c**), 3.50, 3.79 (each d, 4H, J=14 Hz, CH_2Ph for **b** and **c**), 3.72 (dd, 1H, J=10, 7.6 Hz, H-2′ for **b**), 3.75 (dd, 1H, J=8.9, 5.2 Hz, H-2′ for **c**), 4.19 (q, 4H, J=7.3 Hz, OCH_2 for **b** and **c**), 5.75 (d, 1H, J=15.6 Hz, H-2 for **b**), 5.88 (d, 1H, J=15.6 Hz, H-2 for **c**), 6.84 (dd, 1H, J=15.6, 10 Hz, H-3 for **b**), 6.87 (dd, 1H, J=15.6, 8.9 Hz, H-3 for **c**), 7.19–7.32 (m, 10 H, Ph for **b** and **c**); ^{13}C NMR (100 MHz): δ 14.4 (q, OCH_2CH_3 for **b** and **c**), 16.7 (q, 5′-Me for **c**), 19.6 (q, 5′-Me for **b**), 28.1 (q, CMe_3 for **b** and **c**), 33.6 (t, C-4′ for **b**), 34.8 (t, C-4′ for **c**), 46.9 (d, C-3′ for **b**), 49.1 (d, C-3′ for **c**), 51.3, 51.9 (t, CH_2Ph for **b** and **c**), 54.7, 55.3 (d, C-5′ for **b** and **c**), 60.3, 60.4 (t, OCH_2 for **b** and **c**), 64.2, 65.1 (d, C-2′ for **b** and **c**), 80.7 (s, CMe_3 for **b** and **c**), 123.2 (d, C-2 for **c**), 124.9 (d, C-2 for **b**), 126.6, 127.9, 128.0, 128.1, 128.3 (5d, 10C in Ph for **b** and **c**), 139.3 (s, 2C in Ph for **b** and **c**), 144.3 (d, C-3 for **b**), 148.1 (d, C-3 for **c**), 165.4, 166.0 (s, C-1 for **b** and **c**), 170.9, 172.8 (s, CO_2 for **b** and **c**).

4.4.8. Ethyl (*Z*)-5-[(*E*)-*N*-benzylideneamino]-3-hexenoate (21). An oil; IR ($CHCl_3$): 1720 (C=O), 1635 cm^{-1} (C=N); ^{1}H NMR (400 MHz): δ 1.24 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.35 (d, 3H, J=6.6 Hz, 3H-3), 3.17 (ddd, 2H, J=7.3, 3.4, 1.7 Hz, 2H-2), 4.13 (q, 2H, J=7.1 Hz, OCH_2), 4.25–4.33 (m, 1H, H-5), 5.66 (dtd, 1H, J=11.0, 7.3, 1.0 Hz, H-3), 5.78–5.85 (m with ddt-character, 1H, J=11, 8, 2 Hz, H-4), 7.37–7.42, 7.71–7.74 (each m, 5H, Ph), 8.31 (s, 1H, N=CH); ^{13}C NMR (100 MHz): δ 14.3 (q, OCH_2CH_3), 23.2 (q, C-6), 33.6 (t, C-2), 60.7 (t, OCH_2), 62.9 (d, C-5), 120.9 (d, C-3), 128.0, 128.4, 130.4 (3, 5C in Ph), 135.9 (d, C-4), 136.1 (s, C in Ph), 159.3 (d, N=C), 171.2 (s, C-1); EI-MS m/z 245 (M^+, 16%), 230 (6), 200 (16), 172 (31), 158 (100), 131 (11), 106 (23), 91 (27), 67 (15), 55 (11); HRMS calcd for $C_{15}H_{19}NO_2$: 245.1416, found: 245.1417.

4.5. Reactions of 3-phenylaziridines 5 and 6 with alkenes

A 0.060 mol L^{-1} solution of aziridines **5** and **6** in dry acetonitrile with 10 equiv of *tert*-butyl acrylate was irradiated with a low-pressure mercury lamp in a quartz test tube at room temperature. After removal of the solvent, flash column chromatography afforded the adducts. A 0.060 mol L^{-1} solution of aziridines **5** and **6** in xylene with 10 equiv of *tert*-butyl acrylate was heated under reflux. The results are summarized in Table 2.

4.5.1. Ethyl (*E*,2′*RS*,3′*RS*,5′*RS*)-3-(1-benzyl-3-*tert*-butyloxycarbonyl-5-phenylpyrrolidin-2-yl)acrylate [(*E*)-22a]. An oil; IR ($CHCl_3$): 1710 cm^{-1} (C=O); ^{1}H NMR (500 MHz): δ 1.26 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.39 (s, 9H, CMe_3), 2.17 (t, 2H, J=8.5 Hz, H-4′), 2.99–3.06 (m with q-character, 1H, J=9 Hz, H-3′), 3.45, 3.75 (each d, 2H, J=14.0 Hz, CH_2Ph), 3.67–3.73 (m with q-character, 2H, J=8 Hz, H-2′, H-5′), 4.15 (q, 2H, J=7.0 Hz, OCH_2), 5.87 (dd, 1H, J=15.6, 0.6 Hz, H-2), 6.78 (dd, 1H, J=15.6, 8 Hz, H-3), 7.03–7.47 (m, 10H, 2Ph); ^{13}C NMR (100 MHz): δ 14.4 (q, OCH_2CH_3), 28.1 (q, CMe_3), 37.7 (t, C-4′), 47.8 (d, C-3′), 54.1 (t, CH_2Ph), 60.2 (t, OCH_2), 64.2, 66.9 (2d, C-2′, C-5′), 81.0 (s, CMe_3), 122.6 (d, C-2), 126.9, 127.3, 127.6, 127.8, 128.4, 129.8 (6d, 10C in 2Ph), 136.3 (s, C in CH_2Ph), 141.9 (s, C in 5′-Ph), 147.3 (d, C-3), 165.8 (C-1), 170.8 (s, CO_2); EI-MS m/z 435 (M^+, 6%), 378 (10), 362 (6), 344 (24), 334 (7), 288 (34), 216 (11), 104 (8), 91 (100), 57 (13); HRMS calcd for $C_{27}H_{33}NO_4$: 435.2410, found: 435.2415.

4.5.2. Ethyl (*E*,2′*RS*,3′*RS*,5′*SR*)-3-(1-benzyl-3-*tert*-butyloxycarbonyl-5-phenylpyrrolidin-2-yl)acrylate [(*E*)-22b]. An oil; IR ($CHCl_3$): 1715 cm^{-1} (C=O); ^{1}H NMR (500 MHz): δ 1.29 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.34 (s, 9H, CMe_3), 1.97 (ddd, 1H, J=13.7, 9.8, 5.5 Hz, H-4′), 2.84 (td, 1H, J=13.7, 9.8 Hz, H-4′), 3.38–3.42 (m, 1H, H-3′), 3.40, 3.60 (each d, 2H, J=13.7 Hz, CH_2Ph), 3.93 (dd, 1H, J=10.5, 7.0 Hz, H-2′), 4.14 (dd, 1H, J=9.8, 5.5 Hz, H-5′), 4.22 (q, 2H, J=7.2 Hz, OCH_2), 5.72 (d, 1H, J=15.6 Hz, H-2), 6.97 (dd, 1H, J=15.6, 10.5 Hz, H-3), 7.20–7.50 (10H, m, 2Ph); ^{13}C NMR (100 MHz): δ 14.4 (q, OCH_2CH_3), 28.1 (q, CMe_3), 35.3 (t, C-4′), 47.4 (d, C-3′), 51.7 (t, CH_2Ph), 60.4 (t, OCH_2), 63.4, 65.0 (2d, C-2′, C-5′), 80.9 (s, CMe_3), 125.8 (d, C-2), 126.7, 127.1, 127.4, 128.0, 128.3, 128.4 (6d, 10C in 2Ph), 138.7 (s, C in CH_2Ph), 142.8 (d, C-3), 144.0 (s, C in 5′-Ph), 165.3 (C-1), 170.5 (s, CO_2); EI-MS m/z 435 (M^+, 6%), 378 (41), 362 (14), 344 (100), 288 (86), 216 (15), 91 (80); HRMS calcd for $C_{27}H_{33}NO_4$: 435.2410, found: 435.2412.

4.5.3. Ethyl (*E*,2′*RS*,3′*SR*,5′*RS*)-3-(1-benzyl-3-*tert*-butyloxycarbonyl-5-phenylpyrrolidin-2-yl)acrylate [(*E*)-22c]. An oil; IR ($CHCl_3$): 1710 cm^{-1} (C=O); ^{1}H NMR (400 MHz): δ 1.28 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.39 (s, 9H, CMe_3), 1.88–1.96 (m, 1H, H-4′), 2.35 (ddd, 1H, J=12.5, 8, 5 Hz, H-4′), 2.72–2.79 (m, 1H, H-3′), 3.47, 3.76 (each d, 2H, J=13.7 Hz, CH_2Ph), 3.53–3.56 (m with t-character, 1H, J=8 Hz, H-2′), 3.78–3.82 (m with t-character, 1H, J=8 Hz, H-5′), 4.16 (q, 2H, J=7.1 Hz, OCH_2), 5.90 (d, 1H, J=15.6 Hz, H-2), 6.79 (dd, 1H, J=15.6, 7.8 Hz, H-3), 7.07–7.47 (m, 10H, 2Ph); ^{13}C NMR (100 MHz): δ 14.4 (q, OCH_2CH_3), 28.2 (q, CMe_3), 37.8 (t, C-4′), 49.0 (d, C-3′), 54.9 (t, CH_2Ph), 60.3 (t, OCH_2), 66.8, 67.3 (2d, C-2′, C-5′), 80.9 (s, CMe_3), 121.9 (d, C-2), 126.9, 127.2, 127.4, 127.8, 128.4, 129.7 (6d, 10C in 2Ph), 136.5 (s, C in CH_2Ph), 142.6 (s, C in 5′-Ph), 149.3 (d, C-3), 166.0 (C-1), 172.6 (s, CO_2); EI-MS m/z 435 (M^+, 37%), 378 (68), 362 (21), 344 (44), 334 (9), 306 (26), 288 (48), 202 (9), 91 (100); HRMS calcd for $C_{27}H_{33}NO_4$: 435.2410, found: 435.2404.

4.5.4. Ethyl (2*E*,2′*RS*,3′*SR*,5′*SR*)-3-(1-benzyl-3-*tert*-butyloxycarbonyl-5-phenylpyrrolidin-2-yl)acrylate [(*E*)-22d]. An oil; IR ($CHCl_3$): 1720, 1715 cm^{-1} (C=O); ^{1}H NMR (500 MHz): δ 1.30 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.45 (s, 9H, CMe_3), 2.33 (ddd, 1H, J=13.4, 7.5, 5 Hz, H-4′), 2.59 (ddd, 1H, J=13.4, 9.5, 8.2 Hz, H-4′), 2.74 (ddd, 1H, J=9.5, 5, 2.7 Hz, H-3′), 3.33, 3.60 (each d, 2H, J=14.0 Hz, CH_2Ph), 4.01–4.05 (m with t-character, 1H, J=8 Hz, H-5′), 4.08 (dd, 1H, J=9.8, 2.7 Hz, H-2′), 4.22 (q, 2H, J=7.2 Hz, OCH_2), 5.74 (d, 1H, J=15.6 Hz, H-2), 7.00 (dd, 1H, J=15.6, 9.8 Hz, H-3), 7.20–7.40 (m, 10H, 2Ph);

^{13}C NMR (100 MHz): δ 14.4 (q, OCH_2CH_3), 28.2 (q, CMe_3), 36.4 (t, C-4′), 48.5 (d, C-3′), 50.9 (t, CH_2Ph), 60.5 (t, OCH_2), 64.0, 65.3 (2d, C-2′, C-5′), 80.8 (s, CMe_3), 124.1 (d, C-2), 126.5, 127.3, 127.8, 127.9, 128.0, 128.3 (6d, 10C in 2Ph), 138.8 (s, C in CH_2Ph), 142.6 (s, C in 5′-Ph), 145.5 (d, C-3), 165.8 (C-1), 172.4 (s, CO_2); EI-MS *m*/*z* 435 (M^+, 49%), 378 (66), 362 (20), 344 (33), 334 (10), 306 (37), 288 (51), 216 (10), 91 (100); HRMS calcd for $C_{27}H_{33}NO_4$: 435.2410, found: 435.2414.

4.5.5. Ethyl (*E*,2′*RS*,4′*RS*,5′*SR*)-3-(1-benzyl-4-*tert*-butyloxycarbonyl-5-phenylpyrrolidin-2-yl)acrylate [(*E*)-23a]. An oil contaminated with ca. 65% of (*E*)-**22a**; ^{1}H NMR (500 MHz): δ 0.97 (s, 9H, CMe_3), 1.30 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.99 (ddd, 1H, J=12.8, 8.2, 6 Hz, H-3′), 2.25 (dt, 1H, J=12.8, 10.1 Hz, H-3′), 3.09 (td, 1H, J=10, 8.2 Hz, H-4′), 3.37–3.42 (m, 1H, H-2′), 3.52, 3.76 (each d, 2H, J=14.0 Hz, CH_2Ph), 4.04 (d, 1H, J=10.4 Hz, H-5′), 4.20 (q, 2H, J=7.0 Hz, OCH_2), 5.97 (d, 1H, J=15.6 Hz, H-2), 6.91 (dd, 1H, J=15.6, 8.2 Hz, H-3), 7.03–7.53 (m, 10H, 2Ph); ^{13}C NMR (100 MHz): δ 14.4 (q, OCH_2CH_3), 27.5 (q, CMe_3), 34.2 (t, C-3′), 48.7 (d, C-4′), 54.1 (t, CH_2Ph), 60.3 (t, OCH_2), 63.1, 68.0 (2d, C-2′, C-5′), 80.2 (s, CMe_3), 122.0 (d, C-2), 126.9, 127.2, 127.8, 128.4, 129.0, 129.8 (6d, 10C in 2Ph), 135.8 (s, C in CH_2Ph), 139.9 (s, C in 5′-Ph), 150.1 (d, C-3), 166.0 (C-1), 170.8 (s, CO_2).

4.5.6. Ethyl (*E*,2′*RS*,4′*SR*,5′*RS*)-3-(1-benzyl-4-*tert*-butyloxycarbonyl-5-phenylpyrrolidin-2-yl)acrylate [(*E*)-23b]. An oil; IR ($CHCl_3$): 1710 cm^{-1} (C=O); ^{1}H NMR (300 MHz): δ 0.97 (s, 9H, CMe_3), 1.31 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.88 (ddd, 1H, J=13.2, 8.8, 2.4 Hz, H-3′), 2.77 (ddd, 1H, J=13.2, 10.6, 8.1 Hz, H-3′), 3.33, 3.63 (each d, 2H, J=13.8 Hz, CH_2Ph), 3.47–3.57 (m, 1H, H-4′), 3.82–3.90 (m, 1H, H-2′), 4.21 (q, 2H, J=7.2 Hz, OCH_2), 4.33 (d, 1H, J=9.7 Hz, H-5′), 5.81 (dd, 1H, J=15.6, 0.6 Hz, H-2), 6.98 (dd, 1H, J=15.6, 9.0 Hz, H-3), 7.16–7.31 (m, 10H, 2Ph); ^{13}C NMR (75 MHz): δ 14.4 (q, OCH_2CH_3), 27.5 (q, CMe_3), 32.6 (t, C-3′), 48.1 (d, C-4′), 51.9 (t, CH_2Ph), 60.5 (t, OCH_2), 60.9 (d, C-2′), 67.2 (d, C-5′), 80.3 (s, CMe_3), 122.8 (d, C-2), 126.7, 127.4, 127.8, 128.0, 128.4, 129.2 (6d, 10C in 2Ph), 138.8, 139.4 (2s, 2C in CH_2Ph, 5′-Ph), 147.9 (d, C-3), 166.0 (C-1), 170.8 (s, CO_2); EI-MS *m*/*z* 435 (M^+, 3%), 378 (28%), 362 (10), 344 (76), 288 (100), 216 (10), 91 (54); HRMS calcd for $C_{27}H_{33}NO_4$: 435.2410, found: 435.2412.

4.5.7. Ethyl (*E*,2′*RS*,3′*RS*,5′*SR*)-3-(3-methyloxycarbonyl-5-phenylpyrrolidin-2-yl)acrylate [(*E*)-24b]. An oil; IR ($CHCl_3$): 3400 (N–H), 1720 cm^{-1} (C=O); ^{1}H NMR (400 MHz): δ 1.29 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.94 (br s, 1H, NH), 1.96–2.06 (m, 1H, H-4′), 2.68 (ddd, 1H, J=13.7, 8, 6 Hz H-4′), 3.33–3.39 (m, 1H, H-3′), 3.67 (s, 3H, OCH_3), 4.20 (q, 2H, J=7.1 Hz, OCH_2), 4.27–4.31 (m with t-character, 1H, J=7 Hz, H-2′), 4.66–4.70 (m with t-character, 1H, J=8 Hz, H-5′), 6.02 (dd, 1H, J=15.6 Hz, 1.0, H-2), 6.95 (dd, 1H, J=15.6, 7.1 Hz, H-3), 7.22–7.37 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 14.4 (q, OCH_2CH_3), 37.2 (t, C-4′), 48.6 (d, C-3′), 51.8 (q, OCH_3), 60.3, 61.5 (2d, C-2′, C-5′), 60.5 (t, OCH_2), 122.3 (d, C-2), 126.0, 126.8, 128.4 (3d, 5C in Ph), 144.7 (s, C in Ph), 145.2 (d, C-3), 165.8 (C-1), 172.6 (s, CO_2); EI-MS *m*/*z* 303 (M^+, 16%), 274 (21), 258 (12), 230 (16), 199 (15), 144 (29), 126 (12), 119 (100), 112 (17), 104 (10); HRMS calcd for $C_{17}H_{21}NO_4$: 303.1471, found: 303.1465.

4.6. Reactions of aziridines 3 and 5 with molecular oxygen

4.6.1. Aziridine (*Z*)-3a and oxygen. A solution of (*Z*)-**3a** (200 mg, 1.01 mmol) in acetonitrile was irradiated with a low-pressure mercury lamp (conversion 83%) in a quartz test tube under bubbling oxygen for 2 h at room temperature. After removal of the solvent, flash column chromatography [hexane–ethyl acetate (3:1)] of the residue afforded adducts **26** (46.1 mg, 24%).[14]

(*Z*)-(4-Benzyl-5-methyl-1,2,4-dioxazolidin-3-yl)acrylonitrile (**26**), an oil; IR ($CHCl_3$): 2220 cm^{-1} (C≡N); ^{1}H NMR (400 MHz): δ 1.24 (d, 3H, J=5.4 Hz, 5′-CH_3), 4.01, 4.11 (each d, 2H, J=12.9 Hz, CH_2Ph), 4.72 (q, 1H, J=5.4 Hz, H-5′), 5.37 (d, 1H, J=11.0 Hz, H-2), 5.43 (d, 1H, J=7.8 Hz, H-3′), 6.48 (dd, 1H, J=11.0, 7.8 Hz, H-3), 7.26–7.38 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 18.5 (q, 5′-CH_3), 57.8 (t, CH_2Ph), 93.8 (d, C-3′), 95.3 (d, C-5′), 100.9 (d, C-2), 114.5 (s, C-1), 127.7, 128.6, 128.7 (3d, 5C in Ph), 136.8 (s, C in Ph), 149.4 (d, C-3); EI-MS *m*/*z* 230 (M^+, 1%), 198 (33), 149 (6), 107 (63), 91 (100), 77 (9), 65 (12), 50 (9); HRMS calcd for $C_{13}H_{14}N_2O_2$: 230.1055, found: 230.1057.

4.6.2. Aziridine (*E*)-5b and oxygen. By analogy with the photoreactions of (*Z*)-**3a**, a solution of (*E*)-**5b** (41.2 mg, 0.13 mmol) in acetonitrile (3 mL) was irradiated (conversion 100%) under bubbling oxygen for 1.5 h. Preparative TLC [hexane–ethyl acetate (5:1)] of the reaction mixture afforded benzaldehyde (4.1 mg, 30%), *N*-benzylbenzamide (7.5 mg, 28%), and ester **27** (6.1 mg, 20%).[14]

Ethyl 4-benzylamino-4-oxocrotonate (**27**), as colorless crystals; mp 110–111 °C (hexane–ethyl acetate); IR ($CHCl_3$): 3430 (N–H), 1720 (C=O), 1670 cm^{-1} (C=O); ^{1}H NMR (400 MHz): δ 1.25 (d, 3H, J=7.2 Hz, OCH_2CH_3), 4.15 (q, 2H, J=7.2 Hz, OCH_2), 4.52 (d, 2H, J=5.6 Hz, CH_2Ph), 6.15 (br s, 1H, NH), 6.89 (d, 1H, J=15.6 Hz, H-2), 6.92 (d, 1H, J=15.6 Hz, H-3), 7.21–7.39 (m, 5H, Ph); ^{13}C NMR (100 MHz): δ 14.3 (q, OCH_2CH_3), 44.1 (t, CH_2Ph), 61.2 (t, OCH_2), 127.7, 127.8, 128.7 (3d, 5C in Ph), 130.7 (d, C-2), 135.8 (d, C-3), 137.2 (s, C in Ph), 163.2 (s, C-4), 165.3 (s, C-1); EI-MS *m*/*z* 233 (M^+, 19%), 187 (11), 128 (8), 106 (100), 99 (11), 91 (20), 79 (5); HRMS calcd for $C_{13}H_{15}NO_3$: 233.1052, found: 233.1057.

4.7. Reactions of aziridines 7–9 possessing diester, dinitrile, and butadiene functional groups with various alkenes

A 0.060 mol L^{-1} solution of aziridines **7–9** in dry acetonitrile with 10 equiv of alkenes was irradiated with a low-pressure mercury lamp in a quartz test tube at room temperature. After removal of the solvent, flash column chromatography afforded the adducts. The results are summarized in Table 3.

4.7.1. Diester 7 and acrylonitrile. Dimethyl (2′*RS*,3′*RS*)-(3-cyano-1-tritylpyrrolidin-2-yl)methylenemalonate (**29**), an oil;

IR ($CHCl_3$): 2240 (C≡N), 1720 cm^{-1} (C=O); ^1H NMR (400 MHz): δ 1.38–1.48 (m, 1H, H-4), 1.81–1.91 (m, 1H, H-4), 1.97–2.05 (m with q-character, 1H, J=9 Hz, H-3), 3.07 (ddd, 1H, J=12.7, 8.3, 6.1 Hz, H-5), 3.53–3.60 (m, 1H, H-5), 3.56, 3.84 (each s, 6H, $2OCH_3$), 4.69 (dd, 1H, J=10.0, 7.6 Hz, H-2), 7.15 (d, 1H, J=10.0 Hz, 2-CH), 7.18–7.28 (m, 9H, 3Ph), 7.46–7.49 (m, 6H, 3Ph); ^{13}C NMR (100 MHz): δ 29.9 (t, C-4), 33.1 (d, C-3), 48.7 (t, C-5), 52.1, 52.7 (2q, $2OCH_3$), 61.1 (d, C-2), 77.5 (s, CPh_3), 118.5 (s, CN), 126.5, 127.8, 128.9 (3d, 15C in 3Ph), 127.0 [s, $C(CO_2Me)_2$], 143.4 (s, 3C in 3Ph), 163.9, 164.3 (2s, $2CO_2$); EI-MS m/z 480 (M^+, 1%), 449 (1), 362 (14), 403 (1), 243 (100), 237 (15), 205 (5), 165 (41), 91 (4), 83 (5), 77 (4); HRMS calcd for $C_{30}H_{28}N_2O_4$: 480.2049, found: 480.2055.

4.7.2. Dinitrile 8 and acrylonitrile. (2*RS*,3*RS*)-(3-Cyano-1-tritylpyrrolidin-2-yl)methylenemalononitrile (**30**), colorless crystals, mp 201–203 °C (hexane–ethyl acetate); IR ($CHCl_3$): 2210 cm^{-1} (C≡N); ^1H NMR (400 MHz): δ 1.52–1.61 (m, 1H, H-4), 1.85–1.95 (m, 1H, H-4), 2.18–2.26 (m, 1H, H-3), 3.06 (ddd, 1H, J=12.2, 7.6, 6.8 Hz, H-5), 3.56 (ddd, 1H, J=12.2, 7.8, 5.9 Hz, H-5), 4.45–4.50 (m with dd-character, 1H, J=10, 8 Hz, H-2), 7.23–7.38, 7.47–7.50 (2m, 16H, 2-CH, 15H in 3Ph); ^1H NMR (400 MHz; acetone-d_6): δ 1.71–1.80 (m with dtd-character, 1H, J=13, 8, 5 Hz, H-4), 1.99–2.10 (m with dtd-character, 1H, J=13, 9, 7 Hz, H-4), 2.40–2.48 (m with q-character, 1H, J=8.5 Hz, H-3), 3.14 (ddd, 1H, J=12.0, 8.1, 6.8 Hz, H-5), 3.66 (ddd, 1H, J=12.0, 8.5, 5.3 Hz, H-5), 4.63 (dd, 1H, J=9.8, 7.8 Hz, H-2), 7.20–7.29 (m, 9H, 3Ph), 7.57–7.60 (m, 6H, 3Ph), 7.93 (d, 1H, J=9.8 Hz, 2-CH); ^{13}C NMR (100 MHz; acetone-d_6): δ 29.7 (t, C-4), 33.7 (d, C-3), 49.2 (t, C-5), 63.8 (d, C-2), 78.0 (s, CPh_3), 89.7 [s, $C(CN)_2$], 111.1, 112.9, 118.7 (3s, 3CN), 127.9, 129.0, 130.1 (3d, 15C in 3Ph), 144.1 (s, 3C in 3Ph), 167.0 [d, C(2)*C*H]; EI-MS m/z 414 (M^+, 1%), 337 (9), 243 (100), 228 (10), 215 (7), 165 (67), 117 (5), 91 (5); HRMS calcd for $C_{28}H_{22}N_4$: 414.1845, found: 414.1841.

4.7.3. Dinitrile 8 and vinyl acetate. (2*RS*,3*RS*)-2-(2,2-Dicyanovinyl)-1-tritylpyrrolidin-3-yl acetate (**31**), colorless crystals, mp 154–157 °C (hexane–ethyl acetate); IR ($CHCl_3$): 2230 (C≡N), 1740 cm^{-1} (C=O); ^1H NMR (500 MHz): δ 1.27–1.35 (m, 1H, H-4), 1.52–1.59 (m, 1H, H-4), 1.99 (s, 3H, CH_3), 2.97 (ddd, 1H, J=11.9, 7.9, 5.5 Hz, H-5), 3.45 (dt, 1H, J=11.9, 7.3 Hz, H-5), 4.49 (dd, 1H, J=9.5, 7.0 Hz, H-2) 4.63–4.68 (m, 1H, H-3), 7.19–7.33, 7.47–7.51 (2m, 16H, H-1′, 15H in 3Ph); ^{13}C NMR (125 MHz): δ 20.7 (q, CH_3), 30.7 (t, C-4), 47.5 (t, C-5), 62.8 (d, C-2), 75.9 (d, C-3), 76.8 (s, CPh_3), 88.4 [s, $C(CN)_2$], 110.0, 112.1 (2s, 2CN), 127.1, 128.1, 129.4 (3d, 15C in 3Ph), 142.8 (s, 3C in 3Ph), 167.8 (d, C-1′), 169.5 (s, CO_2); EI-MS m/z 447 (M^+, 1%), 404 (1), 370 (6), 243 (100), 228 (8), 215 (4), 165 (48), 91 (4), 43 (6); HRMS calcd for $C_{29}H_{25}N_3O_2$: 447.1947, found: 447.1954.

4.7.4. Dinitrile 8 and isoprene. (2*RS*,3*RS*)-(3-Isopropenyl-1-tritylpyrrolidin-2-yl)methylenemalononitrile (**32**), an oil; IR ($CHCl_3$): 2230 cm^{-1} (C≡N); ^1H NMR (400 MHz): δ 1.25–1.39 (m, 1H, H-3), 1.42 (s, 3H, CH_3), 1.48–1.55 (m, 1H, H-4), 1.71–1.80 (m, 1H, H-4), 2.75–2.83 (m with td-character, 1H, J=10, 7 Hz, H-5), 3.43–3.48 (m with t-character, 1H, J=9 Hz, H-5), 4.21–4.26 (m with dd-character, 1H, J=10, 8 Hz, H-2), 4.51, 4.69 (each br s, 2H, $C(CH_3)$:CH_2), 7.06 (d, 1H, J=9.8 Hz, 2-CH), 7.10–7.25 (m, 9H, 3Ph), 7.46–7.49 (m, 6H, 3Ph); ^{13}C NMR (100 MHz; C_6D_6; 65 °C): δ 23.2 (q, CH_3), 28.0 (t, C-4), 49.2 (t, C-5), 50.6 (d, C-3), 63.8 (d, C-2), 78.3 (s, CPh_3), 88.5 [s, $C(CN)_2$], 111.4, 113.0 (2s, 2CN), 112.8 (t, $C(CH_3)$:CH_2), 127.3, 128.3, 130.1 (3d, 15C in 3Ph), 141.6, 142.8 (s, $C(CH_3)$:CH_2 and 3C in 3Ph), 168.3 [d, C(2)*C*H]; EI-MS m/z 429 (M^+, 1%), 352 (4), 243 (100), 228 (9), 215 (5), 165 (53), 146 (4), 91 (4), 77 (2); HRMS calcd for $C_{30}H_{27}N_3$: 429.2204, found: 429.2202.

4.7.5. Butadinene 9 and acrylonitrile. (2*RS*,3*RS*,1′*E*)-2-(1,3-Butadienyl)-1-tritylpyrrolidine-3-carbonitrile [(*E*)-**33**], an oil; IR ($CHCl_3$): 2210 cm^{-1} (C≡N); ^1H NMR (400 MHz): δ 1.24 (ddd, 1H, J=10.7, 8.5, 6.8 Hz, H-3), 1.60–1.69 (m, with dtd-character, 1H, J=13, 9, 4 Hz, H-4), 1.76–1.87 (m with dtd-character, 1H, J=13, 10, 8 Hz, H-4), 3.00 (ddd, 1H, J=2.7, 8.8, 7.6 Hz, H-5), 3.44 (ddd, 1H, J=12.7, 9.8, 3.9 Hz, H-5), 4.03–4.06 (m with t-character, 1H, J=7 Hz, H-2), 5.17–5.20 (m with d-character, 1H, J=10 Hz, H-4′), 5.31–5.36 (m with d-character, 1H, J=17 Hz, H-4′), 5.89 (dd, 1H, J=14.4, 6.1 Hz, 1′-H), 6.42–6.57 (m, 2H, H-2′, H-3′), 7.16–7.32 (m, 9H, 3Ph), 7.54–7.56 (6H, m, 3Ph); ^{13}C NMR (100 MHz): δ 29.1 (t, C-4), 31.8 (d, C-3), 48.3 (t, C-5), 63.4 (d, C-2), 78.0 (s, CPh_3), 117.6 (t, C-4′), 119.7 (s, CN), 126.5, 127.7, 128.9 (3d, 15C in 3Ph), 129.1, 133.1, 136.2 (3d, C-1′, C-2′, C-3′), 144.1 (s, 3C in 3Ph); EI-MS m/z 390 (M^+, 1%), 313 (3), 243 (100), 228 (4), 183 (5), 165 (33), 105 (5), 91 (2), 77 (4); HRMS calcd for $C_{28}H_{26}N_2$: 390.2096, found: 390.2090.

(2*RS*,3*RS*,1′*Z*)-2-(1,3-Butadienyl)-1-tritylpyrrolidine-3-carbonitrile [(*Z*)-**33**], an oil; ^1H NMR (400 MHz): δ 1.40–1.48 (m with td-character, 1H, J=10, 7 Hz, H-3), 1.62–1.72 (m with dtd-character, 1H, J=13, 9.0, 4.6 Hz, H-4), 1.84–1.95 (m with dtd-character, 1H, J=13, 9.5, 7.1 Hz, H-4), 3.00 (ddd, 1H, J=12.7, 8.9, 7.1 Hz, H-5), 3.50 (ddd, 1H, J=12.7, 9.5, 4.6 Hz, H-5), 4.35 (dd, 1H, J=10.0, 7.1 Hz, H-2), 5.07–5.10 (m with d-character, 1H, J=10 Hz, H-4′), 5.23–5.28 (m with d-character, 1H, J=14 Hz, H-4′), 5.61–5.67 (m with t-character, 1H, J=10 Hz, 1′-H), 6.16–6.27 (m, 2H, H-2′, H-3′), 7.15–7.27 (m, 9H, 3Ph), 7.52–7.55 (m, 6H, 3Ph); ^{13}C NMR (100 MHz): δ 29.7 (t, C-4), 32.6 (d, C-3), 48.1 (t, C-5), 60.1 (d, C-2), 77.9 (s, CPh_3), 119.2 (t, C-4′), 119.8 (s, CN), 126.3, 127.8, 128.9 (3d, 15C in 3Ph), 128.0, 130.1, 131.3 (3d, C-1′, C-2′, C-3′), 144.0 (s, 3C in 3Ph).

4.8. Application to the synthesis of indolizidine fragment of stellettamides 10

4.8.1. (2*RS*,3*RS*,1′*E*)-2-(4-Hydroxy-1-butenyl)-1-tritylpyrrolidine-3-carbonitrile (34). To a solution of butadiene (*E*)-**33** (606 mg, 1.55 mmol) in dry THF (3 mL) was added dropwise 9-BBN (4.7 mL, 0.5 M in THF) at 0 °C. After the mixture had been stirred for 4 h at room temperature, the reaction mixture was cooled to 0 °C. Water (0.1 mL), 30% aqueous H_2O_2 (0.68 mL), and 3 M aqueous NaOH (0.68 mL) were added, the resulting mixture was stirred for 2 h at room temperature and extracted with ether. The organic extract was washed with brine, dried with $MgSO_4$,

and concentrated in vacuo, giving a residue that was subjected to flash column chromatography [hexane–ethyl acetate (2:1)] to afford **34** (159 mg, 25%) as a white amorphous solid: IR ($CHCl_3$): 3530 (O–H), 2240 cm^{-1} (C≡N); ^1H NMR (400 MHz): δ 1.28–1.36 (m with ddd-character, 1H, J=10, 9, 6 Hz, H-3), 1.61–1.70 (m with dtd-character, 1H, J=13, 9, 4 Hz, H-4), 1.75 (br s, 1H, OH), 1.85 (dtd, 1H, J=12.6, 10.0, 7.6 Hz, H-4), 2.40–2.45 (m, 2H, 2H-3′), 2.99 (ddd, 1H, J=12.5, 8.8, 7.6 Hz, H-5), 3.45 (ddd, 1H, J=12.5, 9.8, 4.2 Hz, H-5), 3.69–3.75 (m, 2H, 2H-4′), 3.93–3.97 (m with t-character, 1H, J=6 Hz, H-2), 5.69–5.81 (m, 2H, H-1′, H-2′), 7.16–7.28 (m, 9H, 3Ph), 7.53–7.57 (m, 6H, 3Ph); ^{13}C NMR (100 MHz): δ 29.1 (t, C-4), 32.5 (d, C-3), 36.0 (t, C-3′), 48.3 (t, C-5), 61.9 (t, C-4′), 64.4 (d, C-2), 77.9 (s, CPh_3), 120.8 (s, CN), 126.4, 127.7, 129.0 (3d, 15C in 3Ph), 129.7, 131.0 (2d, C-1′, C-2′), 144.0 (s, 3C in 3Ph); FAB-MS (magic bullet) m/z 409 [(M+1)$^+$]; HRMS (FAB) calcd for $C_{28}H_{29}N_2O$ (M+H): 409.2280, found: 409.2282.

4.8.2. *tert*-Butyl (2*RS*,3*RS*,1′*E*)-3-cyano-2-(4-hydroxy-1-butenyl)pyrrolidine-1-carboxylate (35). To a solution of butene **34** (147 mg, 0.36 mmol) in chloroform (0.36 mL) and methanol (0.36 mL) was added dropwise trifluoroacetic acid (TFA; 0.55 mL, 7.2 mmol) at 0 °C. After the mixture had been stirred for 2 h at 0 °C, the reaction mixture was evaporated under reduced pressure giving a detritylated compound that was used for the next step without further purification. To a solution of the compound in THF/H_2O=2:1 (0.72 mL) was added 10% aqueous NaOH (0.36 mL) at 0 °C, the resulting mixture was stirred for 15 min at 0 °C and then di-*tert*-butyl dicarbonate (0.127 mL, 0.53 mmol) was added dropwise. After the mixture was stirred for 38 h at room temperature, the reaction was quenched with H_2O and extracted with ether. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo, giving a residue that was subjected to flash column chromatography [hexane–ethyl acetate (1:1)] to afford **35** (75.5 mg, 79%) as a colorless oil: IR (neat): 3460 (O–H), 2250 (C≡N), 1685 cm^{-1} (C=O); ^1H NMR (400 MHz): δ 1.44 [s, 9H, C(CH_3)$_3$], 2.16–2.34 (m, 3H, OH, 2H-4), 2.34–2.40 (m with q-character, 2H, J=6 Hz, 2H-3′), 3.13–3.20 (m with dt-character, 1H, J=11, 7 Hz, H-3), 3.37–3.45, 3.53–3.60 (each m, 2H, 2H-5), 3.65–3.69 (m with t-character, 2H, J=6 Hz, 2H-4′), 4.47–4.54 (m, 1H, H-2), 5.53–5.60 (m with dd-character, 1H, J=15, 7 Hz, H-1′), 5.66–5.74 (m with dt-character, 1H, J=15, 7 Hz, H-2′); ^{13}C NMR (100 MHz): δ 28.4 [q, C(CH_3)$_3$], 28.4 (t, C-4), 33.7 (d, C-3), 35.6 (t, C-3′), 44.9 (t, C-5), 59.6 (d, C-2), 61.4 (t, C-4′), 80.3 [s, C(CH$_3$)$_3$], 118.3 (s, CN), 128.2, 131.9 (2d, C-1′, C-2′), 153.5 (s, CO); FAB-MS (glycerol) m/z 267 [(M+1)$^+$]; HRMS (FAB) calcd for $C_{14}H_{23}N_2O_3$ (M+H): 267.1708, found: 267.1716.

4.8.3. *tert*-Butyl (2*RS*,3*RS*)-3-cyano-2-(4-hydroxybutyl)-pyrrolidine-1-carboxylate (36). A solution of butenol **35** (74.1 mg, 0.28 mmol) in ethanol (1.7 mL) with 10% Pd/C (37 mg) under hydrogen was stirred for 21 h at room temperature. The reaction mixture was filtered with Celite, and the filtrate was concentrated in vacuo, giving a residue that was subjected to flash column chromatography (hexane) to afford **36** (70.9 mg, 95%) as a colorless oil: IR (neat): 3400 (O–H), 2245 (C≡N), 1690 cm^{-1} (C=O); ^1H NMR (400 MHz): δ 1.46 [s, 9H, C(CH_3)$_3$], 1.45–1.79 (m, 7H, 5H in the side chain, H-4, OH), 2.16–2.34 (m, 2H, 1H in the side chain, H-4), 2.34–2.40 (m with q-character, 2H, J=6 Hz, 2H-3′), 3.13 (dt, 1H, J=9.8, 7.3 Hz, H-3), 3.40–3.53 (m, 2H, 2H-5), 3.62–3.68 (m, 2H, 2H-4′), 4.02–4.13 (m, 1H, H-2); ^{13}C NMR (100 MHz): δ 22.5, 28.5, 28.6, 32.4 (4t, C-1′, C-2′, C-3′, C-4), 28.5 [q, C(CH_3)$_3$], 32.4 (d, C-3), 44.7 (t, C-5), 57.5 (d, C-2), 62.3 (t, C-4′), 80.2 [s, C(CH$_3$)$_3$], 118.7 (s, CN), 154.0 (s, CO); FAB-MS (glycerol) m/z 269 [(M+1)$^+$]; HRMS (FAB) calcd for $C_{14}H_{25}N_2O_3$ (M+H): 269.1865, found: 269.1861.

4.8.4. *tert*-Butyl (2*RS*,3*RS*)-3-cyano-2-[4-(*p*-toluenesulfonyl)oxybutyl]pyrrolidine-1-carboxylate (37). A solution of *p*-toluenesulfonyl chloride (42 mg, 0.22 mmol) in dry pyridine (0.6 mL) under argon was added to a solution of butanol **36** (48.6 mg, 0.18 mmol) in dry pyridine (0.6 mL) at −20 °C. After 12 h, a solution of *p*-toluenesulfonyl chloride (27 mg, 0.14 mmol) in dry pyridine (0.4 mL) was added moreover, and the mixture was stirred for 17 h at −20 °C and for 23 h at −10 °C. Furthermore, a solution of *p*-toluenesulfonyl chloride (17 mg, 0.09 mmol) in dry pyridine (0.25 mL) was added, and the mixture was stirred for 33 h at −5 °C. The reaction was quenched with H_2O and extracted with methylene chloride. The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo, giving a residue that was subjected to flash column chromatography [hexane–ethyl acetate (2:1)] to afford **37** (57.8 mg, 79%) as a colorless oil: IR (neat): 2240 (C≡N), 1685 cm^{-1} (C=O); ^1H NMR (400 MHz): δ 1.25–1.48, 1.60–1.78, 2.12–2.30 (3m, 8H, 2H-1′, 2H-2′, 2H-3′, 2H-4), 1.46 [s, 9H, C(CH_3)$_3$], 2.45 (s, 3H, Me), 3.08 (dt, 1H, J=10.0, 7.3 Hz, H-3), 3.37–3.51 (m, 2H, 2H-5), 4.01–4.09 (m, 3H, H-2, 2H-4′), 7.35, 7.79 (each d, 4H, J=8 Hz, Ar); ^{13}C NMR (100 MHz): δ 21.8 (q, Me), 22.4, 28.5, 28.9, 31.9 (4t, C-1′, C-2′, C-3′, C-4), 28.5 [q, C(CH_3)$_3$], 32.6 (d, C-3), 44.6 (t, C-5), 57.4 (d, C-2), 70.2 (t, C-4′), 80.4 [s, C(CH$_3$)$_3$], 118.5 (s, CN), 127.7, 129.7 (2d, 4C in Ar), 133.0, 144.5 (2s, 2C in Ar), 153.9 (s, CO); FAB-MS (glycerol) m/z 423 [(M+1)$^+$]; HRMS (FAB) calcd for $C_{21}H_{31}N_2O_5S$ (M+H): 423.1953, found: 423.1952.

4.8.5. (1*RS*,8a*RS*)-1,2,3,5,6,7,8,8a-Octahydroindolizine-1-carbonitrile (38). A solution of **37** (15.0 mg, 0.036 mmol) in 4 M HCl–dioxane solution (0.07 mL) was stirred for 4 h at room temperature. After methylene chloride was added, the mixture was extracted with H_2O (two times). The combined aqueous layer was adjusted to pH 14 with 1 M aqueous NaOH and stirred for 2.5 h at room temperature. The reaction mixture was extracted with methylene chloride. The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated, giving **38** (4.7 mg, 89%) as a colorless oil: IR (neat): 2240 cm^{-1} (C≡N); ^1H NMR (400 MHz): δ 1.20–1.34 (m, 1H,), 1.52–1.67 (m, 3H), 1.80–1.99 (m, 4H), 2.05–2.17 (m, 3H), 2.96–3.02 (m, 1H), 3.11–3.17 (m, 2H); ^{13}C NMR (100 MHz): δ 24.0, 25.0, 27.4, 28.5 (4t), 32.6 (d, C-1), 52.9, 53.2 (2t, C-3, C-5), 64.4 (d, C-8a), 121.1 (s, CN); EI-MS m/z 150 (M$^+$, 28%), 121 (8), 97 (100), 83 (6), 69 (25), 55 (10), 41 (16); HRMS calcd for $C_9H_{14}N_2$: 150.1157, found: 150.1155.

Compound **38**[18]—^1H NMR: δ 1.16–1.29 (m, 1H), 1.42–1.62 (m, 3H), 1.73–2.14 (m, 7H), 2.94–3.16 (m, 3H); δ_C 23.9, 24.9, 27.3, 28.4, 32.5, 52.9, 53.1, 64.4, 121.2.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.098.

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An efficient synthetic methodology of chiral isoquinuclidines by the enantioselective Diels–Alder reaction of 1,2-dihydropyridines using chiral cationic palladium–phosphinooxazolidine catalyst

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Abstract—High purity chiral isoquinuclidines (97% ee) were obtained from the enantioselective Diels–Alder reaction of 1-phenoxycarbonyl-1,2-dihydropyridine with 1-benzyl-2-acryloylpyrazolidin-3-one using chiral cationic palladium–phosphinooxazolidine (Pd–POZ) catalyst. The obtained DA adduct was easily converted to the chiral piperidine derivative bearing three stereogenetic centers in the structure.

1. Introduction

The 2-azabicyclo[2.2.2]octanes (isoquinuclidines) are found widely in natural products such as iboga-type indole alkaloids, which have varied and interesting biological properties (Fig. 1).[1] Typical iboga-alkaloids include catharanthine **1**, which is the precursor of pharmacologically important vinca alkaloids such as vinblastine **3a** and vincristine **3b**.[2] Most recently, it was also indicated that ibogaine **2** reduces cravings for alcohol and other drugs by means of its ability to boost the levels of a growth factor known as glial cell line-derived neurotrophic factor (GDNF).[3] Furthermore, isoquinuclidines are also valuable intermediates in the synthesis of other alkaloids[4] and in medicinal chemistry.[5] Therefore, it is important to establish an effective asymmetric synthetic methodology for chiral isoquinuclidines. A well-established route to this ring system is through the Diels–Alder (DA) reaction of 1,2-dihydropyridines with dienophiles. However, little research on the asymmetric version of this reaction has been reported, and most reports are of diastereoselective versions of the reaction, which used 1,2-dihydropyridines or dienophiles attached to a chiral auxiliary.[6] Despite the obvious advantages of its catalytic enantioselective version, to the best of our knowledge,

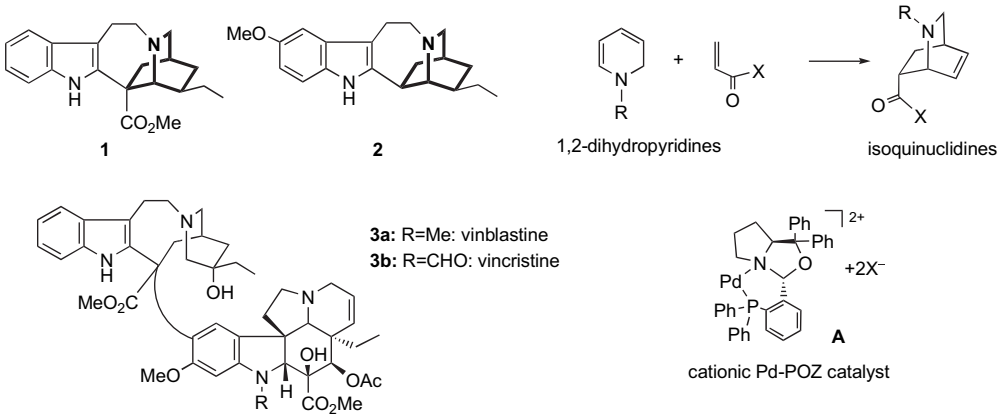

Figure 1.

Keywords: Enantioselective Diels–Alder reaction; 1,2-Dihydropyridine; Chiral cationic palladium–phosphinooxazolidine catalyst; Chiral isoquinuclidines; Chiral piperidines.
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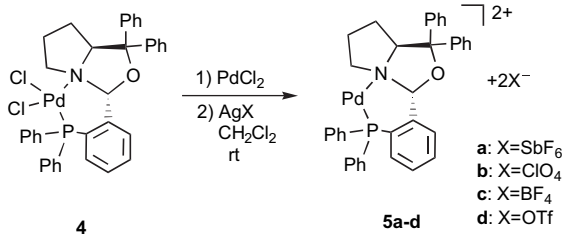
only one example employing a Cr–BINAM catalyst has been reported to date by Rawal et al. for the catalytic enantioselective version of the DA reaction. However, the reaction afforded only modest asymmetric induction (up to 85% ee).[7] Most recently, we have reported that the enantioselective DA reaction of 1,2-dihydropyridines with 1-substituted acryloylpyrazolidin-3-ones using a Pd–POZ catalyst is an efficient synthetic methodology for obtaining chiral isoquinuclidines at synthetically useful levels of enantiomeric excess (ee).[8]

In this paper, we describe the details of the first successful enantioselective DA reaction of 1,2-dihydropyridines with 1-substituted acryloylpyrazolidin-3-ones using a Pd–POZ catalyst,[8] and also the convenient transformation of the obtained DA adduct to the chiral piperidine derivative bearing three chiral carbon centers in the structure.

2. Results and discussion

2.1. Diels–Alder reaction with acryloyl-1,3-oxazolidine-2-one

We first tested the DA reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **6a** or 1-benzyloxycarbonyl-1,2-dihydropyridine **6b** with common 2-acryloyl-1,3-oxazolidine-2-one **7**. The reaction was carried out at 0 °C or −25 °C in CH_2Cl_2 in the presence of 10 mol % of the cationic Pd–POZ catalysts **5a–d** that were prepared by the reactions of $PdCl_2$–POZ complex **4** and the corresponding AgX (X=SbF_6, ClO_4, BF_4, OTf) using our previously reported procedure (Scheme 1).[9] As a result, antimonate catalyst **5a** at −25 °C and perchlorate catalyst **5b** at 0 °C gave the *endo*-DA adduct **8a** in good chemical yields and enantioselectivities (entries 2 and 5, Table 1). The other 1,2-dihydropyridine, 1-benzyloxycarbonyl-1,2-dihydropyridine **6b**, was also used in the same reaction. Although the reaction proceeded with an excellent chemical yield to afford **8b**, the enantioselectivity was moderate. In both reactions, enantioselectivity over 90% ee was not achieved as in the results of Rawal et al.[7]

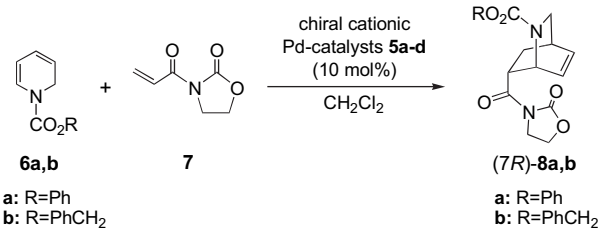


Scheme 1. Preparations of cationic POZ complexes **5a–d**.

2.2. Diels–Alder reaction with 1-substituted 2-acryloylpyrazolidin-3-ones

In order to improve the enantioselectivity of the reaction, we explored the possibilities presented in a report by Sibi et al.,[10] who examined a novel 1-substituted 2-crotonylpyrazolidin-3-one as a dienophile based on the concept of 'chiral relay', and reported that the combination of this dienophile and nonoptimized Cu–bis-oxazoline catalyst can bring about an excellent asymmetric induction in the DA reaction with cyclopentadiene as a diene. However, a fairly high level of catalytic loading (50 mol %) was needed for the achievement of satisfactory enantioselectivity in the reaction. We applied the 1-substituted 2-pyrazolidin-3-one dienophile to the DA reactions of 1,2-dihydropyridines **6a–c** using cationic Pd–POZ catalysts **5a–d**.

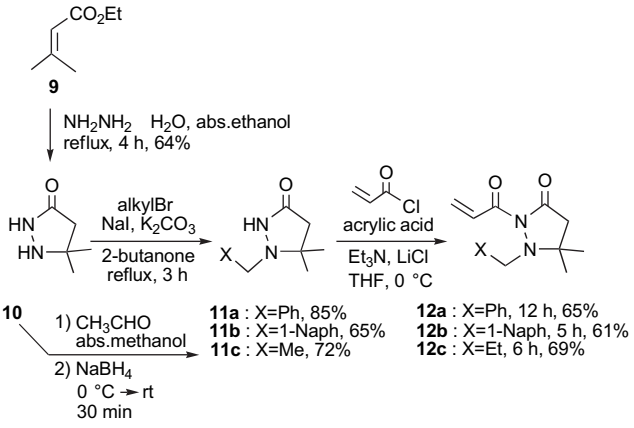
Table 1. Enantioselective DA reactions of 1,2-dihydropyridines **6a**,**b** with 2-acryloyl-1,3-oxazolidine-2-one **7**



Entry	Diene	Catalyst	Temp (°C)	Time (h)	DA adduct	Yield (%)[a]	ee (%)[b]
1	**6a**	**5a**	0	24	**8a**	98	76
2	**6a**	**5b**	0	24	**8a**	90	84
3	**6a**	**5c**	0	24	**8a**	46	88
4	**6a**	**5d**	0	24	**8a**	37	74
5	**6a**	**5a**	−25	48	**8a**	84	82
6	**6a**	**5b**	−25	48	**8a**	73	82
7	**6b**	**5a**	0	24	**8b**	90	74

[a] Isolated yields.
[b] Enantiomeric excess of *endo*-isomer was determined by chiral HPLC using a Daicel AD or AD-H column.

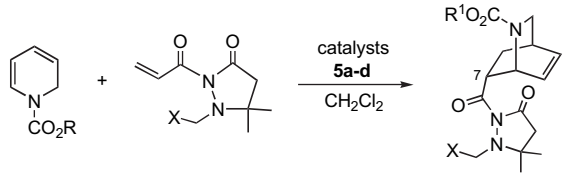
Although Sibi et al. used 1-substituted 2-crotonylpyrazolidin-3-ones as a dienophile, we applied the simplest 1-substituted 2-acryloylpyrazolidin-3-ones to our DA reaction. 2-Acryloylpyrazolidin-3-ones **12a–c** were prepared following the procedure reported by Sibi et al.[10] and Perri et al.[11] (Scheme 2). Thus, 3,3-dimethylacrylate **9** was converted to 5,5-dimethylpyrazolidin-3-one **10** by the reaction with hydrazine monohydrate. N-Alkylation of **10**, followed by the reactions of **11a**,**b** with acryloyl chloride, afforded the dienophiles **12a**[10] and **b** in moderate to good yields. On the other hand, dienophile **12c** was obtained from the condensation of **10** with acetaldehyde, followed by the reduction of the imino moiety and then the reaction of the obtained **11c** with acryloyl chloride in a moderate yield.



Scheme 2. Preparations of dienophiles **12a–c**.

First, we examined the effectiveness of dienophiles **12a–c** using superior antimonate catalyst **5a**. The reactions of diene **6a** with dienophiles **12a–c** were carried out at 0 °C in the presence of 10 mol % of the prepared Pd–POZ catalysts **5a–d** to give the corresponding *endo*-DA adducts **13a–c**. The results are summarized in Table 2. A significant difference was observed in chemical yield and enantioselectivity corresponding to the different substituent groups on the nitrogen at the 1-position. A dramatic increase in enantioselectivity to 97% ee was accomplished with good chemical yield when 1-benzyl substituted derivative **12a** was used as a dienophile (80%, entry 1). Despite our expectations, the bulkier 1-naphthylmethyl derivative **12b** brought about a decrease in both chemical yield and enantioselectivity (entry 2). Similarly, the reaction using the less bulky 1-ethyl substituted derivative **12c** was also sluggish, although the reasons for this remain unclear (entry 3). Next, we examined the effects of other counterions such as perchlorate, tetrafluoroborate, and triflate on the reaction with superior dienophile **12a**. As a result, cationic perchlorate catalyst **5b** and tetrafluoroborate catalyst **5c** afforded the DA adduct **13a** in high enantioselectivities with good chemical yields (entries 4 and 5). In particular, **5c** showed the best enantioselectivity (97% ee) with 76% yield (entry 5), the results are almost identical to those achieved with antimonate catalyst **5a**. However, triflate catalyst **5d** did not give satisfactory reactivity and enantioselectivity (60%, 89% ee, entry 6). The reactions with superior cationic catalysts **5a** and **c** at −25 °C did not afford better results for chemical yields and enantioselectivities than the results at 0 °C (entries 7 and 8). Furthermore, the effect of reducing the molar ratio of catalyst **5a** was examined. At low catalytic loading to 5 mol % of **5a**, equally satisfactory results (78%, 95% ee) were obtained, but the use of 2.5 mol % greatly decreased both the chemical yield and enantioselectivity (59 and 84% ee, entries 9 and 10). These results indicate that the antimonate POZ catalyst **5a** and 1-benzylpyrazolidin-3-one dienophile **12a** were most effective in obtaining chiral isoquinuclidines **13a** with excellent enantioselectivity. Other 1,2-dihydropyridines **6b**[6g] and **c**[6g] were also examined using superior antimonate catalyst **5a** and dienophile **12a** (entries 11 and 12). The reactions were carried out at 0 °C in the presence of 10 mol % of the prepared Pd–POZ catalysts **5a** to give the corresponding *endo*-DA adducts **13d** and **e**, respectively. However, the results of both reactions did not exceed the result of diene **6a**.

Table 2. Enantioselective DA reactions of dienes **6a–c** with **12a–c**



6a-c
a: R=Ph
b: R=CH_2Ph
c: R=Bu^t

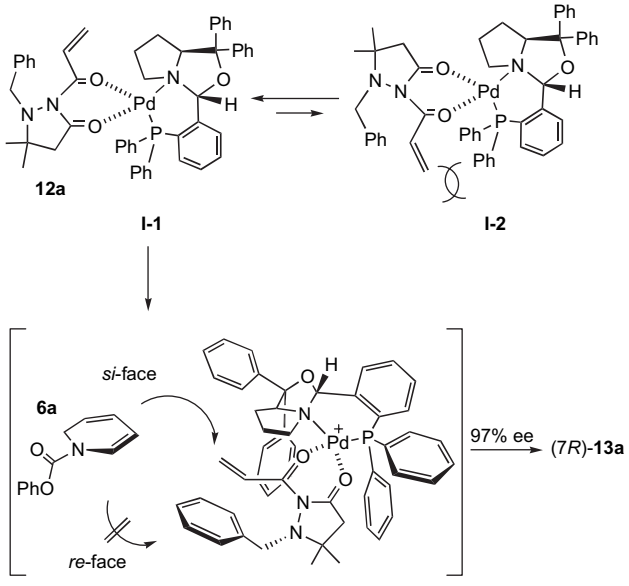
12a-c
a: X=Ph
b: X=1-Naph
c: X=Me

[7*R*]-**13a-e**
a: R=Ph, X=Ph
b: R=Ph, X=1-Naph
c: R=Ph, X=Me
d: R=CH_2Ph, X=Ph
e: R=Bu^t, X=Ph

Entry	Diene	Dienophile	Cat. (mol %)	Temp (°C)	Time (h)	DA adduct	Yield[a] (%)	ee[b] (%)
1	**6a**	**12a**	**5a** (10)	0	24	**13a**	80	97
2	**6a**	**12b**	**5a** (10)	0	72	**13b**	47	33
3	**6a**	**12c**	**5a** (10)	0	72	**13c**	44	43
4	**6a**	**12a**	**5b** (10)	0	24	**13a**	87	94
5	**6a**	**12a**	**5c** (10)	0	24	**13a**	76	97
6	**6a**	**12a**	**5d** (10)	0	24	**13a**	60	89
7	**6a**	**12a**	**5a** (10)	−25	48	**13a**	76	95
8	**6a**	**12a**	**5c** (10)	−25	48	**13a**	76	89
9	**6a**	**12a**	**5a** (5)	0	24	**13a**	78	95
10	**6a**	**12a**	**5a** (2.5)	0	24	**13a**	59	84
11	**6b**	**12a**	**5a** (10)	0	24	**13d**	74	89
12	**6c**	**12a**	**5a** (10)	0	24	**13e**	85	67

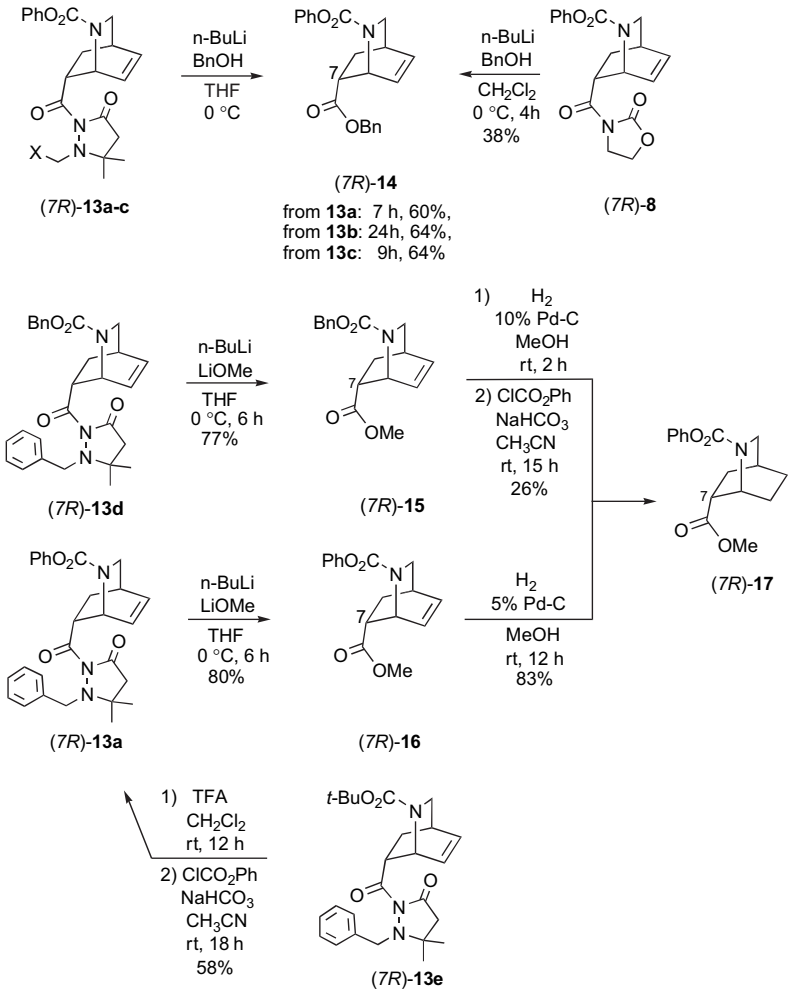
[a] Isolated yields.
[b] Enantiomeric excess of *endo*-isomer was determined by HPLC analysis using a DAICEL Chiralcel AD-H column.

Based on the X-ray structure of $PdCl_2$–POZ complex **4**[9a] and the high enantiopurity (97% ee) of the chiral DA adduct (7*R*)-**13a** that was obtained from the reaction of diene **6a** with dienophile **12a**, a model of the enantioselective reaction course was proposed as follows (Scheme 3). Thus, the reaction might be through the intermediate **I-1** that has a less steric interaction between the diphenylphosphino substituent on the phenyl group in the catalyst and the olefin part of the dienophile. Then, the diene might attack from the *si*-face of the acryloyl group on the dienophile rather than the *re*-face that was masked by the 1-benzyl group on the dienophile to afford (7*R*)-**13a**.



Scheme 3. Plausible reaction course for DA reaction of **6a** with **12a**.

The absolute stereochemistry assignments of the new DA adducts **13a–e** were carried out as follows (Scheme 4). For the assignments of **13a–c**, both **13a–c** and the known (7*R*)-**8a** were converted to benzyl ester **14**. Thus, the reactions of **13a–c** or (7*R*)-**8** with BnOH using *n*-BuLi as a base in THF afforded (7*R*)-benzyl ester **14** in moderate yields (**13a**: 60%; **13b**: 64%; **13c**: 64%; **7**: 38%). Furthermore, both the DA adducts **13d** and (7*R*)-**13a** were converted to methyl esters **15** and (7*R*)-**16**, respectively, by the reactions with LiOMe for the assignment of **13d**. And then, the reduction of the olefin moiety in **15**, followed by the exchange from the benzyloxycarbonyl group to the phenoxycarbonyl



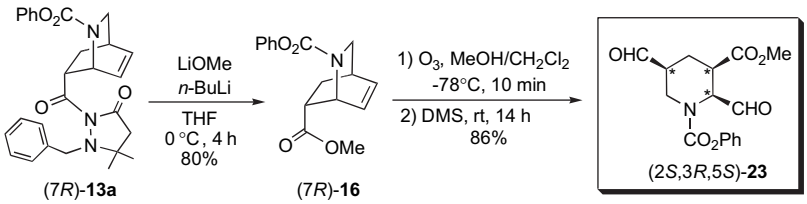
Scheme 4. Absolute configurations of DA adducts **13a**–**e**.

group on nitrogen at the 2-position afforded the compound (7*R*)-**17** in 26% yield. Similarly, (7*R*)-**16** was also transformed to (7*R*)-**17** in a good yield. In addition, the DA adduct **13e** was converted to (7*R*)-**13a** by the decarboxylation and the phenoxycarboxylation on nitrogen at the 2-position in a moderate yield.

We also examined the effectiveness of six kinds of chiral catalysts (Pd–hydroxyPOZ-**18a** and **18b**,[9b] 2-azanorbornane-based Pd–POZ-**19**,[9b] Cu–bis-oxazoline-**20**,[10] Pd–BINAP-**21**,[12] and phosphinooxazoline-**22**[13] catalysts) in the DA reaction of superior diene **6a** with dienophile **12a**. The reactions were carried out at 0 °C in the presence of 10 mol % of catalysts **18**–**22** to give the corresponding DA adduct **13a**. The results are shown in Table 3. The catalytic abilities of our developed 7-hydroxy-POZ catalysts **18a** and **b** in this reaction were contrastive. Thus, the reaction using the 2,7-*cis*-catalyst **18a** proceeded with 82% yield and 91% ee (entry 1). On the other hand, 2,7-*trans*-catalyst **18b** gave only low chemical and moderate enantioselectivity (44%, 79% ee, entry 2). The contrast of the results between **18a** and **b** might be due to the steric factor of the 7-hydroxy group. The more conformationally constrained cationic POZ catalyst **19**, fusing the 2-azanorbornane ring system, was applied in this reaction. Unfortunately, the catalyst **19** did not afford a better result than the result of **5a** in fusing the pyrrolidine ring system (entry 3). The effective catalyst **20** in Sibi's experiment[10] did not show catalytic activity when 10 mol % of **20** was used (entry 4). Catalyst **21**, acting as a superior catalyst in many reactions, had low reactivity and afforded only moderate chemical yield (57%) even at 72 h of reaction time, although it gave excellent enantioselectivity (96% ee, entry 5). Furthermore, catalyst **22** gave DA adduct **13a** in a low chemical yield (31%), but with 85% ee (entry 6). These results indicated that the combination of the POZ catalyst **8a** and dienophile **12a** was the most effective combination for this reaction.

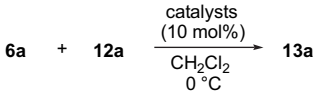
2.3. Transformation from isoquinuclidines to piperidines

Many medicines and biologically active compounds include a piperidine skeleton[14] in their structures. Therefore, it is important to develop an effective and convenient synthetic methodology for chiral piperidines bearing two or more chiral carbon centers in the structure. In order to develop such a methodology, we attempted to obtain the chiral piperidine derivative bearing three carbon centers by means of the ozonolysis of DA adduct **16** converted from **13a** (Scheme 5). The desired chiral piperidine derivative **23** bearing three chiral carbon centers at 2,3,5-positions was obtained with good yield, as well as we expected.



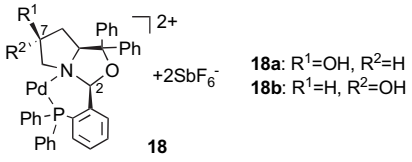
Scheme 5. Transformation from **13a** to piperidine **23**.

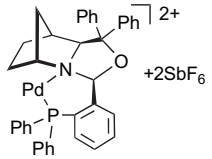
Table 3. Catalyst screen

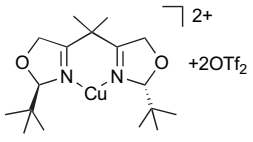


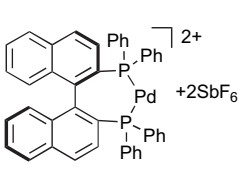
Entry	Catalyst	Time (h)	Yield[a] (%)	ee[b] (%)	Config.[c]
1	**18a**	24	82	91	7*R*
2	**18b**	24	44	79	7*R*
3	**19**	24	54	10	7*S*
4	**20**	72	No reaction	—	—
5	**21**	72	57	96	7*S*
6	**22**	24	31	85	7*S*

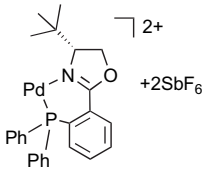
[a] Isolated yields.
[b] Enantiomeric excess of *endo*-isomer was determined by HPLC analysis using a DAICEL Chiralcel AD column.
[c] After conversion to benzyl ester [7*R*]-**14**, the absolute configuration was determined.











3. Conclusion

In conclusion, we have developed an efficient methodology for obtaining the chiral isoquinuclidines that are the precursor of pharmacologically important compounds. Thus, the DA reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **6a** with 1-benzyl-2-acryloylpyrazolidin-3-one **12a** as a dienophile using cationic antimonate Pd–POZ catalyst **5a** afforded the corresponding DA adduct **13a** at 97% ee with good chemical yield. Furthermore, the obtained DA adduct **13a** was easily transformed to the chiral piperidine **23** that bears three chiral carbon centers in the structure. Compound **23** might have a high potential utility as the synthetic intermediate of the pharmacologically important chiral piperidines and other alkaloids. In addition, these results indicate that the combination of Pd–POZ catalyst **5** with 1-substituted pyrazolidin-3-one dienophile **12** is useful not only in the DA reaction of 1,2-dihydropyridine but also in other asymmetric processes.

4. Experimental

4.1. General information

Melting points are uncorrected. IR spectra were recorded as KBr pellets (solids) or thin films (liquids). ^{1}H NMR spectra were recorded at 270 and 400 MHz. ^{13}C NMR spectra were recorded at 67.5 and 100 MHz. The chemical shifts are reported in parts per million downfield to TMS (δ=0) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ=77.0) for ^{13}C NMR. Mass spectra were obtained by EI. The enantiomeric excess (ee) of the products was determined by chiral HPLC. Optical rotations were recorded at the sodium D line with a polarimeter at room temperature. Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Chromatography refers to flash chromatography on silica gel (230–400 mesh), unless otherwise noted.

4.2. General procedure for the DA reaction of 1,2-dihydropyridines 6a,b with 2-acryloyl-1,3-oxazolidine-2-one 7 catalyzed by cationic Pd–POZ complexes 5a–d

A suspension of $PdCl_2$–POZ complex **4** (0.07 mmol) and AgX (X=SbF_6, ClO_4, BF_4, OTf) (2 equiv) in CH_2Cl_2 (1 mL) was stirred at room temperature for 1 h under Ar. The suspension was cooled to 0 °C and diene **6a** or **b** (3.5 mmol) and dienophile **7** (0.7 mmol) were added. The reaction mixture was stirred under Ar. The mixture was then quenched with satd $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtrated, and concentrated under a reduced pressure. The residue was purified by flash chromatography (hexane/AcOEt, 1/1) to afford **8**. The reaction conditions, chemical yields, and optical yields are shown in Table 1.

4.2.1. (1*R*,4*R*,7*R*)-7-(2′-Oxo-oxazolidine-3′-carbonyl)-2-azabicyclo[2.2.2]oct-5-ene-1-carboxylic acid benzyl ester (8b). Yield 118 mg, 90%; white solid (*n*-hexane), mp 37–38 °C; IR (KBr) 2929, 2342, 1781, 1694, 697 cm^{-1}; ^{1}H NMR (DMSO-d_6, 100 °C) δ 1.54–1.63 (m, 1H), 2.05 (ddd, *J*=2.6, 9.8, 12.6 Hz, 1H), 2.84 (m, 1H), 2.92 (dt, *J*=2.7, 10.2 Hz, 1H), 3.28 (d, *J*=10.1 Hz, 1H), 3.80–3.89 (m, 2H), 4.00 (ddd, *J*=2.7, 5.4, 9.8 Hz, 1H), 4.32–4.38 (m, 2H),

4.92 (m, 1H), 5.08 (s, 2H), 6.32–6.44 (m, 2H), 7.28–7.36 (m, 5H); ^{13}C NMR (DMSO-d_6, 100 °C) δ 26.88, 29.72, 42.13, 43.33, 46.24, 46.37, 61.84, 65.54, 126.80 (2C), 127.06, 127.73 (2C), 130.66, 133.44, 152.50, 153.69, 163.65, 171.59; MS *m/z* 356 (M^+); HRMS (EI) calcd for $C_{19}H_{20}N_2O_5$ (M^+) 356.1372, found 356.1365. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.12, H, 5.70; N, 7.72. The enantiomeric excess (ee) was determined by HPLC (DAICEL Chiralcel AD-H, 0.5 mL/min; *n*-hexane/2-propanol, 1/1; t_R (minor)=28.5 min, t_R (major)=35.4 min).

4.3. General procedure for the preparation of pyrazolidin-3-ones 12b,c

To a solution of acrylic acid (1.53 mmol) and Et_3N (2.95 mmol) in THF (10 mL) was added acryloyl chloride (1.60 mmol) at −25 °C and the mixture was stirred for 1 h under Ar. Lithium chloride (1.30 mmol) was added, followed by the pyrazolidin-3-ones, **11b** (1.18 mmol) or **11c** (1.18 mmol). The mixture was allowed to warm to room temperature and stirred for 6 h. The reaction was quenched by satd NaCl and THF was removed under a reduced pressure. The residue was partitioned between AcOEt and satd NaCl. The organic layer was washed with satd Na_2CO_3. The organic layers were then dried over anhydrous $MgSO_4$, filtrated, and concentrated under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 1/1) to afford **12b** and **12c**, respectively.

4.3.1. 2-Acryloyl-1-(1-naphthylmethyl)-5,5-dimethylpyrazolidin-3-one (12b). Yield 223 mg, 61%; white solid (*n*-hexane), mp 120–122 °C; IR (KBr) 1599, 1669, 1766 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 6H), 2.75 (s, 2H), 4.45 (br s, 2H), 5.01 (m, 1H), 5.84 (d, *J*=15.9 Hz, 1H), 6.36 (m, 1H), 7.36 (t, *J*=4.2 Hz, 1H), 7.48 (t, *J*=1.2 Hz, 2H), 7.56 (t, *J*=1.5 Hz, 1H), 7.77 (d, *J*=8.3 Hz, 1H), 7.82 (d, *J*=8.3 Hz, 1H), 8.17 (d, *J*=8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.93, 30.89, 43.00, 55.20, 61.45, 123.22, 125.33, 125.59, 126.29, 127.54, 128.72, 128.74, 129.31, 129.41, 133.63, 163.38, 173.96; MS *m/z* 308 (M^+); HRMS (EI) calcd for $C_{19}H_{20}N_2O_2$ (M^+) 308.1525, found 308.1539. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.12; H, 6.51; N, 8.87.

4.3.2. 2-Acryloyl-1-ethyl-5,5-dimethylpyrazolidin-3-one (12c). Yield 158 mg, 72%; pale yellow oil; IR (NaCl) 1694, 1749 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (t, *J*=7.2 Hz, 3H), 1.33 (s, 6H), 2.60 (s, 2H), 3.01 (q, *J*=7.1 Hz, 2H), 5.86 (d, *J*=12.2 Hz, 1H), 6.55 (d, *J*=17.1 Hz, 1H), 7.27 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 12.79, 25.75, 43.79, 47.31, 60.67, 128.57, 131.30, 163.76, 175.11; MS *m/z* 196 (M^+); HRMS (EI) calcd for $C_{10}H_{16}N_2O_2$ (M^+) 196.1212, found 196.1226. Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.28; H, 8.31; N, 14.16.

4.4. General procedure for the DA reaction of 1,2-dihydropyridine 6a with 2-acryloylpyrazolidin-3-ones 12a–c using cationic Pd–POZ complexes 5a–d

A suspension of $PdCl_2$–POZ complex **4** (10 mol %: 28 mg, 5 mol %: 14 mg, 2.5 mol %: 7 mg) and AgX (X=SbF_6, ClO_4, BF_4, OTf) (2 equiv) in CH_2Cl_2 (1 mL) was stirred at room temperature for 1 h under Ar. The suspension was cooled to 0 °C and diene **6a** (402 mg, 2.0 mmol) and pyrrazolidin-3-ones **12a–c** (0.4 mmol) in CH_2Cl_2 (1 mL) were added under Ar. The reaction mixture was stirred under Ar. The reaction was then quenched with satd $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtrated, and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 1/1) to afford **13a–c**. The reaction conditions, chemical yields, and optical yields are shown in Table 2.

4.4.1. (1*R*,4*R*,7*R*)-7-(1′-Benzyl-5′,5′-dimethyl-3′-oxo-pyrazolidin-2′-carbonyl)-2-azabicyclo[2.2.2]oct-5-ene-1-carboxylic acid phenyl ester (13a). White solid (AcOEt/*n*-hexane), mp 165–168 °C; $[\alpha]_D^{20}$ −52.94 (*c* 0.68, $CHCl_3$); IR (KBr) 1216, 1524, 1644, 3020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12–1.24 (m, 6H), 1.59 (m, 1H), 2.06 (m, 1H), 2.58 (m, 1H), 2.67 (m, 1H), 2.84 (br s, 1H), 3.06 (d, *J*=10.6 Hz, 0.5H), 3.18 (d, *J*=10.3 Hz, 0.5H), 3.35 (d, *J*=10.6 Hz, 0.5H), 3.50 (d, *J*=10.3 Hz, 0.5H), 4.00 (br s, 1H), 4.03 (br s, 2H), 5.07 (br s, 1H), 6.39–6.44 (m, 2H), 7.13 (m, 1H), 7.13–7.38 (m, 7H), 7.43–7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.80, 26.65, 27.51, 30.76, 43.50, 45.54, 46.79, 47.20, 57.10, 60.93, 121.78, 121.83, 125.13, 127.45, 127.50, 128.37, 128.88, 128.99, 129.18, 129.23, 130.84, 133.65, 137.58, 151.36, 153.38, 169.68, 173.91; MS *m/z* 459 (M^+); HRMS (EI) calcd for $C_{27}H_{29}N_3O_4$ (M^+) 459.2158, found 459.2176. Anal. Calcd for $C_{27}H_{29}N_3O_4$: C, 70.57; H, 6.36; N, 9.14. Found: C, 70.62; H, 6.21; N, 9.25. The ee was determined by HPLC (DAICEL Chiralcel AD-H, 0.5 mL/min; *n*-hexane/2-propanol, 1/1; t_R (minor)=12.70 min, t_R (major)=14.38 min).

4.4.2. (1*R*,4*R*,7*R*)-7-(1′-Naphthylmethyl-5′,5′-dimethyl-3′-oxo-pyrazolidin-2′-carbonyl)-2-azabicyclo[2.2.2]oct-5-ene-1-carboxylic acid phenyl ester (13b). White solid (AcOEt/*n*-hexane), mp 170–172 °C; $[\alpha]_D^{20}$ −20.13 (*c* 1.49, $CHCl_3$); IR (KBr) 1238, 1596, 1717, 2969 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35–1.41 (m, 6H), 1.58 (m, 1H), 2.18 (m, 1H), 2.63–2.71 (m, 2H), 2.83 (m, 1H), 3.00–3.13 (m, 2H), 3.54 (m, 1H), 4.32 (m, 1H), 4.57 (m, 1H), 4.87 (m, 1H), 6.10 (t, *J*=6.5 Hz, 0.5H), 6.18 (t, *J*=6.7 Hz, 0.5H), 6.28 (m, 1H), 7.12 (d, *J*=7.6 Hz, 1H), 7.17–7.22 (m, 2H), 7.35–7.40 (m, 3H), 7.42–7.58 (m, 2H), 7.65 (m, 1H), 7.78 (t, *J*=7.4 Hz, 1H), 7.86 (t, *J*=7.9 Hz, 1H), 8.21 (t, *J*=9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.92, 27.22, 30.33, 30.58, 43.22, 46.50, 46.90, 47.44, 54.98, 55.18, 121.72, 121.74, 123.25, 123.33, 125.13, 125.15, 125.35, 125.45, 125.74, 125.85, 126.39, 128.48, 128.76, 129.23, 129.27, 131.77, 133.71, 151.40, 151.43, 153.15, 173.85; MS *m/z* 509 (M^+); HRMS (EI) calcd for $C_{31}H_{31}N_3O_4$ (M^+) 509.2315, found 509.2336. Anal. Calcd for $C_{31}H_{31}N_3O_4$: C, 73.06; H, 6.13; N, 8.25. Found: C, 73.11; H, 6.01; N, 8.36. The ee was determined by HPLC (DAICEL Chiralcel AD-H, 0.5 mL/min; *n*-hexane/2-propanol, 1/1; t_R (minor)=15.00 min, t_R (major)=17.98 min).

4.4.3. (1*R*,4*R*,7*R*)-7-(1′-Ethyl-5′,5′-dimethyl-3′-oxo-pyrazolidin-2′-carbonyl)-2-azabicyclo[2.2.2]oct-5-ene-1-carboxylic acid phenyl ester (13c). White solid (AcOEt/*n*-hexane), mp 130–133 °C; $[\alpha]_D^{20}$ −33.98 (*c* 1.53, $CHCl_3$); IR (KBr) 1207, 1596, 1711, 2979 cm^{-1}; ^{1}H NMR ($CDCl_3$)

δ 1.02–1.07 (m, 3H), 1.24–1.31 (m, 6H), 1.70 (m, 1H), 2.21 (m, 1H), 2.53–2.64 (m, 2H), 2.89 (br s, 1H), 2.90–3.01 (m, 2H), 3.09 (d, J=10.5 Hz, 0.5H), 3.22 (d, J=10.2 Hz, 0.5H), 3.40 (d, J=10.5 Hz, 0.5H), 3.55 (d, J=10.2 Hz, 0.5H), 4.12 (m, 1H), 5.17 (m, 0.5H), 5.19 (m, 0.5H), 6.44–6.54 (m, 2H), 7.11–7.21 (m, 3H), 7.31–7.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.95, 25.77, 25.99, 30.84, 44.04, 45.70, 45.87, 47.03, 47.94, 121.78, 121.90, 125.09, 125.18, 129.15, 129.22, 132.19, 133.53, 134.36, 151.40, 152.96, 153.37; MS m/z 397 (M^+); HRMS (EI) calcd for $C_{22}H_{27}N_3O_4$ (M^+) 397.2002, found 397.1996. Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.57; H, 6.94; N, 10.38. The ee was determined by HPLC (DAICEL Chiralcel AD-H, 0.5 mL/min; *n*-hexane/2-propanol, 1/1; t_R (minor)=9.96 min, t_R (major)=11.75 min).

4.5. General procedure for the DA reaction of 1,2-dihydropyridines 6b,c with 2-acryloylpyrazolidin-3-one 12a

A suspension of $PdCl_2$–POZ complex **4** (0.03 mmol) and $AgSbF_6$ (0.06 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 1 h under Ar. The suspension was cooled to 0 °C and the solution of dienophile **12a** (0.26 mmol) in CH_2Cl_2 (1 mL) and **6b** (1.30 mmol) or **6c** (1.30 mmol) was added at that temperature. The reaction mixture was stirred under Ar for 24 h. The mixture was then quenched with satd $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 1/1) to afford the corresponding DA adducts **13d** and **13e**, respectively. The reaction conditions, chemical yields, and optical yields are shown in Table 2.

4.5.1. (1*R*,4*R*,7*R*)-7-(1′-Benzyl-5′,5′-dimethyl-3′-pyrazolidin-2′-carbonyl)-2-azabicyclo[2.2.2]oct-5-ene-1-carboxylic acid benzyl ester (13d). White solid (AcOEt/*n*-hexane), mp 158–162 °C; $[\alpha]_D^{20}$ −25.20 (*c* 1.23, $CHCl_3$); IR (KBr) 1232, 1495, 1689, 1755, 2957 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.81–1.27 (m, 6H), 1.54 (m, 1H), 2.05 (br s, 1H), 2.52–2.67 (m, 2H), 2.77 (m, 1H), 3.01 (m, 1H), 3.31 (m, 1H), 3.99 (d, J=6.6 Hz, 1H), 4.01–4.08 (m, 2H), 5.05 (m, 1H), 5.11–5.17 (m, 2H), 6.28–6.37 (m, 2H), 7.21–7.33 (m, 4H), 7.35–7.39 (m, 5H), 7.44 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.87, 26.60, 26.63, 27.55, 30.73, 43.52, 45.57, 46.65, 46.78, 57.00, 66.81, 127.39, 127.47, 127.66, 127.83, 127.89, 127.94, 128.01, 128.34, 128.36, 128.45, 128.84, 128.91, 131.65, 133.67, 136.91, 137.69, 154.96; MS m/z 473 (M^+); HRMS (EI) calcd for $C_{28}H_{31}N_3O_4$ (M^+) 473.2315, found 473.2320. Anal. Calcd for $C_{28}H_{31}N_3O_4$: C, 71.01; H, 6.60; N, 8.87. Found: C, 71.18; H, 6.72; N, 8.98. The ee was determined by HPLC (DAICEL Chiralcel AD-H, 0.5 mL/min; *n*-hexane/2-propanol, 1/1; t_R (minor)=12.97 min, t_R (major)=14.55 min).

4.5.2. (1*R*,4*R*,7*R*)-7-(1′-Benzyl-5′,5′-dimethyl-3′-oxo-pyrazolidin-2′-carbonyl)-2-azabicyclo[2.2.2]oct-5-ene-1-carboxylic acid-*tert*-butyl ester (13e). White solid (AcOEt/*n*-hexane), mp 155–158 °C; $[\alpha]_D^{20}$ −30.98 (*c* 1.42, $CHCl_3$); IR (KBr) 1236, 1496, 1688, 1756, 2981 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19–1.23 (m, 6H), 1.45–1.48 (m, 9H), 1.53 (m, 1H), 2.01 (m, 1H), 2.54–2.66 (m, 2H), 2.72 (d, J=1.8 Hz, 1H), 2.90 (d, J=10.3 Hz, 0.5H), 2.94 (d, J=10.6 Hz, 0.5H), 3.23 (t, J=5.1 Hz, 1H), 3.90 (br s, 1H), 4.03 (d, J=1.7 Hz, 2H), 4.80 (br s, 0.5H), 5.00 (br s, 0.5H), 6.28–6.37 (m, 2H), 7.22–7.31 (m, 3H), 7.45 (d, J=7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 25.99, 26.50, 27.63, 28.50, 28.54, 30.63, 30.90, 31.23, 43.54, 45.84, 46.58, 47.10, 60.81, 127.34, 128.31, 128.35, 128.77, 128.82, 131.23, 133.42, 134.00, 137.80, 154.23, 154.46; MS m/z 439 (M^+); HRMS (EI) calcd for $C_{25}H_{33}N_3O_4$ (M^+) 439.2471, found 439.2452. Anal. Calcd for $C_{25}H_{33}N_3O_4$: C, 68.31; H, 7.57; N, 9.56. Found: C, 70.48; H, 7.65; N, 9.78. The ee was determined by HPLC (DAICEL Chiralcel AD-H, 0.5 mL/min; *n*-hexane/2-propanol, 1/1; t_R (minor)=7.89 min, t_R (major)=12.97 min).

4.6. Determinations of the absolute stereochemistries of 13a–c, d, and e

4.6.1. General procedure for the conversion of DA adducts 8 or 13a–c to benzyl ester 14. To a stirred solution of benzyl alcohol (0.1 mL, 1.0 mmol) in anhydrous THF (6 mL) was added *n*-BuLi (1.0 M in *n*-hexane, 0.73 mL, 0.78 mmol) at −78 °C under Ar. The reaction mixture was stirred for 5 min and then the solution of (7*R*)-**8** or **13a–c** (0.52 mmol) in THF was added to the mixture at 0 °C. After being stirred for 3 h, the reaction was quenched by satd NH_4Cl and the solvent was removed under a reduced pressure, diluted with water, and extracted with $CHCl_3$. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under a reduced pressure. The residue was purified by flash chromatography ($CHCl_3$/AcOEt, 1/3) to afford (7*R*)-**14** (**8**: 75 mg, 38%; **13a**: 113 mg, 57%; **13b**: 121 mg, 61%; **13c**: 127 mg, 64%). The absolute stereochemistries of **13a–c** were determined in comparison with the optical rotation of (7*R*)-**14** derived from (7*R*)-**8**.

4.6.2. (1*R*,4*R*,7*R*)-1-Phenoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-benzylcarboxylate (14). Colorless oil [**14** (from **8**, 76% ee): $[\alpha]_D^{21}$ −47.77 (*c* 0.90, $CHCl_3$); **14** (from **13a**, 97% ee): $[\alpha]_D^{21}$ −59.92 (*c* 2.52, $CHCl_3$); **14** (from **13b**, 33% ee): $[\alpha]_D^{21}$ −12.50 (*c* 0.64, $CHCl_3$); **14** (from **13c**, 43% ee): $[\alpha]_D^{21}$ −33.33 (*c* 0.75, $CHCl_3$)]; IR (NaCl) 1216, 1595, 1713, 3019 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.91–2.07 (m, 2H), 2.91 (br s, 1H), 3.05 (d, J=10.6 Hz, 0.5H), 3.16 (d, J=10.3 Hz, 0.5H), 3.24 (m, 1H), 3.35 (d, J=10.6 Hz, 0.5H), 3.49 (d, J=10.3 Hz, 0.5H), 5.07–5.16 (m, 2H), 5.26 (m, 1H), 6.36 (m, 1H), 6.52 (m, 1H), 7.04–7.13 (m, 2H), 7.19 (m, 1H), 7.30–7.41 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 26.00, 30.67, 43.87, 46.96, 47.58, 66.61, 121.69, 121.76, 125.22, 128.11, 128.20, 128.25, 128.55, 128.59, 129.21, 129.25, 130.15, 135.26, 151.27, 153.06, 153.62, 172.36; MS m/z 363 (M^+); HRMS (EI) calcd for $C_{22}H_{21}NO_4$ (M^+) 363.1471, found 363.1471.

4.6.3. (1*R*,4*R*,7*R*)-1-Benzyloxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-methylcarboxylate (15). To the solution of lithium methoxide (1.0 M in methanol, 0.6 mL, 0.6 mmol) in THF (3 mL) at −78 °C was added *n*-BuLi (1.0 M in *n*-hexane, 0.42 mL, 0.45 mmol) and the solution of **13d** (89% ee, 140 mg, 0.3 mmol) in THF (8 mL) was added at that temperature. The mixture was stirred at 0 °C

for 6 h. The reaction was quenched by satd NH_4Cl and extracted with $CHCl_3$. The organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under a reduced pressure. The residue was purified by flash chromatography ($CHCl_3$/AcOEt, 3/1) to afford (7*R*)-**15** (70 mg, 77% yield). Colorless oil; $[\alpha]_D^{20}$ −74.75 (*c* 1.03, $CHCl_3$); IR (NaCl) 1216, 1587, 1692, 1732, 3019 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85–1.87 (m, 2H), 2.84 (m, 1H), 3.00 (m, 1H), 3.09 (m, 1H), 3.31 (m, 1H), 3.66 (s, 3H), 5.09 (m, 1H), 5.12–5.20 (m, 2H), 6.35 (m, 1H), 6.45 (m, 1H), 7.28–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.98, 30.61, 43.73, 46.73, 47.09, 51.95, 66.88, 127.84, 127.91, 127.95, 127.99, 128.46, 128.50, 130.23, 130.63, 135.14, 135.45; MS *m*/*z* 301 (M^+); HRMS (EI) calcd for $C_{17}H_{19}NO_4$ (M^+) 301.1314, found 301.1288.

4.6.4. (1*R*,4*R*,7*R*)-1-Phenoxycarbonyl-2-azabicyclo-[2.2.2]octane-7-methylcarboxylate (17). A suspension of **15** (50 mg, 0.17 mmol) and 10% Pd–C (18 mg, 0.17 mmol) in methanol (5 mL) was stirred under H_2 at room temperature for 2 h. Pd–C (10%) was filtered off and the filtrate was concentrated under a reduced pressure. The obtained residue without purification was dissolved in CH_3CN (1.5 mL). To the solution, phenyl chloroformate (0.02 mL, 0.17 mmol) and $NaHCO_3$ (43 mg, 0.51 mmol) were added and the mixture was stirred at room temperature for 15 h under Ar. The reaction was quenched by satd NH_4Cl and extracted with $CHCl_3$. The organic layers were dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 3/2) to afford (7*R*)-**17** (13 mg, 26% yield). White solid (AcOEt/*n*-hexane), mp 68–70 °C; $[\alpha]_D^{20}$ −56.80 (*c* 1.02, $CHCl_3$); IR (KBr) 1202, 1591, 1704, 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59–1.79 (m, 3H), 1.85–2.09 (m, 2H), 2.22 (m, 1H), 3.07 (m, 1H), 3.45 (s, 1H), 3.58 (m, 1H), 3.68–3.74 (m, 3H), 4.47 (br s, 0.5H), 4.53 (br s, 0.5H), 7.09–7.21 (m, 3H), 7.32–7.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.0, 23.3, 23.7, 25.9, 42.7, 45.5, 46.5, 49.2, 121.7, 121.8, 125.1, 129.2 (2C), 129.3, 151.4, 153.6; MS *m*/*z* 289 (M^+); HRMS (EI) calcd for $C_{16}H_{19}NO_4$ (M^+) 289.1314, found 289.1290.

4.6.5. (1*R*,4*R*,7*R*)-1-Phenoxycarbonyl-2-azabicyclo-[2.2.2]oct-5-ene-7-methylcarboxylate (16). To a solution of lithium methoxide (1.0 M in methanol, 1.70 mL, 1.70 mmol) in THF (10 mL) were added *n*-BuLi (1.0 M in *n*-hexane, 1.20 mL, 1.30 mmol) and the solution of **13a** (>99% ee, 400 mg, 0.87 mmol) in THF (23 mL) at −78 °C. The mixture was stirred at 0 °C for 4 h. The reaction was quenched by satd NH_4Cl and extracted with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under a reduced pressure. The residue was purified by flash chromatography (AcOEt/$CHCl_3$, 1/3) to afford (7*R*)-**16** (199 mg, 80% yield). White solid (AcOEt/*n*-hexane), mp 76–78 °C; $[\alpha]_D^{20}$ −68.18 (*c* 1.98, $CHCl_3$); IR (KBr) 1204, 1570, 1703, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90–1.98 (m, 2H), 2.92 (br s, 1H), 3.05 (d, *J*=10.6 Hz, 0.5H), 3.16–3.22 (m, 1.5H), 3.5 (d, *J*=10.3 Hz, 0.5H), 3.48 (m, 0.5H), 3.67–3.71 (m, 3H), 5.21 (m, 0.5H), 5.27 (m, 0.5H), 6.42 (m, 1H), 6.52 (m, 1H), 7.07–7.14 (m, 2H), 7.19 (m, 1H), 7.31–7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.96, 30.61, 30.87, 43.61, 46.85, 47.50, 51.95, 121.64, 121.69, 125.15, 125.22, 129.16, 129.21, 135.19, 135.69, 151.23; MS *m*/*z* 287 (M^+); HRMS (EI) calcd for $C_{16}H_{17}NO_4$ (M^+) 287.1158, found 287.1176.

4.6.6. Conversion of 16 to 17. The suspension of **16** (103 mg, 0.36 mmol) and 5% Pd–C (8 mg, 0.36 mmol) in methanol (12 mL) was stirred under H_2 at room temperature for 12 h. Pd–C (5%) was filtered off and the solvent was removed under a reduced pressure to give the (7*R*)-**17** [86 mg, 83% yield, $[\alpha]_D^{20}$ −61.03 (*c* 1.00, $CHCl_3$)].

4.6.7. Conversion of 13e to 13a. To the solution of **13e** (67% ee, 33 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (TFA) (0.01 mL, 0.11 mmol), and the mixture was stirred at room temperature for 12 h. The reaction was quenched by 1 N HCl and extracted with $CHCl_3$. The organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under a reduced pressure. The obtained residue was dissolved in CH_3CN, phenyl chloroformate (0.01 mL, 0.08 mmol) and $NaHCO_3$ (21 mg, 0.25 mmol) were added to the solution. The solution was stirred at room temperature for 18 h. The reaction was quenched by satd NH_4Cl and extracted with $CHCl_3$. The organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 2/1) to afford (7*R*)-**13a** [23 mg, 38% yield, $[\alpha]_D^{20}$ −24.99 (*c* 1.36, $CHCl_3$)].

4.7. General procedure for the DA reaction of 1,2-dihydropyridine 6a with 2-acryloylpyrazolidin-3-one 12a using cationic Pd–POZ complexes 18a,b and 19

A suspension of $PdCl_2$–POZ complexes (0.04 mmol) and $AgSbF_6$ (0.08 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 1 h under Ar. To the suspension of the obtained catalysts **18a**,**b** or **19** was added the solution of **12a** (0.4 mmol) in CH_2Cl_2 (1 mL) and **6a** (2.0 mmol) at 0 °C. The reaction was stirred at that temperature for 24 h under Ar. The mixture was then quenched with satd $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 1/1) to afford **13a**. The reaction conditions, chemical yields, and optical yields are shown in Table 3.

4.8. General procedure for the DA reaction of 1,2-dihydropyridine 6a with 2-acryloyl-1,3-oxazolidine-2-one 12a using cationic Pd–POZ complexes 20–22

To a suspension of chiral catalysts **20**–**22** (0.04 mmol) prepared by the previous reported methods[6g,12,13] in CH_2Cl_2 (1 mL) was added the solution of **12a** (0.4 mmol) in CH_2Cl_2 (1 mL) and **6a** (2.0 mmol) at 0 °C and the suspension was stirred at that temperature under Ar. The reaction conditions are shown in Table 3. The mixture was then quenched with satd $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 1/1) to afford **13a**. The reaction conditions, chemical yields, and optical yields are shown in Table 3.

4.9. Transformation of 16 to chiral piperidine derivative 23

4.9.1. (2*S*,3*R*,5*S*)-2,5-Diformyl-1-phenoxycarbonyl-piperidin-3-methylcarboxylate (23). O_3 was bubbled through a MeOH/CH_2Cl_2 (1/1) (6 mL) of DA adduct **16** (115 mg, 0.4 mmol) at −78 °C. After 10 min, the ozone stream from the blue solution was immediately removed from the mixture, which was then purged with N_2 for 5 min. Excess dimethyl sulfide (1 mL) was quickly added and the solution was allowed to reach room temperature slowly (12 h), and then quenched with brine and extracted with AcOEt. The organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under a reduced pressure. The residue was purified by flash chromatography (*n*-hexane/AcOEt, 2/1) to give the product **23** (110 mg, 86%). Pale yellow solid (AcOEt/*n*-hexane), mp 63–65 °C; $[\alpha]_D^{20}$ −54.37 (*c* 1.84, $CHCl_3$); IR (KBr) 1413, 1594, 1719, 2954, 3446 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61–1.71 (m, 1H), 2.57–2.60 (m, 2H), 2.63–3.00 (m, 2H), 3.78–3.81 (m, 3H), 4.63 (m, 1H), 5.51 (d, J=5.1 Hz, 1H), 7.12–7.16 (m, 2H), 7.25 (m, 1H), 7.38–7.42 (m, 2H), 9.68 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 23.28, 42.03, 47.78, 52.44, 60.40, 60.63, 121.45, 121.52, 125.93, 125.99, 128.70, 129.50, 129.78, 197.97, 199.77; MS *m*/*z* 319 (M^+); HRMS (EI) calcd for $C_{16}H_{17}NO_6$ (M^+) 319.1056, found 319.1049.

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$Pd(OAc)_2$/DABCO-catalyzed Suzuki–Miyaura cross-coupling reaction in DMF

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Abstract—The scope and limitations of the $Pd(OAc)_2$/DABCO (1,4-diaza-bicyclo[2.2.2]octane)-catalyzed Suzuki–Miyaura cross-coupling reactions have been demonstrated. The results showed that the effect of solvent had a fundamental influence on the reaction. In the presence of $Pd(OAc)_2$ and DABCO, both aryl bromides and aryl chlorides all worked well with arylboronic acids to form biaryls, heteroaryl-aryls, and biheteroaryls in moderate to excellent yields using DMF as the solvent. Additionally, the reactions of aryl bromides were conducted under relatively mild conditions.

1. Introduction

Palladium-catalyzed cross-coupling of aryl halides with organoboronic acids, namely Suzuki–Miyaura cross-coupling reaction, is a versatile and utilized reaction for the selective formation of carbon–carbon bonds, in particular for the synthesis of biaryls.[1–7] Recently, efforts have been focused on the development of efficient and selective catalytic systems for the Suzuki–Miyaura reaction. However, many catalytic systems are limited to the couplings of aromatic iodides and bromides.[2] In recent years, employing readily available aryl chlorides in these transformations have received increasing attention, and a number of effective catalytic systems have been developed for this purpose.[2–4] In these processes, the use of sterically hindered and electron-rich ligands played crucial roles in the coupling of these challenging substrates. One of the notable examples is the use of bulky trialkylphosphines.[4] However, many of those phosphine ligands are sensitive to air and/or moisture besides expensive, which place significant limits on their synthetic applications. Very recently, we have reported that DABCO (1,4-diaza-bicyclo[2.2.2]octane) was an inexpensive, stable, and highly efficient ligand for the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction.[6] After checking our previous results carefully, we found that the scopes of the Suzuki–Miyaura reactions catalyzed by our catalytic system relied on the solvents. In the presence of $Pd(OAc)_2$ and DABCO, only aryl iodides and bromides were coupled with arylboronic acids efficiently using acetone as the solvent,[6a] whereas the scope was extended to the activated aryl chlorides when PEG-400[6b] or H_2O[6c] was used as the media. Furthermore, the deactivated aryl chlorides could be coupled smoothly with PEG-400 to afford moderate yields with the aid of TBAB (tetrabutylammonium bromide). The results encouraged us to further explore the effects of the solvents on the scope and limitations of the $Pd(OAc)_2$/DABCO-catalyzed Suzuki–Miyaura cross-coupling reactions.[2] We were happy to discover that the scope of the protocol could be extended to aryl chlorides to construct biaryls, heteroaryl-aryl, and biheteroaryls when DMF was employed as the media. Moreover, the couplings of aryl bromides in DMF could be conducted under relatively mild conditions. Here, we wish to report the results of this methodology in detail (Eq. 1).

$$\mathrm{Ar{-}X} + \mathrm{Ar'{-}B(OH)_2} \xrightarrow[\mathrm{Cs_2CO_3,\ DMF}]{\mathrm{Pd(OAc)_2/DABCO}} \mathrm{Ar{-}Ar'} \quad (1)$$

Ar, Ar' = aryl, heteroaryl
X = Br, Cl

2. Results and discussion

2.1. Effect of solvents on the $Pd(OAc)_2$/DABCO-catalyzed Suzuki–Miyaura reaction

The $Pd(OAc)_2$/DABCO-catalyzed Suzuki–Miyaura reaction between 1-chloro-4-nitro-benzene (**1a**) and phenylboronic acid (**2a**) was chosen as a model reaction to evaluate the effects of the solvents, and the results are summarized in

Keywords: $Pd(OAc)_2$/DABCO; Suzuki–Miyaura cross-coupling reaction; Aryl halide; Arylboronic acids.
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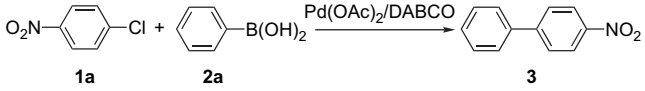
Table 1. Effect of solvents on $Pd(OAc)_2$/DABCO-catalyzed Suzuki–Miyaura cross-coupling reaction of 1-chloro-4-nitrobenzene with phenylboronic acid[a]



1a 2a 3

Entry	Solvent	Time (h)	Isolated yield (%)
1	Acetone (5 mL)	2	18 (Ref. 6a)
2[b]	Acetone (5 mL)	2	40
3	PEG-400 (2 g)	3	60 (Ref. 6b)
4[c]	PEG-400 (2 g)	3	92 (Ref. 6b)
5	Dioxane (3 mL)	19	45
6[b]	H_2O (5 mL)	24	Trace (Ref. 6c)
7[b]	CH_3CH_2OH/H_2O (1:4; 5 mL)	24	50 (Ref. 6c)
8	DMF (3 mL)	19	100
9[d]	DMF (3 mL)	17	100
10[d,e]	DMF (3 mL)	33	94
11[d,f]	DMF (3 mL)	42	72

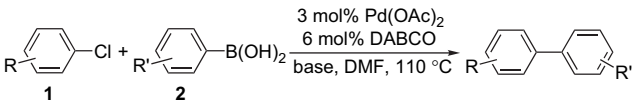
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.7 mmol), $Pd(OAc)_2$ (3 mol %), DABCO (6 mol %), and K_2CO_3 (3 equiv) at 110 °C.
[b] PEG-400 (0.2 equiv).
[c] TBAB (0.1 equiv).
[d] Cs_2CO_3 (3 equiv).
[e] $Pd(OAc)_2$ (1 mol %) and DABCO (2 mol %).
[f] $Pd(OAc)_2$ (0.1 mol %) and DABCO (0.2 mol %).

Table 1. In our initial communication,[6a] acetone was used as the media. Unfortunately, only an 18% yield of the target product **3** was isolated in acetone when 1-chloro-4-nitrobenzene (**1a**) was treated with phenylboronic acid (**2a**), $Pd(OAc)_2$ (3 mol %), DABCO (6 mol %), and K_2CO_3 (3 equiv) at 110 °C (entry 1). We found that the yield of **3** was enhanced to 40% when 0.2 equiv of PEG-400 was added (entry 2). Thus, PEG-400 employed as the medium was tested, and a 60% yield was provided (entry 3).[6b] It was interesting to observe that the yield of **3** was increased sharply to 92% using PEG-400 as the media and TBAB as an additional promoter (entry 4). Dioxane, the reported excellent solvent by Tao and Boykin,[5] gave only a 45% yield of **3** (entry 5). The reaction performed in aqueous media was also investigated.[6c] Trace amount of **3** was isolated in water (entry 6), but the yield was increased to 50% when ethanol was used as the co-solvent (entry 7). We were happy to see that the quantitative yield of **3** was obtained when the reaction was carried out in DMF (entry 8). The results also indicated that effects of bases could affect the reaction to some extent. Cs_2CO_3 in place of K_2CO_3 as the base could shorten the reaction time (entries 8 and 9). It is noteworthy that the reaction performed in DMF can be conducted at 0.1 mol % loading Pd together with a good yield after prolonged reaction time (94% yield at 1 mol % Pd and 72% yield at 0.1 mol % Pd; entries 10 and 11).

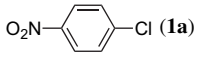
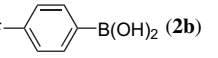
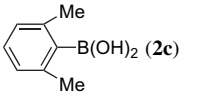
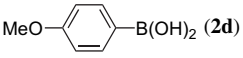
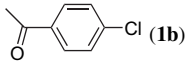
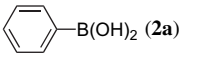
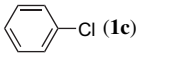
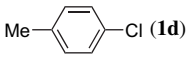
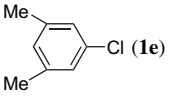
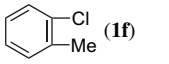
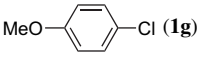
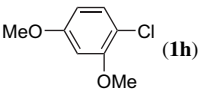
2.2. $Pd(OAc)_2$/DABCO-catalyzed Suzuki–Miyaura reaction to synthesize biaryls

The coupling reaction between a range of substrates and several arylboronic acids was then conducted to explore the general effectiveness of the $Pd(OAc)_2$/DABCO/DMF system (Table 2). Under the above optimized reaction conditions, a wide range of aryl chlorides **1a–h**, whether electron-rich or electron-deficient, all worked well with arylboronic acids **2a–d**. Moreover, *ortho*-substituents on the aromatic rings could also be tolerated as well, leading to the corresponding hindered coupling products in moderate yields. As shown in Table 2, the $Pd(OAc)_2$/DABCO/DMF system was proved exceptionally active for the couplings of the activated chlorides **1a** and **1b**, but the yields relied on arylboronic acids. For example, treatment of **1a** with boronic acid **2b** or **2d** afforded the target products in excellent yields (a 99% yield for **2b** and a 93% yield for **2d**; entries 1 and 3), whereas only a moderate yield was observed when **1a** reacted with the hindered boronic acid **2c** (entry 2). Although the efficiency of the $Pd(OAc)_2$/DABCO/DMF system was also decreased for more challenging deactivated aryl chlorides, moderate yields of the corresponding hindered coupling products were still achieved (entries 7–9 and 14). Unfortunately, an attempt to coupling of the deactivated

Table 2. $Pd(OAc)_2$/DABCO-catalyzed Suzuki–Miyaura cross-coupling reaction of aryl chlorides with arylboronic acids in DMF[a]



1 2

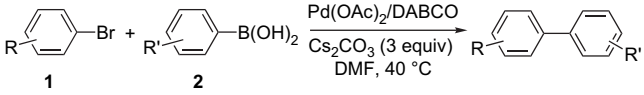
Entry	ArX	$ArB(OH)_2$	Yield (%)[b]
1	 (**1a**)	 (**2b**)	99 (**4**)
2	(**1a**)	 (**2c**)	52 (**5**)
3	(**1a**)	 (**2d**)	93 (**6**)
4[c]	 (**1b**)	 (**2a**)	100 (**7**)
5	 (**1c**)	(**2a**)	65 (**8**)
6	 (**1d**)	(**2a**)	53 (**9**)
7	 (**1e**)	(**2a**)	64 (**10**)
8	 (**1f**)	(**2a**)	60 (**11**)
9	(**1f**)	(**2d**)	58 (**12**)
10	 (**1g**)	(**2a**)	61 (**13**)
11	(**1g**)	(**2b**)	71 (**14**)
12	(**1g**)	(**2c**)	Trace (**15**)
13	(**1g**)	(**2d**)	52 (**16**)
14	 (**1h**)	(**2a**)	63 (**17**)
15	1-Iododecane (**1i**)	(**2a**)	— (**18**)

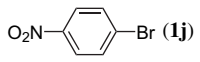
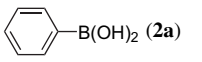
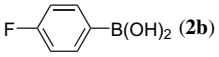
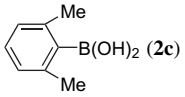
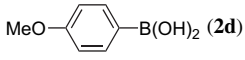
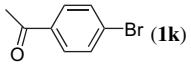
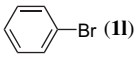
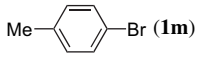
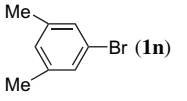
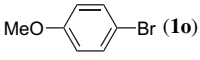
[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (0.5 mmol), **2** (0.7 mmol), $Pd(OAc)_2$ (3 mol %), DABCO (6 mol %), and Cs_2CO_3 (3 equiv) in DMF (3 mL) at 110 °C for 19 h.
[b] Isolated yield.
[c] For 17 h.

chloride **1g** with the bulky boronic acid **2c** was unsuccessful (entry 12). Finally, we also screened the reaction between 1-iododecane (**1i**) and phenylboronic acid (**2a**), but no target product was obtained (entry 15).

With the excellent reaction conditions in hand, we then decided to explore the couplings of aryl bromides again. Gratifyingly, the reactions between aryl bromides and arylboronic acids were able to conduct under mild conditions (Table 3). At 40 °C, aryl bromides **1j–m** and **1o** reacted well with **2a** to afford the corresponding cross-coupling products in excellent yields (entries 2–8 and 11). The hindered bromide **1n** required higher reaction temperature.

Table 3. $Pd(OAc)_2$/DABCO-catalyzed Suzuki–Miyaura cross-coupling reactions of aryl bromides with arylboronic acids in DMF[a]



Entry	ArX	$ArB(OH)_2$	Yield (%)[b]
1[c]	 (**1j**)	 (**2a**)	Trace (**3**)
2	(**1j**)	(**2a**)	100 (**3**)
3	(**1j**)	 (**2b**)	81 (**3**)
4	(**1j**)	 (**2c**)	Trace (**5**)
5	(**1j**)	 (**2d**)	90 (**3**)
6	 (**1k**)	(**2a**)	96 (**7**)
7	 (**1l**)	(**2a**)	94 (**8**)
8	 (**1m**)	(**2a**)	89 (**9**)
9	 (**1n**)	(**2a**)	40 (**10**)
10[d]	(**1n**)	(**2a**)	92 (**10**)
11	 (**1o**)	(**2a**)	90 (**13**)
12	(**1o**)	(**2b**)	37 (**14**)
13[d]	(**1o**)	(**2b**)	82 (**14**)
14	(**1o**)	(**2d**)	30 (**16**)
15[d,e]	(**1o**)	(**2d**)	96 (**16**)

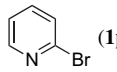
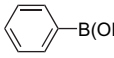
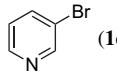
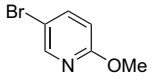
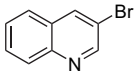
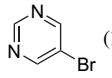
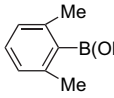
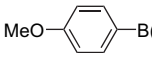
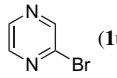
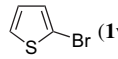
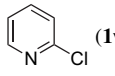
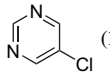
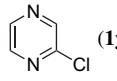
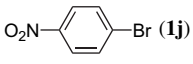
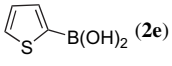
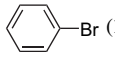
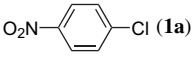
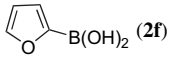
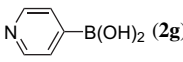
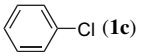
[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (0.5 mmol), **2** (0.7 mmol), $Pd(OAc)_2$ (3 mol %), DABCO (6 mol %), and Cs_2CO_3 (3 equiv) in DMF (3 mL) at 40 °C for 16 h.
[b] Isolated yield.
[c] At room temperature.
[d] At 80 °C.
[e] For 25 h.

Only a 40% yield of the target product **10** was isolated from the reaction of **1n** with **1a** at 40 °C, but the yield of **10** was enhanced to 92% when the reaction was performed at 80 °C (entries 9 and 10). The couplings of the substrates **1j** and **1o** with the other boronic acids were also examined. The results demonstrated that the yields of the desired products were varied with different boronic acids (entries 3–5 and 12–15). The bromide **1j** treated with **2b–d**, $Pd(OAc)_2$, DABCO, and Cs_2CO_3 at 40 °C to offer the corresponding products in 81%, trace, and 90% yields, respectively (entries 3–5). We also observed that bromide **1o** with the other boronic acid **2b** or **2d** required the couplings performing at higher temperature to produce good results (entries 12–15). For example, the reaction of bromide **1o** with **2b** provided only 37% of the desired coupled product **14** at 40 °C (entry 12). However, the yield was increased to 82% when the reaction was carried out at 80 °C (entries 13).

2.3. $Pd(OAc)_2$/DABCO-catalyzed Suzuki–Miyaura reaction to synthesize heteroaryl-aryls and biheteroaryls

Construction of biaryl containing heteroaryl rings via the palladium-catalyzed Suzuki–Miyaura reaction is another interesting area.[2,7] There are a few transformations for general cross-coupling reactions of both aryl halides and heteroaryl halides with arylboronic acids including heteroarylboronic acids to synthesize biaryls containing heteroaryl rings. However, most of the transformations required the phosphine ligands to improve them as well as limited to aryl bromides. To our delight, the $Pd(OAc)_2$/DABCO/DMF system was also effective for the reactions of aryl halides with heteroarylboronic acids (Table 4). Solvent was also found to play a crucial role in the reaction (entries 1–4). In acetone, treatment of **1p** with **2a**, $Pd(OAc)_2$, DABCO, and Cs_2CO_3 afforded a 34% yield of the target product **19** in 48 h. In dioxane, the yield of **19** was increased slightly to 49% for 48 h (entry 2). We were happy to find that the yield of **19** was enhanced to 66% for 22 h when the reaction was conducted in DMF. Under the same optimized reaction conditions, the other heteroaryl bromides **1q–v**, including nitrogen- or sulfur-containing heteroaryl bromides, coupled with arylboronic acids were carried out efficiently to produce the corresponding products in moderate to excellent yields (entries 4–12). For example, 5-bromopyrimidine **1t** reacted with three kinds of arylboronic acids, including a challenging boronic acid **2d**, smoothly to give the corresponding desired products **23–25** in 98, 50, and 98% yields, respectively (entries 7–9). The sulfur-containing substrate **1v** coupled with **2a** offered a moderate yield of the target product **27** under the same reaction conditions (entry 11). It was pleased to find that the yield of **27** was increased sharply to 98% when K_2CO_3 was employed as the base (entry 12). However, the best base for the couplings of heteroaryl chlorides **1w–y** was KOH (entries 13–17). Treatment of chloride **1w** with **2a**, $Pd(OAc)_2$, DABCO, and Cs_2CO_3 provided a 40% of the desired product **19** (entry 13), whereas the yield of **19** was enhanced dramatically to 58% using KOH as the base (entry 14). In the presence of $Pd(OAc)_2$, DABCO, KOH, and DMF, the other chlorides **1x** and **1y** underwent the coupling with **2a** smoothly to afford the corresponding products in moderate yields (entries 15 and 16).

Table 4. $Pd(OAc)_2$/DABCO-catalyzed Suzuki–Miyaura cross-coupling reaction of aryl halides with heteroarylboronic acids to synthesize heteroaryl-aryls[a]

Entry	ArX	$ArB(OH)_2$	Time (h)	Yield (%)[b]
1[c]	 (**1p**)	 (**2a**)	48	34 (**19**)
2[d]	(**1p**)	(**2a**)	48	49 (**19**)
3	(**1p**)	(**2a**)	22	66 (**19**)
4	 (**1q**)	(**2a**)	22	81 (**20**)
5	 (**1r**)	(**2a**)	21	65 (**21**)
6	 (**1s**)	(**2a**)	22	94 (**22**)
7	 (**1t**)	(**2a**)	4	98 (**23**)
8	(**1t**)	 (**2c**)	12	50 (**24**)
9	(**1t**)	 (**2d**)	10	98 (**25**)
10	 (**1u**)	(**2a**)	46	94 (**26**)
11	 (**1v**)	(**2a**)	22	65 (**27**)
12[e]	(**1v**)	(**2a**)	22	98 (**27**)
13	 (**1w**)	(**2a**)	48	40 (**19**)
14[f]	(**1w**)	(**2a**)	46	58 (**19**)
15[f]	 (**1x**)	(**2a**)	46	52 (**23**)
16[f]	 (**1y**)	(**2a**)	46	54 (**26**)
17	 (**1j**)	 (**2e**)	10	98 (**28**)
18	 (**1l**)	(**2e**)	12	95 (**27**)
19	 (**1a**)	(**2e**)	19	93 (**28**)
20	(**1a**)	 (**2f**)	19	90 (**29**)
21	(**1a**)	 (**2g**)	24	58 (**30**)
22	 (**1c**)	(**2e**)	24	88 (**27**)
23	(**1c**)	(**2f**)	24	74 (**31**)

[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (0.5 mmol), **2** (0.7 mmol), $Pd(OAc)_2$ (3 mol %), DABCO (6 mol %), and Cs_2CO_3 (3 equiv) in DMF (3 mL) at 110 °C.
[b] Isolated yield.
[c] In acetone (3 mL).
[d] In dioxane (3 mL).
[e] K_2CO_3 (3 equiv) instead of Cs_2CO_3.
[f] KOH (3 equiv) instead of Cs_2CO_3.

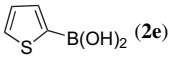
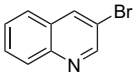
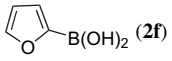
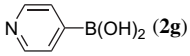
Subsequently, the couplings between aryl halides and heteroarylboronic acids were conducted under the same optimized conditions. The results indicated that the reactions of aryl bromides **1j** or **1l** with heteroarylboronic acid **2e** produced the corresponding products in excellent yields using $Pd(OAc)_2$/DABCO as the catalytic system and DMF as the solvent (entries 17 and 18). Moderate to good yields were still achieved when aryl chlorides **1a** or **1c** were treated with heteroarylboronic acids under the same reaction conditions (entries 19–23). For example, the reaction of substrate **1a** with **2e–g** afforded the corresponding products **28–30** in 93, 90, and 58%, respectively, in the presence of $Pd(OAc)_2$, DABCO, Cs_2CO_3, and DMF (entries 19–21).

The reactions of heteroaryl halides with heteroarylboronic acids were also performed smoothly under the $Pd(OAc)_2$/DABCO/DMF system and the results are summarized in Table 5. In the presence of $Pd(OAc)_2$ and DABCO, a number of heteroaryl bromides reacted with sulfur- and oxygen-containing heteroarylboronic acids to afford the corresponding products in high yields using KOH or K_2CO_3 as the base and DMF as the solvent (entries 1–6), but with nitrogen-containing heteroarylboronic acid (**2g**) provided a moderate yield (entry 7). For example, the reaction of substrate **1u** with **2e** gave the desired product **37** in a 98% yield, whereas treatment of **1u** with **2g**, a nitrogen-containing heteroarylboronic acid, produced only a 65% yield of the target product **38** (entries 6 and 7). To our surprise, only a 16% yield of the desired coupled product **32** was isolated together with a 56% yield of 2-(pyridin-2-yl)pyridine, a homocoupling product of 2-bromopyridine (**1p**) (entry 1). Under the same reaction conditions, the reaction of 2-chloropyridine **1w** was also unsuccessful (entry 8). However, another chloride **1y** coupled with **2e** was carried out smoothly to offer the desired product **37** in a moderate yield (entry 9).

3. Conclusion

In summary, we have discussed the effect of solvents on the scope and limitations of the $Pd(OAc)_2$/DABCO-catalyzed Suzuki–Miyaura cross-coupling reaction. On the base of the results, several features are established: (1) the effect of the solvents has a fundamental influence on the scope and limitations of the current reaction, and the results demonstrate the broad substrate scope of the $Pd(OAc)_2$/DABCO/DMF system for the Suzuki–Miyaura coupling. In acetone,

Table 5. $Pd(OAc)_2$/DABCO-catalyzed Suzuki–Miyaura cross-coupling reactions of heteroaryl halides with heteroarylboronic acids to provide biheteroaryls[a]

Entry	ArX	$ArB(OH)_2$	Time (h)	Yield (%)[b]
1	 (**1p**)	 (**2e**)	39	16 (**32**)
2	 (**1s**)	(**2e**)	23	93 (**33**)
3	(**1s**)	 (**2f**)	21	98 (**34**)
4[c]	 (**1t**)	(**2e**)	17	96 (**35**)
5[c]	(**1t**)	(**2f**)	22	93 (**36**)
6	 (**1u**)	(**2e**)	23	98 (**37**)
7	(**1u**)	 (**2g**)	23	65 (**38**)
8	 (**1w**)	(**2e**)	41	Trace (**32**)
9	 (**1y**)	(**2e**)	38	50 (**37**)

[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (0.5 mmol), **2** (0.7 mmol), $Pd(OAc)_2$ (3 mol %), DABCO (6 mol %), and KOH (3 equiv) in DMF (3 mL) at 110 °C.
[b] Isolated yield.
[c] K_2CO_3 (3 equiv) instead of KOH.

only aryl iodides and bromides were coupled with arylboronic acids efficiently,[6a] whereas in PEG-400[6b] or PEG-400/H_2O[6c] the scope was extended to the activated aryl chlorides. In addition, some deactivated aryl chlorides could be coupled smoothly when TBAB was added to PEG-400.[6b] However, DMF was proved here to be the more effective solvent for a wide range of aryl halides including the deactivated aryl chlorides and heteroaryl halides. Moreover, the couplings of aryl bromides in DMF were conducted under mild conditions. The reason that DMF is the most effective medium here may be that DMF is a highly polar solvent and may play as a ligand to promote the reaction.[2] (2) The reaction showed excellent substituent tolerance on the aromatic rings. (3) DABCO is considerably inexpensive and readily available, which emerged as an attractive alternative to the phosphine ligand for the Suzuki–Miyaura cross-coupling reaction. Given these advantage, design, and application of these ligands on the base of the DABCO skeleton in other palladium-catalyzed cross-coupling transformations should be attractive.

4. Experimental

4.1. Typical experimental procedure for the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction in DMF

A mixture of aryl halide **1** (0.5 mmol), arylboronic acid **2** (0.7 mmol), $Pd(OAc)_2$ (3 mol %), DABCO (6 mol %), base (3 equiv), and DMF (3 mL) was stirred at the indicated reaction temperature for the desired time until complete consumption of starting material as monitored by TLC. After the mixture was poured into diethyl ether, then washed with water, extracted with diethyl ether, dried by anhydrous Na_2SO_4, and evaporated under vacuum, the residue was purified by flash column chromatography (hexane or hexane/ethyl acetate) to afford the desired coupled products **3**–**14**, **16**, **17**, and **19**–**38**.

4.1.1. 4-Nitro-biphenyl (3).[3] Yellow solid; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.30 (d, J=8.8 Hz, 2H), 7.74 (d, J=8.8 Hz, 2H), 7.64 (d, J=6.9 Hz, 2H), 7.52–7.44 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.6, 147.1, 138.8, 129.2, 128.91, 127.8, 127.4, 124.1; LRMS (EI, 20 eV) m/z (%): 199 (M^+, 100).

4.1.2. 4-Nitro-4′-fluorobiphenyl (4).[3] Yellow solid; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.30 (d, J=8.8 Hz, 2H), 7.70 (d, J=8.8 Hz, 2H), 7.59 (dd, J=5.6 Hz, 5.6 Hz, 2H), 7.20 (t, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.6, 162.1, 146.5, 134.9, 129.1 (d, J=8.6 Hz, 1C), 127.6, 124.2, 116.2 (d, J=21.7 Hz, 1C); LRMS (EI, 20 eV) m/z (%): 217 (M^+, 100).

4.1.3. 4-Nitro-2′,6′-dimethylbiphenyl (5).[3] Yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.31 (d, J=9.0 Hz, 2H), 7.35 (d, J=8.7 Hz, 2H), 7.25–7.20 (m, 1H), 7.15–7.13 (m, 2H), 2.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.4, 146.8, 139.5, 135.3, 130.7, 128.0, 127.6, 123.8, 20.7; LRMS (EI, 20 eV) m/z (%): 227 (M^+, 100).

4.1.4. 4-Nitro-4′-methoxybiphenyl (6).[3] Yellow solid; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.25 (d, J=9.0 Hz, 2H), 7.68 (d, J=9.0 Hz, 2H), 7.57 (d, J=9.0 Hz, 2H), 7.02 (d, J=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.4, 147.2, 146.5, 131.0, 128.5, 127.0, 124.1, 114.6, 55.4; LRMS (EI, 20 eV) m/z (%): 229 (M^+, 100).

4.1.5. 1-Biphenyl-4-yl-ethanone (7).[3] White solid; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, J=8.4 Hz, 2H), 7.69 (d, J=8.4 Hz, 2H), 7.64 (d, J=7.6 Hz, 2H), 7.50–7.40 (m, 3H), 2.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.1, 146.1, 140.2, 136.2, 130.1, 129.2, 128.6, 127.6, 118.5, 27.0; LRMS (EI, 20 eV) m/z (%): 196 (M^+, 100).

4.1.6. Biphenyl (8).[3] White solid; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.59 (d, J=8.4 Hz, 4H), 7.43 (t, J=7.2 Hz, 4H), 7.36 (t, J=7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.6, 129.1, 127.6, 127.5; LRMS (EI, 20 eV) m/z (%): 154 (M^+, 100).

4.1.7. 4-Methyl-biphenyl (9).[3] White solid; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.59 (t, J=7.6 Hz, 2H), 7.49 (d, J=8.0 Hz, 2H), 7.42 (t, J=7.6 Hz, 2H), 7.31 (t, J=7.6 Hz, 1H), 7.24 (d, J=8.0 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.1, 138.3, 137.0, 129.5, 128.7, 127.3, 127.2, 127.0, 21.1; LRMS (EI, 20 eV) m/z (%): 168 (M^+, 100).

4.1.8. 3,5-Dimethyl-biphenyl (10).[3] Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, J=8.4 Hz, 2H), 7.44–7.40 (m, 2H), 7.31–7.28 (m, 1H), 7.19 (d, J=8.4 Hz, 2H), 6.98 (d, J=9.2 Hz, 1H), 2.35 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.5, 138.1, 128.9, 128.7, 127.9,

127.2, 127.1, 125.1, 21.4; LRMS (EI, 20 eV) *m/z* (%): 182 (M^+, 100).

4.1.9. 2-Methyl-biphenyl (11).[3] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (t, J=7.2 Hz, 2H), 7.32 (t, J=6.8 Hz, 3H), 7.25–7.23 (m, 4H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.9, 135.3, 130.3, 129.8, 129.2, 128.0, 127.2, 126.7, 125.7, 125.6, 20.4; LRMS (EI, 20 eV) *m/z* (%): 168 (M^+, 100).

4.1.10. 2-Methyl-4′-methoxy-biphenyl (12).[3] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26–7.22 (m, 6H), 6.95 (d, J=8.4 Hz, 2H), 3.85 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5, 141.5, 135.5, 134.3, 130.3, 130.2, 129.9, 127.0, 125.8, 113.5, 55.3, 20.6; LRMS (EI, 20 eV) *m/z* (%): 198 (M^+, 100).

4.1.11. 4-Methoxy-biphenyl (13).[3] White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54 (t, J=8.4 Hz, 4H), 7.42 (t, J=7.8 Hz, 2H), 7.31 (t, J=7.5 Hz, 1H), 6.98 (d, J=9.0 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3; LRMS (EI, 20 eV) *m/z* (%): 184 (M^+, 100).

4.1.12. 4-Fluoro-4′-methoxy-biphenyl (14).[3] White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50–7.45 (m, 4H), 7.09 (t, J=8.4 Hz, 2H), 6.96 (d, J=8.7 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.7, 160.4, 159.0, 132.7, 128.2 (d, J=9.3 Hz, 1C), 128.0, 115.5 (d, J=28.2 Hz, 1C), 114.2, 55.3; LRMS (EI, 20 eV) *m/z* (%): 202 (M^+, 100).

4.1.13. 4,4′-Dimethoxy-biphenyl (16).[3] White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (d, J=8.4 Hz, 4H), 6.95 (d, J=8.87 Hz, 4H), 3.84 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.7, 133.5, 127.7, 114.1, 59.3; LRMS (EI, 20 eV) *m/z* (%): 214 (M^+, 100).

4.1.14. 2,4-Dimethoxy-biphenyl (17).[3] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (d, J=8.1 Hz, 2H), 7.40 (t, J=7.5 Hz, 2H), 7.34 (t, J=9.0 Hz, 1H), 6.95–6.82 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.6, 138.3, 129.4, 128.0, 127.0, 116.6, 116.0, 113.0, 112.8, 112.5, 56.2, 55.8; LRMS (EI, 20 eV) *m/z* (%): 214 (M^+, 100).

4.1.15. 2-Phenylpyridine (19).[3] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (d, J=4.8 Hz, 1H), 7.99 (d, J=6.8 Hz, 2H), 7.78–7.71 (m, 2H), 7.48 (t, J=8.8 Hz, 2H), 7.42 (t, J=7.2 Hz, 1H), 7.26–7.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.4, 149.6, 139.3, 136.7, 128.9, 128.7, 126.9, 122.1, 120.5; LRMS (EI, 20 eV) *m/z* (%): 155 (M^+, 100).

4.1.16. 3-Phenylpyridine (20).[3] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.85 (s, 1H), 8.59 (d, J=6.4 Hz, 1H), 7.88 (d, J=12.0 Hz, 1H), 7.60 (d, J=8.4 Hz, 2H), 7.49 (t, J=7.2 Hz, 2H), 7.43–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.4, 148.3, 137.8, 136.6, 134.3, 129.0, 128.1, 127.1, 123.5; LRMS (EI, 20 eV) *m/z* (%): 155 (M^+, 100).

4.1.17. 2-Methoxy-5-phenylpyridine (21). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (s, 1H), 7.79 (d, J=2.8 Hz, 1H), 7.54–7.52 (m, 2H), 7.46 (t, J=7.2 Hz, 2H), 7.35 (t, J=7.6 Hz, 1H), 6.82 (d, J=8.8 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.6, 145.0, 137.9, 137.4, 130.1, 128.9, 127.3, 126.7, 110.8, 53.5; LRMS (EI, 20 eV) *m/z* (%): 185 (M^+, 100); HRMS (EI) for $C_{12}H_{11}NO$ (M^+): calcd, 185.0841; found, 185.0840.

4.1.18. 3-Phenylquinoline (22).[8] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.19 (s, 1H), 8.30 (s, 1H), 8.15 (d, J=8.8 Hz, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.72 (d, J=7.2 Hz, 3H), 7.60–7.51 (m, 3H), 7.44 (t, J=7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.9, 147.3, 137.8, 133.8, 133.2, 129.4, 129.2, 129.1, 128.1, 128.0 (2C), 127.4, 127.0; LRMS (EI, 20 eV) *m/z* (%): 205 (M^+, 100).

4.1.19. 5-Phenylpyrimidine (23).[3] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.21 (s, 1H), 8.96 (s, 2H), 7.58 (d, J=8.8 Hz, 2H), 7.53 (t, J=8.8 Hz, 2H), 7.47 (t, J=7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.3, 154.8, 134.2, 134.1, 129.3, 128.9, 126.7; LRMS (EI, 20 eV) *m/z* (%): 156 (M^+, 100).

4.1.20. 5-(2,6-Dimethylphenyl)pyrimidine (24). White solid, mp 50–52 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.23 (s, 1H), 8.60 (s, 2H), 7.26 (t, J=8.0 Hz, 1H), 7.17 (d, J=8.4 Hz, 2H), 2.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.3, 157.1, 136.4, 134.6, 133.8, 128.7, 127.8, 21.0; LRMS (EI, 20 eV) *m/z* (%): 184 (M^+, 100); HRMS (EI) for $C_{12}H_{12}N_2$ (M^+): calcd, 184.1001; found, 184.1000.

4.1.21. 5-(4-Methoxyphenyl)pyrimidine (25). White solid, mp 91–93 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.16 (s, 1H), 8.92 (s, 2H), 7.53 (d, J=8.4 Hz, 2H), 7.05 (d, J=8.4 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3, 156.8, 154.3, 133.8, 128.0, 126.4, 114.8, 55.3; LRMS (EI, 20 eV) *m/z* (%): 186 (M^+, 100); HRMS (EI) for $C_{11}H_{10}N_2O$ (M^+): calcd, 186.0793; found, 186.0791.

4.1.22. 2-Phenylpyrazine (26).[9] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.04 (d, J=1.6 Hz, 2H), 8.65 (s, 1H), 8.52 (d, J=2.4 Hz, 1H), 8.02 (d, J=8.0 Hz, 2H), 7.51 (t, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.8, 144.2, 142.9, 142.2, 136.3, 129.9, 129.0, 126.9; LRMS (EI, 20 eV) *m/z* (%): 156 (M^+, 100).

4.1.23. 2-Phenylthiophene (27).[10] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61–7.57 (m, 2H), 7.35 (t, J=7.6 Hz, 2H), 7.29–7.23 (m, 2H), 7.05 (t, J=4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.4, 134.3, 128.8, 127.9, 127.4, 125.9, 124.7, 123.0; LRMS (EI, 20 eV) *m/z* (%): 160 (M^+, 100).

4.1.24. 2-(4-Nitrophenyl)thiophene (28).[11] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (d, J=8.8 Hz, 2H), 7.74 (d, J=9.6 Hz, 2H), 7.48 (d, J=4.0 Hz, 1H), 7.44 (d, J=5.2 Hz, 1H), 7.15 (t, J=4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.6, 141.6, 140.6, 128.7, 127.7, 126.0, 125.7, 124.4; LRMS (EI, 20 eV) *m/z* (%): 205 (M^+, 100).

4.1.25. 2-(4-Nitrophenyl)furan (29).[11] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (d, J=8.8 Hz, 2H), 7.78 (d, J=7.8 Hz, 2H), 7.57 (d, J=1.2 Hz, 1H), 6.87

(d, J=2.4 Hz, 1H), 6.55 (t, J=3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.7, 146.4, 144.1, 136.4, 124.3, 123.3, 112.4, 108.6; LRMS (EI, 20 eV) m/z (%): 189 (M^+, 100).

4.1.26. 4-(4-Nitrophenyl)pyridine (30). Yellow solid, mp 128.4–129.4 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (d, J=6.0 Hz, 2H), 8.36 (d, J=8.8 Hz, 2H), 7.81 (d, J=8.8 Hz, 2H), 7.55 (d, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.6, 148.1, 145.7, 144.4, 127.9, 124.3, 121.7; LRMS (EI, 20 eV) m/z (%): 200 (M^+, 100).

4.1.27. 2-Phenylfuran (31).[12] White solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 (d, J=8.8 Hz, 1H), 7.60 (d, J=8.8 Hz, 2H), 7.46–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.0, 128.7, 128.6, 127.3, 127.2, 127.1, 123.7, 111.6; LRMS (EI, 20 eV) m/z (%): 144 (M^+, 100).

4.1.28. 3-(Thiophen-2-yl)quinoline (33). White solid, mp 73.4–73.9 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.18 (s, 1H), 8.21 (s, 1H), 8.08 (d, J=8.0 Hz, 1H), 7.77 (d, J=8.4 Hz, 1H), 7.66 (t, J=7.6 Hz, 1H), 7.51 (t, J=7.6 Hz, 1H), 7.45 (s, 1H), 7.35 (d, J=4.8 Hz, 1H), 7.12 (t, J=4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.5, 147.1, 140.6, 131.2, 129.2, 129.1, 128.3, 127.8, 127.7, 127.4, 127.1, 126.0, 124.3; LRMS (EI, 20 eV) m/z (%): 211 (M^+, 100); HRMS (EI) for $C_{13}H_9NS$ (M^+): calcd, 211.0456; found, 211.0455.

4.1.29. 3-(Furan-2-yl)quinoline (34). Pale solid, mp 81.7–82.0 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.21 (s, 1H), 8.33 (s, 1H), 8.07 (d, J=8.4 Hz, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.66 (t, J=8.8 Hz, 1H), 7.56–7.51 (m, 2H), 6.85 (d, J=3.2 Hz, 1H), 6.54 (d, J=5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.3, 147.1, 143.1, 129.3, 129.2, 129.0, 127.9, 127.8, 127.1, 124.0, 111.9, 106.7; LRMS (EI, 20 eV) m/z (%): 195 (M^+, 100); HRMS (EI) for $C_{13}H_9NO$ (M^+): calcd, 195.0684; found, 195.0684.

4.1.30. 5-(Thiophen-2-yl)pyrimidine (35). White solid, mp 77.2–78.0 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.13 (s, 1H), 8.96 (s, 1H), 7.46 (d, J=6.0 Hz, 2H), 7.43 (d, J=5.2 Hz, 1H), 7.18 (t, J=3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.2, 153.4, 136.2, 128.6 (2C), 127.3, 125.2; LRMS (EI, 20 eV) m/z (%): 162 (M^+, 100); HRMS (EI) for $C_8H_6N_2S$ (M^+): calcd, 162.0252; found, 162.0251.

4.1.31. 5-(Furan-2-yl)pyrimidine (36).[13] Slight yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.10 (s, 1H), 9.01 (s 2H), 7.59 (d, J=1.6 Hz, 1H), 6.85 (d, J=3.6 Hz, 1H), 6.55 (t, J=1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.0, 151.3, 147.9, 144.0, 125.0, 112.1, 107.9; LRMS (EI, 20 eV) m/z (%): 146 (M^+, 100).

4.1.32. 2-(Thiophen-2-yl)pyrazine (37).[13] Slight yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (s, 1H), 8.51 (s, 1H), 8.40 (s, 1H), 7.69 (d, J=4.0 Hz, 1H), 7.49 (d, J=5.6 Hz, 1H), 7.16 (t, J=4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.5, 143.9, 142.3, 141.3, 140.6, 129.0, 128.4, 125.7; LRMS (EI, 20 eV) m/z (%): 162 (M^+, 100).

4.1.33. 2-(Pyridin-4-yl)pyrazine (38). Slight yellow solid, mp 87.6–88.4 °C (uncorrected); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.11 (s, 1H), 8.79 (d, J=6.0 Hz, 2H), 8.72 (s, 1H), 8.64 (s, 1H), 7.93 (d, J=6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.7, 150.1, 144.7, 144.6, 143.5, 142.3, 120.9; LRMS (EI, 20 eV) m/z (%): 157 (M^+, 100); HRMS (EI) for $C_9H_7N_3$ (M^+): calcd, 157.0640; found, 157.0640.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.103.

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Palladium(II)-catalyzed tandem intramolecular aminopalladation of alkynylanilines and conjugate addition for synthesis of 2,3-disubstituted indole derivatives

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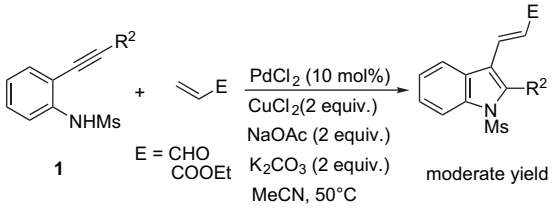
Abstract—An efficient method for the synthesis of 2,3-disubstituted indoles with high selectivity from 2-ethynylaniline derivatives and α,β-unsaturated carbonyl compounds was developed. This Pd(II)-catalyzed reaction involves tandem intramolecular aminopalladation, olefin insertion and protonolysis of the carbon-palladium bond with the regeneration of Pd(II) species in the presence of halide ions.

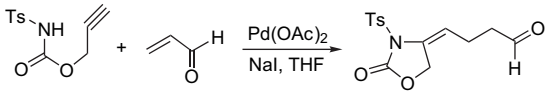
1. Introduction

The construction of the pyrrole ring incorporated into the indole system under the catalysis of the Pd complexes has been extensively studied.[1] The intramolecular cyclization of 2-ethynylaniline under the catalysis of Pd species belongs to one of the most useful methods for the systhesis of indoles.[1a] Yasuhara reported that the reaction of *N*-protected 2-alkynylanilines with electron-deficient alkenes in the presence of a palladium(II) catalyst and copper chloride as an oxidant in acetonitrile gave products of β-H elimination (Heck reaction), namely, 2-substituted 3-alkenylindoles with moderate yields (Eq. 1).[2]



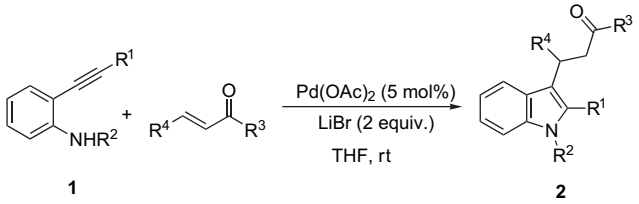
(1)

In our previous work, we reported the synthesis of oxazolidinones, imidazolidinones or lactams under the catalysis of a divalent palladium species with high chemo- and stereoselectivity from the intramolecular aminopalladation of alkynes, followed by insertion of acrolein, and finally, protonolysis of the newly formed-palladium bond (tandem aminopalladation and conjugate addition) (Eq. 2).[3] It is worth noting that in this reaction, the β-hydride elimination could be inhibited in the presence of an equivalent amount of NaI or LiBr.[4] Thus, the halide ions are crucial for this reaction.



(2)

Herein, we wished to report the Pd(II)-catalyzed reaction of 2-ethynylaniline with α,β-unsaturated carbonyl compounds in the presence of LiBr affording corresponding 2,3-disubstituted indoles without the occurrence of β-hydride elimination (Scheme 1).



Scheme 1. Tandem reaction of intramolecular aminopalladation and conjugate addition.

Keywords: Indole; Palladium; Aminopalladation; Conjugate addition.
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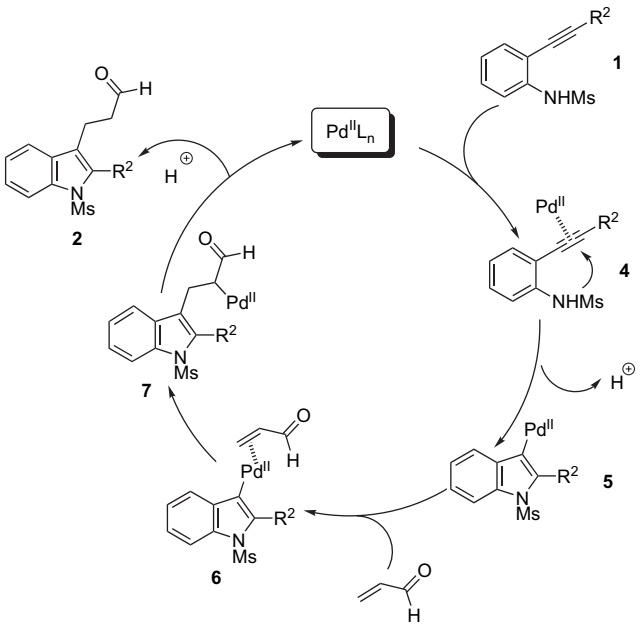
2. Results and discussion

The reaction conditions for the intramolecular aminopalladation of *N*-mesyl-2-ethynylaniline **1a** and the succeeding conjugate addition reaction with acrolein were examined as shown in Table 1.

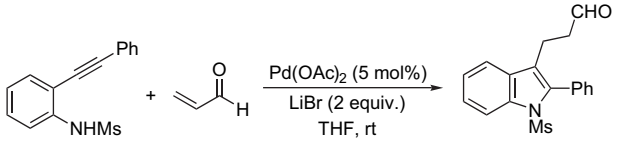
As a result, using 3 equiv of acrolein, the tandem reaction of 2-ethynylaniline proceeded smoothly in the presence of $Pd(OAc)_2$ (5 mol%) as catalyst and LiBr (2 equiv) as additive in THF at room temperature yielding the expected product **2a** in 85% yield without the occurrence of β-hydride elimination (Table 1, entry 2).

Under the same reaction conditions, different 2-ethynylaniline derivatives (**1b–1l**) and α,β-unsaturated carbonyl compounds were investigated as shown in Table 2. All the substrates with a sulfonyl group (tosyl or mesyl) on the nitrogen atom gave the good yield. It is worth noting that when the substituted group on nitrogen was trifluoroacetyl, acetyl or hydrogen, the reaction did not occur or gave a mixture of unknown products (Table 2, entries 4,7 and 10). This may be due to the requirement of a more acidic hydrogen on the nitrogen atom to facilitate the aminopalladation step.[3] For substrates with a variety of R^1 groups on the triple bond, including Ph, *n*-Bu, CH_2OCH_3 and even the bulky TMS group, the reaction could afford products in good to excellent yield (Table 2, entries 1–3, 5,6 and 8). However, the yield of the reaction greatly decreased for the substrates with a terminal alkyne (**1j**, Table 2, entry 9). Beside acrolein, the reaction of **1a** with crotonaldehyde gave the expected product **2a′** in 81% yield (Table 2, entry 11). In the meanwhile, the reaction of compound **1c** with methyl vinyl ketone afforded the product **2c′** in 76% yield (Table 2, entry 12).



Scheme 2. Mechanism of the reaction.

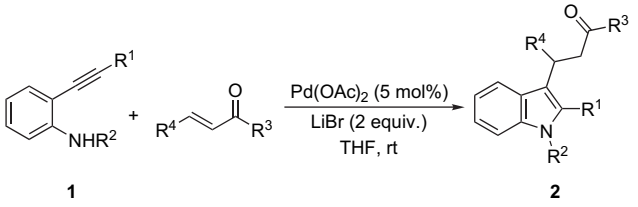
Table 1. Palladium(II)-catalyzed tandem reaction with different amounts of acrolein[a]



Entry	Time (day)	Acrolein (equiv)	Yield (%)[b]
1	1	10	71
2	1	3.0	85
3	2	1.5	78

[a] Conditions: substrate **1a** (0.22 mmol), LiBr (2 equiv), THF (1.1 mL).
[b] Isolated yield.

Table 2. Palladium(II)-catalyzed tandem reaction for the synthesis of indoles from 2-alkynylaniline and α,β-unsaturated carbonyl compounds[a]



Entry	1	R^1	R^2	R^3	R^4	Time	Yield (%)[b]
1	**1b**	Ph	Ts	H	H	Overnight	83 (**2b**)
2	**1c**	*n*-Bu	Ts	H	H	Overnight	88 (**2c**)
3	**1d**	*n*-Bu	Ms	H	H	Overnight	75 (**2d**)
4	**1e**	*n*-Bu	Ac	H	H	6 d	Trace
5	**1f**	CH_2OCH_3	Ms	H	H	1 d	89 (**2f**)
6	**1g**	CH_2OCH_3	Ts	H	H	Overnight	94 (**2g**)
7	**1h**	CH_2OCH_3	$COCF_3$	H	H	5 d	N.R.
8	**1i**	TMS	Ms	H	H	4 d	72 (**2i**)
9	**1j**	H	Ms	H	H	3 d	27 (**2j**)
10	**1l**	Ph	H	H	H	5 d	Disordered
11	**1a**	Ph	Ms	H	CH_3	4 d	81 (**2a′**)
12	**1c**	*n*-Bu	Ts	CH_3	H	2 d	76 (**2c′**)

[a] Conditions: substrate **1a** (0.22 mmol), α,β-unsaturated carbonyl compounds (3 equiv), LiBr (2 equiv), THF (1.1 mL).
[b] Isolated yield.

The following mechanism is proposed for this reaction: first, the Pd(II) species will coordinate with the triple bond of the substrate **1**. Trans attack of mesyl or tosyl amide anion to the coordinated triple bond may afford indole palladium intermediate **5** (aminopalladation),[5] followed by insertion of the double bond of the acrolein and protonolysis of the newly formed carbon–palladium bond via the palladium enolate **7** in the presence of halide ions to yield aldehyde **2** and regenerate the divalent palladium species to complete the catalytic cycle (Scheme 2).[4b,6] The key point in this tandem reaction is that the halide ions can block the β-hydride elimination of a (2-oxoalkyl)-palladium species, giving preferentially the protonolysis product in acidic media.[4b] This also indicates the reason that a sulfonamide amino group (more acidic) is preferential for this reaction.

3. Conclusion

In summary, we developed an efficient method for the synthesis of 2,3-disubstituted indoles with high selectivity from 2-alkynylaniline derivatives and α,β-unsaturated carbonyl compounds. This Pd(II)-catalyzed reaction involves tandem intramolecular aminopalladation, olefin insertion and protonolysis of the carbon-palladium bond.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained on a Varian EM-360 at 300 and 75 MHz, respectively. The mass spectra were run using a Hewlett–Packard MS-Engine 5989A instrument. Infrared spectra were recorded on a Bio-Rad FTS-185 machine. 2-Ethynylaniline derivative **1a**–**1d**,[7] **1f**–**1g**,[7] **1i**,[7] **1g**,[7] **1e**,[8] **1h**[9] and **1j**[10] was prepared according to the literature. LiBr was purified according to the standard method.

4.2. General procedure for the reaction of 2-alkynylaniline derivatives with α,β-unsaturated carbonyl compounds under the catalysis of Pd(II)

A solution of **1** (0.22 mmol), LiBr (0.44 mmol), α,β-unsaturated carbonyl compounds (0.66 mmol), $Pd(OAc)_2$ (5 mol%, 2.5 mg) in dry THF (1.1 mL) was stirred under nitrogen at room temperature. After the reaction was finished as monitored by TLC, silica gel (100–200 mesh) was added into the mixture and the solvent was evaporated under reduced pressure. The residues were purified by flash chromatography on silica gel with petroleum ether–ethyl acetate (10/1–4/1 (v/v)) as the eluent to afford the white solid **2**.

4.2.1. 3-(*N*-Mesyl-2′-phenylindol-3′-yl)propanal (2a). White solid, 85% yield, mp: 135–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (t, J=7.2 Hz, 2H), 2.83 (s, 3H), 2.91 (t, J=7.2 Hz, 2H), 7.35–7.48 (m, 7H), 7.55–7.58 (m, 1H), 8.12–8.15 (m, 1H), 9.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 40.4, 43.4, 115.3, 119.0, 121.2, 124.1, 125.3, 128.0, 129.0, 129.7, 130.7, 130.8, 136.6, 136.9, 201.0; IR (KBr): ν 2932, 1714, 1450, 1355, 1171 cm^{-1}; MS (EI) *m/z*: 327 (M)$^+$, 271, 230, 218, 205, 204, 115, 55; Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28. Found: C, 66.22; H, 5.30; N, 4.08.

4.2.2. 3-(*N*-Tosyl-2′-phenylindol-3′-yl)propanal (2b). White solid, 83% yield, mp: 159–160 °C (recrystallization from petroleum ether–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.49–2.54 (m, 2H), 2.78–2.83 (m, 2H), 7.08 (d, J=8.1 Hz, 2H), 7.26–7.46 (m, 10H), 8.33–8.36 (m, 1H), 9.59 (t, J=1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 21.5, 43.3, 116.0, 118.7, 121.5, 123.8, 125.1, 126.7, 127.6, 128.8, 129.3, 129.9, 130.9, 131.1, 135.2, 136.97, 137.01, 144.5, 201.1; IR (KBr): ν 2836, 2737, 1720, 1366, 1172 cm^{-1}; MS (EI) *m/z*: 403 (M)$^+$, 402 (M−1)$^+$, 346, 230, 203, 91, 57, 56, 55; Anal. Calcd for $C_{24}H_{21}NO_3S$: C, 71.44; H, 5.25; N, 3.47. Found: C, 71.31; H, 5.38; N, 3.18.

4.2.3. 3-(*N*-Tosyl-2′-*n*-butylindol-3′-yl)propanal (2c). Oil, 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J=7.2 Hz, 3H), 1.35–1.48 (m, 2H), 1.60–1.65 (m, 2H), 2.32 (s, 3H), 2.69 (t, J=7.8 Hz, 2H), 2.90–3.00 (m, 4H), 7.14 (d, J=8.1 Hz, 2H), 7.23–7.27 (m, 2H), 7.33–7.36 (m, 1H), 7.52–7.55 (m, 2H), 8.16–8.19 (m, 1H), 9.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 16.6, 21.4, 22.7, 26.2, 33.1, 43.7, 115.4, 118.0, 119.1, 123.5, 124.1, 126.1, 129.6, 130.0, 135.8, 136.7, 138.3, 144.4, 201.1; IR (neat): ν 2959, 2929, 1724, 1454, 1365, 1174 cm^{-1}; MS (EI) *m/z*: 383 (M)$^+$, 382 (M−1)$^+$, 326, 155, 143, 115, 105, 91, 55; HRMS Calcd for $C_{22}H_{25}NO_3S$: 383.1555, found: 383.1566.

4.2.4. 3-(*N*-Mesyl-2′-*n*-butylindol-3′-yl)propanal (2d). White solid, 75% yield, mp: 62–63 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J=7.2 Hz, 3H), 1.37–1.45 (m, 2H), 1.57–1.67 (m, 2H), 2.79 (t, J=6.9 Hz, 2H), 2.94 (s, 3H), 2.92–3.03 (m, 4H), 7.28–7.32 (m, 2H), 7.44–7.47 (m, 1H), 8.00–8.04 (m, 1H), 9.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 16.6, 22.7, 25.9, 33.0, 40.0, 43.8, 114.6, 118.3, 118.7, 123.7, 124.4, 130.0, 136.3, 138.3, 201.1; IR (KBr): ν 3033, 2958, 1721, 1456, 1351, 1166 cm^{-1}; MS (EI) *m/z*: 307 (M)$^+$, 251, 222, 143, 130, 115, 55, 40; Anal. Calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56. Found: C, 62.49; H, 7.00; N, 4.27.

4.2.5. 3-(*N*-Mesyl-2′-methoxymethylindol-3′-yl)propanal (2f). Oil, 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (t, J=7.5 Hz, 2H), 3.09 (m, 2H), 3.21 (s, 3H), 3.45 (s, 3H), 4.77 (s, 2H), 7.27–7.39 (m, 2H), 7.52–7.54 (m, 1H), 8.08 (d, J=7.5 Hz, 1H), 9.83 (t, J=0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 40.9, 44.0, 58.1, 63.4, 114.3, 119.1, 121.6, 123.3, 125.4, 128.5, 132.3, 136.3, 200.9; IR (neat): ν 2931, 1715, 1362, 1172 cm^{-1}; MS (EI) *m/z*: 295 (M$^+$), 172, 156, 144, 143, 142, 130, 115, 45; HRMS Calcd for ($C_{14}H_{17}NO_4S$+Na$^+$): 318.0770, found: 318.0775.

4.2.6. 3-(*N*-Tosyl-2′-methoxymethylindol-3′-yl)propanal (2g). White solid, 94% yield, mp: 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.75 (dt, J_1=0.9, J_2=7.2 Hz, 2H), 3.04 (t, J=7.2 Hz, 2H), 3.41 (s, 3H), 4.83 (s, 2H), 7.16–7.46 (m, 5H), 7.80–7.83 (m, 2H), 8.14–8.17 (m, 1H), 9.78 (t, J=0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 21.5, 44.0, 57.9, 63.5, 115.0, 118.9, 122.8, 123.3, 125.3, 126.9, 128.9, 129.4, 132.8, 135.8, 136.4, 144.5, 201.1; IR (KBr): ν 3065, 1716, 1368, 1179 cm^{-1}; MS (EI) *m/z*: 371 (M)$^+$, 370 (M−1)$^+$, 172, 156, 130, 115, 105, 91, 77, 45; HRMS Calcd for $C_{20}H_{21}NO_4S$: 371.1191, found: 371.1199.

4.2.7. 3-(*N*-Mesyl-2′-trimethylsilylindol-3′-yl)propanal (2i). Yellow solid, 72% yield, mp: 57–58 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.47 (s, 9H), 2.79 (s, 3H), 2.77–2.82 (m, 2H), 3.17–3.22 (m, 2H), 7.31–7.41 (m, 2H), 7.49–7.52 (m, 1H), 8.01–8.04 (m, 1H), 9.86 (t, J=1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.3, 17.9, 38.4, 45.0, 114.8, 119.0, 123.8, 125.9, 131.7, 134.6, 137.6, 139.1, 200.7; IR (KBr): ν 3015, 2976, 2830, 1717, 1359, 1178 cm^{-1}; MS (EI) *m/z*: 323 (M^+), 154, 143, 137, 75, 73, 59, 45, 43; HRMS Calcd for $C_{15}H_{21}NO_3SSi$: 323.1011, found: 323.1021.

4.2.8. 3-(*N*-Mesyl-indol-3′-yl)propanal (2j). White solid, 27% yield, mp: 82–83 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (t, J=7.2 Hz, 2H), 3.06 (s, 3H), 3.03–3.08 (m, 2H), 7.22 (s, 1H), 7.30–7.41 (m, 2H), 7.57 (d, J=8.1 Hz, 1H), 7.90 (d, J=8.1 Hz, 1H), 9.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 40.4, 42.8, 113.2, 119.5, 121.2, 122.7, 123.4, 125.2, 130.4, 135.3, 200.9; IR (KBr): ν 3128, 3019, 2926, 1732, 1446, 1354, 1168 cm^{-1}; MS (EI) *m/z*: 251 (M^+), 195, 144, 143, 130, 116, 115, 55; HRMS Calcd for $C_{12}H_{13}NO_3S$: 251.0616, found: 251.0613.

4.2.9. 3-(*N*-Mesyl-2′-phenylindol-3′-yl)-3-methylpropanal (2a′). White solid, 81% yield, mp: 134–136 °C (recrystallization from petroleum ether–dichloromethane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, J=7.2 Hz, 3H), 2.73 (ddd, J_1=1.8, J_2=7.2, J_3=16.8 Hz, 1H), 2.88 (s, 3H), 2.85–2.93 (m, 1H), 3.36–3.44 (m, 1H), 7.33–7.49 (m, 7H), 7.69–7.72 (m, 1H), 8.14–8.17 (m, 1H), 9.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 25.9, 40.7, 49.2, 115.4, 120.2, 123.7, 125.0, 128.0, 128.4, 129.1, 130.8, 131.1, 131.2, 136.0, 136.9, 201.1; IR (KBr): ν 3014, 2967, 1721, 1365, 1175 cm^{-1}; MS (EI) *m/z*: 341 (M^+), 340 ($M-1)^+$, 219, 218, 187, 185, 135, 77, 40; HRMS Calcd for $C_{19}H_{19}NO_3S$: 341.1086, found: 341.1091.

4.2.10. 4-(*N*-Mesyl-2′-*n*-butylindol-3′-yl)but-2-one (2c′). White solid, 76% yield, mp: 62–63 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J=7.5 Hz, 3H), 1.25–1.46 (m, 2H), 1.56–1.68 (m, 2H), 2.17 (s, 3H), 2.75 (t, J=7.8 Hz, 2H), 2.91–2.97 (m, 7H), 7.26–7.33 (m, 2H), 7.44–7.47 (m, 1H), 8.00–8.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 18.1, 22.6, 25.8, 30.0, 33.0, 39.8, 43.3, 114.6, 118.4, 119.2, 123.6, 124.2, 130.2, 136.3, 138.1, 207.6; IR (KBr): ν 3035, 2952, 1714, 1351, 1165, 746 cm^{-1}; MS (EI) *m/z*: 321 (M^+), 320 ($M-1)^+$, 222, 184, 156, 144, 143, 44, 43; HRMS Calcd for ($C_{17}H_{23}NO_3S$+Na^+): 344.1291, found: 344.1297.

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A versatile route to the synthesis of 1-substituted β-carbolines by a single step Pictet–Spengler cyclization

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Abstract—A one-step conversion of L-tryptophan and activated aldehydes (1,2-dicarbonyl compounds) directly to 1-substituted β-carbolines without formation of the tetrahydro derivatives under modified Pictet–Spengler conditions was described. Moreover, a practical application for the synthesis of a natural 1-substituted β-carboline, luzongerine A, isolated from *Illigera luzonensis* was also successfully carried out utilizing this protocol. The effects of synthetic compounds **11** and **11a** on nitric oxide (NO) production in LPS/IFN-γ stimulated RAW 264.7 macrophage cells were evaluated in vitro. They displayed significant dose-dependent inhibition of inducible nitric oxide synthase (iNOS).

1. Introduction

Pyrido[3,4-*b*]indoles, commonly known as β-carbolines represent a deeply investigated family of indole alkaloids that possess a wide diversity of important biological activities, particularly concerning the central nervous system.[1] Due to their unique rigid heterocyclic skeleton, many β-carbolines are known to bind with high affinity to benzodiazepine (BzR), serotonin, and dopamine receptors sites and to inhibit monoamine oxidase A.[2] It has also been reported that the medicinal activities of β-carbolines were improved by the introduction of appropriate susbstitutions into position 1.[3] Also, 1-substituted β-carbolines widely exist in nature, and there have been many methodologies concerning their syntheses.[4] For almost one century, the Pictet–Spengler reaction has remained as one of the most powerful methods for the formation of this ring system via C–C bond formation using tryptophan as the starting material.[2] In general, this reaction can be characterized by the formation of an iminium salt after an acid-catalyzed condensation of tryptophan and tryptamine derivatives with an aldehyde and then *endo* cyclization is effected between a carbon nucleophile of a sufficiently reactive aromatic moiety and the activated iminium ion resulting in an *N*-heterocyclic ring via a new C–C bond.[5] Over the years, several groups have studied the detail mechanistic aspects of this reaction and it is interesting to note that the method still continues to be a significant focus of research as chemists continue to improve upon the methodology by applying new reaction conditions.[6] In order to investigate the structure–activity relationship of a series of iNOS inhibitors, we required a robust and general synthetic methodology for the preparation of 1-alkyl or aryl substituted β-carboline nucleus. In this context, Behforouz and co-workers described a useful approach for the preparation of 1-acetyl β-carboline derivatives via acid mediated coupling of methyl ester of DL-tryptophan and pyruvaldehyde.[7] The ease of this one-pot oxidation reaction prompted us to investigate the scope and synthesis of variety of 1-substituted β-carboline derivatives. As a result, we recognized the conversion of L-tryptophan and phenylglyoxal directly to 1-substituted β-carbolines in the presence of acid via a single step Pictet–Spengler reaction. This strategy improved the scope of the Pictet–Spengler cyclization and allows product diversification at C-1 by the use of inexpensive and commercially available L-tryptophan and activated aldehydes like pyruvaldehyde and phenylglyoxal. Herein we wish to describe this single step synthetic methodology, which would be an alternative for the preparation of 1-substituted β-carbolines, and successful application of this reaction to the synthesis of naturally occurring 1-substituted β-carbolines.

2. Results and discussions

By virtue of the readily synthetic availability, L-tryptophan was chosen as the model substrate. Initial attention was

Keywords: 1-Substituted β-carbolines; Pictet–Spengler cyclization; *Illigera luzonensis*; iNOS inhibitors.
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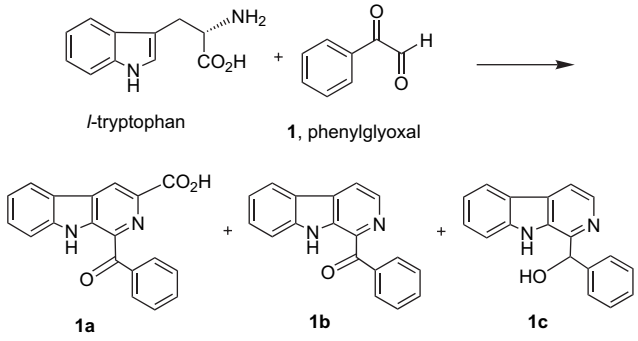
focused on the use of phenylglyoxal as an electrophile employing its cyclocondensation with L-tryptophan in H_2SO_4 as model reaction leading to **1a**, **1b**, and **1c** as the major products (Scheme 1). The transformation was next explored using H_2SO_4, *p*-TsOH, and HCl as acids, different solvent systems (MeOH, acetone, MeCN, THF, 1,4-dioxane, DMSO, and DMF), reaction temperatures, reaction time, and equivalents of L-tryptophan. A representative collection of results is summarized in Table 1. Among these conditions, addition of *p*-TsOH to the mixture of L-tryptophan and phenylglyoxal in MeOH at 50 °C for 2 h (entry 7) provided the best results, and it is common in acid-catalytic reactions that mild conditions were preferred. Temperature was found to have a profound effect on the reaction course, a decrease in the reaction temperature lengthened the reaction time (entries 5 and 6). In process of optimization of yields, it was found that 1.3 equiv of L-tryptophan was necessary to ensure the complete conversion of phenylglyoxal to **1a–c** in satisfactory yields. Overall yields of **1b** and **1c** are 80%, and under oxidation condition, **1c** could be easily converted into **1b**. A decrease in the polarity of solvent, by using acetone, MeCN, THF, or 1,4-dioxane (entries 11–14), resulted in the quite lower conversion of L-tryptophan probably due to its poor solubility and thus low yield of products. No product was obtained using polar aprotic solvents, such as DMF and DMSO in Pictet–Spengler condensation under optimized reaction conditions. In every case, the crude product obtained after work up was easily purified by silica gel chromatography using the mixture of *n*-hexane and ethyl acetate as an eluent and characterized by mass and NMR spectroscopic methods.

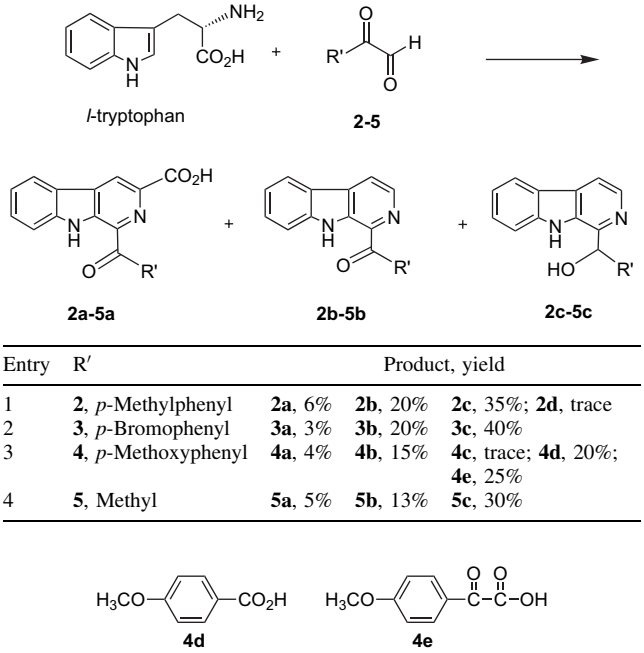


Scheme 1. Condensation between L-tryptophan and phenylglyoxal.

Having established a useful set of reaction conditions, these optimized conditions were subsequently applied to reactions of L-tryptophan with aliphatic and otherwise functionalized aromatic aldehydes, generally furnishing of products as shown in Table 2. However, no general conclusions on the electronic effects could be deduced. Both the electron-releasing (**2** and **5**) and electron-withdrawing (**3**) groups gave similar yields of the two major products. In the first entry of Table 2, a minor product **2d** was also confirmed with the yield of less than 1%. With these selected electrophiles, both HCl and *p*-TsOH catalyses afforded similar yields. Surprisingly, only a trace amount of **4c** was obtained in the case of **4** (electron-releasing group). It may be due to the formation of oxidized products **4d** and **4e**, which interrupt the successive cyclization and aromatization.

In general, the classical Pictet–Spengler reaction is a two-step method and involves acid-catalyzed condensation of an aliphatic amine attached to a sufficiently reactive aromatic

Table 2. Preparation of 1-substituted β-carboline derivatives by direct condensation of L-tryptophan with selected activated aldehydes



Entry	R′	Product, yield		
1	**2**, *p*-Methylphenyl	**2a**, 6%	**2b**, 20%	**2c**, 35%; **2d**, trace
2	**3**, *p*-Bromophenyl	**3a**, 3%	**3b**, 20%	**3c**, 40%
3	**4**, *p*-Methoxyphenyl	**4a**, 4%	**4b**, 15%	**4c**, trace; **4d**, 20%; **4e**, 25%
4	**5**, Methyl	**5a**, 5%	**5b**, 13%	**5c**, 30%

Table 1. Optimization of reaction involving preparation of 1-substituted β-carbolines using L-tryptophan and phenylglyoxal under different Pictet–Spengler protocols

Entry	Acid (equiv)	L-Tryptophan (equiv)	Solvent	Conditions (*T* (°C), time (h))	Yield (%)		
					1a	**1b**	**1c**
1	H_2SO_4 (1)	1.1[a]	MeOH	rt, 24	3	2	4
2	H_2SO_4 (1)	1.1[a]	MeOH	50 °C, 2	3	3	5
3	HCl (1)	1.1[a]	MeOH	50 °C, 2	5	7	10
4	*p*-TsOH (1)	1.1[a]	MeOH	50 °C, 2	5	6	9
5	HCl (1)	1.3	MeOH	50 °C, 2	4	32	42
6	HCl (1)	1.3	MeOH	rt, 48	5	24	35
7	*p*-TsOH (1)	1.3	MeOH	50 °C, 2	4	35	45
8	H_2SO_4 (1)	1.3	MeOH	50 °C, 2	12	13	20
9	HCl (1)	1.3	MeOH	50 °C, 2	6	28	35
10	*p*-TsOH (1)	1.3	MeOH	50 °C, 2	5	20	25
11	HCl (1)	1.3	Acetone	50 °C, 2	5	6	11
12	HCl (1)	1.3	MeCN	50 °C, 2	14	3	15
13	HCl (1)	1.3	THF	50 °C, 2	2	3	6
14	HCl (1)	1.3	1,4-Dioxane	50 °C, 2	12	2	17

[a] The phenylglyoxal was monitored by HPLC and not completely consumed.

nucleus with aldehydes.[5] In the first step an imine is formed, which may be activated by acids and in the second step *endo* cyclization is affected between a carbon nucleophile of a sufficiently reactive aromatic moiety and the activated iminium ion resulting in an *N*-heterocyclic ring via a new C–C bond and forming tetrahydro-β-carboline (THBC), which on dehydrogenation leads to β-carboline.[8] However, in our experiments, treatment of L-tryptophan with *p*-tolylglyoxal under acidic conditions did not produce the tetrahydro-β-carbolines but rather afforded directly a dehydrogenated β-carboline product **2c** and its oxidized product **2b** as major along with minor amounts of **2a** and **2d** in a single step.[9] These observations can be rationalized by the mechanism proposed in Figure 1. In the presence of acid, the aldehyde is activated to allow nucleophilic attack of tryptophan forming tetrahydro-β-carboline-3-carboxylic acid intermediate **6**. Successive dehydrogenation and oxidative decarboxylation as described in the literature[10] leads to the β-carboline **2b** as major product accompanied by a minor product **2a**. However, if the intermediate **7** tautomerizes in the acidic condition, **2c** could be afforded through an enol intermediate. The other minor product **2d** could be rationalized through decarboxylation process occurred at the expense of an oxazolidine-5-one intermediate **9** formed by intramolecular cyclization of the Schiff's base **8**,[11] followed by an intermediate **10** prone to cyclize to form hydration product **2d**.

Encouraged by our success on 1-substituted β-carbolines synthesis, we have applied the developed methodology for the synthesis of luzongerine A (**11**),[12] a minor 1-substituted β-carboline, isolated from *Illigera luzonensis*. Compound **11** was prepared under the optimized reaction conditions using **4** and 5-methoxy-tryptophan as the starting materials (Scheme 2). As a result, compound **11** was afforded in 40% yield along with a minor product **11a** in 5% yield. Physical and spectral data of synthetic sample coincided well with those of the isolated one. Thus, the described method is applicable to the synthesis of the natural 1-substituted β-carbolines.

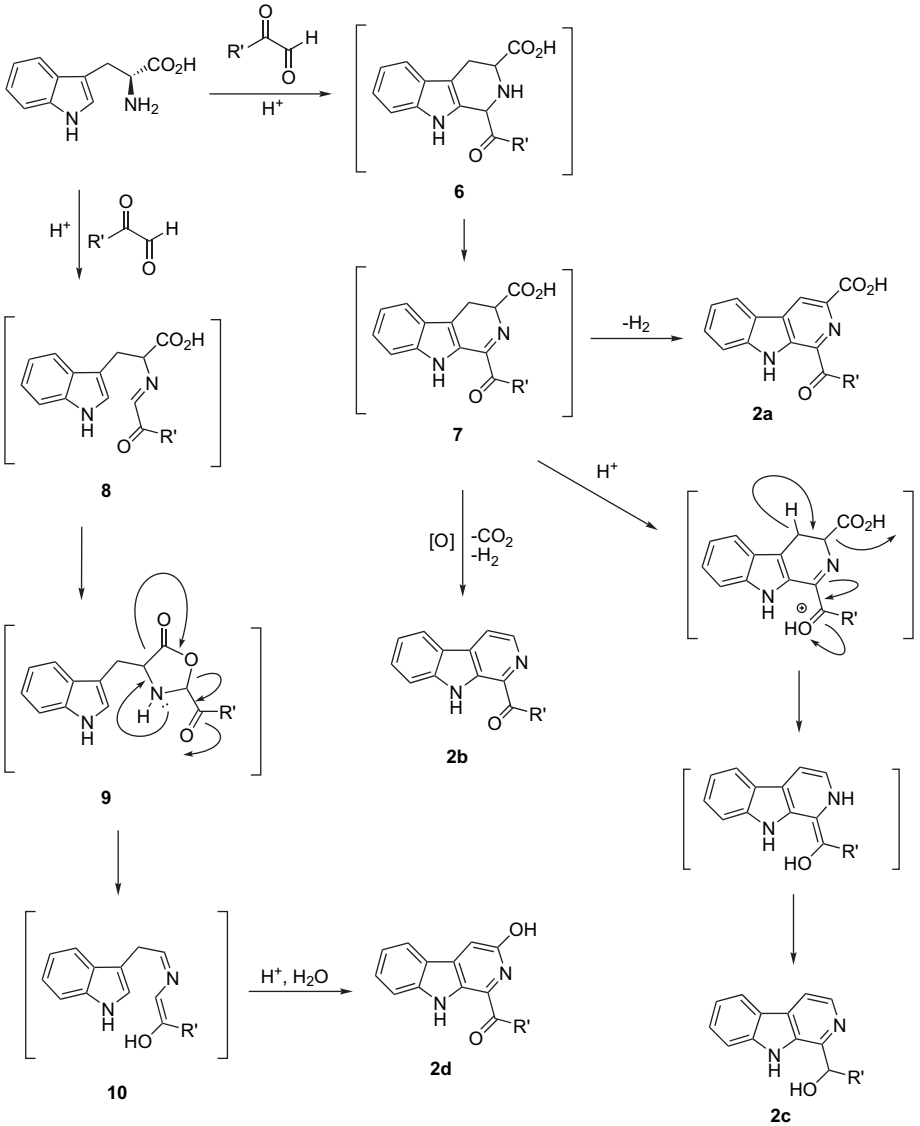
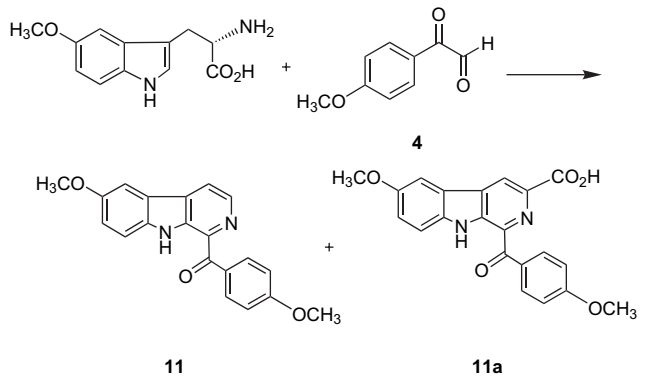


Figure 1. Proposed mechanism for **2a–d** formation.



Scheme 2. Synthesis of **11** and **11a** by the reported modified Pictet–Spengler method.

Table 3. Effects of tested compounds on LPS/IFN-γ-induced nitrite production of RAW 264.7 macrophage cells

Compound	IC_{50} (μM)	Potency
11	12.67±2.39	3.2×
11a	18.39±6.09	2.2×
Aminoguanidine (iNOS inhibitor)	40.96±5.04	1.0×

Nitric oxide (NO) is a molecular messenger that is synthesized by nitric oxide synthase (NOS) enzymes. NO is implicated in a variety of physiological and pathological processes.[13] Excessive NO generated by inducible nitric oxide synthase (iNOS) is known to be an important mediator of acute and chronic inflammations.[14] Naturally occurring 1-substituted β-carboline alkaloids were shown to inhibit the expression of iNOS in various cell systems.[15] Thus, the inhibition effects of the synthetic analogues on the generation of NO were examined in LPS/IFN-γ stimulated RAW 264.7 macrophages according to the method reported in the literature.[16] Tested compounds **11** and **11a** (1, 3, 10, and 30 μM) alone did not affect basal nitrite production, however, significantly and dose-dependently suppressed LPS/IFN-γ stimulated nitrite accumulation with IC_{50} values of 12.67±2.39 and 18.39±6.09 μM, respectively, as shown in Table 3. The cytotoxic effects of the synthetic compounds were measured using the MTT assay; no detectable cytotoxicity was observed at all the concentrations tested (1, 3, 10, and 30 μM) and the viability effects of treated cells were all greater than 95%.

3. Conclusions

In conclusion, a new application of Pictet–Spengler reaction for the synthesis of 1-substituted β-carboline derivatives has been developed. A variety of aryl and alkyl substituted activated aldehydes undergoes this process and allows product diversification at C-1 in overall good yields. This strategy improved the scope of Pictet–Spengler cyclization, giving access directly to a new family of β-carbolines in a single step without the need of aromatization step. Compounds **11** and **11a** displayed significant iNOS inhibition activity. Thus, the method met our criteria for simplicity and generality and has provided us with a vehicle for the preparation of a diverse set of 1-substituted β-carboline derivatives for a SAR evaluation. Currently work is in progress in our lab with several second generation substrates designed on the basis of our new concept for the Pictet–Spengler reaction and will be reported soon.

4. Experimental

4.1. General

Melting points were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. IR spectra were obtained with a Shimadzu FT-IR DR-8011 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on Bruker Avance-300 NMR spectrometers, with tetramethylsilane (TMS) as internal standard. EI and HREIMS spectra were recorded on a VG 70-250 S spectrometer. FAB and HRFABMS were measured on a Jeol JMS-700 mass spectrometer. Elementary Analyses were performed on an Elementar vario EL III analyzer.

4.2. Typical preparation procedure of 1a–5c

To a stirred suspension of 0.174 g (0.854 mmol, 1.3 equiv) of L-tryptophan in 1.0 equiv of *p*-toluenesulfonic acid monohydrate, 0.09 g (0.657 mmol, 1.0 equiv) of phenylglyoxal monohydrate was added. The resulting solution was stirred at 50 °C for 2 h, and the phenylglyoxal was monitored by HPLC to be completely consumed. The reaction mixture was poured into water and the precipitate was filtered and purified by silica gel column chromatography eluted with a gradient of *n*-hexane and ethyl acetate to afford **1a**, **1b**, and **1c**. Compounds **2a**–**5c** were prepared with the similar procedures.

4.2.1. 1-Benzoyl-9*H*-β-carboline-3-carboxylic acid (1a). Yellow powder (EtOAc–MeOH), mp 281–283 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.97 (1H, br s, D_2O exchangeable, CO_2H), 12.40 (1H, br s, D_2O exchangeable, NH), 9.17 (1H, s, H-4), 8.48 (1H, d, J=7.8 Hz, H-5), 8.40 (2H, d, J=7.4 Hz, H-2′ and -6′), 7.85 (1H, d, J=8.2 Hz, H-8), 7.72–7.57 (4H, m, H-7, -3′, -4′, and -5′), 7.37 (1H, t, J=7.5 Hz, H-6); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 192.8, 166.6, 142.3, 137.1, 136.9, 136.4, 135.9, 133.0, 131.7, 131.4, 129.6, 128.3, 122.4, 121.2, 120.7, 120.7, 113.5; EIMS *m*/*z* 316 $[M]^+$ (43), 271 (24), 242 (23), 105 (38), 77 (100); HREIMS *m*/*z* 316.0850 $[M]^+$ (calcd for $C_{19}H_{12}N_2O_3$, 316.0848). Anal. Calcd for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.82; N, 8.86. Found: C, 72.16; H, 3.80; N, 8.90.

4.2.2. (9*H*-β-Carbolin-1-yl)-phenyl-methanone (1b). Yellow needle (EtOAc), mp 135–138 °C; IR (KBr) ν_{max} 3432, 1642, 1621 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.06 (1H, br s, D_2O exchangeable, NH), 8.53 (1H, d, J=4.7 Hz, H-3), 8.46 (1H, d, J=4.7 Hz, H-4), 8.33 (1H, d, J=7.8 Hz, H-5), 8.18 (2H, d, J=7.5 Hz, H-2′ and -6′), 7.81 (1H, d, J=8.3 Hz, H-8), 7.69–7.55 (4H, m, H-7, -3′, -4′, and -5′), 7.32 (1H, t, J=7.8 Hz, H-6); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 194.1, 141.9, 137.7, 137.3, 136.5, 136.1, 132.4, 131.2, 131.0, 129.4, 128.1, 121.9, 120.4, 120.3, 119.0, 113.2; EIMS *m*/*z* 272 $[M]^+$ (100), 244 (91), 167 (23), 149 (50); HREIMS *m*/*z* 272.0953 $[M]^+$ (calcd for $C_{18}H_{12}N_2O$, 272.0950). Anal. Calcd for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.54; H, 4.40; N, 10.33.

4.2.3. (9*H*-β-Carbolin-1-yl)-phenyl-methanol (1c). Yellow powder (EtOAc), mp 141–144 °C; IR (KBr) ν_{max} 3352, 1627 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.26 (1H, br s, D_2O exchangeable, NH), 8.23 (1H, d, J=5.0 Hz, H-3), 8.17 (1H, d, J=7.8 Hz, H-5), 7.98 (1H, d, J=5.0 Hz, H-4), 7.72 (1H, d, J=8.2 Hz, H-8), 7.60 (2H, d, J=7.4 Hz, H-2′ and -6′), 7.50 (1H, t, J=7.5 Hz, H-7), 7.29–7.17 (3H, m, H-3′, -5′, and -6), 6.51 (1H, d, J=3.8 Hz, OH), 6.14 (1H, d, J=3.8 Hz, C*H*OH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 147.7, 144.0, 140.9, 137.1, 132.4, 128.9, 128.2, 127.2, 126.5, 121.6, 120.6, 119.4, 113.8, 112.8, 76.1. EIMS m/z 274 $[M]^+$ (50), 255 (100); HREIMS m/z 274.1109 $[M]^+$ (calcd for $C_{18}H_{14}N_2O$, 274.1106). Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.62; H, 5.24; N, 10.07.

4.2.4. 1-(4-Methyl-benzoyl)-9*H*-β-carboline-3-carboxylic acid (2a). Yellow powder (EtOAc–MeOH), mp 259–260 °C; IR (KBr) ν_{max} 3256, 1766, 1731, 1639, 1620 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.35 (1H, br s, D_2O exchangeable, NH), 9.15 (1H, s, H-4), 8.46 (1H, d, J=7.7 Hz, H-5), 8.34 (2H, d, J=7.6 Hz, H-2′ and -6′), 7.83 (1H, d, J=7.9 Hz, H-8), 7.63 (1H, t, J=7.5 Hz, H-7), 7.38 (2H, d, J=7.8 Hz, H-3′ and -5′), 7.35 (1H, t, J=7.5 Hz, H-6), 2.42 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 192.2, 166.7, 143.4, 142.2, 136.8, 136.4, 136.1, 134.4, 131.6, 131.5, 129.5, 128.9, 122.4, 121.1, 120.7, 120.5, 113.4, 21.4; EIMS m/z 330 $[M]^+$ (100), 315 (35), 302 (18), 285 (79), 271 (22), 258 (70); HREIMS m/z 330.1007 $[M]^+$ (calcd for $C_{20}H_{14}N_2O_3$, 330.1004). Anal. Calcd for $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.27; N, 8.48. Found: C, 72.91; H, 4.35; N, 8.51.

4.2.5. (9*H*-β-Carbolin-1-yl)-*p*-tolyl-methanone (2b). Yellow needle (EtOAc), mp 158–161 °C; IR (KBr) ν_{max} 3395, 1621, 1604 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.02 (1H, br s, D_2O exchangeable, NH), 8.52 (1H, d, J=5.0 Hz, H-3), 8.44 (1H, d, J=5.0 Hz, H-4), 8.32 (1H, d, J=7.6 Hz, H-5), 8.14 (2H, d, J=8.0 Hz, H-2′ and -6′), 7.79 (1H, d, J=7.9 Hz, H-8), 7.60 (1H, dd, J=7.9, 7.4 Hz, H-7), 7.38 (2H, d, J=8.0 Hz, H-3′ and -5′), 7.31 (1H, dd, J=7.6, 7.4 Hz, H-6), 2.42 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 193.4, 142.9, 141.8, 137.3, 136.8, 135.9, 134.9, 131.2, 131.1, 129.1, 128.8, 122.0, 120.3, 120.2, 118.9, 113.1, 21.4; EIMS m/z 286 $[M]^+$ (100), 271 (74), 258 (100); HREIMS m/z 286.1102 $[M]^+$ (calcd for $C_{19}H_{14}N_2O$, 286.1106). Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.92; H, 5.03; N, 9.84.

4.2.6. (9*H*-β-Carbolin-1-yl)-*p*-tolyl-methanol (2c). Yellow powder (EtOAc), mp 184–185 °C; IR (KBr) ν_{max} 3360, 1625 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.23 (1H, br s, D_2O exchangeable, NH), 8.22 (1H, d, J=5.2 Hz, H-3), 8.17 (1H, d, J=7.6 Hz, H-5), 7.97 (1H, d, J=5.2 Hz, H-4), 7.72 (1H, d, J=7.9 Hz, H-8), 7.50 (1H, dd, J=7.9, 7.4 Hz, H-7), 7.47 (2H, d, J=7.7 Hz, H-2′ and -6′), 7.19 (1H, dd, J=7.6, 7.4 Hz, H-6), 7.07 (2H, d, J=7.7 Hz, H-3′ and -5′), 6.46 (1H, d, J=4.0 Hz, OH), 6.10 (1H, d, J=4.0 Hz, C*H*OH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 147.8, 140.9, 140.8, 137.0, 136.1, 132.3, 128.7, 128.7, 128.0, 126.4, 121.5, 120.5, 119.2, 113.7, 112.7, 75.8, 20.8; EIMS m/z 288 $[M]^+$ (100), 269 (56), 255 (92); HREIMS m/z 288.1265 $[M]^+$ (calcd for $C_{19}H_{16}N_2O$, 288.1263). Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.27; H, 5.66; N, 9.72.

4.2.7. (3-Hydroxy-9*H*-β-carbolin-1-yl)-*p*-tolyl-methanone (2d). Orange powder (EtOAc), mp 171–175 °C; IR (KBr) ν_{max} 3360, 1659, 1631 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.56 (1H, br s, D_2O exchangeable, NH), 10.33 (1H, br s, D_2O exchangeable, OH), 8.21 (1H, d, J=8.6 Hz, H-5), 8.18 (2H, d, J=8.4 Hz, H-2′ and -6′), 7.69 (1H, s, H-4), 7.67 (1H, d, J=8.1 Hz, H-8), 7.53 (1H, t, J=7.5 Hz, H-7), 7.36 (2H, d, J=8.1 Hz, H-3′ and -5′), 7.20 (1H, t, J=7.5 Hz, H-6), 2.41 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 192.6, 154.8, 143.4, 142.7, 136.0, 135.2, 132.9, 132.0, 131.2, 129.4, 128.8, 122.3, 120.0, 119.6, 112.8, 104.6, 21.4; EIMS m/z 302 $[M]^+$ (100), 287 (34); HREIMS m/z 302.1058 $[M]^+$ (calcd for $C_{19}H_{14}N_2O_2$, 302.1055).

4.2.8. 1-(4-Bromo-benzoyl)-9*H*-β-carboline-3-carboxylic acid (3a). Yellow powder (EtOAc–MeOH), mp 290–291 °C; IR (KBr) ν_{max} 3276, 1731, 1640, 1621 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.41 (1H, br s, D_2O exchangeable, NH), 9.16 (1H, s, H-4), 8.47 (1H, d, J=7.8 Hz, H-5), 8.34 (2H, d, J=8.2 Hz, H-2′ and -6′), 7.84 (1H, d, J=8.8 Hz, H-8), 7.81 (2H, d, J=8.2 Hz, H-3′ and -5′), 7.65 (1H, t, J=7.5 Hz, H-7), 7.37 (1H, t, J=7.5 Hz, H-6); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 191.9, 166.7, 142.4, 137.0, 136.6, 136.2, 135.5, 133.5, 131.9, 131.5, 129.8, 127.3, 122.6, 121.4, 121.0, 120.8, 113.6; EIMS m/z 396 $[M+2]^+$ (22), 394 $[M]^+$ (23), 349 (13), 322 (12), 271 (12), 241 (12); HREIMS m/z 393.9957 $[M]^+$ (calcd for $C_{19}H_{11}N_2O_3Br$, 393.9953).

4.2.9. (4-Bromo-phenyl)-(9*H*-β-carbolin-1-yl)-methanone (3b). Yellow needle (EtOAc), mp 194–196 °C; IR (KBr) ν_{max} 3389, 1644 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.09 (1H, br s, D_2O exchangeable, NH), 8.51 (1H, d, J=4.9 Hz, H-3), 8.44 (1H, d, J=4.9 Hz, H-4), 8.31 (1H, d, J=7.8 Hz, H-5), 8.15 (2H, d, J=8.5 Hz, H-2′ and -6′), 7.82 (1H, d, J=8.2 Hz, H-8), 7.77 (2H, d, J=8.5 Hz, H-3′ and -5′), 7.60 (1H, t, J=7.5 Hz, H-7), 7.31 (1H, t, J=7.5 Hz, H-6); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 192.8, 141.9, 137.4, 136.6, 136.0, 133.0, 131.3, 131.2, 129.2, 126.5, 122.0, 120.4, 120.2, 119.3, 113.2; EIMS m/z 352 $[M+2]^+$ (17), 350 $[M]^+$ (18), 322 (14), 279 (27), 185 (71), 183 (79), 167 (44), 149 (100); HREIMS m/z 350.0055 $[M]^+$ (calcd for $C_{18}H_{11}N_2OBr$, 350.0055). Anal. Calcd for $C_{18}H_{11}N_2OBr$: C, 61.56; H, 3.16; N, 7.98. Found: C, 61.76; H, 3.21; N, 7.94.

4.2.10. (4-Bromo-phenyl)-(9*H*-β-carbolin-1-yl)-methanol (3c). Yellow powder (EtOAc), mp 157–159 °C; IR (KBr) ν_{max} 3441, 1628 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.27 (1H, br s, D_2O exchangeable, NH), 8.23 (1H, d, J=5.3 Hz, H-3), 8.17 (1H, d, J=7.6 Hz, H-5), 7.99 (1H, d, J=5.3 Hz, H-4), 7.71 (1H, d, J=8.0 Hz, H-8), 7.55 (2H, d, J=8.5 Hz, H-2′ and -6′), 7.51 (1H, dd, J=8.0, 7.5 Hz, H-7), 7.47 (2H, d, J=8.5 Hz, H-3′ and -5′), 7.20 (1H, dd, J=7.6, 7.5 Hz, H-6), 6.62 (1H, d, J=4.1 Hz, OH), 6.14 (1H, d, J=4.1 Hz, C*H*OH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 147.1, 143.3, 140.9, 137.1, 132.4, 131.1, 129.0, 128.7, 128.2, 121.6, 120.6, 120.3, 119.4, 114.0, 112.7, 75.2; EIMS m/z 354 $[M+2]^+$ (34), 352 $[M]^+$ (35), 335 (24),

333 (22), 255 (100); HREIMS *m/z* 352.0211 $[M]^+$ (calcd for $C_{18}H_{13}N_2OBr$, 352.0211). Anal. Calcd for $C_{18}H_{13}N_2OBr$: C, 61.21; H, 3.71; N, 7.93. Found: C, 61.18; H, 3.81; N, 7.72.

4.2.11. 1-(4-Methoxy-benzoyl)-9*H*-β-carboline-3-carboxylic acid (4a). Yellow powder (EtOAc–MeOH), mp 264–266 °C; IR (KBr) ν_{max} 3273, 1703 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.33 (1H, br s, D_2O exchangeable, NH), 9.14 (1H, s, H-4), 8.53 (2H, d, *J*=8.8 Hz, H-2′ and -6′), 8.46 (1H, d, *J*=7.6 Hz, H-5), 7.82 (1H, d, *J*=8.2 Hz, H-8), 7.63 (1H, dd, *J*=8.2, 7.8 Hz, H-7), 7.35 (1H, dd, *J*=7.8, 7.6 Hz, H-6), 7.13 (2H, d, *J*=8.8 Hz, H-3′ and -5′), 3.89 (3H, s, OCH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 190.6, 166.7, 163.4, 142.2, 136.8, 136.6, 136.3, 134.0, 131.4, 129.5, 129.5, 122.4, 121.0, 120.7, 120.4, 113.8, 113.4, 55.8; EIMS *m/z* 346 $[M]^+$ (100), 317 (15), 302 (20), 299 (21), 274 (32), 135 (82); HREIMS *m/z* 346.0951 $[M]^+$ (calcd for $C_{20}H_{14}N_2O_4$, 346.0954). Anal. Calcd for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.59; H, 4.10; N, 8.07.

4.2.12. (9*H*-β-Carbolin-1-yl)-(4-methoxy-phenyl)-methanone (4b). Yellow needle (EtOAc), mp 185–187 °C; IR (KBr) ν_{max} 3423, 1597 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.98 (1H, br s, D_2O exchangeable, NH), 8.52 (1H, d, *J*=4.8 Hz, H-3), 8.41 (1H, d, *J*=4.8 Hz, H-4), 8.31 (2H, d, *J*=8.9 Hz, H-2′ and -6′), 8.30 (1H, d, *J*=7.7 Hz, H-5), 7.79 (1H, d, *J*=8.0 Hz, H-8), 7.59 (1H, dd, *J*=8.0, 7.4 Hz, H-7), 7.29 (1H, dd, *J*=7.7, 7.4 Hz, H-6), 7.10 (2H, d, *J*=8.9 Hz, H-3′ and -5′), 3.87 (3H, s, OCH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 191.8, 163.0, 141.8, 137.2, 137.1, 135.9, 133.6, 131.0, 130.0, 129.0, 122.0, 120.3, 118.6, 113.6, 113.1, 55.7; EIMS *m/z* 302 $[M]^+$ (100), 273 (75), 135 (41); HREIMS *m/z* 302.1056 $[M]^+$ (calcd for $C_{19}H_{14}N_2O_2$, 302.1055). Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.48; H, 4.66; N, 9.27.

4.2.13. (9*H*-β-Carbolin-1-yl)-(4-methoxy-phenyl)-methanol (4c). Yellow syrup; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.22 (1H, br s, D_2O exchangeable, NH), 8.21 (1H, d, *J*=5.2 Hz, H-3), 8.17 (1H, d, *J*=7.6 Hz, H-5), 7.96 (1H, d, *J*=5.2 Hz, H-4), 7.71 (1H, d, *J*=7.8 Hz, H-8), 7.49 (1H, dd, *J*=7.8, 7.4 Hz, H-7), 7.48 (2H, d, *J*=8.6 Hz, H-2′ and -6′), 7.19 (1H, dd, *J*=7.6, 7.4 Hz, H-6), 6.82 (2H, d, *J*=8.6 Hz, H-3′ and -5′), 6.41 (1H, d, *J*=3.9 Hz, OH), 6.08 (1H, d, *J*=3.9 Hz, C*H*OH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 158.5, 148.0, 140.8, 137.0, 136.0, 132.3, 128.8, 128.1, 127.7, 121.5, 120.6, 119.3, 113.7, 113.6, 112.7, 75.6, 55.2; EIMS *m/z* 304 $[M]^+$ (100), 285 (98), 272 (76), 255 (73), 242 (30); HREIMS *m/z* 304.1215 $[M]^+$ (calcd for $C_{19}H_{16}N_2O_2$, 304.1212).

4.2.14. 4-Methoxy-benzoic acid (4d). Yellow powder (benzene), mp 190–192 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.60 (1H, br s, D_2O exchangeable, OH), 7.88 (2H, d, *J*=8.7 Hz, H-2′ and -6′), 7.00 (2H, d, *J*=8.7 Hz, H-3′ and -5′), 3.81 (3H, s, OCH_3).

4.2.15. (4-Methoxy-phenyl)-oxo-acetic acid (4e). Yellow powder (benzene), mp 223–226 °C; IR (KBr) ν_{max} 1651, 1608 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.82 (2H, d, *J*=8.6 Hz, H-2′ and -6′), 7.02 (2H, d, *J*=8.6 Hz, H-3′ and -5′), 3.82 (3H, s, OCH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 193.5, 169.7, 163.4, 131.6, 127.0, 114.1, 55.7.

4.2.16. 1-Acetyl-9*H*-β-carboline-3-carboxylic acid (5a). Yellow powder (EtOAc–MeOH), mp 292 °C (dec); ^1H NMR (DMSO-d_6, 300 MHz) δ 12.23 (1H, br s, D_2O exchangeable, NH), 9.14 (1H, s, H-4), 8.44 (1H, d, *J*=8.0 Hz, H-5), 7.84 (1H, d, *J*=8.0 Hz, H-8), 7.62 (1H, t, *J*=8.0 Hz, H-7), 7.34 (1H, t, *J*=8.0 Hz, H-6), 2.87 (3H, s, $COCH_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 201.3, 166.5, 142.5, 136.5, 135.3, 135.2, 131.7, 129.5, 122.4, 121.2, 121.2, 120.4, 113.6, 26.0; EIMS *m/z* 254 $[M]^+$ (100), 236 (16), 210 (32), 194 (39), 182 (35); HREIMS *m/z* 254.0688 $[M]^+$ (calcd for $C_{14}H_{10}N_2O_3$, 254.0691).

4.2.17. 1-(9*H*-β-Carbolin-1-yl)-ethanone (5b). Yellow needle (EtOAc), mp 207–209 °C; IR (KBr) ν_{max} 3333, 1669 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.88 (1H, br s, D_2O exchangeable, NH), 8.50 (1H, d, *J*=4.8 Hz, H-3), 8.43 (1H, d, *J*=4.8 Hz, H-4), 8.29 (1H, d, *J*=7.8 Hz, H-5), 7.80 (1H, d, *J*=8.1 Hz, H-8), 7.58 (1H, t, *J*=7.8 Hz, H-7), 7.29 (1H, t, *J*=7.8 Hz, H-6), 2.79 (3H, s, $COCH_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 201.5, 142.0, 137.6, 136.1, 134.2, 131.1, 129.1, 122.0, 120.4, 120.0, 119.6, 113.3, 26.1; EIMS *m/z* 210 $[M]^+$ (98), 182 (52), 168 (100), 140 (35); HREIMS *m/z* 210.0796 $[M]^+$ (calcd for $C_{13}H_{10}N_2O$, 210.0793).

4.2.18. 1-(9*H*-β-Carbolin-1-yl)-ethanol (5c). Yellow powder (EtOAc), mp 168–170 °C; IR (KBr) ν_{max} 3288, 1628 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.22 (1H, br s, D_2O exchangeable, NH), 8.22 (1H, d, *J*=5.1 Hz, H-3), 8.17 (1H, d, *J*=8.4 Hz, H-5), 7.98 (1H, d, *J*=5.1 Hz, H-4), 7.68 (1H, d, *J*=8.1 Hz, H-8), 7.50 (1H, t, *J*=8.1 Hz, H-7), 7.20 (1H, t, *J*=7.5 Hz, H-6), 5.68 (1H, d, *J*=4.5 Hz, OH), 5.19 (1H, qd, *J*=6.5, 4.5 Hz, C*H*OH), 1.54 (3H, d, *J*=6.5 Hz, $COCH_3$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 148.9, 140.7, 136.8, 132.5, 128.5, 128.0, 121.6, 120.7, 119.3, 113.7, 112.6, 69.5, 23.1; EIMS *m/z* 212 $[M]^+$ (75), 193 (100), 184 (56), 168 (77).

4.3. Preparation of (6-methoxy-9*H*-β-carbolin-1-yl)-(4-methoxy-phenyl)-methanone (11)

To a stirred suspension of 0.093 g (0.397 mmol, 1.3 equiv) of 5-methoxy-tryptophan in 1.0 equiv of *p*-toluenesulfonic acid, 0.050 g (0.305 mmol, 1.0 equiv) of **4** was added. The resulting solution was stirred at 50 °C for 2 h. The reaction mixture was poured into water and the precipitate was filtered and purified by silica gel column chromatography eluted with a gradient of *n*-hexane and ethyl acetate to afford **11** and **11a**, respectively. Compound **11**: yellow needle (EtOAc), mp 135–138 °C; IR (KBr) ν_{max} 3432, 1642, 1621 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.82 (1H, br s, D_2O exchangeable, NH), 8.48 (1H, d, *J*=5.0 Hz, H-3), 8.41 (1H, d, *J*=5.0 Hz, H-4), 8.31 (2H, d, *J*=8.8 Hz, H-2′ and -6′), 7.87 (1H, d, *J*=2.4 Hz, H-5), 7.69 (1H, d, *J*=8.9 Hz, H-7), 7.24 (1H, dd, *J*=8.9, 2.4 Hz, H-8), 7.11 (2H, d, *J*=8.8 Hz, H-3′ and -5′), 3.87 (6H, s, $OCH_3\times2$); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 191.8, 162.9, 154.1, 137.2, 136.6, 136.3, 133.6, 131.0, 130.0, 120.7, 119.0, 118.8, 113.9, 113.6, 103.8, 55.8, 55.7; EIMS *m/z* 332 $[M]^+$ (100), 317 (10), 303 (25), 289 (28); HREIMS *m/z* 332.1163 $[M]^+$ (calcd for $C_{20}H_{16}N_2O_3$, 332.1161). Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 71.97; H, 4.96; N, 8.30. Compound **11a**: yellow needle

(EtOAc–MeOH), mp 135–138 °C; IR (KBr) ν_{max} 3432, 1642, 1621 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.18 (1H, br s, D_2O exchangeable, NH), 9.16 (1H, s, H-4), 8.54 (2H, d, J=8.8 Hz, H-2′ and -6′), 8.07 (1H, d, J=2.1 Hz, H-5), 7.72 (1H, d, J=8.9 Hz, H-8), 7.27 (1H, dd, J=8.9, 2.1 Hz, H-7), 7.12 (2H, d, J=8.8 Hz, H-3′ and -5′), 3.89 (3H, s, OCH_3), 3.88 (3H, s, OCH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 190.6, 166.8, 163.4, 154.7, 137.1, 136.9, 136.6, 135.6, 134.0, 131.6, 131.3, 129.6, 121.3, 120.7, 119.5, 114.3, 114.0, 113.8, 104.2, 55.9, 55.8; EIMS m/z 376 $[M]^+$ (100), 332 (46), 301 (14), 224 (16); HREIMS m/z 376.1056 $[M]^+$ (calcd for $C_{21}H_{16}N_2O_5$, 376.1059).

4.4. Bioassay

4.4.1. Cell culture. Raw 264.7 cells (American Type Culture Collection ATCC, TIB 71, Rockville, MD) suspending in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat-inactivated fetal calf serum (FCS), penicillin (100 U mL^{-1}), and streptomycin (100 μg/mL) were seeded onto 96-well plated (Corning-Costar). LPS (1 μg/mL) plus IFN-γ (50 U/mL) was added to the medium for 24 h to stimulate NO production. Tested compounds and iNOS inhibitor (aminoguanidine) were added together with LPS/IFN-γ.[13]

4.4.2. Nitrite measurement. Nitrite formation, an indicator of NO synthesis, was measured by adding 100 μL of Griess reagent (1% sulfanilamide and 0.1% naphthylenediamine in 5% phosphoric acid) to 100 μL samples of medium. The optical density at 550 nm (OD_{550}) was measured with a microplate reader. Concentrations were calculated by comparison with OD_{550} of standard solutions of sodium nitrite prepared in culture medium.

4.4.3. Cell viability. Cell viability was assessed by the mitochondria-dependent reduction of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] to formazan. The extent of reduction of MTT to formazan within cells was quantitated by measurement of OD_{570} against OD_{630}.

4.4.4. Statistical evaluation. The results are expressed as mean±SE and NO production is indicated as absolute concentrations in micromolars. Computation of 50% inhibitory concentration (IC_{50}) and the slope of regression line were computer-assisted (PHARM/PCS v.4.2).

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Alkaline hydrolysis of *N*-bromoiminothianthrene derivatives

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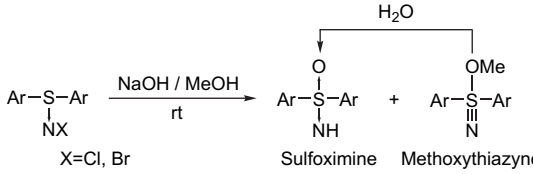
Abstract—5-(*N*-Bromo)iminothianthrene (**2**) and 5-(*N*-bromo)iminothianthrene 10-oxide (**5**) and 10,10-dioxide (**8**) were prepared and their alkaline hydrolyses were studied. The compound **2** and *cis*-5-(*N*-bromo)iminothianthrene 10-oxide (*cis*-**5**) afforded the corresponding sulfoximine exclusively. While, unexpectedly, both *trans*-5-(*N*-bromo)iminothianthrene 10-oxide (*trans*-**5**) and **8** afforded mainly de-brominated products, *trans*-5-iminothianthrene 10-oxide (*trans*-**4**) and 5-iminothianthrene 10,10-dioxide (**7**), respectively. In these cases, 5-iminothianthrene 5,10-dioxide (**6**) (*Z*- and *E*-mixture) and 5-iminothianthrene 5,10,10-trioxide (**9**) and further de-iminated products were also formed respectively as minor products. The stereochemical considerations on the S_N reactions are described in view of the steric effect and 'flip-flap' motion of the thianthrene framework.

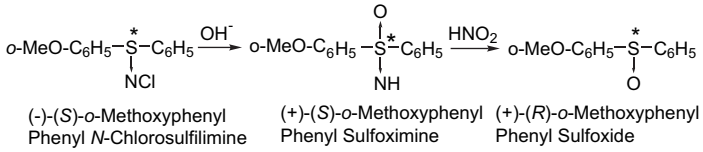
1. Introduction

N-Halosulfilimines are interesting derivatives that can be obtained easily by treating the corresponding *N*-unsubstituted sulfilimines with halogenating reagents.[1–4] However, their reactivities have been left still uncovered. It is reported that alkaline hydrolysis of diaryl *N*-halosulfilimines with sodium hydroxide in methanol afforded diaryl sulfoximine.[1–3,5] This reaction is synthetically useful for the preparation of diaryl sulfoximines. In 1987, from the results of stereochemical study using optically active (−)-(*S*)-*o*-methoxyphenyl phenyl *N*-chlorosulfilimine and other observations, Oae et al. suggested that the alkaline hydrolyses proceed by a nucleophilic attack of hydroxide ion with the retention of configuration on the sulfur atom (Scheme 1).[3]

In 1989 Yoshimura et al. have found that the novel intermediate diaryl methoxythiazyne, having a unique SN triple bond, incipiently formed in this reaction, and this intermediate is finally hydrolyzed to give diaryl sulfoximines (Scheme 2).[6] They fully examined the kinetic behavior of alkaline hydrolysis of diaryl *N*-halosulfilimines in MeOH/H_2O solution under various kinetic conditions and concluded that the alkaline hydrolysis of these derivatives proceeds via two concurrent mechanisms, the S_N1 mechanism involving nitridosulfonium cation $(Ph_2S{=}N)^+$ as an intermediate and the S_N2' mechanism with the transition state in which the N–X bond cleavage progressed more than the S–O bond formation with nucleophiles (HO^- and MeO^-).[7]



Scheme 2. Formation of diaryl methoxythiazyne and its conversion to diaryl sulfoximine.



Scheme 1. Hydrolysis of *o*-methoxyphenyl phenyl *N*-chlorosulfilimine and the determination of the stereochemical reaction course.

Keywords: Thianthrene; Sulfilimine; *N*-Bromosulfilimine; Sulfoximine; S_N reaction on sulfur; Steric hindrance; 'Flip-flap' motion.
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In order to extend this study in the thianthrene system and to obtain a clue for the hydrolysis mechanism of *N*-halosulfilimines and particularly for the formation of *N*-unsubstituted sulfilimines, we carried out the alkaline hydrolysis of **2** and its oxides at 10-*S*-position, such as *cis*-**5**, *trans*-**5**, and **8**.

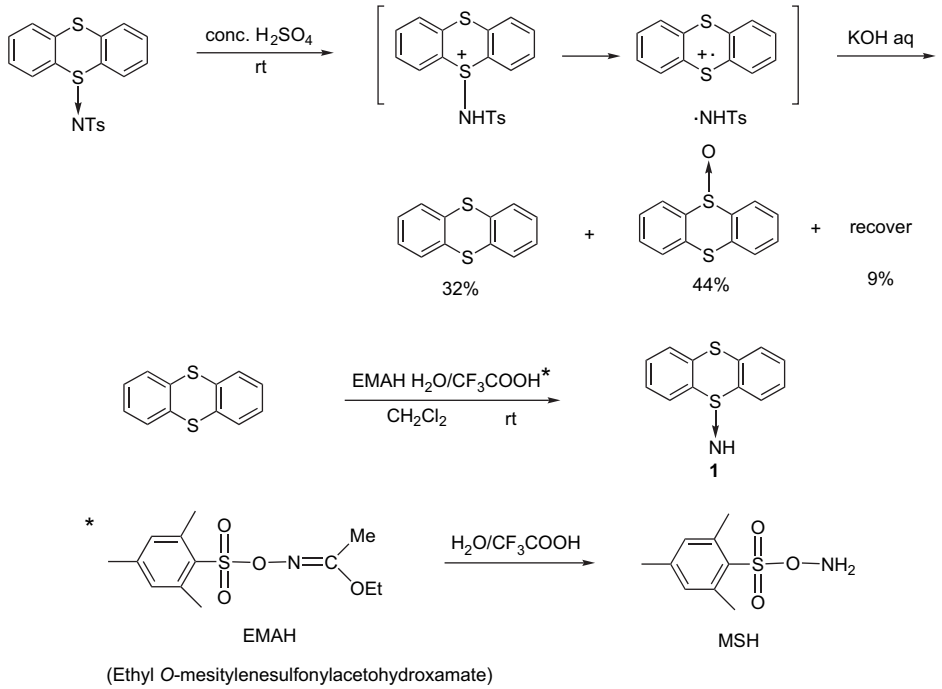
2. Results and discussion

For the preparation of 5-iminothianthrene (**1**), we tried the hydrolysis of thianthrene *N*-tosylsulfilimine in 95% concentrated sulfuric acid following the literature.[8,9] However, this reaction only afforded thianthrene and thianthrene 5-oxide probably via thianthrene cation radical. The desired *N*-unsubstituted thianthrene sulfilimine was successfully obtained by the reaction of thianthrene with *O*-(mesitylenesulfonyl)-hydroxylamine (MSH) obtained in situ by trifluoroacetic acid catalyzed hydrolysis of ethyl *O*-mesitylenesulfonylacetohydroxamate by the modified literature procedure[10] as shown in Scheme 3.

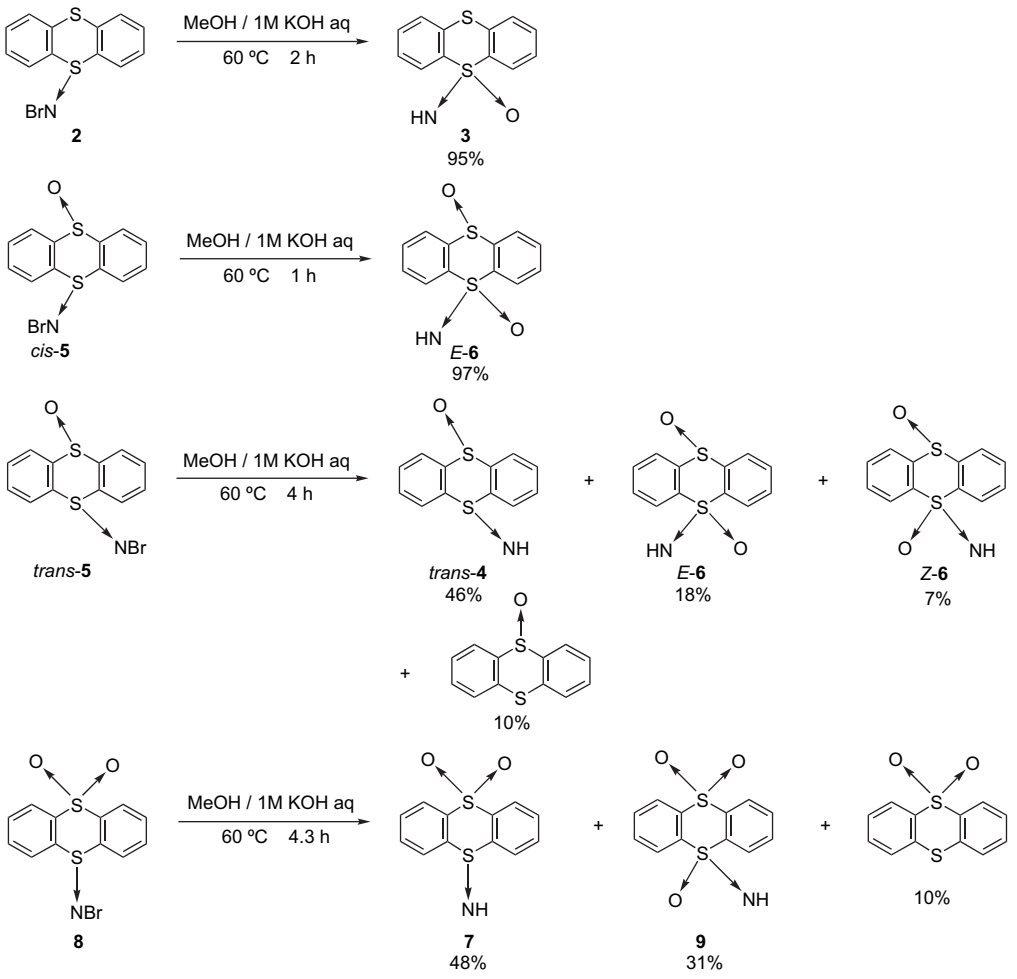
cis-5-Iminothianthrene 10-oxide (*cis*-**4**), *trans*-**4**, and 5-iminothianthrene 10,10-dioxide (**7**) were obtained by the hydrolysis reaction of the corresponding *N*-tosylsulfilimines with concentrated sulfuric acid.[11] Then, further *N*-bromination of the corresponding unsubstituted sulfilimines was performed with NBS to afford **2**, *cis*- and *trans*-**5**, and **8** in good yields.

In the case of hydrolysis of **2** with KOH in MeOH/H_2O at 60 °C for 2 h, the isolated products were 5-iminothianthrene 5-oxide (**3**, 95%). Under the same conditions for 1 h, *cis*-**5** led to (*E*)-5-iminothianthrene 5,10-dioxide (*E*-**6**) exclusively in 97% yield with the retention of configuration on sulfur atom at 5-*S*-position. However, *trans*-**5** afforded a rather complex reaction mixture even slowly (4 h), forming *trans*-**4**, *E*-**6**, *Z*-**6**, and thianthrene 5-oxide in 46%, 18%, 7%, and 10% yields, respectively. Similarly, in the reaction of **8**, the corresponding *N*-unsubstituted sulfilimine (**7**) was formed in 48%, with further de-iminated product thianthrene 5,5-dioxide in 10%, and the expected sulfoximine **9** in 31% yield. In both cases the de-brominated products *trans*-**4** and **7** are thought to be formed by nucleophilic attack of a nucleophile (HO^- or MeO^-) on bromine atom of *trans*-**5** or **8** with retention of configuration. Successively, *trans*-**4** and **7** were de-iminated partially to give the corresponding thianthrene 5-oxide and 5,5-dioxide. On the other hand, products *E*-**6**, *Z*-**6**, and **9** are apparently formed through nucleophilic attack of HO^- and/or MeO^- on sulfur atom at 5-*S*-position of *cis*- and *trans*-**5** and **8** (Scheme 4).

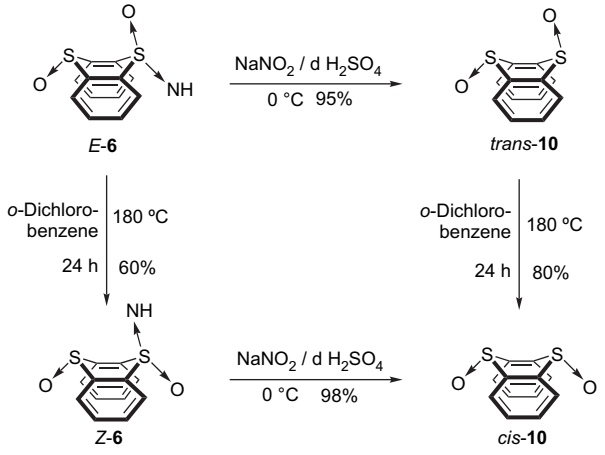
Concerning the stereochemistry of *E*- and *Z*-**6**, the determination of the configuration of NH group on sulfur atom at 5-*S*-position was performed by the de-imination procedure in the literature.[3] Thus, in order to distinguish between these two isomers, the de-imination reactions of *E*- or *Z*-**6** via diazotization with sodium nitrite in 45% aqueous sulfuric acid at 0 °C were carried out. The de-imination of compound *E*-**6** led to only *trans*-thianthrene 5,10-dioxide (*trans*-**10**) in 95% yield, while in the same procedure using compound *Z*-**6**, *cis*-thianthrene 5,10-dioxide (*cis*-**10**) was formed in 98% yield. According to the de-imination mechanism on sulfur atom with nitrous acid it has been known to proceed with the retention of configuration.[12–15] Thus, the stereochemical assignment for the de-imination from *E*-**6** and *Z*-**6** to *trans*-**10** and *cis*-**10**, respectively, in Scheme 5 was confirmed definitely as the results of product analysis depicted in Scheme 4.



Scheme 3. Reaction of 5-(*N*-*p*-tosyl)iminothianthrene with concd H_2SO_4 and imination of thianthrene with MSH.



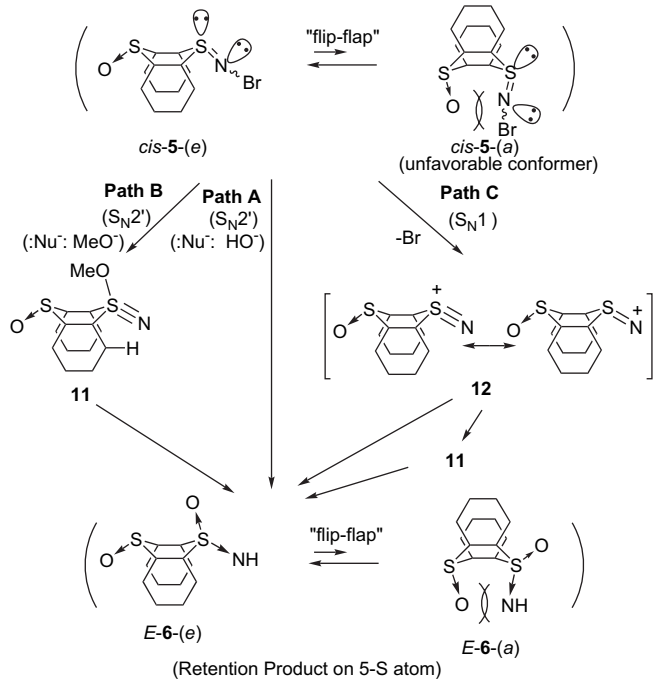
Scheme 4. Product analysis for the reaction of 5-(*N*-bromo)iminothianthrenes in KOH/(MeOH–H_2O) solution.



Scheme 5. Determination of the stereochemistry of sulfoximines *E*- and *Z*-**6** and the thermal conversion of *E*-**6** to *Z*-**6**.

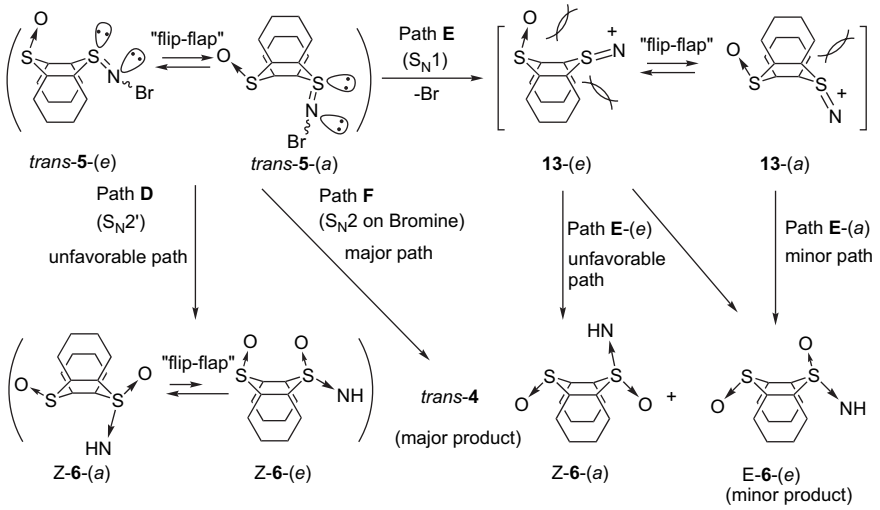
In Scheme 5, the result of thermal isomerization from *E*-**6** to *Z*-**6** (via thermal pyramidal inversion at 10-*S*-atoms, followed by successive 'flip-flap' motion, or vice versa) was also presented together with the *trans*- to *cis*-**10** isomerization.[11] This result seems to suggest that *Z*-**6** is more thermodynamically stable than *E*-**6** in *o*-dichlorobenzene and hence, unsubstituted sulfilimino group (–S–NH) is more stable at axial than equatorial position. However, the reason is unclear. According to the stability of these two conformations, the ab initio MO calculation will be performed in near future.

The confirmed configurational assignment of the products *E*- and *Z*-**6**, is suggestive to explain the mechanistic pathway on the stereochemistry in the alkaline hydrolysis of *trans*- and *cis*-**5**. In the alkaline hydrolysis of *cis*-**5**, the mechanistic aspect will be discussed as follows as illustrated in Scheme 6. In the thianthrene system, there is a possibility to exist as the mixture of 'flip-flap' inter-convertible confomers around S–S axis of the dithiin framework. Therefore, *cis*-**5** will exist as a mixture of two comformers of *cis*-**5**-(*e*) and *cis*-**5**-(*a*) (*e*: equatorial SN bond, *a*: axial SN bond). Comparison between these two conformers indicates clearly that *cis*-**5**-(*a*) is less stable than *cis*-**5**-(*e*) due to the 1,4-diaxial interaction between SO and *N*-bromosulfimide groups. Hence, HO^- attacks 5-*S*-position of *cis*-**5**-(*e*) more preferentially than *cis*-**5**-(*a*) via the S_N2' mechanism (Path **A**), resulting in the formation of *E*-**6**. Methoxide nucleophile also attacks 5-*S*-position of *cis*-**5**-(*e*) similarly (Path **B**), resulting in the concurrent formation of the intermediate methoxythiazyne **11** that is hydrolyzed rapidly to *E*-**6** spontaneously. Another possible route to *E*-**6** is via S_N1 mechanism (Path **C**) that leads to nitridosulfonium cation intermediate **12** initially,

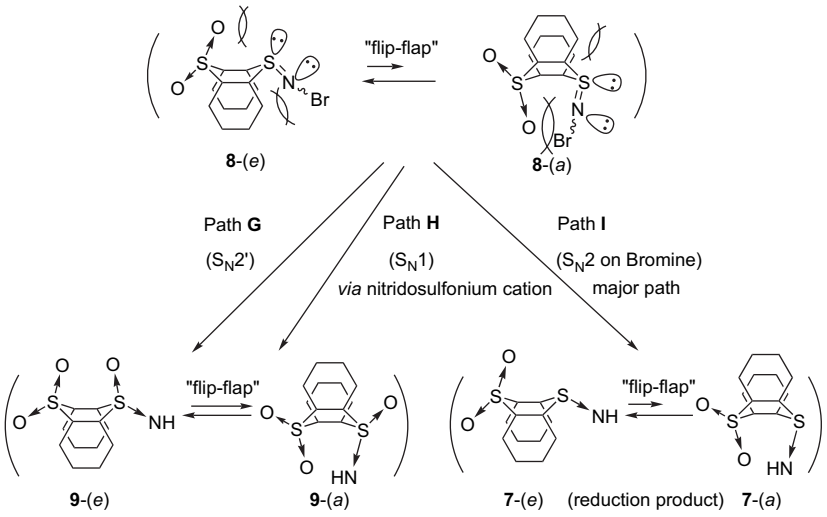


Scheme 6. Reaction mechanism of *cis*-**5** in KOH/(MeOH–H_2O) solution.

and successively to give *E*-**6**. Consequently, in the hydrolysis of *cis*-**5** under the conditions only the product *E*-**6** with retention of configuration was formed. In the alkaline hydrolysis of *trans*-**5**, the reaction path will be accounted for as follows. Similar to the cis-isomer, *trans*-**5** will exist as two conformers of *trans*-**5**-(*e*) and *trans*-**5**-(*a*) (*e* and *a* notations are the same as in case of cis-isomer), that have almost the same stability because of the absence of 1,4-diaxial interaction between SO and *N*-bromosulfimide groups (Scheme 7). However, contrary to *cis*-**5**, it is suggested that the attacking site of nucleophiles in *trans*-**5**-(*e*) was hindered substantially by SO group at 10-*S*-position, and further, *trans*-**5**-(*a*) has the steric hindrance due to *peri*-hydrogens on the fused benzene rings. Therefore, in the S_N2' mechanism the attack of HO^- or MeO^- ion at 5-*S*-position is prevented greatly to afford *Z*-**6** (Path **D**). This path **D** seems to be less important. Another possible route to S_N products *E*- and *Z*-**6** is via S_N1 mechanism. Ionization of *trans*-**5** leads to nitridosulfonium cation intermediates **13**-(*e*) and **13**-(*a*), and successively to give *E*-**6** and *Z*-**6**, as depicted in Scheme 7. In this case, the less-hindered nitridosulfonium cation intermediate **13**-(*a*) seems to be more favorable for attack of H_2O or MeOH than **13**-(*e*), resulting in the formation of *E*-**6** (18%) via path **E**-(*a*) preferentially than *Z*-**6** (7%) via path **E**-(*e*). The de-brominated product *trans*-**4** is formed as the main product in 46% yield, by the attack of HO^- and/or MeO^- on bromine atom, because this route is apparently the most favorable with absence of steric hindrance (Path **F**).



Scheme 7. Reaction route of *trans*-**5** in KOH/(MeOH–H_2O) solution.



Scheme 8. Reaction mechanism of **8** in KOH/(MeOH–H_2O) solution.

However, the precise mechanism of this de-bromination process is not clear at present. Further, these results suggest that S_N2' on sulfur proceeds (Path **D**) faster than both solvolysis (S_N1 process: Path **E**) and de-bromination (S_N2 reaction on bromine atom: Path **F**). *cis*-**5** (1 h; only S_N product, *E*-**6**) was found to react faster than *trans*-**5** (4 h) in which case sterically preferable S_N1 product ratio (via Path **E**) is quite small compared with the de-brominated product, *trans*-**4** (via Path **F**).

The product distribution from **8** under the same conditions also will be accounted for by the similar explanation as in the case of *trans*-**5**, as depicted in Scheme 8. The displacement reaction on sulfur atom to the product **9** via Path **G** (S_N2' mechanism) seems to be difficult. The attacking site for a nucleophile to **8**-(*e*) is sterically hindered by one SO group at 10-*S*-position and also **8**-(*a*) has the steric hindrance against nucleophile by interaction with *peri*-hydrogens on two benzene rings. Therefore, the possible route to **9** seems to be via S_N1 mechanism forming nitridosulfonium cation intermediates via path **H**, subsequently to lead to the product **9** as in the case of *trans*-**5** (Scheme 7). The compound **7** is formed as the major product by the attack of HO^- and/or MeO^- on bromine atom via S_N2 mechanism (Path **I**). The rather slow reaction time (4.3 h), compared to the result of hydrolysis of *cis*-**5** (see Scheme 6), also seems to suggest that S_N1 proceeds more slowly than S_N2'. The mechanism for the further de-imination steps for thianthrene 5-oxide and 5,5-dioxide from *trans*-**4** and **7**, respectively, is not clear at present.

3. Conclusion

The nucleophilic reaction on *N*-halosulfilimine among trivalent sulfur compounds involves many complex viewpoints mechanistically as follows. (1) Attacking site of nucleophile onto sulfur or halogen. (2) Types of transition state (usually trigonal bipyramidal; in this case attacking direction of nucleophile and leaving direction of leaving group are crucial to reflect to the change of the resulting stereochemistry of the products). (3) Berry pseudo-rotation (turnstile rotation) and so on.[16,17] However, in the thianthrene system with rather rigid dibenzodithiin framework these considerations are thought to be restricted greatly, in the direction of both nucleophile and leaving group in the transition state, and particularly in pseudo-rotation behavior. As a consequence, all the discussions shown above seem to explain the difference of the reactivities and the product distribution for **2**, *cis*- and *trans*-**5**, and **8** under the alkaline hydrolysis conditions in MeOH/H_2O.

4. Experimental

4.1. General

All the melting points were uncorrected. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ using TMS as an internal standard. The elemental analyses were performed at Microanalytical Laboratory of the Department of Material Systems Engineering and Life Science, University of Toyama. All the reactions were monitored with TLC using Silica Gel 60 F_{254} TLC plates and the products were separated by column chromatography using Silica Gel 60 and also by preparative layer chromatography using Silica Gel 60 PF_{254} with UV detection. All the reagents were of the highest quality and were further purified by distillation or recrystallization. The solvents were further purified by general methods.

4.1.1. 5-Iminothianthrene (1). Thianthrene (300 mg, 1.39 mmol) was dissolved in 25 mL of CH_2Cl_2 and into this solution 0.27 mL (3.47 mmol) of trifluoroacetic acid and 50 μl (2.77 mmol) of H_2O were added. To this solution was added ethyl *O*-mesitylenesulfonylacetohydroxamate (514.5 mg, 1.80 mmol) in CH_2Cl_2. After stirring for one day at rt, the reaction mixture was basified with aqueous $NaHCO_3$, and then extracted with $CHCl_3$. The chloroform layer was washed with brine, dried over anhydrous $MgSO_4$, and removed at reduced pressure to give **1** (245.7 mg, 76%),[18] that was recrystallized from CH_2Cl_2–hexane (colorless crystal). Mp 152–156 °C (dec 153 °C, lit.[18]); ^1H NMR ($CDCl_3$): δ=7.38–7.42 (m, 2H), 7.52–7.56 (m, 2H),

7.58–7.61 (m, 2H), 8.00–8.03 (m, 2H); IR (KBr): ν= 934 cm^{-1}.

4.1.2. 5-(*N*-Bromo)iminothianthrene (2). To a solution of **1** (217.2 mg, 0.939 mmol) in 25 mL of acetone, *N*-bromosuccinimide (178 mg, 1.13 mmol) in 5 mL of acetone was added at 5 °C. After 15 min, into the reaction mixture sufficient ice-water was added to form yellow precipitate, that was collected by filtration, washed with water to remove the succinimide formed, and dried at reduced pressure to give **2** (243.4 mg, 84.5%) followed by recrystallization from CH_2Cl_2–hexane (yellow crystal). Mp 121–123 °C (dec); ^1H NMR ($CDCl_3$): δ=7.48–7.53 (m, 2H), 7.57–7.66 (m, 4H), 8.00–8.08 (m, 2H); IR (KBr): ν=1437, 881, 757 cm^{-1}. Anal. Calcd for $C_{12}H_8NOS_2Br$: C, 46.46; H, 2.60; N, 4.51. Found: C, 46.58; H, 2.60; N, 4.53.

4.1.3. *cis*-5-(*N*-Bromo)iminothianthrene 10-oxide (*cis*-5). To a solution of *cis*-**4**[10] (203.0 mg, 0.82 mmol) in 34 mL of CH_2Cl_2 was added *N*-bromosuccinimide (173.6 mg, 0.98 mmol) in 17 mL of CH_2Cl_2 at rt. After 30 min the solvent was removed, and the residue was washed with water. Yellow crystalline material was dissolved again in CH_2Cl_2 and dried over anhydrous $MgSO_4$. The solvent was removed at reduced pressure to give *cis*-**5** (261.0 mg, 97%) that was recrystallized from CH_2Cl_2–hexane (yellow crystal). Mp 154–176 °C (dec); ^1H NMR ($CDCl_3$): δ=7.80–7.86 (m, 4H), 8.12–8.15 (m, 4H); ^{13}C NMR ($CDCl_3$): δ=125.0, 127.4, 129.4, 130.8, 131.6, 138.7; IR (KBr): ν=1075, 890 cm^{-1}. Anal. Calcd for $C_{12}H_8NOS_2Br$: C, 44.18; H, 2.47; N, 4.29. Found: C, 44.14; H, 2.42; N, 4.27.

4.1.4. *trans*-5-(*N*-Bromo)iminothianthrene 10-oxide (*trans*-5). To a solution of *trans*-**4**[10] (501.1 mg, 2.03 mmol) in 34 mL of CH_2Cl_2 was added *N*-bromosuccinimide (432.8 mg, 2.43 mmol) in 23 mL of CH_2Cl_2 at rt. After 30 min the solvent was removed, and the residue was washed with water. Yellow crystalline material was dissolved again in CH_2Cl_2 and dried over anhydrous $MgSO_4$. The solvent was removed at reduced pressure to give *trans*-**5** (591 mg, 89%) that was recrystallized from CH_2Cl_2–hexane (yellow crystal). Mp 168–177 °C (dec); ^1H NMR ($CDCl_3$): δ= 7.71–7.75 (m, 2H), 7.81–7.86 (m, 2H), 8.04–8.06 (m, 2H), 8.24–8.26 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=129.8, 130.1, 131.4, 132.4, 136.2, 140.7; IR (KBr): ν=1025, 885 cm^{-1}. Anal. Calcd for $C_{12}H_8NOS_2Br$: C, 44.18; H, 2.47; N, 4.29. Found: C, 44.16; H, 2.16; N, 4.40.

4.1.5. 5-(*N*-Bromo)iminothianthrene 10,10-dioxide (8). To a solution of **7**[11] (150.7 mg, 0.57 mmol) in 5 mL of CH_2Cl_2 was added *N*-bromosuccinimide (123.4 mg, 0.69 mmol) in 14 mL of CH_2Cl_2 at rt. After 30 min the solvent was removed, and the residue was washed with water. Yellow crystalline material was dissolved again in CH_2Cl_2 and dried over anhydrous $MgSO_4$. The solvent was removed at reduced pressure to give **8** (182.0 mg, 93%) that was recrystallized from CH_2Cl_2–hexane (yellow crystal). Mp 180–190 °C (dec); ^1H NMR ($CDCl_3$): δ=7.79–7.83 (m, 2H), 7.87–7.91 (m, 2H), 8.17–8.19 (m, 2H), 8.24–8.27 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=126.2, 128.3, 131.4, 133.0, 136.1, 139.4; IR (KBr): ν=1320, 1165, 890 cm^{-1}. Anal. Calcd for $C_{12}H_8NO_2S_2Br$: C, 42.11; H, 2.35; N, 4.09. Found: C, 42.17; H, 2.06; N, 4.14.

4.1.6. Hydrolysis of 2. To a suspension of **2** (46.5 mg, 0.15 mmol) in 6 mL of methanol was added 3 mL of 1 M aqueous KOH solution. After stirring for 2 h at 60 °C, the solution was neutralized with aqueous ammonium chloride and extracted with $CHCl_3$. The chloroform layer was washed with water and dried over anhydrous $MgSO_4$, and removed at reduced pressure to give 5-iminothianthrene 5-oxide (**3**, 39.2 mg, 95%) that was recrystallized from acetone–hexane (colorless crystal). Mp 117–118 °C; ^1H NMR ($CDCl_3$): δ=7.49–7.56 (m, 4H), 7.63–7.67 (m, 2H), 8.12–8.27 (m, 2H); IR (KBr): ν=3292, 1232, 978, 755 cm^{-1}. Anal. Calcd for $C_{12}H_9NO_2S_2$: C, 58.27; H, 3.67; N, 5.66. Found: C, 58.11; H, 3.74; N, 5.57.

4.1.7. Hydrolysis of *cis*-5. To a suspension of *cis*-**5** (50.2 mg, 0.15 mmol) in 6 mL of methanol was added 3 mL of 1 M aqueous KOH solution. After stirring for 1 h at 60 °C, the solution was neutralized with aqueous H_2SO_4 and extracted with $CHCl_3$. The chloroform layer was washed with water and dried over anhydrous $MgSO_4$, and removed at reduced pressure to give *E*-**6** (39.2 mg, 97%) that was recrystallized from EtOAc–hexane (colorless crystal). Mp 225–227 °C; ^1H NMR ($CDCl_3$): δ=3.52 (s, 1H), 7.64–7.68 (m, 2H), 7.70–7.75 (m, 2H), 8.11–8.14 (m, 2H), 8.18–8.20 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=124.8, 125.7, 130.3, 132.3, 136.6, 147.2; IR (KBr): ν=3170, 1240, 1095, 1050, 950 cm^{-1}. Anal. Calcd for $C_{12}H_9NO_2S_2$: C, 54.73; H, 3.44; N, 5.31. Found: C, 54.42; H, 3.26; N, 5.34.

4.1.8. Hydrolysis of *trans*-5. To a suspension of *cis*-**5** (50.3 mg, 0.15 mmol) in 20 mL of methanol was added 10 mL of 1 M aqueous KOH solution. After stirring for 4 h at 60 °C, the solution was neutralized with aqueous H_2SO_4 and extracted with $CHCl_3$. The chloroform layer was washed with 3% aqueous H_2SO_4 and water, and dried over anhydrous $MgSO_4$, and removed at reduced pressure and then the residue was purified by preparative layer chromatography (silica gel; EtOAc–$CHCl_3$=1:20) to give *E*-**6** (7.5 mg, 18%), (*Z*)-5-iminothianthrene 5,10-dioxide (*Z*-**6**, 3.0 mg, 7%), and thianthrene 5-oxide (3.5 mg, 10%). Neutralization of aqueous H_2SO_4 layer gave *trans*-**4** (17.4 mg, 46%). Compound *Z*-**6** (colorless crystal): mp 239–241 °C (recrystallization from EtOAc–hexane); ^1H NMR ($CDCl_3$): δ=7.66–7.70 (m, 2H), 7.73–7.77 (m, 2H), 8.11–8.15 (m, 4H); ^{13}C NMR ($CDCl_3$): δ=125.1, 126.1, 130.4, 132.5, 136.5, 146.8; IR (KBr): ν=3190, 1240, 1095, 1070, 980 cm^{-1}. Anal. Calcd for $C_{12}H_9NO_2S_2$: C, 54.73; H, 3.44; N, 5.31. Found: C, 54.34; H, 3.48; N, 5.27.

4.1.9. Hydrolysis of 8. To a suspension of **8** (50.8 mg, 0.15 mmol) in 14 mL of methanol was added 7 mL of 1 M aqueous KOH solution. After stirring for 4.3 h at 60 °C, the solution was neutralized with aqueous sulfuric acid and extracted with $CHCl_3$. The chloroform layer was washed with 3% aqueous H_2SO_4 and water and dried over anhydrous $MgSO_4$, and removed at reduced pressure and then the residue was purified by preparative layer chromatography (silica gel; EtOAc–Hexane=1:1) to give **9** (13.0 mg, 31%) and thianthrene 5,5-dioxide (3.6 mg, 10%). Neutralization of aqueous H_2SO_4 layer gave **7** (18.9 mg, 48%). Compound **9** (colorless crystal): mp 262–266 °C (dec); ^1H NMR ($CDCl_3$): δ=7.77–7.84 (m, 4H), 8.24–8.27 (m, 2H), 8.28–8.30 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=125.7, 125.8, 133.0,

133.8, 138.4, 142.4; IR (KBr): ν=3210, 1315, 1250, 1165, 980 cm^{-1}. Anal. Calcd for $C_{12}H_9NO_3S_2$: C, 51.60; H, 3.25; N, 5.01. Found: C, 51.74; H, 3.31; N, 4.93.

4.1.10. De-imidation of *E*-6 to *trans*-10. To a solution of *E*-**6** (50.2 mg, 0.19 mmol) in 7 mL of 45% aqueous H_2SO_4 was added sodium nitrite (27.6 mg, 0.40 mmol) in 1.5 mL of water at 0 °C. After 30 min the solution was extracted with $CHCl_3$. The chloroform layer was washed with water and dried over anhydrous $MgSO_4$ and the solvent was removed at reduced pressure to give *trans*-**10**[11] (44.9 mg, 95%) that was identified by ^1H NMR and IR spectral data.

4.1.11. De-imidation of *Z*-6 to *cis*-10. To a solution of *Z*-**6** (40.1 mg, 0.15 mmol) in 4 mL of 45% aqueous H_2SO_4 was added sodium nitrite (22.4 mg, 0.32 mmol) in 1.5 mL of water at 0 °C. After 30 min the solution was extracted with $CHCl_3$. The chloroform layer was washed with water and dried over anhydrous Mg_2SO_4 and the solvent was removed at reduced pressure to give *cis*-**10**[11] (37.0 mg, 98%) that was identified by ^1H NMR and IR spectral data.

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Chemical predisposition in synthesis: application to the preparation of the pyrrolidine natural products, plakoridines A and B

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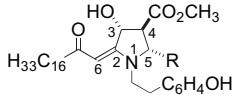
Abstract—The pyrrolidine natural products, plakoridines A and B, as well as an array of unnatural analogues, have been prepared using a five-step synthetic sequence modelled on a biogenetic theory. The key transformation involves a 'Mannich/Michael/internal-redox' cascade, which proceeds in yields of 31–63%.

1. Introduction

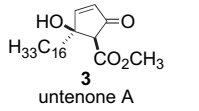
Marine sponges of the genus *Plakortis* are a rich source of oxidised fatty acid derivatives (oxylipins), many of which display quite potent bioactivities.[1] Plakoridines A and B (**1** and **2**) are two novel heterocyclic natural products belonging to this class of compounds, which were first isolated during the last decade from Japanese sponges collected in Okinawan waters (Fig. 1).[2,3] These unusual secondary metabolites have unprecedented structures containing a tyramine unit as well as a fully substituted pyrrolidine ring: initial biological studies have shown that **1** is cytotoxic towards murine lymphoma L1210 cells. In 2000, Ma and Sun described an elegant 14-step asymmetric synthesis of (−)-plakoridine A, which indicated that the natural products were essentially racemic (natural **1**: $[\alpha]_D^{20}$ −0.4 (*c* 0.5, $CHCl_3$); (−)-**1**: $[\alpha]_D^{22}$ −43.0 (*c* 0.5, $CHCl_3$)).[4]



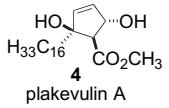
R = C_3H_7 : plakoridine A **1**
R = $C_{15}H_{31}$: plakoridine B **2**

Figure 1.

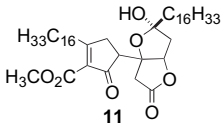
The plakoridines are members of a biogenetically related group of natural products, many of which have been isolated by the research group of Professor J. Kobayashi and which include untenone A (**3**),[5] plakevulin A (**4**),[6,7] manzamenones (e.g., **5**–**11**)[2,8,9] and plakorsins (e.g., plakorsin A (**12**)) (Fig. 2).[10] The members of this family of compounds are



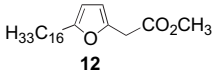
3
untenone A



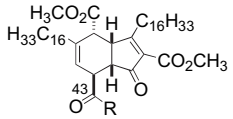
4
plakevulin A



11
manzamenone K



12
plakorsin A



manzamenone A **5** R = OH
manzamenone C **6** R = OEt
manzamenone D **7** R = NH_2
manzamenone E **8**

manzamenone F **9** R = OC_4H_9
manzamenone H **10** R = $HN(CH_2)_2C_6H_4OH$

Figure 2.

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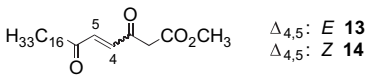
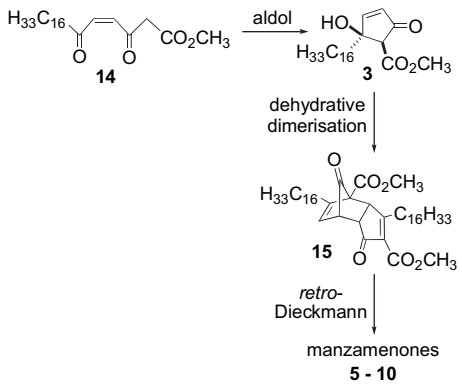


Figure 3.

characterised by the common structural features of at least one β-oxygenated carboxyl group and at least one fully saturated unbranched C_{16} alkyl chain.

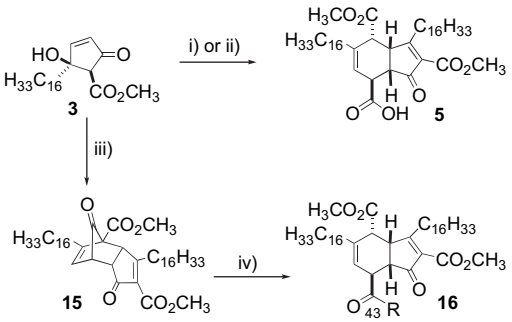
Kobayashi noted that many members of this family of oxylipins possess structures, which could be derived biosynthetically from (*E*)/(*Z*)-methyl-3,6-dioxo-4-docosenoate (**13**, **14**) (Fig. 3).

Prompted by this observation, we have suggested a plausible biosynthetic pathway, which interrelates (*Z*)-methyl-3,6-dioxo-4-docosenoate (**14**), untenone A (**3**) and many of the manzamenones (Scheme 1).[11–14] According to this proposal, aldol cyclisation of **14** leads to untenone A (**3**), which then undergoes dehydrative dimerisation to give the tricyclic adduct **15**. Subsequent attack at the reactive bridging carbonyl of **15** by different nucleophiles RH, followed by *retro*-Dieckmann ring-opening, gives a conjugated enol(ate), which undergoes kinetic protonation at the α-position and on the convex surface to give the bicyclic structure common to the majority of the manzamenones. An attractive feature of this scheme is that the inherent reactivity of the tricyclic intermediate **15** is ultimately manifested in differential functionalisation at C43 of the manzamenone skeleton, which is the natural locus of diversification.



Scheme 1.

Successful syntheses of several natural as well as unnatural manzamenones using approaches modelled on the biogenetic theory have provided support for the plausibility of the proposal (Scheme 2). Thus, simply stirring a mixture of **3** in water, at ambient temperature and in the presence of either a Brønsted acid surfactant combined catalyst (dodecyl-benzenesulfonic acid: 0.1 equiv) or a Lewis acid surfactant combined catalyst (scandium trisdodecylsulfate: 0.1 equiv) provided manzamenone A (**5**) in reproducible yields of 65–80%.[14] Alternatively, dehydrative dimerisation of untenone A to give adduct **15** has been achieved using trifluoroacetic anhydride: subsequent exposure of **15** to a range of O and N centred nucleophiles has provided a variety of manzamenone analogues differing with respect to the acyl substituent at C43.[15]



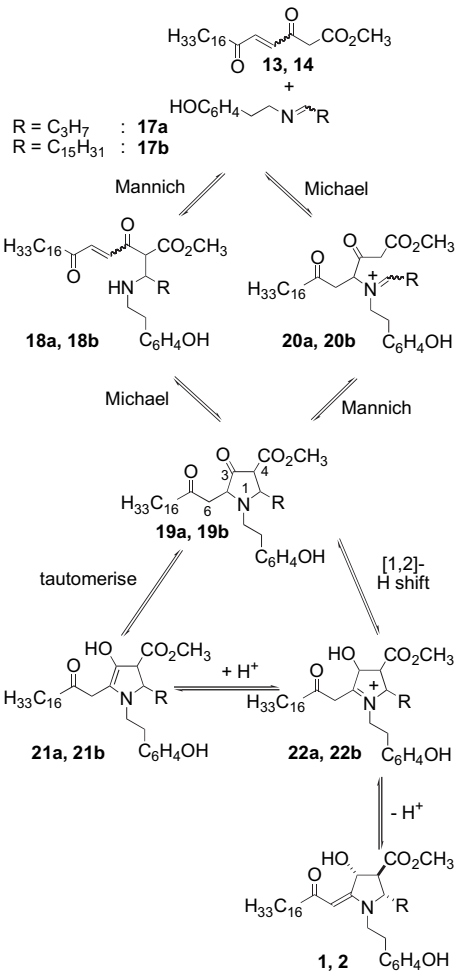
Scheme 2. Reagents and conditions: (i) scandium trisdodecylsulphate (0.1 equiv), H_2O, 25 °C, 1–24 h, 70–80%; (ii) dodecyl-benzenesulfonic acid (0.1 equiv), H_2O, 25 °C, 7–24 h, 65–70%; (iii) TFAA, $CDCl_3$, rt, 24 h; (iv) for ester derivatives: RH, rt, 24 h, 15–63% from **3**; for amide derivatives: RH, CH_2Cl_2, rt, 24 h, 10–15% from **3**.

Chemical predisposition refers to the kinetic reaction preferences bestowed on the functional groups in a molecule by their specific molecular context.[16] In the 'arena' of biochemical evolution, chemically predisposed reactions may be viewed as the starting points from which nature, the 'quintessential process development chemist',[17] evolves efficient enzyme-catalysed processes. The transformation of untenone A (**3**) into the manzamenones bears the hallmarks of a predisposed biochemical process and this is supported experimentally by the ease with which the transformations can be carried out in the laboratory.

It occurred to us that the plakoridines may also be products of a predisposed biochemical pathway, which commences with either (*E*)- or (*Z*)-methyl-3,6-dioxo-4-docosenoate (**13**, **14**) (Scheme 3).[18]

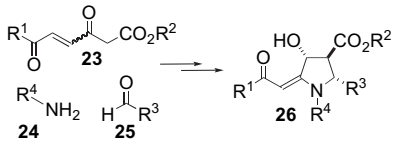
According to our proposal, reaction of **13** or **14** with the aldimines derived from tyramine and either butyraldehyde or hexadecanal would give pyrrolidinones **19a**, **19b**: this transformation might proceed by initial Mannich reaction followed by a '5-*exo*' Michael-type cyclisation, or alternatively by initial Michael reaction to give iminium species **20a**, **20b** followed by a '5-*endo*' Mannich cyclisation. The conversion of pyrrolidinones **19a**, **19b** to plakoridines A and B (**1**, **2**) involves, formally, an internal redox reaction whereby the ketone moiety of **19a**, **19b** is reduced to an alcohol and the exocyclic C–C single bond at C2 is oxidised to an alkene: the thermodynamic driving force for the transformation being formation of the vinylogous amide moiety present in the plakoridines. Mechanistically, this process might occur via a series of prototropic shifts somewhat akin to those which occur during the Amadori rearrangement: thus tautomerism of **19a**, **19b** could lead to enaminols **21a**, **21b**, which upon protonation would give iminium species **22a**, **22b**. Deprotonation of the *exo*-methylene group at C2 of **22a**, **22b** would then furnish the plakoridines. Iminium species **22a**, **22b** could alternatively be generated directly from pyrrolidinones **19a**, **19b** via a concerted [1,2]-hydrogen shift. The reversibility of the individual transformations of this sequence means that the relative stereochemistry of the plakoridines would be expected to be a consequence of thermodynamic control.

The challenging and quite unprecedented cascade sequence of reactions leading to the plakoridines inspired us to initiate



Scheme 3.

an investigation into the synthesis of these unusual natural products using an approach modelled on the biogenetic theory. Reports in the literature that plakoridine A (**1**),[19] as well as other members of this family of oxylipins,[20] displays inhibitory properties towards DNA polymerases α and β have provided additional stimulus for us to exploit the multi-component nature of the biosynthetic sequence in the preparation of novel analogues of the plakoridines. In this paper, we provide details of our investigations into the synthesis of an array of analogues of the plakoridines, which possess general structure **26** (Scheme 4). The successful outcome of these investigations will ultimately facilitate the generation of important SAR-data regarding the structural features, which are important for optimal bioactivity of this class of compounds towards DNA polymerases.

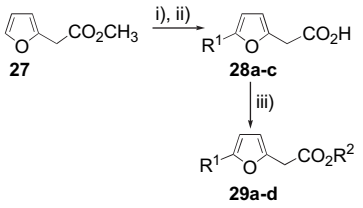


R^1= linear alkyl; R^2 = linear or branched alkyl;
R^3 = linear alkyl or aryl; R^4 = terminally substituted alkyl.

Scheme 4.

2. Results and discussion

Analogues of the furan fatty acid derivative, plakorsin A (e.g., **29a–d**), were envisaged to be the key intermediates for our synthetic investigations. Previously, we have reported full details of the synthesis of plakorsin A (**12**) starting from 2-furan acetonitrile;[13] our preferred starting material for the synthesis of analogues **29a–d** in the studies reported here was the methyl ester of 2-furanacetic acid (**27**) (Scheme 5). Acylation of **27** with the appropriate acid chloride followed by ketone reduction using the Huang-Minlon modification of the Wolff–Kishner conditions[21a,b] gave 5-alkyl-furan-2-yl acetic acids **28a–c** in acceptable yields. Subsequent esterification either under acid-catalysed conditions or in the presence of DCCI gave the desired ester derivatives **29a–d**. Representative yields for the individual transformations of this sequence are provided in Table 1.



Scheme 5. Reagents and conditions: (i) RCOCl, $SnCl_4$, CH_2Cl_2, −5 °C, 1 h; (ii) H_2NNH_2, NaOH, $HOCH_2CH_2OH$, Δ, 72 h; (iii) R^2OH, Amberlite® IR-120 (H), Δ, 72 h or R^2OH, DCCI, CH_2Cl_2, 0 °C, 1 h.

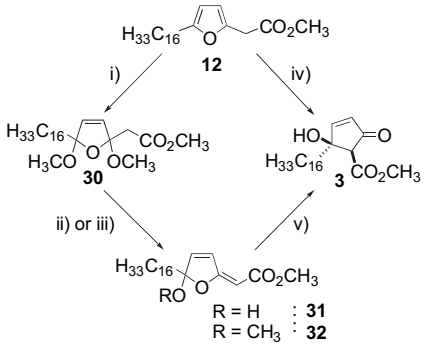
Table 1. Yields of individual transformations for the conversion of methyl ester **27** to plakorsin analogues **29a–d**

	R^1	R^2	Yield (%)		
			(i)	(ii)	(iii)
a	C_2H_5	CH_3	96	96	91
b	$C_{12}H_{25}$	CH_3	89	47	76
c	$C_{16}H_{33}$	C_2H_5	99	59	98
d	$C_{16}H_{33}$	$CH(CH_3)_2$	—	—	99

It was envisaged that under appropriately controlled conditions, oxidative cleavage of the furan ring in the plakorsin analogues would provide (*E*)- or (*Z*)-enediones analogous to **13** and **14**. Therefore, using plakorsin A (**12**) as a test substrate, we carried out investigations into the outcome of exposure of the 2,5-disubstituted furan ring-system to a variety of oxidation conditions.

As we have described previously, treatment of plakorsin A (**12**) with bromine in methanol gave the bis-acetal **30** as a mixture of diastereoisomers in good yield.[12,13,22] This compound is a masked form of (*Z*)-methyl-3,6-dioxo-4-docosenoate (**14**) and, accordingly, exposure of **30** to mildly acidic hydrolytic conditions[23] furnished **31**, a cyclic hemiketal tautomer of **14**. The structural identity of **31** was confirmed by comparison of its spectroscopic data with those of methyl ketal **32**, which was prepared in unambiguous fashion, by base-mediated elimination of methanol from **30** (Scheme 6).

Low temperature oxidation of **12** using a peracid (*m*-CPBA)[24] followed by a mildly basic aqueous work-up



Scheme 6. Reagents and conditions: (i) Br_2, CH_3OH, Na_2CO_3, rt, 2 h, 84%; (ii) 0.005 M H_2SO_4, H_2O, dioxane, rt, 1.5 h; (iii) KHMDS, THF, −78 °C to rt, 79%; (iv) *m*-CPBA, CH_2Cl_2, −10 °C to rt, 2 h then work-up with $NaHCO_{3(aq)}$, 63%; (v) $NaHCO_3$, H_2O, dioxane, rt, 1 h, 82% from **30**.

furnished untenone A (**3**) as the major product and as a single diastereoisomer. This transformation almost certainly proceeds via the intermediacy of (*Z*)-enedione **14**, or a tautomer thereof, and accordingly, exposure of cyclic hemiketal **31** to mildly basic conditions also furnished untenone A (**3**) in good yield.

These studies indicated that (*Z*)-enedione **14** has a propensity to undergo aldol cyclisation to give untenone A. This observation prompted us to conclude that the diastereoisomeric (*E*)-enedione **13** would be a more appropriate substrate for our synthetic studies towards the plakoridines. A useful procedure for the preparation of (*E*)-enediones from furan derivatives, which utilises pyridinium chlorochromate (PCC) as the oxidant, has been described by Piancatelli and co-workers.[25] Disappointingly, exposure of plakorsin A (**12**) to the conditions described by these authors gave (*E*)-enedione **13**, as its enol tautomer **33**, in variable and quite unsatisfactory yields. Fortunately, however, a satisfactory procedure for the preparation of **33** was developed, based on a report by Jurczak and Pikul:[26] thus, after much experimentation, it was found that treatment of a solution of **12** in a 5:1 mixture of acetone and water (pre-cooled to −20 °C) with 1 equiv of bromine, provided **33** in a yield of 63% after purification by flash chromatography (82% yield based on recovered **12**) (Scheme 7). If the reaction was carried out at temperatures higher than −10 °C, or if excess bromine was added, competitive bromination of the enolic product resulted in an erosion of the isolated yield of **33**. The generality of this procedure has been demonstrated by the preparation, in acceptable yields, of other analogues of **33** (e.g., **34**–**36**).

The C4/C5 double bond geometry of the products of these reactions was indicated as (*E*) by the magnitude of the vicinal coupling constants between C(4)*H* and C(5)*H* (15–16 Hz). Further confirmation of the structure of the products was provided by X-ray crystallographic analysis of a sample of the short-chain analogue **34** (Fig. 4).

With compounds **33**–**36** in-hand, we were in a position to investigate the reaction cascade leading to the core skeleton of the plakoridines. The ultimate aim of our investigations (vide supra) was to develop a procedure suitable for the preparation of a range of analogues of **1**, **2**. In the first instance therefore, we decided to investigate the reaction of the putative biosynthetic precursor **33** with an imine, which differed slightly from the one implicated in the biosynthesis of the natural products. Using the excellent procedure of Tashiro and co-workers, imine **37** was prepared under aqueous conditions from phenethylamine and propionaldehyde.[27] We were then pleased to discover that prolonged incubation at rt of a solution of this imine and enol **33** in $CDCl_3$ resulted in the generation of two isomeric plakoridine-type structures: clean samples of both compounds were obtained following careful purification by flash chromatography (Scheme 8).[18] The close similarity of the ^1H NMR spectral data of the major isomer **38** with those of plakoridine A,[2] and in particular, the similar magnitude of the vicinal coupling constants between the ring hydrogens of the respective pyrrolidine cores ($J_{3,4} \approx J_{4,5} \approx 6.0$ Hz for **38**; $J_{3,4}=J_{4,5}=5.5$ Hz for **1**) were in accord with the structural assignment shown for **38**. Furthermore, a significant NOE observed from C(3)*H* to C(5)*H* was consistent with a *syn* relative stereochemistry at these two centres in **38**. Tentative structural assignment of the minor isomer **39** as the C3 epimer of **38** was based on two pieces of evidence: an increased vicinal coupling constant between C(3)*H* and C(4)*H* ($J_{3,4}=8.5$ Hz) and the absence of an observable NOE from C(3)*H* to C(5)*H*.

The potential for interconversion of the two isomers **38** and **39** was confirmed by the finding that prolonged storage of a sample of the minor isomer **39** in $CDCl_3$ at rt, resulted in slow isomerisation to give a mixture of **38** and **39** enriched

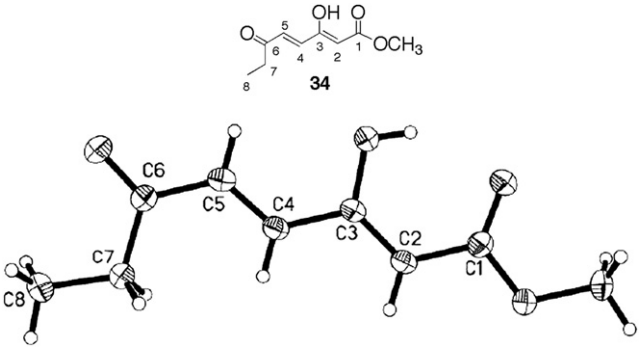
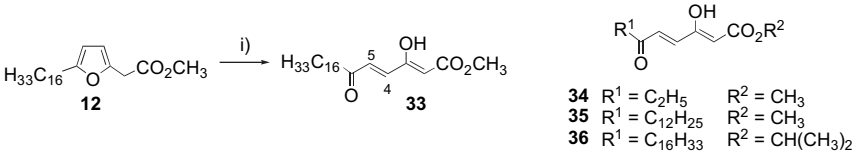
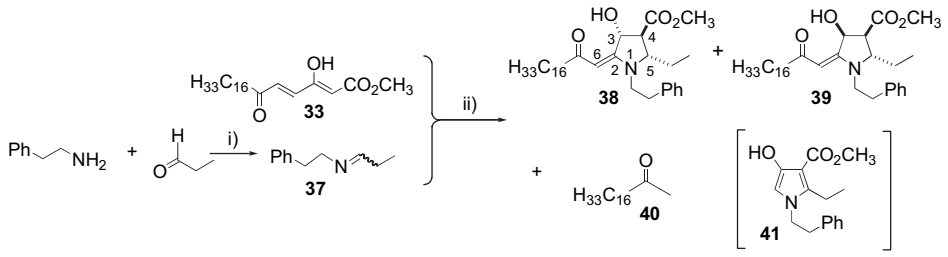


Figure 4. Crystal structure of **34** with ellipsoids at 50% probability.



Scheme 7. Reagents and conditions: (i) Br_2, acetone/H_2O (5:1), −20 to −10 °C, 6 h, 63% for **33**, 52% for **34**, 61% for **35**, 43% for **36**.



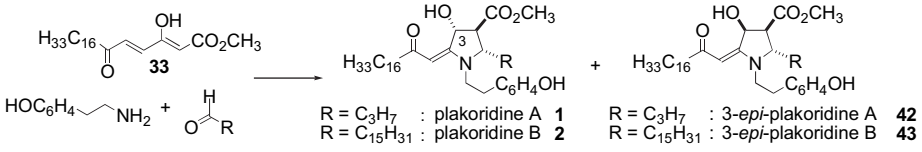
Scheme 8. Reagents and conditions: (i) H_2O, rt, 3 h, 97%; (ii) $CDCl_3$, rt, 12 days, 38% for **38**, 4% for **39**, 15% for **40**.

in the former (ratio of **38**:**39** 3:2 after 55 days). This observation is in accord with our initial suggestion that the relative stereochemistry of the natural plakoridines may be under thermodynamic control. Intriguingly, a third nonpolar compound was also isolated from the initial incubation reaction, which was identified as octadecan-2-one (**40**). Although a number of plausible mechanisms may result in the formation of this ketone, it seems likely that **40** is derived from a *retro*-Mannich reaction of an initial cyclised pyrrolidinone intermediate of type **19** (Scheme 3). A transformation of this kind would benefit from the generation of a hydroxylated pyrrole **41** (or tautomer thereof), but unfortunately, isolation of such an entity has not been possible.

The successful outcome of this initial study prompted us to investigate the preparation of the natural products themselves (Scheme 9).

It transpired that the imines necessary for the preparation of plakoridines A and B (**1** and **2**), derived from condensation of tyramine with either butyraldehyde or hexadecanal were unstable in a concentrated form. An alternative procedure was developed therefore, whereby the prerequisite imines were prepared in $CDCl_3$ in the presence of $MgSO_4$. The drying agent was then removed and a solution of enol **33** in $CDCl_3$ was added. The reactions were monitored by ^{1}H NMR spectroscopy and after a period of several days, substantial conversion to the natural products had occurred. A minor isomer was again generated in each case, believed to be the C3 epimer of the natural products (crude ratio of major isomer:minor isomer; ~3:1). Following purification by flash chromatography, plakoridines A and B (**1** and **2**) were isolated in 43 and 36% yields, respectively. The structural identity of our synthetic sample of **1** was confirmed by comparison of its ^{1}H NMR spectrum with that of (−)-plakoridine A[4] (Fig. 5).

The generality of the three-component coupling procedure outlined above for the synthesis of plakoridine-type structures has allowed the preparation of an array of analogues



Scheme 9.

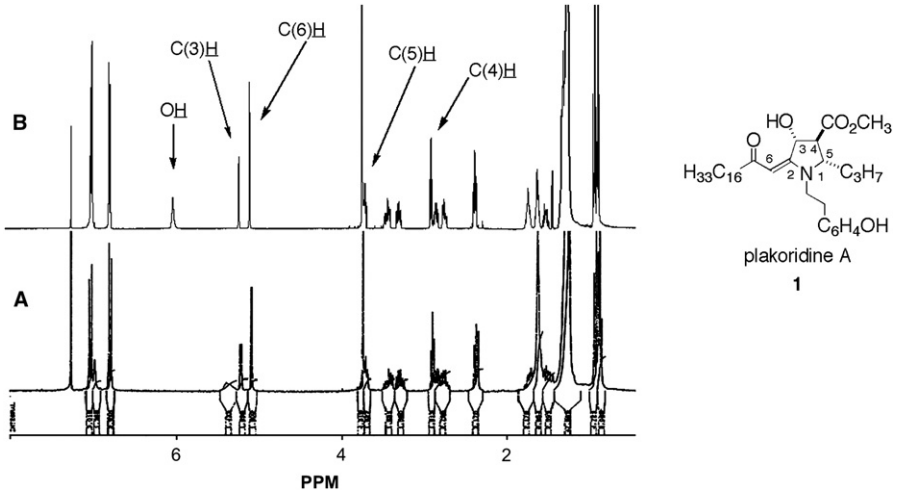


Figure 5. ^{1}H NMR spectra for (−)-plakoridine A[4] and (+/−)-plakoridine A, prepared according to Scheme 9. (A) ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of (−)-plakoridine A (reprinted with the kind permission from Professor Dawei Ma); (B) ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of (+/−)-plakoridine A.

of the natural products, using compounds **33**–**36** as substrates. Two alternative procedures were employed for these reactions, which differed with respect to the method of imine generation: method A involved preparation of the imines in an aqueous medium and method B, generally used for imines derived from long-chain aldehydes and/or from tryptamine, utilised dichloromethane as the reaction solvent. The crude product isomer ratios, as well as the isolated yields of the major products, are listed in Table 2: we feel that the yields of the reactions, which range between 31 and 63%, are acceptable given the complexity of the cascade sequence. Although it was feasible to isolate pure samples of the major 'natural' isomers from many of these reactions, it proved impossible, in most cases, to isolate pure samples of the minor isomeric components.

The progress of each of the reactions was monitored by ^{1}H NMR spectroscopy and in many cases, this provided evidence for the intermediacy of a pyrrolidinone intermediate, which was present as a mixture of two diastereoisomers. For example, in the case of the synthesis of compound **52**, the appearance and relatively slow disappearance of two ABX coupled systems were consistent with the formation of diastereoisomeric intermediates having general structure **55** (Fig. 6).

We reasoned that the use of an aromatic amine in the cascade sequence might lessen the thermodynamic drive for the formation of the vinylogous amide moiety of the plakoridine structures and allow the isolation of a pyrrolidinone intermediate. Accordingly, we exposed the short-chain enol **34** to Schiff's base **56** derived from aniline and benzaldehyde. After stirring for a period of 24 h, the enol **34** had been completely consumed to be replaced by three new principal compounds (ratio ~7:3:1). Continued monitoring by ^{1}H NMR over a period of 3 days indicated no further changes and, in particular, no evidence for the formation of plakoridine-type structures. The major product from this reaction was isolated by crystallisation from ethyl acetate, however, it proved impossible to grow crystals suitable for X-ray analysis. The ^{1}H NMR spectrum of this material was consistent with that expected for a pyrrolidinone intermediate: the observation of NOEs between C(2)*H* and C(4)*H*, as well as between both C(2)*H* and C(4)*H* and the *ortho* hydrogens of the phenyl substituent at C(5) are in accord with the relative stereostructure **57** depicted in Scheme 10.

Storage of a sample of **57** in either $CDCl_3$ or C_6D_6 resulted in quite rapid equilibration with two other species, which were the same as those generated in the original incubation reaction. We believe the major of these to be enol tautomer **58**

Table 2. Isomer ratios and isolated yields for preparation of plakoridine analogues **44**–**54**

Compound number	R^1	R^2	R^3	R^4	Synthetic method[a]	Isomer ratio[b] (major:minor)	Yield of major isomer (%)
44	$C_{16}H_{33}$	CH_3	C_6H_5	3-Indolyl-$(CH_2)_2$	B	28:1	38
45	$C_{16}H_{33}$	CH_3	C_6H_5	$C_6H_5(CH_2)_2$	A	19:1	39[c]
46	$C_{16}H_{33}$	CH_3	$C_{15}H_{31}$	$C_6H_5(CH_2)_2$	B	4:1	60
47	$C_{16}H_{33}$	CH_3	$C_{15}H_{31}$	3-Indolyl-$(CH_2)_2$	B	6:1	63
48	$C_{16}H_{33}$	$CH(CH_3)_2$	C_2H_5	$C_6H_5(CH_2)_2$	A	3:1	63
49	$C_{12}H_{25}$	CH_3	C_6H_5	$C_6H_5(CH_2)_2$	A	19:1	60
50	$C_{12}H_{25}$	CH_3	C_6H_5	3-Indolyl-$(CH_2)_2$	B	28:1	38
51	$C_{12}H_{25}$	CH_3	C_2H_5	$C_6H_5(CH_2)_2$	A	3:1	40
52	$C_{12}H_{25}$	CH_3	C_6H_5	$C_6H_5CH_2$	A	7:1	31[d]
53	C_2H_5	CH_3	C_6H_5	$C_6H_5CH_2$	A	8:1	57
54	C_2H_5	CH_3	$C_{15}H_{31}$	$C_6H_5(CH_2)_2$	B	3:1	55

[a] Method A: imine was prepared by stirring a mixture of the appropriate aldehyde and amine in water for 3 h at rt; method B: imine was prepared by stirring a mixture of the appropriate aldehyde and amine in dichloromethane for 3 h at rt.
[b] Isomer ratios were estimated by comparison of the integrals for C(6)*H* in the ^{1}H NMR spectra of the crude product mixtures.
[c] Sample was contaminated with <5% of the minor isomer.
[d] Sample was contaminated with <10% of the minor isomer.

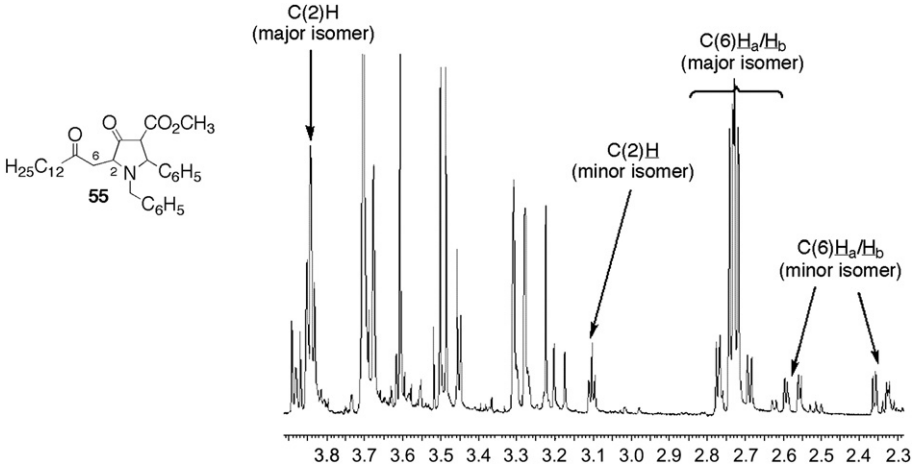
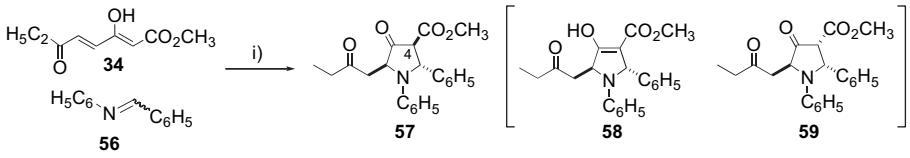


Figure 6. ^{1}H NMR spectrum of the intermediate product mixture from reaction of enol **35** with benzylidene benzylamine.



Scheme 10. Reagents and conditions: (i) $CDCl_3$, rt, 24h, 55%.

and we have assigned the minor component **59** to be the C4 epimer of **57**: the gradual disappearance of the ^1H NMR signal for C(4)*H* of **57** in the presence of D_2O is in accord with these conclusions.

3. Conclusions

In conclusion, we have prepared the plakoridines A (**1**) and B (**2**) as well as an array of analogues of the natural products, in five linear steps from the methyl ester of 2-furanacetic acid (**27**). The synthetic approach was modelled on a plausible and apparently unprecedented biosynthetic pathway involving a three-component Mannich/Michael reaction sequence followed by an 'internal redox' process. We consider that the yield of the key biomimetic transformation (31–63%) is reasonable given the complexity of the cascade sequence. Spectroscopic evidence for the intermediacy of a pyrrolidinone intermediate has been provided and a sample of such a species has been obtained by altering the amine and aldehyde partners in the cascade process. Further studies have indicated that the relative stereochemistry of the natural products may be under thermodynamic control. The successful preparation of an array of natural and unnatural plakoridines will allow further assessment of the inhibitory properties of this unusual structural type towards DNA polymerases α and β.[15] The full results of these SAR studies will be reported in due course.

4. Experimental

4.1. General

Solvents were dried and distilled before use. Chromatography was performed over Merck silica gel 60 (40–63 μm). IR spectra were recorded on a Perkin–Elmer 881 spectrometer, an AT1-Mattson Genesis Series FTIR spectrometer or a JASCO FT/IR-4100 spectrometer. ^1H and ^{13}C spectra were recorded on a Varian Inova 400 MHz spectrometer, a Varian Inova 300 MHz spectrometer or a Bruker AMX 500 MHz spectrometer. Chemical shifts are referenced to the residual solvent peak. Mass spectra were recorded on a Micromas Trio 2000 quadrupole spectrometer (EI/CI, low resolution), a Thermo Finigan MAT 95 XP spectrometer (EI/CI, high resolution) and a Micromass Platform spectrometer (electrospray). Melting points were recorded using a Sanyo Gallenkamp MPD350 heater and are uncorrected.

For the purpose of consistency and clarity, the numbering scheme employed for the presentation of spectroscopic data for the plakoridine analogues is depicted in Figure 7 for compound **38**.

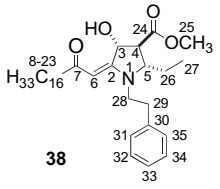


Figure 7.

4.2. Representative procedure for Friedel–Crafts acylation of 2-furanacetic acid methyl ester

4.2.1. (5-Dodecanoylfuran-2-yl)acetic acid methyl ester. A 1 M solution of tin tetrachloride in dichloromethane (43 mL, 43 mmol) was added dropwise via cannula to a solution of dodecanoyl chloride (8.2 mL, 35.5 mmol) in dichloromethane (10 mL) at −5 °C. The reaction mixture was stirred at this temperature for 45 min. A solution of 2-furanacetic acid methyl ester (**27**) (5.0 g, 35.5 mmol) in dichloromethane (10 mL) was then added dropwise over a period of 10 min and the reaction mixture was stirred at −5 °C for a further 45 min. The mixture was poured onto ice, stirred for 30 min and the resulting two-phase mixture was separated. The organic layer was washed with water, dried ($MgSO_4$) and then concentrated in vacuo. The residue was dissolved in diethyl ether and filtered through a pad of Celite® to remove tin residues. The filtrate was concentrated in vacuo to give the title compound as an orange solid (10.2 g, 89%); R_f 0.31 (petroleum ether:ethyl acetate, 6:1); mp 35.5–37.8 °C; ν_{max} (film)/cm^{-1} 2925s (C–H), 1746m (C═O, ester), 1679m (C═O, ketone), 1517m, 1464w, 1438w, 1264w, 1214m; δ_H (300 MHz, $CDCl_3$) 0.85 (3H, t, *J* 6.7, C(18)H_3), 1.24–1.29 (16H, m, C(10)H_2–C(17)H_2), 1.63–1.72 (2H, m, C(9)H_2), 2.74 (2H, t, *J* 7.5, C(8)H_2), 3.72 (3H, s, CO_2CH_3), 3.76 (2H, s, C(2)H_2), 6.39 (1H, d, *J* 3.0, C(4)*H*), 7.11 (1H, d, *J* 3.0, C(5)*H*); δ_C (75 MHz, $CDCl_3$) 14.3 (*C*(18)H_3), 22.9, 24.7, 29.57, 29.65, 29.7, 29.8, 32.1 (*C*(9)H_2 to *C*(17)H_2, some overlapping), 34.3 (*C*(2)H_2), 38.6 (*C*(8)H_2), 52.7 (CO_2CH_3), 111.1 (*C*(4)H), 118.5 (*C*(5)H), 152.5 (*C*(3) and *C*(6)), 169.0 (*C*(1)O), 189.6 (*C*(7)O); *m*/*z* (CI/NH_3) 340 ($[M+NH_4]^+$, 100%), 323 ($[M+H]^+$, 15), 199 (10); found 340.2484, $C_{19}H_{34}NO_4$ ($[M+NH_4]^+$) requires 340.2482.

4.2.2. Data for (5-acetylfuran-2-yl)acetic acid methyl ester. Pale yellow oil; R_f 0.21 (petroleum ether:diethyl ether, 1:1); ν_{max} (film)/cm^{-1} 3123w and 2955w (C–H), 1742s (C═O, ester), 1674s (C═O, ketone), 1517s, 1437m, 1296s, 1218s, 1019m; δ_H (300 MHz, $CDCl_3$) 2.37 (3H, s, C(8)H_3), 3.70 (3H, s, CO_2CH_3), 3.72 (2H, s, C(2)H_2), 6.37 (1H, d, *J* 3.6, C(4)*H*), 7.08 (1H, d, *J* 3.6, C(5)*H*); δ_C (75 MHz, $CDCl_3$) 26.0 (*C*(8)H_3), 34.2 (*C*(2)H_2), 52.6 (CO_2CH_3), 111.2 (*C*(4)H), 119.0 (*C*(5)H), 152.4, 152.8 (*C*(3) and *C*(6)), 168.9 (*C*(1)O), 186.5 (*C*(7)O); *m*/*z* (CI/NH_3) 200 ($[M+NH_4]^+$, 100%), 183($[M+H]^+$, 15).

4.2.3. Data for (5-hexadecanoylfuran-2-yl)acetic acid methyl ester. Orange solid; mp 65.4–66.7 °C; ν_{max} (solid state)/cm^{-1} 2918s and 2848s (C–H), 1732s (C═O, ester), 1664s (C═O, ketone), 1520m, 1217s; δ_H (300 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.7, C(22)H_3), 1.15–1.35 (24H, m, C(10)H_2 to C(21)H_2), 1.62–1.73 (2H, m, C(9)H_2), 2.75 (2H, t, *J* 7.5, C(8)H_2), 3.73 (3H, s, CO_2CH_3), 3.77 (2H, s, C(2)H_2), 6.40 (1H, d, *J* 3.3, C(4)*H*), 7.12 (1H, d, *J* 3.3, C(5)*H*); δ_C (75 MHz, $CDCl_3$) 14.3 (*C*(22)H_3), 22.9, 24.7, 29.5, 29.56, 29.59, 29.65, 29.7, 29.8, 29.89, 29.92, 32.1 (*C*(9)H_2 to *C*(21)H_2, some overlapping), 34.3 (*C*(2)H_2), 38.6 (*C*(8)H_2), 52.6 (CO_2CH_3), 111.1 (*C*(4)H), 118.5 (*C*(5)H), 152.4 and 152.5 (*C*(3) and *C*(6)), 169.0 (*C*(1)O), 189.7 (*C*(7)O); *m/z* (CI/NH_3) 396 ([M+NH_4]$^+$, 100%), 379 ([M+H]$^+$, 15) (+ve ion electrospray); found 378.2766, $C_{23}H_{38}O_4$ (M$^+$) requires 378.2765.

4.3. Representative procedure for the preparation of (5-alkylfuran-2-yl)acetic acids

4.3.1. (5-Dodecylfuran-2-yl)acetic acid (28b). A mixture of (5-dodecanoylfuran-2-yl)acetic acid methyl ester (10.2 g, 31.5 mmol) and hydrazine monohydrate (18.3 mL, 378 mmol) in ethylene glycol (85 mL) was heated under reflux for 1 h. Potassium hydroxide pellets (10.2 g, 181 mmol) were added cautiously and the reaction mixture was heated under reflux for a further 72 h and then allowed to cool. Water (40 mL) was added and the reaction mixture was heated to ~60 °C and stirred for 30 min. The reaction mixture was cooled to room temperature and acidified to pH 4 with 2 M aqueous hydrochloric acid solution. The product was extracted into diethyl ether (3×30 mL), the combined organic extracts were dried ($MgSO_4$) and then concentrated in vacuo. Purification by flash column chromatography (petroleum ether:ethyl acetate, 6:1) afforded the title compound as a colourless solid (4.38 g, 47%); R_f 0.24 (SiO_2; petroleum ether: ethyl acetate, 6:1); mp 56.3–57.5 °C; ν_{max} (film)/cm^{-1} 2918m (C–H), 1712m (C═O, carboxylic acid), 1467w, 1444w, 1254w, 1179w; δ_H (300 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.6, C(18)H_3), 1.21–1.31 (18H, m, C(9)H_2 to C(17)H_2), 1.57–1.67 (2H, m, C(8)H_2), 2.59 (2H, t, *J* 7.6, C(7)H_2), 3.69 (2H, s, C(2)H_2), 5.93 (1H, d, *J* 3.0, C(5)*H*), 6.13 (1H, d, *J* 3.0, C(4)*H*); δ_C (75 MHz, $CDCl_3$) 14.4 (*C*(18)H_3), 23.0, 28.2, 28.3, 29.4, 29.6, 29.8, 29.92, 29.94, 32.2 (*C*(7)H_2 to *C*(17)H_2, some overlapping), 34.2 (*C*(2)H_2), 105.8 (*C*(5)H), 109.2 (*C*(4)H), 145.0 and 156.8 (*C*(3) and *C*(6)), 176.3 (*C*(1)O); *m/z* (CI/NH_3) 312 ([M+NH_4]$^+$, 100%), 295 ([M+H]$^+$, 8), 250 (10), 95 (12); found 312.2532, $C_{18}H_{34}NO_3$ ([M+NH_4]$^+$) requires 312.2533.

4.3.2. (5-Ethylfuran-2-yl)acetic acid (28a) and (5-hexadecylfuran-2-yl)acetic acid (28c). Data for (5-ethylfuran-2-yl)acetic acid (**28a**) and (5-hexadecylfuran-2-yl)acetic acid (**28c**) were as described previously.[13]

4.4. Representative procedures for esterification of (5-alkylfuran-2-yl)acetic acids

4.4.1. Method 1: preparation of methyl ester derivatives.

4.4.1.1. (5-Dodecylfuran-2-yl)acetic acid methyl ester (29b). Amberlite® IR-120 (H) (4.20 g) was added to a solution of (5-dodecylfuran-2-yl)acetic acid (**28b**) (4.20 g, 14.2 mmol) in methanol (40 mL) and the reaction mixture was heated under reflux for 72 h. The resin was then removed by hot filtration and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2; petroleum ether:ethyl acetate, 25:1) furnished the title compound as a colourless oil (3.33 g, 76%); R_f 0.46 (petroleum ether:ethyl acetate, 25:1); ν_{max} (film)/cm^{-1} 2925s (C–H), 1745s (C═O, ester), 1463w, 1436w, 1268w, 1223w, 1141w; δ_H (300 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.7, C(18)H_3), 1.22–1.31 (18H, m, C(9)H_2 to C(17)H_2), 1.57–1.64 (2H, m, C(8)H_2), 2.58 (2H, t, *J* 7.6, C(7)H_2), 3.65 (2H, s, C(2)H_2), 3.73 (3H, s, CO_2CH_3), 5.91 (1H, d, *J* 3.0, C(5)*H*), 6.10 (1H, d, *J* 3.0, C(4)*H*); δ_C (75 MHz, $CDCl_3$) 14.4 (*C*(18)H_3), 23.0, 28.27, 28.30, 29.5, 29.62, 29.64, 29.8, 29.91, 29.94, 32.2 (*C*(7)H_2 to *C*(17)H_2, many overlapping), 34.3 (*C*(2)H_2), 52.5 (CO_2CH_3), 105.7 (*C*(5)H), 108.7 (*C*(4)H), 145.7 and 156.6 (*C*(3) and *C*(6)), 170.4 (*C*(1)O); *m/z* (CI/NH_3) 326 ([M+NH_4]$^+$, 100%), 309 ([M+H]$^+$, 13), 249 (3); found 326.2689, $C_{19}H_{36}NO_3$ ([M+NH_4]$^+$) requires 326.2690.

4.4.1.2. (5-Ethylfuran-2-yl)acetic acid methyl ester (29a) and plakorsin A (12). Data for (5-ethylfuran-2-yl)-acetic acid methyl ester (**29a**) and plakorsin A (**12**) were as described previously.[13]

4.4.2. Method 2: preparation of ethyl and isopropyl ester derivatives.

4.4.2.1. (5-Hexadecylfuran-2-yl)acetic acid ethyl ester (29c). A solution of (5-hexadecylfuran-2-yl)acetic acid (**28c**) (270 mg, 0.77 mmol), ethanol (54 mL, 0.93 mmol) and 4-dimethylaminopyridine (9 mg, 0.077 mmol) in dichloromethane (5.7 mL) was cooled to 0 °C. A solution of *N*,*N*′-dicyclohexylcarbodiimide (191 mg, 0.93 mmol) in dichloromethane (2 mL) was added and the reaction mixture was stirred at 0 °C for 1 h. The precipitated dicyclohexylurea was removed by filtration, washed with ice-cold dichloromethane and the filtrate was concentrated in vacuo. Residual dicyclohexylurea was removed by trituration with a minimum volume of ice-cold dichloromethane followed by filtration. Purification by flash column chromatography (SiO_2; petroleum ether:diethyl ether, 18:1) yielded the title compound as a colourless oil, which solidified on standing (286 mg, 98%); R_f 0.57 (petroleum ether:diethyl ether, 7:3); mp 33.4–34.1 °C; ν_{max} (film)/cm^{-1} 2921s and 2851s (C–H), 1742s (C═O, ester), 1567w, 1467m, 1218m, 1174m, 1138m; δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.7, C(22)H_3), 1.23–1.40 (26H, m, C(9)H_2 to C(21)H_2), 1.31 (3H, t, *J* 7.2, OCH_2CH_3), 1.60–1.70 (2H, m, C(8)H_2), 2.61 (2H, t, *J* 7.5, C(7)H_2), 3.66 (2H, s, C(2)H_2), 4.22 (2H, q, *J* 7.2, $CO_2CH_2CH_3$), 5.94 (1H, d, *J* 3.0, C(5)*H*), 6.13 (1H, d, *J* 3.0, C(4)*H*); δ_C (75 MHz, $CDCl_3$) 14.4 (*C*(22)H_3), 23.0, 28.3, 29.5, 29.7, 29.8, 29.96, 29.99, 32.2 (*C*(7)H_2 to *C*(21)H_2 and OCH_2CH_3, many overlapping), 34.5 (*C*(2)H_2), 61.3 ($CO_2CH_2CH_3$), 105.7 (*C*(5)H), 108.6 (*C*(4)H), 145.9 and 156.4 (*C*(3) and *C*(6)), 170.0 (*C*(1)O); *m/z* (CI/NH_3) 396 ([M+NH_4]$^+$, 100%), 379 ([M+H]$^+$, 70), 167 (40), 88 (45), 74 (80); found 396.3478, $C_{24}H_{46}O_3N$ ([M+NH_4]$^+$) requires 396.3472.

4.4.2.2. Data for (5-hexadecylfuran-2-yl)acetic acid isopropyl ester (29d). Colourless solid; R_f 0.69 (petroleum ether:diethyl ether, 7:3); mp 28.3–29.0 °C; ν_{max} (film)/cm^{-1} 2924s and 2853s (C–H), 1740s (C═O, ester), 1566w,

1466m, 1374w, 1266m, 1223m, 1179m, 1108s; δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.6, C(22)H_3), 1.23–1.37 (32H, m, C(9)H_2 to C(21)H_2 and OCH(CH_3)$_2$), 1.60–1.69 (2H, m, C(8)H_2), 2.61 (2H, t, *J* 7.6, C(7)H_2), 3.61 (2H, s, C(2)H_2), 5.08 (1H, septet, *J* 6.3, $CO_2CH(CH_3)_2$), 5.94 (1H, d, *J* 3.0, C(5)*H*), 6.12 (1H, d, *J* 3.0, C(4)*H*); δ_C (75 MHz, $CDCl_3$) 14.4 (*C*(22)H_3), 22.0 (OCH(*C*H_3)$_2$), 23.0, 28.3, 29.5, 29.7, 29.9, 30.0, 32.2 (*C*(7)H_2 to *C*(21)H_2, many overlapping), 34.9 (*C*(2)H_2), 68.7 (CO_2CH(CH$_3$)$_2$), 105.7 (*C*(5)H), 108.5 (*C*(4)H), 146.1, 156.3 (*C*(3) and *C*(6)), 169.5 (*C*(1)O); *m/z* (CI/NH_3) 410 ([M+NH_4]$^+$, 100%), 393 ([M+H]$^+$, 50), 305 (30), 96 (30); found 392.3279, $C_{25}H_{44}O_3$ (M^+) requires 392.3285.

4.5. One-pot procedure for the conversion of plakorsin A (12) to (+/−)-untenone A (3)

meta-Chloroperbenzoic acid (46 mg, 0.27 mmol) was added to a stirred solution of plakorsin A (**12**) (75 mg, 0.21 mmol) in dichloromethane (3 mL) at −10 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2.5 h when it was washed thoroughly with a saturated aqueous solution of sodium hydrogen carbonate (3×10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash column chromatography (SiO_2; petroleum ether:ethyl acetate, 9:1) furnished the title compound as a colourless solid (44 mg, 56%); analytical data were as described previously.[13]

4.6. Representative procedure for the oxidation of (5-alkylfuran-2-yl)acetates to give (*E*)-enediones

4.6.1. (2*Z*,4*E*)-3-Hydroxy-6-oxo-docosa-2,4-dienoic acid methyl ester (33). A solution of bromine (42 μL, 0.82 mmol) in a mixture of acetone and water (5:1, 1 mL) was added to a solution of plakorsin A (**12**) (300 mg, 0.82 mmol) in a mixture of acetone and water (5:1, 6.5 mL) at −20 °C. The reaction mixture was stirred at −20 °C for 3 h and then warmed to −10 °C. After a further 3 h, the reaction mixture was poured into diethyl ether (15 mL) and the resulting two-phase mixture was separated. The organic layer was washed with brine (3×10 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2; petroleum ether:ethyl acetate, 25:1) yielded the title compound as a colourless solid (196 mg, 63% [82% based on recovered starting material]); R_f 0.19 (petroleum ether:ethyl acetate, 25:1); mp 82.5–83.5 °C; ν_{max} (film)/cm^{-1} 3019m, 2927m and 2855m (C–H), 1659m (C=O, ketone), 1588m, 1216s; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.7, C(22)H_3), 1.21–1.36 (26H, m, C(9)H_2 to C(21)H_2), 1.59–1.68 (2H, m, C(8)H_2), 2.61 (2H, t, *J* 7.3, C(7)H_2), 3.79 (3H, s, CO_2CH_3), 5.34 (1H, s, C(2)*H*), 6.77 (1H, d, *J* 15.3, C(4)*H*), 6.93 (1H, d, *J* 15.3, C(5)*H*), 11.64 (1H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 14.4 (*C*(22)H_3), 23.0, 24.1, 29.5, 29.64, 29.67, 29.73, 29.9, 30.0, 32.2 (*C*(8)H_2 to *C*(21)H_2, many overlapping), 42.5 (*C*(7)H_2), 51.9 (CO_2CH_3), 96.9 (*C*(2)H), 132.0 (*C*(5)H), 134.5 (*C*(4)H), 166.7 (*C*(3)O), 171.6 (*C*(1)O), 200.0 (*C*(6)O); *m/z* (APCI) 379 ([M−H]$^-$, 70%), 348 ([M−CH_3OH]$^-$, 100); found 379.2841, $C_{23}H_{39}O_4$ [M−H]$^-$ requires 379.2854.

4.6.2. Data for (2*Z*,4*E*)-3-hydroxy-6-oxo-octa-2,4-dienoic acid methyl ester (34). Colourless crystals; mp 70.2–71.9 °C; R_f 0.45 (petroleum ether:ethyl acetate, 3:1); ν_{max} (solid state)/cm^{-1} 3070br w (O–H), 2976w and 2937w (C–H), 1657s (C=O, ketone), 1583s, 1446s, 1336s, 1188s; δ_H (300 MHz, $CDCl_3$) 1.12 (3H, t, *J* 7.3, C(8)H_3), 2.65 (2H, q, *J* 7.3, C(7)H_2), 3.78 (3H, s, CO_2CH_3), 5.34 (1H, s, C(2)*H*), 6.78 (1H, dd, *J* 15.7, 1.5, C(4)*H*), 6.92 (1H, d, *J* 15.7, C(5)*H*), 11.60 (1H, d, *J* 1.5, O*H*); δ_C (75 MHz, $CDCl_3$) 8.0 (*C*(8)H_3), 35.6 (*C*(7)H_2), 51.9 (CO_2CH_3), 96.9 (*C*(2)H), 131.8 (*C*(5)H), 134.5 (*C*(4)H), 166.7 (*C*(3)O), 172.5 (*C*(1)O), 200.4 (*C*(6)O); *m/z* (CI/NH_3) 202 ([M+NH_4]$^+$, 100%), 185 ([M+H]$^+$, 22); found 184.0729, $C_9H_{12}O_4$ (M^+) requires 184.0730.

4.6.3. Data for (2*Z*,4*E*)-3-hydroxy-6-oxo-octadeca-2,4-dienoic acid methyl ester (35). Colourless solid; R_f 0.16 (petroleum ether:ethyl acetate, 25:1); mp 74.5–75.0 °C; ν_{max} (film)/cm^{-1} 3453br w (O–H), 3019s and 2927s (C–H), 1710m (C=O, ester), 1658m (C=O, ketone), 1588m, 1447m, 1216s; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.6, C(18)H_3), 1.19–1.30 (18H, m, C(9)H_2 to C(17)H_2), 1.58–1.66 (2H, m, C(8)H_2), 2.60 (2H, t, *J* 7.3, C(7)H_2), 3.79 (3H, s, CO_2CH_3), 5.34 (1H, s, C(2)*H*), 6.80 (1H, dd, *J* 15.6, 1.6, C(4)*H*), 6.93 (1H, d, *J* 15.6, C(5)*H*), 11.61 (1H, d, *J* 1.6, O*H*); δ_C (75 MHz, $CDCl_3$) 14.4 (*C*(18)H_3), 23.0, 24.2, 29.5, 29.6, 29.66, 29.73, 29.90, 29.92, 32.2, 42.5 (*C*(8)H_2, to *C*(17)H_2), 47.9 (*C*(7)H_2), 52.0 (CO_2CH_3), 97.0 (*C*(2)H), 132.0 (*C*(5)H), 134.6 (*C*(4)H), 166.7 (*C*(3)O), 172.6 (*C*(1)O), 200.0 (*C*(6)O); *m/z* (CI/NH_3) 342 ([M+NH_4]$^+$, 75%), 325 ([M+H]$^+$, 35); found 324.2294, $C_{19}H_{32}O_4$ (M^+) requires 324.2295.

4.6.4. Data for (2*Z*,4*E*)-3-hydroxy-6-oxo-docosa-2,4-dienoic acid isopropyl ester (36). Colourless solid; R_f 0.23 (petroleum ether:ethyl acetate, 25:1); mp 85.1–86.9 °C; ν_{max}(KBr disc)/cm^{-1} 2914s and 2849s (C–H), 1695m (C=O, ester), 1640s (C=O, ketone), 1590s, 1473s, 1375m, 1239s, 1110m; δ_H (300 MHz, $CDCl_3$) 0.91 (3H, t, *J* 6.6, C(22)H_3), 1.22–1.40 (26H, m, C(9)H_2 to C(21)H_2), 1.32 (6H, d, *J* 6.3, OCH(CH_3)$_2$), 1.62–1.71 (2H, m, C(8)H_2), 2.63 (2H, t, *J* 7.4, C(7)H_2), 5.15 (1H, septet, *J* 6.3, $CO_2CH(CH_3)_2$), 5.32 (1H, s, C(2)*H*), 6.80 (1H, dd, *J* 15.6, 1.5, C(4)*H*), 6.95 (1H, d, *J* 15.6, C(5)*H*), 11.80 (1H, d, *J* 1.5, O*H*); δ_C (75 MHz, $CDCl_3$) 14.4 (*C*(22)H_3), 22.1 (OCH(*C*H_3)$_2$), 23.0, 24.2, 29.5, 29.63, 29.67, 29.7, 29.8, 29.93, 29.96, 32.2 (*C*(8)H_2 to *C*(21)H_2, some overlapping), 42.5 (*C*(7)H_2), 68.7 (CO_2CH(CH$_3$)$_2$), 97.8 (*C*(2)H), 131.7 (*C*(5)H), 134.7 (*C*(4)H), 166.5 (*C*(3)O), 171.9 (C(1)O), 200.2 (*C*(6)O); *m/z* (−ve ion electrospray) 407 ([M−H]$^-$, 100%), 273 (80) (+ve ion electrospray); found 431.3132, $C_{25}H_{44}O_4Na$ [M+Na]$^+$ requires 431.3132.

4.7. Representative procedures for the preparation of plakoridine analogues using isolated imines

Imines were prepared and isolated using one of the two alternative procedures.

4.7.1. Method A. The amine (1 equiv) was added to a rapidly stirred mixture of the appropriate aldehyde (1 equiv) and water (*c*=0.85 M). The resulting suspension was stirred at room temperature for 3 h and the reaction mixture was

then extracted three times with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to yield the required imine, which was used, when required, without further purification.

4.7.2. Method B. The amine (1 equiv) was added to a 0.03 M solution of the appropriate aldehyde (1 equiv) in dichloromethane. The reaction mixture was stirred at room temperature for 3 h when $MgSO_4$ was added and the reaction mixture was stirred for a further 30 min. The magnesium sulfate was removed by filtration and the filtrate was concentrated in vacuo to yield the required imine, which was used, when required, without further purification.

4.7.3. (3*R,4*S**,5*S**)-1-(2-(1*H*-Indol-3-yl)-ethyl)-2-(2′-oxo-octadec-*E*-ylidene)-3-hydroxy-5-phenyl-pyrrolidine-4-carboxylic acid methyl ester (44).** A solution of benzylidine-2-(1*H*-indol-3-yl)ethylamine (76 mg, 0.31 mmol) in deuterochloroform (1.0 mL) was added to (2*Z*,4*E*)-3-hydroxy-6-oxo-docosa-2,4-dienoic acid methyl ester (**33**) (117 mg, 0.31 mmol). The reaction mixture was stirred at room temperature for 10 days and then concentrated in vacuo. Purification by flash column chromatography (SiO_2; petroleum ether:ethyl acetate, 4:1) yielded the title compound as a pale yellow oil (74 mg, 38%); R_f 0.13 (petroleum ether:ethyl acetate, 3:1); ν_{max} (film)/cm^{-1} 3300br (O–H), 2923s and 2852s (C–H), 1739s (C=O, ester), 1618m (C=O, vinylogous amide), 1526s, 1458s, 1250m, 1173m; δ_H (300 MHz, $CDCl_3$) 0.93 (3H, t, *J* 6.8, C(23)H_3), 1.24–1.42 (26H, m, C(10)H_2 to C(22)H_2), 1.61–1.71 (2H, m, C(9)H_2), 2.38 (2H, ~t, *J* 7.8, C(8)H_2), 2.81–2.91 (1H, m, one of C(33)H_2), 3.04–3.22 (2H, m, one of C(32)H_2 and one of C(33)H_2), 3.23 (1H, ~t, *J* 7.1, C(4)*H*), 3.44–3.54 (1H, m, one of C(32)H_2), 3.71 (3H, s, CO_2CH_3), 4.63 (1H, d, *J* 7.5, C(5)*H*), 5.25 (1H, s, C(6)*H*), 5.34 (1H, d, *J* 6.6, C(3)*H*), 6.96 (1H, d, *J* 2.4, C(35)*H*), 7.08–7.42 (9H, m, C(27)*H* to C(31)*H* and C(38)*H* to C(41)*H*), 7.46 (1H, br s, O*H*), 8.34 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 14.4 (*C*(23)H_3), 21.6 (*C*(33)H_2), 23.0, 26.6, 29.7, 29.87, 29.96, 30.0, 32.2 (*C*(9)H_2 to *C*(22)H_2, many overlapping), 44.8 (*C*(8)H_2), 45.5 (*C*(32)H_2), 52.8 (CO_2CH_3), 57.0 (*C*(4)H), 69.5 (*C*(5)H), 76.1 (*C*(3)H), 90.9 (*C*(6)H), 111.7, 112.1, 118.5, 119.8, 122.52, 122.55, 127.2, 128.2, 129.3, 129.4 (*C*(27)H and *C*(31)H, *C*(28)H and *C*(30)H, *C*(29)H, *C*(35)H, *C*(38)H to *C*(41)H and 2× quaternary), 136.6, 138.4 (2×quaternary), 166.2 (*C*(2)), 172.2 (*C*(24)O), 200.6 (*C*(7)O); *m/z* (+ve ion electrospray) 651 ([M+Na]$^+$, 73%), 629 ([M+H]$^+$, 55), 196 (55); found 629.4323, $C_{40}H_{57}N_2O_4$ ([M+H]$^+$), requires 629.4313.

4.7.4. Data for (3*R,4*S**,5*S**)-1-phenethyl-2-(2′-oxo-octadec-*E*-ylidene)-3-hydroxy-5-phenylpyrrolidine-4-carboxylic acid methyl ester (45).** A pale yellow oil; R_f 0.47 (petroleum ether:ethyl acetate, 3:1); ν_{max} (film)/cm^{-1} 3426m (O–H), 2924s and 2853s (C–H), 1741m (C=O, ester), 1626w (C=O, vinylogous amide), 1528m, 1458m; δ_H (500 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.0, C(23)H_3), 1.18–1.27 (26H, m, C(10)H_2 to C(22)H_2), 1.54–1.60 (2H, m, C(9)H_2), 2.34 (2H, ~td, *J* 7.0, 2.5, C(8)H_2), 2.56 (1H, ddd, *J* 13.8, 8.5, 5.0, one of C(33)H_2), 2.76–2.82 (1H, m, one of C(33)H_2), 2.94–3.00 (1H, m, one of C(32)H_2), 3.12 (1H, ~t, *J* 7.0, C(4)*H*), 3.30 (1H, ddd, *J* 13.8, 9.0, 5.0, one of C(32)H_2), 3.63 (3H, s, CO_2CH_3), 4.47 (1H, d, *J* 7.2, C(5)*H*), 5.13 (1H, s, C(6)*H*), 5.22 (1H, d, *J* 6.6, C(3)*H*), 6.94–6.96 (2H, m, Ar-C*H*), 7.14–7.33 (8H, m, Ar-C*H*); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(23)H_3), 22.8, 25.4, 29.5, 29.7, 29.8, 31.5 (*C*(9)H_2 to *C*(22)H_2, many overlapping), 32.0 (*C*(33)H_2), 43.7 (*C*(8)H_2), 46.3 (*C*(32)H_2), 52.6 (*C*(4)H), 56.7 (CO_2CH_3), 69.3 (*C*(5)H), 75.7 (*C*(3)H), 90.8 (*C*(6)H), 126.8 (Ar-*C*H), 127.8 (Ar-*C*H), 128.6 (Ar-*C*H), 128.7 (Ar-*C*H), 129.0 (Ar-*C*H), 129.1 (Ar-*C*H), 137.9, 138.1 (*C*(26) and *C*(34)), 165.6 (*C*(2)), 171.7 (*C*(24)O), 200.1 (*C*(7)O); *m/z* (+ve ion electrospray) 590 ([M+H]$^+$, 100%); found 590.4203, $C_{34}H_{56}NO_4$ ([M+H]$^+$), requires 590.4204.

4.7.5. Data for (3*R,4*S**,5*S**)-1-phenethyl-2-(2′-oxo-octadec-*E*-ylidene)-3-hydroxy-5-pentadecylpyrrolidine-4-carboxylic acid methyl ester (46).** A pale yellow oil; R_f 0.21 (petroleum ether:ethyl acetate, 9:1); ν_{max} (film)/cm^{-1} 3225br (O–H), 2925s, 2853s, 1741s (C=O, ester), 1626m (C=O, vinylogous amide), 1538s, 1466m, 1172w; δ_H (500 MHz, $CDCl_3$) 0.81 (6H, ~t, *J* 6.8, C(23)H_3 and C(40)H_3), 1.10–1.30 (52H, m, C(10)H_2 to C(22)H_2 and C(27)H_2 to C(39)H_2), 1.40–1.47 (1H, m, one of C(26)H_2), 1.51–1.56 (2H, m, C(9)H_2), 1.65–1.70 (1H, m, one of C(26)H_2), 2.29 (2H, td, *J* 7.8, 2.8, C(8)H_2), 2.75 (1H, ddd, *J* 14.4, 8.9, 5.8, one of C(42)H_2), 2.81–2.87 (1H, m, one of C(42)H_2), 2.84 (1H, ~t, *J* 5.7, C(4)*H*), 3.26 (1H, ddd, *J* 14.4, 8.9, 5.8, one of C(41)H_2), 3.39 (1H, ddd, *J* 14.4, 8.9, 5.8, one of C(41)H_2), 3.63–3.76 (1H, m, C(5)*H*), 3.67 (3H, s, CO_2CH_3), 5.03 (1H, br s, C(6)*H*), 5.13 (1H, d, *J* 5.7, C(3)*H*), 6.89 (1H, br s, O*H*), 7.11 (2H, d, *J* 7.4, C(44)*H* and C(48)*H*), 7.18 (1H, t, *J* 7.4, C(46)*H*), 7.25 (2H, t, *J* 7.4, C(45)*H* and C(47)*H*); δ_C (75 MHz, $CDCl_3$) 14.4 (*C*(23)H_3 and *C*(40)H_3, coincident), 23.0, 24.5, 26.5, 29.6, 29.7, 29.79, 29.84, 29.88, 29.9, 30.0, 32.2, 32.4, 33.3 (*C*(9)H_2 to *C*(22)H_2, *C*(26)H_2 to *C*(39)H_2 and *C*(42)H_2, many overlapping), 43.8 (*C*(8)H_2), 46.2 (*C*(41)H_2), 52.5 (*C*(4)H), 52.8 (CO_2CH_3), 65.6 (*C*(5)H), 76.1 (*C*(3)H), 90.0 (*C*(6)H), 127.2 (*C*(46)H), 128.9 (*C*(44)H and *C*(48)H), 129.1 (*C*(45)H and *C*(47)H), 138.3 (*C*(43)), 165.9 (*C*(2)), 173.0 (*C*(24)O), 200.0 (*C*(7)O); *m/z* (+ve ion electrospray) 746 ([M+Na]$^+$, 100%), 724 ([M+H]$^+$, 93); found 724.6229, $C_{47}H_{82}NO_4$ ([M+H]$^+$) requires 724.6238.

4.7.6. Data for (3*R,4*S**,5*S**)-1-(2-(1*H*-indol-3-yl)-ethyl)-2-(2′-oxo-octadec-*E*-ylidene)-3-hydroxy-5-pentadecylpyrrolidine-4-carboxylic acid methyl ester (47).** A pale yellow oil; R_f 0.25 (petroleum ether:ethyl acetate, 3:1); ν_{max} (film)/cm^{-1} 3300br (O–H), 2923s and 2852s (C–H), 1739m (C=O, ester), 1618w (C=O, vinylogous amide), 1526s, 1465m; δ_H (500 MHz, $CDCl_3$) 0.81 (6H, ~t, *J* 6.9, C(23)H_3 and C(40)H_3), 1.10–1.26 (52H, m, C(10)H_2 to C(22)H_2 and C(27)H_2 to C(39)H_2), 1.40–1.51 (3H, m, C(9)H_2 and one of C(26)H_2), 1.64–1.70 (1H, m, one of C(26)H_2), 2.18 (2H, t, *J* 7.6, C(8)H_2), 2.83 (1H, ~t, *J* 6.1, C(4)*H*), 2.89–2.94 (1H, m, one of C(42)H_2), 3.00–3.06 (1H, m, one of C(42)H_2), 3.33–3.39 (1H, m, one of C(41)H_2), 3.46–3.52 (1H, m, one of C(41)H_2), 3.66 (3H, s, CO_2CH_3), 3.69 (1H, ddd, *J* 8.9, 6.1, 2.8, C(5)*H*), 5.00 (1H, s, C(6)*H*), 5.12 (1H, d, *J* 6.1, C(3)*H*), 6.94 (1H, d, *J* 2.4, C(44)*H*), 7.00 (1H, br s, O*H*), 7.09 (1H, t, *J* 7.6, C(48)*H* or C(49)*H*), 7.15 (1H, t, *J* 7.6, C(48)*H* or C(49)*H*), 7.31 (1H, d, *J* 7.6, C(47)*H* or C(50)*H*), 7.52 (1H, d, *J* 7.6, C(47)*H* or C(50)*H*), 8.06 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 14.4 (*C*(23)H_3 and *C*(40)H_3, coincident), 22.2, 23.0, 24.5, 26.6, 29.6, 29.7, 29.81, 29.83, 29.9, 29.95, 29.99, 32.2, 33.3

($C(9)H_2$ to $C(22)H_2$, $C(26)H_2$ to $C(39)H_2$ and $C(42)H_2$, many overlapping), 43.7 ($C(8)H_2$), 45.0 ($C(41)H_2$), 52.6 ($C(4)$H), 52.8 (CO_2CH_3), 65.5 ($C(5)$H), 76.3 ($C(3)$H), 90.4 ($C(6)$H), 111.7, 112.3, 118.5, 120.0, 122.5, 122.7, 127.3, 136.6 ($C(43)$, C(44)H, $C(46)$, $C(47)$H to $C(50)$H and $C(51)$), 166.2 ($C(2)$), 173.2 ($C(24)$O), 200.0 ($C(7)$O); *m/z* (+ve ion electrospray) 785 ($[M+Na]^+$, 100%); found 785.6165, $C_{49}H_{82}N_2O_4Na$ ($[M+Na]^+$) requires 785.6167.

4.7.7. Data for (3*R,4*S**,5*S**)-1-phenethyl-2-(2′-oxo-octadec-*E*-ylidene)-3-hydroxy-5-ethylpyrrolidine-4-carboxylic acid isopropyl ester (48).** A pale yellow oil; R_f 0.16 (petroleum ether:ethyl acetate, 9:1); ν_{max} (film)/cm^{-1} 3222br (O–H), 2924s and 2853s (C–H), 1732s (C=O, ester), 1625m (C=O, vinylogous amide), 1535s, 1466s, 1249m, 1180m, 1107s; δ_H (300 MHz, $CDCl_3$) 0.79–0.84 (6H, m, C(23)H_3 and C(26)H_3), 1.10–1.28 (32H, m, C(10)H_2 to C(22)H_2 and $OCH(CH_3)_2$), 1.48–1.57 (3H, m, C(9)H_2 and one of C(25)H_2), 1.72–1.80 (1H, m, one of C(25)H_2), 2.29 (2H, td, *J* 7.5, 3.2, C(8)H_2), 2.72–2.78 (1H, m, one of C(28)H_2), 2.77 (1H, ~t, *J* 6.0, C(4)*H*), 2.84 (1H, ddd, *J* 14.4, 9.0, 4.5, one of C(28)H_2), 3.25 (1H, ddd, *J* 14.4, 9.0, 4.5, one of C(27)H_2), 3.40 (1H, ddd, *J* 14.4, 9.0, 4.5, one of C(27)H_2), 3.58–3.62 (1H, m, C(5)*H*), 4.98 (1H, septet, *J* 6.2, $CO_2CH(CH_3)_2$), 5.03 (1H, br s, C(6)*H*), 5.13 (1H, d, *J* 6.0, C(3)*H*), 6.88 (1H, br s, O*H*), 7.12 (2H, d, *J* 7.0, C(30)*H* and C(34)*H*), 7.17–7.20 (1H, m, C(32)*H*), 7.26 (2H, d, *J* 7.0, C(31)*H* and C(33)*H*); δ_C (75 MHz, $CDCl_3$) 8.7, 14.4 ($C(23)H_3$ and $C(26)H_3$), 21.9, 22.0, 23.0, 25.9, 26.5, 29.4, 29.82, 29.85, 29.9, 30.0, 32.2, 32.3 ($C(9)H_2$ to $C(22)H_2$, $OCH(CH_3)_2$, $C(25)H_2$ and $C(28)H_2$, many overlapping), 43.7 ($C(8)H_2$), 46.1 ($C(27)H_2$), 52.4 ($C(4)$H), 66.7 ($C(5)$H), 69.3 ($CO_2CH(CH_3)_2$), 76.0 ($C(3)$H), 90.5 ($C(6)$H), 127.2 ($C(32)$H), 128.9 ($C(30)$H and $C(34)$H), 129.1 ($C(31)$H and $C(33)$H), 138.3 ($C(29)$), 166.3 ($C(2)$), 172.1 ($C(24)$O), 200.0 ($C(7)$O); *m/z* (+ve ion electrospray) 592 ($[M+Na]^+$, 13%), 570 ($[M+H]^+$, 100); found 570.4509, $C_{36}H_{60}NO_4$ ($[M+H]^+$) requires 570.4517.

4.7.8. Data for (3*R,4*S**,5*S**)-1-phenethyl-2-(2′-oxo-tetradec-*E*-ylidene)-3-hydroxy-5-phenylpyrrolidine-4-carboxylic acid methyl ester (49).** A pale yellow oil; R_f 0.19 (petroleum ether:ethyl acetate, 5:1); ν_{max} (film)/cm^{-1} 3255br (O–H), 2924s and 2852s (C–H), 1739s (C=O, ester), 1625m (C=O, vinylogous amide), 1533s, 1457m, 1251m; δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.6, C(19)H_3), 1.24–1.41 (18H, m, C(10)H_2 to C(18)H_2), 1.64–1.73 (2H, m, C(9)H_2), 2.43–2.48 (2H, m, C(8)H_2), 2.67 (1H, ddd, *J* 13.8, 8.7, 5.0, one of C(29)H_2), 2.86–2.96 (1H, m, one of C(29)H_2), 3.00–3.13 (1H, m, one of C(28)H_2), 3.23 (1H, ~t, *J* 6.9, C(4)*H*), 3.41 (1H, ddd, *J* 13.8, 8.7, 5.0, one of C(28)H_2), 3.74 (3H, s, CO_2CH_3), 4.59 (1H, d, *J* 6.9, C(5)*H*), 5.25 (1H, s, C(6)*H*), 5.33 (1H, d, *J* 6.9, C(3)*H*), 7.05–7.08 (2H, m, 2×aromatic C*H*), 7.25–7.43 (8H, m, 8×aromatic C*H*); δ_C (75 MHz, $CDCl_3$) 14.4 ($C(19)H_3$), 23.0, 26.6, 29.6, 29.8, 29.9, 30.0, 31.7, 32.2 ($C(9)H_2$ to $C(18)H_2$ and $C(29)H_2$, some overlapping), 43.9 ($C(8)H_2$), 46.5 ($C(28)H_2$), 52.8 (CO_2CH_3), 56.9 ($C(4)$H), 69.6 ($C(5)$H), 76.0 ($C(3)$H), 91.0 ($C(6)$H), 127.1, 128.1, 128.9, 129.1, 129.4 ($C(23)$H and $C(27)$H, $C(24)$H and $C(26)$H, $C(25)$H, $C(31)$H and $C(35)$H, $C(32)$H and $C(34)$H and $C(33)$H), 138.2, 138.5 ($C(22)$ and $C(30)$), 165.9 ($C(2)$), 172.1 ($C(20)$O), 200.5 ($C(7)$O); *m/z* (+ve ion electrospray) 556 ($[M+Na]^+$, 100%); found 556.3405, $C_{34}H_{47}NO_4Na$ ($[M+Na]^+$) requires 556.3397.

4.7.9. Data for (3*R,4*S**,5*S**)-1-(2-(1*H*-indol-3-yl)-ethyl)-2-(2′-oxo-tetradec-*E*-ylidene)-3-hydroxy-5-phenyl-pyrrolidine-4-carboxylic acid methyl ester (50).** A yellow oil; R_f 0.47 (petroleum ether:ethyl acetate, 3:1); ν_{max} (film)/cm^{-1} 3326br (O–H), 2924s and 2852m (C–H), 1738s (C=O, ester), 1618w (C=O, vinylogous amide), 1525s, 1457m, 1437w, 1250w; δ_H (300 MHz, $CDCl_3$) 0.94 (3H, t, *J* 6.6, C(19)H_3), 1.25–1.40 (18H, m, C(10)H_2 to C(18)H_2), 1.62–1.70 (2H, m, C(9)H_2), 2.38 (2H, t, *J* 7.6, C(8)H_2), 2.82–2.93 (1H, m, one of C(29)H_2), 3.05–3.24 (2H, m, one of C(28)H_2 and one of C(29)H_2), 3.24 (1H, ~t, *J* 7.2, C(4)*H*), 3.45–3.58 (1H, m, one of C(28)H_2), 3.72 (3H, s, CO_2CH_3), 4.63 (1H, d, *J* 7.2, C(5)*H*), 5.25 (1H, s, C(6)*H*), 5.35 (1H, d, *J* 6.3, C(3)*H*), 7.00 (1H, d, *J* 2.1, C(31)*H*), 7.10–7.43 (10H, m, C(23)*H* to C(27)*H*, C(34)*H* to C(37)*H* and O*H*), 8.35 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$) 14.4 ($C(19)H_3$), 21.6 ($C(29)H_2$), 23.0, 26.6, 29.7, 29.9, 29.96, 29.99, 32.2 ($C(9)H_2$ to $C(18)H_2$, some overlapping), 43.8 ($C(8)H_2$), 45.5 ($C(28)H_2$), 52.8 (CO_2CH_3), 57.0 ($C(4)$H), 69.5 ($C(5)$H), 76.1 ($C(3)$H), 90.9 ($C(6)$H), 111.7, 112.1, 118.5, 119.8, 122.6, 127.3, 128.2, 129.3, 129.4 ($C(23)$H and $C(27)$H, $C(24)$H and $C(26)$H, $C(25)$H, $C(34)$H, $C(35)$H, $C(36)$H, $C(37)$H and 2×quaternary *C*), 136.6, 138.4 (2×quaternary *C*), 166.3 ($C(2)$), 172.3 ($C(20)$O), 200.6 ($C(7)$O); *m/z* (+ve ion electrospray) 595 ($[M+Na]^+$, 20%), 573 ($[M+H]^+$, 70), 295 (25); found 573.3689, $C_{36}H_{49}N_2O_4$ ($[M+H]^+$) requires 573.3687.

4.7.10. Data for (3*R,4*S**,5*S**)-1-phenethyl-2-(2′-oxo-tetradec-*E*-ylidene)-3-hydroxy-5-ethylpyrrolidine-4-carboxylic acid methyl ester (51).** A yellow oil; R_f 0.47 (petroleum ether:ethyl acetate, 3:1); ν_{max} (film)/cm^{-1} 2924s and 2853s (C–H), 1740s (C=O, ester), 1624m (C=O, vinylogous amide), 1535s, 1463m, 1248w; δ_H (300 MHz, $CDCl_3$) 0.93 (3H, t, *J* 6.9, C(19)H_3 or C(23)H_3), 0.94 (3H, t, *J* 7.5, C(19)H_3 or C(23)H_3), 1.26–1.37 (18H, m, C(10)H_2 to C(18)H_2), 1.61–1.71 (3H, m, C(9)H_2 and one of C(22)H_2), 1.82–1.93 (1H, m, one of C(22)H_2), 2.39–2.45 (2H, m, C(8)H_2), 2.87 (1H, ddd, *J* 14.8, 9.0, 5.8, one of C(25)H_2), 2.93–3.02 (1H, m, one of C(25)H_2), 2.96 (1H, ~t, *J* 6.0, C(4)*H*), 3.37 (1H, ddd, *J* 14.8, 9.0, 5.8, one of C(24)H_2), 3.53 (1H, ddd, *J* 14.8, 9.0, 5.8, one of C(24)H_2), 3.74–3.82 (1H, m, C(5)*H*), 3.80 (3H, s, CO_2CH_3), 5.16 (1H, s, C(6)*H*), 5.26 (1H, d, *J* 6.0, C(3)*H*), 7.23–7.42 (5H, m, C(27)*H* to C(31)*H*); δ_C (75 MHz, $CDCl_3$) 8.6, 14.4 ($C(19)H_3$ and $C(23)H_3$), 23.0, 25.7, 26.6, 29.4, 29.8, 29.9, 30.0, 32.2, 32.3 ($C(9)H_2$ to $C(18)H_2$, $C(22)H_2$ and $C(25)H_2$, some overlapping), 43.8 ($C(8)H_2$), 46.1 ($C(24)H_2$), 51.9 ($C(4)$H), 52.8 (CO_2CH_3), 66.3 ($C(5)$H), 76.0 ($C(3)$H), 90.6 ($C(6)$H), 127.2 ($C(29)$H), 128.9 (either $C(27)$H and $C(31)$H or $C(28)$H and $C(30)$H), 129.1 (either $C(27)$H and $C(31)$H or $C(28)$H and $C(30)$H), 138.2 (C(26)), 166.1 ($C(2)$), 173.0 ($C(20)$O), 200.1 ($C(7)$O); *m/z* (+ve ion electrospray) 508 ($[M+Na]^+$, 90%), 486 ($[M+H]^+$, 100), 417, (10), 212 (38); found 486.3574, $C_{30}H_{48}NO_4$ ($[M+H]^+$) requires 486.3578.

4.7.11. Data for (3*R,4*S**,5*S**)-1-benzyl-2-(2′-oxo-tetradec-*E*-ylidene)-3-hydroxy-5-phenylpyrrolidine-4-carboxylic acid methyl ester (52).** A pale yellow oil

contaminated with <10% of a minor diastereoisomer; R_f 0.50 (petroleum ether:ethyl acetate, 3:1); ν_{max} (film)/cm^{-1} 2925s and 2853m (C–H), 1739m (C=O, ester), 1628w (C=O, vinylogous amide), 1535s, 1457m, 1250w; δ_H (300 MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.6, C(19)H_3), 1.24–1.37 (18H, m, C(10)H_2 to C(18)H_2), 1.47–1.65 (2H, m, C(9)H_2), 2.36–2.41 (2H, m, C(8)H_2), 3.21 (1H, ~t, *J* 6.4, C(4)*H*), 3.75 (3H, s, CO_2CH_3), 3.97 (1H, d, *J* 16.1, one of C(28)H_2), 4.48 (1H, d, *J* 16.1, one of C(28)H_2), 4.89 (1H, d, *J* 6.4, C(5)*H*), 5.34 (1H, s, C(6)*H*), 5.41 (1H, d, *J* 6.4, C(3)*H*), 7.07–7.43 (11H, m, C(23)*H* to C(27)*H* and C(30)*H* to C(34)*H* and O*H*); δ_C (75 MHz, $CDCl_3$) 14.4 (*C*(19)H_3), 23.0, 26.4, 29.6, 29.7, 29.8, 29.9, 32.2 (*C*(9)H_2 to *C*(18)H_2), 43.9 (*C*(8)H_2), 48.3 (*C*(28)H_2), 52.9 (CO_2CH_3), 56.7 (*C*(4)H), 69.2 (*C*(5)H), 76.1 (*C*(3)H), 91.6 (*C*(6)H), 127.4, 128.1, 128.2, 129.1, 129.3, 129.4 (*C*(23)H and *C*(27)H, *C*(24)H and *C*(26)H, *C*(25)H, *C*(30)H and *C*(34)H, *C*(31)H and *C*(33)H and *C*(32)H), 134.6, 138.3 (*C*(22) and *C*(29)), 166.6 (*C*(2)), 172.4 (*C*(20)O), 201.0 (*C*(7)O); *m/z* (+ve ion electrospray) 520 ([M+H]$^+$, 100%); found 520.3422, $C_{33}H_{46}NO_4$ [M+H]$^+$ requires 520.3421.

4.7.12. Data for (3*R,4*S**,5*S**)-1-benzyl-2-(2′-oxo-but-*E*-ylidene)-3-hydroxy-5-phenylpyrrolidine-4-carboxylic acid methyl ester (53).** A pale yellow oil; R_f 0.12 (petroleum ether:ethyl acetate, 5:1); ν_{max} (film)/cm^{-1} 3185br (O–H), 2972m (C–H), 1737s (C=O, ester), 1628m (C=O, vinylogous amide), 1535s, 1457s, 1251m; δ_H (300 MHz, $CDCl_3$) 1.13 (3H, t, *J* 7.5, C(9)H_3), 2.43 (2H, q, *J* 7.4, C(8)H_2), 3.32 (1H, ~t, *J* 6.0, C(4)*H*), 3.75 (3H, s, CO_2CH_3), 3.97 (1H, d, *J* 15.9, one of C(18)H_2), 4.48 (1H, d, *J* 15.9, one of C(18)H_2), 4.90 (1H, d, *J* 6.6, C(5)*H*), 5.34 (1H, s, C(6)*H*), 5.41 (1H, d, *J* 6.0, C(3)*H*), 7.07–7.10 (2H, m, 2×aromatic C*H*), 7.15 (1H, br s, O*H*), 7.29–7.43 (8H, m, 8×aromatic C*H*); δ_C (75 MHz, $CDCl_3$) 36.7 (*C*(8)H_2), 48.3 (*C*(18)H_2), 52.9 (CO_2CH_3), 56.7 (*C*(4)H), 69.2 (*C*(5)H), 76.1 (*C*(3)H), 91.1 (*C*(6)H), 127.4, 128.1, 129.1, 129.3, 129.4 (*C*(13)H and *C*(17)H, *C*(14)H and *C*(16)H, *C*(15)H, *C*(20)H and *C*(24)H, *C*(21)H and *C*(23)H and *C*(22)H), 134.6, 138.3 (*C*(12) and *C*(19)), 166.5 (*C*(2)), 172.4 (*C*(10)O), 201.3 (*C*(7)O); *m/z* (+ve ion electrospray) 402 ([M+Na]$^+$, 15%), 380 ([M+H]$^+$, 12); found 380.1863, $C_{23}H_{26}NO_4$ ([M+H]$^+$) requires 380.1856.

4.7.13. Data for (3*R,4*S**,5*S**)-1-phenethyl-2-(2′-oxo-but-*E*-ylidene)-3-hydroxy-5-pentadecylpyrrolidine-4-carboxylic acid methyl ester (54).** A pale yellow oil; R_f 0.25 (petroleum ether:ethyl acetate, 5:1); ν_{max} (film)/cm^{-1} 3205br (O–H), 2925s and 2854m (C–H), 1740s (C=O, ester), 1627m (C=O, vinylogous amide), 1537s, 1466s, 1172m; δ_H (500 MHz, $CDCl_3$) 0.67 (3H, t, *J* 7.0, C(26)H_3), 0.92 (3H, t, *J* 7.5, C(9)H_3), 0.97–1.16 (26H, m, C(13)H_2 to C(25)H_2), 1.27–1.34 (1H, m, one of C(12)H_2), 1.52–1.58 (1H, m, one of C(12)H_2), 2.20 (2H, qd, *J* 7.5, 2.5, C(8)H_2), 2.61 (1H, ddd, *J* 14.7, 9.1, 6.0, one of C(28)H_2), 2.68–2.73 (1H, m, one of C(28)H_2), 2.70 (2H, ~t, *J* 5.8, C(4)*H*), 3.13 (1H, ddd, *J* 14.7, 9.1, 6.0, one of C(27)H_2), 3.26 (1H, ddd, *J* 14.7, 9.1, 6.0, one of C(27)H_2), 3.50–3.54 (1H, m, C(5)*H*), 3.53 (3H, s, CO_2CH_3), 4.90 (1H, br s, C(6)*H*), 5.01 (1H, d, *J* 5.5, C(3)*H*), 6.72 (1H, br s, O*H*), 6.97–7.13 (5H, m, C(30)*H* to C(34)*H*); δ_C (75 MHz, $CDCl_3$) 10.3 (*C*(9)H_3), 14.4 (*C*(26)H_3), 23.0, 24.5, 29.6, 29.7, 29.8, 29.87, 29.92, 29.95, 31.2, 32.4, 33.3 (*C*(12)H_2 to *C*(25)H_2 and *C*(28)H_2, some overlapping), 36.5 (*C*(8)H_2), 46.2 (*C*(27)H_2), 52.4 (*C*(4)H), 52.7 (CO_2CH_3), 65.6 (*C*(5)H), 76.1 (*C*(3)H), 89.9 (*C*(6)H), 128.9 (either *C*(30)H and *C*(34)H or *C*(31)H and *C*(33)H), 129.1 (either *C*(30)H and *C*(34)H or *C*(31)H and *C*(33)H), 138.3 (*C*(29)), 165.9 (*C*(2)), 173.0 (*C*(10)O), 200.4 (*C*(7)O); *m/z* (+ve ion electrospray) 550 ([M+Na]$^+$, 70%), 528 ([M+H]$^+$, 100); found 528.4048, $C_{33}H_{54}NO_4$ [M+H]$^+$ requires 528.4047.

4.7.14. (3*R,4*S**,5*S**)-1-Phenethyl-2-(2′-oxo-octadec-*E*-ylidene)-3-hydroxy-5-ethylpyrrolidine-4-carboxylic acid methyl ester (38) and (3*R**,4*R**,5*R**)-1-phenethyl-2-(2′-oxo-octadec-*E*-ylidene)-3-hydroxy-5-ethylpyrrolidine-4-carboxylic acid methyl ester (39).** Data for (3*R**,4*S**,5*S**)-1-phenethyl-2-(2′-oxo-octadec-*E*-ylidene)-3-hydroxy-5-ethylpyrrolidine-4-carboxylic acid methyl ester (**38**) and (3*R**,4*R**,5*R**)-1-phenethyl-2-(2′-oxo-octadec-*E*-ylidene)-3-hydroxy-5-ethylpyrrolidine-4-carboxylic acid methyl ester (39) were as reported previously.[18]

4.8. Representative procedure for the preparation of the natural plakoridines

4.8.1. (+/−)-Plakoridine B (2). Tyramine (28.8 mg, 0.21 mmol) was added to a solution of hexadecanal (50.4 mg, 0.21 mmol) in $CDCl_3$ (12 mL). The reaction mixture was stirred at room temperature for 3 h when $MgSO_4$ was added and the reaction mixture was stirred for a further 30 min. The $MgSO_4$ was removed by filtration and the filtrate was added to (2*Z*,4*E*)-3-hydroxy-6-oxo-docosa-2,4-dienoic acid methyl ester (**33**) (80 mg, 0.21 mmol). The reaction mixture was stirred at room temperature for 11 days and then concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, petroleum ether:ethyl acetate, 5:1) yielded the title compound as a pale yellow oil (56 mg, 36%). R_f 0.30 (petroleum ether:-ethyl acetate, 3:1); ν_{max} (film)/cm^{-1} 3252br (O–H), 2923s and 2853s (C–H), 1741s (C=O, ester), 1613m (C=O, vinylogous amide), 1516s, 1466s, 1247m; δ_H (500 MHz, $CDCl_3$) 0.89 (6H, ~t, *J* 6.9, C(23)H_3 and C(40)H_3), 1.21–1.35 (54H, m, C(10)H_2 to C(22)H_2 and C(27)H_2 to C(39)H_2), 1.48–1.55 (1H, m, one of C(26)H_2), 1.58–1.65 (2H, m, C(9)H_2), 1.72–1.78 (1H, m, one of C(26)H_2), 2.35–2.39 (2H, m, C(8)H_2), 2.74 (1H, ddd, *J* 14.1, 8.8, 5.6, one of C(42)H_2), 2.82–2.88 (1H, m, one of C(42)H_2), 2.91 (1H, ~t, *J* 5.8, C(4)*H*), 3.26–3.32 (1H, m, one of C(41)H_2), 3.43 (1H, ddd, *J* 14.1, 8.8, 5.6, one of C(41)H_2), 3.71 (1H, ddd, *J* 8.8, 5.8, 2.9, C(5)*H*), 3.75 (3H, s, CO_2CH_3), 5.09 (1H, s, C(6)*H*), 5.22 (1H, d, *J* 5.8, C(3)*H*), 5.53 (1H, br s, O*H*), 6.80 (2H, d, *J* 8.6, C(45)*H* and C(47)*H*), 7.01 (1H, br s, O*H*), 7.04 (2H, d, *J* 8.6, C(44)*H* and C(48)*H*); δ_C (75 MHz, $CDCl_3$) 14.4 (*C*(23)H_3 and *C*(40)H_3), 23.0, 24.5, 26.7, 29.6, 29.7, 29.8, 29.89, 29.94, 31.5, 32.2, 33.3 (*C*(9)H_2 to *C*(22)H_2, *C*(26)H_2 to *C*(39)H_2 and *C*(42)H_2, many overlapping), 43.7 (*C*(8)H_2), 46.5 (*C*(41)H_2), 52.4 (*C*(4)H), 52.9 (CO_2CH_3), 65.8 (*C*(5)H), 76.2 (*C*(3)H), 90.5 (*C*(6)H), 116.0 (*C*(45)H and *C*(47)H), 129.7 (*C*(46)), 130.0 (*C*(44)H and *C*(48)H), 155.4 (*C*(43)), 166.3 (*C*(2)), 173.0 (*C*(24)O), 200.2 (*C*(7)O); *m/z* (+ve ion electrospray) 762 ([M+Na]$^+$, 100%); found 740.6188, $C_{47}H_{82}NO_5$ ([M+H]$^+$) requires 740.6188.

4.8.2. Data for (+/−)-Plakoridine A (1). A pale yellow oil; R_f 0.18 (petroleum ether:ethyl acetate, 3:1); ν_{max} (film)/cm^{-1} 3300br (O–H), 2924s and 2853s (C–H), 1740s (C=O, ester), 1613m (C=O, vinylogous amide), 1516s, 1466s, 1236m; δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, J 7.1, C(23)H_3 or C(28)H_3), 0.93 (3H, t, J 7.4, C(23)H_3 or C(28)H_3), 1.21–1.35 (28H, m, C(10)H_2 to C(22)H_2 and C(27)H_2), 1.47–1.55 (1H, m, one of C(26)H_2), 1.59–1.65 (2H, m, C(9)H_2), 1.70–1.77 (1H, m, one of C(26)H_2), 2.36–2.39 (2H, m, C(8)H_2), 2.74 (1H, ddd, J 14.2, 8.9, 5.5, one of C(30)H_2), 2.82–2.88 (1H, m, one of C(30)H_2), 2.91 (1H, ~t, J 5.6, C(4)H), 3.27–3.33 (1H, m, one of C(29)H_2), 3.44 (1H, ddd, J 14.2, 8.9, 5.5, one of C(29)H_2), 3.70–3.75 (1H, m, C(5)H), 3.74 (3H, s, CO_2CH_3), 5.10 (1H, br s, C(6)H), 5.24 (1H, d, J 5.6, C(3)H), 6.03 (1H, br s, OH), 6.81 (1H, d, J 8.6, C(33)H and C(35)H), 7.02–7.05 (3H, m, C(32)H, C(36)H and OH); δ_C (75 MHz, $CDCl_3$) 14.2, 14.4 (C(23)H_3 and C(28)H_3), 17.9, 23.0, 26.7, 29.6, 29.8, 30.0, 31.5, 32.2 (C(9)H_2 to C(22)H_2, C(27)H_2 and C(30)H_2, many overlapping), 35.5 (C(26)H_2), 43.7 (C(8)H_2), 46.5 (C(29)H_2), 52.4 (C(4)H), 52.9 (CO_2CH_3), 65.7 (C(5)H), 76.2 (C(3)H), 90.5 (C(6)H), 116.0 (C(33)H and C(35)H), 129.8 (C(34)), 130.0 (C(32)H and C(36)H), 155.3 (C(31)), 166.2 (C(2)), 173.0 (C(24)O), 200.2 (C(7)O); m/z (+ve ion electrospray) 594 ([M+Na]$^+$, 100%), 572 ([M+H]$^+$, 12); found 572.4313, $C_{35}H_{58}NO_5$ [M+H]$^+$ requires 572.4310.

4.9. Synthesis of (2*R**,4*R**,5*S**)-1-phenyl-2-(2′-oxo-butyl)-3-oxo-5-phenylpyrrolidine-4-carboxylic acid methyl ester (57)

A solution of benzylidine-aniline (135 mg, 0.74 mmol) in deuterochloroform (0.6 mL) was added to (2*Z*,4*E*)-3-hydroxy-6-oxo-octa-2,4-dienoic acid methyl ester (**34**) (125 mg, 0.74 mmol). The reaction mixture was stirred at room temperature for 24 h and then concentrated in vacuo and the residue was triturated with ether. The resulting solid was recrystallised from ethyl acetate to yield the title compound as a colourless microcrystalline solid (149 mg, 55%); mp 130.2–132.1 °C (decomp.); R_f 0.15 (petroleum ether:diethyl ether, 5:1); ν_{max} (film)/cm^{-1} 3002w, 2952w and 2900w (C–H), 1760m (C=O, five-membered ketone), 1731s (C=O, ester), 1704s (C=O, ketone), 1597m, 1501m, 1337s, 1258s, 1223s, 1110s; δ_H (500 MHz, $CDCl_3$) 0.87 (3H, t, J 7.3, C(9)H_3), 2.08 (1H, dq, J 17.5, 7.3, C(8)H_2), 2.19 (1H, dq, J 17.5, 7.3, one of C(8)H_2), 3.04 (1H, dd, J 18.0, 3.5, one of C(6)H_2), 3.41 (1H, dd, J 18.0, 4.8, one of C(6)H_2), 3.65 (1H, d, J 8.3, C(4)H), 3.88 (3H, s, CO_2CH_3), 4.81 (1H, ~t, J 4.0, C(2)H), 5.62 (1H, d, J 8.3, C(5)H), 6.64 (2H, d, J 7.6, C(13)H and C(17)H), 6.74 (1H, t, J 7.6, C(15)H), 7.12 (2H, t, J 7.6, C(14)H and C(16)H), 7.22 (1H, t, J 7.4, C(21)H), 7.29 (2H, t, J 7.4, C(20)H and C(22)H), 7.39 (2H, d, J 7.4, C(19)H and C(23)H); m/z (+ve ion electrospray) 388 ([M+Na]$^+$, 100%), 366 ([M+H]$^+$, 35%).

4.10. X-ray crystallographic analysis of (2*Z*,4*E*)-3-hydroxy-6-oxo-octa-2,4-dienoic acid methyl ester (34)

Crystal data for **34**: $C_9H_{12}O_4$, M=184.19, monoclinic, space group $P2_1/c$, Z=4, a=3.970(5), b=25.875(5), c=9.245(5) Å, β=101.507(5)°, U=930.6(13)Å^3, d_{calcd}=1.315 Mg/m^3. Intensity data were collected using a Mo Kα Bruker Apex CCD diffractometer;[28] 5280 reflections were collected, of which 1917 were unique, R_{int}=0.0777. Data processing was carried out using SAINT[29] and the structure was solved by direct methods using SHELXS97.[30] All nonhydrogen atoms were refined anisotropically, and hydrogens were included in calculated positions using the riding method. Refinement on F^2 was carried out using SHELXL97,[30] Final $R1$=0.0410, $wR2$=0.0844 for 1044 data with $I>2\sigma(I)$. All calculations were carried out using the SHELXTL package.[28] Crystallographic data (excluding structure factors) have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 612879. 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 email: deposit@ccdc.cam.ac.uk].

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Tetrahedron

An entry to 7-amino- and to 2-ethoxycarbonyl-5-dethia-5-oxa-cephams from 1,3-alkylidene-L-erythritol

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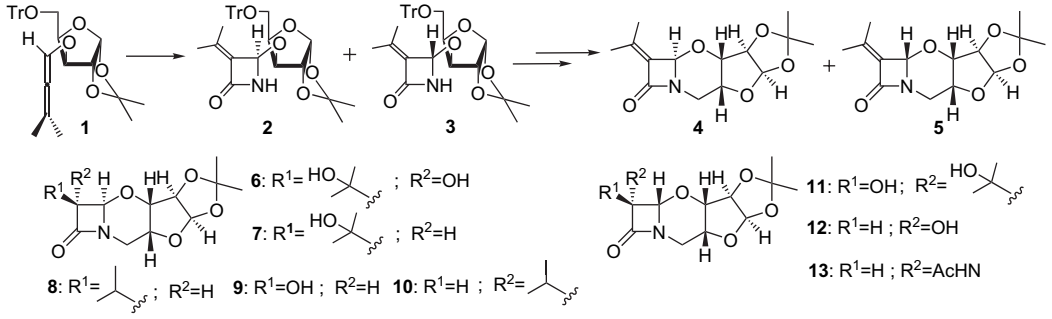
Abstract—The alkoxyallene derived from 1,3-benzylidene-L-erythritol when treated with chlorosulfonyl isocyanate provided diastereomeric β-lactams with moderate stereoselectivity. After the intramolecular alkylation of the nitrogen atom, these afforded compounds having oxa-cepham skeletons. The *exo*-isopropylidene group enabled the introduction of a variety of substituents to the C-7 carbon atom of the cepham, whereas removal of the benzylidene protection followed by the oxidation of 3-OH to the ketone allowed carboxylation of the C-2 carbon atom.

1. Introduction

Recently, we have demonstrated that the [2+2]cycloaddition of chlorosulfonyl isocyanate (CSI) to alkoxyallene **1** derived from the 1,2-*O*-isopropylidene-D-xylofuranose provided β-lactams **2** and **3** with a moderate stereoselectivity.[1] The intramolecular alkylation of the nitrogen atom in **2** and **3** afforded cephams **4** and **5** having an *exo*-isopropylidene group (Scheme 1). Compounds **4** and **5** were used as substrates for a variety of transformations leading to the introduction of isopropyl, hydroxyisopropyl, oxygen, and nitrogen functions at the α position to the β-lactam carbonyl group (**6**–**13**).[2] These transformations followed, in part, Buynak and co-workers[3] study on the functionalization of 3-alkylidene-azetidin-2-ones. Reactions described by us proceeded in high stereoselectivity, with control of the configuration of the cephams thus formed. The introduction of the amino function (**13**) was successfully performed for the cepham **5** only, having the (*S*) configuration at the bridgehead carbon atom.[2]

Due to the specific multifunctional character of the 1,2-*O*-isopropylidene-D-xylofuranose scaffold, however, the cephams obtained are of limited value, since the acid catalyzed hydrolysis of the acetal center derived from the sugar precursor could not be made without the opening of the azetidinone ring. The successful opening of the furanoid fragment was performed as a base induced β-elimination process.[4]

The [2+2]cycloaddition of CSI to alkoxyallene **14** derived from benzylidene erythritol provided azetidinones **15** and



Scheme 1.

Keywords: Alkoxyallenes; β-Lactams; 5-Oxacephams.
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16, which were subjected to intramolecular alkylation affording corresponding tricyclic cephams.[5] Compounds **17** and **18** were synthesized with the intention to introduce a carboxylic function to the C-2 atom and a variety of substituents to the C-7 carbon atom of the 3,4-disubstituted 5-oxacepham skeleton (Chart 1).

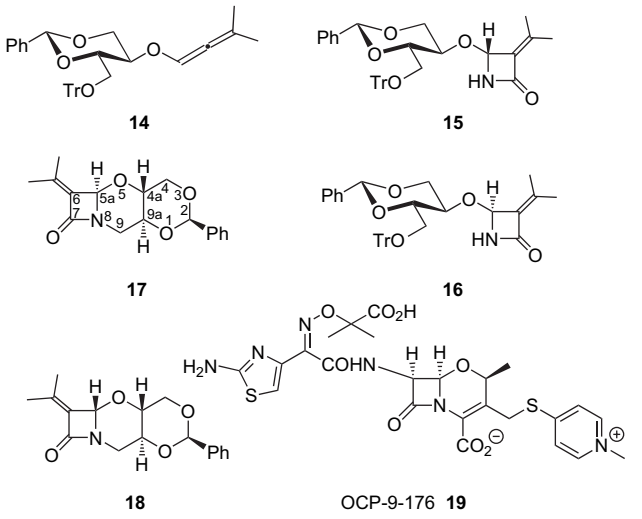
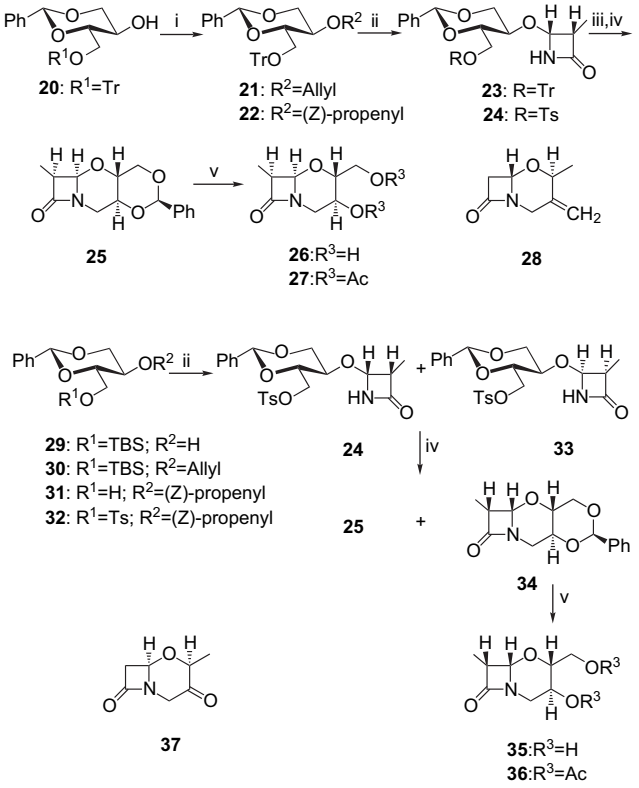


Chart 1.



Scheme 2. (i) (a) NaH/DMF, CH_2=$CHCH_2Br$; (b) *t*-BuOK/DMSO; (ii) CSI, Na_2CO_3/Red-Al; (iii) (a) TsOH/MeOH; (b) TsCl/Py; (iv) K_2CO_3, Bu_4NBr/CH_3CN; and (v) (a) Pd/C, H_2; (b) Ac_2O/Py.

2. Results and discussion

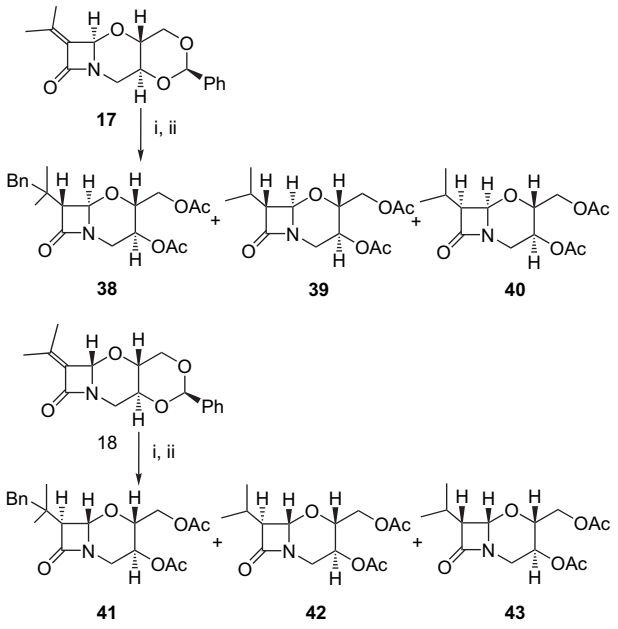
Introduction of the benzylidene grouping to the L-erythritol is a crucial step for successful functionalization of the 5-oxacepham skeleton, since the reductive removal of the protection should be performed easily without any decomposition of the β-lactam ring. The debenzylidation leaves a free OH group at C-3 of the cepham, which after oxidation to the ketone should allow us to introduce an alkoxycarbonyl function to the C-2 carbon atom.[6] Moreover, the cepham obtained contains the hydroxymethyl group at C-4, which may increase its biological activity. At the end of the eighties the Merck and Meiji groups[7] reported a new 4-methyl-cephalosporin **19**, which offers the stability toward β-lactamases together with a significant antibacterial activity.

The usefulness of the benzylidene erythritol scaffold[8] was demonstrated using simple diastereomeric models **25** and **34** obtained by the standard reaction sequence developed for the ethylidene congeners (Scheme 2).[9,20] [2+2]Cycloaddition of chlorosulfonyl isocyanate to **20** proceeded with excellent stereoselectivity, and provided, after intramolecular alkylation of the β-lactam nitrogen atom, only one oxacepham **25**. Its diastereomer **34**, having the (*S*) configuration at the bridgehead carbon atom, was obtained by the same reaction sequence, starting from the tosyloxymethyl propenyl ether **32**, which gave lower stereoselectivity in the cycloaddition. The minor product of the cycloaddition (**33**) after the intramolecular alkylation provided the cepham **34**. All these reactions followed our earlier observations made for ethylidene analogs.[9]

As it was expected, hydrogenation of **25** over palladium gave **26** in a very good yield. Removal of the benzylidene fragment caused the inversion in the conformation of the six-membered oxazine ring. Consequently hydroxymethyl and hydroxy groups switched from diequatorial geometry coerced by the rigid trans decalin system to the distorted diaxial geometry of the oxazine ring. This was demonstrated by the change of coupling constants $J_{3,4}$ from about 9.5 Hz to 2.2 Hz. Similar conformation of the six-membered oxazine ring has been found by us recently for cepham **28**.[10] Such a conformational switch demonstrates the angular strain existing in **25**. Contrary to that, the hydrogenation of the alternative diastereomer **34**, having *syn* protons at C-5a and C-6a carbon atoms, provided cepham **36**, which did not show an inversion in the conformation of the six-membered oxazine ring in comparison with the decalin precursor **34**. The coupling constant $J_{3,4}$=9.8 Hz remains large, proving the diaxial position of both protons. This shows that the conformation of the oxacepham having the β-lactam ring fused to the six-membered oxazine is well defined. The bridgehead proton H-6 of the molecule must be located in the pseudoaxial position. One can compare X-ray structures of **28** and **37** reported by us recently.[10] The reverse conformational arrangement can occur only if the cepham fragment is a part of the bigger rigid molecule, for example, a trans decalin system.

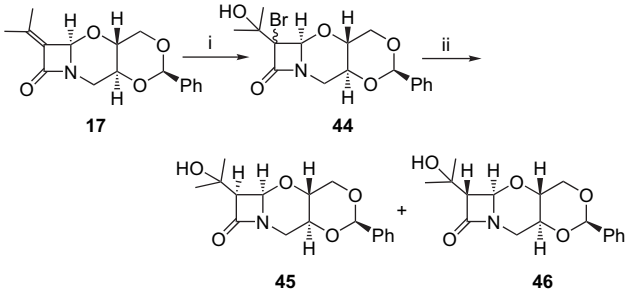
Readily available oxacepham **17** and its C-6 epimer **18**[5] were selected to demonstrate both functionalizations, i.e., introduction of substituents at the C-7 carbon atom and alkoxycarbonylation of the C-2. The sodium in liquid ammonia reduction of compound **17**, which should remove the benzylidene protection and reduce the double bond, led to the

mixture of three products **38**, **39**, and **40** in a ratio of about 1.3:1.2:1, respectively, whereas compound **18** under the same conditions provided a corresponding mixture of **41**, **42**, and **43** in the ratio of about 2:2:1 (Scheme 3). The transfer of the benzyl radical or anion to the α,β-unsaturated amide is worth mentioning. Addition of acrylamide to the reaction mixture in order to trap the reactive intermediate did not change significantly the proportion of the reaction products. Low stereoselectivity of reduction of the double bond was another feature that differentiated reduction of **17** or **18** from that of **4**, which proceeded exclusively to the trans arrangement of protons at C-6 and C-7 of the cepham skeleton.[2]



Scheme 3. (i) Na/NH_3 and (ii) Ac_2O/Py.

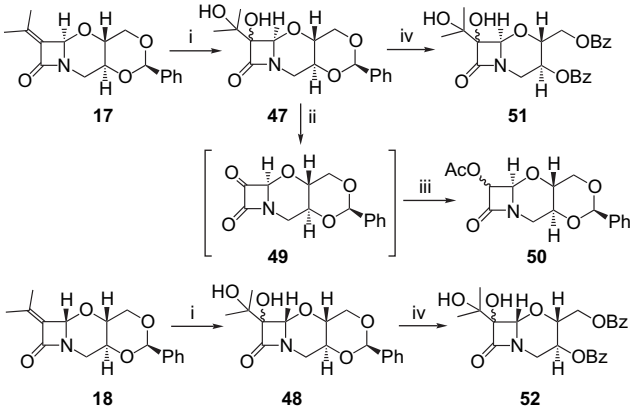
The isopropylidene group in compound **17** can be easily transformed into hydroxyisopropyl by the sequence of reactions involving the bromohydrin formation followed by the reductive removal of the bromine atom (Scheme 4).



Scheme 4. (i) NBS/DMSO–H_2O and (ii) Bu_3SnH/AIBN/toluene.

The treatment of **17** with NBS in wet DMSO,[11] according to the known procedure,[3f] provided a mixture of bromohydrins **44**, which upon treatment with tributyltin hydride gave two diastereomers **45** and **46** in the ratio of 4.4:1, respectively (Scheme 4). The relatively high stereoselectivity of debromination, which did not depend upon the proportion of bromohydrins, was in agreement with the previous observations.[2]

Since ozonolysis of the *exo* double bond in β-lactams led to the decomposition of the azitidin-2-one ring,[12] we used a cis hydroxylation–glycolic cleavage sequence to split the double bonds in **17** and **18**. Introduction of substituents to the C-3 carbon atom of the azetidin-2-one ring via 2,3-dione stage has been reported recently.[13] Oxidation of the cephams **17** and **18** independently with $RuCl_3/NaIO_4$ in $H_2O/CH_3CN/CHCl_3$ mixture, for 30 min,[14] afforded corresponding mixtures of diols **47** and **48** in a good yields (Scheme 5). Glycolic cleavage of **47**[15], followed by reduction of unstable ketone **49** with sodium borohydride provided a mixture of alcohols in a very low yield, which were characterized as acetates **50**. This low yield could be explained by the mentioned above strain, which exists in (6*R*) β-lactam ring fused to the trans decalin system and is manifested by the easy opening of the four-membered β-lactam ring.

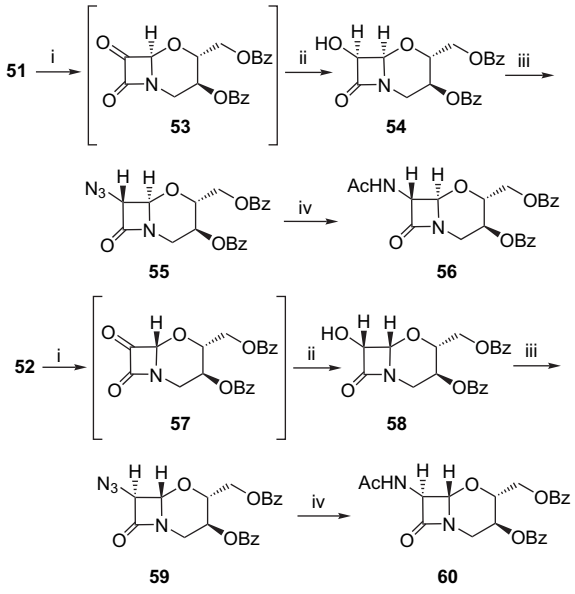


Scheme 5. (i) $RuCl_3/NaIO_4$, $H_2O/CH_3CN/CHCl_3$; (ii) H_5IO_6/AcOEt; (iii) (a) $NaBH_4$; (b) Ac_2O/Py; and (iv) (a) H_2, Pd/C; (b) BzCl/Py.

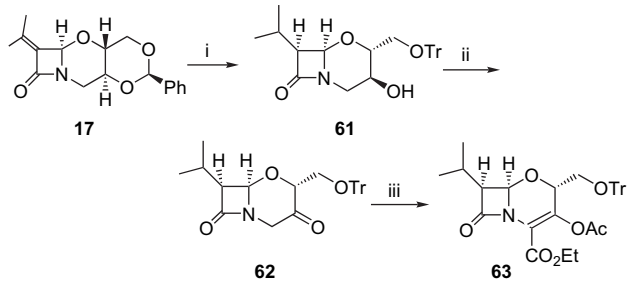
The hydrogenolysis of the benzylidene fragment in diol **47** released the conformational strain providing a tetraol, which was protected at the primary and secondary hydroxyl groups and gave compound **51**. Glycolic cleavage performed on diol **51** proceeded in much better yield. Unstable 7-keto compound **53** was thus obtained, which without purification was immediately reduced to the corresponding 7-ol **54**. Subsequent triflation of the hydroxyl group, followed by nucleophilic substitution with azide, provided **55** with the inversion in the configuration at C-7 carbon atom. Hydrogenation of the azide **55** and acetylation of the resulting amino group ended the reaction sequence affording **56**. The same reaction sequence was performed on **48**, yielding the corresponding acetamide **60**. All transformations proceeded in good yield (Scheme 6).

Hydrogenation of compound **17** over palladium followed by tritylation of the primary hydroxyl group provided only one diastereomer **61** having cis located H-6 and H-7 protons. Subsequent oxidation of the secondary hydroxyl group afforded the ketone **62**. Reaction of **62** with 1.1 equiv of KHMDS at −78 °C in toluene followed by the addition of ethyl cyanoformate provided, after acetylation, the cepham **63** in 60% yield (Scheme 7). This relatively high yield of ethoxycarbonylation was in contrast to our previous observations.[6]

Oxacephams **17**, **18**, **56**, and **63** were tested for their biological activity. An inhibition of the DD-carboxypeptidase activity and,



Scheme 6. (i) H_5IO_6/AcOEt; (ii) $NaBH_4/H_2O$; (iii) (a) Tf_2O/Py; (b) NaN_3/DMF; and (iv) (a) Pd/C, H_2; (b) Ac_2O, Py.



Scheme 7. (i) (a) Pd/C, H_2; (b) TrCl, Py; (ii) PCC, MS 4 Å, CH_2Cl_2, reflux; and (iii) (a) KHMDS, $NCCO_2Et$, toluene; (b) Ac_2O, Py.

separately, an inhibition of β-lactamase was measured.[16–19] Within studied series, all tested oxacephams showed low activity of DD-peptidase. All tested compounds did not show any significant activity as inhibitors of the β-lactamase either.

3. Conclusions

In summary, we have demonstrated that the [2+2]cycloadducts of CSI to 2-*O*-allenyl-1,3-benzylidene-L-erythritol are versatile intermediates for the preparation of a wide range of 7-substituted-5-oxacephams and for the introduction of carboxylic function to the C-2 carbon atom. Except the cycloaddition reaction that proceeded with a moderate stereoselectivity, the other transformations offer high stereoselectivities, and therefore may provide substituents at C-7, existing in many active β-lactam antibiotics.

4. Experimental

4.1. General remarks

Melting points were determined on a Koefler hot-stage apparatus. NMR spectra were recorded using Bruker Avance 500 and Varian Mercury 400 instruments. IR spectra were recorded on a Perkin–Elmer FTIR Spectrum 200 spectrophotometer. Mass spectra were recorded using AMD-604 Inectra GmbH and HPLC–MS with Mariner and API 356 detectors. Optical rotations were measured using JASCO P 3010 polarimeter at 22±3 °C. Column chromatography was performed using E. Merck Kiesel Gel (230–400 mesh).

Compounds **21**–**25** and **30**–**34** were obtained according to the procedures reported previously for ethylidene analogs.[9] Detailed procedures, spectral and analytical data are provided in Supplementary data.[20]

4.1.1. (3*S*,4*R*,6*R*,7*S*)-3-Hydroxy-4-hydroxymethyl-7-methyl-5-oxa-cepham (26). Compound **25** (0.07 g, 0.25 mmol) dissolved in MeOH (10 mL) was hydrogenated in the presence of 5% Pd/C (0.007 g) for 1.5 h. Subsequently the mixture was filtered through Celite and evaporated. The crude product was purified by chromatography using AcOEt/MeOH, 4:1 v/v as an eluent to afford **26** (0.04 g, 83%). $[\alpha]_D^{22}$ +21.7 (*c* 0.1, CH_2Cl_2). IR (film): 1740, 3367 cm^{-1}. HRMS (ESI), *m*/*z* $(M+H)^+$, calcd for $C_8H_{15}O_4N$: 188.0917, found: 188.0922. ^1H NMR (400 MHz, D_2O) *δ*: 1.24 (d, *J*=7.5 Hz, 3H, CH_3), 3.38 (ddd, *J*=1.8, 2.9, 14.7 Hz, 1H, H-2), 3.50 (ddq, *J*=1.8, 3.7, 7.5 Hz, 1H, H-7), 3.64 (ddd, *J*=1.1, 2.0, 14.7 Hz, 1H, H-2′), 3.77–3.85 (m, 2H, H-3, CH_AH_BOH), 4.06–4.14 (m, 2H, H-4, CH_AH_BOH), 5.29 (d, 1H, *J*=3.7 Hz, H-6). Acetate **27**. $[\alpha]_D^{22}$ +83.3 (*c* 0.5, CH_2Cl_2). IR (film): 1745, 1770 cm^{-1}. HRMS (ESI), *m*/*z* $(M+Na)^+$, calcd for $C_{12}H_{17}O_6NNa$: 294.0948, found: 294.0953. ^1H NMR (500 MHz, C_6D_6) *δ*: 1.19 (d, *J*=7.5 Hz, 3H, CH_3), 1.59, 1.67 (2s, 6H, 2Ac), 2.51 (ddd, *J*=1.4, 3.0, 15.1 Hz, 1H, H-2), 2.86 (ddq, *J*=1.4, 3.6, 7.5 Hz, 1H, H-7), 3.66 (dd, *J*=4.9, 12.0 Hz, 1H, CH_AH_BOAc), 3.67 (dt, *J*=1.3, 1.8, 15.1 Hz, 1H, H-2′), 4.00 (m, 1H, H-4), 4.13 (dd, *J*=7.7, 12.0 Hz, 1H, CH_AH_BOAc), 4.25 (ddd, *J*=1.8, 2.2, 3.0 Hz, 1H, H-3), 4.58 (d, *J*=3.6 Hz, 1H, H-6).

4.1.2. (3*S*,4*R*,6*S*,7*R*)-3-Hydroxy-4-hydroxymethyl-7-methyl-5-oxa-cepham (35). Compound **34** was hydrogenated according to the procedure described above to afford **35** (85%). $[\alpha]_D^{22}$ −10.8 (*c* 0.5, CH_2Cl_2). IR (film): 1743, 3378 cm^{-1}. HRMS (ESI), *m*/*z* $(M+H)^+$, calcd for $C_8H_{15}O_4N$: 188.0917, found: 188.0906. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 1.20 (d, *J*=7.5 Hz, 3H, CH_3), 2.77 (ddd, *J*=2.6, 9.7, 13.1 Hz, 1H, H-2), 3.36 (ddq, *J*=1.7, 3.7, 7.5 Hz, 1H, H-7), 3.49 (m, 1H, CH_AH_BOH), 3.78 (m, 1H, H-3), 3.91 (m, 2H, H-4, CH_AH_BOH), 4.11 (dd, *J*=6.2, 13.1 Hz, H-2′), 4.97 (d, *J*=3.7 Hz, 1H, H-6). Acetate **36**: $[\alpha]_D^{22}$ −15.1 (*c* 0.1, CH_2Cl_2). IR (film): 1746, 1773 cm^{-1}. HRMS (ESI), *m*/*z* $(M+Na)^+$, calcd for $C_{12}H_{17}O_6NNa$: 294.0948, found: 294.0925. ^1H NMR (500 MHz, C_6D_6) *δ*: 1.08 (d, *J*=7.5 Hz, 3H, CH_3), 1.53, 1.61 (2s, 6H, 2Ac), 2.25 (ddd, *J*=1.6, 9.5, 13.0 Hz, 1H, H-2), 2.79 (ddq, *J*=1.6, 3.7, 7.5 Hz, 1H, H-7), 3.22 (ddd, *J*=2.9, 4.6, 9.8 Hz, 1H, H-4), 4.09 (dd, *J*=2.9, 12.1 Hz, 1H, CH_AH_BOAc), 4.12 (dd, *J*=4.6, 12.1 Hz, 1H, CH_AH_BOAc), 4.17 (dd, *J*=6.3, 13.0 Hz, 1H, H-2′), 4.19 (d, *J*=3.7 Hz, 1H, H-6), 4.66 (dt, *J*=6.4, 9.5, 9.8 Hz, 1H, H-3).

4.1.3. (3*S*,4*R*,6*R*,7*R*)-3-Acetoxy-4-(acetoxymethyl)-7-(1′-benzyl-1′-methyl-ethyl)-5-oxa-cepham (38), (3*S*,4*R*,6*R*,7*R*) and (3*S*,4*R*,6*R*,7*S*)-7-isopropyl-3-acetoxy-4-(1′-acetoxymethyl)-5-oxa-cepham (39 and 40). To a stirring solution

of sodium (0.040 g, 1.7 mmol) in liquid ammonia (40 mL) at 60 °C, compound **17** (0.050 g, 0.166 mmol) in dry THF (4 mL) was added dropwise. The temperature was maintained for 40 min. Subsequently NH_4Cl (0.5 g) was added and the mixture was left until evaporation of ammonia. To the residue, 10 mL of water was added and the mixture was extracted with AcOEt (3×20 mL). The extract was dried and evaporated. The crude products were acetylated with Ac_2O/pyridine mixture. Standard workup and chromatographical separation using hexane/AcOEt, 7:3 v/v as an eluent provided compound **38** (0.013 g, 20%) and a mixture **39/40** (0.017 g, 34%) in a ratio of about 1.2:1, respectively.

Compound **38**: $[\alpha]_D^{22}$ +44.2 (*c* 0.4, CH_2Cl_2). IR (film): 1745, 1769 cm^{-1}. HRMS (ESI), *m/z* $(M+Na)^+$, calcd for $C_{21}H_{27}NO_6Na$: 412.1731, found: 412.1756. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 0.97 and 1.03 (2s, 6H, $2CH_3$), 2.11 (s, 6H, 2Ac), 2.63 and 2.68 (2d, *J*=13.2 Hz, 2H, CH_2Ph), 3.06 (s, 1H, H-7), 3.32 (dd, *J*=3.51, 15.03 Hz, 1H, H-2), 3.87 (m, 1H, H-2′), 4.20 (m, 1H, H-4), 4.25 (m, 1H, CH_AH_BOAc), 4.53 (dd, *J*=6.12, 11.13 Hz, 1H, CH_AH_BOAc), 4.70 (m, 1H, H-3), 4.95 (s, 1H, H-6), 7.18–7.28 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) *δ*: 20.76, 21.02, 24.35, 25.22, 33.95, 39.60, 47.14, 60.88, 64.39, 68.97, 72.96, 75.57, 126.25, 127.87, 128.32, 130.88, 137.43, 169.99, 170.36.

Compounds **39** and **40**, taken for the mixture. IR (film): 1745, 1769 cm^{-1}. HRMS (ESI), *m/z* $(M+Na)^+$, calcd for $C_{14}H_{21}NO_6Na$: 322.1261, found: 322.1275. ^1H NMR (500 MHz, $CDCl_3$) *δ*: **39**: 1.01 (d, *J*=6.7 Hz, 3H, CH_3), 1.06 (d, *J*=6.7 Hz, 3H, CH_3), 1.98 (m, 1H, C*H*–$(CH_3)_2$), 2.10 and 2.12 (2s, 6H, 2Ac), 2.98 (d, *J*=6.7 Hz, 1H, H-7), 3.30 (dd, *J*=3.4, 15.1 Hz, 1H, H-2), 3.86 (m, 1H, H-2′), 4.22 (m, 1H, H-4), 4.30 (m, 1H, CH_AH_BOAc), 4.56 (dd, *J*=6.5, 11.2 Hz, 1H, CH_AH_BOAc), 4.70 (m, 1H, H-3), 4.95 (s, 1H, H-6). Compound **40**: 0.96 (d, *J*=6.6 Hz, 3H, CH_3), 1.16 (d, *J*=6.7 Hz, 3H, CH_3), 2.10 and 2.11 (2s, 6H, 2Ac), 2.24 (m, 1H, C*H*–$(CH_3)_2$), 2.95 (ddd, *J*=1.4, 3.5, 10.9 Hz, 1H, H-7), 3.30 (ddd, *J*=1.4, 3.3, 15.0 Hz, 1H, H-2), 3.84 (m, 1H, H-2′), 4.24 (m, 1H, H-4), 4.28 (dd, *J*=5.5, 11.8 Hz, 1H, CH_AH_BOAc), 4.54 (dd, *J*=6.7, 11.8 Hz, 1H, CH_AH_BOAc), 4.70 (m, 1H, H-3), 5.18 (d, *J*=3.5 Hz, 1H, H-6).

4.1.4. (3*S*,4*R*,6*S*,7*S*)-3-Acetoxy-4-(acetoxymethyl)-7-(1′-benzyl-1′-methyl-ethyl)-5-oxa-cepham (41), (3*S*,4*R*,6*S*,7*S*) and (3*R*,4*R*,6*S*,7*R*)-7-isopropyl-3-acetoxy-4-(1′-acetoxymethyl)-5-oxa-cepham (42 and 43). Compound **41** (23%) and a mixture **42/43** (32%) were obtained from compound **18** according to the procedure described for compounds **38**–**40**.

Compound **41**: $[\alpha]_D^{22}$ +36.4 (*c* 0.1, CH_2Cl_2). IR (film): 1746, 1765 cm^{-1}. HRMS (ESI), *m/z* $(M+Na)^+$, calcd for $C_{21}H_{27}NO_6Na$: 412.1731, found: 412.1755. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 0.98, 1.04 (2s, 6H, $2CH_3$), 2.17 (s, 6H, 2Ac), 2.61 and 2.73 (2d, *J*=13.3 Hz, 2H, CH_2Ph), 2.78 (dd, *J*=9.5, 13.0 Hz, 1H, H-2a), 3.03 (s, 1H, H-7), 3.72 (ddd, *J*=2.4, 5.1, 9.9 Hz, 1H, H-4), 4.19 (dd, *J*=2.4, 12.2 Hz, 1H, CH_AH_BOAc), 4.25 (dd, *J*=5.1, 12.2 Hz, 1H, CH_AH_BOAc), 4.33 (dd, *J*=6.3, 13.0 Hz, 1H, H-2b), 4.73 (dt, *J*=6.5, 9.5, 9.9 Hz, 1H, H-3), 4.78 (s, 1H, H-6), 7.19–7.29 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) *δ*: 20.75, 21.00, 24.36, 25.23, 33.95, 39.62, 47.17, 60.92, 64.42, 69.01, 72.98, 75.61, 126.26, 127.87, 130.88, 137.45, 169.98, 170.34, 170.36.

Compounds **42** and **43**, taken for the mixture. IR (film): 1732, 1772 cm^{-1}. HRMS (ESI), *m/z* $(M+Na)^+$, calcd for $C_{14}H_{21}NO_6Na$: 322.1261, found: 322.1279. ^1H NMR (500 MHz, $CDCl_3$) *δ*: **42**: 1.01 (d, *J*=6.8, 3H, CH_3), 1.06 (d, *J*=6.7 Hz, 3H, CH_3), 2.00 (m, 1H, C*H*–$(CH_3)_2$), 2.06 and 2.09 (2s, 6H, 2Ac), 2.77 (dd, *J*=9.5, 13.0 Hz, 1H, H-2), 2.96 (d, *J*=6.7 Hz, 1H, H-7), 3.7 (m, 1H, H-4), 4.20 (dd, *J*=2.4, 12.2 Hz, 1H, CH_AH_BOAc), 4.24 (m, 1H, CH_AH_BOAc), 4.40 (dd, *J*=6.4, 13.0 Hz, 1H, H-2′), 4.72 (dt, *J*=6.4, 9.5 Hz, 1H, H-3), 4.80 (s, 1H, H-6). **43**: 0.95 (d, *J*=6.5 Hz, 3H, CH_3), 1.13 (d, *J*=6.7 Hz, 3H, CH_3), 2.06 and 2.08 (2s, 6H, 2 Ac), 2.15 (m, 1H, C*H*–$(CH_3)_2$), 2.75 (ddd, *J*=1.6, 9.5, 13.0 Hz, 1H, H-2a), 2.94 (ddd, *J*=1.6, 3.6, 10.9 Hz, 1H, H-7), 3.75 (m, 1H, H-4), 4.23 (m, 2H, CH_2OAc), 4.29 (dd, *J*=6.4, 13.0 Hz, 1H, H-2b), 4.71 (m, 1H, H-3), 4.98 (d, *J*=3.6 Hz, 1H, H-6).

4.1.5. (2*R*,4a*R*,5a*R*,6*R*,9a*S*) and (2*R*,4a*R*,5a*R*,6*S*,9a*S*)-6-Bromo-6-(1′-hydroxy-1′-methyl-ethyl)-2-phenyl-1,3,5-trioxa-8-aza-cyclobuta[*b*]decalin-7-on (44). To a stirring solution of **17** (0.040 g, 0.13 mmol) in water (0.01 mL, 0.55 mmol) and DMSO (5 mL) NBS (0.034 g, 0.19 mmol) was added. Stirring was continued at room temperature for 12 h. Subsequently the mixture was poured into water (10 mL) and extracted with Et_2O (2×20 mL). Organic layer was dried and evaporated. The residue was purified by chromatography using hexane/AcOEt, 1:1 v/v as an eluent to afford **44** as a mixture of two diastereomers in a ratio of about 10:1 (0.032 g, 62%). HRMS (ESI) taken for the mixture, *m/z* $(M+Na)^+$, calcd for $C_{17}H_{20}BrNO_5Na$: 420.0417, found: 420.0439. ^1H NMR (500 MHz, $CDCl_3$) *δ*: the major isomer: 1.42 and 1.54 (2s, 6H, $2CH_3$), 3.66 (dd, *J*=7.2, 12.7 Hz, 1H, H-9), 3.78 (m, 2H, H-4, H-9a), 4.12 (m, 2H, H-4a, H-9′), 4.44 (dd, *J*=2.1, 10.7 Hz, 1H, H-4′), 5.31 (s, 1H, H-2), 5.55 (s, 1H, H-5a), 7.36–7.46 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$) *δ*: 26.27, 26.41, 41.82, 65.40, 68.74, 72.11, 73.97, 79.99, 80.26, 102.05, 126.14, 128.33, 128.39, 129.39, 136.64, 165.68.

4.1.6. (2*R*,4a*R*,5a*R*,6*S*,9a*S*) and (2*R*,4a*R*,5a*R*,6*R*,9a*S*)-6-(1′-Hydroxy-1′-methyl-ethyl)-2-phenyl-1,3,5-trioxa-8-aza-cyclobuta[*b*]decalin-7-on (45 and 46). A solution of tri-*n*-butyltin hydride (0.37 mL, 0.14 mmol) and AIBN (0.021 g, 0.16 mmol) in toluene (2 mL) was added to a hot solution (95 °C) of bromohydrins **44** (0.027 g, 0.07 mmol) in toluene (3 mL). The stirring and temperature was maintained for additional 40 min. Subsequently the temperature of the mixture was cooled to room temperature and the solvent was evaporated. The residue was purified by chromatography using hexane/AcOEt, 1:1 v/v as an eluent to afford a mixture of **45/46** in a ratio of about 4.4:1 (0.019 g, 85%). IR (film): 1755, 3457 cm^{-1}. HRMS (ESI) taken for the mixture, *m/z* $(M+Na)^+$, calcd for $C_{17}H_{21}NO_5Na$: 342.1312, found: 342.1317. ^1H NMR (500 MHz, $CDCl_3$) *δ*: major component **45**: 1.38 and 1.46 (2s, 6H, $2CH_3$), 3.23 (dd, *J*=1.9, 3.4 Hz, 1H, H-6), 3.59 (ddd, *J*=1.9, 7.1, 12.0 Hz, 1H, H-9), 3.74 (dd, *J*=8.7, 10.9 Hz, 1H, H-4), 3.76 (dd, *J*=9.5, 12.0 Hz, 1H, H-9′), 4.05 (m, *J*=4.9, 8.7, 9.5 Hz,

1H, H-4a), 4.12 (dt, *J*=7.1, 9.5, 9.5 Hz, 1H, H-9a), 4.34 (dd, *J*=4.9, 10.9 Hz, 1H, H-4′), 5.37 (d, *J*=3.4 Hz, 1H, H-5a), 5.55 (s, 1H, H-2), 7.36–7.45 (m, 5H, Ph). Compound **46** inter alia: 1.34 and 1.40 (2s, 6H, $2CH_3$), 3.20 (s, 1H, H-6), 4.4 (dd, *J*=5.0, 10.7 Hz, 1H, H-4′), 5.24 (s, 1H, H-5a), 5.54 (s, 1H, H-2).

4.1.7. (2*R*,4a*R*,5a*R*,6*S*,9a*S*) and (2*R*,4a*R*,5a*R*,6*R*,9a*S*)-6-Hydroxy-6-(1′-hydroxy-1′-methyl-ethyl)-2-phenyl-1,3,5-trioxa-8-aza-cyclobuta[*b*]decalin-7-on (47). A solution of **17** (0.070 g, 0.23 mmol) in CH_3CN (10 mL), $CHCl_3$ (2 mL), and water (5 mL) was treated with $NaIO_4$ (0.245 g, 1.15 mmol) and $RuCl_3 \cdot H_2O$ (0.001 g). The stirring was continued until disappearance of the substrate (TLC), about 30 min. The mixture was treated with water (10 mL) and extracted with AcOEt (3×20 mL). Organic layer was dried and evaporated. The residue was purified by chromatography using hexane/AcOEt, 7:3 v/v as an eluent to afford **47** as a mixture of diastereoisomers in a ratio of about 2.8:1 (0.067 g, 87%). IR (film): 3293, 3222, 1755 cm^{-1}. HRMS (ESI) taken for the mixture, *m*/*z* $(M+Na)^+$, calcd for $C_{17}H_{21}NO_6Na$: 358.1261, found: 358.1271. ^1H NMR (500 MHz, $CDCl_3$) *δ*: major component: 3.63–3.82 (m, 3H, H-4, H-9, H-9′), 3.92 (m, 1H, H-9a), 4.16 (m, 1H, H-4a), 4.33 (dd, *J*=5.0, 10.9 Hz, 1H, H-4′), 5.15 (s, 1H, H-2), 5.54 (s, 1H, H-5a), 7.34–7.46 (m, 5H, Ph). Minor component inter alia: 4.43 (dd, *J*=5.0, 10.9 Hz, 1H, H-4), 5.22 (s, 1H, H-2), 5.55 (s, 1H, H-5a).

4.1.8. (2*R*,4a*R*,5a*S*,6*S*,9a*S*) and (2*R*,4a*R*,5a*S*,6*R*,9a*S*)-6-Hydroxy-6-(1′-hydroxy-1′-methyl-ethyl)-2-phenyl-1,3,5-trioxa-8-aza-cyclobuta[*b*]decalin-7-on (48). Compound **48** (90%) in a ratio of about 4.5:1 was obtained from **18** following procedure described for **47**. IR (film): 1756, 3220, 3292 cm^{-1}. HRMS (ESI), *m*/*z*, $(M+Na)^+$, calcd for $C_{17}H_{21}NO_6Na$: 358.1261, found: 358.1271. ^1H NMR (500 MHz, $CDCl_3$) major product *δ*: 1.28 and 1.39 (2s, 6H, $2CH_3$), 3.04 (dd, *J*=10.0, 12.6 Hz, 1H, H-9), 3.62 (ddd, *J*=4.8, 9.1, 9.9 Hz, 1H, H-4a), 3.68–3.74 (m, 2H, H-4, H-9a), 4.17 (dd, *J*=5.7, 12.6 Hz, 1H, H-9′), 4.30 (dd, *J*=4.8, 10.7 Hz, 1H, H-4′), 5.00 (s, 1H, H-2), 5.52 (s, 1H, H-5a), 7.18–7.38 (m, 5H, Ph).

4.1.9. (2*R*,4a*R*,5a*R*,6*S*,9a*S*) and (2*R*,4a*R*,5a*R*,6*R*,9a*S*)-6-Acetoxy-2-phenyl-1,3,5-trioxa-8-aza-cyclobuta[*b*]decalin-7-on (50). A solution of **47** (0.065 g, 0.19 mmol) in AcOEt (5 mL) was treated with H_5IO_6 (0.043 g, 0.19 mmol). Upon stirring at temperature 0–5 °C, $NaBH_4$ (0.01 g, 0.026 mmol) in water (2 mL) was added. After 20 min, 10 mL of water was added and the mixture was extracted with AcOEt (3×20 mL). The extract was dried and evaporated. The crude product was acetylated with Ac_2O/Py mixture to afford, after standard workup, compound **50** in a ratio of about 5.5:1 (0.003 g, 5%). IR (film): 1755, 1782 cm^{-1}. HRMS (ESI), *m*/*z* $(M+Na)^+$, calcd for $C_{16}H_{17}NO_6Na$: 342.0948, found: 342.0953. ^1H NMR (500 MHz, C_6D_6) major isomer (6*S*) *δ*: 3.00 (ddd, *J*=1.2, 7.6, 12.4 Hz, 1H, H-9), 3.32 (m, 1H, H-9′), 3.44 (dd, *J*=9.9, 10.3 Hz, 1H, H-4), 3.80 (m, 2H, H-9a, H-4a), 4.19 (dd, *J*=5.1, 10.3 Hz, 1H, H-4′), 4.79 (d, *J*=2.5 Hz, 1H, H-5a), 5.25 (s, 1H, H-2), 5.31 (dd, *J*=1.7, 2.5 Hz, 1H, H-6), 7.27–7.62 (m, 5H, Ph). Minor isomer (6*S*) inter alia: 4.86 (s, 1H, H-5a), 5.19 (s, 1H, H-2), 5.54 (s, 1H, H-6).

4.1.10. (3*S*,4*R*,6*R*,7*R*) and (3*S*,4*R*,6*R*,7*S*)-3-Benzoyloxy-4-benzoyloxymethyl-7-hydroxy-7-(1′-hydroxy-1′-methyl-ethyl)-5-oxa-cepham (51). Compound **47** (0.060 g, 0.18 mmol) in MeOH (10 mL) was treated with 10% Pd/C (3 mg) and stirred under a hydrogen atmosphere for 2 h. Subsequently the mixture was filtered and evaporated. The residue was treated with BzCl/Py mixture. After standard workup, compound **51** was obtained (0.063 g, 77%) in a ratio 6:1. IR (film): 3331, 1787, 1747, 1724 cm^{-1}. HRMS (ESI), *m*/*z* $(M+Na)^+$, calcd for $C_{24}H_{25}NO_8Na$: 478.1472, found: 478.1487. ^1H NMR (500 MHz, $CDCl_3$) major isomer *δ*: 1.33 and 1.45 (2s, 6H, $2CH_3$), 3.62 (dd, *J*=3.3, 15.1 Hz, 1H, H-2), 4.00 (m, 1H, H-2′), 4.60 (m, 2H, H-4, CH_AH_BOBz), 4.80 (dd, *J*=6.3, 12.0 Hz, 1H, CH_AH_BOBz), 5.08 (m, 1H, H-3), 5.28 (s, 1H, H-6), 7.19–8.02 (m, 10H, 2×Ph).

4.1.11. (3*S*,4*R*,6*S*,7*R*) and (3*S*,4*R*,6*S*,7*S*)-3-Benzoyloxy-4-benzoyloxymethyl-7-hydroxy-7-(1′-hydroxy-1′-methyl-ethyl)-5-oxa-cepham (52). Compounds **52** (75%) in a ratio 2.1:1 were obtained from **48** according to the procedure described for **51**. IR (film): 1721, 1761, 3423, 3519 cm^{-1}. HRMS (ESI), *m*/*z* $(M+Na)^+$, calcd for $C_{24}H_{25}NO_8Na$: 478.1472, found: 478.1498. ^1H NMR (500 MHz, $CDCl_3$) major isomer *δ*: 1.35, 1.46 (2s, 6H, $2CH_3$), 3.08 (dd, *J*=9.5, 12.9 Hz, 1H, H-2), 4.26–4.34 (m, 1H, H-4), 4.53 (dd, *J*=4.2, 12.3 Hz, 1H, CH_AH_BOBz), 4.56 (dd, *J*=6.3, 12.3 Hz, 1H, CH_AH_BOBz), 4.67 (dd, *J*=2.6, 12.9 Hz, 1H, H-2′), 5.10 (s, 1H, H-6), 5.18 (dt, *J*=6.4, 9.5, 9.5 Hz, 1H, H-3), 7.43–8.00 (m, 10H, 2×Ph).

4.1.12. (3*S*,4*R*,6*R*,7*S*)-3-Benzoyloxy-4-benzoyloxymethyl-7-hydroxy-5-oxa-cepham (54). A solution of compound **51** (0.055 g, 0.12 mmol) in AcOEt (5 mL) was treated with H_5IO_6 (0.027 g, 0.12 mmol) and stirred at room temperature for 45 min. Subsequently the mixture was cooled to −5 °C and a solution of $NaBH_4$ (0.01 g, 0.026 mmol) in water (2 mL) was added. Stirring was continued for 30 min and then water (10 mL) was added and the mixture was extracted with AcOEt (3×20 mL). Organic layer was dried and evaporated. The residue was purified by chromatography using hexane/AcOEt, 3:2 v/v as an eluent to afford **54** (0.031 g, 65%). $[\alpha]_D^{22}$ +10.4 (*c* 0.2, CH_2Cl_2). IR (film): 1721, 1757, 3394 cm^{-1}. HRMS (ESI), *m*/*z* $(M+Na)^+$, calcd for $C_{21}H_{19}NO_7Na$: 420.1054, found: 420.1072, ^1H NMR (500 MHz, $CDCl_3$) *δ*: 3.58 (m, 1H, H-2), 4.07 (m, 1H, H-2′), 4.63–4.70 (m, 2H, H-4, CH_AH_BOBz), 4.93–4.99 (m, 2H, H-7, CH_AH_BOBz), 5.13 (m, 1H, H-3), 5.44 (dd, *J*=3.2 Hz, 1H, H-6), 7.48–8.07 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$) *δ*: 39.55, 61.78, 65.59, 73.47, 74.80, 78.86, 128.56, 2×128.67, 128.97, 129.72, 129.92, 2×133.66, 165.57, 165.91, 172,39.

4.1.13. (3*S*,4*R*,6*R*,7*R*)-7-Azido-3-benzoyloxy-4-benzoyloxymethyl-5-oxa-cepham (55). Tf_2O (0.047 g, 0.17 mmol) was added to pyridine (2 mL) at −20 °C under argon. After 5 min a solution of **54** (0.056 g, 0.14 mmol) in pyridine (2 mL) was added and the mixture was left for 30 min. Subsequently the solvent was removed under diminished pressure. The residue was dissolved in DMF (10 mL), treated with NaN_3 (0.065 g, 1.0 mmol) and heated to 70 °C for 30 min until disappearance of the triflate (TLC). Subsequently, the mixture was cooled to room temperature, treated

with water (20 mL) and extracted with AcOEt (3×20 mL). Organic layer was dried and evaporated. The crude product was purified by chromatography using hexane/AcOEt, 9:1 v/v as an eluent to afford **55** (44 mg, 75%). $[\alpha]_D^{22}$ +69.4 (*c* 1.8, CH_2Cl_2). IR (film): 1722, 1782, 2114 cm^{-1}. HRMS (ESI), *m/z* $(M+Na)^+$, calcd for $C_{21}H_{18}N_4O_6Na$: 445.1119, found: 445.1133. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.65 (dd, *J*=3.1, 15.0 Hz, 1H, H-2), 4.08 (m, 1H, H-2′), 4.58 (s, 1H, H-7), 4.61 (m, 2H, H-4, CH_AH_BOBz), 4.86 (m, 1H, CH_AH_BOBz), 5.10 (m, 1H, H-3), 5.29 (s, 1H, H-6), 7.47–8.06 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$) δ: 40.70, 60.02, 64.74, 72.39, 73.62, 79.65, 128.65, 128.73, 128.98, 128.99, 129.73, 129.82, 133.72, 133.74, 163.80, 165.48, 165.89.

4.1.14. (3*S*,4*R*,6*R*,7*R*)-7-Acetamino-3-benzoyloxy-4-benzoyloxymethyl-5-oxa-cepham (56). Compound **55** (0.030 g, 0.07 mmol) and 5% Pd/C in AcOEt (10 mL) were hydrogenated for 2 h. Subsequently the mixture was filtered through Celite and evaporated. The residue was acetylated with Ac_2O/Py mixture. Subsequently the mixture was evaporated and purified by chromatography using AcOEt to afford **56** (0.028 g, 90%). $[\alpha]_D^{22}$ +38.6 (*c* 0.4, CH_2Cl_2). IR (film): 1722, 1775, 3300 cm^{-1}. HRMS (ESI), *m/z* $(M+Na)^+$, calcd for $C_{23}H_{22}N_2O_7Na$: 461.1319, found: 461.1341. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.04 (s, 3H, Ac), 3.68 (dd, *J*=3.2, 14.9 Hz, 1H, H-2), 4.08 (m, 1H, H-2′), 4.60 (m, 1H, H-4), 4.64 (m, 1H, CH_AH_BOBz), 4.82 (dd, *J*=5.2, 11.0 Hz, 1H, CH_AH_BOBz), 4.86 (d, *J*=7.6 Hz, 1H, H-7), 5.10 (m, 1H, H-3), 5.38 (s, 1H, H-6), 6.01 (d, *J*=7.6 Hz, 1H, NH), 7.46–8.05 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$) δ: 22.86, 40.62, 62.10, 64.99, 65.68, 73.40, 80.72, 128.60, 128.67, 2×129.08, 129.76, 129.85, 133.60, 133.65, 165.52, 165.64, 165.95, 170.20.

4.1.15. (3*S*,4*R*,6*S*,7*R*)-3-Benzoyloxy-4-benzoyloxymethyl-7-hydroxy-5-oxa-cepham (58). Compound **58** was obtained from the mixture **52** (74%) according to the procedure described for **54**. $[\alpha]_D^{22}$ +46.7 (*c* 3, CH_2Cl_2). IR (film): 1722, 1759, 3424 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.03 (m, 1H, H-2), 4.27 (ddd, *J*=2.7, 5.6, 9.8 Hz, 1H, H-4), 4.50 (m, 2H, CH_AH_BOBz, H-7), 4.69 (dd, *J*=2.7, 12.2 Hz, 1H, CH_AH_BOBz), 4.93 (ddd, *J*=1.2, 3.2, 11.8 Hz, 1H, H-2′), 5.12 (dt, *J*=6.3, 9.5, 9.8 Hz, 1H, H-3), 5.14 (d, *J*=3.2 Hz, 1H, H-6), 7.42–8.02 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$) δ: 41.59, 63.37, 63.99, 75.17, 78.19, 79.48, 128.47, 128.59, 128.74, 129.4, 129.75, 129.81, 133.33, 133.74, 164.84, 166.22, 171.12.

4.1.16. (3*S*,4*R*,6*S*,7*R*)-7-Azido-3-benzoyloxy-4-benzoyloxymethyl-5-oxa-cepham (59). Compound **59** was obtained from **58** (85%) according to the procedure described for compound **55**. $[\alpha]_D^{22}$ −15.43 (*c* 0.3, CH_2Cl_2). IR (film): 1732, 1783, 2113 cm^{-1}. HRMS (ESI), *m/z* $(M+Na)^+$, calcd for $C_{21}H_{18}N_4O_6Na$: 445.1119, found: 445.1130. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.06 (dd, *J*=9.4, 13.1 Hz, 1H, H-2), 4.16 (ddd, *J*=2.6, 5.5, 9.8 Hz, 1H, H-4), 4.41 (dd, *J*=5.5, 12.3 Hz, 1H, CH_AH_BOBz), 4.53 (dd, *J*=6.4, 13.1 Hz, 1H, H-2′), 4.56 (s, 1H, H-7), 4.70 (dd, *J*=2.6, 12.3 Hz, 1H, CH_AH_BOBz), 5.02 (s, 1H, H-6), 5.08 (dt, *J*=6.4, 9.8, 1H, H-3), 7.42–8.02 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$) δ: 42.37, 63.13, 63.70, 70.92, 75.62, 83.14, 128.40, 128.50, 128.56, 129.26, 129.68, 129.73, 133.284, 133.77, 161.94, 164.73, 166.00.

4.1.17. (3*S*,4*R*,6*S*,7*R*)-7-Acetamino-3-benzoyloxy-4-benzoyloxymethyl-5-oxa-cepham (60). Compound **60** was obtained from **59** (92%) according to the procedure described for **56**. $[\alpha]_D^{22}$ +17.9 (*c* 0.4, CH_2Cl_2). IR (film): 1722, 1777, 3313 cm^{-1}. HRMS (ESI), *m/z* $(M+Na)^+$, calcd for $C_{23}H_{22}N_2O_7Na$: 461.1319, found: 461.1338. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.02 (s, 3H, Ac), 3.08 (dd, *J*=9.4, 13.0 Hz, 1H, H-2), 4.14 (ddd, *J*=2.7, 5.4, 9.7 Hz, 1H, H-4), 4.42 (dd, *J*=5.4, 12.2 Hz, 1H, CH_AH_BOBz), 4.52 (dd, *J*=6.4, 13.0 Hz, 1H, H-2′), 4.62 (d, *J*=7.35 Hz, 1H, H-7), 4.66 (dd, *J*=2.7, 12.2 Hz, 1H, CH_AH_BOBz), 5.07 (dt, *J*=6.4, 9.7, 1H, H-3), 5.24 (s, 1H, H-6), 5.20 (d, *J*=7.4 Hz, 1H, NH), 7.34–8.05 (10H, m, 2×Ph). ^{13}C NMR ($CDCl_3$) δ: 22.78, 42.28, 63.33, 64.07, 64.32, 75.49, 84.04, 128.41, 128.58, 128.74, 129.47, 129.76, 129.79, 133.24, 133.72, 164.06, 164.93, 166.20, 170.64.

4.1.18. (3*S*,4*R*,6*R*,7*S*)-7-Isopropyl-3-hydroxy-4-trityloxymethyl-5-oxa-cepham (61). Compound **17** (0.13 g, 0.43 mmol) in MeOH (10 mL) was hydrogenated in the presence of a catalytic amount of 10% Pd/C for 4 h. Subsequently the mixture was filtered and evaporated. The crude product was treated with TrCl in pyridine at 70 °C for 2 h. After standard workup and chromatographical purification, compound **61** was obtained (0.176 g, 90%). $[\alpha]_D^{22}$ +44.1 (*c* 0.4, CH_2Cl_2). IR (film): 1748, 3431 cm^{-1}. HRMS (ESI), *m/z* $(M+Na)^+$, calcd for $C_{29}H_{31}NO_4Na$: 480.2145, found: 480.2154. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.97 (d, *J*=6.5 Hz, 3H, CH_3), 1.15 (d, *J*=6.7 Hz, 3H, CH_3), 2.20 (m, 1H, $CH(CH_3)_2$), 2.86 (ddd, *J*=1.4, 3.5, 11.3 Hz, 1H, H-7), 3.04 (dd, *J*=1.4, 3.1, 14.1 Hz, 1H, H-2), 3.41 (dd, *J*=6.4, 10.1 Hz, 1H, CH_AH_BOTr), 3.51 (dd, *J*=5.6, 10.1 Hz, 1H, CH_AH_BOTr), 3.64 (dt, *J*=1.3, 14.1 Hz, 1H, H-2′), 3.74 (m, 1H, H-3), 4.15 (m, 1H, H-4), 5.00 (d, *J*=3.5 Hz, 1H, H-6), 7.27–7.44 (m, 15H, OTr).

4.1.19. (3*S*,4*R*,6*R*,7*S*)-7-Isopropyl-3-oxo-4-trityloxymethyl-5-oxa-cepham (62). Compound **61** (0.1 g, 0.22 mmol) in CH_2Cl_2 (10 mL) was treated with PCC (0.056 g, 0.26 mmol) and molecular sieves MS 4 Å (0.02 g). The reaction mixture was stirred under reflux until disappearance of the substrate (4 h, TLC). Subsequently it was filtered by Celite and concentrated. The residue was filtered by chromatography using hexane/AcOEt, 7:3 v/v as an eluent to afford **62** (0.09 g, 90%). $[\alpha]_D^{22}$ +77.13 (*c* 0.3, CH_2Cl_2). IR (film): 1763, 1778 cm^{-1}. HRMS (ESI), *m/z* $(M+Na)^+$, calcd for $C_{29}H_{29}NO_4Na$: 478.1989, found: 478.2009. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.99 (d, *J*=6.4 Hz, 3H, CH_3), 1.18 (dd, *J*=6.7 Hz, 3H, CH_3), 2.55 (m, 1H, $CH(CH_3)_2$), 3.06 (ddd, *J*=1.6, 3.5, 11.6 Hz, 1H, H-7), 3.56 (dd, *J*=2.3, 10.4 Hz, 1H, CH_AH_BOTr), 3.69 (dd, *J*=4.7, 10.4 Hz, 1H, CH_AH_BOTr), 3.84 (dt, *J*=1.6, 19.5 Hz, 1H, H-2), 4.41 (m, 1H, H-4), 4.47 (d, *J*=19.5 Hz, 1H, H-2′), 5.74 (d, *J*=3.5 Hz, 1H, H-6), 7.27–7.38 (m, 15H, OTr). ^{13}C NMR ($CDCl_3$) δ: 20.49, 21.48, 24.51, 60.34, 62.33, 65.66, 77.52, 79.80, 87.78, 127.36, 128.00, 128.52, 143.08, 172.51, 201.37.

4.1.20. (4*R*,6*R*,7*S*)-3-Acetoxy-7-isopropyl-2-ethoxycarbonyl-4-trityloxymethyl-5-oxa-2-cephem (63). Compound **62** (0.017 g, 0.038 mmol) in toluene (5 mL) at −45 °C under argon was treated with KHMDS (0.045 mmol, 0.091 mL, 0.5 M in toluene). After 30 min

ethyl cyanoformate (0.045 mmol, 0.004 mL) was added. Stirring was continued for 30 min and then the solution was treated with Ac_2O (0.5 mL) in pyridine (5 mL) with catalytic amount of DMAP. The mixture was stirred for 4 h at room temperature and then brine (10 mL) was added. The mixture was extracted with AcOEt (3×20 mL). The extract was dried and evaporated. The residue was purified by chromatography using hexane/AcOEt, 95:5 v/v as an eluent to afford **63** (0.012 g, 60%). $[\alpha]_D^{22}$ −54.3 (*c* 0.1, CH_2Cl_2). IR (film): 1727, 1776 cm^{-1}. HRMS (ESI), *m/z* $(M+Na)^+$, calcd for $C_{34}H_{35}NO_7Na$: 592.2306, found: 592.2329. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 1.02 (d, *J*=6.4, 3H, CH_3), 1.14 (d, *J*=6.7 Hz, 3H, CH_3), 1.32 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 2.04 (s, 3H, OAc), 2.25 (m, 1H, $CH(CH_3)_2$), 3.10 (dd, *J*=3.9, 11.8 Hz, 1H, H-7), 3.31 (dd, *J*=2.6, 10.6 Hz, 1H, CH_AH_BOTr), 3.39 (dd, *J*=4.7, 10.6 Hz, 1H, CH_AH_BOTr), 4.24 (dq, *J*=10.7, 7.1 Hz, 1H, $OCH_AH_BCH_3$), 4.34 (dq, *J*=10.8, 7.1 Hz, 1H, $OCH_AH_BCH_3$), 4.59 (m, 1H, H-4), 5.44 (d, *J*=3.9 Hz, 1H, H-6), 7.25–7.43 (15H, m, OTr). ^{13}C NMR ($CDCl_3$) *δ*: 14.07, 20.36, 20.46, 21.64, 24.20, 60.37, 61.43, 61.63, 63.57, 72.89, 76.19, 87.15, 119.49, 127.26, 127.93, 128.65, 143.26, 159.74, 167.32, 169.18.

4.1.21. Assay of DD-carboxypeptidase activity. The enzyme activity was measured as described previously.[16,17] Samples for the assay of the DD-carboxypeptidase activity consisted of 10 μL of DD-carboxypeptidase from *Saccharopolyspora erythraea* PZH TZ 64-575 (40 units/mg), 20 μL of substrate solution containing 4.52 mg/mL *N*α,*N*ε-diacetyl-L-lysyl-D-alanyl-D-alanine in 0.1 M phosphate buffer, pH 8.0 and 10 μL of 0.1 M phosphate buffer, pH 8.0. Standard sample contained 20 μL of D-alanine in distilled water.

Reaction mixture for assay of the DD-carboxypeptidase activity consisted of 60 μL of 0.05 mg/mL flavin adenine dinucleotide in 0.1 M phosphate buffer, pH 8.0, 10 μL of 0.05 mg/mL horseradish peroxidase (1230 units/mg) in distilled water, 5 μL of 5 mg/mL *o*-dianisidine in methanol, and 2 μL of 11.77 mg/mL D-amino acid oxidase from porcine kidney (6.7 units/mg) in 0.1 M phosphate buffer, pH 8.0.

Samples were incubated for 30 min at 37 °C and then boiled for 2 min. After cooling, 77 μL of the reaction mixture was added, and all samples were incubated for 10 min at 37 °C. Next, to each sample 350 μL of mixture consisting of methanol, distilled water, and sulfuric acid (5:5:6 by volume) were added. Extinction of the resulting solution was measured at 540 nm.

The inhibition of DD-peptidase 64-575 by the oxacephams discussed above was evaluated.[17,18] Mixtures of 10 μL of DD-peptidase 64-575 (40 units/mg), 5 μL solution of an oxacepham in methanol, and 5 μL of 0.1 M phosphate buffer, pH 8.0 were incubated for 45 min at 37 °C. The concentration of a cepham in the mixture was from 2.3×10^{-2} to 1.3×10^{-5} M. Following the incubation, 20 μL of substrate solution was added to 20 μL of each sample and resulted mixtures were incubated again.

The inhibition of penicillinase was evaluated following the literature method.[19] The samples for the assay of inhibition of β-lactamase consisted of 10 μL of penicillinase (Penase, 5×10^6 IU/mL, Bacto), 20 μL, 0.1 M phosphate buffer, pH 7.0 and 10 μL solution of oxacephams in methanol. The samples were incubated for 30 min at 37 °C. Then 30 mL of nitrocephin and 430 μL, 0.1 M phosphate buffer pH 7.0 were added, and all the samples were incubated for 10 min at 37 °C. Absorption was measured at 482 nm.

The following oxacephams were tested for both activities: **17**, **18**, **56**, and **63**.

Acknowledgements

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Supplementary data

Supplementary data including spectral and analytical data for compounds **21**–**25** and **31**–**34** are available on the www under http://www.sciencedirect.com or from the authors. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.074.

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Synthesis of a β-strand mimetic based on a pyridine scaffold

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Abstract—A synthetic route to a 2,4-disubstituted pyridine as a potential β-strand mimetic has been developed and applied in the synthesis of a tripeptidomimetic of Leu-Gly-Gly. The pyridine scaffold replaces the central glycine, and is substituted with analogues of leucine and glycine in positions 4 and 2, respectively. 2-Fluoro-4-iodopyridine was chosen as the functionalized scaffold and was substituted with protected leucinal in position 4 via a Grignard exchange reaction using *iso*-propyl magnesium chloride. The glycine moiety was introduced in position 2 via a nucleophilic aromatic substitution reaction (S_NAr) facilitated by microwave irradiation. The synthetic sequence involved 12 steps with an overall yield of 7%.

1. Introduction

A β-strand is a saw-toothed arrangement where amino acid side chains alternate above and below a linear peptide backbone.[1] There are no intramolecular hydrogen bonds between the amino acids that make up a β-strand. However, by reversing the overall direction of the peptide backbone via a turn or a loop, a second β-strand may hydrogen bond to the first one, thereby initiating β-sheet formation. β-Strands are thus key elements in β-sheet secondary structures[2] and are also known to be important in protein–protein and protein–ligand interactions in various biological systems.[2]

Our research group is involved in studies of two systems where interactions between β-strands and proteins are crucial for the biological outcome. The molecular machinery of pilus assembly in uropathogenic *Escherichia coli* (UPEC) constitutes one system.[3,4] Adhesive pili, which are supramolecular protein appendages that anchor the UPEC to host tissue, are required for the pathogenicity of the bacterium. Such pili are formed through a highly conserved process called the chaperone/usher pathway, where interactions between β-strands are required both in the folding of pilus subunits and in the assembly of the subunits into functional pili.[3,4] Recently it was shown that peptides derived from β-strands of pilus subunits can inhibit the protein–protein interactions required for pilus assembly,[5] suggesting that β-strand mimetics may constitute leads for the development of a novel class of antibiotics targeting pilus assembly in UPECs.[6,7] The second system involves binding and presentation of a glycopeptide from type II collagen by major histocompatibility complex (MHC) molecules in an animal model for rheumatoid arthritis (RA).[8] This glycopeptide–MHC interaction has been found to be essential for the development of arthritis in mice, and further studies have shown that vaccination with the glycopeptide epitope has a protective effect.[9] A recent study identified the minimal, active glycopeptide epitope to consist of an octapeptide,[10] thereby setting the stage for developing β-strand mimetics as immunomodulators for treatment of RA.[11]

The important biological functions of peptides, together with their generally poor pharmacokinetic properties, make the development of peptidomimetics highly desirable. β-Strand mimetics have been developed by incorporation of a wide range of amide bond bioisosters,[2] including olefins[12] in the peptide backbone. Introduction of cyclic systems[13–17] to reduce flexibility and/or to induce extended conformations has also been used. Among cyclic systems, pyrrolinones have been particularly successful in retaining the biological activity of the original peptide.[15–17,18]

In this study a synthetic route to β-strand mimetics **2**, based on a 2,4-disubstituted pyridine scaffold (Fig. 1), has been developed. In mimetic **2**, which was designed using semiempirical and molecular mechanic calculations,[19] the pyridine scaffold replaces the central amino acid of a tripeptide sequence. Residues corresponding to the N-terminal and the C-terminal amino acids are attached at positions 4 and 2 of the pyridine ring, respectively.[19] As reported previously the scaffold permits introduction of a residue in position 3 of

Keywords: β-Strand mimetic; 2-Aminopyridine; Grignard exchange reaction; Nucleophilic aromatic substitution.
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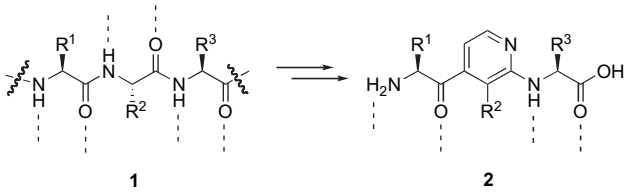


Figure 1. β-Strand mimetic **2**, which mimics tripeptide fragment **1**, was designed[19] based on a 2,4-disubstituted pyridine scaffold. Mimetic **2** lacks the two central amide bonds of tripeptide fragment **1**, but retains some of the hydrogen bonding capacity of **1**.

the pyridine ring, which corresponds to the side chain of the central amino acid of the tripeptide.[19,20] The two amide bonds have been replaced by a keto functionality at position 4 of the pyridine scaffold and by an amine at position 2, which thus serve as amide bioisosters. Additionally, the pyridine nitrogen atom is positioned with potential to mimic the carbonyl oxygen atom in the amide bond between the second and third residues of the original tripeptide. As a consequence of this modified hydrogen bonding pattern the β-strand mimetic maintains the ability to form hydrogen bonds with a complementary β-strand in one, but not in the other direction (Fig. 1).

2. Results and discussion

In order to establish the synthetic conditions that allow the synthesis of β-strand mimetics **2**, we choose Leu-Gly-Gly tripeptide mimetic **4** as our first target (Fig. 2). This requires the central pyridine scaffold to be substituted with a leucine and a glycine moiety in positions 4 and 2, respectively. Model compound **4** was thus chosen so as to contain a stereogenic center adjacent to the carbonyl group of the N-terminal moiety, while the C-terminal residue was kept simple at this stage. A retrosynthetic analysis revealed that mimetic **4** could be prepared from protected leucinal **5**, 2-fluoro-4-iodopyridine (**6**), and a glycine equivalent (**7**).

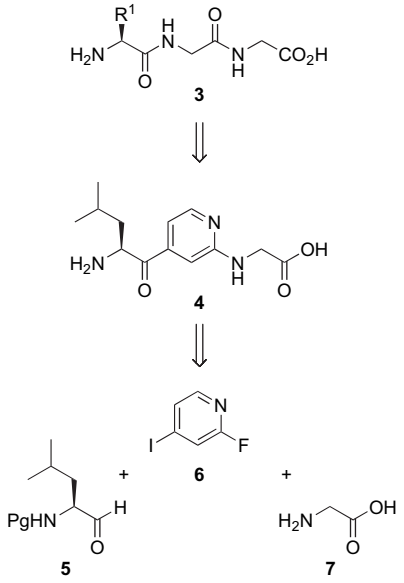
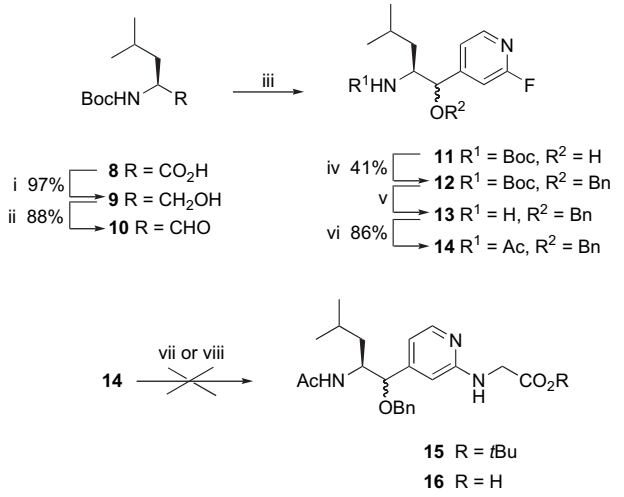


Figure 2. A retrosynthetic analysis suggests that β-strand mimetic **4** can be prepared from protected leucinal **5**, 2-fluoro-4-iodo-pyridine (**6**), and a glycine equivalent (**7**).

2-Fluoro-4-iodopyridine is a key building block and can be synthesized in two steps from 2-fluoropyridine.[21] The moiety in mimetic **4**, which corresponds to the leucine residue was intended to be introduced at position 4 of the pyridine scaffold via a Grignard exchange reaction[22] of the iodine atom with protected *S*-leucinal as electrophile.[20] Introduction of the glycine equivalent, which corresponds to the third amino acid of the tripeptide, was thereafter planned to be achieved by displacement of the fluorine atom of the scaffold via a nucleophilic aromatic substitution reaction (S_NAr).

The synthetic route started by reduction[23] of Boc-protected leucine **8** to alcohol **9** in 97% yield (Scheme 1). This was achieved via activation of the carboxyl group of **8** as a mixed anhydride using *iso*-butyl chloroformate, followed by reduction using sodium borohydride. Alcohol **9** was subsequently oxidized[24] to aldehyde **10** by treatment with Dess–Martin periodinane (88%). By keeping the product cold during work-up and continuing directly with the next step without further purification, epimerization of this sensitive intermediate was avoided.[25,26] In order to couple the central pyridine scaffold to aldehyde **10**, 2-fluoro-4-iodopyridine was treated with *iso*-propyl magnesium chloride at room temperature for 3 h to conduct a Grignard exchange reaction.[20] Addition of aldehyde **10** to the Grignard reagent then afforded alkylated pyridine **11** without affecting the fluorine atom in position 2 of the pyridine ring. Purification of alkylated pyridine **11** turned out to be more problematic than expected. Therefore, the alcohol functionality of crude **11** was directly protected as a benzyl ether under phase transfer conditions,[27] which allowed facile purification to give ether **12** (41% from **10**).

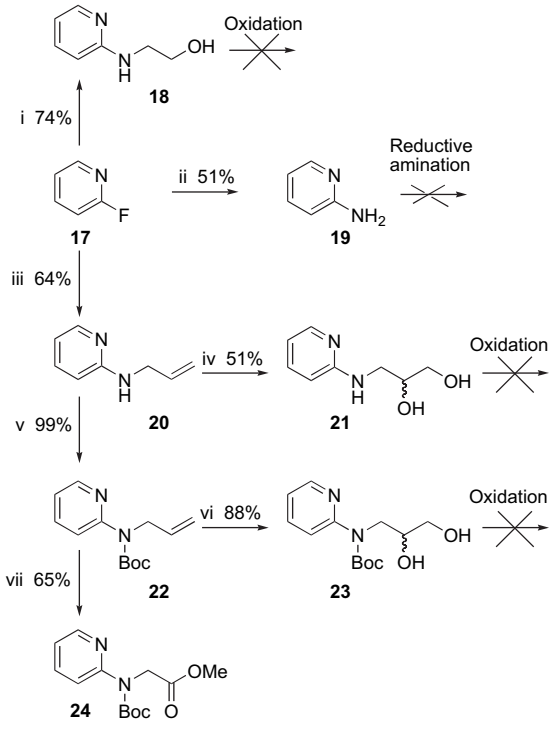


Scheme 1. Reagents and conditions: (i) NMM, *iso*-butyl chloroformate, $NaBH_4$, MeOH, THF, −15 °C, 97%; (ii) Dess–Martin periodinane, CH_2Cl_2, 88%; (iii) *iso*-PrMgCl, 2-fluoro-4-iodopyridine, THF; (iv) benzyl bromide, $QHSO_4$, 50% NaOH (aq), toluene, 41% from **10**; (v) formic acid; (vi) Ac_2O, DMAP, CH_2Cl_2, 86% from **12**; (vii) H_2N-Gly-O*t*Bu, pyridine, 150→180 °C; (viii) H_2N-Gly-OH, satd $NaHCO_3$ aq, 160 °C.

The C-terminal glycine moiety of the target β-strand mimetic was planned to be introduced by replacing the fluorine atom of **12** in an S_NAr reaction. In contrast to the substitution of 2-fluoropyridine analogues of **12** with oxygen nucleophiles, which has been accomplished under relatively mild conditions,[19,20] substitution of **12** with amines turned out

to be a significant challenge. Preferably the amino group of a glycine derivative would serve as a nucleophile in the substitution reaction. Initial attempts to accomplish this substitution resulted in partial cleavage of the Boc-group of **12**. The Boc-group was therefore removed using formic acid to give **13** and replaced by an acetyl group by treatment with acetic anhydride in dichloromethane to afford **14** (86% from **12**). As revealed by LCMS analysis, microwave irradiation of **14** at 150 °C for 1 h with glycine *tert*-butyl ester in pyridine gave the desired substitution product **15**, but only in trace amounts (appr. 1% yield). Raising the temperature to 180 °C did not increase the yield of **15**, instead this resulted in formation of a black solid in the reaction mixture, almost certainly by decomposition and polymerization of glycine *tert*-butyl ester. This was confirmed by running the same experiment without **14** present, which also resulted in a black solid. Based on the finding that the problems originated from the *tert*-butyl ester of glycine, substitution of **14** was attempted with unprotected glycine. In order to dissolve glycine, aqueous sodium hydrogen carbonate was used as solvent in the microwave assisted substitution reaction. When carried out at 160 °C for 1 h the desired product **16** was indeed obtained, but in an unsatisfactory yield (<10% according to LCMS) and accompanied by equal amounts of the product resulting from attack of water at position 2 of the pyridine ring.

In view of the difficulties encountered in the nucleophilic substitutions of **14** it was decided to study the reactions between 2-fluoropyridine (**17**) and various amines as model systems (Scheme 2). Just as for **14**, attempts to react glycine

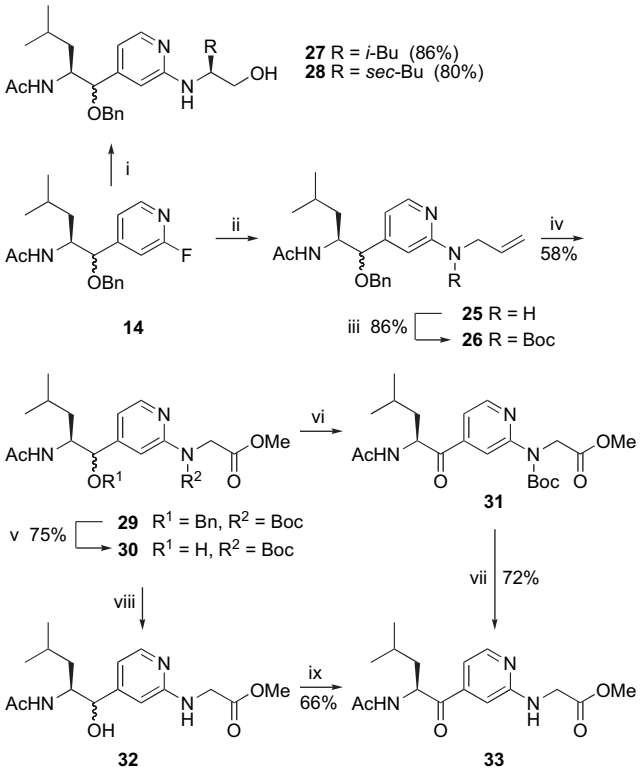


Scheme 2. Reagents and conditions: (i) ethanolamine, 2-fluoropyridine, pyridine, 210 °C, 74%; (ii) 25% NH_3 in H_2O, ~140 °C, 51%; (iii) allylamine, 2-fluoropyridine, pyridine, 190 °C, 64%; (iv) potassium osmate, NMO, H_2O, THF, acetone, 51%; (v) Boc_2O, DMAP, CH_2Cl_2, 99%; (vi) potassium osmate, NMO, H_2O, THF, acetone, 88%; (vii) NaOH (2 M in MeOH), CH_2Cl_2, O_3, −78 °C→rt, 65%.

or the *tert*-butyl ester of glycine with 2-fluoropyridine under different conditions using microwave irradiation failed; no reaction was observed with glycine while the *tert*-butyl ester of glycine polymerized into an insoluble black solid. Therefore, other glycine equivalents were explored as nucleophiles. Microwave irradiation of ethanolamine and 2-fluoropyridine in pyridine at 210 °C for 1 h gave derivative **18** (74%). Unfortunately, attempted oxidation of the alcohol functionality in **18** with Dess–Martin periodinane to give the corresponding aldehyde, or with ruthenium trichloride to the corresponding acid was unsuccessful. In an attempt to circumvent the problematic oxidation step, 2-fluoropyridine was converted to 2-aminopyridine[28] (**19**) by heating in 25% aqueous ammonia in a sealed steel cylinder. Anisaldehyde was then used to investigate different conditions for reductive amination of **19**. At best, a modest 36% yield could be obtained when sodium triacetoxyborohydride was used as the reducing agent in 1,2-dichloroethane under basic conditions.[29] Disappointingly, when these conditions were applied to reductive amination of 2-aminopyridine with glyoxylic acid, or with the more soluble *tert*-butyl glyoxylate[30] neither of the products were obtained.

Nucleophilic substitution of 2-fluoropyridine (**17**) was then investigated using allylamine as nucleophile, with the alkene part intended as a carboxylic acid precursor. Substitution was achieved by microwave irradiation of 2-fluoropyridine and allylamine in pyridine at 190 °C for 1 h to give substituted pyridine **20** (64%). Oxidation of the alkene moiety of **20** was accomplished by a catalytic amount of potassium osmate with *N*-methyl morpholine *N*-oxide as co-oxidant in a solvent mixture of water, tetrahydrofuran, and acetone to give diol **21** (51%). Further oxidation of diol **21** was first attempted with lead tetraacetate in toluene to give the corresponding aldehyde, and then with sodium periodate and bromine in methanol to give an ester functionality,[31] but neither of the desired products were obtained. Also, when direct oxidation[32] of the olefin in **20** to a methyl ester was attempted by ozonolytic cleavage in a mixture of methanolic sodium hydroxide and dichloromethane, all starting materials were consumed but no product was formed. To eliminate the possibility that the anilinic proton of **20** interferes during oxidation, aminopyridine **20** was protected[33] using Boc-anhydride and a catalytic amount of 4-dimethylaminopyridine to give derivative **22** (99%). Just as for **20** oxidation of **22** to diol **23** (88%) was successful, but again further oxidation of the diol failed. However, when Boc-protected aminopyridine **22** was treated with ozone in methanolic sodium hydroxide and dichloromethane,[34] the olefin was oxidized to give the desired ester **24** (65%).

Synthesis of the Leu-Gly-Gly β-strand mimetic from building block **14** was then brought to completion based on the learnings from the model study. Consequently, **14** was subjected to microwave irradiation in neat allylamine (2.5 h, 17 bar, ~150 °C) to give substituted pyridine **25** which, after aqueous work-up, was protected[33] with a Boc-group to afford protected 2-aminopyridine **26** (86% from **14**, Scheme 3). In order to investigate if more sterically demanding amino acid derivatives than the glycine equivalents ethanolamine and allylamine could be employed in the critical aromatic substitution of **14**, leucinol and *iso*-leucinol were chosen as nucleophiles. Building block **14** was first



Scheme 3. Reagents and conditions: (i) (a) leucinol, microwave irradiation 200 °C, to give **27**, 86%; (b) *iso*-leucinol, microwave irradiation 200–210 °C, to give **28**, 80%; (ii) allylamine, microwave irradiation (17 bar, ~150 °C); (iii) Boc_2O, DMAP, CH_2Cl_2, 86% from **14**; (iv) NaOH (2 M in MeOH), CH_2Cl_2, O_3, −78 °C→rt, 58%; (v) Pd/C, H_2 (1 atm), MeOH, AcOH, 75%; (vi) Dess–Martin periodinane, CH_2Cl_2; (vii) formic acid, 72% from **30**; (viii) 25% TFA in CH_2Cl_2; (ix) Dess–Martin periodinane, CH_2Cl_2, 66% from **30**.

dissolved in leucinol (appr. 20 equiv) and heated to 200 °C by microwave irradiation, which afforded substituted pyridine **27** (86%). Encouraged by this result, the even more sterically hindered *iso*-leucinol was used as nucleophile and gave the desired compound **28** (80%) when heating to 210 °C. Further attempts to convert derivatives **27** and **28**, or analogues thereof, into more complex β-strand mimetics will be the subject of future studies. Instead the synthetic sequence continued with oxidation of the olefinic part of **26** to methyl ester **29** (58%) by ozonolytic cleavage in basic methanolic solution.[32] Careful adjustment of the reaction time was necessary to avoid oxidation of the benzyl ether in **29** to an undesired benzoyl ester. Thereafter the benzyl ether of **29** was removed by hydrogenolysis in a mixture of methanol and acetic acid to give **30** (75%). Oxidation to ketone **31** using Dess–Martin periodinane followed by removal of the Boc-protective group afforded the desired β-strand mimetic **33** (72% from **30**). Somewhat surprisingly, chiral chromatography of mimetic **33** on a silica based column, revealed that partial epimerization (~60% ee) of the chiral center of **33** had occurred. However, ketone **31**, the direct precursor of **33**, was found to be enantiomerically pure as determined by chiral chromatography. It was therefore concluded that cleavage of the Boc-group of pure **31**, under acidic conditions had caused the epimerization via enolization of the ketone. To circumvent this problem, acidic removal of the Boc-group was performed already on alcohol **30** using trifluoroacetic acid (25%) in dichloromethane to give amine **32**. Finally, oxidation of the alcohol moiety of **32** using Dess–Martin periodinane gave β-strand mimetic **33** (66% from **30**) in enantiomerically pure form according to chiral chromatography. In conclusion, the synthesis of β-strand mimetic **33** was accomplished in a 12-step synthetic sequence with an overall yield of 7%.

3. Experimental

3.1. General

^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ or in CD_3OD at 298 K. ^1H NMR and ^{13}C NMR signals are assigned with support from appropriate 2D-NMR and are presented in Supplementary data. For compounds that contain an uneven mixture of diastereomers (**12**–**14** and **25**–**30**), only signals for the major diastereomer are assigned. All microwave irradiations were performed in a Smithcreator with Emrys™ process vials (2–5 mL for compounds **18**, **20**, and **25**, or 0.5–1.5 mL for compounds **27** and **28**), temperature and pressure measurements were performed by infrared detection. Chiral HPLC was run on a Pirkle covalent (*S*,*S*) whelk-O1 10/100 Krom FCC, with heptane/CH_2Cl_2/2-propanol 48:48:4 for compounds **33** and **33***rac*, 49:49:2 for compounds **31** and **31***rac* as eluent. Chromatograms of both **33** and **33***rac* are presented in Supplementary data.

3.2. Procedures

3.2.1. *tert*-Butyl [(1*S*)-1-(hydroxymethyl)-3-methylbutyl]carbamate (9). Boc-Leu-OH·H_2O (**8**, 7.0 g, 28 mmol) was evaporated from toluene and dissolved in THF (80 mL). *N*-Methyl morpholine (3.3 mL, 29 mmol) was added and the reaction was cooled to −20 °C. The reaction was treated with *iso*-butyl chloroformate (4.4 mL, 29 mmol) and stirred for 30 min. The formed precipitate was removed by filtration and rinsed with THF (30 mL). To the clear filtrate $NaBH_4$ (3.2 g, 84 mmol) was added in one portion followed by careful addition of methanol (200 mL) at −20 °C. After 1 h the reaction was quenched with satd NH_4Cl aq followed by addition of EtOAc. The two phases were separated and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel pretreated with triethylamine) EtOAc/heptane 1:4→1:2 to give alcohol **9** (5.9 g, 97%) as a clear oil; $[\alpha]_D^{20}$ −25.8 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.62 (d, J=8.0 Hz, 1H), 3.76–3.59 (m, 2H), 3.53–3.44 (m, 1H), 2.72 (s, 1H), 1.71–1.59 (m, 1H), 1.43 (s, 9H), 1.34–1.25 (m, 2H), 0.92 (d, J=1.7 Hz, 3H), 0.91 (d, J=1.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 79.6, 66.5, 51.0, 40.5, 28.4, 24.8, 23.0, 22.2; IR (neat): 3590–3138, 1688, 1529 cm^{-1}; FABHRMS calcd for $C_{11}H_{24}NO_3$ (M+H): 218.1756, found: 218.1756.

3.2.2. *tert*-Butyl [(1*S*)-1-formyl-3-methylbutyl]carbamate (10). Alcohol **9** (0.11 g, 0.51 mmol) was dissolved in CH_2Cl_2 (3 mL) and treated with Dess–Martin periodinane in CH_2Cl_2 (1.6 mL, 15 wt % in CH_2Cl_2, 0.76 mmol). After 1 h a white precipitate was formed and sodium bisulfite (1.0 g, 5.3 mmol) in satd $NaHCO_3$ aq was added. The organic layer was washed with satd $NaHCO_3$ aq, dried

over Na_2SO_4, and concentrated under reduced pressure at 0 °C to give aldehyde **10** (96 mg, 88%) as a clear oil, which was used without further purification for the next step.

3.2.3. *tert*-Butyl {(1*S*)-1-[(*RS*)-(benzyloxy)(2-fluoropyridin-4-yl)methyl]-3-methylbutyl}carbamate (12). 2-Fluoro-4-iodopyridine (1.2 g, 5.4 mmol) and *iso*-propyl magnesium chloride (2.6 mL, 5.5 mmol) was stirred in THF (2 mL) for 3 h. To this solution aldehyde **10** (0.56 g, 2.6 mmol) dissolved in THF (2 mL) was added and the mixture was stirred for another 15 h. The reaction was quenched with satd NH_4Cl aq followed by addition of satd $NaHCO_3$ aq and brine and extraction with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. To the residue toluene (40 mL) and NaOH aq (50%, 30 mL) were added. The vigorously stirred two phase system was treated with benzyl bromide (0.31 mL, 2.8 mmol) and tetrabutylammonium hydrogen sulfate (0.10 g, 0.30 mmol). After 3 h water was added followed by extraction with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography EtOAc/heptane 1:9→1:4 to give **12** (0.43 g, 41%) as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J=5.1 Hz, 1H), 7.40–7.27 (m, 5H), 7.12 (d, J=5.1 Hz, 1H), 6.92 (s, 1H), 4.60 (d, J=9.9 Hz, 1H), 4.56 (d, J=12 Hz, 1H), 4.43 (d, J=1.7 Hz, 1H), 4.32 (d, J=12 Hz, 1H), 3.94–3.85 (m, 1H), 1.64–1.51 (m, 1H), 1.44–1.36 (m, 2H), 1.30 (s, 9H), 0.91 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (d, J_{C-F}=239 Hz), 155.1, 147.5 (d, J_{C-F}=15 Hz), 137.1, 128.5, 128.1, 128.0, 119.9, 107.7 (d, J_{C-F}=37 Hz), 80.5, 79.3, 71.8, 53.2, 41.2, 28.2, 24.7, 23.0, 22.1; IR (neat): 1703, 1612 cm^{-1}; FABHRMS calcd for $C_{23}H_{32}FN_2O_3$ (M+H): 403.2397, found: 403.2389.

3.2.4. *N*-{(1*S*)-1-[(*RS*)-(Benzyloxy)(2-fluoropyridin-4-yl)-methyl]-3-methylbutyl}acetamide (14). Boc-protected amine **12** (0.31 g, 0.77 mmol) was treated with formic acid (12 mL) for 3 h. Formic acid was removed under reduced pressure and the residue was dissolved in EtOAc and washed with satd $NaHCO_3$ aq and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (7.5 mL) followed by addition of acetic anhydride (0.08 mL, 0.86 mmol) and 4-dimethylaminopyridine (0.1 g, 0.82 mmol). After 2 h a 1:3 mixture of satd $NaHCO_3$ aq and brine was added and the two phases were separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography EtOAc/heptane 3:2 to give **14** (0.23 g, 86%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J=5.2 Hz, 1H), 7.41–7.28 (m, 5H), 7.10 (d, J=5.2 Hz, 1H), 6.88 (s, 1H), 5.53 (d, J=9.7 Hz, 1H), 4.57 (d, J=11 Hz, 1H), 4.47 (d, J=2.7 Hz, 1H), 4.34 (d, J=11 Hz, 1H), 4.31–4.23 (m, 1H), 1.85 (s, 3H), 1.55–1.46 (m, 1H), 1.45–1.39 (m, 2H), 0.91 (d, J=6.5 Hz, 3H), 0.89 (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 164.0 (d, J_{C-F}=237 Hz), 154.9 (d, J_{C-F}=7 Hz), 147.6 (d, J_{C-F}=15 Hz), 136.9, 128.6, 128.3, 128.1, 119.7 (d, J_{C-F}=4 Hz), 107.5 (d, J_{C-F}= 38 Hz), 80.0, 72.0, 51.7, 41.1, 24.8, 23.1, 23.0, 22.2; IR (neat): 1652, 1552 cm^{-1}; FABHRMS calcd for $C_{20}H_{26}FN_2O_2$ (M+H): 345.1978, found: 345.1977.

3.2.5. 2-(Pyridin-2-ylamino)ethanol (18). 2-Fluoropyridine (0.3 mL, 3.5 mmol) was dissolved in pyridine (1 mL) and ethanolamine (2.1 mL, 35 mmol). The reaction was subjected to microwave irradiation at 210 °C for 1 h. Satd $NaHCO_3$ aq and EtOAc were added to the reaction and the two phases were separated. The aqueous layer was extracted with EtOAc and CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give alcohol **18** (0.36 g, 74%) as a colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02–7.97 (m, 1H), 7.34 (ddd, J=9.2, 7.1, and 1.9 Hz, 1H), 6.57–6.52 (m, 1H), 6.42 (d, J=8.4 Hz, 1H), 5.06 (br s, 1H), 4.92 (br s, 1H), 3.77 (t, J=4.8 Hz, 2H), 3.49–3.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 147.1, 137.5, 112.9, 108.3, 63.0, 45.2; IR (neat): 3347–3132, 1607, 1524 cm^{-1}; FABHRMS calcd for $C_7H_{11}N_2O$ (M+H): 139.0871, found: 139.0878.

3.2.6. Allyl-pyridin-2-yl-amine (20). Allylamine (0.79 mL, 10.5 mmol) and 2-fluoropyridine (0.3 mL, 3.5 mmol) were dissolved in pyridine (2 mL) and subjected to microwave irradiation to 190 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography EtOAc/heptane 2:1 to give aminopyridine **20** (0.3 g, 64%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.05 (m, 1H), 7.39 (ddd, J=8.8, 7.1, and 1.9 Hz, 1H), 6.55 (ddd, J=7.1, 5.1, and 0.9 Hz, 1H), 6.37 (d, J=8.8 Hz, 1H), 5.99–5.88 (m, 1H), 5.28–5.22 (m, 1H), 5.16–5.11 (m, 1H), 4.78 (br s, 1H), 3.94–3.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 148.1, 137.3, 135.0, 115.8, 112.9, 106.6, 44.6; IR (neat): 3371–3178, 1601, 1571, 1510 cm^{-1}; FABHRMS calcd for $C_8H_{11}N_2$ (M+H): 135.0922, found: 135.0932.

3.2.7. 3-(Pyridin-2-ylamino)propane-1,2-diol (21). Alkene **20** (0.12 g, 0.92 mmol) was dissolved in H_2O (5.5 mL), acetone (5.5 mL), and THF (5.5 mL). Potassium osmate(VI) dihydrate (5 mg, 14 μmol) and *N*-methyl morpholine *N*-oxide (0.23 g, 1.96 mmol) were added and the reaction was stirred for 15 h. The solvents were removed under reduced pressure with toluene as azeotrope. The residue was purified by flash chromatography EtOH/toluene 1:6 to give diol **21** (0.78 g, 51%) as a colorless amorphous solid; ^{1}H NMR (400 MHz, CD_3OD) δ 7.92–7.87 (m, 1H), 7.41 (ddd, J=9.2, 7.0, and 1.9 Hz, 1H), 6.58–6.51 (m, 2H), 3.80–3.72 (m, 1H), 3.53 (d, J=5.6 Hz, 2H), 3.45 (dd, J=14.1 and 4.6 Hz, 1H), 3.32 (dd, J=14.1 and 6.3 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.6, 147.5, 138.8, 113.4, 110.2, 72.7, 64.8, 45.6; IR (neat): 3292, 1611, 1575 cm^{-1}; FABHRMS calcd for $C_8H_{13}N_2O_2$ (M+H): 169.0977, found: 169.0984.

3.2.8. *tert*-Butyl allyl(pyridin-2-yl)carbamate (22). Aminopyridine **20** (55 mg, 0.41 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and treated with di-*tert*-butyl dicarbonate (0.19 g, 0.86 mmol) and a catalytic amount of 4-dimethylaminopyridine (5 mg, 41 μmol). After 15 h satd $NaHCO_3$ aq was added and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4 and concentrated under

reduced pressure. The residue was purified by flash chromatography EtOAc/heptane 1:7 to give Boc-protected aminopyridine **22** (96 mg, 99%) as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38–8.34 (m, 1H), 7.67–7.57 (m, 2H), 7.01–6.96 (m, 1H), 6.00–5.89 (m, 1H), 5.18–5.06 (m, 2H), 4.58–4.53 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 154.2, 147.7, 136.9, 134.8, 119.6, 119.4, 115.8, 81.2, 49.2, 28.3; IR (neat): 1706, 1650, 1588, 1551 cm^{-1}; FABHRMS calcd for $C_{13}H_{19}N_2O_2$ (M+H): 235.1447, found: 235.1447.

3.2.9. *tert*-Butyl (2,3-dihydroxypropyl)pyridin-2-ylcarbamate (23). Boc-protected aminopyridine **22** (96 mg, 0.41 mmol) was dissolved in H_2O (2.5 mL), acetone (2.5 mL), and THF (2.5 mL). Potassium osmate(VI) dihydrate (5 mg, 14 μmol) and *N*-methyl morpholine *N*-oxide (0.10 g, 0.88 mmol) were added and the reaction was stirred for 15 h. Brine, satd $NaHCO_3$, and EtOAc were added and the two phases were separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography EtOAc/heptane 2:1 to give diol **23** (97 mg, 88%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29–8.25 (m, 1H), 7.69–7.63 (m, 1H), 7.59–7.54 (m, 1H), 7.08–7.03 (m, 1H), 4.01–3.91 (m, 2H), 3.87–3.79 (m, 1H), 3.64 (dd, *J*=12 and 4.8 Hz, 1H), 3.58 (dd, *J*=12 and 4.8 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 153.9, 146.4, 137.7, 120.3, 120.1, 82.2, 70.6, 64.1, 51.2, 28.1; IR (neat): 3605–3064, 1705, 1594, 1572 cm^{-1}; FABHRMS calcd for $C_{13}H_{21}N_2O_4$ (M+H): 269.1501, found: 269.1494.

3.2.10. (*tert*-Butoxycarbonyl-pyridin-2-yl-amino)-acetic acid methyl ester (24). Boc-protected aminopyridine **22** (0.10 g, 0.44 mmol) was dissolved in CH_2Cl_2 (3.5 mL) and a 2 M solution of NaOH in methanol (0.90 mL) and cooled to −78 °C. O_3 was passed through the solution, which turned bright yellow at first and gradually decolorized. A colorless precipitate was formed and the solution turned blue and the excess of O_3 was purged from the solution with a stream of oxygen. Water and Et_2O were added and the two phases were separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give ester **24** (75 mg, 65%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30–8.27 (m, 1H), 7.83 (br d, *J*=8.6 Hz, 1H), 7.62 (ddd, *J*=8.6, 7.3, and 1.9 Hz, 1H), 6.97 (ddd, *J*=7.3, 4.9, and 0.9 Hz, 1H), 4.71 (s, 2H), 3.73 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 153.5, 153.5, 147.1, 137.0, 119.2, 118.2, 82.0, 51.9, 47.7, 28.1; IR (neat): 1758, 1720, 1590 cm^{-1}; FABHRMS calcd for $C_{13}H_{19}N_2O_4$ (M+H): 267.1345, found: 267.1344.

3.2.11. *tert*-Butyl{4-[(1*RS*,2*S*)-2-(acetylamino)-1-(benzyloxy)-4-methylpentyl]pyridin-2-yl}allylcarbamate (26). Fluoropyridine **14** (0.23 g, 0.66 mmol) was dissolved in allylamine (4 mL) and subjected to microwave irradiation to 17 bar (~150 °C) for 2.5 h. Allylamine was removed under reduced pressure and the residue was dissolved in CH_2Cl_2, followed by addition of a 1:3 mixture of satd $NaHCO_3$ aq and brine. The two phases were separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL) and treated with di-*tert*-butyl dicarbonate (0.36 g, 1.65 mmol) and 4-dimethylaminopyridine (0.01 g, 0.082 mmol). After 20 h a 1:3 mixture of satd $NaHCO_3$ aq and brine was added and the two phases were separated. The aqueous layer was extracted with EtOAc and the combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography EtOAc/heptane 1:1 to give **26** (0.27 g, 86%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J*=5.1 Hz, 1H), 7.62 (s, 1H), 7.40–7.29 (m, 5H), 6.98 (dd, *J*=5.1 and 1.1 Hz, 1H), 6.03–5.92 (m, 1H), 5.52 (d, *J*=9.5 Hz, 1H), 5.16 (dd, *J*=17 and 1.6 Hz, 1H), 5.10 (dd, *J*=10 and 1.6 Hz, 1H), 4.59 (d, *J*=12 Hz, 1H), 4.56–4.52 (m, 2H), 4.47 (d, *J*=2.4 Hz, 1H), 4.37 (d, *J*=12 Hz, 1H), 4.35–4.27 (m, 1H), 1.91 (s, 3H), 1.51 (s, 9H), 1.49–1.41 (m, 1H), 1.32–1.24 (m, 2H), 0.91 (d, *J*=2.7 Hz, 3H), 0.89 (d, *J*=2.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 154.4, 154.1, 149.2, 147.4, 137.6, 134.8, 128.5, 128.1, 128.0, 117.6, 115.8, 81.1, 80.5, 71.7, 51.4, 49.1, 40.4, 28.3, 24.7, 23.2, 23.1, 22.2; IR (neat): 1704, 1650, 1601, 1555 cm^{-1}; FABHRMS calcd for $C_{28}H_{40}N_3O_4$ (M+H): 482.3019, found: 482.3023.

3.2.12. {4-[(1*RS*,2*S*)-2-(Acetylamino)-1-(benzyloxy)-4-methylpentyl]pyridin-2-ylamino}-*S*-leucinol (27). Fluoropyridine **14** (0.18 g, 0.53 mmol) was dissolved in *S*-leucinol (1.2 mL, 9.3 mmol) and heated by microwave irradiation (200 °C, 90 min). The reaction mixture was put on a silica gel column and eluted with EtOH/toluene 1:15→1:8 to give **27** (0.20 g, 86%) as a white foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J*=5.3 Hz, 1H), 7.38–7.26 (m, 5H), 6.49 (d, *J*=5.3 Hz, 1H), 6.38 (s, 1H), 5.70 (d, *J*=9.4 Hz, 1H), 4.76 (d, *J*=6.9 Hz, 1H), 4.55 (d, *J*=11.7 Hz, 1H), 4.31 (d, *J*=11.7 Hz, 1H), 4.29 (d, *J*=3.2 Hz, 1H), 4.28–4.20 (m, 1H), 3.88–3.80 (m, 1H), 3.71 (dd, *J*=11 and 3.2 Hz, 1H), 3.49 (dd, *J*=11 and 6.6 Hz, 1H), 1.86 (s, 3H), 1.77–1.67 (m, 1H), 1.55–1.45 (m, 1H), 1.43–1.36 (m, 4H), 0.97–0.85 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 158.9, 149.9, 147.0, 137.5, 128.3, 127.9, 127.8, 111.3, 106.1, 80.5, 71.5, 67.1, 52.7, 51.6, 41.0, 40.6, 24.9, 24.7, 23.1, 23.0, 22.9, 22.4, 22.1; IR (neat): 3371–3129, 1649, 1620, 1560 cm^{-1}; FABHRMS calcd for $C_{26}H_{40}N_3O_3$ (M+H): 442.3070, found: 442.3069.

3.2.13. {4-[(1*RS*,2*S*)-2-(Acetylamino)-1-(benzyloxy)-4-methylpentyl]pyridin-2-ylamino}-*S*-*iso*-leucinol (28). Fluoropyridine **14** (0.10 g, 0.30 mmol) was dissolved in *S*-*iso*-leucinol (1.1 g, 9.2 mmol) and heated by microwave irradiation (200 °C, 90 min and 210 °C, 30 min). The reaction mixture was put on a silica column and eluted with EtOH/toluene 1:15→1:10 to give **28** (0.11 g, 80%) as a white foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J*=5.2 Hz, 1H), 7.37–7.27 (m, 5H), 6.49 (dd, *J*=5.2 and 1.1 Hz, 1H), 6.38 (s, 1H), 5.73 (d, *J*=9.7 Hz, 1H), 4.92 (d, *J*=7.0 Hz, 1H), 4.55 (d, *J*=12 Hz, 1H), 4.31 (d, *J*=12 Hz, 1H), 4.29 (d, *J*=3.2 Hz, 1H), 4.28–4.20 (m, 1H), 3.75 (d, *J*=8.7 Hz, 1H), 3.63–3.55 (m, 2H), 1.86 (s, 3H), 1.74–1.64 (m, 1H), 1.58–1.46 (m, 2H), 1.42–1.35 (m, 2H), 1.26–1.15 (m, 1H), 0.97–0.86 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 159.1, 149.9, 147.1, 137.5, 128.3, 127.8, 127.8, 111.1, 106.1, 80.5, 71.4, 64.1, 58.8, 51.6, 40.5, 36.8, 25.8, 24.7, 23.0, 23.0, 22.1, 15.4, 11.6; IR (neat): 3474–3117,

1649, 1609, 1561, 1516 cm^{-1}; FABHRMS calcd for $C_{26}H_{40}N_3O_3$ (M+H): 442.3070, found: 442.3066.

3.2.14. Methyl *N*-{4-[(1*RS*,2*S*)-2-(acetylamino)-1-(benzyloxy)-4-methylpentyl]pyridin-2-yl}-*N*-(*tert*-butoxycarbonyl)glycinate (29). Olefin **26** (0.27 g, 0.57 mmol) was dissolved in CH_2Cl_2 (10 mL) and a solution of 2 M NaOH in methanol (0.56 mL) and cooled to −78 °C. O_3 was passed through the solution, which turned bright yellow at first and was decolorized gradually. A colorless solid was formed and the solution turned light blue and the excess of O_3 was purged from the solution with a stream of oxygen. Water and Et_2O were added and the two phases were separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified by flash chromatography EtOAc/heptane 3:2 to give **29** (0.17 g, 58%) as a colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J=5.1 Hz, 1H), 7.80 (s, 1H), 7.40–7.28 (m, 5H), 6.98 (d, J=5.1 Hz, 1H), 5.53 (d, J=9.8 Hz, 1H), 4.75 (d, J=18 Hz, 1H), 4.67 (d, J=18 Hz, 1H), 4.58 (d, J=11 Hz, 1H), 4.47 (d, J=2.7 Hz, 1H), 4.36 (d, J=11 Hz, 1H), 4.34–4.25 (m, 1H), 3.75 (s, 3H), 1.92 (s, 3H), 1.51 (s, 9H), 1.49–1.41 (m, 1H), 1.34–1.23 (m, 2H), 0.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.6, 153.6, 153.5, 149.5, 147.1, 137.5, 128.4, 128.1, 127.9, 117.5, 116.5, 82.0, 80.5, 71.6, 52.0, 51.4, 47.8, 40.4, 28.1, 24.7, 23.2, 23.1, 22.1; IR (neat): 1754, 1715, 1655, 1602 cm^{-1}; FABHRMS calcd for $C_{28}H_{40}N_3O_6$ (M+H): 514.2917, found: 514.2917.

3.2.15. Methyl *N*-{4-[(1*RS*,2*S*)-2-(acetylamino)-1-hydroxy-4-methylpentyl]pyridin-2-yl}-*N*-(*tert*-butoxycarbonyl)glycinate (30). Benzyl protected alcohol **29** (0.16 g, 0.30 mmol) and Pd/C (0.15 g) were added to a mixture of MeOH (15 mL) and AcOH (0.15 mL). The reaction was stirred vigorously under H_2 atmosphere (1 atm) for 30 h. Pd/C was removed by filtration through Celite and the solvent was removed under reduced pressure. The residue was purified by flash chromatography EtOAc/heptane 2:1 → 1:0 to give **30** (0.096 g, 75%) as a colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J=5.2 Hz, 1H), 7.75 (s, 1H), 7.01 (d, J=5.2 Hz, 1H), 5.73 (d, J=9.1 Hz, 1H), 4.74–4.67 (m, 1H), 4.69 (s, 2H), 4.16–4.06 (m, 1H), 3.92 (s, 1H), 3.74 (s, 3H), 1.94 (s, 3H), 1.67–1.57 (m, 1H), 1.51 (s, 9H), 1.45–1.37 (m, 2H), 0.92 (d, J=2.3 Hz, 3H), 0.90 (d, J=2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.7, 153.6, 153.4, 152.1, 147.1, 117.1, 115.7, 82.1, 74.7, 53.5, 52.0, 47.8, 39.5, 28.1, 24.8, 23.2, 23.1, 21.9; IR (neat): 3280, 3254, 1713, 1607, 1603, 1529 cm^{-1}; FABHRMS calcd for $C_{21}H_{34}N_3O_6$ (M+H): 424.2448, found: 424.2457.

3.2.16. (2*S*)-{[4-(2-Acetylamino-4-methyl-pentanoyl)-pyridin-2-yl]-*tert*-butoxycarbonyl-amino}-acetic acid methyl ester (31). Alcohol **30** (96 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (3 mL) and treated with Dess–Martin periodinane (0.80 mL, 15 wt % in CH_2Cl_2, 0.34 mmol) for 20 min. Sodium disulfite (0.49 g, 2.55 mmol) in satd $NaHCO_3$ aq was added and the two phases were separated and the aqueous phase was extracted with EtOAc followed by a wash with satd $NaHCO_3$ aq. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography EtOAc/heptane 3:1 to give ketone **31** (77 mg, 81%) as a colorless oil; $[\alpha]_D^{20}$ +4.4 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, J=5.1 and 0.6 Hz, 1H), 8.40 (s, 1H), 7.44 (dd, J=5.1 and 1.5 Hz, 1H), 6.13 (d, J=8.2 Hz, 1H), 5.61–5.54 (m, 1H), 4.74 (s, 2H), 3.75 (s, 3H), 2.05 (s, 3H), 1.79–1.59 (m, 2H), 1.53 (s, 9H), 1.46–1.36 (m, 1H), 1.07 (d, J=6.5 Hz, 3H), 0.89 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 170.3, 169.8, 154.9, 153.2, 148.3, 142.2, 116.5, 116.5, 82.7, 53.0, 52.1, 47.7, 42.1, 28.1, 25.2, 23.3, 23.2, 21.6; IR (neat): 1753, 1709, 1652, 1598, 1554 cm^{-1}; FABHRMS calcd for $C_{21}H_{32}N_3O_6$ (M+H): 422.2291, found: 422.2298.

3.2.17. (2*R*,*S*)-{[4-(2-Acetylamino-4-methyl-pentanoyl)-pyridin-2-yl]-*tert*-butoxycarbonyl-amino}-acetic acid methyl ester (31*rac*). Prepared in the same way as **33***rac* starting with compound **31** (4 mg, 9.5 μmol) to give **31***rac* (3 mg, 75%) as determined by chiral HPLC; $[\alpha]_D^{20}$ 0 (*c* 0.25, $CHCl_3$); ^{1}H NMR identical as for compound **31**.

3.2.18. (2*S*)-[4-(2-Acetylamino-4-methyl-pentanoyl)-pyridin-2-ylamino]-acetic acid methyl ester (33). Boc-protected amine **30** (28 mg, 66 μmol) was dissolved in CH_2Cl_2 (6 mL) and treated with trifluoroacetic acid (2 mL) for 1.5 h. The reaction mixture was concentrated under reduced pressure and coevaporated from $CHCl_3$. The residue was dissolved in CH_2Cl_2 and treated with Dess–Martin periodinane (0.22 mL, 15 wt % in CH_2Cl_2, 99 μmol). After 4 min sodium bisulfite (0.19 g, 0.97 mmol) in satd $NaHCO_3$ aq was added. The organic layer was washed with satd $NaHCO_3$ aq, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography EtOAc/heptane 2:1 → 4:1 to give β-strand mimetic **33** (0.014 g, 66%) as a yellow oil. $[\alpha]_D^{20}$ +11.5 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J=5.2 Hz, 1H), 7.03 (d, J=5.2 Hz, 1H), 6.98 (s, 1H), 6.27 (d, J=8.1 Hz, 1H), 5.55–5.46 (m, 1H), 5.35 (t, J=5.5 Hz, 1H), 4.19 (d, J=5.5 Hz, 2H), 3.77 (s, 3H), 2.03 (s, 3H), 1.76–1.64 (m, 1H), 1.62–1.52 (m, 1H), 1.44–1.35 (m, 1H), 1.01 (d, J=6.5 Hz, 3H), 0.87 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 171.4, 169.9, 158.4, 149.2, 142.6, 111.0, 107.0, 52.6, 52.3, 43.5, 41.9, 25.1, 23.3, 23.2, 21.8; IR (neat): 3447–3166, 1741, 1700, 1651, 1608 cm^{-1}; FABHRMS calcd for $C_{16}H_{24}N_3O_4$ (M+H): 322.1767, found: 322.1768.

3.2.19. (2*R*,*S*)-[4-(2-Acetylamino-4-methyl-pentanoyl)-pyridin-2-ylamino]-acetic acid methyl ester (33*rac*). β-Strand mimetic **33** (5 mg, 16 μmol) was dissolved in THF (2 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (25 μL, 167 μmol) was added. The reaction was subjected to microwave irradiation, 80 °C for 0.5 h. The reaction was concentrated under reduced pressure and the residue was filtered through a short path of silica gel with EtOAc as eluent to give **33***rac* (4 mg, 80%) as determined by chiral HPLC; $[\alpha]_D^{20}$ 0 (*c* 0.25, $CHCl_3$); ^{1}H NMR identical as for β-strand mimetic **33**.

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Supplementary data

^{1}H NMR and ^{13}C NMR spectra for all new isolated compounds as well as chiral chromatograms of compounds **33** and **33***rac* are included. This material is available free of charge via the Internet at http://www.sciencedirect.com. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.080.

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Oxidation and ring cleavage reactions of 3-benzhydrylchromones. Generation of triarylmethine cations from methylidenechroman-4-ones and benzopyrano[4,3-*c*]pyrazoles

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Abstract—The oxidation of 3-[bis-(diaryl)methyl]chromones **2** with *p*-chloranil affords novel acetals, 3-[bis-(diaryl)methylene]-2-methoxychroman-4-ones, **4** through interception of a pyrylium type intermediate. Oxidation of 3-(2-hydroxyphenyl)-4-[bis-(diaryl)methyl]pyrazoles **8**, derived from **2** and hydrazines, gave 4,4-diarylbenzopyrano[4,3-*c*]pyrazoles **15**. The electronic absorption spectra of **4** and **15** upon protonation are comparable with those of triarylmethine cationic dyes.

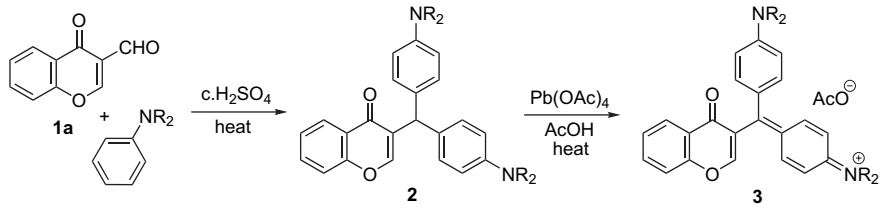
1. Introduction

Chromone-3-carboxaldehyde (4-oxo-4*H*[1]benzopyran-3-carboxaldehyde) **1a** displays a rich and varied chemistry.[1] It can be readily converted into a broad range of heterocyclic systems, e.g., xanthones[2] and pyranobenzopyranones[3] by cycloaddition strategies,[2] pyrazolopyrimidines,[4] benzopyranopyridopyrimidines,[5] pyrimidopyrimidines,[6] benzopyranobenz-thiazepines, -oxazepines and -diazepines,[7] furobenzopyranones[8] and *o*-hydroxyphenyl substituted azoles[9] and pyrimidines[9,10] through condensation with a variety of bis-nucleophiles. Harnish has investigated the addition of tertiary aromatic amines to the formyl group of **1a** and obtained the diarylmethyl analogues **2**, which were subsequently oxidised with $Pb(OAc)_4$ in AcOH to the triarylmethine dyes **3** (Scheme 1).[11]

We were interested in exploring some chemistry of **2**, particularly their reaction with bis-nucleophiles and their oxidation with *p*-chloranil. The addition of bis-nucleophiles to chromone and substituted chromones that do not have an electron withdrawing substituent at C-3 has been shown to be critically dependant upon the reaction conditions.[12] This feature is conveniently illustrated by the addition of hydroxylamine to chromone, which under anhydrous conditions affords the simple oxime, whereas using aqueous ethanol results in pyran ring cleavage to afford a mixture of isomeric (*o*-hydroxyphenyl)isoxazoles.[13]

2. Discussion

Chromone-3-carboxaldehyde **1a** was efficiently obtained (74%) in a single step from *o*-hydroxyacetophenone by



Scheme 1.

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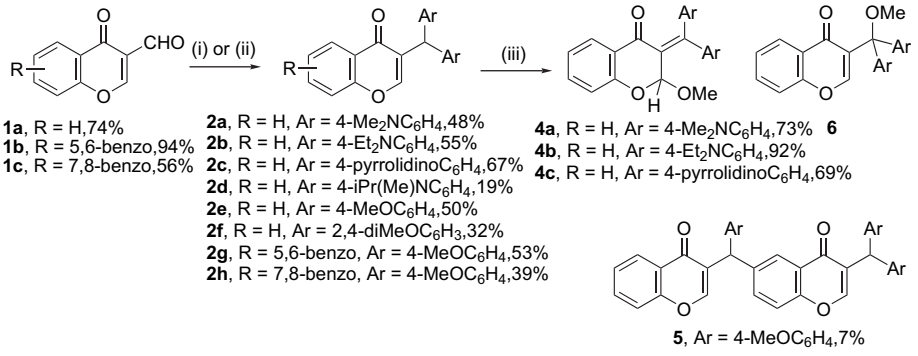
a double Vilsmeier formylation reaction.[11] The benzologues **1b** and **1c** were similarly obtained in 94 and 56% yield from 1-acetyl-2-hydroxynaphthalene and 2-acetyl-1-hydroxynaphthalene, respectively. The acid-catalysed condensation of **1a** with a range of tertiary aromatic amines gave the 3-[bis-(4-aminophenyl)methyl]chromones (benzhydrylchromones) **2a–d** in moderate yield. The aminoaryl groups of **2a–d** are equivalent affording signals in their ^{1}H NMR spectra at ~δ 6.6 and δ 7.0 due to the aromatic protons *ortho* and *meta* to the amino function, respectively. The low field signal at ca. δ 8.2 is assigned to 5-H as a consequence of its *peri* relationship with the C=O group and the methine proton resonates at ~δ 5.6. 2-H appears as a doublet ($J \approx 1.0$ Hz) at ~δ 7.4, shifted upfield relative to 2-H (δ 7.88) in chromone[14] as a consequence of shielding by the diarylmethine unit. Our attempts to obtain 3-[bis-(4-methoxyphenyl)methyl]chromone **2e** using this methodology were unsuccessful. Similar attempts to obtain **2e** by treatment of **1a** in anisole with a catalytic amount of TFA failed.[15] However, **2e** was accessed in 50% yield by heating **1a** in dichloromethane containing 2.1 equiv of anisole and 6 equiv of $BF_3 \cdot OEt_2$ for 20 h with purification effected by column chromatography and recrystallisation from EtOAc and hexane. The ^{1}H NMR spectrum of **2e** displayed the expected singlet at δ 5.7 and the equivalent methoxy groups resonated at δ 3.8. A second component was isolated from the reaction mixture, which displayed two methine signals (δ 5.54 and δ 5.92) and two overlapping signals for 5-H, *peri* to a chromone type C=O function, at δ 8.14. The presence of three 4-methoxyphenyl units was confirmed by the two signals at δ 3.73 (6H) and δ 3.74 (3H). Furthermore, two chromone C=O units were present as indicated by signals at δ 176.6 and δ 176.7 in the ^{13}C NMR spectrum. These data and a molecular ion (electrospray, M+H$^+$) m/z=637.2217 Da suggest the bis-adduct, structure **5** (7%). Chromones have been reported to undergo S_EAr at the 6-position[16] particularly in the absence of electron donating groups in the pyranone and it is probable that **5** is formed by interception of a carbocationic intermediate, derived from **1a** and 1 mol of anisole, by the substituted chromone **2e**. Compound **2f** (32%) was similarly obtained from **1a** and 1,3-dimethoxybenzene though the reaction time was somewhat shorter (7 h) than that of **2e**.

The benzologues **2g** (53%), **h** (39%) were obtained using a similar protocol to that employed for **2e**. The ^{1}H NMR spectra of **2g** and **2h** displayed a singlet at ~δ 5.7 assigned to the methine protons. Of greater significance is the chemical shift of 10-H in **2g**, which appears at δ 10.1 and the corresponding proton (5-H) in **2h**, which resonates at δ 8.4; a feature, which enables these isomers to be readily distinguished.

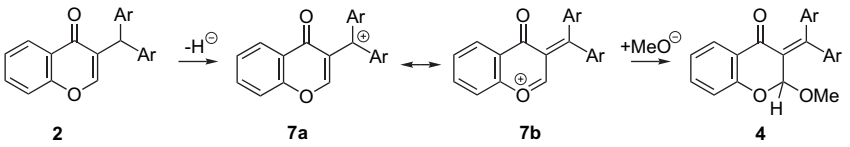
There are few reports pertaining to the use of *p*-chloranil for the oxidation of triarylmethanes to triarylmethanols.[17] Refluxing a methanolic solution of **2a** containing a slight excess of *p*-chloranil for ca. 4 h and treatment of the cooled reaction mixture with NaOMe to remove the tetrachlorohydroquinone by-product gave a new orange-red compound. The ^{1}H NMR spectrum of this product was not in agreement with the expected methoxytriarylmethane **6** (Ar=4-$Me_2NC_6H_4$), the precursor of dyes **3**, since the dimethylaminophenyl groups are non-equivalent to the NMe_2 groups resonating at δ 2.98 and δ 3.04. Interestingly, the ^{1}H NMR spectrum of this product also contained a singlet at δ 3.43 (3H) and a singlet at δ 5.56 (1H). Furthermore, the furthest downfield signal appeared at δ 7.95, which suggests that the relationship between the C=O group and 5-H has changed. Examination of the literature reveals that the chemical shift of 5-H is extremely sensitive to the level of oxidation of the benzopyranone unit. Typically, 5-H in chromones (4-oxo-4*H*[1]benzopyrans) resonates at ca. δ 8.2, whereas in the reduced analogues, the chromanones (2,3-dihydro-4-oxo-4*H*[1]benzopyrans), 5-H usually appears at ca. δ 7.9.[18] Furthermore, the singlet at δ 5.56 is in a region typically associated with the methine proton of an acetal unit.[19] With this information in hand, we proposed that this compound is the acetal **4a**. The treatment of **2b**, **c** under identical conditions afforded the corresponding acetals **4b**, **c**, respectively, with similar spectroscopic properties to **4a** (Scheme 2).

Our attempts to oxidise **2e**, **f** and **g** with *p*-chloranil failed and instead starting material was recovered. The use of triphenylcarbenium fluoroborate in anhydrous CH_2Cl_2 at room temperature[20] was also investigated for the oxidation step but again unchanged starting material was recovered. Presumably, the oxidation fails as a consequence of the less efficient resonance stabilisation of the cation **7a** (Scheme 3) by the methoxyphenyl groups compared with the *N*,*N*-dialkylaminophenyl units of **2a–c**.

The formation of **4** is thought to proceed by initial hydride abstraction by the *p*-chloranil to generate the carbocation



Scheme 2. Reagents and conditions: (i) aq H_2SO_4, *N*,*N*-dialkylaminobenzene, 110 °C; (ii) (di)methoxybenzene, $BF_3 \cdot OEt_2$, CH_2Cl_2, reflux; (iii) *p*-chloranil, methanol, reflux then NaOMe, rt.



Scheme 3.

7a that is efficiently resonance stabilised, not only by the adjacent aminophenyl groups, but also by the oxygen atom of the pyran ring. This latter resonance stabilisation may be likened to a pyrylium type cation **7b**. Nucleophilic addition of pyrylium salts to C-2 is well established[21] and in this instance interception of the less hindered oxonium ion by methoxide affords **4** (Scheme 3).

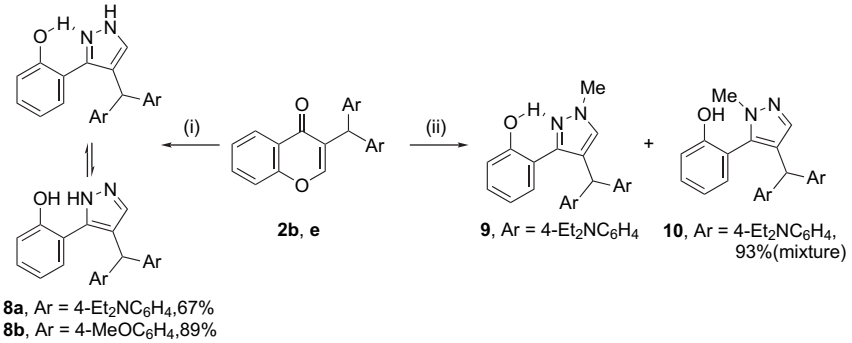
Treatment of **2b**, **e** with hydrazine hydrate in refluxing ethanol gave the *o*-hydroxyphenyl pyrazoles **8a** and **8b** in 67 and 89% yield, respectively (Scheme 4). Their formation is readily explained by the conjugate addition of hydrazine to the enone unit of **2** followed by enol–keto tautomerism to regenerate the benzylic C═O group; a 5-*exo-trig* ring closure completes the sequence to the pyrazole. Despite the possibility of annular prototropy of the pyrazole ring,[22] the ^{1}H NMR spectrum of **8a** was well resolved with only the OH (δ 11.0) and NH (δ 10.0) signals exhibiting broadening. The pyrazole ring proton (5-H) appeared as a singlet at ~δ 7.1.

The ^{1}H NMR spectrum of the product of the reaction between **2b** and methylhydrazine was more complex and indicated that two isomeric pyrazoles **9** and **10** had been formed. The ratio of the two isomers was determined as 2:3 based upon comparison of the integrals for the *N*-methyl signals at δ 3.62 (major) and δ 3.84 and the methine signals at δ 4.85 (major) and δ 5.40. Interestingly, simple (2-hydroxyaryl)pyrazoles obtained from α-hydroxymethylene–acetophenones and hydrazines have been evaluated as UV absorbers with an energy quenching proton transfer process similar to that of 2′-hydroxybenzophenones and hydroxyphenylbenzotriazoles;[23] the new hydroxyphenylpyrazoles **8**, **9** and **10** may offer similar photophysical properties.

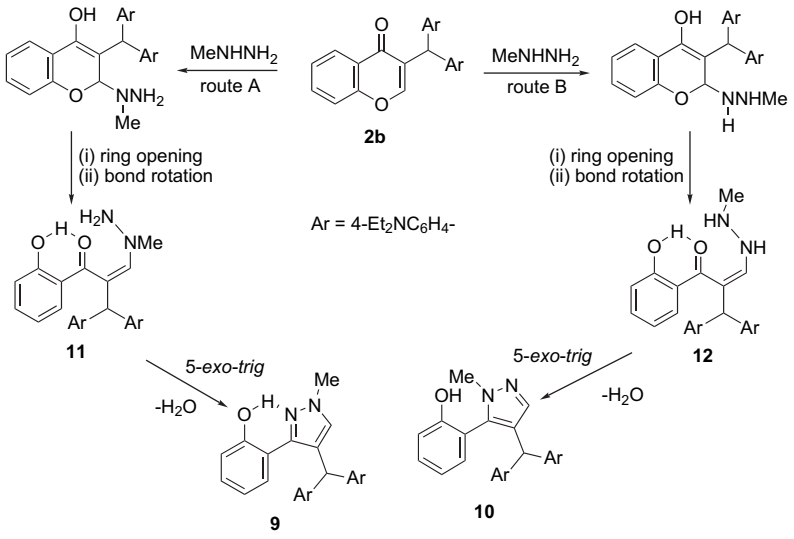
The formation of these isomeric methyl pyrazoles may be conveniently rationalised by considering the differing nucleophilicities of the hydrazine N atoms. In route A (Scheme 5) N-1 of methylhydrazine attacks C-2 of **2b**. Regeneration of the C-2–C-3 double bond with elimination of phenoxide results in **11**, which contains a stabilising intramolecular H-bond, after rotation of the *o*-hydroxyphenyl function. Dehydrative ring closure affords pyrazole **9**. In route B attack by N-2 initiates the sequence to afford, after ring-opening and bond rotation, enaminone **12** that affords pyrazole **10** on cyclisation.

The pyrazole **8a** was readily oxidised with *p*-chloranil using the procedure for the oxidation of **2**. The ^{1}H NMR spectrum of the product displayed a single set of signals for the NEt_2 functions suggesting their equivalence, a feature, which precludes the diazafulvene **13**. Additionally, 3-H resonates at δ 7.25, a chemical shift typical to some simple 4,4-dialkyl substituted benzo- and benzothio-pyrano[4,3-*c*]pyrazoles.[24] The possibility that the oxidation product was the hydroxyphenylpyrazole **14** was eliminated by the addition of D_2O since only one exchangeable signal was noted, whereas **14** has three such protons. The structure of the product was thus proposed as the benzopyrano[4,3-*c*]pyrazole **15**. Further evidence for this benzopyranopyrazole accrued from the ^{13}C NMR spectrum, which displayed a signal at δ 84.4 (4-C), which is in the typical range for *gem* diaryl substituted carbon atom in benzo- and naphtho-pyrans (Scheme 6).[25]

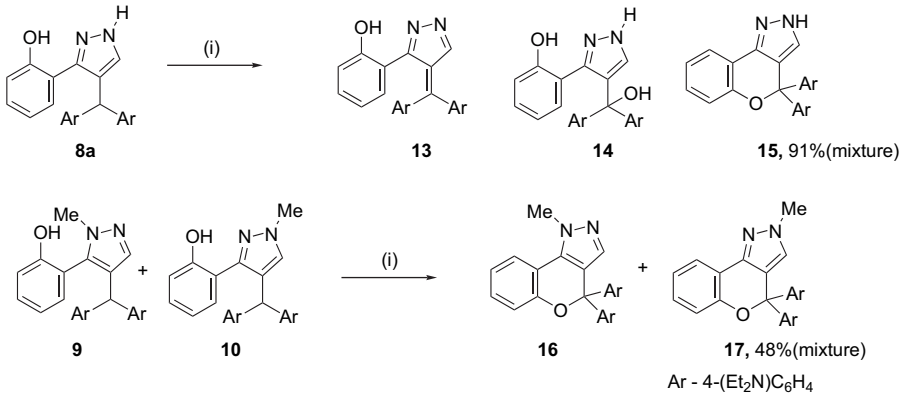
The structure of **15** was firmly established as the benzopyranopyrazole by X-ray crystallography (Fig. 1).[26] Interestingly, **15** exists as a hydrogen bonded dimer composed of two crystallographically different units in the solid state. The bond lengths and angles of the pyrazole ring of **15** compare favourably with those of pyrazole itself.[27] The length of the N1–C3 (1.338 Å) and C2–C4 (1.375 Å) bonds (crystallographic numbering) is suggestive for double bond character and confirms the location of the H atom on N2 (N2–H, 0.88 Å). The most significant difference between the independent units of the dimer is a twist of one of the *N*-ethyl groups. The O1–C1 bond (1.486 Å) of the pyran ring is longer than the typical O–C ether bond (1.42 Å)[28] and compares favourably with the O–C bond (ca. 1.46 Å) of diaryl substituted naphthopyrans.[29]



Scheme 4. Reagents and conditions: (i) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux; (ii) $MeNHNH_2$, EtOH, reflux.



Scheme 5.



Scheme 6. Reagents and conditions: (i) *p*-chloranil, methanol, reflux, then NaOMe, rt.

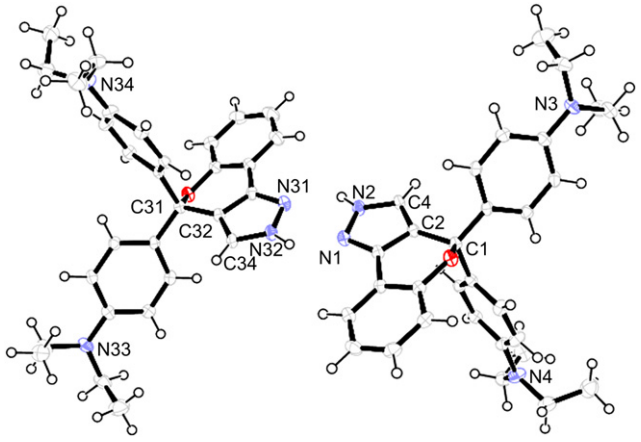
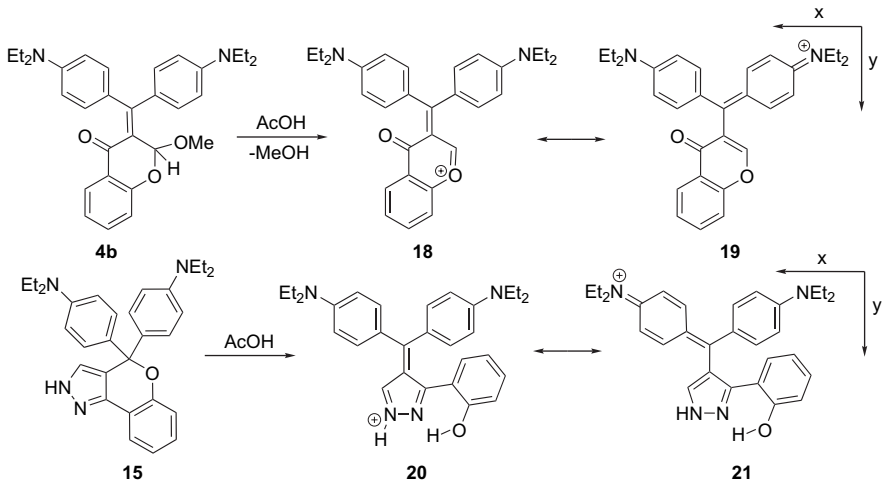


Figure 1. X-ray crystallographic structure of benzopyranopyrazole **15**.

Similarly, oxidation of the mixture of N-Me pyrazoles **9** and **10** gave a mixture of benzopyranopyrazoles **16** and **17** (48%). The isomer ratio was calculated as 2:3, again established by comparison of the relative intensities of the *N*-methyl signals at δ 3.92 (minor) and 4.16 (major). Attempts to oxidise the pyrazole **8b** with either *p*-chloranil or triphenylcarbenium fluoroborate failed. The formation of pyrazoles **15**, **16** and **17** involves the trapping of the carbocationic intermediate that results from the abstraction of hydride ion by *p*-chloranil from the diarylmethine moiety by the pendant 2-hydroxyphenyl unit. This intramolecular pyran ring forming protocol constitutes a new route to the fused benzopyranopyrazole ring system; previous approaches rely upon the construction of the pyrazole ring by condensation of a hydrazine derivative with a suitably functionalised benzopyranone.[30] Interestingly, the colour forming properties of 4,4-diarylbenzopyranopyrazoles have been previously reported; however, these compounds were obtained by an alternative procedure involving the $POCl_3$ promoted condensation of Michler's ketone and a substituted 5-(2-hydroxyphenyl)pyrazole.[31]

The electronic absorption spectra of **4** and pyrazoles **15**, **16** and **17** were investigated, since protonation of these compounds generates an intensely coloured cationic species (Scheme 7). Dissolution of **4a–c** and pyrazoles **15** and mixture **16**, **17** in acetic acid resulted in the instantaneous development of an intense green colour. The visible spectra of these compounds (ca. 2×10^{-5} mol dm^{-3} in 98% aqueous acetic acid) are displayed in Figures 2 and 3. The visible spectra of cations **18/19** developed from **4** show two distinct absorption bands; a weak short wavelength band at 428 nm



Scheme 7.

and a significantly more intense band at ca. 640 nm. The spectra of the pyrazoles also display two bands with the short wavelength band appearing at ca. 453 nm and the long wavelength band at ca. 630 nm. The molar extinction coefficients for the long wavelength bands of **18/19** are comparable with those of triarylmethine dyes[32] and are in the range

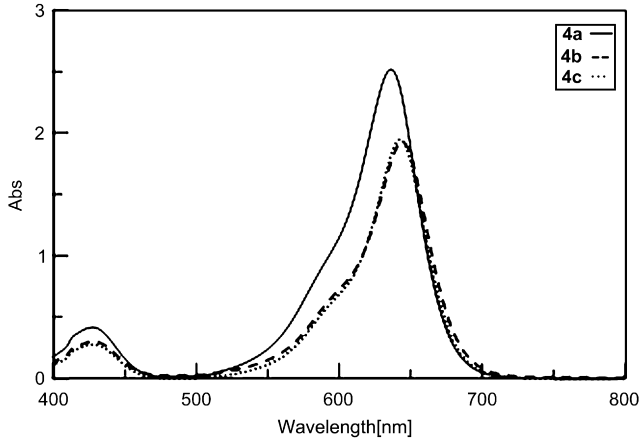


Figure 2. Visible spectra of benzopyranones **4** in acetic acid.

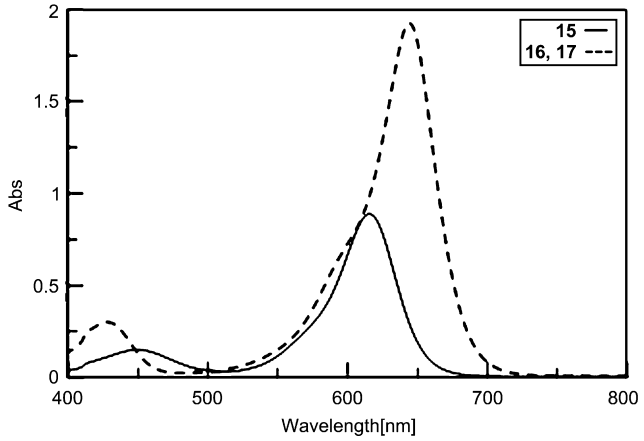


Figure 3. Visible spectra of benzopyranopyrazoles **15** and mixture **16**, **17** in acetic acid.

80–110,000 $mol^{-1}\,dm^3\,cm^{-1}$ (Table 1), whereas those for the cations **20/21** developed from the pyrazoles are lower.

The evolution of the absorption bands is comparable with those of triarylmethine dyes where the long wavelength absorption (x) band may be considered to arise from electronic transitions associated with the cyanine type resonance structures **19** and **21** (N-donor, N-acceptor), whereas the short wavelength (y) band results from electronic transitions associated to resonance structures **18** and **20** (Scheme 7).[33]

We were interested in further exploring the structure of the cationic species that result from protonation of **4b** and **15** by NMR spectroscopy using CD_3CO_2D as the solvent. In the ^1H NMR spectrum of **4b** recorded in CD_3CO_2D the terminal NEt_2 groups are now equivalent and resonate at δ 1.36 (t, J=6.8 Hz, CH_3) and δ 3.76 (q, J=6.8 Hz, NCH_2); the latter group shifted downfield by ca. 0.4 ppm on protonation. Interestingly, the signal for the MeOD unit, derived from the elimination of methanol from **4b** upon deuteration, appears at δ 3.46 as a singlet presumably, as a consequence of rapid deuterium exchange. 2-H now resonates at δ 8.34, significantly deshielded compared with non-protonated **4b** (δ 5.57), and appears further downfield of the chemical shift range normally associated with 2-H of chromones (ca. δ 7.8) but not as far downfield as 2-H in benzopyrylium salts (ca. δ 9.6).[18] The ^{13}C NMR spectrum of **4b** in CD_3CO_2D shows a singlet at δ 13.1 and δ 46.9 accounting for equivalent NEt_2 groups. The low field signal at δ 177.1 is assigned to a chromone-like C=O group [chromone δ C=O 176.9 ($CDCl_3$)[18]] and resonates further upfield of the chromanone-like C=O group in non-protonated **4b**. These NMR data are suggestive of a cationic dye structure in which form **19** predominates.

Table 1. Spectroscopic data for compounds **4**, **15**, **16** and **17** in acetic acid

No.	Wavelength (nm)	$\varepsilon\times10^4$ ($mol^{-1}\,dm^3\,cm^{-1}$)
4a	428, 636	11.0
4b	428, 642	8.1
4c	428, 644	9.4
15	450, 616	3.6
16, **17**	456, 644	6.5

The ^{1}H NMR spectrum of **15** recorded in CD_3CO_2D at 20 °C was less informative as a consequence of incomplete ring-opening of the pyran ring as indicated by the presence of two signals (ratio 1:2) for the methyl groups of the terminal NEt_2 units at δ 1.13 and δ 1.29 (minor, ring-opened form). A similar ratio was observed for the pyrazole ring protons, which appeared at δ 7.56 (major, ring-closed form) and at δ 7.84 (minor, ring-opened form). The ^{1}H NMR spectrum of a solution of **15** equilibrated at 75 °C for 1 h showed significant broadening of the aromatic signals but did however results in complete conversion to the ring-opened form as indicated by the absence of a signal at δ 1.13. This shift in the equilibrium between the ring-closed and -opened forms on warming confirms that the diaryl substituted pyranopyrazole system offers potential as a thermochromic material.

3. Experimental

3.1. General

Melting points were determined in capillary tubes and are uncorrected. Visible spectra were recorded for solutions in spectroscopic grade glacial acetic acid (98% aq) in 10 mm quartz cells at 20 °C using an Analytik Jena Specord S100 diode array spectrophotometer. Infrared spectra were recorded on a Perkin–Elmer Spectrum Spotlight infrared spectrophotometer. NMR spectra were recorded on a Bruker Avance 400 MHz instrument for solutions in $CDCl_3$. The formyl benzo-(naphtho)-pyrans **1a**, **1b** and **1c** were obtained according to the method described by Harnish.[11]

3.2. General method for the preparation of 3-[bis-(4-aminophenyl)methyl]benzopyranones

A solution of concentrated sulfuric acid (5 mL) and water (4 mL) was added to a stirred mixture of 3-formyl-4*H*[1]benzopyran-4-one (8.7 g, 50 mmol) and an aromatic tertiary amine (100 mmol). The mixture was maintained at 110 °C for 8 h and then upon cooling to ca. 60 °C was diluted with aqueous NaOAc solution [($NaOAc \cdot 3H_2O$ (30 g, 220 mmol), water (150 mL)]. The resulting suspension was extracted with CH_2Cl_2 (6×50 mL) and the combined extracts were washed with water (2×50 mL). Removal of the dried (anhydrous Na_2SO_4) solvent gave the crude adduct, which was recrystallised from EtOAc/hexane.

3.2.1. 3-[Bis-(4-dimethylaminophenyl)methyl]-4*H*[1]-benzopyran-4-one (2a). Pale green microcrystals (9.6 g, 48%); mp 169–171 °C; ν_{max} 1646, 1611 cm^{-1}; δ_H 2.91 (12H, s, $(NMe_2)_2$), 5.60 (1H, s, methine), 6.67 (4H, m, Ar-H), 7.06 (4H, m, Ar-H), 7.35 (1H, m, 6-H), 7.39 (1H, dd, *J*=8.2, 0.9 Hz, 8-H), 7.43 (1H, d, *J*=1.2 Hz, 2-H), 7.62 (1H, m, 7-H), 8.20 (1H, dd, *J*=8.1, 1.2 Hz, 5-H) (found: C, 78.1; H, 6.6; N, 6.9. $C_{26}H_{26}N_2O_2$ requires C, 78.4; H, 6.5; N, 7.0%).

3.2.2. 3-[Bis-(4-diethylaminophenyl)methyl]-4*H*[1]benzopyran-4-one (2b). Bright yellow microcrystals (12.5 g, 55%); mp 132–134 °C [lit. mp 131–131.5 °C[11]]; ν_{max} 1650, 1611 cm^{-1}; δ_H 1.13 (12H, t, *J*=7.2 Hz, $(N(CH_2CH_3)_2)_2$), 3.30 (8H, q, *J*=7.2 Hz, $(N(CH_2CH_3)_2)_2$), 5.57 (1H, s, methine), 6.60 (4H, m, Ar-H), 7.02 (4H, m, Ar-H), 7.35 (1H, m, 6-H), 7.40 (1H, dd, *J*=8.1, 1.0 Hz, 8-H), 7.47 (1H, d, *J*=0.9 Hz, 2-H), 7.61 (1H, m, 7-H), 8.20 (1H, dd, *J*=8.0, 1.3 Hz, 5-H); δ_C 13.1, 44.8, 45.4, 112.3, 118.4, 124.5, 125.1, 126.7, 129.3, 129.6, 130.2, 133.6, 146.8, 155.6, 156.7, 177.4.

3.2.3. 3-[Bis-(4-pyrrolidinophenyl)methyl]-4*H*[1]benzopyran-4-one (2c). Off-white microcrystals (15.1 g, 67%); mp 178–180 °C; ν_{max} 1642, 1612 cm^{-1}; δ_H 1.97 (8H, m, $((CH_2)_2)_2$), 3.25 (8H, m, $(N(CH_2)_2)_2$), 5.59 (1H, s, methine), 6.49 (4H, m, Ar-H), 7.04 (4H, m, Ar-H), 7.34 (1H, m, 6-H), 7.39 (1H, dd, *J*=8.2, 1.1 Hz, 8-H), 7.43 (1H, d, *J*=0.8 Hz, 2-H), 7.61 (1H, m, 7-H), 8.20 (1H, dd, *J*=8.1, 1.6 Hz, 5-H) (found: C, 79.6; H, 6.6; N, 6.2. $C_{30}H_{30}N_2O_2$ requires C, 80.0; H, 6.7; N, 6.2%).

3.2.4. 3-{Bis-[4-(*N*-isopropyl-*N*-methylamino)phenyl]-methyl}-4*H*[1]benzopyran-4-one (2d). Pale yellow microcrystals (4.3 g, 19%); mp 161–163 °C; ν_{max} 1649, 1611 cm^{-1}; δ_H 1.13 (12H, d, *J*=6.6 Hz, $(CH(CH_3)_2)_2$), 2.69 (6H, s, $(NMe)_2$), 4.04 (2H, sept, *J*=6.6 Hz, $(CH(CH_3)_2)_2$), 5.59 (1H, s, methine), 6.70 (4H, m, Ar-H), 7.03 (4H, m, Ar-H), 7.35 (1H, m, 6-H), 7.41 (1H, dd, *J*=8.0, 0.9 Hz, 8-H), 7.44 (1H, d, *J*=1.0 Hz, 2-H), 7.63 (1H, m, 7-H), 8.20 (1H, dd, *J*=8.0, 1.6 Hz, 5-H) (found: C, 79.0; H, 7.6; N, 6.2. $C_{30}H_{34}N_2O_2$ requires C, 79.3; H, 7.5; N, 6.2%).

3.3. General method for the preparation of [bis-(methoxyphenyl)methyl]benzopyranones

$BF_3 \cdot OEt_2$ (21.8 mL, 172 mmol) was added in a single portion to a stirred solution of the formylbenzo- or -naphthopyran (29 mmol) and the methoxybenzene (60 mmol) in dry CH_2Cl_2 (70 mL) at room temperature. The solution was heated to reflux and followed by TLC. On completion of the reaction the cooled mixture was poured into water (400 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and then the combined CH_2Cl_2 extracts were washed with water (2×50 mL), dried (anhyd Na_2SO_4) and evaporated to afford the crude product. The crude product was eluted from silica with 30% EtOAc in hexane to afford the title compounds, which were further purified by recrystallisation from EtOAc and hexane.

3.3.1. 3-[Bis-(4-methoxyphenyl)methyl]-4*H*[1]benzopyran-4-one (2e) and 6-[(4-methoxyphenyl)-(4-oxo-4*H*[1]benzopyran-3-yl)methyl]-3-bis(4-methoxyphenyl)-methyl-4*H*[1]benzopyran-4-one (5). Elution from silica gave two fractions. Fraction 1: 3-[bis-(4-methoxyphenyl)-methyl]-4*H*[1]benzopyran-4-one (**2e**) from anisole and (**1a**) as off-white microcrystals (5.4 g, 50%); mp 98–101 °C; ν_{max} 1636, 1608, 1509, 1242, 759 cm^{-1}; δ_H 3.77 (6H, s, $(OMe)_2$), 5.67 (1H, s, methine), 6.82 (4H, m, Ar-H), 7.11 (4H, m, Ar-H), 7.39 (3H, m, 6-H, 8-H, 2-H), 7.64 (1H, m, 7-H), 8.19 (1H, dd, *J*=8.1, 1.5 Hz, 5-H) (found: C, 77.4; H, 5.3; [M+H$^+$] 373.1429. $C_{24}H_{20}O_4$ requires C, 77.4; H, 5.4%; [M+H$^+$] 373.1434). Fraction 2: 6[(4-methoxyphenyl)-(4-oxo-4*H*[1]benzopyran-3-yl)methyl]-3-bis(4-methoxyphenyl)methyl-4*H*[1]benzopyran-4-one (**5**) as off-white microcrystals (1.29 g, 7%); mp 170–174 °C; ν_{max} 1635, 1608, 1464, 1242, 755 cm^{-1}; δ_H 3.73 (6H, s, $(OMe)_2$), 3.74 (3H, s, OMe), 5.54 (1H, s, methine), 5.92 (1H, d, *J*=4.8 Hz, methine), 6.74 (5H, m, Ar-H), 6.81 (1H,

dd, J=8.4, 2.8 Hz, Ar-H), 6.99 (5H, m, Ar-H), 7.29 (2H, m, Ar-H), 7.35 (4H, m, Ar-H), 7.63 (2H, m, Ar-H), 8.14 (2H, m, 5-H); δ_C 40.0, 45.3, 45.4, 55.1, 55.2, 55.6, 110.7, 113.7, 113.8, 117.9, 118.0, 123.9, 124.7, 124.8, 126.1, 127.4, 128.4, 129.7 (6), 129.7 (9), 129.8 (4), 130.3, 133.1, 133.2, 133.3 (6), 133.4, 154.1, 154.5, 155.0, 155.1, 155.6, 156.1, 156.2, 156.3, 158.0 (6), 158.1, 176.6, 176.7 (found: C, 77.2; H, 5.1; [M+H$^+$] 637.2217. $C_{41}H_{32}O_7$ requires C, 77.3; H, 5.1%; [M+H$^+$] 637.2226).

3.3.2. 3-[Bis-(2,4-dimethoxyphenyl)methyl]-4*H*[1]benzopyran-4-one (2f). Obtained from 1,3-dimethoxybenzene and **1a** as pale yellow microcrystals (4.0 g, 32%); mp 178–181 °C; ν_{max} 1638, 1610, 1584, 1463, 1137, 1033, 753 cm^{-1}; δ_H 3.74 (6H, s, $(OMe)_2$), 3.79 (6H, s, $(OMe)_2$), 6.15 (1H, s, methine), 6.35 (2H, dd, J=8.4, 2.4 Hz, Ar-H), 6.47 (2H, d, J=2.4 Hz, Ar-H), 6.81 (2H, d, J=8.4 Hz, Ar-H), 7.29 (1H, d J=1.1 Hz, 2-H), 7.34 (1H, m, 6-H), 7.40 (1H, dd, J=8.0, 1.9 Hz, 8-H), 7.61 (1H, m, 7-H), 8.20 (1H, dd, J=8.0, 1.7 Hz, 5-H) (found: C, 72.2; H, 5.6. $C_{26}H_{24}O_6$ requires C, 72.2; H, 5.6%).

3.3.3. 2-[Bis-(4-methoxyphenyl)methyl]-1*H*-naphtho[2,1-*b*]pyran-1-one (2g). Obtained from anisole and **1b** as cream microcrystals (6.5 g, 53%); mp 138–140 °C; ν_{max} 1639, 1610, 1596, 1438, 1237 cm^{-1}; δ_H 3.77 (6H, s, $(OMe)_2$), 5.78 (1H, s, methine), 6.84 (4H, m, Ar-H), 7.14 (4H, m, Ar-H), 7.42 (1H, d, J=1.1 Hz, 2-H), 7.46 (1H, d, J=9.2 Hz, Ar-H), 7.59 (1H, m, Ar-H), 7.68 (1H, m, Ar-H), 7.88 (1H, dd, J=8.9, 1.8 Hz, Ar-H), 8.08 (1H, d, J=8.7 Hz, Ar-H), 10.10 (1H, dd, J=8.8, 2.2 Hz, 10-H) (found: C, 79.6; H, 5.2. $C_{28}H_{22}O_4$ requires C, 79.6; H, 5.2%).

3.3.4. 3-[Bis-(4-methoxyphenyl)methyl]-4*H*-naphtho[1,2-*b*]pyran-4-one (2h). Obtained from anisole and **1c** as a pale brown glass (4.8 g, 39%); ν_{max} 1639, 1608, 1239, 1029 cm^{-1}; δ_H 3.78 (6H, s, $(OMe)_2$), 5.74 (1H, s, methine), 6.85 (4H, m, Ar-H), 7.14 (4H, m, Ar-H), 7.58 (1H, d, J=1.2 Hz, 2-H), 7.65 (3H, m, Ar-H), 7.91 (1H, d, J=8.8 Hz, Ar-H), 8.14 (1H, d, J=8.9 Hz, Ar-H), 8.40 (1H, d, J=8.7 Hz, 5-H) (found: C, 79.3; H, 5.2. $C_{28}H_{22}O_4$ requires C, 79.6; H, 5.2%).

3.4. General method for the oxidation of 3-[bis(4-aminophenyl)methyl]benzopyranones and hydroxyphenylpyrazoles

p-Chloranil (1.1 g, 4.5 mmol) was added in a single portion to a stirred suspension of the 3-[bis(4-aminophenyl)methyl]-benzopyranone or hydroxyphenylpyrazole (4.0 mmol) in anhydrous methanol (50 mL). The mixture was refluxed until no starting material remained by TLC examination (ca. 4 h). Sodium methoxide [from sodium (0.46 g, 20 mmol) and anhydrous methanol (40 mL)] was added to the cold solution and the resulting precipitate was collected by vacuum filtration, washed well with cold methanol (3×20 mL) and air dried. Analytically pure material was obtained by recrystallisation from EtOAc/hexane.

3.4.1. 3-[Bis-(4-dimethylaminophenyl)methylene]-2,3-dihydro-2-methoxy-4*H*[1]benzopyran-4-one (4a). Obtained from **2a** as orange-red crystals (1.3 g, 73%); mp 180–182 °C; ν_{max} 1655, 1603 cm^{-1}; δ_H 2.98 (6H, s, NMe_2), 3.04 (6H, s, NMe_2), 3.43 (3H, s, 2-OMe), 5.56 (1H, s, 2-H), 6.58 (2H, m, Ar-H), 6.67 (2H, m, Ar-H), 7.07 (4H, m, 6-H, 8-H, Ar-H), 7.19 (2H, br m, Ar-H), 7.46 (1H, m, 7-H), 7.95 (1H, dd, J=7.8, 1.9 Hz, 5-H) (found: C, 75.5; H, 6.4; N, 6.4; [M+H$^+$] 429.2176. $C_{27}H_{28}N_2O_3$ requires C, 75.7; H, 6.5; N, 6.5%; [M+H$^+$] 429.2173).

3.4.2. 3-[Bis-(4-diethylaminophenyl)methylene]-2,3-dihydro-2-methoxy-4*H*[1]benzopyran-4-one (4b). Obtained from **2b** as lustrous red crystals (1.8 g, 92%); mp 209–211 °C; ν_{max} 1651, 1602 cm^{-1}; δ_H 1.16 (6H, t, J=6.8 Hz, $N(CH_2CH_3)_2$), 1.21 (6H, t, J=6.8 Hz, $N(CH_2CH_3)_2$), 3.35 (8H, m, $(N(CH_2CH_3)_2)_2$), 3.44 (3H, s, 2-OMe), 5.57 (1H, s, 2-H), 6.51 (2H, m, Ar-H), 6.62 (2H, m, Ar-H), 7.01 (4H, m, 6-H, 8-H, Ar-H), 7.17 (2H, br m, Ar-H), 7.45 (1H, m, 7-H), 7.96 (1H, dd, J=7.9, 1.8 Hz, 5-H); δ_C 12.6, 12.7, 44.2, 44.3, 55.2, 104.8, 110.1, 117.7, 121.5, 123.1, 123.9, 127.0, 127.3, 127.5, 133.0, 133.2, 134.6, 138.1, 148.7, 148.9, 155.9, 158.6, 183.3; δ_H (CD_3CO_2D) 1.36 (12H, t, J=6.8 Hz, $N(CH_2CH_3)_2$), 3.46 (3H, s, OMe), 3.76 (8H, m, $(N(CH_2CH_3)_2)_2$), 7.06 (4H, m, Ar-H), 7.64 (1H, m, 6-H), 7.75 (1H, d, J=8.4 Hz, 8-H), 7.96 (1H, m, 7-H), 8.29 (1H, dd, J=8.0, 1.9 Hz, 5-H), 8.37 (1H, s, 2-H); δ_C (CD_3CO_2D) 13.1, 46.9, 49.8, 114.8, 119.7, 125.7, 127.5, 127.8, 128.1, 136.5, 141.2, 156.7, 157.4, 162.8, 165.9, 170.8, 177.1; (found: C, 76.8; H, 7.5; N, 5.6; [M+H$^+$] 485.2799. $C_{31}H_{36}N_2O_3$ requires C, 76.9; H, 7.4; N, 5.8%; [M+H$^+$] 485.2799).

3.4.3. 3-[Bis-(4-pyrrolidinophenyl)methylene]-2,3-dihydro-2-methoxy-4*H*[1]benzopyran-4-one (4c). Obtained from **2c** as red microcrystals (1.3 g, 69%); mp 215–218 °C; ν_{max} 1659, 1604 cm^{-1}; δ_H 1.97 (4H, m, $(CH_2)_2$), 2.04 (4H, m, $(CH_2)_2$), 3.31 (8H, m, $(N(CH_2)_2)_2$), 3.42 (3H, s, 2-OMe), 5.56 (1H, s, 2-H), 6.41 (2H, m, Ar-H), 6.52 (2H, m, Ar-H), 7.01 (4H, m, 6-H, 8-H, Ar-H), 7.19 (2H, br m, Ar-H), 7.45 (1H, m, 7-H), 7.95 (1H, dd, J=7.8, 1.6 Hz, 5-H) (found: C, 77.4; H, 6.6; N, 5.5; [M+H$^+$] 481.2478. $C_{31}H_{32}N_2O_3$ requires C, 77.3; H, 6.7; N, 5.8%; [M+H$^+$] 481.2468).

3.4.4. 4,4-Bis-(4-diethylaminophenyl)-1*H*,4*H*[1]benzopyrano[4,3-*c*]pyrazole (15). Obtained from **8a** as green blocks (1.7 g, 91%); mp 179–181 °C; ν_{max} 3220, 2969, 1603, 1516, 1462, 1189, 1143 cm^{-1}; δ_H 1.12 (12H, t, J=7.0 Hz, $(N(CH_2CH_3)_2)_2$), 3.30 (8H, q, J=7.0 Hz, $(N(CH_2CH_3)_2)_2$), 6.55 (4H, m, Ar-H), 6.91 (1H, m, 8-H), 7.05 (1H, d, J=8.0 Hz, 6-H), 7.15 (5H, m, Ar-H), 7.25 (1H, s, 3-H), 7.63 (1H, d, J=7.9 Hz, 9-H), 9.41 (1H, br s, NH); δ_C 12.6, 44.2, 84.4, 104.5, 110.6, 118.4, 120.6, 121.2, 122.0, 129.0, 129.4, 130.9, 147.1, 153.7; δ_H (CD_3CO_2D, 75 °C) 1.29 (12H, t, J=6.8 Hz, $(N(CH_2CH_3)_2)_2$), 3.64 (8H, q, J=6.8 Hz, $(N(CH_2CH_3)_2)_2$), 6.73 (1H, br s, Ar-H), 6.82 (4H, br m, Ar-H), 7.11 (2H, br s, Ar-H), 7.53 (4H, m, Ar-H), 7.83 (1H, br s, pyrazole-H) (found: C, 77.2; H, 7.3; N, 11.7; [M+H$^+$] 467.2808. $C_{30}H_{34}N_4O$ requires C, 77.3; H, 7.3; N, 12.0%; [M+H$^+$] 467.2805).

3.4.5. 4,4-Bis-(4-diethylaminophenyl)-1-methyl-1*H*,4*H*[1]benzopyrano[3,4-*d*]pyrazole (16) and 4,4-bis-(4-diethylaminophenyl)-2-methyl-2*H*,4*H*[1]benzopyrano[4,3-*c*]pyrazole (17). Obtained from mixture **9**, **10** as pale green microcrystals (0.9 g, 48%); mp 69–70 °C; ν_{max} 3647, 3389, 2966, 1605, 1514, 1239, 1150 cm^{-1}; δ_H 1.12

(24H, t, J=7.1 Hz, ($N(CH_2CH_3)_2)_2$), 3.30 (16H, q, J=7.1 Hz, ($N(CH_2CH_3)_2)_2$), 3.92 (3H, s, NMe minor), 4.16 (3H, s, NMe major), 6.54 (8H, m, Ar-H), 6.90 (2H, m, Ar-H), 7.02 (2H, m, Ar-H), 7.09–7.20 (12H, m, Ar-H, pyrazole-H), 7.48 (1H, dd, J=7.8, 1.4 Hz, 9-H major), 7.67 (1H, dd, J=7.7, 1.4 Hz, 9-H minor); δ_C 12.6, 39.1, 39.3, 44.2, 83.8, 84.9, 110.5, 110.6, 116.4, 118.3, 118.6, 118.9, 121.0, 121.2, 121.7, 121.8, 121.9, 128.0, 128.9, 129.1, 129.3, 130.6, 131.2, 133.2, 135.6, 143.6, 147.0, 147.1, 153.4, 153.7 (found: C, 77.1; H, 7.5; N, 11.6; [M+H$^+$] 481.2961. $C_{31}H_{36}N_4O$ requires C, 77.5; H, 7.5; N, 11.7%; [M+H$^+$] 481.2962).

3.5. General method for the preparation of hydroxyphenylpyrazoles

The hydrazine (19.8 mmol) was added in a single portion to a solution of the 3-[bis(aryl)methyl]benzopyranone (6.6 mmol) in anhydrous ethanol (40 mL). The mixture was refluxed until no benzopyranone remained by TLC examination (ca. 6 h). The cooled mixture was diluted with water (250 mL) and extracted with EtOAc (4×50 mL). The combined EtOAc extracts were washed with water (3×50 mL), dried (anhyd Na_2SO_4) and evaporated to afford a dark green gum, which was recrystallised from EtOAc and hexane.

3.5.1. 4-[Bis-(4-diethylaminophenyl)methyl]-3-(2-hydroxyphenyl)-1*H*-pyrazole (8a). Obtained from **2b** and hydrazine hydrate as pale green microcrystals (2.1 g, 67%); mp 155–158 °C; ν_{max} 3378, 1613, 1570, 1229 cm^{-1}; δ_H 1.13 (12H, t, J=7.2 Hz, ($N(CH_2CH_3)_2)_2$), 3.29 (8H, q, J=7.2 Hz, ($N(CH_2CH_3)_2)_2$), 5.43 (1H, s, methine), 6.59 (4H, m, Ar-H), 6.74 (1H, m, Ar-H), 6.97 (4H, m, Ar-H), 7.01 (1H, dd, J=8.0, 1.6 Hz, Ar-H), 7.10 (1H, s, 5-H), 7.15 (1H, m, Ar-H), 7.44 (1H, dd, J=7.9, 1.5 Hz, Ar-H), 10.02 (1H, br s, NH), 11.06 (1H, br s, OH) (found: C, 76.7; H, 7.8; N, 11.7. $C_{30}H_{36}N_4O$ requires C, 76.9; H, 7.7; N, 12.0%).

3.5.2. 4-[Bis-(4-methoxyphenyl)methyl]-3-(2-hydroxyphenyl)-1*H*-pyrazole (8b). Obtained from **2e** and hydrazine hydrate as a pale brown viscous oil (2.3 g, 89%), which decomposed on attempted purification by vacuum distillation; ν_{max} 3279, 1606, 1582, 1232, 749 cm^{-1}; δ_H 3.76 (6H, s, $(OMe)_2$), 5.55 (1H, s, methine), 6.68 (1H, m, Ar-H), 6.80 (4H, m, Ar-H), 7.01 (6H, m, Ar-H, 5-H), 7.12 (1H, m, Ar-H), 7.31 (1H, dd, J=8.3, 1.4 Hz, Ar-H), 10.18 (1H, br s, NH), 11.09 (1H, br s, OH).

3.5.3. 4-[Bis-(4-diethylaminophenyl)methyl]-3-(2-hydroxyphenyl)-1-methyl-1*H*-pyrazole (minor isomer) (9) and 4-[bis-(4-diethylaminophenyl)methyl]-5-(2-hydroxyphenyl)-1-methyl-1*H*-pyrazole (major isomer) (10). Obtained from **2b** and methylhydrazine as pale green microcrystals (3.0 g, 93%); mp (mixture) 161–166 °C; ν_{max} 3290, 1609, 1514, 1263 cm^{-1}; δ_H 0.90 (12H, t, J=7.0 Hz, ($N(CH_2CH_3)_2)_2$ minor), 1.01 (12H, t, J=7.0 Hz, ($N(CH_2CH_3)_2)_2$ major), 3.20 (8H, q, J=7.0 Hz, ($N(CH_2CH_3)_2)_2$ minor), 3.25 (8H, q, J=7.0 Hz, ($N(CH_2CH_3)_2)_2$ major), 3.62 (3H, s, NMe major), 3.84 (3H, s, NMe minor), 4.85 (1H, s, methine major), 5.40 (1H, s, methine minor), 6.60 (8H, m, Ar-H major and minor), 6.74 (1H, s, Ar-H minor), 6.89–7.02 (13H, m, Ar-H major and minor, 5-H minor), 7.14 (1H, m, Ar-H minor), 7.31 (1H, m, Ar-H major), 7.40 (1H, dd, J=8.3, 1.9 Hz, Ar-H minor), 7.44 (1H, s, 3-H major), 8.51 (1H, br s, OH major) 11.10 (1H, s, OH minor) (found: C, 76.8; H, 8.0; N, 11.4. $C_{31}H_{38}N_4O$ requires C, 77.2; H, 7.9; N, 11.6%).

4. Conclusion

The oxidation of 3-[bis-(diaryl)methyl]chromones **2** with *p*-chloranil provides novel acetals, 3-[bis-(diaryl)methylene]-2-methoxychroman-4-ones, **4** through interception of a pyrylium type intermediate. Treatment of **4** with acid unmasks the acetal and generates an intensely coloured cationic dye. Condensation of **2** with hydrazines affords 3-(2-hydroxyphenyl)-4-[bis-(diaryl)methyl]pyrazoles **8**, **9** and **10**. Oxidation of these (2-hydroxyphenyl)pyrazoles affords 4,4-diarylbenzopyrano[4,3-*c*]pyrazoles **15**, **16** and **17** via interception of a diarylmethine cation; a process, which constitutes a new route to benzopyranopyrazoles. The electronic absorption spectra of **15**, **16** and **17** in acid solution are comparable with those of triphenylmethine cationic dyes.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.090.

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General method of obtaining deuterium-labeled heterocyclic compounds using neutral D_2O with heterogeneous Pd/C

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Abstract—A protocol of a versatile H–D exchange reaction of heterocyclic compounds catalyzed by heterogeneous Pd/C in D_2O is described. The reaction of various nitrogen-containing heterocycles with 10% Pd/C (10 wt % of the substrate) under hydrogen atmosphere in D_2O as a deuterium source at 110–180 °C for 24 h afforded the corresponding deuterated compounds with satisfactory efficiency of deuteration in moderate to excellent isolated yields. Furthermore, the Pd/C–H_2–D_2O system can be extended to the direct deuteration of biologically active compounds such as sulfamethazine, which is used as a synthetic antibacterial drug for fat stocks and would be applied as a general method for the preparation of the standard materials for the analysis of residual chemicals in foods and so on.

1. Introduction

Deuterium-labeled compounds have found extensive applications in such research areas as pharmaceutical, bioanalytical, biological, and environmental chemistry to analyze drug metabolism mechanisms, residual agrochemicals in foods using mass spectrometry (MS), structure of biomolecules, and so on.[1,2] Access to the deuterium-labeled compounds has been facilitated by the adoption of the post-synthetic H–D exchange reaction instead of the laborious and costly multi-step synthetic processes starting from originally deuterium-labeled small synthons. Although a huge number of post-synthetic H–D exchange reactions have been reported in the literature, they usually require high temperature and pressure,[3] stoichiometric reagents,[4] expensive or inaccessible reagents,[5] strong bases or acids,[2e,3a–c,3g–j,6] special apparatus,[2e,6f] and/or deuterium atmosphere.[4a–4c,5a,7] Furthermore, some of the methods involve structural transformations[3m,3q,8] or a low degree of deuterium-efficiency.[6c,7g,7m,9] Hence, the development of new, post-synthetic, and deuterium-efficient H–D exchange reactions is still a challenging subject.

We recently developed a regioselective H–D exchange reaction at the benzylic positions using Pd/C as a catalyst in deuterium oxide under hydrogen atmosphere (Pd/C–H_2–D_2O system) at room temperature,[10] and found that the application of heat could promote the H–D exchange reaction not only at the benzylic positions, but also on the non-activated carbons.[11] Since heterocyclic compounds such as indole, pyridine, pyrimidine, and quinoline ring systems are often seen in natural products, pharmaceuticals, veterinary medicines, agrochemicals, and so on, the deuterated heterocycles are of interest as building blocks of such bioactive materials needed as internal standards in GC–MS or LC–MS assays. Taking into consideration the establishment of a general deuteration method of heterocycles as the core nuclei of biologically active compounds using the Pd/C–H_2–D_2O system, we studied the deuteration of a wide range of heterocyclic substrates.

2. Results and discussion

A variety of heterocyclic substrates were heated at 110–180 °C (bath temperature) in the presence of a catalytic amount of 10% Pd/C (10% of the weight of the substrate, Aldrich) in D_2O. The reaction was carried out under ca. 1 atm H_2 pressure and reflux conditions (110–160 °C of the heating head or bath temperature) using ChemiStation™ or reflux condenser (Dimroth type); the inner reaction temperature was at ca. 104 °C (boiling point of D_2O). When a sealed tube was employed as a reaction vessel, the reaction mixture was stirred at 160 or 180 °C under <2.5 atm H_2 pressure (the inner gas pressure was measured by a pressure gauge). The deuterated positions and deuterium-efficiency of the obtained products were determined by ^{1}H NMR (DSS, *p*-anisic acid or dioxane as an internal standard), ^{2}H NMR, and mass spectra. It is noteworthy that water

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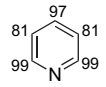
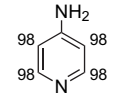
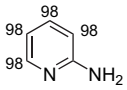
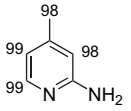
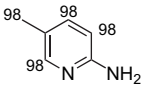
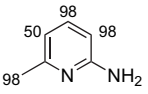
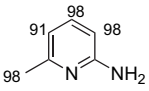
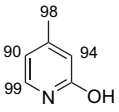
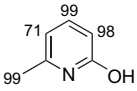
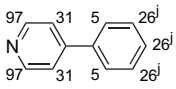
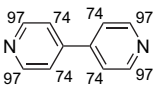
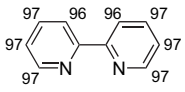
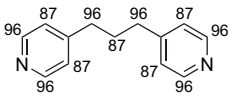
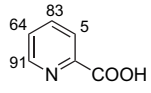
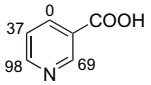
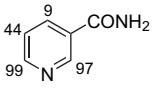
Table 1. H–D exchange reaction of pyridine derivatives in D_2O catalyzed by 10% Pd/C–H_2[a]

Substrate $\xrightarrow[D_2O,\ 24\ h]{10\%\ Pd/C,\ H_2}$ Product-d_n

Entry	Temp (°C)[b]	D content (%)[c]	Yield (%)[d]
1[e,f]	110		83[k]
2[f]	160		100
3[g]	180		100
4[g]	180		69
5[g]	180		91
6[g]	180		51
7[g,h]	180		49
8[g]	180		99
9[f]	160		100
10	160		88
11	160		84
12	160		80
13	160		97
14[f]	160		99
15[f,i]	160		98
16[f]	160		100

(*continued*)

Table 1. (*continued*)

[a] Unless otherwise noted, 0.5 mmol of the substrate was used. Reactions were carried out in a sealed tube under ordinary H_2 pressure using 10% Pd/C (10 wt % of the substrate) in D_2O (2 mL) for 24 h.
[b] Temperature of oil bath or heating head of ChemiStation™.
[c] D content was determined by ^1H NMR.
[d] Isolated yield, unless otherwise stated.
[e] Substrate (1 mmol) was used in D_2O (4 mL).
[f] The reaction was carried out using the ChemiStation™.
[g] Substrate (500 mg) was used in D_2O (17 mL).
[h] Pd/C [10% (10 wt % of the substrate)] and Pt/C [5% (20 wt % of the substrate)] were used.
[i] Substrate (0.25 mmol) was used in D_2O (1 mL).
[j] Indicated as the average D content.
[k] Determined by GC.

(D_2O)-insoluble substrates are also acceptable for this H–D exchange reaction.

2.1. H–D exchange reaction of pyridine derivatives

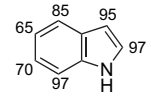
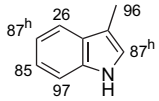
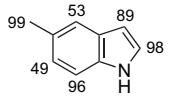
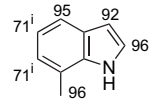
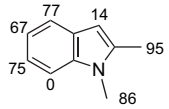
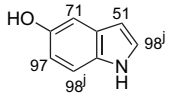
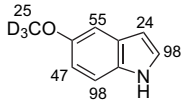
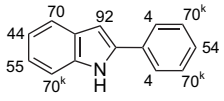
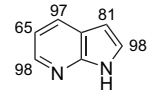
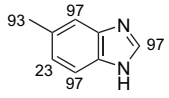
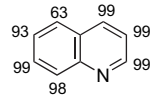
As shown in Table 1, the H–D exchange reaction proceeded well on the pyridine nucleus to give the desired multi-deuterated products in satisfactory deuterium-efficiency and isolated yields. In particular, aminopyridine and hydroxypyridine derivatives showed remarkably excellent deuterium-efficiency at 160–180 °C (entries 2–5, 7, and 8). It is noteworthy to mention that the 5-position of 2-amino-6-methylpyridine where the H–D exchange was inefficient only with Pd/C could be deuterated easily by using 5% Pt/C together with 10% Pd/C (entries 6 vs 7). In general, higher efficiency of deuteration at the positions adjacent to the nitrogen atoms on the pyridine rings was observed rather than at other positions. On the other hand, lower incorporation of deuterium at the neighboring positions of a carbon substituent (*ortho*-positions to the substituent) such as CH_2, CO_2H, and $CONH_2$ (entries 10–16) was observed presumably due to steric hindrance. Moreover, as shown in entries 15 and 16, the H–D exchange reaction efficiently proceeded even at the *ortho*-position to the substituent if the position was adjacent to the nitrogen atom in the pyridine ring. It is apparent that the nitrogen atom profoundly influences the deuteration reaction using the Pd/C–H_2–D_2O system. It is expected that the Pd metal can be located in the vicinity of the nitrogen atom of the pyridine ring since Pd metal has a quite high affinity for the nitrogen lone pair. This could be the reason why the 2-position of the pyridine ring was effectively deuterated.

2.2. H–D exchange reaction of indole derivatives

Excellent deuterium incorporation was observed at the methyl substituents as well as at the positions adjacent to the nitrogen atoms on the indole, azaindole, benzimidazole, and quinoline rings, while the efficiency of the deuteration at the neighboring positions of the methyl groups was usually

Table 2. H–D exchange reaction of indole, azaindole, benzimidazole, quinoline derivatives in D_2O catalyzed by 10% Pd/C–H_2[a]

Substrate $\xrightarrow[D_2O,\ 24\ h]{10\%\ Pd/C,\ H_2}$ Product-d_n

Entry	Temp (°C)[b]	D content (%)[c]	Yield (%)[d]
1	160		80
2	160		94
3[e,f]	160		98
4	160		91
5[f]	140		95
6	160		98
7[f]	160		99
8[e]	160		96
9	160		99
10	160		99
11[g]	180		83

[a] Unless otherwise noted, 0.5 mmol of the substrate was used. Reactions were carried out in a sealed tube under ordinary H_2 pressure using 10% Pd/C (10 wt % of the substrate) in D_2O (2 mL).
[b] Temperature of oil bath or heating head of ChemiStation™.
[c] D content was determined by ^1H NMR.
[d] Isolated yield.
[e] Substrate (0.25 mmol) was used in D_2O (1 mL).
[f] The reaction was carried out using the ChemiStation™.
[g] Substrate (500 mg) was used in D_2O (17 mL).
[h–k] Indicated as the average D content.

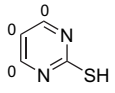
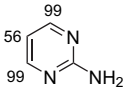
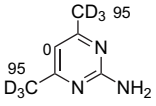
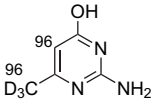
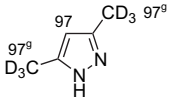
low compared to the position adjacent to the hydroxyl group (Table 2, entries 1–7 and 9–11). In addition, the 7-position of the indole and benzimidazole rings, which are regarded as the *ortho*-positions to the amino groups of the benzene rings, were deuterated efficiently (entries 1–3, 6, 7, and 10). On the other hand, no incorporation was found at the 7-position when 1,2-dimethylindole was used as a substrate (entry 5). The above results also demonstrate that this deuterating method is highly affected by both electronic and steric factors.

2.3. H–D exchange reaction of pyrimidine and imidazole derivatives

When 2-mercaptopyrimidine was used as a substrate, no H–D exchange reaction was observed and dimerization proceeded as a result of the formation of a disulfide linkage (Table 3, entry 1). Probably because the sulfur atom acted as a catalytic poison, the H–D exchange reaction was completely suppressed. On the other hand, when the thiol moiety was replaced with an amino group, the deuteration, especially at the 4- and 6-positions, proceeded smoothly with high efficiency (entry 2). When two methyl groups were introduced to the 4- and 6-positions of 2-aminopyrimidine, no deuterium incorporation at the 5-position was observed, whereas the 5-position, which was adjacent to the hydroxyl group, was deuterated quantitatively when 2-amino-4-hydroxy-6-methylpyrimidine was used as

Table 3. H–D exchange reaction of pyrimidine, pyrazole derivatives in D_2O catalyzed by 10% Pd/C–H_2[a]

Substrate $\xrightarrow[D_2O,\ 24\ h]{10\%\ Pd/C,\ H_2}$ Product-d_n

Entry	Temp (°C)[b]	D content (%)[c]	Yield (%)[d]
1	160		NA[h]
2	160		99
3[e]	110		100
4[e]	110		100
5[f]	160		81

[a] Unless otherwise noted, 0.5 mmol of the substrate was used. Reactions were carried out using the ChemiStation™ under ordinary H_2 pressure using 10% Pd/C (10 wt % of the substrate) in D_2O (2 mL).
[b] Temperature of oil bath or heating head of ChemiStation™.
[c] D content was determined by ^1H NMR.
[d] Isolated yield.
[e] The mixture was heated under reflux for 24 h.
[f] The reaction was carried out in a sealed tube.
[g] Indicated as the average D content.
[h] Disulfide of 2-mercaptopyrimidine was formed as a product.

a substrate (entries 3 vs 4). Furthermore, the use of 3,5-dimethylpyrazole led to almost quantitative deuterium incorporation at the 4-position (entry 5). These results suggest that introduction of an appropriate substituent into the substrate may enable us to establish a regioselective H–D exchange reaction by taking advantage of the steric hindrance and/or neighboring effect of the substituent.

2.4. H–D exchange reaction of biologically active compounds

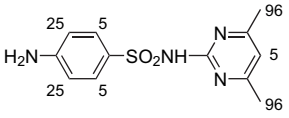
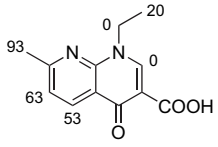
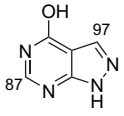
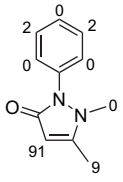
The applications of stable isotope (SI)-labeled compounds for clinical pharmacokinetic studies and the analysis of residual agrochemicals in the environment have rapidly increased in recent years. Since the chemical properties of SI-labeled compounds are similar to those of non-labeled compounds, SI-labeled compounds are the most valuable tracers for these studies and analyses using GC–MS or LC–MS. In spite of the usefulness of SI-labeled isotope tracers, there are often problems incurred in getting a desired labeled tracer because of the difficulties in the synthesis of SI-labeled compounds. Heating a variety of biologically active compounds in the Pd/C–H_2–D_2O system led to efficient introduction of deuterium atoms. The results are summarized in Table 4.

The H–D exchange reactions at the methyl groups in sulfamethazine and nalidixic acid, both of which are antibacterial agents, proceeded effectively (Table 4, entries 1 and 2), but the efficiency of the deuteration at the methyl group of antipirine, an analgesic agent, was seriously reduced (entry 4). Instead, antipirine was regioselectively deuterated on the pyrazolidinone ring (entry 4). When allopurinol, an antiurolithic agent, was used as a substrate, the H–D exchange reaction proceeded effectively (entry 3).

Deuterated drugs often have different actions from the protonated forms in vivo.[12] Some deuterated drugs show different transport processes. Since many deuterated drugs are more resistant to metabolic changes by the isotope effect derived from bulky deuterium, it can be expected that deuterium-labeled drugs demonstrate the feasibility of developing new sustained-release dosage by virtue of the isotope effect. The deuteration method we demonstrated in this paper could be a general method for the preparation of new prolonged drugs as well as the standard materials for the studies of metabolism and the analysis of residual chemicals in the environment.

Table 4. H–D exchange reaction of bioactive compounds in D_2O catalyzed by 10% Pd/C–H_2[a]

Substrate $\xrightarrow[D_2O,\ 24\ h]{10\%\ Pd/C,\ H_2}$ Product-d_n

Entry	Temp (°C)[b]	D content (%)[c]	Yield (%)[d]
1	160		97
2	160		96
3	160		99
4[e]	160		98

[a] Substrate (0.25 mmol) was used. Reactions were carried out in a sealed tube under ordinary H_2 pressure using 10% Pd/C (10 wt % of the substrate) in D_2O (1 mL).
[b] Temperature of oil bath or heating head of ChemiStation™.
[c] D content was determined by ^1H NMR.
[d] Isolated yield.
[e] The reaction was carried out using the ChemiStation™.

3. Conclusion

In summary, we have developed an efficient and extensive deuterium incorporation method using a heterogeneous Pd/C–H_2–D_2O system for a wide range of substrates including bioactive substances in moderate to excellent deuterium-efficiency. The results presented here provide a deuterium gas-free, totally catalytic, and post-synthetic deuterium labeling method in D_2O medium. The simplicity of this method makes it an attractive new tool for medicinal, analytical, and organic chemists.

4. Experimental

4.1. General

All the substances examined in this study were obtained commercially and were used without further purification. Pd/C (10%) was purchased from Aldrich Chemical Co. and deuterium oxide (99.9% isotopic purity) was purchased from Cambridge Isotope Laboratories.

ChemiStation™ is a personal organic synthesizer from TOKYO RIKAKIKAI CO., LTD (EYELA). ^1H and ^2H NMR spectra were recorded on a JEOL AL-400 spectrometer or JEOL EX-400 spectrometer (^1H NMR: 400 MHz, ^2H NMR: 61 MHz). Chemical shifts (δ) are given in parts per million relative to residual solvent or internal standard (3-trimethylsilyl-1-propanesulfonic acid sodium salt (DSS), *p*-anisic acid, or dioxane). EI and FAB mass spectra were recorded on a JEOL JMS-SX102A spectrometer. GC spectra were recorded on a SHIMADZU GC-17A spectrometer. Preparative thin-layer chromatography was performed using Merk PLC plate (silica gel 60 F254).

4.2. General procedure for H–D exchanges

Method A: A substrate (0.25–0.50 mmol) and 10% Pd/C (10 wt % of the substrate) in D_2O (1–2 mL) were stirred at 160 °C using the ChemiStation™ under H_2 atmosphere for

24 h. After cooling, the reaction mixture was diluted with methanol (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex®-LG, 0.20 μm) to remove the catalyst. The filtered catalyst was washed with methanol (2×10 mL) and the filtrate was concentrated in vacuo.

Method B: A substrate (0.25–0.50 mmol) and 10% Pd/C (10 wt % of the substrate) in D_2O (1–2 mL) were stirred at 160 °C using the ChemiStation™ under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex®-LG, 0.20 μm) to remove the catalyst. The filtered catalyst was washed with diethyl ether (2×10 mL). The combined organic phases were washed with H_2O (2×30 mL) and brine (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford deuterated forms.

Method C: A substrate (500 mg, 4.6–5.3 mmol) and 10% Pd/C (50 mg, 10 wt % of the substrate) in D_2O (17 mL) were stirred at 180 °C in a sealed tube under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with methanol (20 mL) and the mixture was filtered through a filter paper to remove the catalyst. The filtered catalyst was washed with methanol (2×5 mL) and the filtrate was concentrated in vacuo.

Method D: A substrate (0.25–0.50 mmol) and 10% Pd/C (10 wt % of the substrate) in D_2O (1–2 mL) were stirred at 160 °C in a sealed tube under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex®-LG, 0.20 μm) to remove the catalyst. The filtered catalyst was washed with diethyl ether (2×10 mL). The combined organic phases were washed with H_2O (2×30 mL) and brine (30 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford deuterated forms.

Method E: A substrate (0.5 mmol) and 10% Pd/C (10 wt % of the substrate) in D_2O (2 mL) were heated under reflux for 24 h. After cooling, the reaction mixture was diluted with methanol (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex®-LG, 0.20 μm) to remove the catalyst. The filtered catalyst was washed with methanol (2×10 mL) and the filtrate was concentrated in vacuo.

4.2.1. [^{2}H]-Pyridine (Table 1, entry 1). A mixture of pyridine (80 μL, 1.0 mmol) and 10% Pd/C (7.9 mg, 10 wt % of the substrate) in D_2O (4 mL) was refluxed under H_2 atmosphere for 24 h. After cooling, the reaction mixture was filtered through a membrane filter (Millipore Millex®-LG, 0.20 μm) to remove the catalyst. The yield was determined by GC analysis of the crude filtrate (83% yield). Isotope distribution (EIMS): 1% d_1, 2% d_2, 10% d_3, 30% d_4, 53% d_5. ^{1}H NMR (D_2O, DSS as an internal standard) δ 8.51 (s, 0.03H), 7.83 (s, 0.03H), 7.45 (s, 0.38H).

4.2.2. [^{2}H]-4-Aminopyridine (Table 1, entry 2). Method A, 100% yield as a colorless solid. Isotope distribution (EIMS): 4% d_2, 10% d_3, 79% d_4, 7% d_5. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 7.97 (s, 0.03H), 6.46 (s, 0.04H), 5.96 (br s, 2H). ^{2}H NMR (DMSO) δ 7.96 (br s), 6.45 (br s).

4.2.3. [^{2}H]-2-Aminopyridine (Table 1, entry 3). Method C. Purification by preparative thin-layer chromatography (silica gel, ethyl acetate) gave 2-aminopyridine-d_n as a colorless solid (100% yield). Isotope distribution (EIMS): 1% d_1, 2% d_2, 9% d_3, 82% d_4, 6% d_5. ^{1}H NMR (CD_2Cl_2, dioxane as an internal standard) δ 8.02 (s, 0.02H), 7.41 (s, 0.02H), 6.61 (s, 0.02H), 6.49 (s, 0.02H), 4.44 (br s, 2H). ^{2}H NMR (CH_2Cl_2) δ 8.06 (br s), 7.45 (br s), 6.66 (br s), 6.54 (br s).

4.2.4. [^{2}H]-2-Amino-4-methylpyridine (Table 1, entry 4). 2-Amino-4-methylpyridine (500 mg, 4.6 mmol) and 10% Pd/C (50 mg, 10 wt % of the substrate) in D_2O (17 mL) were stirred at 180 °C under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with ethyl acetate (20 mL) and the mixture was filtered through a filter paper to remove the catalyst. The filtered catalyst was washed with ethyl acetate (2×5 mL). The combined organic phases were washed with H_2O (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by preparative thin-layer chromatography (silica gel, ethyl acetate) gave 2-amino-4-methylpyridine-d_n as a colorless solid (69% yield). Isotope distribution (EIMS): 1% d_3, 2% d_4, 13% d_5, 76% d_6, 6% d_7, 2% d_8. ^{1}H NMR ($CDCl_3$, dioxane as an internal standard) δ 7.93 (s, 0.01H), 6.48 (s, 0.01H), 6.32 (s, 0.02H), 4.35 (br s, 2H), 2.20 (s, 0.07H). ^{2}H NMR ($CHCl_3$) δ 7.94 (br s), 6.53 (br s), 6.37 (br s), 2.20 (br s).

4.2.5. [^{2}H]-2-Amino-5-methylpyridine (Table 1, entry 5). Method C, 91% yield as a pale yellow crystal. Isotope distribution (EIMS): 1% d_2, 3% d_3, 18% d_4, 12% d_5, 61% d_6, 5% d_7. ^{1}H NMR (CD_2Cl_2, dioxane as an internal standard) δ 7.85 (s, 0.02H), 7.25 (s, 0.02H), 6.43 (s, 0.02H), 4.32 (br s, 2H), 2.12 (s, 0.07H). ^{2}H NMR (CH_2Cl_2) δ 7.89 (br s), 7.30 (br s), 6.48 (br s), 2.14 (br s).

4.2.6. [^{2}H]-2-Amino-6-methylpyridine (Table 1, entry 6). Method C. Purification by preparative thin-layer chromatography (silica gel, ethyl acetate) gave 2-amino-6-methylpyridine-d_n as a pale yellow solid (51% yield). Isotope distribution (EIMS): 1% d_3, 7% d_4, 48% d_5, 41% d_6, 3% d_7. ^{1}H NMR (CD_3OD, dioxane as an internal standard) δ 7.33 (s, 0.02H), 6.45 (s, 0.50H), 6.40 (s, 0.02H), 2.26 (s, 0.07H). ^{2}H NMR (CH_3OH) δ 7.35 (br s), 6.47 (br s), 6.40 (br s), 2.25 (br s).

4.2.7. [^{2}H]-2-Amino-6-methylpyridine (Table 1, entry 7). Method C. Purification by preparative thin-layer chromatography (silica gel, ethyl acetate) gave 2-amino-6-methylpyridine-d_n as a pale yellow solid (49% yield). Isotope distribution (EIMS): 3% d_4, 17% d_5, 75% d_6, 5% d_7. ^{1}H NMR ($CDCl_3$, dioxane as an internal standard) δ 7.31 (s, 0.02H), 6.50 (s, 0.09H), 6.30 (s, 0.02H), 4.39 (br s, 2H), 2.34 (s, 0.06H). ^{2}H NMR ($CHCl_3$) δ 7.35 (br s), 6.53 (br s), 6.34 (br s), 2.34 (br s).

4.2.8. [^{2}H]-2-Hydroxy-4-methylpyridine (Table 1, entry 8). Method C, 99% yield as a colorless solid. Isotope distribution (EIMS): 3% d_4, 19% d_5, 72% d_6, 6% d_7. ^{1}H NMR (CD_2Cl_2, dioxane as an internal standard) δ 13.03 (br s,

1H), 7.24 (s, 0.01H), 6.31 (s, 0.06H), 6.11 (s, 0.10H), 2.17 (s, 0.06H). ^{2}H NMR (CH_2Cl_2) δ 7.28 (br s), 6.35 (br s), 6.17 (br s), 2.18 (br s).

4.2.9. [^{2}H]-2-Hydroxy-6-methylpyridine (Table 1, entry 9). Method A. Boiling ethanol was used instead of methanol, 100% yield as an off-white solid. Isotope distribution (EIMS): 3% d_4, 35% d_5, 56% d_6, 6% d_7. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 11.6 (br s, 1H), 7.32 (s, 0.01H), 6.13 (s, 0.02H), 5.97 (s, 0.29H), 2.14 (s, 0.04H). ^{2}H NMR (DMSO) δ 7.32 (br s), 6.12 (br s), 5.97 (br s), 2.09 (br s).

4.2.10. [^{2}H]-4-Phenylpyridine (Table 1, entry 10). Method D, 88% yield as a colorless solid. Isotope distribution (EIMS): 5% d_0, 8% d_1, 24% d_2, 30% d_3, 21% d_4, 9% d_5, 3% d_6. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 8.67–8.65 (m, 0.07H), 7.84 (d, J=7.24 Hz, 1.91H), 7.74 (s, 1.38H), 7.58–7.51 (m, 2.23H). ^{2}H NMR (DMSO) δ 8.67 (br s), 7.73 (br s), 7.55 (br s).

4.2.11. [^{2}H]-4,4′-Bipyridyl (Table 1, entry 11). Method D. Ethyl acetate was used instead of diethyl ether, 84% yield as a colorless solid. Isotope distribution (EIMS): 1% d_3, 6% d_4, 14% d_5, 25% d_6, 30% d_7, 24% d_8. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 8.76 (s, 0.13H), 7.86 (s, 1.05H). ^{2}H NMR (DMSO) δ 8.74 (br s), 7.86 (br s).

4.2.12. [^{2}H]-2,2′-Bipyridyl (Table 1, entry 12). Method D. Ethyl acetate was used instead of diethyl ether, 80% yield as a colorless solid. Isotope distribution (EIMS): 1% d_4, 6% d_5, 19% d_6, 21% d_7, 53% d_8. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 8.72 (s, 0.07H), 8.42 (s, 0.09H), 7.98 (s, 0.06H), 7.48 (s, 0.06H). ^{2}H NMR (DMSO) δ 8.72 (br s), 8.42 (br s), 7.98 (br s), 7.49 (br s).

4.2.13. [^{2}H]-1,3-Di(4-pyridyl)propane (Table 1, entry 13). Method D. Ethyl acetate was used instead of diethyl ether, 97% yield as a colorless solid. Isotope distribution (EIMS): 3% d_{10}, 8% d_{11}, 23% d_{12}, 36% d_{13}, 30% d_{14}. ^{1}H NMR (DMSO-d_6, p-anisic acid as an internal standard) δ 8.40 (s, 0.15H), 7.29 (s, 0.51H), 2.68 (s, 0.15H), 2.00–1.96 (m, 0.27H). ^{2}H NMR (DMSO) δ 8.42 (br s), 7.31 (br s), 2.65 (br s), 1.93 (br s).

4.2.14. [^{2}H]-Picolinic acid (Table 1, entry 14). Method A, 99% yield as a colorless solid. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 8.73 (s, 0.09H), 8.07 (s, 0.88H), 8.03–8.01 (m, 0.24H), 7.64 (s, 0.36H). ^{2}H NMR (DMSO) δ 8.72 (br s), 8.00 (br s), 7.64 (br s).

4.2.15. [^{2}H]-Nicotinic acid (Table 1, entry 15). Method A. Boiling water was used instead of methanol, 98% yield as a colorless solid. Isotope distribution (EIMS): 1% d_0, 15% d_1, 46% d_2, 34% d_3, 4% d_4. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 13.4 (br, 1H), 9.10 (s, 0.31H), 8.79 (s, 0.02H), 8.30–8.28 (m, 1H), 7.57 (d, J=7.82 Hz, 0.63H). ^{2}H NMR (DMSO) δ 9.08 (br s), 8.81 (br s), 7.57 (br s).

4.2.16. [^{2}H]-Nicotinamide (Table 1, entry 16). Method A. Boiling ethanol was used instead of methanol, 100% yield as a colorless solid. Isotope distribution (EIMS): 2% d_1, 38% d_2, 50% d_3, 9% d_4, 1% d_5. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 9.05 (s, 0.03H), 8.72 (s, 0.01H), 8.24–8.22 (m, 0.91H), 8.19 (br s, 1H), 7.62 (br s, 1H), 7.52 (d, J=7.81 Hz, 0.56H). ^{2}H NMR (DMSO) δ 9.05 (br s), 8.72 (br s), 8.23 (br s), 7.53 (br s).

4.2.17. [^{2}H]-Indole (Table 2, entry 1). Method D, 80% yield as a pale red solid. Isotope distribution (EIMS): 1% d_2, 3% d_3, 10% d_4, 27% d_5, 36% d_6, 23% d_7. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 7.52–7.50 (m, 0.15H), 7.36–7.32 (m, 0.03H), 7.19 (s, 0.03H), 7.05 (s, 0.30H), 6.96 (s, 0.35H), 6.40 (s, 0.05H). ^{2}H NMR (CH_3OH) δ 7.56 (br s), 7.39 (br s), 7.23 (br s), 7.10 (br s), 7.01 (br s), 6.46 (br s).

4.2.18. [^{2}H]-3-Methylindole (Table 2, entry 2). Method D, 94% yield as a pale red solid. Isotope distribution (EIMS): 1% d_1, 1% d_2, 5% d_3, 16% d_4, 29% d_5, 23% d_6, 16% d_7, 7% d_8, 1% d_9. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 7.46 (s, 0.74H), 7.30 (s, 0.03H), 7.06 (s, 0.15H), 6.97 (s, 0.26H), 2.26 (s, 0.11H). ^{2}H NMR (CH_3OH) δ 7.31 (br s), 7.07 (br s), 6.98 (br s), 2.23 (br s).

4.2.19. [^{2}H]-5-Methylindole (Table 2, entry 3). Method B, 98% yield as a pale red solid. Isotope distribution (EIMS): 1% d_1, 1% d_2, 4% d_3, 14% d_4, 30% d_5, 24% d_6, 23% d_7, 3% d_8. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 7.29 (s, 0.45H), 7.22–7.20 (m, 0.04H), 7.14 (s, 0.02H), 6.89 (s, 0.51H), 6.30 (s, 0.11H), 2.33 (s, 0.04H). ^{2}H NMR (CH_3OH) δ 7.27 (br s), 7.18 (br s), 6.35 (br s), 2.33 (br s).

4.2.20. [^{2}H]-7-Methylindole (Table 2, entry 4). Method D, 91% yield as an off-white solid. Isotope distribution (EIMS): 1% d_2, 2% d_3, 9% d_4, 26% d_5, 25% d_6, 23% d_7, 11% d_8, 1% d_9. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 7.35 (s, 0.05H), 7.19 (s, 0.04H), 6.86 (s, 0.58H), 6.40 (s, 0.08H), 2.48–2.42 (m, 0.12H). ^{2}H NMR (CH_3OH) δ 7.39 (br s), 7.22 (br s), 6.92 (br s), 6.45 (br s), 2.43 (br s).

4.2.21. [^{2}H]-1,2-Dimethylindole (Table 2, entry 5). Method B, 95% yield as a wine-red solid. Isotope distribution (EIMS): 6% d_4, 9% d_5, 14% d_6, 21% d_7, 23% d_8, 16% d_9, 11% d_{10}. ^{1}H NMR (DMSO-d_6, p-anisic acid as an internal standard) δ 7.40–7.39 (m, 0.23H), 7.33 (s, 1H), 7.05–7.02 (m, 0.25H), 6.94 (s, 0.33H), 6.17 (s, 0.86H), 3.64–3.59 (m, 0.43H), 2.35 (s, 0.14H). ^{2}H NMR (DMSO) δ 7.43 (br s), 7.07 (br s), 6.98 (br s), 6.22 (br s), 3.60 (br s), 2.34 (br s).

4.2.22. [^{2}H]-5-Hydroxyindole (Table 2, entry 6). Method D, 98% yield as a brown solid. Isotope distribution (EIMS): 3% d_2, 18% d_3, 38% d_4, 33% d_5, 7% d_6, 1% d_7. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 10.8 (br s, 1H), 8.60 (s, 1H), 7.22 (s, 0.02H), 7.19 (s, 0.02H), 6.86 (s, 0.29H), 6.61 (s, 0.03H), 6.23 (s, 0.49H). ^{2}H NMR (DMSO) δ 7.21 (br s), 6.87 (br s), 6.62 (br s), 6.26 (br s).

4.2.23. [^{2}H]-5-Methoxylindole (Table 2, entry 7). Method B, 99% yield as a brown solid. Isotope distribution (EIMS): 12% d_3, 34% d_4, 27% d_5, 17% d_6, 7% d_7, 2% d_8, 1% d_9. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 7.23 (s, 0.02H), 7.16 (s, 0.02H), 7.03 (s, 0.45H), 6.73 (s, 0.53H), 6.33 (s, 0.76H), 3.78 (s, 2.26H). ^{2}H NMR (CH_3OH) δ 7.26 (br s), 7.18 (br s), 7.06 (br s), 6.76 (br s), 6.37 (br s), 3.89–3.67 (m).

4.2.24. [^{2}H]-2-Phenylindole (Table 2, entry 8). Method D, 96% yield as a yellow solid. Isotope distribution (EIMS): 2% d_0, 5% d_1, 9% d_2, 11% d_3, 12% d_4, 13% d_5, 16% d_6, 16% d_7, 12% d_8, 3% d_9, 1% d_{10}. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 11.5 (br s, 1H), 7.89 (s, 1.93H), 7.56–7.54 (m, 0.31H), 7.50–7.41 (m, 0.92H), 7.33 (s, 0.46H), 7.12–7.10 (m, 0.45H), 7.04–7.00 (m, 0.57H), 6.92 (s, 0.08H). ^{2}H NMR (DMSO) δ 7.48 (br s), 6.98 (br).

4.2.25. [^{2}H]-7-Azaindole (Table 2, entry 9). Method A. The reaction was carried out in a sealed tube, 99% yield as a pale yellow solid. Isotope distribution (EIMS): 1% d_1, 2% d_2, 12% d_3, 41% d_4, 39% d_5, 5% d_6. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 11.6 (br s, 1H), 8.24–8.20 (m, 0.02H), 7.98–7.96 (m, 0.03H), 7.47 (s, 0.08H), 7.06 (s, 0.35H), 6.46 (s, 0.19H). ^{2}H NMR (CH_3OH) δ 8.20 (br s), 7.95 (br s), 7.46 (br s), 7.05 (br s), 6.44 (br s).

4.2.26. [^{2}H]-5-Methylbenzimidazole (Table 2, entry 10). Method A. The reaction was carried out in a sealed tube, 99% yield as a colorless solid. Isotope distribution (EIMS): 2% d_2, 11% d_3, 28% d_4, 24% d_5, 27% d_6, 7% d_7, 1% d_8. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 8.06 (s, 0.03H), 7.48–7.46 (m, 0.03H), 7.38 (s, 0.03H), 7.08–7.07 (m, 0.77H), 2.44–2.40 (m, 0.22H). ^{2}H NMR (CH_3OH) δ 8.07 (br s), 7.47 (br s), 7.40 (br s), 7.09 (br s), 2.38 (br s).

4.2.27. [^{2}H]-Quinoline (Table 2, entry 11). Quinoline (500 mg, 3.9 mmol) and 10% Pd/C (50 mg, 10 wt % of the substrate) in D_2O (17 mL) were stirred at 180 °C under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with ethyl acetate (20 mL) and the mixture was filtered through a filter paper to remove the catalyst. The filtered catalyst was washed with ethyl acetate (2×5 mL). The combined organic phases were washed with H_2O (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by preparative thin-layer chromatography (silica gel, ethyl acetate–hexane, 1:4 v/v) gave quinoline-d_n as pale yellow oil (83% yield). Isotope distribution (EIMS): 1% d_2, 1% d_3, 5% d_4, 12% d_5, 39% d_6, 42% d_7. ^{1}H NMR ($CDCl_3$, dioxane as an internal standard) δ 8.93 (s, 0.01H), 8.17 (s, 0.02H), 8.12 (s, 0.01H), 7.83 (s, 0.37H), 7.73 (s, 0.01H), 7.58–7.52 (m, 0.07H), 7.40 (s, 0.01H). ^{2}H NMR ($CHCl_3$) δ 9.01 (br s), 8.26 (br s), 7.92 (br s), 7.82 (br s), 7.65 (br s), 7.47 (br s).

4.2.28. [^{2}H]-2-Aminopyrimidine (Table 3, entry 2). Method A, 99% yield as a colorless solid. Isotope distribution (EIMS): 4% d_1, 31% d_2, 52% d_3, 13% d_4. ^{1}H NMR (CD_3OD, *p*-anisic acid as an internal standard) δ 8.16 (s, 0.03H), 6.54 (s, 0.42H). ^{2}H NMR (CH_3OH) δ 8.26 (br s), 6.67 (br s).

4.2.29. [^{2}H]-2-Amino-4,6-dimethylpyrimidine (Table 3, entry 3). Method E, 100% yield as a colorless solid. Isotope distribution (EIMS): 3% d_4, 16% d_5, 72% d_6, 8% d_7, 1% d_8. ^{1}H NMR (CD_3OD, *p*-anisic acid as an internal standard) δ 6.37 (s, 1H), 2.17–2.13 (m, 0.28H). ^{2}H NMR (CH_3OH) δ 2.22 (br s).

4.2.30. [^{2}H]-2-Amino-4-hydroxy-6-methylpyrimidine (Table 3, entry 4). Method E, 100% yield as a colorless solid. Isotope distribution (EIMS): 1% d_2, 14% d_3, 77% d_4, 8% d_5. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 10.7 (br s, 1H), 6.49 (br s, 2H), 5.40 (s, 0.04H), 1.97 (s, 0.11H). ^{2}H NMR (DMSO) δ 5.40 (br s), 1.92 (br s).

4.2.31. [^{2}H]-3,5-Dimethylpyrazole (Table 3, entry 5). Method D, 81% yield as a yellow solid. Isotope distribution (EIMS): 1% d_1, 1% d_3, 7% d_4, 34% d_5, 13% d_6, 41% d_7, 3% d_8. ^{1}H NMR (DMSO-d_6, *p*-anisic acid as an internal standard) δ 12.3 (br s, 1H), 5.72 (s, 0.03H), 2.07 (s, 0.17H). ^{2}H NMR (DMSO) δ 5.75 (br s), 2.06 (br s).

4.2.32. [^{2}H]-Sulfamethazine (Table 4, entry 1). Method A. The reaction was carried out in a sealed tube, 97% yield as a colorless solid. Isotope distribution (FABMS, Gly): 1% d_2, 1% d_3, 2% d_4, 9% d_5, 29% d_6, 33% d_7, 17% d_8, 6% d_9, 2% d_{10}. ^{1}H NMR (CD_3OD, DSS as an internal standard) δ 7.74–7.71 (m, 1.89H), 6.67 (s, 0.95H), 6.61 (d, J=9.28 Hz, 1.51H), 2.25 (s, 0.22H). ^{2}H NMR (CH_3OH) δ 6.66 (br s), 2.24 (br s).

4.2.33. [^{2}H]-Nalidixic acid (Table 4, entry 2). Method D. Chloroform was used instead of diethyl ether, 96% yield as a colorless solid. Isotope distribution (EIMS): 4% d_0, 3% d_1, 7% d_2, 12% d_3, 18% d_4, 28% d_5, 16% d_6, 8% d_7, 4% d_8. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 9.23 (s, 1H), 8.66–8.64 (m, 0.47H), 7.64–7.63 (m, 0.37H), 4.67 (q, J=7.08 Hz, 2H), 2.71 (s, 0.22H), 1.45 (t, J=7.08 Hz, 2.40H). ^{2}H NMR (DMSO) δ 8.62 (br s), 7.63 (br s), 2.65 (br s), 1.36 (br s).

4.2.34. [^{2}H]-Allopurinol (Table 4, entry 3). Allopurinol (68.1 mg, 0.5 mmol) and 10% Pd/C (6.8 mg, 10 wt % of the substrate) in D_2O (2 mL) were stirred at 160 °C under H_2 atmosphere for 24 h. After cooling, the reaction mixture was diluted with boiling water (10 mL) and the mixture was filtered through a membrane filter (Millipore Millex®-LG, 0.20 μm) to remove the catalyst. The filtered catalyst was washed with boiling water (2×10 mL) and the filtrate was concentrated in vacuo, 99% yield as an off-white solid. Isotope distribution (EIMS): 8% d_0, 19% d_1, 65% d_2, 8% d_3. ^{1}H NMR (DMSO-d_6, DSS as an internal standard) δ 13.7 (br, 1H), 12.1 (br, 1H), 8.15 (br s, 0.13H), 8.03 (s, 0.03H). ^{2}H NMR (DMSO-d_6) δ 8.11 (br s), 8.00 (br s).

4.2.35. [^{2}H]-Antipirine (Table 4, entry 4). Method A, 98% yield as a pale yellow solid. Isotope distribution (EIMS): 17% d_0, 65% d_1, 15% d_2, 5% d_3. ^{1}H NMR (DMSO-d_6, *p*-anisic acid as an internal standard) δ 7.48–7.44 (m, 1.97H), 7.31–7.24 (m, 3H), 5.27 (s, 0.09H), 3.03 (s, 3H), 2.22 (s, 2.73H). ^{2}H NMR (DMSO-d_6) δ 5.31 (br s), 2.17 (br s).

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An easy and general protocol for multicomponent coupling reactions of aldehydes, amides, and dienophiles

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Abstract—An improved procedure for the three-component coupling reaction of *a*ldehydes, *a*mides, and *d*ienophiles (AAD-reaction) has been developed. The use of microwave technology enables the *endo*-selective synthesis of *N*-acyl cyclohexenylamines via condensation of readily available aldehydes and amides, and subsequent Diels–Alder reaction with electron-deficient dienophiles in significantly improved yields. Advantageously, there is no need of employing additional solvents and reaction times are drastically reduced compared to similar thermal reactions.

1. Introduction

Multicomponent[1] and domino reactions[2] offer significant advantages compared to the classical step by step formation of individual bonds due to their higher synthetic efficiency. The resulting reduced number of synthetic and purification steps for a given target molecule increases the attractiveness and practicability of the process. As a special benefit, often MCRs also enable the enhancement of structural diversity in an unprecedented way. Due to the wide variation of the starting materials, various opportunities arise for the synthesis of compound libraries. Therefore, in the last decade research in academia and industry has increasingly emphasized the use of MCRs as well as domino reaction sequences for a broad range of products.[3]

Based on our general interest in homogeneous catalysis, we studied transition metal-catalyzed three- and four-component coupling reactions such as the hydroaminomethylation of olefins,[4] and the amidocarbonylation of aldehydes.[5] With respect to the latter work,[6] we discovered multicomponent reactions of *a*ldehydes, *a*mides, and *d*ienophiles (AAD-reaction) for the straightforward synthesis of a large variety of carbo- and heterocyclic amides.[7] As shown in Scheme 1, the underlying mechanism involves an Oppolzer–Overman-type 1-(*N*-acylamino)-1,3-butadiene, which easily undergoes Diels–Alder addition to an electron-deficient dienophile.[8] The synthesized three-component adducts exhibit a high degree of diversity, which is based upon structural variations of the simple, ubiquitous components carboxamide, aldehyde, and olefin. More recently, such coupling reactions of aldehydes and dienophiles could be extended from amides to anhydrides (ANAD-reaction), orthoesters (ALAD-reaction), and even to isocyanates (IAD-reaction) (Scheme 1). Covering this broad range of substrates, the generality of the methods has been demonstrated in the synthesis of more than 200 carbo- and heterocyclic compounds.

The versatility of isolated functionalized 1,3-butadienes for Diels–Alder chemistry[8] has also been demonstrated in the preparation of pumiliotoxin,[9] gephyrotoxin,[10] dendrobine,[11] and tabersonine.[12] Furthermore, we have recently demonstrated the synthetic applicability of our MCRs in the preparation of highly substituted aniline,[13] bicyclo[2.2.2]-oct-2-ene,[14] enantiomerically pure cyclohexenol,[15] and cyclohexenylamine,[7e] phthalic acid,[7d] luminol,[16] phenanthridone[17] as well as lactam[18] derivatives.

Here, we wish to report an improved protocol for the coupling of aldehydes, amides, and dienophiles. Taking advantage of microwave radiation functionalized 1-amido-2-cyclohexene derivatives are synthesized in good to excellent yields. To the best of our knowledge, such strategy has not been used for multicomponent couplings of aldehydes and dienophiles till date.

2. Results and discussion

Typically, three-component coupling reactions of aldehydes, amides, and dienophiles have been carried out at 80–120 °C

Keywords: Aldehydes; Dienophiles; Diels–Alder reaction; Multicomponent reaction; Microwaves.
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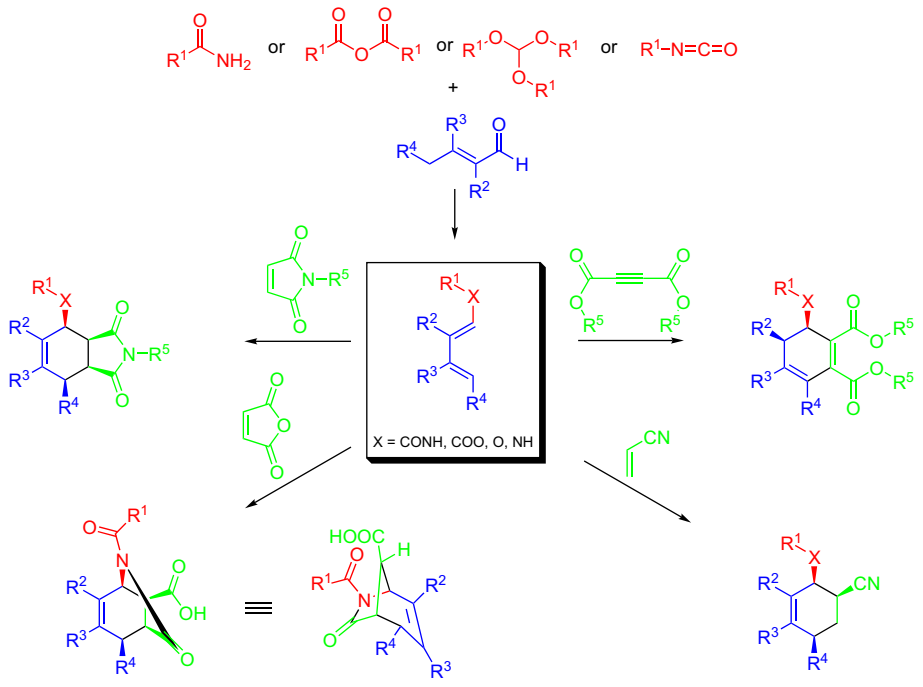


Scheme 1. Schematic representation of the AAD-, ANAD-, ALAD-, IAD-reaction protocols.

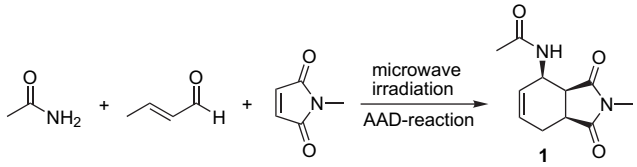
in dipolar, aprotic solvents like NMP (so-called first generation protocol). Despite the generality of these conditions, sometimes aldol-type side-products arise and the purification of the desired product is troublesome. By studying the condensation of amides with more sensitive arylacetylaldehydes in detail, we observed that the presence of aromatic solvents such as toluene or xylene improves the yield of the corresponding MCR-product (so-called second generation protocol). Nevertheless, a drawback of both procedures is the comparatively long reaction time (16–120 h), which is required for full conversion. In order to synthesize compound libraries in a faster manner, we were particularly interested in the development of a short term procedure. For this purpose the application of microwave technology has become the method of choice.[19] For instance, several groups reported on the beneficial use of microwaves for the considerable acceleration of reactions.[20]

As a model reaction we started screening the conversion of crotonaldehyde in the presence of acetamide and *N*-methylmaleimide (Table 1), applying the professional CEM monomode microwave Discover®.[21] It is important to note that all reactions were carried out at maximum microwave power of 50 W. In the first set of experiments, we examined the influence of various reaction media (toluene, 1,4-dioxane, no solvent) and the temperature. Fixing the time and temperature to 20 min and 180 °C, respectively, we observed full conversion and the formation of 4-*N*-acetylamino-2-methyl-*cis*-3a,4,7,7a-tetrahydroisoindole-1,3-dione **1** in 38% yield using the aromatic solvent toluene (Table 1, entry 1). Applying the polar, aprotic solvent 1,4-dioxane, a slightly increased yield of 49% is observed (Table 1, entry 2).

A similar result is obtained for the neat reaction (51%, Table 1, entry 3). Decreasing the reaction temperature to 150 °C did not change the product yield for both solvents (Table 1, entries 4 and 5). Surprisingly, the reaction yield was remarkably increased for the solvent-free reaction (73%, Table 1, entry 6). Additional experiments at a lower temperature of 110 °C resulted in drastically reduced product yields (Table 1, entries 7–9).

Next, we studied the variation of reaction times at 150 °C. However, improved yields were obtained neither for shorter

Table 1. Microwave-assisted synthesis of 4-*N*-acetylamino-2-methyl-*cis*-3a,4,7,7a-tetrahydroisoindole-1,3-dione (**1**)



Entry	Solvent	*T* [°C]	*t* [min]	Additives	Yield [%]
1	Toluene	180	20	—	38
2	Dioxane	180	20	—	49
3	—	180	20	—	51
4	Toluene	150	20	—	38
5	Dioxane	150	20	—	49
6	—	150	20	—	73
7	Toluene	110	20	—	19
8	Dioxane	110	20	—	31
9	—	110	20	—	54
10		150	10	—	47
11	—	150	30	—	63
12	—	150	60	—	58
13	—	150	20	1 mmol crotonaldehyde	85
14	—	150	20	1 mmol crotonaldehyde, 1 mmol Ac_2O	90
15	Toluene	110	960	—	61[a]

Conditions: 1 mmol acetamide, 1 mmol crotonaldehyde, 1.5 mmol *N*-methylmaleimide, 2 mol % *p*-TSA, 2 mL solvent, max 50 W microwave irradiation.
[a] Second generation procedure: 5 mmol acetamide, 5 mmol crotonaldehyde, 7.5 mmol *N*-methylmaleimide, 5 mmol Ac_2O, 2 mol % *p*-TSA, 20 mL toluene.

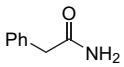
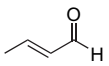
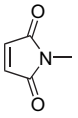
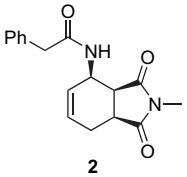
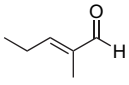
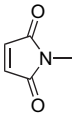
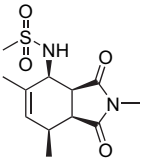
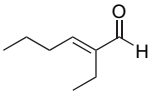
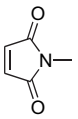
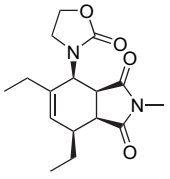
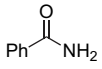
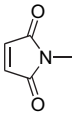
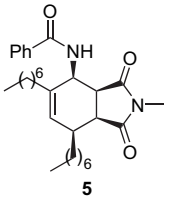
nor for longer reaction times (Table 1, entries 10–12). Increasing the amount of crotonaldehyde to 2 equiv (with respect to acetamide) resulted in 85% yield of the desired tetrahydroisoindole-1,3-dione derivative (Table 1, entry 13). In accordance with experiments under thermal conditions, the addition of acetic acid anhydride as water removing reagent to the reaction mixture led to an additional beneficial effect. Hence, the model product **1** is obtained in an excellent yield of 90% (Table 1, entry 14).[22] It is worth mentioning that the classical first and second generation AAD-procedures resulted, at their standard conditions, in <61% product yield, requiring a nearly fifty times longer reaction time of 16 h (Table 1, entry 15).

In order to prove the generality of the optimized set of conditions, we applied the microwave-assisted protocol to other starting materials. Here, differently functionalized amide derivatives were reacted with aliphatic as well as α,β-unsaturated aldehydes in the presence of suitable dienophiles providing a series of 1-acylamino-2-cyclohexene derivatives. For a number of reactions the use of NMP (first generation protocol), toluene (second generation protocol), and the solvent-free, microwave-assisted procedure were compared under optimized conditions. As shown in Table 2, in most cases studied, the new protocol gave higher yields compared to our previous procedures. For example, aliphatic and aromatic amides, as well as sulfonamides react nearly quantitatively with α,β-unsaturated aldehydes and *N*-methylmaleimide (79–96% yield; Table 2, entries 1, 2, 5).

Only in the case of the cyclic oxazolidin-2-one, a lower yield of 52% is obtained (Table 2, entry 3). In addition, aliphatic aldehydes furnish the corresponding products in excellent yields (81–95% yield; Table 2, entries 4, 6). In order to study the influence of other dienophiles also, we employed maleic acid anhydride, diethyl but-2-ynedioate, and acrylonitrile as substrates, which gave the corresponding products in 26–31% yield (Table 2, entries 7–9). Interestingly, in the case of diethyl but-2-ynedioate, for the first time a 1,4-cyclohexadiene derivative is obtained as product.

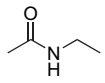
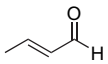
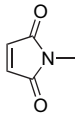
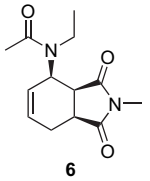
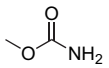
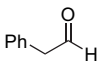
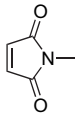
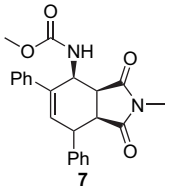
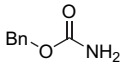
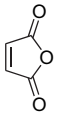
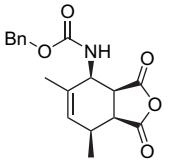
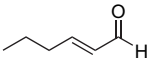
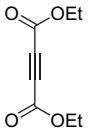
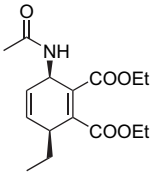
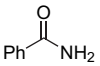
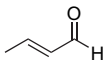
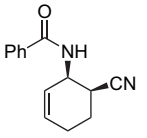
For all products one- and two-dimensional NMR experiments unambiguously established the stereochemical structure. Although up to four stereogenic centers are created, only one diastereomer is formed selectively. In agreement with our previously reported multicomponent coupling reactions, we observe the selective *endo* addition of the dienophile during the Diels–Alder step. Thus, analyses of the ^{1}H–^{1}H coupling constants of the amido-, as well as the other alkyl-substituents on the cyclohexene ring reveal the exclusive formation of the all-*syn* product. This results in bowl- or crown-shaped cyclohexene derivatives with all substituents on one side of the ring.

Table 2. Microwave-assisted synthesis of various AAD-products

Entry	Amide	Aldehyde	Dienophile	AAD-product	First generation yield [%]	Second generation yield [%]	Third generation yield [%]
1				 **2**	58	72	96
2				 **3**	nd	88	85
3				 **4**	nd	73	52
4				 **5**	nd	70	95

(*continued*)

Table 2. (*continued*)

Entry	Amide	Aldehyde	Dienophile	AAD-product	First generation yield [%]	Second generation yield [%]	Third generation yield [%]
5				 **6**	0	69	79
6				 **7**	5	70	81
7				 **8**	nd	72	31
8				 **9**	nd	0	26
9				 **10**	76	8	31[a]

Reaction conditions: 1 mmol amide, 2 mmol α,β-unsaturated aldehyde or 4 mmol aldehyde, 1.5 mmol dienophile, 1 mmol Ac_2O, 2 mol % *p*-TSA, 150 °C, 20 min, max 50 W microwave irradiation.

[a] Acrylonitrile: 5 mmol; 120 min.

3. Conclusion

In summary, we have developed an improved multicomponent reaction of aldehydes, amides, and dienophiles, which features the domino formation of three carbon–carbon and one carbon–nitrogen bonds. The described methodology constitutes probably the most simple and direct approach to 1-amido-2-cyclohexenes. Taking advantage of microwave irradiation, reaction times could be significantly reduced, and often product yields are improved compared to our previous AAD-protocols. With regard to green chemistry, there is no need of adding solvents and it is interesting to emphasize that the ubiquitous, off-shelf starting materials readily react even without special exclusion of air and water.

Acknowledgements

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21. For more information regarding the CEM monomode microwave Discover® see: www.cem.com.
22. (a) Procedure for the synthesis of *N*-(2,3,3a,4,7,7a-hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-7-yl)-acetamide (**1**): acetamide (1 mmol), *N*-methylmaleimide (1.5 mmol), and *p*-toluenesulfonic acid monohydrate (2 mol %) were combined in a CEM-Discover microwave pressure tube and crotonaldehyde (2 mmol) and Ac_2O (1 mmol) were added. Then, the reaction was stirred at 150 °C for 20 min at max 50 W microwave irradiation. After cooling, the crude mixture was dissolved in NMP and hexadecane (1 mmol) was added as an internal standard for the determination of product yield by GC. R_f (SiO_2, *n*-heptane/EtOAc=1/1): 0.21. Yield: 90 %. ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.10 (d, *J*=7.6 Hz, CON*H*), 5.87 and 5.73 (m, 1H and dt, *J*=9.3 Hz and *J*=3.0 Hz, 1H, C*H*=C*H*), 4.43 (m, 1H, C*H*NH), 3.38 (m, 1H, CHC*H*CO), 3.19 (m, 1H, CH_2CHCO), 2.76 (s, 3H, CONCH_3), 2.50 and 2.17 (both m, both 1H, CH_2), 1.88 (s, 3H, CH_3CO). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=179.6 and 177.2 (2 CH*C*ON), 169.0 (*C*ONH), 130.9 and 127.8 (*C*H=*C*H), 45.2 (*C*HNH), 44.9 and 38.6 (2 C*H*CON), 24.4 (CON*C*H$_3$), 23.4 (*C*H$_2$), 22.6 (*C*H$_3$CO). MS (EI, 70 eV): *m*/*z* (%)=222 (2) [M]$^+$, 179 (100) [M−Ac]$^+$, 94 (35), 69 (43), 43 (23) [Ac]$^+$, no other peaks >10%. IR (KBr): 1/λ=3255 (s), 3086 (m), 2956 (w), 2874 (w), 1775 (m), 1692 (vs), 1644 (m), 1571 (s), 1441 (s), 1288 (s), 1119 (s), 1010 (m), 793 (m), 722 (m), 605 (m), 579 (m) cm^{-1}. HRMS (EI): calcd for $C_{14}H_{14}N_2O$: 222.10120; found: 222.10045 [M]$^+$.(b) Procedure for the synthesis of diethyl 3-acetamido-6-ethyl-cyclohexa-1,4-diene-1,2-dicarboxylate (**9**): acetamide (1 mmol), diethyl but-2-ynedioate (1.5 mmol), and *p*-toluenesulfonic acid monohydrate (2 mol %) were combined in a CEM-Discover microwave pressure tube and hex-2-enal (2 mmol) and Ac_2O (1 mmol) were added. Then, the reaction was stirred

at 150 °C for 20 min at max 50 W microwave irradiation. After cooling, all volatile compounds were removed under reduced pressure. Silicagel column chromatography afforded the corresponding product as a colorless oil. R_f (SiO_2, *n*-heptane/EtOAc=1/1): 0.41. Yield: 26%. ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.95 (d, J=8.52 Hz, 1H, CON*H*), 5.81 and 5.61 (both m, both 1H, C*H*=C*H*), 5.17 (m, 1H, C*H*NH), 4.15–4.01 (m, 4H, 2 OCH_2), 2.98 (m, 1H, CH_2C*H*), 1.77 (s, 3H, CH_3CO), 1.72–1.59 (m, 2H, CH_3CH_2CH), 1.18 and 1.13 (both t, J=7.23 Hz and J=7.63 Hz, both 3H, 2 CH_3CH$_2$O), 0.84 (t, J=7.53 Hz, CH_3CH$_2$CH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=168.5 and 166.9 (2 *C*OO), 166.0 (*C*ONH), 139.0 and 132.7 (*C*=*C*), 128.8 and 124.7 (*C*H=*C*H), 60.8 and 60.6 (2 OCH_2), 43.0 (*C*HNH), 37.6 (CH_2*C*H), 26.2 (CH_3*C*H_2CH), 22.3 (*C*H_3CO), 13.7 (2 *C*H_3CH$_2$O), 10.4 (*C*H_3CH$_2$CH). MS (EI, 70 eV): m/z (%)=309 (1) [M]$^+$, 234 (81), 190 (22), 164 (100), 148 (17), 43 (68) [Ac]$^+$, no other peaks >10%. IR (KBr): 1/λ=3465 (s), 3051 (w), 2951 (w), 1678 (m), 1604 (s), 1436 (m), 1384 (m), 1346 (m), 1281 (m), 1250 (m), 1170 (m), 1119 (m), 1034 (m), 978 (m), 930 (w), 840 (w), 793 (w), 671 (w), 580 (w) cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{23}NO_5$: 309.15762; found: 310.16517 [M]$^+$.

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Improvement and simplification of synthesis of 3-aryloxy-1,2-epoxypropanes using solvent-free conditions and microwave irradiations. Relation with medium effects and reaction mechanism

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Abstract—Some 3-aryloxy-1,2-epoxypropanes, interesting as potential synthons in β-adrenergic receptor antagonists preparation, were obtained in excellent yields (65–96% within 2–17 min) by microwave activation (monomode system) using solid–liquid solvent-free phase transfer catalysis (PTC). The best results for the O-alkylation of some phenols with epichlorohydrin were obtained using TBAB and $NaOH/K_2CO_3$ (1:4 mol/mol) as phase transfer catalyst and more acceptable basic system, respectively. These new procedure is compared with classical methods. Significant specific microwave effect (non-purely thermal) was evidenced in all cases. They were discussed in terms of reaction medium and mechanism, taking into account the variations in polarity of the systems.

1. Introduction

During last 10 years our interest in an efficient and economical technology for the preparation of some organic synthons has promoted the research in the field of microwave irradiation.[1–3] The use of such non-conventional reaction conditions reveals several features like: a short reaction time compared to conventional heating, ease of work-up after a reaction, and reduction in the usual thermal degradation and better selectivity.[4–5] In recent years some important reviews, concerning study of microwave assisted organic reactions, have been published.[6–7]

Generally, interpretation of microwave enhancements in organic synthesis is now well-demonstrated and fully acknowledged.[8] Their interpretation lies in a consideration of the concept of dielectric polarization[9] and, more precisely, *dipolar polarization*, which is at the origin of microwave heating due to the alignment of polar molecules along an electromagnetic field. As microwaves consist in an alternating electric field of high frequency (ν=2450 MHz, λ=12.2 cm), inversion in the dipole orientation at each alternance results in the stirring and friction of molecules, inducing energy dissipation into internal homogenous heating. Among other physical phenomena concerned in dielectric polarization, *ionic polarization* can be involved. It results in the separation of positive and negative charges induced by the electromagnetic field. Therefore, this phenomenon can also be considered in the acceleration of organic synthesis under microwave irradiation after the generation of more reactive species by ionic dissociation.

In this work, we want to check this second hypothesis as a possible cause, like dipolar polarization effects, of microwave enhancement. For this purpose we assume that the acceleration observed previously[10] in the case of O-alkylation reactions of some phenols with epichlorohydrin, could also have consequences for the reaction selectivity. In previous paper we reported preliminary results for O-alkylation of some selected phenols **1c**,**f**,**g**,**j** with epichlorohydrin by microwave irradiation under solid–liquid solvent-free phase transfer catalysis.[10] The aim of this work was to reproduce some of these reactions in classical conditions (aqueous solution of NaOH) and in solvent-free conditions under microwave irradiation (MW) or classical heating (Δ). These conditions were extended to another case of phenols such as: **1a**–**b**,**d**–**e**,**h**–**i** (Scheme 1). It is important to note that the alkylation of phenols to give aromatic ethers is well known (Williamson reaction). However, in classical conditions the reaction time is very long. The phase transfer catalysis technique[11,12] under classical heating[13] or microwave irradiation[14] has been successfully applied to the Williamson ether synthesis. Concerning 3-aryloxy-1,2-epoxypropanes

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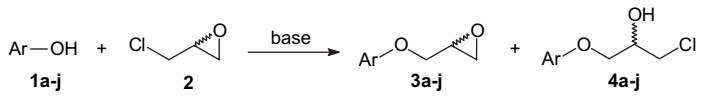


Scheme 1. **Ar**=**a**: C_6H_5–, **b**: 2-CH_3–C_6H_4–, **c**: 3-CH_3–C_6H_4–, **d**: 4-CH_3–C_6H_4–, **e**: 4-Cl–C_6H_4–, **f**: 3-CH_3–4-Cl–C_6H_3–, **g**: 1-naphthyl-, **h**: 2-CH_3O–C_6H_4–, **i**: 2,6-Cl–C_6H_3–, **j**: 2-CN–C_6H_4.

3, the simplest and more popular method for their preparation consist in one-step O-alkylation of the suitably substituted phenol **1** with epichlorohydrin **2** in the presence of base (Stephenson procedure).[15] Generally, in all procedures described, the epichlorohydrin is used in a significant excess and the reaction is carried out in an aqueous solution of a base (NaOH, KOH, K_2CO_3, etc.) or in an organic solvent containing pyridine or piperidine.[16,17] Concerning chemical industry and high scale, only last methods were used.[16i,j] Depending on the substituent position or nature in the phenol **1**, it takes 6–20 h at reflux or 24–26 h at room temperature to complete the reaction. It is important to note that, these classical methods can suffer from some inconvenience due to moderate isolated yields (50–70%), moderate purity of products and poor reaction selectivity (1-chloro-3-aryloxypropan-2-ols **4** were formed in an important amount as non-suitable by-product[15,16a]). Some from these inconvenience may be limited by addition of the phase transfer catalyst (e.g. benzyltriethylammonium chloride) to the aqueous solution of base (K_2CO_3, etc.).[16a,h,k,n,17a,i,r] However, as described by Bevinakatti and Banerji,[16h] the acceptable reaction rates, selectivities and isolated yields of product **3** were obtained, in PTC procedures, only by using very high concentrations of the base.

We have sought to develop a general method of the O-alkylation of phenols **1a–j** with epichlorohydrin **2**. Such a procedure should retain the convenience of PTC methods but should be free from some limitations related to PTC systems and much faster. Therefore, we decided to explore the use of microwave heating under solvent-free phase transfer catalysis (PTC) conditions.

2. Results and discussion

The conditions for O-alkylation of various phenols **1a–j** with epichlorohydrin **2** were optimized according to the conventional scheme described in the literature (Scheme 1). In the first time, one selected classical procedure was tested, in term of conversion, selectivity and isolated yield. In second time, the same reactions were performed in non-classical conditions by using solid–liquid PTC catalysis under microwave irradiation or classical heating. Concerning all method tested, the effects of nature and position of the substituent on the phenyl ring were evaluated on conversion, selectivity and isolated yield of suitable product **3**.

2.1. Classical conditions

Generally, it is always difficult to anticipate the best choice of classical method for the preparation, in high scale, of 3-aryloxy-1,2-epoxypropanes **3**. On the other hand, for these compounds, the correlations between nature or position of substituent on the aromatic ring and conversion, selectivity or reaction yield were newer evaluated. In a first series of experiments, the efficiency of known classical procedure described by Biniecki,[17g] for O-alkylation of various phenols with epichlorohydrin, was investigated. For this purpose, various phenols **1a–i** were treated, at reflux, with 1.26 equiv of epichlorohydrin in an aqueous sodium hydroxide (Scheme 1).

The reactions were performed in high scale (0.19 mol of phenol and 0.24 mol of epichlorohydrin) and monitored by GC. The 3-aryloxy-1,2-epoxypropanes **3** were separated by silica gel column chromatography from the corresponding 1-chloro-3-aryloxypropan-2-ols **4**, which were formed as by-products. The main results are given in Table 1.

The results presented in Table 1 clearly show that the conditions described by Biniecki were sligthly acceptable, concerning selectivity and isolated yield of suitable product **3**. It is important to note that, for all phenols tested **1a–i**, the arylglycidyl ethers **3** were formed as major product with moderate yields (yield of **3**=58–76%). On the other hand, the quantities of non-suitable by-product **4**, determined in the reaction mixture by GC analysis, were important (10–32%, yield of **4**=5–23%). Generally, we observe a notable effect of the phenyl-ring substituent in terms of reaction time (94–99% conversion within 5–12 h). Concerning selectivity, the values of ratio **3**:**4** depend only slightly on the nature and position of the phenyl-ring substituent. In fact, the values of ratio **3**:**4** were only slightly different when the electronic effects of the substituent changed (e.g.: 76:24 for 4-CH_3–C_6H_4–, 70:30 for 2-CH_3O–C_6H_4–, 68:32 for 4-Cl–C_6H_4–). Concerning 1-naphthol **1g**, the value of ratio **3**:**4** was notably higher (ratio **3**:**4**=90:10) than in all other cases. Finally, we note that when the reaction conversion

Table 1. Reaction of epichlorohydrin **2** with several phenols **1a–i** by using aqueous solution of NaOH at reflux[a]

Phenol **1**	Ar	Time (h)	Conv. (%)[b,c]	Ratio **3**:**4**[d]	Yield of **3** (%)[e]	Yield of **4** (%)[e]
a	C_6H_5–	5	98	80:20	69	14
		10	99	85:15	75	7
b	2-CH_3–C_6H_4–	7	97	68:32	58	18
		14	99	75:25	66	13
c	3-CH_3–C_6H_4–	11	98	70:30	63	19
		19	99	78:22	77	16
d	4-CH_3–C_6H_4–	6	98	76:24	70	16
e	4-Cl–C_6H_4–	7	97	68:32	61	22
f	4-Cl–3-CH_3–C_6H_3–	12	96	82:18	65	11
g	1-Naphthyl	6	94	90:10	69	5
h	2-CH_3O–C_6H_4–	7	98	70:30	68	23
i	2,6-Di-Cl–C_6H_3–	8	>99	81:19	76	10

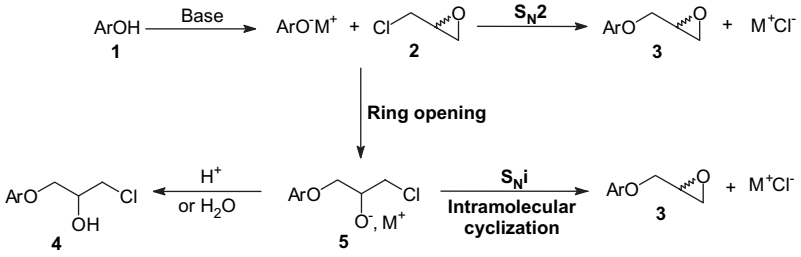
[a] Conditions: **1a–i** (0.19 mol), epichlorohydrin **2** (0.24 mol) in 100 mL of aqueous solution of NaOH (0.24 mol) under reflux.
[b] Determined by GC and ^{1}H NMR.
[c] Complement to 100% conversion is an unreacted substrate phenol.
[d] Determined by GC and ^{1}H NMR.
[e] Yields calculated after purification and separation by chromatography on silica gel 60.

was 97–98%, the further prolongation of the reaction time produce only slight increase in the yield of product **3** and as a consequence the yield of non-suitable by-product **4** decreased. For example, in the case of phenol **1a**, the isolated yield of **3a** increase from 69 to 75% when the reaction time was prolonged from 5 to 10 h, but in this case the yield of corresponding chloroalcohol **4** was decreased from 14 to 7%. This last observations can justify our thesis that in the reaction mixture exists permanent competition of two different mechanisms (Scheme 2) *mechanism 1*=the direct nucleophilic substitution (S_N2) of phenate ion (ArO^-) on epichlorohydrin **2** with destruction of C–Cl bond and *mechanism 2*=the ring opening of epichlorohydrin **2** with ArO^- followed by intramolecular cyclization (S_Ni) of corresponding alcoholate **5** formed in situ.

2.2. Non-classical conditions

In second series of experiments, the O-alkylations were performed by mixing selected phenol **1**, the solid base, the solid phase transfer catalyst [tetrabutylammonium bromide (TBAB)], and the liquid alkylating agent epichlorohydrin **2**, without any organic solvent in the relative amounts indicated in the Tables 2 and 3. All reactions were performed under atmospheric pressure by using microwave irradiation (MW, power=60 W) or classical heating in a thermostated oil bath (Δ). The microwave irradiations were carried out using a monomode Synthewave 402 Prolabo reactor[18] fitted with an infrared detector to measure the temperature throughout the reaction. The interest of a monomode reactor lies in its focalization of the electromagnetic waves using an accurately proportioned waveguide, which allows a homogeneous distribution of the field. It can be used with a low emitted power and therefore produces a high energetic yield. The use of such an apparatus was shown to lead to considerable improvements in organic synthesis at very low emitted powers and with a good temperature homogeneity. In order to check for the possible intervention of specific (not purely thermal) effects of microwaves (such as those that might be due to a different temperature increase profile, better temperature homogeneity, or modifications of the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$), reactions were performed with the two activation methods, microwave irradiation (MW) and classical heating (Δ), keeping the reaction time, final temperature and pressure the same. In control experiments performed by using microwave irradiation and classical heating, it was shown that the reaction did not proceed in the absence of phase transfer catalyst (TBAB) and base within the reaction time indicated in the Tables 2 and 3, concerning all bases and phenols tested. The temperature of sample was measured in each experiment immediately upon termination of the microwave exposure. Reference reactions were then carried out at this temperature with conventional heating. In all cases of reactions performed by using microwave irradiation, the ^{1}H NMR, IR and GC analyses revealed that the reaction product was pure 3-aryloxy-1,2-epoxypropane **3** and not mixture of **3** and **4**. The main results are given in Tables 2 and 3.

2.2.1. Effect of the base. The effect of the base nature on the selectivity, conversion and reaction yield of some O-alkylation reactions is well documented in the literature. Therefore, in a first series of experiments, the influence of the base nature on the selectivity, conversion and reaction yield



Scheme 2.

Table 2. Reaction of epichlorohydrin **2** with phenol **1f** by using different solid bases under focused microwave irradiation (MW) or classical heating (Δ)[a]

Entry	Base	Relative amounts **1f/2**/TBAB/(base)	Activation mode[b]	Temp (°C)[c]	Time (min)	Conv. (%)[d,e]	Ratio **3f**:**4f**[d]	Yield of **3f** (%)[f]	Yield of **4f** (%)[f]
1	NaOH	1/1.5/0.1/(1)	MW	105	5	65	100:0	51	—
			Δ	105	5	20	65:35	9	6
2	K_2CO_3	1/1.5/0.1/(4)	MW	108	5	20	100:0	16	—
			Δ	108	5	9	75:25	5	2
3	$NaOH/K_2CO_3$	1/1.5/0.1/(1:4)	MW	110	5	99	100:0	81	—
			Δ	110	5	56	85:15	36	8
4	$NaOH/Al_2O_{3basic}$	1/1.5/0.1/(1:4)	MW	112	7	28	100:0	21	—
			Δ	112	7	8	95:5	5	—
5	$NaOH/Ca(OH)_2$	1/1.5/0.1/(1:4)	MW	114	15	70	97:3	64	—
			Δ	114	15	23	69:31	10	5

[a] Conditions: **1f** (20 mmol), epichlorohydrin **2** (30 mmol), TBAB (2 mmol), solid base as presented in the table, under atmospheric pressure, without solvent under microwave irradiation (power=60 W) or classical heating in a thermostated oil bath.
[b] Incident emitted power all along the reaction.
[c] Temperature at the end of the microwave irradiation (MW) or classical heating (Δ).
[d] Determined by GC and ^{1}H NMR.
[e] Complement to 100% conversion is an unreacted substrate phenol.
[f] Yields calculated after purification and separation by chromatography on silica gel 60.

Table 3. Reaction of epichlorohydrin **2** with several phenols **1a–i** by using of solid–liquid solvent-free phase transfer catalysis under microwave irradiation (MW) or classical heating (Δ)[a]

Entry	Phenol **1**	Ar	Activation mode[b]	Temp[c] (°C)	Time (min)	Conv. (%)[b,c]	Ratio **3**:**4**[d]	Yield of **3** (%)[e]	Yield of **4** (%)[e]
1	**a**	C_6H_5–	MW	113	6	99	100:0	90	—
			Δ	113	6	48	76:24	31	10
2	**b**	2-CH_3–C_6H_4–	MW	110	7	96	95:5	89	2
			Δ	110	7	38	83:17	26	6
3	**c**	3-CH_3–C_6H_4–	MW	112	5	99	100:0	95	—
			Δ	112	5	50	66:34	29	15
4	**d**	4-CH_3–C_6H_4–	MW	110	7	98	95:5	87	4
			Δ	110	7	41	88:12	30	5
5	**e**	4-Cl–C_6H_4–	MW	113	11	95	99:1	68	—
			Δ	113	11	40	69:31	20	9
6	**f**	4-Cl–3-CH_3–C_6H_3–	MW	110	5	99	100:0	81	—
			Δ	110	5	56	85:15	36	8
7	**g**	1-Naphthyl-	MW	116	2	99	99:1	96	—
			Δ	116	2	55	76:24	38	12
8	**h**	2-CH_3O–C_6H_4–	MW	111	5	98	99:1	87	—
			Δ	111	5	36	66:34	19	10
9	**i**	2,6-Di-Cl–C_6H_3–	MW	110	12	96	100:0	65	—
			Δ	110	12	57	73:27	28	10
10	**j**	2-CN–C_6H_4–	MW	106	17	98	100:0	67	—
			Δ	106	17	33	80:20	20	5

[a] Conditions: **1a–i** (0.19 mol), epichlorohydrin **2** (0.24 mol) in 100 mL of aqueous solution of NaOH (0.24 mol) under reflux and atmospheric pressure.
[b] Determined by GC and ^{1}H NMR.
[c] Complement to 100% conversion is an unreacted substrate phenol.
[d] Determined by GC and ^{1}H NMR.
[e] Yields calculated after purification and separation by chromatography on silica gel 60.

of TBAB catalyzed O-alkylation of phenol **1f**, taken as model substrate, with epichlorohydrin was investigated. The reactions were carried out by employing dry powdered bases or basic systems such as: NaOH, K_2CO_3, NaOH/K_2CO_3 (1:4 mol/mol), NaOH/Al_2O_{3basic} (1:4 mol/mol), NaOH/$Ca(OH)_2$ (1:4 mol/mol). Concerning all reactions performed under microwave irradiation, it is important to note, that the power=60 W was sufficient to maintain the temperature at a limited imposed value 105–114 °C. The main results and the reaction conditions are presented in Table 2.

It can be clearly seen from Table 2, that it is possible to run the O-alkylation of phenol **1f** with epichlorohydrin **2** by microwave activation or classical heating using solid–liquid solvent-free phase transfer catalysis (PTC). Generally, for all bases the tested results of these reaction were significantly better in the case of microwave irradiation when compared to classical heating, concerning conversion, selectivity and the yield of isolated product **3f**. It also indicates the presence of a specific microwave effect (non-purely thermal) on the O-alkylation of phenol **1f** with epichlorohydrin **2**, conforming thus some conclusions already described in the literature for other types of reactions. In fact, for all the bases tested conversions of phenol **1f** as well as the isolated yields of suitable product **3f** were significantly higher under microwave irradiation when compared to classical heating, concerning the same conditions like: time, temperature and pressure. It is important to note that, all reactions performed by using microwave irradiation were totally selective and the suitable arylglycidyl ether **3f** was obtained as an unique product of the reaction (ratio **3f**:**4f**=100:0). As expected, the reaction performed by using NaOH/$Ca(OH)_2$ as basic system is not totally selective. In this case the traces of by-product **4f** were observed in the reaction mixture by GC analysis (ratio **3f**:**4f**=97:3). On the other hand, in the case of the reactions performed by using classical heating, the by-product **4f** was formed in an important amount (35, 25, 15, 5 and 31% for NaOH, K_2CO_3, NaOH/K_2CO_3, NaOH/Al_2O_{3basic} and NaOH/$Ca(OH)_2$, respectively).

Finally, we showed that the best conditions for O-alkylation of phenol **1f** with epichlorohydrin **2** were obtained by using the mixture NaOH/K_2CO_3 (1:4 mol/mol) as basic system, concerning microwave irradiation and classical heating. However, using of microwave irradiation result in both significantly higher conversion and isolated yield of product **3f** (conv. of **1a**=99% and yield of **3f**=81%) when compared to classical heating (conv. of **1a**=56% and yield of **3f**=36%), concerning the same conditions like: time (5 min), temperature (110 °C) and pressure. On the other hand, changing the base from pure NaOH (1 mol) or pure K_2CO_3 (4 mol) to the mixture of both bases cited NaOH/K_2CO_3 (1:4 mol/mol) produce high increase in the reaction rate (conversion increased from 65 and 20 to 99%, respectively) and isolated yield of **3f** (yield of **3f** increased from 51% and 16%–81%, respectively). Finally, changing the base from K_2CO_3 to Al_2O_{3basic} or to $Ca(OH)_2$ in the mixture with NaOH induces important decrease in the reaction rate and consequently in the isolated yield of product **3f**. In fact, we observe 70% of conversion within 15 min when the mixture of NaOH/$Ca(OH)_2$ was used under microwave irradiation at 114 °C. On the other hand, the use of NaOH in the mixture with basic Al_2O_3 at 112 °C under microwave irradiation results in only 28% of conversion within 7 min. Evidently, in both cases cited the results obtained under microwave irradiation were significantly better when compared to classical heating (8 and 23% conversion within 7 and 15 min, respectively).

2.2.2. Effects of nature and position of the substituent on the phenyl ring. Finally, in order to investigate the influence of the nature and position of the substituent on the phenyl ring various phenols **1a–j** were used as substrates

in O-alkylation with epichlorohydrin **2**. All reactions were carried out in the best conditions previously selected for phenol **1f**. In fact, tetrabutylammonium bromide (TBAB) and the mixture $NaOH/K_2CO_3$ (1:4 mol/mol) were used as phase transfer catalyst and basic system, respectively, concerning microwave irradiation (MW) and classical heating (Δ). The results are collected in Table 3.

The comparative analysis of the results presented in Table 3 clearly showed that, all reactions performed under microwave irradiation were totally (ratio **3**:**4**=100:0 and 99:1 for **1a**, **1c**, **1f**, **1i–j** and for **1e**, **1g–h**) or highly selective (ratio **3**:**4**=95:5 for **1b** and **1d**). On the other hand, we observe that the nature of the substituent on the phenyl ring produces an important effect on the conversion and isolated yield of product **3**. In fact, the excellent yields of product **3** were obtained (yield of **3**=87–95% within 96–99% conversion), when the substituent of phenol was an electron-releasing group (2-CH_3–, 3-CH_3–, 4-CH_3–, 2-CH_3O–). However, the yields of suitable product **3** were significantly lower when the substituent of the phenol was an electron withdrawing group such as: 4-Cl–, 2,6-di-Cl– or 2-CN– (yield of **3**=65–68% within 95–99% conversion). It is important to note that for all phenols **1a–j** tested the results of O-alkylation reaction with epichlorohydrin **2** were significantly better under microwave irradiation when compared to classical heating, concerning the same conditions like: time, temperature and pressure. Finally, the results summarized in Table 3 and Figures 1 and 2 indicates the presence of a specific microwave effect (non-purely thermal). Figure 1 shows the course of the conversion of selected phenols, **1a** and **1e**, under microwave irradiation (MW) and classical heating (Δ), with time. The reactions of **1a** and **1e** under MW irradiation lead to a nearly 100% conversion within 6 and 11 min, respectively, with a final temperature of 113 °C. Heating in an oil bath gave only 48 and 40% conversion, respectively, under similar conditions of temperature, reaction time and pressure. The temperature–time profiles for the reactions of **1a** and **1e** under MW irradiation and in an oil bath are shown in Figure 2. It is important to note that, under classical heating (Δ) the conversion of **1a** can be enhanced up to 63% by increasing the reaction time to 13 min (Fig. 1).

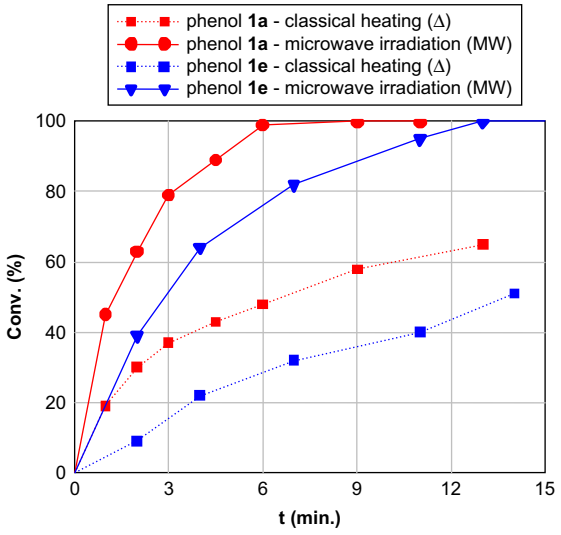


Figure 1. Conversion versus time for the reaction of epichlorohydrin **2** with phenol **1a** and **1e** by using of solid–liquid solvent-free phase transfer catalysis under microwave irradiation (MW) or classical heating in an oil bath (Δ).

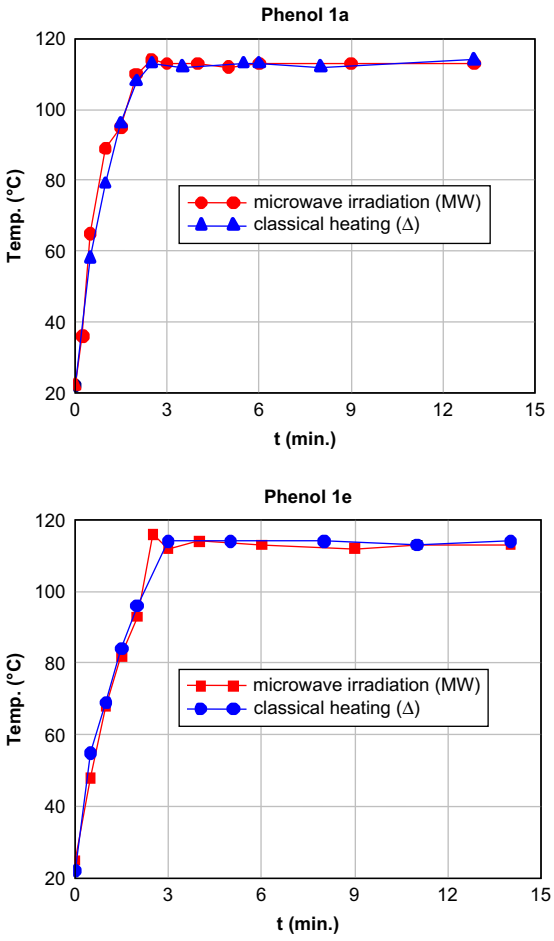


Figure 2. Thermal behaviour of the reaction mixture for phenols **1a** and **1e** under microwave irradiation (MW) and in an oil bath (Δ).

3. Effects according to reaction mechanism

Generally, microwave effects[19] result from material-wave interactions and, due to the dipolar polarization phenomenon, the greater the polarity of a molecule (such as the solvent) the more pronounced the microwave effect when the rise in temperature is considered. In terms of reactivity and kinetics, the specific effect has therefore to be considered according to the reaction mechanism and particularly with regard to how the polarity of the system is altered during the progress of the reaction. Specific microwave effects can be expected for the polar mechanism, when the polarity is increased during the reaction from the ground state (**GS**) towards the transition state (**TS**). The outcome is essentially dependent on the medium and the reaction mechanism. If stabilization of the transition state (**TS**) is more effective than that of the ground state (**GS**), this results in an enhancement of reactivity by a decrease in the activation energy ($\Delta G^{\neq}$) (Fig. 3). It is important to note that this decrease in the activation energy provoke direct increase in the rate constant (k) according to the Eyring equation:[19a]

$$k = A\exp(-\Delta G^{\neq}/RT).$$

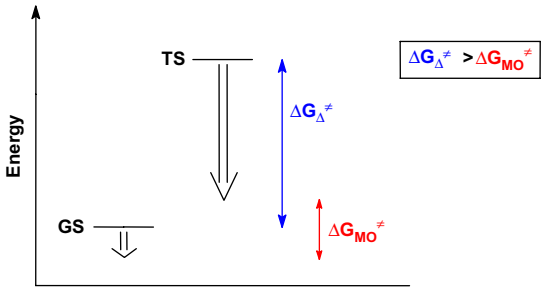
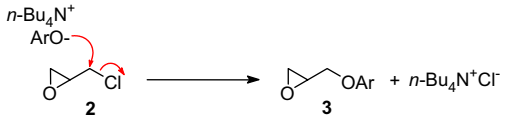


Figure 3. Relative stabilization of a more polar **TS** when compared to the **GS** (polar mechanism).

It is important to note that the reaction between any substituted phenol **1** and epichlorohydrin **2** may be considered as an *anionic bimolecular reaction involving neutral electrophile, which is epichlorohydrin* **2**. Generally, this case of reaction involve the reactivity of anionic species Nu^- associated as ion pairs having several possible structures with counterions M^+. The main results presented in Table 3 clearly show that the reaction between the phenate ion (ArO^-) and epichlorohydrin **2** reveals two competitive mechanisms (Schemes 3 and 4):

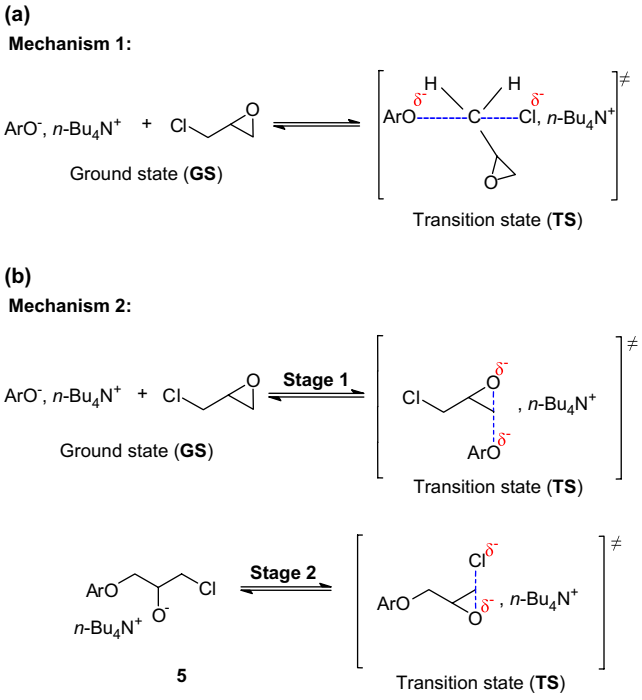


Scheme 3.

Mechanism 1. One-step nucleophilic substitution (mechanism S_N2) with cleavage of C–Cl bond (Scheme 3).

Mechanism 2. Ring opening of epichlorohydrin **2** with ArO^- (mechanism S_Ni) followed by intramolecular cyclization (S_Ni) of corresponding alcoholate **5**, containing one atom of chlorine in β-position, formed in situ (Scheme 4).

In both cases of mechanism (Schemes 3 and 4), the ground-states (**GS**) were identical and composed, on the first hand, of an ion pair between anionic species as ArO^-, formed in situ, and counterions $n\text{-}Bu_4N^+$ coming from the phase transfer catalyst, and on the other hand, from epichlorohydrin **2**. The transition states (**TS**) were composed, in both cases of mechanism, of loose ion pairs in so far as they involve a charge delocalized anion possessing one atom of chlorine, thereby conferring an enhancement in polarity with respect to the ground state (in which the ion pairs are tighter) due to an increase in anionic dissociation as the more bulky product anion formed. As a consequence, specific microwave effects, directly connected to polarity enhancement were observed (Scheme 5a and b). It is important to note that in the case of O-alkylation reaction performed in two stages (under mechanism 2) the conversion and selectivity should be increased under microwave irradiation thanks to acceleration of both stages and we suppose that this acceleration is probably more important for second stage due to more marked localization of negative charge on the oxygen atom in the alcoholate **5**, which is the intermediate of this reaction.



Scheme 5.

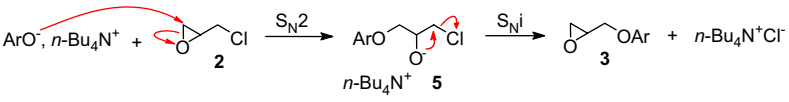
4. Conclusion

In this paper we present a general procedure to realize selective O-alkylation of diversely substituted phenols **1a–j**. High reaction selectivities and high isolated yields of corresponding 3-aryloxy-1,2-epoxypropanes **3a–j** were obtained using solvent-free phase transfer catalysis (PTC) coupled with microwave irradiation (MW). We have shown that the best conditions for O-alkylation were obtained using the mixture $NaOH/K_2CO_3$ (1:4 mol/mol) as basic system and tetrabutylammonium bromide (TBAB) as phase transfer catalyst. It is important to note that the results obtained under microwave irradiation were much better than those derived from classical methods described in the literature, concerning selectivity, conversion and yield of suitable product. Generally, our procedure is very mild, inexpensive and very easy to operate and can replace advantageously the classical ones.

5. Experimental

5.1. General methods

All the commercially available chemicals were obtained from Aldrich and Fluka. Solvents of analytical-grade quality were purchased from Lab Scan Ltd. and Aldrich.



Scheme 4.

5.2. Analytical methods

Microanalyses were performed by the Laboratoire Central de Microanalyse du CNRS, Gif sur Yvette, France. ^{1}H (200 or 250 MHz) and ^{13}C (50.23 or 62.9 MHz) NMR spectra were recorded on Bruker AC-200 or 250 spectrometer in $CDCl_3$ with TMS as an internal standard. Chemical shifts (δ) are given in parts per million. Gas chromatographic analyses were run on a 6000 Vega Series instrument equipped with a FID detector and Spectra-Physics SP 4290 integrator and an OV_1 column (12 m). The detector and the injector temperatures were set at 300 °C and 290 °C, respectively. Column temperature was programmed in the range 70–280 °C (10 °C min^{-1}) for **3a** and **4a**, and 100–280 °C (10 °C min^{-1}) for **3b–j**, and **4b–j**. The retention times (t_R/min) were as follows for 3-aryloxy-1,2-epoxypropanes: **3a**: 5.18; **3b**: 4.29; **3c**: 4.32; **3d**: 4.51; **3e**: 5.47; **3f**: 5.63; **3g**: 9.21; **3h**: 5.32; **3i**: 6.37; **3j**: 6.01 and were as follows for corresponding 1-chloro-3-aryloxypropan-2-ols: **4a**: 7.15; **4b**: 5.93; **4c**: 5.66; **4d**: 6.51; **4e**: 7.35; **4f**: 7.18; **4g**: 11.36; **4h**: 6.94; **4i**: 8.23; **4j**: 8.33. Column chromatography was performed on Merck silica gel 60 (230–400 mesh). TLC was carried out using glass sheets pre-coated with silica gel 60 F_{254} prepared by Merck. The reaction under microwave irradiations was performed in a monomode microwave reactor (Synthewave 402 from Prolabo), fitted with a stirring system and an IR temperature detector, which indicates the surface temperature.

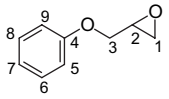
5.3. Typical O-alkylation procedure of phenols 1a–i with epichlorohydrin under classical conditions (aqueous solution of NaOH)

To a stirred solution of 9.6 g of sodium hydroxide (0.24 mol) in 100 mL of water, 0.19 mol of the phenol **1** (0.19 mol) was added. The solution was stirred for 15 min at room temperature and the alkylating agent, epichlorohydrin (0.24 mol, 22.2 g) was added. The final solution was stirred under reflux and monitored by thin layer chromatography (TLC). After the appropriate time (Table 1), the stirring was stopped and the reaction solution was extracted with diethyl ether (3×50 mL). The collected solutions were dried over anhydrous $MgSO_4$ and evaporated to dryness under reduced pressure. The crude mixture of two products, 3-aryloxy-1,2-epoxy-propane **3** and by-product 1-chloro-3-aryloxypropan-2-ol **4**, was separated by flash chromatography on silica gel with *n*-hexane/ethyl acetate (10:1 and 15:1 v/v, for phenol **1a–d**,**1g–h** and **1e–f**,**1i**, respectively) as the eluent.

5.4. Typical O-alkylation procedure for phenols 1a–j with epichlorohydrin using solvent-free phase transfer catalysis conditions (PTC) under microwave irradiation and classical heating

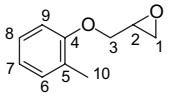
Into a Pyrex tube (2 cm diameter) were introduced 20 mmol of phenol **1**, 0.8 g (20 mmol) of powdered sodium hydroxide, 11.6 g (80 mmol) of anhydrous potassium carbonate and 0.6 g (2 mmol) of tetrabutylammonium bromide (TBAB). After stirring at room temperature during 2 min, 2.76 g (30 mmol) of epichlorohydrin was added. The reaction mixture was either introduced into the monomode microwave reactor (Synthewave 402 from Prolabo, power= 60 W) or in a thermostated oil bath for the times indicated in Tables 2 and 3. It is important to note that all reactions performed under microwave reactor or in an oil bath were agitated by using mechanical stirring. After cooling to room temperature, 100 mL of water was added to the reaction mixture to remove mineral salts and the obtained solution was extracted with diethyl ether (3×50 mL). The collected ethereal extract was washed with water and dried over anhydrous $MgSO_4$. Finally, the organic solution was evaporated to dryness under reduced pressure. The products, suitable 3-aryloxy-1,2-epoxypropane **3** and/or by-product 1-chloro-3-aryloxypropan-2-ol **4**, were purified by flash chromatography on silica gel with *n*-hexane/ethyl acetate (10:1 and 15:1 v/v, for phenol **1a–d**,**1g–h** and **1e–f**,**1i–j**, respectively) as the eluent. The purity of products was checked by GC analysis and their structure was confirmed by ^{1}H, ^{13}C NMR and MS spectra, IR data as well as micro-analyses. ^{1}H and ^{13}C NMR spectra of 3-aryloxy-1,2-epoxypropanes **3a–j** were identical with those presented in the literature. ^{1}H, ^{13}C NMR and MS spectra, IR data as well as micro-analyses of **3a–j** are as follows.

5.4.1. 3a: 1,2-Epoxy-3-phenoxypropane.



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.74–2.81 (1H, dd, J_{gem}=4.89 Hz, J_{1-2}=2.70 Hz, H1), 2.80–2.91 (1H, m, H1′), 3.35–3.46 (1H, m, H2), 3.80–4.10 (1H, dd, J_{gem}=11.0 Hz, J_{3-2}=5.40 Hz, H3), 4.18–4.32 (1H, dd, J_{gem}=10.99 Hz, $J_{3'-2}$=2.99 Hz, H3′), 6.70–7.09 (3H, m, H5, H7, H9), 7.13–7.42 (2H, m, H6, H8); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 44.36 (*C*H$_2$, Cl), 68.50 (*C*H$_2$, C3), 114.52 (C_{arom}, C5, C9), 120.99 (C_{arom}, C7), 130.41 (C_{arom}, C6, C8), 156.73 (C_{arom}, C4). IR (neat, cm^{-1}): 1245 cm^{-1}: C–O–C; Anal. Calcd for $C_9H_{10}O_2$ (150.17): C, 71.98; H, 6.71. Found: C, 71.91; H, 6.61. MS (electr. impact, 70 eV, *m*/*z*): $(M)^{+\bullet}$=150 (53), $(M-CH_2O)^+$=120 (13.6), $(M-C_2H_3O)^+$=107 (13), $(M-C_3H_4O)^+$=94 (64), $(M-C_3H_5O_2)^+$=77 (41.8), $(M-C_4H_5O_2)^+$=65 (31), $(M-C_6H_7O_2)^+$=39 (100). Colourless oil, bp=244–246 °C, $bp_{Lit.}$=245 °C.[20a]

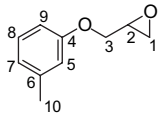
5.4.2. 3b: 1,2-Epoxy-3-(2-methylphenoxy)propane.



^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.26 (3H, s, H10), 2.72–2.84 (1H, dd, J_{gem}=4.96 Hz, J_{1-2}=2.61 Hz, H1), 2.85–2.95 (1H, m, H1′), 3.30–3.41 (1H, m, H2), 3.88–4.05 (1H, dd, J_{gem}=11.07 Hz, J_{3-2}=5.44 Hz, H3), 4.15–4.30 (1H, dd, J_{gem}=11.09 Hz, $J_{3'-2}$=3.04 Hz, H3′), 6.70–6.92 (2H, m, H7, H9), 7.05–7.20 (2H, m, H6, H8); ^{13}C NMR (50.23 MHz, $CDCl_3$, ppm): δ 16.13 (*C*H$_3$, Cl0), 44.56 (*C*H$_2$, Cl), 50.25 (*C*H, C2), 68.55 (*C*H$_2$, C3), 111.13 (C_{arom}, C9), 120.82 (C_{arom}, C7), 126.69 (C_{arom}, C8), 126.93 (C_{arom}, C5), 130.71 (C_{arom}, C6), 156.53 (C_{arom}, C4). IR (neat, cm^{-1}): 1240 cm^{-1}: C–O–C; Anal. Calcd for $C_{10}H_{12}O_2$

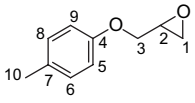
(164.20): C, 73.15; H, 7.36. Found: C, 73.02; H, 7.28. Colourless oil, bp=109–110 °C/0.2 mmHg.

5.4.3. 3c: 1,2-Epoxy-3-(3-methylphenoxy)propane.



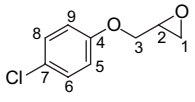
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.34 (3H, s, H10), 2.71–2.81 (1H, dd, J_{gem}=4.95 Hz, J_{1-2}=2.62 Hz, H1), 2.84–2.93 (1H, m, H1′), 3.31–3.43 (1H, m, H2), 3.83–4.01 (1H, dd, J_{gem}=11.10 Hz, J_{3-2}=5.36 Hz, H3), 4.13–4.28 (1H, dd, J_{gem}=11.13 Hz, $J_{3'-2}$=3.10 Hz, H3′), 6.76–7.92 (3H, m, H5, H7, H9), 7.18 (1H, m, H8); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 21.63 (CH_3, Cl0), 44.61 (CH_2, Cl), 50.09 (*C*H, C2), 68.83 (CH_2, C3), 112.00 (C_{arom}, C9), 114.99 (C_{arom}, C5), 122.12 (C_{arom}, C7), 129.43 (C_{arom}, C8), 139.82 (C_{arom}, C6), 157.99 (C_{arom}, C4). IR (neat, cm^{-1}): 1244 cm^{-1}: $\overset{O}{C'-C}$; Anal. Calcd for $C_{10}H_{12}O_2$ (164.20): C, 73.15; H, 7.36. Found: C, 73.09; H, 7.24. Colourless oil, bp=112–113 °C/0.1 mmHg, $bp_{Lit.}$=112–115 °C/0.1 mmHg.[10]

5.4.4. 3d: 1,2-Epoxy-3-(4-methylphenoxy)propane.



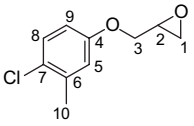
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.28 (3H, s, H10), 2.70–2.81 (1H, dd, J_{gem}=4.92 Hz, J_{1-2}=2.60 Hz, H1), 2.86–2.95 (1H, m, H1′), 3.28–3.40 (1H, m, H2), 3.85–4.02 (1H, dd, J_{gem}=11.02 Hz, J_{3-2}=5.59 Hz, H3), 4.12–4.22 (1H, dd, J_{gem}=11.04 Hz, $J_{3'-2}$=3.23 Hz, H3′), 6.77–6.89 (2H, m, H5, H9), 7.03–7.15 (2H, m, H6, H8); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 20.42 (CH_3, Cl0), 44.70 (CH_2, Cl), 50.17 (*C*H, C2), 68.77 (CH_2, C3), 114.41 (C_{arom}, C5, C9), 129.88 (C_{arom}, C6, C8), 130.40 (C_{arom}, C7), 156.31 (C_{arom}, C4). IR (neat, cm^{-1}): 1245 cm^{-1}: $\overset{O}{C'-C}$; Anal. Calcd for $C_{10}H_{12}O_2$ (164.20): C, 73.15; H, 7.36. Found: C, 73.07; H, 7.26. Colourless oil, bp=121–126 °C/0.2 mmHg.

5.4.5. 3e: 1,2-Epoxy-3-(4-chlorophenoxy)propane.



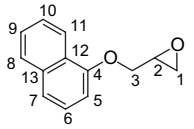
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.70–2.82 (1H, dd, J_{gem}=4.87 Hz, J_{1-2}=2.71 Hz, H1), 2.87–2.98 (1H, m, H1′), 3.29–3.45 (1H, m, H2), 3.80–4.01 (1H, dd, J_{gem}=11.02 Hz, J_{3-2}=5.77 Hz, H3), 4.15–4.30 (1H, dd, J_{gem}=11.00 Hz, $J_{3'-2}$=2.97 Hz, H3′), 6.80–6.95 (2H, m, H5, H9), 7.18–7.32 (2H, m, H6, H8); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 44.53 (CH_2, Cl), 49.98 (*C*H, C2), 68.98 (CH_2, C3), 115.84 (C_{arom}, C5, C9), 126.02 (C_{arom}, C7), 129.31 (C_{arom}, C6, C8), 157.00 (C_{arom}, C4). IR (neat, cm^{-1}): 1240 cm^{-1}: $\overset{O}{C'-C}$; Anal. Calcd for $C_9H_9O_2Cl$ (184.62): C, 58.55; H, 4.91. Found: C, 58.41; H, 4.78; MS (electr. impact, 70 eV, *m/z*): $(M+2)^+$=186 (26), $(M)^{+\bullet}$=184 (73), $(M-CH_2O)^+$=154 (11.5), $(M-C_2H_3O)^+$=141 (21.7), $([M+2]-C_3H_4O)^+$=130 (26.5), $(M-C_3H_4O)^+$=128 (100), $(M-C_3H_5O_2)^+$=111 (26), $(M-C_4H_5O_2)^+$=99 (17.8). Yellowish oil, bp=110–114 °C/0.1 mmHg.

5.4.6. 3f: 1,2-Epoxy-3-(4-chloro-3-methylphenoxy)propane.



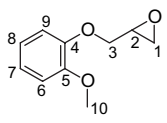
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.39 (3H, s, H10), 2.68–2.80 (1H, dd, J_{gem}=4.89 Hz, J_{1-2}=2.74 Hz, H1), 2.90–2.98 (1H, m, H1′), 3.33–3.47 (1H, m, H2), 3.78–4.03 (1H, dd, J_{gem}=11.06 Hz, J_{3-2}=5.69 Hz, H3), 4.12–4.29 (1H, dd, J_{gem}=11.01 Hz, $J_{3'-2}$=2.99 Hz, H3′), 6.69–6.94 (2H, m, H5, H9), 7.21–7.28 (1H, m, H8); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 20.54 (CH_3, Cl0), 44.59 (CH_2, Cl), 53.17 (*C*H, C2), 68.76 (CH_2, C3), 113.23 (C_{arom}, C9), 116.96 (C_{arom}, C5), 127.00 (C_{arom}, C7), 129.64 (C_{arom}, C8), 137.46 (C_{arom}, C6), 156.24 (C_{arom}, C4). IR (neat, cm^{-1}): 1237 cm^{-1}: $\overset{O}{C'-C}$; Anal. Calcd for $C_{10}H_{11}O_2Cl$ (198.65): C, 60.46; H, 5.58. Found: C, 60.35; H, 5.49. Colourless oil, bp=120–121 °C/0.1 mmHg, $bp_{Lit.}$=119–123 °C/0.1 mmHg.[20b]

5.4.7. 3g: 1,2-Epoxy-3-(1-naphthoxy)propane.



^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 2.80–2.90 (1H, dd, J_{gem}=4.93 Hz, J_{1-2}=2.65 Hz, H1), 2.92–3.01 (1H, m, H1′), 3.42–3.55 (1H, m, H2), 4.03–4.18 (1H, dd, J_{gem}=11.07 Hz, J_{3-2}=5.61 Hz, H3), 4.32–4.45 (1H, dd, J_{gem}=11.08 Hz, $J_{3'-2}$=3.02 Hz, H3′), 6.75–6.87 (1H, m, H5), 7.34–7.61 (4H, m, H6, H7, H10, H11), 7.80–7.90 (1H, m, H9), 8.31–8.45 (1H, m, H8). ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 44.83 (CH_2, Cl), 50.20 (*C*H, C2), 69.89 (CH_2, C3), 104.05 (C_{arom}, C5), 119.80 (C_{arom}, C7), 120.85 (C_{arom}, C11), 125.10 (C_{arom}, C10), 125.48 (C_{arom}, C6, C12), 126.45 (C_{arom}, C9), 127.32 (C_{arom}, C8), 135.00 (C_{arom}, C13), 154.67 (C_{arom}, C4). IR (neat, cm^{-1}): 1248 cm^{-1}: $\overset{O}{C'-C}$; Anal. Calcd for $C_{13}H_{12}O_2$ (200.24): C, 77.98; H, 6.04. Found: C, 77.86; H, 5.92. Colourless oil, bp=148–149 °C/0.5 mmHg, $bp_{Lit.}$=145–149 °C/0.5 mmHg.[20c]

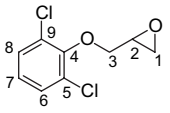
5.4.8. 3h: 1,2-Epoxy-3-(2-methoxyphenoxy)propane.



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.67–2.82 (1H, m, H1), 2.83–2.98 (1H, m, H1′), 3.31–3.49 (1H, m, H2), 3.87 (3H, s,

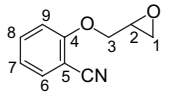
H10), 3.98–4.11 (1H, dd, J_{gem}=11.40 Hz, J_{3-2}=5.61 Hz, H3), 4.17–4.32 (1H, dd, J_{gem}=11.42 Hz, $J_{3'-2}$=3.58 Hz, H3′), 6.78–7.05 (4H, m, H6, H7, H8, H9). ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 44.92 (*C*H_2, Cl), 50.15 (*C*H, C2), 55.80 (*C*H_3, C10), 70.13 (*C*H_2, C3), 111.83 (C_{arom}, C6), 114.12 (C_{arom}, C9), 120.76 (C_{arom}, C7), 121.86 (C_{arom}, C8), 147.88 (C_{arom}, C5), 149.54 (C_{arom}, C4). IR (neat, cm^{-1}): 1245 cm^{-1}: C–O–C; Anal. Calcd for $C_{10}H_{12}O_3$ (180.20): C, 66.65; H, 6.71. Found: C, 66.53; H, 6.58. MS (electr. impact, 70 eV, *m*/*z*): $(M)^{+\bullet}$=180 (99.7), $(M-CH_2O)^+$=150 (11.8), $(M-C_2H_3O)^+$=137 (20.00), $(M-C_3H_4O)^+$=124 (48), $(M-C_3H_5O)^+$=123 (15.7), $(M-C_3H_6O)^+$=122 (21.8), $(M-C_3H_7O)^+$=121 (25), $(M-C_4H_7O)^+$=109 (100), $(M-C_4H_8O_2)^+$=92 (13), $(M-C_4H_7O_3)^+$=77 (83.10), $(M-C_5H_7O_3)^+$=65 (34.70), $(M-C_5H_8O_3)^+$=64 (25.90), $(M-C_5H_9O_3)^+$=63 (35.40), $(M-C_6H_8O_3)^+$=52 (87), $(M-C_6H_9O_3)^+$=51 (55.90). Yellowish oil, bp=110–114 °C/0.03 Torr, $bp_{Lit.}$=115–116 °C/0.03 Torr.[20d]

5.4.9. 3i: 1,2-Epoxy-3-(2,6-bischlorophenoxy)propane.



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.68–2.75 (1H, dd, J_{gem}=4.90 Hz, J_{1-2}=2.57 Hz, H1), 2.86–2.95 (1H, m, H1′), 3.40–3.51 (1H, m, H2), 3.98–4.12 (1H, dd, J_{gem}=10.91 Hz, J_{3-2}=5.97 Hz, H3), 4.17–4.28 (1H, dd, J_{gem}=10.95 Hz, $J_{3'-2}$=3.69 Hz, H3′), 6.92–7.08 (1H, m, H7), 7.22–7.35 (2H, m, H6, H8); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 44.59 (*C*H_2, Cl), 50.03 (*C*H, C2), 74.31 (*C*H_2, C3), 125.33 (C_{arom}, C7), 128.90 (C_{arom}, C6, C8), 129.34 (C_{arom}, C5, C9), 151.01 (C_{arom}, C4). IR (neat, cm^{-1}): 1247 cm^{-1}: C–O–C; Anal. Calcd for $C_9H_8O_2Cl_2$ (219.07): C, 49.34; H, 3.68. Found: C, 49.26; H, 3.56. Yellowish oil.

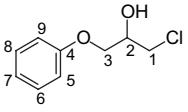
5.4.10. 3j: 1,2-Epoxy-3-(2-cyanophenoxy)propane.



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.74–2.80 (1H, dd, J_{gem}=4.78 Hz, J_{1-2}=2.76 Hz, H1), 2.85–2.96 (1H, m, H1′), 3.28–3.46 (1H, m, H2), 3.10–4.18 (1H, dd, J_{gem}=11.12 Hz, J_{3-2}=5.76 Hz, H3), 4.17–4.48 (1H, dd, J_{gem}=11.13 Hz, $J_{3'-2}$=3.06 Hz, H3′), 6.98–7.39 (4H, m, H6, H7, H8, H9); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 43.28 (*C*H_2, Cl), 48.70 (*C*H, C2), 69.90 (*C*H_2, C3), 97.91 (C_{arom}, C5), 114.62 (C_{arom}, C9), 118.51 (CN, C10), 121.61 (C_{arom}, C7), 133.08 (C_{arom}, C6), 133.77 (C_{arom}, C8), 162.80 (C_{arom}, C4). IR (neat, cm^{-1}): 1245 cm^{-1}: C–O–C; Anal. Calcd for $C_{10}H_9NO_2$ (175.18): C, 68.56; H, 5.18; N, 8.00. Found: C, 68.43; H, 5.03; N, 7.92. Colourless oil, bp=128–129 °C/0.1 mmHg, $bp_{Lit.}$=124–127 °C/0.1 mmHg.[10]

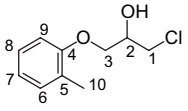
^{1}H NMR (and MS for **4a**) spectra, IR data as well as microanalyses of 1-chloro-3-aryloxypropan-2-ols **4a–j** are as follows.

5.4.10.1. 4a: 1-Chloro-3-phenoxypropan-2-ol.



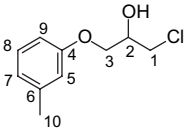
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.49 (1H, s, OH), 3.75 (2H, d, J_{1-2}=3.98 Hz, H1), 4.11–4.27 (3H, m, H2, H3), 6.67–6.98 (3H, m, H5, H7, H9), 7.08–7.35 (2H, m, H6, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_9H_{11}O_2Cl$ (186.64): C, 57.92; H, 5.94. Found: C, 57.85; H, 5.84. MS (electr. impact, 70 eV, *m*/*z*): $(M+2)^+$=188 (5.40), $(M)^{+\bullet}$=186 (18), $(M-CH_3OCl)^+$=119 (7.30), $(M-C_2H_3OCl)^+$=108 (5.90), $(M-C_2H_4OCl)^+$=107 (25.70), $(M-C_3H_4OCl)^+$=95 (24.50), $(M-C_3H_5OCl)^+$=94 (74), $(M-C_3H_6O_2Cl)^+$=77 (100), $(M-C_4H_5O_2Cl)^+$=66 (30), $(M-C_4H_6O_2Cl)^+$=65 (26). Colourless oil.

5.4.10.2. 4b: 1-Chloro-3-(2-methylphenoxy)propan-2-ol.



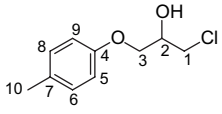
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.14 (3H, s, H10), 2.45 (1H, s, OH), 3.84 (2H, d, J_{1-2}=4.07 Hz, H1), 4.11–4.36 (3H, m, H2, H3), 6.77–6.90 (2H, m, H7, H9), 7.09–7.24 (2H, m, H6, H8). IR (neat, cm^{-1}): 3390 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{13}O_2Cl$ (200.66): C, 59.86; H, 6.53. Found: C, 59.79; H, 6.46. Colourless oil.

5.4.10.3. 4c: 1-Chloro-3-(3-methylphenoxy)propan-2-ol.



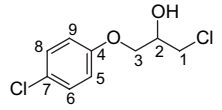
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.24 (3H, s, H10), 2.51 (1H, s, OH), 3.73 (2H, d, J_{1-2}=4.11 Hz, H1), 4.09–4.30 (3H, m, H2, H3), 6.63–6.78 (3H, m, H5, H7, H9), 7.10 (1H, m, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{13}O_2Cl$ (200.66): C, 59.86; H, 6.53. Found: C, 59.76; H, 6.50. Colourless oil.

5.4.10.4. 4d: 1-Chloro-3-(4-methylphenoxy)propan-2-ol.



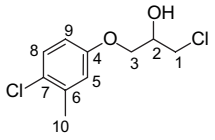
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.19 (3H, s, H10), 2.43 (1H, s, OH), 3.78 (2H, d, J_{1-2}=3.99 Hz, H1), 4.12–4.32 (3H, m, H2, H3), 6.70–6.90 (2H, m, H5, H9), 7.09–7.24 (2H, m, H6, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{13}O_2Cl$ (200.66): C, 59.86; H, 6.53. Found: C, 59.80; H, 6.45. Colourless oil.

5.4.10.5. 4e: 1-Chloro-3-(4-chlorophenoxy)propan-2-ol.



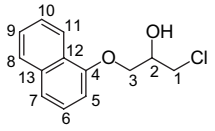
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.50 (1H, s, OH), 3.76 (2H, d, J_{1-2}=4.06 Hz, H1), 4.05–4.41 (3H, m, H2, H3), 6.78–6.89 (2H, m, H5, H9), 7.15–7.29 (2H, m, H6, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_9H_{10}O_2Cl_2$ (221.08): C, 48.90; H, 4.56. Found: C, 48.78; H, 4.50. Yellowish oil.

5.4.10.6. 4f: 1-Chloro-3-(4-chloro-3-methylphenoxy)-propan-2-ol.



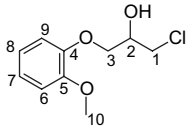
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.29 (3H, s, H10), 2.70 (1H, s, OH), 3.68 (2H, d, J_{1-2}=3.87 Hz, H1), 4.03–4.32 (3H, m, H2, H3), 6.53–6.79 (2H, m, H5, H9), 7.16–7.26 (1H, m, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{12}O_2Cl_2$ (235.11): C, 51.09; H, 5.14. Found: C, 50.95; H, 5.09. Yellowish oil.

5.4.10.7. 4g: 1-Chloro-3-(1-naphthoxy)propan-2-ol.



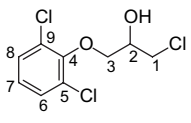
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.63 (1H, d, J=5.48 Hz, OH), 3.84 (2H, d, J_{1-2}=4.05 Hz, H1), 4.23–4.48 (3H, m, H2, H3), 6.68 (1H, m, H5), 7.26–7.71 (4H, m, H6, H7, H10, H11), 7.70–7.89 (1H, m, H9), 8.13–8.22 (1H, m, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_{13}H_{13}O_2Cl$ (236.70): C, 65.97; H, 5.54. Found: C, 65.89; H, 5.44. Colourless oil.

5.4.10.8. 4h: 1-Chloro-3-(2-methoxyphenoxy)propan-2-ol.



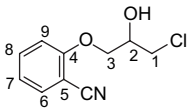
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.50 (1H, s, OH), 3.72 (2H, d, J_{1-2}=3.98 Hz, H1), 3.89 (3H, s, H10), 4.14–4.35 (3H, m, H2, H3), 6.71–7.10 (4H, m, H6, H7, H8, H9). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{13}O_3Cl$ (216.66): C, 55.44; H, 6.05. Found: C, 55.36; H, 5.91. Colourless oil.

5.4.10.9. 4i: 1-Chloro-3-(2,6-bischlorophenoxy)propan-2-ol.



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.46 (1H, s, OH), 3.62 (2H, d, J_{1-2}=4.15 Hz, H1), 4.20–4.33 (3H, m, H2, H3), 6.89–7.06 (1H, m, H7), 7.19–7.31 (2H, m, H6, H8). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_9H_9O_2Cl_3$ (255.53): C, 42.30; H, 3.55. Found: C, 42.21; H, 3.45. Colourless oil.

5.4.10.10. 4j: 1-Chloro-3-(2-cyanophenoxy)propan-2-ol.



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 2.38 (1H, s, OH), 3.81 (2H, d, J_{1-2}=4.19 Hz, H1), 4.09–4.36 (3H, m, H2, H3), 6.80–7.31 (4H, m, H6, H7, H8, H9). IR (neat, cm^{-1}): 3400 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{10}O_2ClN$ (211.65): C, 56.75; H, 4.76. Found: C, 56.67; H, 4.66. Colourless oil.

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A new approach towards peptidosulfonamides: synthesis of potential inhibitors of bacterial peptidoglycan biosynthesis enzymes MurD and MurE

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Dedicated to Professor Miha Tišler on the occasion of his 80th birthday

Abstract—Peptidosulfonamides are an emerging group of peptidomimetics with a variety of applications in medicinal chemistry. We present a novel approach to the synthesis of peptidosulfonamides, and apply it to a series of new potential inhibitors of the bacterial peptidoglycan biosynthesis enzymes MurD and MurE. The synthesis was conducted via *N*-phthalimido β-aminoethanesulfonyl chlorides, which are new building blocks for the synthesis of peptidosulfonamides. In the most crucial step, sulfonic acids or their sodium salts were converted into the corresponding sulfonyl chlorides using an excess of either $SOCl_2$ or $SOCl_2$/DMF, and then coupled to the *C*-protected amino acid. None of the compounds significantly inhibited MurD, however, some inhibited MurE; one had an IC_{50} below 200 μM, which constitutes a promising starting point for further development. Molecular modelling simulations were performed on two analogues to investigate the absence of inhibitory activity of the sulfonamide compounds on MurD.

1. Introduction

Infectious diseases are the second leading cause of death worldwide and the third leading cause of death in developed countries.[1] Due to the emergence and dissemination of resistant bacterial strains, there is an urgent need for the development of novel antibacterial agents.[2] The bacterial cell wall peptidoglycan[3] is an important target for antibiotic research. Many antibacterial agents, like bacitracin, vancomycin, penicillins and cephalosporins, act by inhibiting the late enzymatic steps of bacterial peptidoglycan biosynthesis.[4] On the other hand, the early intracellular steps, catalysed by a series of Mur enzymes (MurA to MurF), have been underexploited as antibacterial targets.[5–7]

Recently, we focused our attention on the D-glutamic acid-adding enzyme (UDP-*N*-acetylmuramoyl-L-alanine:D-glutamate ligase, or MurD), which catalyses the addition of D-Glu to UDP-Mur*N*Ac-L-Ala during the synthesis of the cytoplasmic precursor UDP-Mur*N*Ac-pentapeptide. MurD is an ATP-dependant, amide-forming enzyme that performs the initial phosphorylation of the carboxylic acid (Fig. 1). The resulting acyl-phosphate is then attacked by the incoming amino acid (D-Glu) to form a high-energy tetrahedral intermediate, which finally collapses into the amide product and inorganic phosphate. All Mur ligases act via this mechanism, which has been confirmed by X-ray diffraction analysis,[8] by isotope transfer[9] and rapid quench[10] experiments, and by the chemical trapping method.[11] To date, several phosphinates of general formula **1** have been developed as tetrahedral transition-state analogue inhibitors of MurD,[12–14] and a QSAR study has been done for some of them.[15] Although the most active inhibitors still retain UDP-Mur*N*Ac or structurally closely related fragments, some less complex molecules based on the key phosphinodipeptide L-Ala-Ψ[PO(OH)-CH_2]-D-Glu have been shown to possess good inhibitory activities.[12–14]

To prepare improved inhibitors of MurD, we sought an innovative tetrahedral functional group that could be used as a transition-state mimetic. Over the last decade, the peptidosulfonamides have been recognized as emerging building

Keywords: Peptidosulfonamides; β-Aminosulfonyl chlorides; Transition-state analogue inhibitors.
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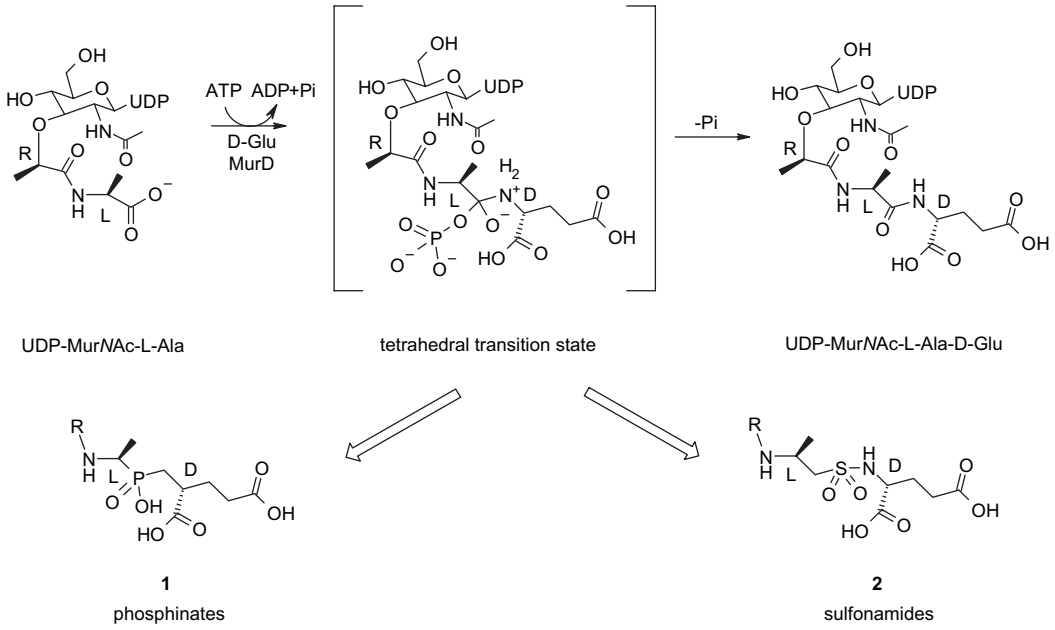


Figure 1. Reaction catalysed by MurD and design of transition-state analogue inhibitors.

blocks for preparing peptidomimetics and enzyme inhibitors.[16] Due to the intrinsic chemical instability of α-peptidosulfonamides, most of the studies of peptides containing the SO_2NH junction have been limited to β-peptidosulfonamides.[17] Sulfonamides possess a geometry similar to that of the tetrahedral intermediate formed during the peptide bond cleavage or formation.[18] Additionally, the stability of peptidosulfonamide peptidomimetics towards degradation by proteases is significantly increased.[19] As this type of transition-state mimetic has not yet been evaluated for inhibition of Mur enzymes, we prepared a series of peptidosulfonamides **2** of general formula R-L-Ala-Ψ(CH_2-SO_2)-D-Glu (Fig. 1) and assayed them for inhibition of MurD.

MurE is another cytoplasmic enzyme that is essential for the biosynthesis of bacterial peptidoglycan. It catalyses the attachment of the third amino acid residue to the product of the MurD reaction (UDP-Mur*N*Ac-L-Ala-D-Glu). Depending on the microorganism species, this amino acid is generally *meso*-diaminopimelic acid, L-lysine or L-ornithine.[20] All compounds designed as transition-state analogue inhibitors of MurD are thus highly interesting as potential inhibitors of MurE, for which they could act as substrate analogues.

2. Results and discussion

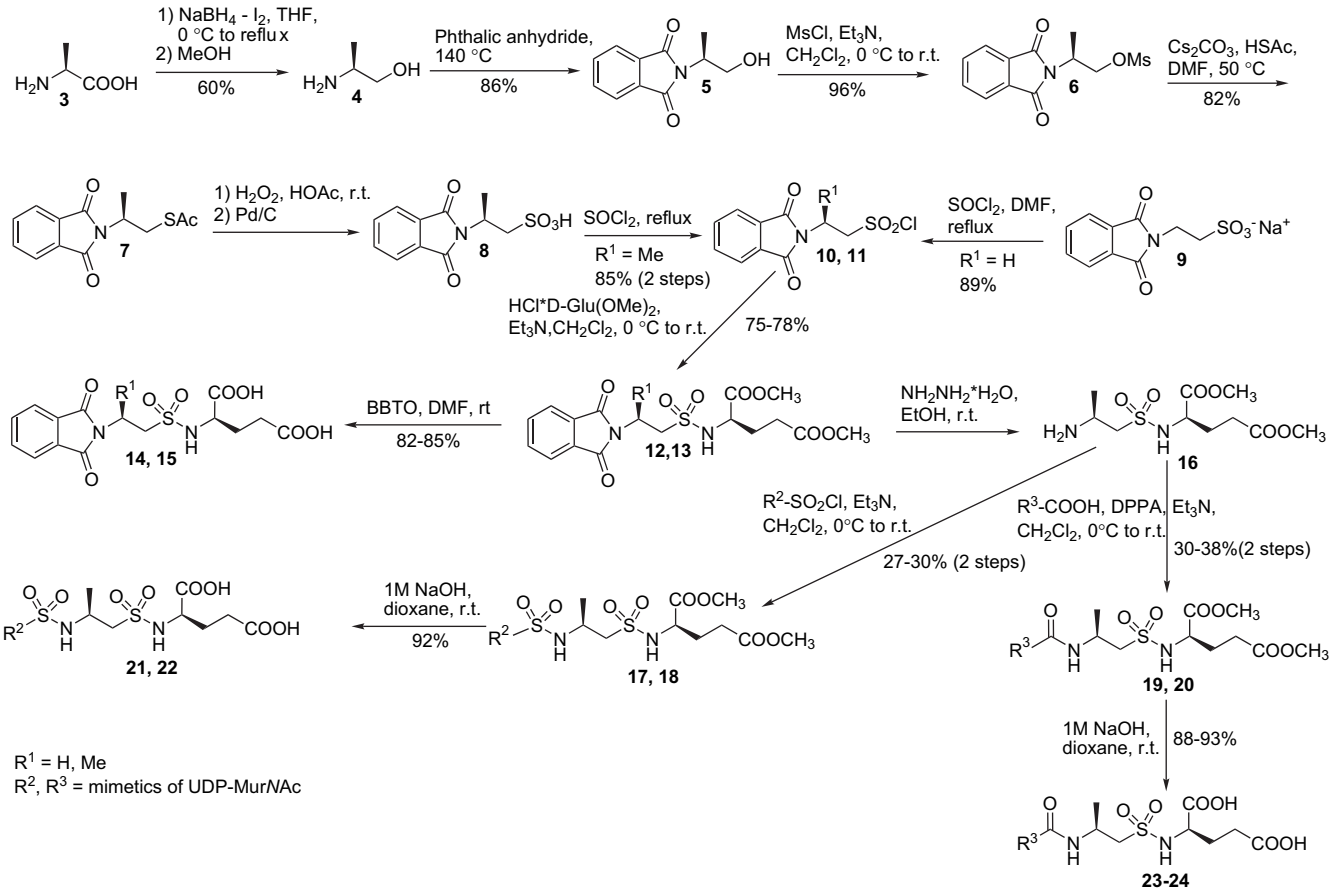
2.1. Synthesis

The crucial step in the synthesis of peptidosulfonamides is the conversion of sulfonic acids into the corresponding sulfonyl chlorides. β-Substituted β-aminoethanesulfonyl chlorides are usually obtained from sulfonic acids or their salts using triphosgene[21–23] or phosgene[24–26] as chlorinating agent. Recently, we developed a new method for the synthesis of *N*-phthalimido β-aminoethanesulfonyl chlorides using thionyl chloride.[27] In this paper we present the application of this method to the synthesis of potential inhibitors of the bacterial peptidoglycan biosynthesis enzymes MurD and MurE.

The synthesis of sulfonamide inhibitors **14**, **15** and **21**–**24** is presented in Scheme 1. We started the synthesis with free L-alanine **3**, which was reduced to amino alcohol **4** using the $NaBH_4/I_2$ system,[28] and phthaloylated with phthalic anhydride to give *N*-phthalimido-protected amino alcohol **5** in high yield. The protected amino alcohol **5** was mesylated with methanesulfonyl chloride and Et_3N in dichloromethane. In the next step, mesylate **6** was added to the mixture of thioacetic acid and Cs_2CO_3 in DMF and stirred at 50 °C for 24 h. Thioacetate **7** was then oxidized to the corresponding sulfonic acid **8** using aqueous hydrogen peroxide and acetic acid; after 24 h at rt, the excess peroxide was destroyed by adding 10% Pd/C. The resulting crude sulfonic acid **8** was finally refluxed in excess thionyl chloride to give sulfonyl chloride **10** in high yield. The sulfonyl chloride of taurine derivative **11** was obtained by a slight modification of the procedure, in which a catalytic amount of dry DMF was added to the reaction mixture to achieve clean and rapid chlorination of sodium salt **9**.

The corresponding sulfonyl chlorides **10** and **11** were coupled with *C*-protected D-glutamic acid to give methyl esters **12** and **13**, respectively, the selective deprotection of which with bis(tributyltin) oxide (BBTO)[29] yielded compounds **14** and **15**, respectively. We found that the reaction displays a high level of chemoselectivity between methyl esters and the phthalimido protecting group.

Hydrazinolysis of the phthalimido protecting group of compound **12** produced the crucial amine intermediate **16**, which was unstable to heat and prolonged storage at rt. Free amine **16** was immediately substituted by different carboxyl or sulfonyl moieties. The resulting compounds **17**–**20** were converted by alkaline hydrolysis into target sulfonamide inhibitors **21**–**24** (Table 1).



Scheme 1. Synthesis of β-sulfonopeptide inhibitors.

2.2. Inhibitory activities

Target compounds **14**, **15** and **21**–**24** were tested for inhibitory activity on MurD from *Escherichia coli* and on MurE from *Staphylococcus aureus*. The results are presented as residual activities (RA) of the enzymes in the presence of 1 mM compound (Table 1).

All target peptidosulfonamides (compounds **14**, **15** and **21**–**24**) proved to be poor inhibitors of MurD. Phosphinate **25** had previously been prepared and evaluated on MurD (IC_{50}=95 μM).[14] The RA of its structurally closely related sulfonamide analogue **24** was 80%, which makes the compound practically inactive against MurD. Compounds **24** and **25** were both designed with the purpose of mimicking the tetrahedral transition-state of the reaction catalysed by MurD. The substituted *trans*-cinnamoyl moiety present in both compounds was introduced to mimic the Mur*N*Ac part of the substrate. However, only phosphinate **25** inhibited MurD, in spite of the fact that it was tested as a mixture of four diastereoisomers, while the related sulfonamidopeptide **24** is diastereomerically pure. The reason for the poor inhibitory activity of peptidosulfonamides might be the elongation of the pseudopeptide backbone caused by the insertion of the additional methylene group, which may disrupt the active conformation of the molecule.

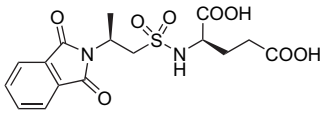
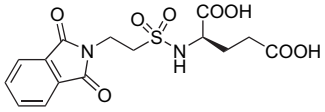
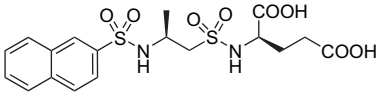
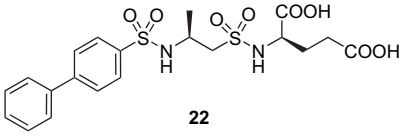
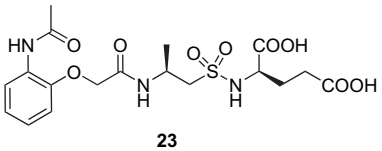
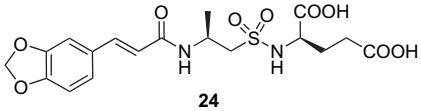
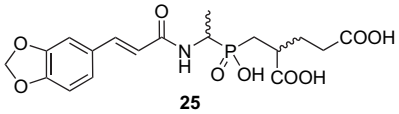
Although the compounds synthesized in this study were designed as potential transition-state analogue inhibitors of MurD, they turned out to be better inhibitors of MurE. In fact, biphenyl derivative **22** is a good inhibitor of MurE, with an IC_{50} in the micromolar range; it thus represents a promising starting point for further structural modifications. It is most likely that sulfonamidopeptide **22** inhibits MurE as a substrate analogue.

2.3. Molecular modelling

A molecular modelling study was performed to examine the differences in inhibitory activity between the sulfonamide (**24**) and phosphinate (**25**) types of inhibitors. To date, no crystallographic data of MurD inhibitors bound to the enzyme active site have been published. However, it is reasonable to assume that the inhibitors possessing the D-Glu functionality mimic the position occupied by the D-Glu moiety of the product UDP-Mur*N*Ac-L-Ala-D-Glu in the active site. Thus, we have considered only the situations where the D-Glu part was docked to the subpocket as defined in an analogous way to the experimental structure with bound UDP-Mur*N*Ac-L-Ala-D-Glu (pdb code 4uag[8]).

In Figures 2 and 3, the crystal structure of UDP-Mur*N*Ac-L-Ala in the active site of MurD from *E. coli* (pdb code 3uag[8]) is compared with modelled structures of compounds **25** and **24**, respectively. When the positions of both compounds in the active site are compared, one important difference can be observed. The phosphinic group of phosphinate inhibitor **25** is perfectly positioned to form a coordinative bond with the

Table 1. Residual activities of the enzymes in the presence of 1 mM inhibitor

Structure	RA (%) MurD	RA (%) MurE
 **14**	74	41
 **15**	77	ND[a]
 **21**	75	60
 **22**	70	12 (IC_{50}=181±18 μM)
 **23**	93	56
 **24**	80	64
 **25**	17[b] (IC_{50}=95±15 μM)[b]	ND[a]

Results represent the means of two independent experiments. Standard deviations were within ±10% of the means.
[a] ND=not determined.
[b] From Ref. 14.

Mn^{2+} ion, as expected for a transition-state analogue. In addition, the dicarboxylic moiety of the compound extents into the D-Glu binding pocket formed by Thr321, Lys348, Phe422 and Ser415. On the other hand, the $–SO_2–$ group of compound **24** can also form a coordinative bond with Mn^{2+}, but this results in an unfavourable position of the sulfonamide –NH– group. Consequently, the α-carboxyl group of D-Glu reorients itself by losing a strong hydrogen bond

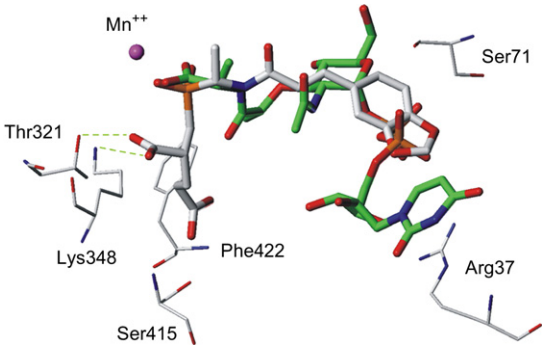


Figure 2. Superposition of phosphinate **25** (carbon atoms coloured grey) and UDP-Mur*N*Ac-L-Ala (carbon atoms coloured green) in the *E. coli* MurD active site. The subpocket into which the D-Glu part of the molecule is anchored is shown (Ser415 and Phe422).

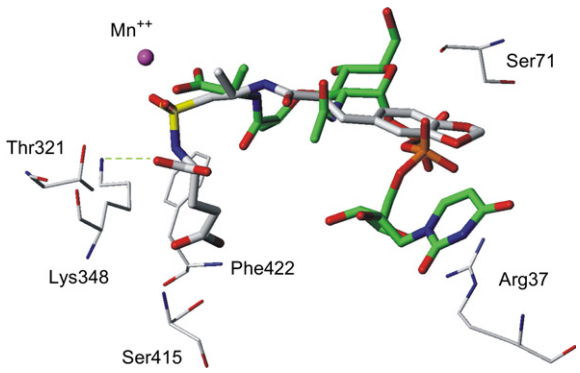


Figure 3. Superposition of sulfonamide **24** and UDP-Mur*N*Ac-L-Ala in the *E. coli* MurD active site. Colour representation as in Figure 2.

with Thr321 (see Figs. 2 and 3). This unfavourable interaction is also recognized in terms of the scoring, where the *F*-score ranked compound **24** (−17.6) much lower than compound **25** (−31.0). However, the sulfonamide bond has no influence on the orientation of 3-(1,3-benzodioxol-5-yl)-cinnamoyl part of compound **24**. This group, which is a good mimetic of the phospho-sugar part of UDP-Mur*N*Ac,[14] binds in a similar way in compounds **24** and **25**, and thus should not be responsible for the differences in biological activity observed.

It has to be pointed out that the geometry of the transition-state analogue at the peak of its free energy profile could be in variation with the transition structure, which is the point of highest potential energy of the molecule along the reaction pathway.[30] Thus, in the modelling of the transition-state structures, other contributions, such as entropic factors,[31] should in principle be considered. In addition, the substitution of the phosphinic group present in compound **25** with the sulfonamido group might result in a weaker coordination bond with the Mn^{2+}, which could consequently contribute to the lower inhibitory activity of compound **24**.

3. Conclusion

We have presented a simple and straightforward synthesis of new peptidosulfonamides as potential inhibitors of the bacterial peptidoglycan biosynthesis enzymes MurD and MurE. The synthesis was conducted via *N*-phthalimido β-aminoethanesulfonyl chlorides, which are new building blocks for the synthesis of peptidosulfonamides. In the most crucial step, sulfonic acids or their sodium salts were converted into the corresponding sulfonyl chlorides using either excess $SOCl_2$ or $SOCl_2$/DMF. From the inhibitory activity results and the molecular modelling study, we can conclude that β-peptidosulfonamides are not suitable for development of transition-state analogue inhibitors of MurD. However, compound **22** had a good inhibitory activity on MurE, and represents a promising starting point for further design of MurE inhibitors that act as substrate analogues.

4. Methods

4.1. Enzyme assays

4.1.1. MurD. Enzymatic assays were performed as previously described,[32] with slight modifications. The compounds were tested for their ability to inhibit the addition of D-[^{14}C]Glu to UDP-Mur*N*Ac-L-Ala in a mixture (final volume: 50 μL) containing 0.1 M Tris/HCl, pH 8.6, 5 mM $MgCl_2$, 25 μM UDP-Mur*N*Ac-L-Ala, 25 μM D-[^{14}C]Glu (50,000 cpm), 5% (v/v) DMSO, purified MurD from *E. coli*[33] (diluted with 20 mM potassium phosphate, pH 7.0, 1 mM dithiothreitol, 1 mg/mL BSA), and 1 mM test compound (all of the compounds were soluble in the enzyme assay mixture containing 5% DMSO). The mixture was incubated for 30 min at 37 °C, and the reaction stopped by adding 10 μL glacial acetic acid. The mixture was lyophilized and taken up in the HPLC elution buffer. The radioactive substrate and product were separated by reverse-phase HPLC with a Nucleosil $5C_{18}$ column (150×4.6 mm) as stationary phase, and isocratic elution at a flow rate of 0.6 mL/min with 50 mM ammonium formate, pH 4.7. The compounds were detected and quantified with an LB 506 C-1 HPLC radioactivity monitor (Berthold France, Thoiry, France) using Quickszint Flow 2 scintillator (Zinsser Analytic, Maidenhead, UK) at 0.6 mL/min. Residual activity was calculated with respect to a similar assay without inhibitor. Values are expressed as the means of two independent experiments. Standard deviations were within ±10% of the means.

4.1.2. MurE. The compounds were tested for their ability to inhibit the addition of L-[^{14}C]Lys to UDP-Mur*N*Ac-L-Ala-D-Glu in a mixture (final volume: 50 μL) containing 0.1 M Tris/HCl, pH 8.6, 15 mM $MgCl_2$, 100 μM UDP-Mur*N*Ac-L-Ala-D-Glu, 200 μM L-[^{14}C]Lys (50,000 cpm), 5% (v/v) DMSO, purified MurE from *S. aureus*[34] (diluted with 20 mM potassium phosphate, pH 7.0, 1 mM dithiothreitol) and 1 mM test compound (all of the compounds were soluble in the assay mixture containing 5% DMSO). The mixture was incubated for 30 min at 37 °C, and the reaction stopped by adding 10 μL glacial acetic acid. Separation and quantification were then performed as described for MurD. The IC_{50} value for compound **22** was determined from a range of inhibitor concentrations; value±standard deviation at 95% of confidence was calculated from the fitted regression equation using the logit/log plot.

4.2. Molecular modelling

Our modelling procedure was based on the crystal structure of the complex of the MurD enzyme from *E. coli* with its ligands UDP-Mur*N*Ac-L-Ala, ADP and Mn^{2+} (pdb entry 3uag[8]). Molecular modelling simulations were performed using the Sybyl7.1 (Tripos, Inc.) programme suite[35] and FlexX, a software package for incremental docking.[36] All of the compounds were initially modelled, then minimized for up to 1000 steps, and finally centred. Standard Gasteiger–Marsili charges[37] were used throughout. Docking of inhibitors into the *E. coli* MurD active site was performed in several independent runs. Residue Lys198 was included in the active site as the carbamoylated form[38] and all crystal water molecules were deleted. In addition, we defined the Mn^{2+} ion as an essential part of the active site since it makes a coordinative bond with the carboxylic functional group of the L-Ala part of UDP-Mur*N*Ac-L-Ala. We also defined residues Ser415 and Phe422 as a subpocket since in the experimentally determined structure of the complex MurD*UDP-Mur*N*Ac-L-Ala-D-Glu (pdb entry 4uag[8]), they bind the D-Glu part of UDP-Mur*N*Ac-L-Ala-D-Glu. For each compound, 100 positions (low energy conformations in the active site) were determined using FlexX as both docking and scoring functions.

5. Experimental

5.1. Materials

Chemicals from Sigma–Aldrich and Acros Organics were used without further purification. Analytical TLC was performed on Merck silica gel ($60F_{254}$) plates (0.25 mm); compounds were visualized with ultraviolet light. Column

chromatography was carried out on silica gel 60 (particle size 240–400 mesh). Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DPX$_{300}$ spectrometer in $CDCl_3$ or DMSO-d_6 solution, with TMS as the internal standard. IR spectra were obtained on a Perkin–Elmer 1600 FTIR spectrometer. Optical rotation was measured on a Perkin–Elmer 1241 MC polarimeter. Microanalyses were performed on a Perkin–Elmer C, H, N analyzer 240 C. Mass spectra were obtained using a VG-Analytical Autospec Q mass spectrometer.

5.2. Synthesis of β-aminoethanesulfonyl chlorides 10, 11

5.2.1. (*S*)-2-Phthalimidopropanol (5). Phthalic anhydride (20.00 g, 135.0 mmol) and (*S*)-alaninol (9.66 g, 128.6 mmol) were fused at 140 °C for 7 h. The reaction mixture was cooled to rt and the resulting solid dissolved in EtOAc (200 mL). The solution was washed successively with saturated aqueous $NaHCO_3$ (60 mL), H_2O (60 mL), citric acid (10% w/w, 60 mL) and brine (60 mL). Drying (Na_2SO_4), followed by concentration in vacuo, produced compound **5** (22.70 g, 86%) as a white solid: R_f=0.48 ($CHCl_3$/MeOH=9/1); mp 79–82 °C (lit.[39] mp 77 °C); $[\alpha]_D^{23}$ +32.7 (*c* 0.312, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (d, 3H, *J*=7.1 Hz, CH_3), 2.70 (br s, 1H, OH), 3.91 (dd, 1H, *J*=11.8, 3.8 Hz, CH_2), 4.05 (dd, 1H, *J*=11.8, 7.5 Hz, CH_2), 4.45–4.63 (m, 1H, CH), 7.70–7.78 (m, 2H, Pht-H), 7.82–7.90 (m, 2H, Pht-H); FABMS: *m*/*z*=206 (M+H)$^+$.

5.2.2. (2*S*)-2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-propyl methanesulfonate (6). To a solution of alcohol **5** (9.76 g, 47.6 mmol) in CH_2Cl_2 (150 mL), Et_3N (8.0 mL, 57.0 mmol) was added. After cooling to 0 °C, methanesulfonyl chloride (4.5 mL, 57.0 mmol) was added dropwise. Stirring was continued overnight at rt, followed by addition of CH_2Cl_2 (100 mL). The mixture was washed with $NaHCO_3$ (5% w/w, 2×100 mL), H_2O (2×100 mL) and brine (80 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated. Mesylate **6** was crystallized from EtOAc/hexane. White crystals were obtained (12.90 g, 96%): R_f=0.64 ($CHCl_3$/MeOH=9/1); mp 71–74 °C; $[\alpha]_D^{23}$ +34.0 (*c* 0.315, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (d, 3H, *J*=6.8 Hz, CH_3), 2.99 (s, 3H, CH_3), 4.45 (dd, 1H, *J*=9.8, 4.4 Hz, CH_2), 4.68–4.90 (m, 2H, CH_2+CH), 7.71–7.80 (m, 2H, Pht-H), 7.82–7.91 (m, 2H, Pht-H); IR (KBr, cm^{-1}): 3012, 1771, 1709, 1467, 1354, 1170, 1042, 992, 821, 719, 517; FABMS: *m*/*z*=284 (M+H)$^+$; Anal. Calcd for $C_{12}H_{13}NO_5S$: C (50.87%), H (4.63%), N (4.94%). Found: C (51.16%), H (4.70%), N (4.96%).

5.2.3. *S*-[(2*S*)-2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]ethanethioate (7). Thioacetate (3.6 mL, 51.0 mmol) was added to a suspension of Cs_2CO_3 (15.25 g, 47.0 mmol) in DMF (70 mL). Mesylate **6** (12.05 g, 42.6 mmol) was added in one portion to the resulting solution and stirring was continued at 50 °C for 24 h, prior to which the reaction flask was covered with aluminium foil. The mixture was poured into distilled H_2O (250 mL), and the aqueous phase extracted with EtOAc (3×150 mL). The combined organic layers were washed with H_2O (150 mL), $NaHCO_3$ (5% w/w, 150 mL) and brine (150 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated. The resulting residue was purified by column chromatography (EtOAc/hexane=1/1) to produce **7** as a white solid (9.20 g, 82%): R_f=0.40 (EtOAc/Hex=1/1); mp 54–57 °C; $[\alpha]_D^{23}$ +170.1 (*c* 0.332, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (d, 3H, *J*=6.9 Hz, CH_3), 2.30 (s, 3H, CH_3), 3.40 (dd, 1H, *J*=13.9, 5.5 Hz, CH_2), 3.52 (dd, 1H, *J*=13.9, 9.7 Hz, CH_2), 4.42–4.58 (m, 1H, CH), 7.68–7.78 (m, 2H, Pht-H), 7.80–7.90 (m, 2H, Pht-H); IR (KBr, cm^{-1}): 3453, 2976, 1698, 1466, 1356, 1106, 944, 884, 714, 630; FABMS: *m*/*z*=264 (M+H)$^+$; Anal. Calcd for $C_{13}H_{13}NO_3S$: C (59.30%), H (4.98%), N (5.32%). Found: C (59.29%), H (4.89%), N (5.23%).

5.2.4. (2*S*)-2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-propanesulfonyl chloride (10). A mixture of H_2O_2 (30% w/w in H_2O, 30 mL) and HOAc (60 mL) was added to a solution of thioacetate **7** (9.05 g, 34.4 mmol) in HOAc (30 mL). After stirring for 24 h at rt, 10% Pd/C was added to destroy the excess peroxide. Filtration, concentration and co-evaporation with toluene (2×20 mL) and ether (2×20 mL) under reduced pressure produced crude sulfonic acid **8**. This compound was dried at 50 °C for 48 h in vacuo over P_2O_5 and NaOH, and afterwards refluxed in $SOCl_2$ (20 mL) for 7 h. Excess $SOCl_2$ was removed by evaporation, followed by co-evaporation with toluene and ether under reduced pressure. The resulting residue was purified through a silica plug (CH_2Cl_2) to give **10** as a white solid (8.41 g, 85%). An analytical sample was obtained by precipitation from CH_2Cl_2/hexane: R_f=0.65 (CH_2Cl_2/acetone=18/1); mp 83–85 °C; $[\alpha]_D^{23}$ +78.1 (*c* 0.310, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66 (d, 3H, *J*=7.2 Hz), 3.97 (dd, 1H, *J*=14.3, 3.6 Hz, CH_2), 4.77 (dd, 1H, *J*=14.3, 9.8 Hz, CH_2), 5.13–5.28 (m, 1H, CH), 7.72–7.81 (m, 2H, Pht-H), 7.84–7.93 (m, 2H, Pht-H); IR (KBr, cm^{-1}): 3467, 1776, 1711, 1374, 1169, 1062, 860, 724, 605, 525; EIMS: 287, 289 (M$^+$); Anal. Calcd for $C_{11}H_{10}ClNO_4S$: C (45.92%), H (3.50%), N (4.87%). Found: C (46.18%), H (3.52%), N (4.68%).

5.2.5. 2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethanesulfonyl chloride (11). To an ice-cooled mixture of sulfonic acid sodium salt **9** (5.00 g, 17.9 mmol), which was prepared as described,[40] and excess thionyl chloride (10 mL), DMF (1 mL) was added dropwise. The mixture was heated under reflux for 5 h. The chlorinating species was removed by evaporation, followed by co-evaporation with toluene and ether under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with H_2O (60 mL), saturated aqueous $NaHCO_3$ (60 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated, and the residue purified through a silica plug (CH_2Cl_2) to yield sulfonyl chloride **11** as a white solid (4.90 g, 89%): R_f=0.63 (CH_2Cl_2/acetone=18/1); mp 160–162 °C (lit.[40] mp 159–162 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.03–4.15 (m, 2H, CH_2SO_2), 4.38 (t, 2H, *J*=6.5 Hz, NCH_2), 7.74–7.83 (m, 2H, Pht-H), 7.86–7.96 (m, 2H, Pht-H); FABMS: *m*/*z*=274 (M+H)$^+$.

5.3. General procedure for the preparation of pseudodipeptides 12, 13

Sulfonyl chloride **10**, **11** (25.0 mmol) was dissolved in CH_2Cl_2 (40 mL) and added dropwise to an ice-cooled mixture of HCl*D-Glu(OMe)$_2$ (25.0 mmol) and Et_3N

(50.0 mmol) in CH_2Cl_2 (50 mL). The resulting mixture was stirred overnight allowing warming to rt. After dilution with CH_2Cl_2 (30 mL), the mixture was washed with ice-cold 2 M HCl (2×50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resulting residue was purified by column chromatography (CH_2Cl_2/acetone=15/1).

5.3.1. Dimethyl *N*-{[(2*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]sulfonyl}-D-glutamate (12). White solid (9.31 g, 78%): R_f=0.37 (CH_2Cl_2/acetone=15/1); mp 89–90 °C; $[\alpha]_D^{23}$ +42.9 (*c* 0.322, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 1.46 (d, 3H, *J*=7.2 Hz, CH_3), 1.69–1.84 (m, 1H, CH_2CH_2CO), 1.92–2.06 (m, 1H, CH_2CH_2CO), 2.36–2.46 (m, 2H, CH_2CH_2CO), 3.48 (dd, 1H, *J*=14.3, 4.5 Hz, CH_2SO_2), 3.59 (s, 3H, $COOCH_3$), 3.65 (s, 3H, $COOCH_3$), 3.80 (dd, 1H, *J*=14.3, 9.4 Hz, CH_2SO_2), 3.93–4.05 (m, 1H, CHCO), 4.64–4.79 (m, 1H, $CHCH_3$), 7.81–7.91 (m, 4H, Ar-H), 7.96 (d, 1H, *J*=9.0 Hz, NH); IR (KBr, cm^{-1}): 3282.9, 2962.5, 1714.7, 1440.7, 1381.5, 1305.2, 1156.1, 978.3, 716.5; FABMS: *m*/*z*=427 $(M+H)^+$; Anal. Calcd for $C_{18}H_{22}N_2O_8S$: C (50.70%), H (5.20%), N (6.57%). Found: C (50.96%), H (5.29%), N (6.39%).

5.3.2. Dimethyl *N*-{[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]sulfonyl}-D-glutamate (13). White solid (5.64 g, 75%): R_f=0.36 (CH_2Cl_2/acetone=15/1); mp 105–108 °C; $[\alpha]_D^{23}$ +14.9 (*c* 0.276, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.90–2.10 (m, 1H, CH_2CH_2CO), 2.45–2.65 (m, 1H, CH_2CH_2CO), 2.36–2.46 (m, 2H, CH_2CH_2CO), 3.25–3.37 (m, 1H, CH_2SO_2), 3.40–3.55 (m, 1H, CH_2SO_2), 3.70 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 4.02–4.17 (m, 1H, NCH_2), 4.20–4.35 (m, 1H, CH), 4.37–4.50 (m, 1H, NCH_2), 5.55 (d, 1H, *J*=9.1 Hz, NH), 7.70–7.80 (m, 2H, Ar-H), 7.85–7.95 (m, 2H, Ar-H); IR (KBr, cm^{-1}): 3485.8, 1641.6, 1438.1, 978.6, 720.4; FABMS: *m*/*z*=413 $(M+H)^+$; Anal. Calcd for $C_{17}H_{20}N_2O_8S$: C (49.51%), H (4.89%), N (6.79%). Found: C (49.46%), H (4.90%), N (6.67%).

5.4. General procedure for the hydrazinolysis of the phthalimido protecting group of pseudodipeptide 12

To a solution of pseudodipeptide **12** (15.0 mmol) in EtOH (40 mL), hydrazine monohydrate (17.0 mmol) was added, and the reaction mixture was stirred at rt for 96 h. The mixture was cooled to 0 °C and filtered to remove phthalhydrazide. The filtrate was concentrated to dryness and the resulting oil was redissolved in a minimum amount of EtOH, cooled to 0 °C, filtered and evaporated under reduced pressure. The resulting pale yellow oil **16** was immediately used for the next reaction step, without further purification.

5.5. General procedure for the preparation of *N*-sulfonyl peptidosulfonamides 17, 18

The required sulfonyl chloride (3.0 mmol) was dissolved in CH_2Cl_2 (15 mL) and added dropwise to an ice-cooled mixture of amine **16** (2.5 mmol) and Et_3N (6.0 mmol) in CH_2Cl_2 (25 mL). The resulting mixture was stirred overnight allowing warming to rt. After dilution with CH_2Cl_2 (50 mL), the mixture was washed with ice-cold 2 M HCl (2×30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resulting residue was purified by column chromatography (CH_2Cl_2/acetone=10/1).

5.5.1. Dimethyl *N*-({(2*S*)-2-[(2-naphthylsulfonyl)amino]-propyl}sulfonyl)-D-glutamate (17). White solid (420 mg, 30%): R_f=0.32 (CH_2Cl_2/acetone=10/1); mp 97–99 °C; $[\alpha]_D^{23}$ −35.1 (*c* 0.297, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 1.06 (d, 3H, *J*=6.8 Hz, $CHCH_3$), 1.64–1.81 (m, 1H, CH_2CH_2CO), 1.85–2.01 (m, 1H, CH_2CH_2CO), 2.34 (t, 2H, *J*=7.4 Hz, CH_2CH_2CO), 3.00–3.23 (m, 2H, CH_2SO_2), 3.58 (s, 3H, $COOCH_3$), 3.60–3.73 (m, 4H, $CHCH_3$+$COOCH_3$), 3.83–3.95 (m, 1H, CHCO), 7.64–8.21 (m, 8H, Naph-H+2×NH), 8.46 (s, 1H, Naph-H); IR (KBr, cm^{-1}): 3299.4, 2949.2, 1734.7, 1439.0, 1330.6, 982.9, 820.3, 665.3; FABMS: *m*/*z*=487 $(M+H)^+$; Anal. Calcd for $C_{20}H_{26}N_2O_8S_2$: C (49.37%), H (5.39%), N (5.76%). Found: C (49.61%), H (5.40%), N (5.75%).

5.5.2. Dimethyl *N*-({(2*S*)-2-[([1,1′-biphenyl]-4-ylsulfonyl)-amino]propyl}sulfonyl)-D-glutamate (18). White solid (390 mg, 27%): R_f=0.36 (CH_2Cl_2/acetone=10/1); mp 136–138 °C; $[\alpha]_D^{23}$ −51.6 (*c* 0.295, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 1.11 (d, 3H, *J*=6.8 Hz, $CHCH_3$), 1.67–1.84 (m, 1H, CH_2CH_2CO), 1.87–2.04 (m, 1H, CH_2CH_2CO), 2.37 (t, 2H, *J*=7.5 Hz, CH_2CH_2CO), 3.08 (dd, 1H, *J*=13.9, 9.4 Hz, CH_2SO_2), 3.20 (dd, *J*=13.9, 3.8 Hz, CH_2SO_2), 3.58 (s, 3H, $COOCH_3$), 3.61–3.74 (m, 4H, $CHCH_3$+$COOCH_3$), 3.87–3.97 (m, 1H, CHCO), 7.41–7.96 (m, 11H, Ar-H+2×NH); IR (KBr, cm^{-1}): 3292.4, 2980.0, 1735.0, 1441.7, 1284.3, 1154.1, 983.5, 922.9, 763.7, 674.6, 577.9; FABMS: *m*/*z*=513 $(M+H)^+$; Anal. Calcd for $C_{22}H_{28}N_2O_8S_2$: C (51.55%), H (5.51%), N (5.47%). Found: C (51.68%), H (5.60%), N (5.45%).

5.6. General procedure for the preparation of *N*-acyl peptidosulfonamides 19, 20

DPPA coupling: to an ice-cooled mixture containing the amine **16** (2.5 mmol) and the required carboxylic acid (2.5 mmol) in dry DMF (20 mL), DPPA was slowly added (3.0 mmol), followed by dropwise addition of Et_3N (5.0 mmol). The reaction mixture was kept at 0 °C for another 2 h, and then allowed to warm up to rt. After 24 h, the reaction mixture was diluted with EtOAc (70 mL) and washed with an aqueous solution of citric acid (10% w/w, 50 mL), H_2O (50 mL), saturated aqueous $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resulting residue was purified by column chromatography (CH_2Cl_2/acetone=10/1).

5.6.1. Dimethyl *N*-{[(2*S*)-2-({2-[2-(acetylamino)phenoxy]acetyl}amino)propyl]sulfonyl}-D-glutamate (19). Colourless oil (370 mg, 30%), used in the next reaction step without further purification: R_f=0.15 ($CHCl_3$/acetone=5/1); ^{1}H NMR (300 MHz, DMSO): δ 1.23 (d, 3H, *J*=6.8 Hz, $CHCH_3$), 1.71–1.87 (m, 1H, CH_2CH_2CO), 1.93–2.06 (m, 1H, CH_2CH_2CO), 2.11 (s, 3H, CH_3CO), 2.38–2.46 (m, 2H, CH_2CH_2CO), 3.10–3.29 (m, 2H, CH_2SO_2), 3.59 (s, 3H, $COOCH_3$), 3.65 (s, 3H, $COOCH_3$), 3.96–4.06 (m, 1H, CHCO), 4.25–4.37 (m, 1H, $CHCH_3$), 4.52 (ABq, 2H, *J*=15.1 Hz, OCH_2CO), 6.90–7.11 (m, 3H, Ar-H), 7.79–7.90 (m, 2H, Ar-H+SO_2NH), 8.28 (d, 1H, *J*=7.5 Hz,

*NH*CH), 9.35 (s, 1H, Ar-*NH*CO); IR (KBr, cm^{-1}): 3283.9, 1736.5, 1669.9, 1536.0, 1455.0, 1120.9, 753.4; FABMS: *m*/*z*=488 (M+H).

5.6.2. Dimethyl *N*-[((2*S*)-2-{[(*E*)-3-(1,3-benzodioxol-5-yl)-2-propenoyl]amino}propyl)sulfonyl]-D-glutamate (20). Colourless oil (150 mg, 38%): R_f=0.13 ($CHCl_3$/acetone=5/1); $[\alpha]_D^{23}$ +30.0 (*c* 0.140, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 1.25 (d, 3H, *J*=6.8 Hz, CH*CH*$_3$), 1.73–1.88 (m, 1H, *CH*$_2$CH$_2$CO), 1.92–2.05 (m, 1H, *CH*$_2$CH$_2$CO), 2.38–2.45 (m, 2H, CH$_2$*CH*$_2$CO), 3.09–3.29 (m, 2H, CH_2SO_2), 3.58 (s, 3H, $COOCH_3$), 3.66 (s, 3H, $COOCH_3$), 3.96–4.06 (m, 1H, CHCO), 4.24–4.36 (m, 1H, *CH*CH_3), 6.07 (s, 2H, OCH_2O), 6.41 (d, 1H, *J*=15.8 Hz, CH*CH*CO), 6.95 (d, 1H, *J*=7.9 Hz, Ar-H), 7.07 (dd, 1H, *J*=7.9, 1.5 Hz, Ar-H), 7.14 (d, 1H, *J*=1.5 Hz, Ar-H), 7.34 (d, 1H, *J*=15.8 Hz, *CH*CHCO), 7.86 (d, 1H, *J*=8.7 Hz, NH), 8.07 (d, 1H, *J*=7.9 Hz, NH); IR (KBr, cm^{-1}): 3276.8, 2953.3, 1735.8, 1654.6, 1616.2, 1491.1, 1447.4, 1251.2, 1148.1, 1037.5, 981.1; FABMS: *m*/*z*=471 $(M+H)^+$; Anal. Calcd for $C_{20}H_{26}N_2O_9S$: C (51.06%), H (5.57%), N (5.95%). Found: C (51.14%), H (5.76%), N (5.86%).

5.7. General procedure for the preparation of peptidosulfonamide inhibitors 21–24. Alkaline hydrolysis of esters

To a stirred solution of dimethyl-protected peptidosulfonamide **17**–**20** (0.4 mmol) in dioxane (2 mL), 1 M NaOH (2 mL) was added, and the reaction mixture was stirred overnight at rt. After the solvent was removed under reduced pressure, the oily residue was redissolved in H_2O (20 mL) and washed with EtOAc (2×20 mL). The aqueous phase was acidified to pH 1–2 using an aqueous solution of 2 M HCl, and extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (1×20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure.

5.7.1. *N*-({(2*S*)-2-[(2-Naphthylsulfonyl)amino]propyl}-sulfonyl)-D-glutamic acid (21). White solid (160 mg, 92%): R_f=0.72 (CH_3CN/MeOH/H_2O=3/1/1); mp 246–248 °C; $[\alpha]_D^{23}$ −44.5 (*c* 0.297, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 1.06 (d, 3H, *J*=6.4 Hz, CH*CH*$_3$), 1.62–1.77 (m, 1H, *CH*$_2$CH$_2$CO), 1.82–1.99 (m, 1H, *CH*$_2$CH$_2$CO), 2.26 (t, 2H, *J*=7.4 Hz, CH$_2$*CH*$_2$CO), 3.07 (dd, 1H, *J*=13.9, 9.0 Hz, CH_2SO_2), 3.20 (dd, 1H, *J*=13.9, 4.0 Hz, CH_2SO_2), 3.58–3.73 (m, 1H, *CH*CH_3), 3.80–3.91 (m, 1H, CHCO), 7.63–8.22 (m, 8H, Naph-H+2×NH), 8.47 (s, 1H, Naph-H), 12.55 (br s, 2H, 2×COOH); IR (KBr, cm^{-1}): 3288.9, 1706.1, 1420.5, 1314.5, 1216.7, 1156.2, 987.9, 821.0, 666.1; FABMS: *m*/*z*=457 $(M-H)^-$; Anal. Calcd for $C_{18}H_{22}N_2O_8S_2$: C (47.15%), H (4.84%), N (6.11%). Found: C (47.05%), H (4.94%), N (6.22%).

5.7.2. *N*-({(2*S*)-2-[([1,1′-Biphenyl]-4-yl-sulfonyl)amino]-propyl}sulfonyl)-D-glutamic acid (22). White solid (170 mg, 92%): R_f=0.76 (CH_3CN/MeOH/H_2O=3/1/1); mp 201–203 °C; $[\alpha]_D^{23}$ −50.1 (*c* 0.316, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 1.11 (d, 3H, *J*=6.8 Hz, CH*CH*$_3$), 1.63–1.81 (m, 1H, *CH*$_2$CH$_2$CO), 1.86–2.02 (m, 1H, *CH*$_2$CH$_2$CO), 2.23–2.33 (m, 2H, CH$_2$*CH*$_2$CO), 3.07 (dd, 1H, *J*=13.9, 9.4 Hz, CH_2SO_2), 3.23 (dd, 1H, *J*=13.9, 3.8 Hz, CH_2SO_2), 3.58–3.71 (m, 1H, *CH*CH_3), 3.79–3.89 (m, 1H, CHCO), 7.40–8.00 (m, 11H, Ar-H+2×NH); IR (KBr, cm^{-1}): 3288.0, 1714.9, 1312.9, 1159.4, 982.5, 765.1, 674.4, 574.8; FABMS: *m*/*z*=486 $(M+H)^+$; Anal. Calcd for $C_{20}H_{24}N_2O_8S_2$: C (49.58%), H (4.99%), N (5.78%). Found: C (49.20%), H (5.10%), N (5.50%).

5.7.3. *N*-{[(2*S*)-2-({2-[2-(Acetylamino)phenoxy]acetyl}-amino)propyl]sulfonyl}-D-glutamic acid (23). White solid (125 mg, 88%): R_f=0.71 (CH_3CN/MeOH/H_2O=3/1/1); mp 108–111 °C; $[\alpha]_D^{23}$ +22.6 (*c* 0.248, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 1.22 (d, 3H, *J*=6.8 Hz, CH*CH*$_3$), 1.66–1.82 (m, 1H, *CH*$_2$CH$_2$CO), 1.90–2.04 (m, 1H, *CH*$_2$CH$_2$CO), 2.11 (s, 3H, CH_3CO), 2.25–2.37 (m, 2H, CH$_2$*CH*$_2$CO), 3.10–3.29 (m, 2H, CH_2SO_2), 3.82–3.94 (m, 1H, CHCO), 4.24–4.39 (m, 1H, *CH*CH_3), 4.51 (s, 2H, OCH_2CO), 6.89–7.12 (m, 4H, Ar-H), 7.85 (d, 1H, *J*=7.5 Hz, SO_2NH), 8.45 (m, 1H, CONH), 9.45 (s, 1H, Ar-*NH*CO); IR (KBr, cm^{-1}): 3386.0, 3224.1, 1717.1, 1652.0, 1536.9, 1263.4, 1158.9, 1050.2, 746.9; FABMS: *m*/*z*=460 $(M+H)^+$; Anal. Calcd for $C_{18}H_{25}N_3O_9S$: C (47.05%), H (5.48%), N (9.15%). Found: C (47.18%), H (5.59%), N (8.76%).

5.7.4. *N*-[((2*S*)-2-{[(*E*)-3-(1,3-Benzodioxol-5-yl)-2-propenoyl]amino}propyl)sulfonyl]-D-glutamic acid (24). White solid (130 mg, 93%): R_f=0.71 (CH_3CN/MeOH/H_2O=3/1/1); mp 115–118 °C; $[\alpha]_D^{23}$ +51.6 (*c* 0.266, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 1.25 (d, 3H, *J*=6.8 Hz, CH*CH*$_3$), 1.73–1.88 (m, 1H, *CH*$_2$CH$_2$CO), 1.92–2.05 (m, 1H, *CH*$_2$CH$_2$CO), 2.38–2.45 (m, 2H, CH$_2$*CH*$_2$CO), 3.09–3.29 (m, 2H, CH_2SO_2), 3.96–4.06 (m, 1H, *CH*CO), 4.24–4.36 (m, 1H, *CH*CH_3), 6.07 (s, 2H, OCH_2O), 6.41 (d, 1H, *J*=15.8 Hz, CH*CH*CO), 6.95 (d, 1H, *J*=7.9 Hz, Ar-H), 7.07 (dd, 1H, *J*=7.9, 1.5 Hz, Ar-H), 7.14 (d, 1H, *J*=1.5 Hz, Ar-H), 7.34 (d, 1H, *J*=15.8 Hz), 7.86 (d, 1H, *J*=8.7, NH), 8.07 (d, 1H, *J*=7.9 Hz, NH); IR (KBr, cm^{-1}): 3314.7, 2965.9, 1717.1, 1653.6, 1525.9, 1448.1, 1338.5, 1252.6, 1123.9, 1038.2, 927.8; FABMS: *m*/*z*=443 $(M+H)^+$; Anal. Calcd for $C_{18}H_{22}N_2O_9S$: C (48.86%), H (5.01%), N (6.33%). Found: C (49.20%), H (5.41%), N (5.96%).

5.8. General procedure for the preparation of peptidosulfonamide inhibitors 14, 15

BBTO cleavage: to a stirred solution of BBTO (3.0 mmol) in toluene (20 mL), dimethyl-protected peptidosulfonamide **12**, **13** (1.0 mmol) was added. The mixture was refluxed for 48 h and the solvent evaporated under reduced pressure. The resulting oil was dissolved in EtOAc (30 mL) and washed with 5% aqueous $NaHCO_3$ (3×20 mL). The aqueous phase was acidified to pH 2–3 using an aqueous solution of 2 M HCl, and extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (1×20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure.

5.8.1. *N*-{[(2*S*)-2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propyl]sulfonyl}-D-glutamic acid (14). Colourless oil (380 mg, 82%): R_f=0.60 (CH_3CN/MeOH/H_2O=3/1/1); $[\alpha]_D^{23}$ +34.5 (*c* 0.330, MeOH); ^{1}H NMR (300 MHz, DMSO): δ 1.46 (d, 3H, *J*=6.8 Hz, CH_3), 1.65–1.79 (m, 1H, *CH*$_2$CH$_2$CO), 1.92–2.05 (m, 1H, *CH*$_2$CH$_2$CO), 2.25–2.37 (m, 2H, CH$_2$*CH*$_2$CO), 3.46 (dd, 1H, *J*=14.3, 4.7 Hz, CH_2SO_2), 3.80 (dd, 1H, *J*=14.3, 9.0 Hz, CH_2SO_2), 3.85–3.93 (m, 1H, CHCO), 4.66–4.80 (m, 1H, *CH*CH_3), 7.75 (d,

1H, J=9.1 Hz, NH), 7.81–7.91 (m, 4H, Pht-H), 12.50 (br s, 2H, 2×COOH); IR (KBr, cm^{-1}): 3528.4, 1704.3, 1396.8, 1152.4, 1022.2, 722.7; FABMS: m/z=399 $(M+H)^+$; Anal. Calcd for $C_{16}H_{18}N_2O_8S$: C (48.24%), H (4.55%), N (7.03%). Found: C (48.50%), H (4.65%), N (6.80%).

5.8.2. *N*-{[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-ethyl]sulfonyl}-D-glutamic acid (15). White solid (320 mg, 85%): R_f=0.60 ($CH_3CN/MeOH/H_2O$=3/1/1); mp 81–84 °C; $[\alpha]_D^{23}$ +7.8 (c 0.355, MeOH); ^1H NMR (300 MHz, DMSO): δ 1.70–1.85 (m, 1H, CH_2CH_2CO), 1.92–2.10 (m, 1H, CH_2CH_2CO), 2.20–2.30 (m, 2H, CH_2CH_2CO), 3.20–3.40 (m, 2H, CH_2SO_2), 3.95–4.05 (m, 3H, NCH_2+CH), 7.75–7.91 (m, 5H, NH+Pht-H), 12.45 (br s, 2H, 2×COOH); IR (KBr, cm^{-1}): 3288.8, 1691.6, 1442.8, 1406.7, 1142.6, 976.2, 720.8; FABMS: m/z=383 $(M-H)^-$; Anal. Calcd for $C_{16}H_{18}N_2O_8S$: C (46.87%), H (4.17%), N (7.29%). Found: C (47.20%), H (4.50%), N (7.05%).

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RuO_4-mediated oxidative polycyclization of linear polyenes. A new approach to the synthesis of the bis-THF diol core of antitumour cis–cis adjacent bis-THF annonaceous acetogenins

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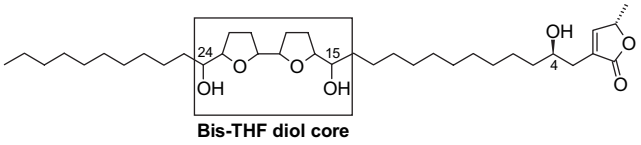
Abstract—The RuO_4-catalyzed oxidative polycyclization of some selected linear polyenes, possessing a repetitive 1,5-diene structural motif, has been investigated. The all-*trans* triene (*E*,*E*,*E*)-acetic acid henicosa-2,6,10-trienyl ester gave the expected bis-tetrahydrofuranyl diol product possessing a *threo-cis-threo-cis-threo* relative configuration, along with a mixture of the corresponding bis-THF ketols. These compounds can be seen as useful intermediates in the synthesis of the bis-THF diol core of adjacent bis-THF antitumour acetogenins possessing a *threo-cis-threo-cis-erythro* relative configuration, such as rolliniastatiin-1, membranacin, rollimembrin and membrarollin. Oxidation of the related all-*trans* tetraene (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester stops at the second cyclization step giving a mixture of a *threo-cis-threo-cis-threo* bis-THF diol and the corresponding ketol products. Oxidation of the triene (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester stops at the monocyclization level failing to give bis-cyclized products, as previously observed for the related isoprenoid triene (*E*,*Z*)-farnesyl acetate. This result confirms the difficulty of closing a second THF ring when the central double bond of the triene possesses a cis configuration. Based on the collected results, a plausible model is proposed that both explains the observed cis/trans stereoselectivity for each ring-closing step in these processes, and rationalize the stereochemical course of the previously studied polycyclization of the isoprenoid polyenes (*E*,*E*)-farnesyl acetate, geranylgeranyl acetate and squalene.

1. Introduction

Annonaceous acetogenins (ACGs) are a group of secondary metabolites isolated from plants of the family *Annonaceae* many of which exhibit high cytotoxic and impressive antitumour activities.[1] The biological effect of these substances are attributed to the inhibition of mammalian mitochondrial NADH-ubiquinone oxidoreductase (complex I), a membrane-bound protein of the mitochondrial electron transport system,[2] and to the inhibition of an ubiquinone-linked NADH oxidase expressed in the plasma membrane of cancerous cells but only transiently expressed in the membranes of 'normal' cells.[3] These mechanisms result in ATP deprivation leading to apoptosis (programmed cell death) in the high energy demanding malignant cells.[4]

From a structural point of view, they are mostly made up of a mono- or bis-THF core flanked by two long alkyl chains, one of which ending with an α,β-unsaturated γ-lactone ring, usually carrying hydroxyl groups along their length (Fig. 1).



Bis-THF diol core

Figure 1. Structural features of some representative adjacent bis-THF ACGs with high antitumour activity. Configuration of the bis-THF diol core (from C_{24} to C_{15}): asimicin *threo–trans–threo–trans–threo*; bullatacin *erythro–trans–threo–trans–threo*; trilobacin *threo–cis–erythro–trans–threo*; rolliniastatin-1 *erythro–cis–threo–cis–threo*.

A common feature shared by the ACGs possessing the highest anticancer activity is the presence of a bis-THF diol portion: two adjacent THF rings each one flanked by a hydroxyl-bearing methine group (Fig. 1). This subgroup is very abundant amounting to more than 40% of all known metabolites of this type. Representative examples of this type of ACGs are asimicin, bullatacin, trilobacin and rolliniastatin-1, only differing in the configuration of the bis-THF diol core (Fig. 1); all these substances have shown an in vitro antitumour potency 10^8 times higher than that exhibited by adriamycin.[5]

The selectivity shown towards diverse human tumour cell lines,[1] including those that exhibit multidrug resistance

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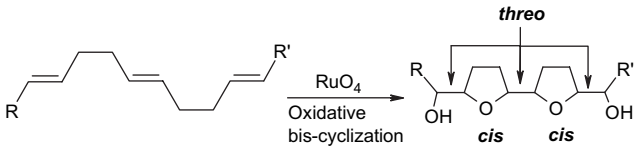
(MDR),[6] as well as their ability to only modestly affect the normal human cells growth,[6] has prompted many research groups to undertake the total synthesis of these substances or to search for suitable analogues to be tested in SAR studies.[7]

Only few adjacent bis-THF ACGs have been isolated that possess an *erythro–cis–threo–cis–threo* relative configuration, for example, rolliniastatin-1, rollimembrin, membrarollin, membranacin; however, they are among the most effective substances of this type. Compared to other annonaceous acetogenins, which are popular targets for total synthesis, there has been limited synthetic activity towards these substances possibly due to the challenges posed by the *erythro–cis–threo–cis–threo* relative configuration of their bis-THF diol portion.

Recently, we have discovered a novel oxidative polycyclization (OP) process involving catalytic amounts of RuO_4 that allows to obtain, in a single step, all-*threo* adjacently linked poly-tetrahydrofuran diol (poly-THF diol) compounds starting from isoprenoid polyenes characterized by a repetitive 1,5-diene structural motif such as (*E*,*E*)-farnesyl acetate [(*E*,*E*)-FA], geranylgeranyl acetate (GGA) and squalene (Scheme 1).[8]

We reasoned that this process could be usefully employed for the synthesis of the bis-THF diol core of the aforementioned cis–cis adjacent bis-THF ACGs provided that it could work well for the OP of linear 1,5,9-trienes as well. In particular, based on the stereochemical course of the first two ring-forming steps in the OP of the above-cited isoprenoid polyenes (a cis–cis bis-THF sequence is obtained in all cases; see Scheme 1),[8] as well as the cis-stereoselectivity of the THF-forming step in the RuO_4-mediated oxidative monocyclization of linear 1,5-dienes,[9] it was expected that a cis,cis adjacent bis-THF diol product would have been obtained from an all-*trans* 1,5,9-triene. In addition, according to the mechanistic hypothesis previously formulated for these cyclizations (*syn* addition of oxygen across each double bond), substantiated by stereochemical evidence collected for all the previously studied OP, it was also expected that this product would possess an all-*threo* arrangement (Scheme 2). In this paper we report on our studies towards this goal.

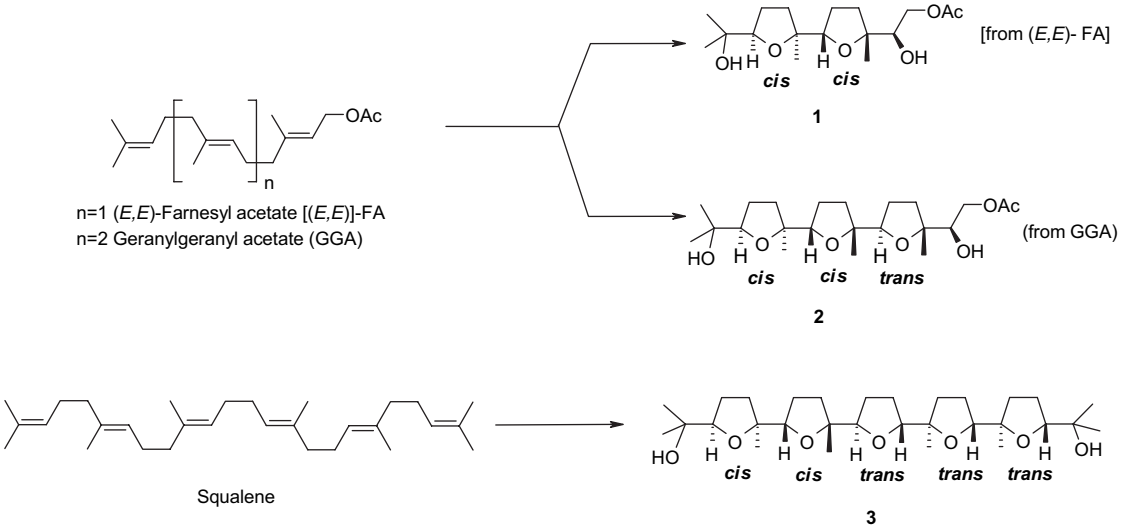


Scheme 2. Expected bis-THF diol product from the RuO_4-catalyzed bis-cyclization of an all-*trans* 1,5,9-triene.

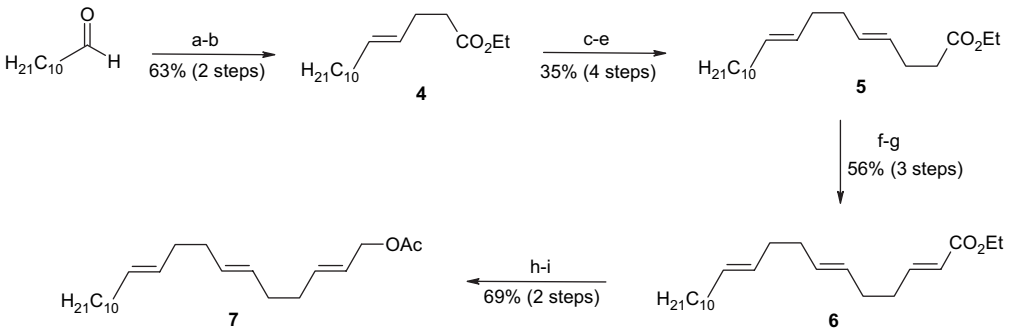
2. Results and discussion

In order to probe the above hypothesis, (*E*,*E*,*E*)-acetic acid henicosa-2,6,10-trienyl ester (**7**) was synthesized as described in the literature for the C_{21} alcohol analogue,[10] starting from undecanal (Scheme 3). Cyclization of triene **7** would have allowed to access a *threo–cis–threo–cis–threo* bis-THF diol product possessing a C_{10} saturated alkyl chain (Scheme 2: R=$C_{10}H_{21}$; R′=CH_2OAc) characterizing rolliniastatin-1-type ACGs.

In particular, Grignard reaction of undecanal with vinylmagnesium bromide followed by *ortho* ester Claisen–Johnson rearrangement of the obtained allylic alcohol allowed elongation of a four-carbon fragment and concomitant stereoselective formation of the first trans double bond to give monounsaturated ester **4**. Conversion of **4** to the double unsaturated ester **5** was accomplished in four steps: transformation of **4** to the corresponding aldehyde (LAH reduction followed by PCC oxidation) followed by the two-step sequence used for the conversion of undecanal into **4**. Then, conversion of **5** into the corresponding aldehyde, as above seen for **4**, followed by Wittig–Horner olefination with triethyl phosphonoacetate gave the all-*trans* triple unsaturated ester **6**. Dibal-H reduction of this one followed by acetylation yielded the required triene **7**.



Scheme 1. Summary of the RuO_4-catalyzed polycyclization of some isoprenoid polyenes. Reagents and conditions: (*E*,*E*)-FA: $RuO_2 \cdot 2H_2O$ (20 mol %), $NaIO_4$ (4 equiv), CH_3CN–EtOAc–H_2O (3:3:1), 0 °C, 30 min. GGA and squalene: as for (*E*,*E*)-FA but $NaIO_4$ 5 equiv and 8 equiv, respectively.



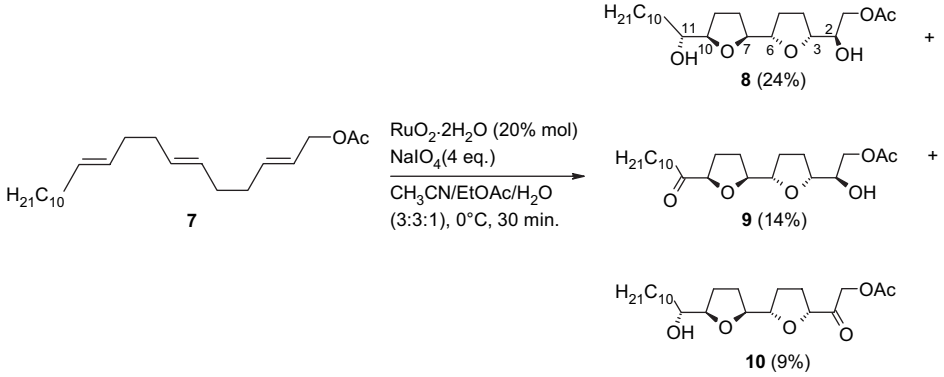
Scheme 3. Synthesis of (*E*,*E*,*E*)-acetic acid henicosa-2,6,10-trienyl ester (**7**). Reagents and conditions: (a) vinylmagnesium bromide, THF, 0 °C; (b) triethyl orthoacetate, propyonic acid (2%), xylene, reflux; (c) $LiAlH_4$, Et_2O, 0 °C→rt; (d) PCC, Celite, CH_2Cl_2, rt; (e) same as for sequence a–b; (f) same as for sequence c–d; (g) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 °C→rt; (h) DIBAL-H, THF, −78 °C; (i) Ac_2O-py, rt.

Oxidation of **7** under the standard conditions previously set up for (*E*,*E*)-FA[8a] (Scheme 4), followed by HPLC separation of the reaction mixture, gave diol **8** as the main bis-THF product (24%) along with the corresponding isomeric bis-THF ketols **9** and **10** (together 23%). The overall 47% yield is not too far from that obtained for (*E*,*E*)-FA (56%) in the same conditions;[8a] the slightly less yield probably reflects the efficiency of the first THF-closing step, in agreement with the difference in the yields previously observed for the monocyclizations of alkylsubstituted 1,5-dienes, such as geranyl acetate,[9b,9c] and linear 1,5-dienes,[11] with RuO_4. The structural relationship among the three bicyclic products **8**–**10** was proven by oxidation of **8** to a mixture of **9** and **10** with $TPAP_{(cat.)}$/NMO.

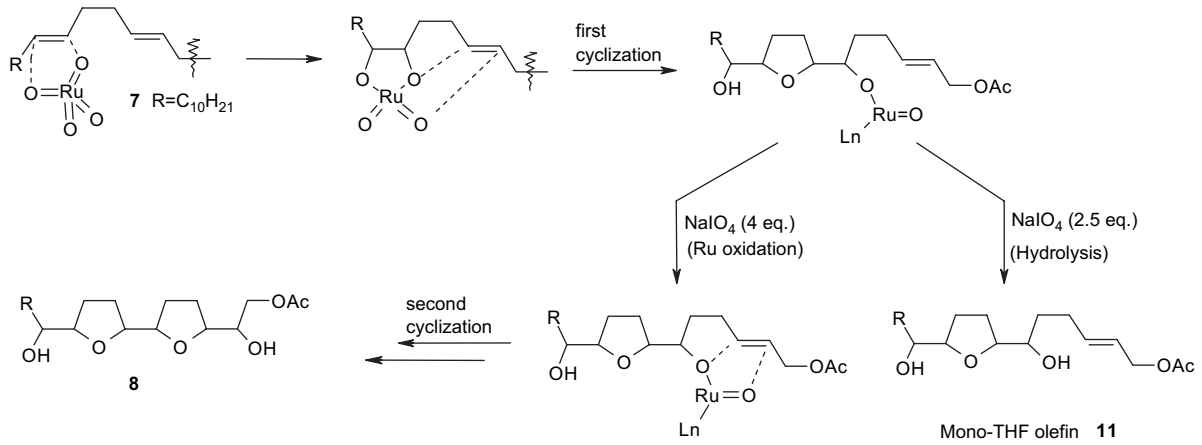
In order to establish the relative configuration of **8** a detailed 2D-NMR analysis of this compound was accomplished. In particular, a resonance specific assignment was achieved using two-dimensional COSY, TOCSY, ^1H–^{13}C HSQC and ^1H–^{13}C HMBC NMR experiments. Subsequently, to assess the stereo-relationship around the bis-THF portion, 2D-ROESY experiments were carried out for **8** both in $CDCl_3$ and DMSO-d_6. In agreement with our expectations, and previous results obtained with related molecules, the experiment performed in $CDCl_3$ evidenced correlations between the resonances at δ 4.02 (H-3) and δ 3.94 (H-6), and between those at δ 3.91 (H-7) and δ 3.81 (H-10) that suggested a cis arrangement for both the proton pairs H-3/H-6 and H-7/H-10 and, therefore, a cis–cis sequence for the two contiguous THF rings. Confirmatory evidences arose from a high-quality 2D-ROESY spectrum performed in DMSO-d_6, which showed the same correlation peaks observed in the ROESY spectrum of **8** recorded in $CDCl_3$.

In an attempt to further increase the yield of the process the effect of ruthenium dioxide and periodate amounts was evaluated (Scheme 5). The increase of the amount of RuO_4, up to one equivalent, had no significant effect on the overall yield of the process and the HPLC profile of the bis-cyclization products. On the other hand, as observed for the oxidation of isoprenoid analogues,[8] reduction of the amount of the co-oxidant (from 4 to 2.5 equiv) depresses the second cyclization step, in accord with the hypothesis that oxidation at ruthenium is indispensable for the process to go ahead, as shown in Scheme 5. In fact, in these conditions mono-THF olefin **11** was obtained as the main reaction product (18%) along with the corresponding ketols (overall 9%), as an inseparable mixture while bis-THF diol **8** was only obtained in a 3% amount. Lower yields in the THF-containing material is probably to be attributed to the further RuO_4 oxidation of the mono-THF compounds at their olefin function.

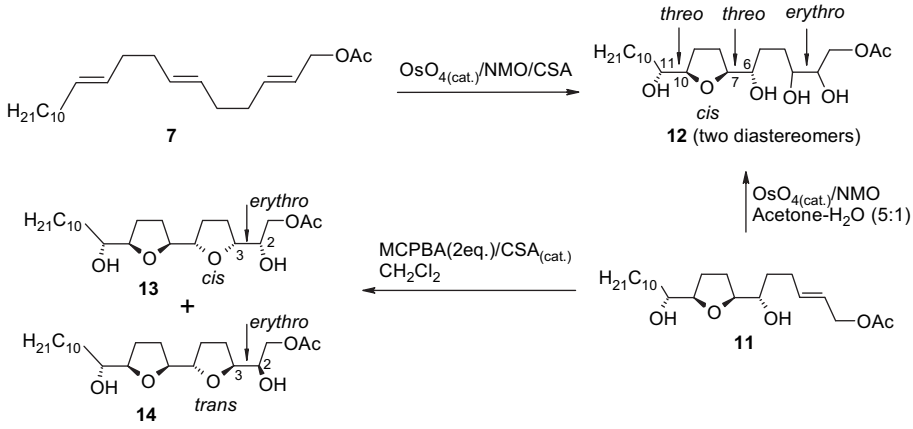
Definitive confirmation for the expected all-*threo* arrangement for compound **8** was provided by simple chemical transformations strictly similar to those previously carried out on isoprenoid analogues (Scheme 6). In particular, cis-stereoselective monocyclization of **7** with $OsO_{4(cat.)}$/NMO/CSA[12] afforded a mixture of diastereomeric mono-THF tetrols **12**, derived from THF-diol formation and further dihydroxylation of the Δ^2 double bond, that resulted identical to the dihydroxylation products of **11** with $OsO_{4(cat.)}$/NMO. This secured a *threo–cis–threo* arrangement for compound **11** and, therefore, this configuration could be inferred for the bis-THF diol **8** as well. The remaining C2/C3 *threo* relationship in **8** was secured by the different spectral and chromatographic (HPLC) properties exhibited by the two C2/C3



Scheme 4. RuO_4-mediated oxidative bis-cyclization of (*E*,*E*,*E*)-acetic acid henicosa-2,6,10-trienyl ester (**7**).



Scheme 5. Proposed mechanism for the bis-cyclization and partial cyclization of triene **7**.



Scheme 6. Demonstration of the all-*threo* arrangement of compound **8**.

erythro bis-THF diol isomers of **8** (**13** and **14**, Scheme 6), synthesized by treatment of mono-THF olefin **11** with MCPBA (2 equiv)/$CSA_{(cat.)}$ in CH_2Cl_2 (one-step epoxidation/acid-catalyzed THF formation), and compound **8** itself.

In summary, our approach to a bis-THF diol fragment suitable for further synthetic elaboration along the route to cis–cis ACGs features the formation of all six chiral centres (five when ketols are formed) of the bis-THF diol portion in a single, stereoselective, step. The starting all-*trans* triene, (*E*,*E*,*E*)-acetic acid henicosa-2,6,10-trienyl ester, is obtained following an easy-to-carry-out procedure based on an iterative reaction sequence that makes use of many inexpensive reagents (the starting aldehyde, PCC, Ac_2O, triethyl orthoacetate). The starting triene is achiral and formation of all chiral centres is deferred to a final single reaction, a ruthenium-catalyzed oxidative bis-cyclization where the true oxidant is sodium periodate, a product commercially available at low price. Only seven different reactions are involved into the synthesis of the starting triene and yields are overall good when considering the cost of the reagents employed. In addition, the right-hand part of our bis-THF diol fragment is functionalized in such a way to allow attachment of the remaining, γ-lactone-containing, portion following, for example, a rather short reaction sequence similar to that recently employed by Brown et al. in the synthesis of membranacin.[13] Only the inversion of configuration at C-24 (Fig. 1), a synthetic manoeuvre generally easy to carry out through well-known chemistry, needs to be accomplished to fix the C-23/C-24 *erythro* relationship that characterizes rolliniastatin-1-type ACGs.[14,15] On the other hand, adjustment of the oxidation state and generation of the proper configuration at the C-2 or C-11 centres in both ketols **9** and **10** can allow the synthetic use of these materials as well, either in the synthesis of the above-cited substances or of their C-15 unnatural epimers. In fact, production of a complete library of adjacent bis-THF acetogenins, and evaluation of their biological properties, appears an important synthetic goal towards which some research groups are currently addressing their efforts.[16]

It seems also worth mentioning that bis-THF diol **8** possesses the same relative configuration as that found in squamocin-N,[17] the sole known ACG with a *threo–cis–threo–cis–threo* configuration of the bis-THF diol portion, whose synthesis has not yet been accomplished (Fig. 2).

Having ascertained the ability of the $RuO_{2(cat.)}/NaIO_4$ oxidizing system to induce the bis-cyclization of the all-*trans* triene **7**, we were interested in probing whether the related all-*trans* tetraene (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester (**16**, Scheme 7) could also be tris-cyclized in the same conditions, as it happens for the isoprenoid tetraene GGA (Scheme 1). This compound was

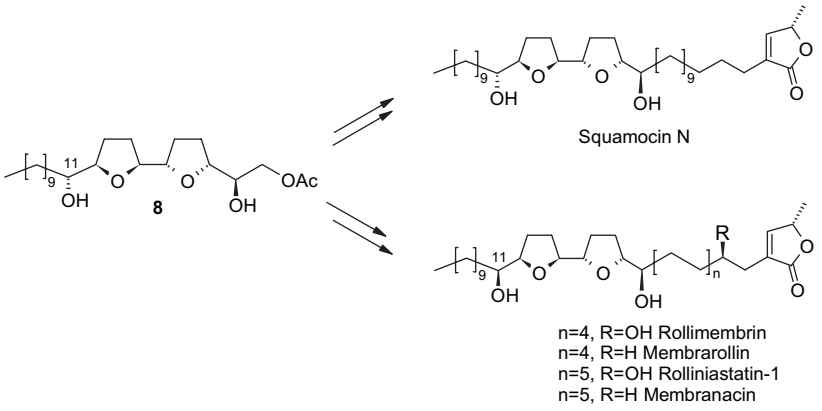
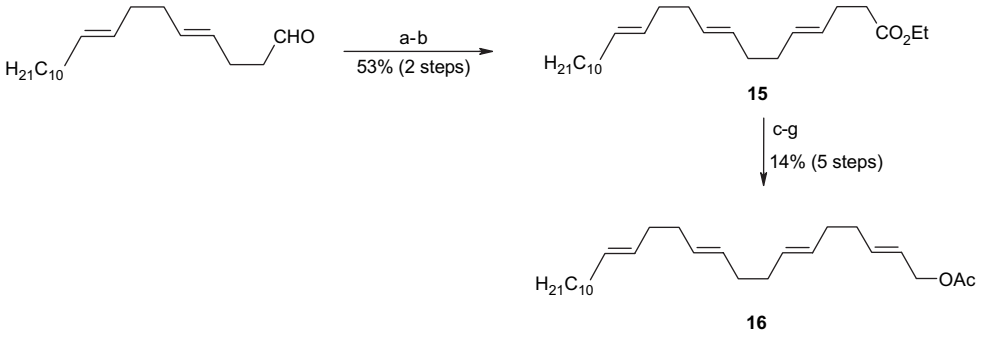


Figure 2. Bis-THF diol **8** can be further elaborated for the synthesis of some cis–cis adjacent bis-THF ACGs.

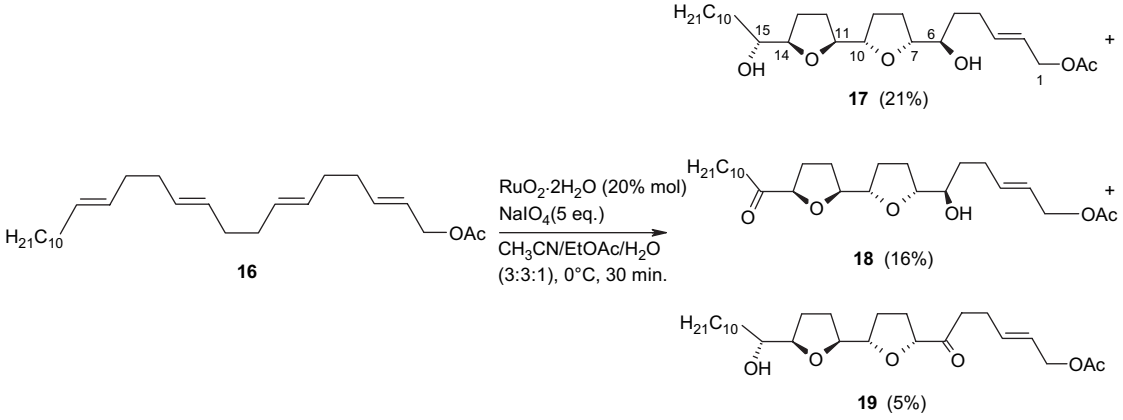
synthesized as depicted in Scheme 7 starting from (*E*,*E*)-nonadeca-4,8-dienal, an intermediate of the synthesis of triene **7**, through the same chemistry employed for the synthesis of the latter, and then subjected to RuO_4 oxidation (Scheme 8). According to the mechanism hypothesized for the process (Scheme 5) and precedents from the oxidation of GGA, the presence of one more double bond in **16**, a 5 equiv amount of co-oxidant (one more equivalent compared to **7**) was expected to be required.

Unexpectedly, contrary to what happens for GGA,[8a] no tris-THF product was obtained from the oxidation of **16**. The process stopped at the bis-cyclization level giving the three related bis-THF compounds **17–19** in an overall 42% yield (Scheme 8). The order of abundance for these products is the same observed for compounds **8–10** obtained from the oxidation of triene **7**: bis-THF diol **17** was the main oxidation product (21%) followed by ketol **18** (16%), with the keto group next to the C_{10} alkyl chain, and ketol **19** (5%). The structural relationship among compounds **17–19** was once again proven by oxidation of **17** to a mixture of **18** and **19** with TPAP/NMO.

Compounds **17–19** were subjected to the same set of 2D-NMR experiments performed for **8**. In particular, inspection of the ROESY spectrum of **17** revealed a strong correlation peak between resonances at δ 3.83 and 3.89 that, due to the pseudo-symmetry of the molecule around its bis-THF diol



Scheme 7. Synthesis of (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester **16**. Reagents and conditions: (a) vinylmagnesium bromide, THF, 0 °C; (b) triethyl orthoacetate, propyonic acid (2%), xylene, reflux; (c) $LiAlH_4$, Et_2O, 0 °C→rt; (d) PCC, Celite, CH_2Cl_2, rt; (e) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 °C→rt; (f) DIBAL-H, THF, −78 °C; (g) Ac_2O-py, rt.

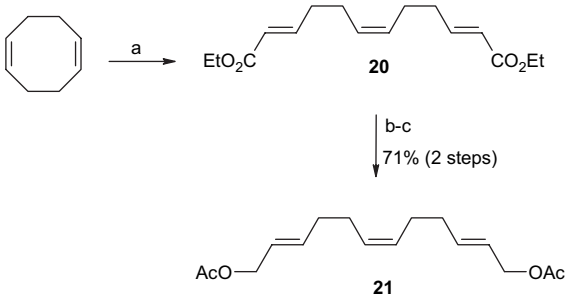


Scheme 8. RuO_4-mediated oxidative bis-cyclization of (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester **16**.

portion, accounted for the H-7/H-14 and H-10/H-11 proton pairs, respectively. This observation preliminarily suggested a cis–cis arrangement of the two adjacent rings. The unambiguous confirmation of this arrangement came from the analysis of ROESY spectra of ketols **18** and **19**. In particular, a strong ROE correlation peak between resonances at δ 4.38 (H-14) and δ 3.95 (H-11) suggested the cis relationship of this proton pair in **18**. The cis relationship between protons H-14 and H-11 was also settled in **19** due to the presence of a cross peak between resonances at δ 3.83 (H-14) and δ 3.92 (H-11). Finally, the cis arrangement of protons H-7 and H-10 in **19** was established thanks to the correlation between resonances at δ 4.37 (H-7) and δ 3.94 (H-10) observed in its ROESY spectrum. Therefore, based on all previous stereochemical evidence for bis-THF diol **8**, isoprenoid poly-THF diols **1**–**3** and the hypothesized mechanism (Scheme 5), an all-*threo* cis–cis relative configuration was assumed for compounds **17**–**19**.

An increasing of RuO_4 up to 50% seems not to affect this process as well, while increasing of the co-oxidant only produces the formation of some more polar products tentatively identified as the dihydroxylation products of initially formed **17**–**19** at their Δ^2 double bond. It cannot be excluded that a further increasing of yields of **17**–**19** could be obtained by employing a minor (4 equiv) amount of co-oxidant (the amount usually used for the bis-cyclization of trienes). This should prevent the residual double bond being further attacked by the oxidant with consequent yield improvement. However, for the time being these conditions were not further explored.

Finally, we probed our oxidative process on (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester (**21**, Scheme 9),



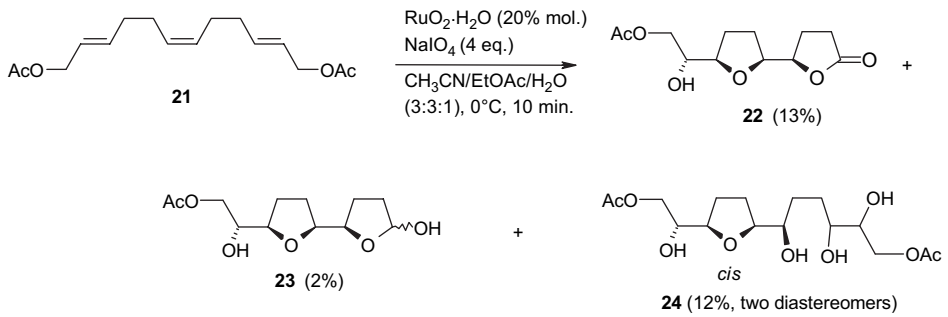
Scheme 9. Synthesis of (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester (**21**). Reagents and conditions: (a) O_3, $CHCl_2$, −78 °C then PPh_3, 1 h, then Ph_3PCHCO_2Et; (b) DIBAL-H, THF, −78 °C; (c) Ac_2O–py, rt.

an easily accessible model triene with the central cis double bond. In particular, we wanted to ascertain whether the change in the configuration of the central double bond from trans (as is in triene **7**) to cis would have affected the cyclization process as had happened for the related isoprenoid triene (*E*,*Z*)-FA,[8b] for which the oxidative process stops at the monocyclization level, contrary to what happened for its isomer (*E*,*E*)-FA that gives a bis-cyclized product (Scheme 1).

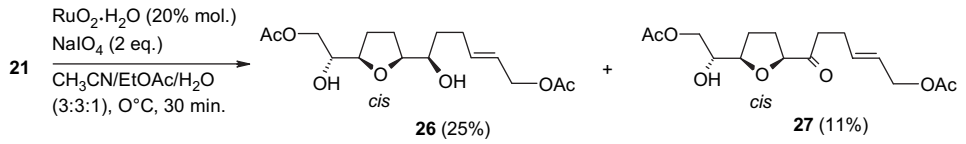
The required compound **21** was synthesized by acetylation of diester **20** in turn obtained starting from commercially available 1,5-cyclooctadiene, following a reported procedure (Scheme 9)[18] and subjected to oxidation with the usual conditions (Scheme 10). HPLC separation of the reaction mixture afforded the structurally related lactone **22** and lactol **23**, in a disappointingly overall 15% yield along with a mixture of THF tetrols **24** (12%) as the main products. All these compounds can be seen to originate from the further attack of the oxidant at the double bond of the initially formed monocyclized product (THF-olefin **26**, Scheme 11) indicating that the process stops at the first cyclization step, in line with the previously observed reactivity of (*E*,*Z*)-FA. No further detailed studies were carried out to ascertain the identity of the remaining material required for mass balance. However, ^1H NMR analysis of some partially purified (HPLC) side products indicated that they could derive from oxidation of the double bond of the initially formed mono-THF olefin **26**, followed by its further evolution.

Therefore, we could conclude that the presence of a cis double bond, immediately following a trans one in the polyenic chain (at least when the latter occupies the Δ^1 position), represents an obstacle for a further cyclization step to take place, irrespective of the fact that the substrate be isoprenoid, such as (*E*,*Z*)-FA, or linear, such as compound **21**.

In one case, the oxidation of **21** gave, besides compounds **22**–**24**, the expected bis-cyclized product **25** (Fig. 3), though in a very low yield (ca. 1%). Unfortunately, we were unable to reproduce this result. Referring to this experiment, it is important to say that careful HPLC and NMR analyses showed that compound **25** was the sole bis-THF product obtained. Accurate 2D-NMR analyses, ES-MS spectra, and symmetry considerations pointed to the bis-THF diol structure **25** for this compound. In particular, the proton spectrum recorded in $CDCl_3$ included, as expected, two acetate signals at 2.087 and 2.093 ppm and 10 distinct resonances for protons geminal to oxygen height of which spanning between



Scheme 10. RuO_4-mediated oxidative cyclization of triene **21**.



Scheme 11. Partial oxidative cyclization of triene **21**.

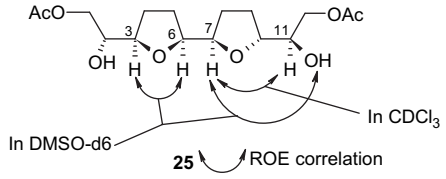


Figure 3. Significant ROE correlations for bis-THF **25**.

3.95 and 4.30 ppm (2×C*H*$_2$OAc and four THF protons) and two in the range 3.62–3.73 attributable to the two C*H*–OH protons. 2D-ROESY experiments carried out both in $CDCl_3$ and DMSO-d_6 showed strong ROE correlation peaks between resonances for the proton pairs H-3/H-6, H-7/H-11 and H-7/OH-11 as shown in Figure 3. This, in conjunction with the absence of a correlation between the H-7 and H-10 protons, were clear evidence for the cis–trans relative configuration of the THF pair. On the other hand, symmetry considerations excluded the structures with *threo–trans–erythro–trans–threo* and *threo–cis–erythro–cis–threo* configuration, incompatible with the observed NMR characteristics of **25**. The presence of a *cis*-THF is also in line with the structure of all the related compounds **22**–**24**, derived from the oxidation of **21**, where the THF ring from the first cyclization invariably possesses a cis configuration.

The above results indicate that, at the present level of optimization, the oxidation of **21**, can hardly have synthetic value; nevertheless, formation of bis-THF **25** has mechanistic relevance as will be explained in the next section.

Stopping oxidation of **21** at the first ring-closing step may have synthetic value, provided that the first-formed mono-THF product does not undergo overoxidation. We reasoned that the use of a lesser amount of periodate (2 equiv) could induce the formation of the first THF ring preventing the successive oxidation of the remaining olefin function. Under these conditions, a mixture of mono-THF olefin compounds **26** and **27** in a 36% overall yield along with a 35% of unreacted triene (Scheme 11). This process is unoptimized but further improvements appear to be feasible by suitably tuning the co-oxidant amount and reaction times.

It is interesting to note that, due to the type of functionalisation at both termini, mono-cyclized products **26** and **27** lend themselves to further synthetic manipulations. In particular, the *threo–cis–erythro* stereochemical relationship around the mono-THF portion suggests their use for the synthesis of acetogenins of the type trilobin and trilobacin (Fig. 4) by using, for example, previously reported chemistry.[5a]

Finally, the structural relationship among compounds **23**–**25** was proven as shown in Scheme 12, through simple chemical transformations involving OsO_4 chemistry.

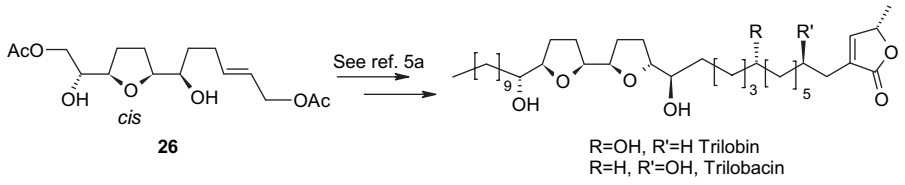
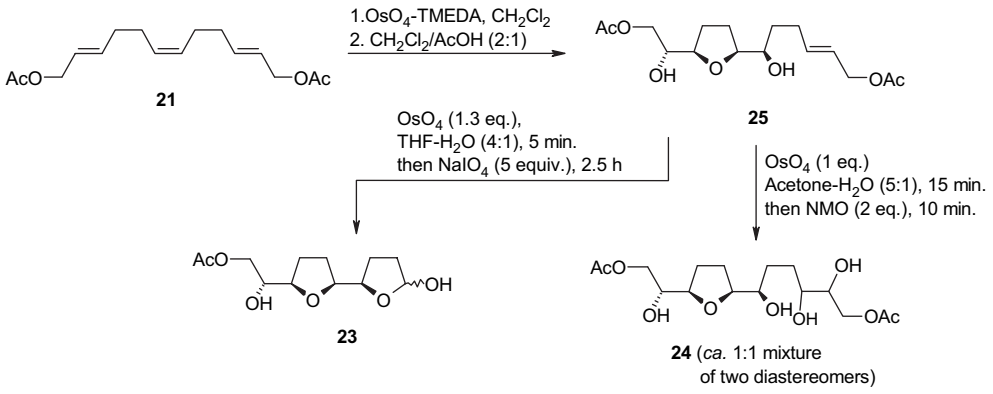


Figure 4.



Scheme 12. Chemical correlation of compounds **23**–**25**.

2.1. An explanation for the diastereoselectivity observed in the OP of polyenes with a repetitive 1,5-diene motif

The following points, emerged, both in the present and in our previous related studies on the OP of isoprenoid polyenes,[8] which need to be explained.

(a) Why in all the studied cases (isoprenoid or linear polyenes) the first two THF rings are invariably obtained with a cis selectivity;
(b) Why a cis double bond immediately following a trans one, as in (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester **21** and in (*E*,*Z*)-FA, prevents the second cyclization step to take place;
(c) Why for the all-*trans* tetraene (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester **16** the polycyclization stops at the bis-THF level contrary to what happens for the isoprenoid analogue GGA that gives a tris-THF product.

2.2. Model for the cis-selective first cyclization

We will now try to give a plausible explanation of the above points taking into account previously developed models for the rhenium(VII)-mediated oxidative cyclization of hydroxy-polyenes[19] as well as reported oxidative chemistry for related metal oxo-species.[9]

The cis selectivity observed for the first cyclization step could be explained as shown in Figure 5. We cannot know the oxidation state of ruthenium during each cyclization step; however, the oxidation states +6 or +8 appear to be the most plausible.[20] Assuming an octahedral geometry for ruthenium[21] in the first-formed Ru(VI) diester **28** and a chair-like conformation of the molecule in the transition state for the cyclization step,[19] a [3+2] cycloaddition,[21] the correct positioning of the double bond involved in the THF closure, close to an O═Ru–O portion, can only occur in the stereochemical arrangement **29**. Though this arrangement suffers for steric repulsions of the pseudoaxially disposed C-2 carbon (numeration relative to the isoprenoid substrate), this appears not to hamper the cyclization event also in isoprenoid polyenes (R=Me). On the other hand, arrangement **31**, similar to **29**, can also exist where the C(2)O–Ru bond underwent hydrolytic cleavage (see **30**) and the free C(2)–OH group is still coordinated to ruthenium, that also would lead to a *cis*-THF.

It is to be noted that the ruthenium ester species **30** could, in principle, also lead to a *trans*-THF via arrangement **32**. In fact, this species is strictly similar to the perrhenate ester involved into the *trans*-diastereoselective cyclization of bishomoallylic alcohols promoted by rhenium (VII) oxo-species. In this case, the steric control model formulated by McDonald[10b,19c] (Fig. 6) could be invoked, with the molecule

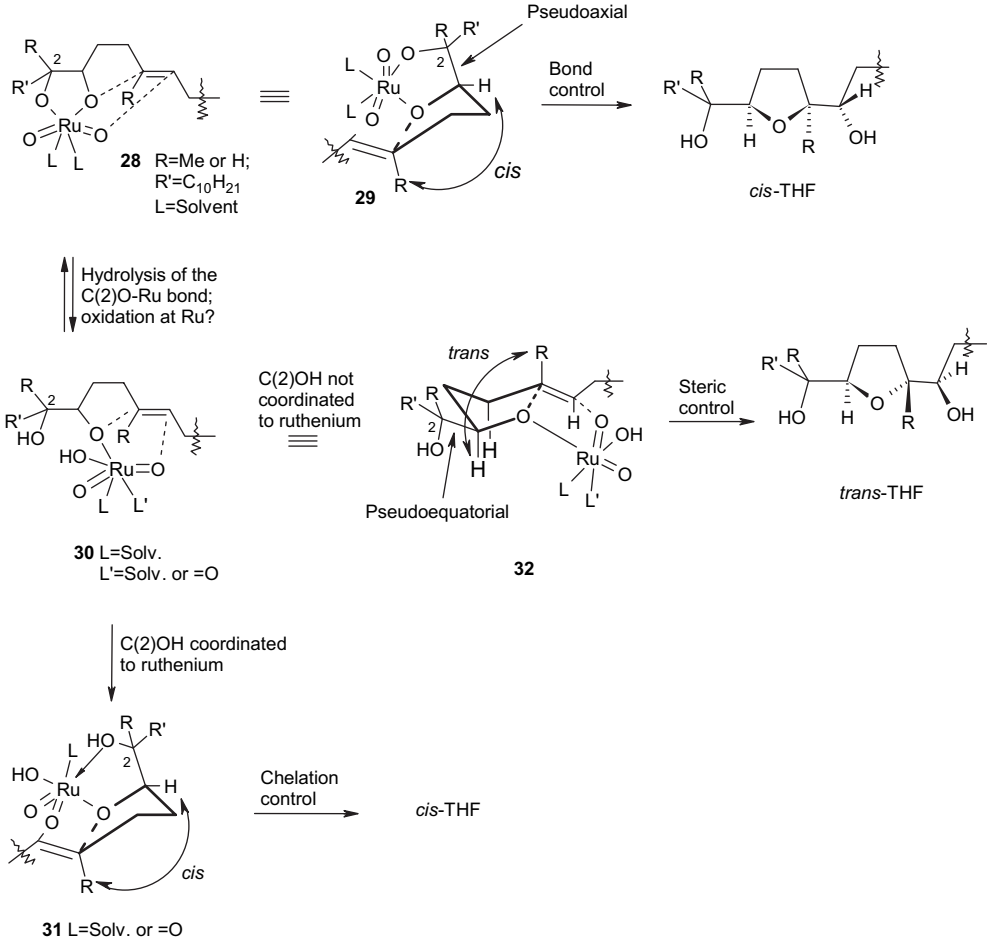


Figure 5. Chelation versus steric control in the first cyclization step of RuO_4-mediated OP process.

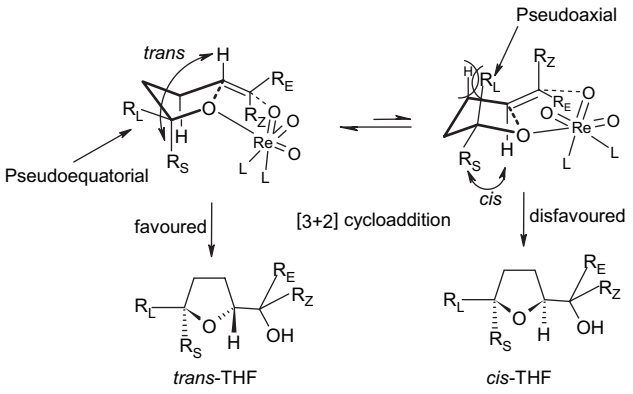


Figure 6. Steric control model for a trans-diastereoselective cyclization of bishomoallylic alcohols promoted by rhenium (VII) oxo-species.[19c]

preferably adopting an arrangement with the bulk group (RR′CHOH) at C-3 pseudoequatorially disposed in the chair-like transition state **32**. That an equilibrium **28/30/32** could exist is substantiated by the formation of minor amounts of *trans*-THF products both in the RuO_4-mediated monocyclization of 1,5-dienes[9] and the partial oxidative cyclization of (*E*,*E*)-FA with the same reagent.[8a] It is also interesting to note here that strictly related monocyclizations processes of 1,5-dienes in the presence of OsO_4,[22] MnO_4^- [23] and RuO_4^- [24] evidently proceed through an intermediate such as **28/29** since the formation of *trans*-THF products has never been observed for these processes a fact that render the involvement of the open ester form **30**, in these cases, not plausible.

The above model is also in accordance with the stereochemical course of the strictly related oxidative cyclization processes promoted by Cr(VI) oxo-species (Fig. 7, top).[25] In particular, the monocyclization of 1,2-dihydroxyalkenes to *cis*-THF's can be explained through the formation of a chromium monoester such as **33** where the coordination of the C-2 OH group to the metal forces the molecule to adopt a spatial arrangement analogous to **31**, thus ensuring the closure of a *cis*-THF ring.[10b] It is to be said, however, that the involvement of a cyclic diester species of the type **28/29** cannot be ruled out in this process as well, owing to the bidentate character of the dihydroxyalkene. Conversely, the same authors reported that the cyclization of a monodentate hydroxydiene such as **34** with PCC[25d] gives a *trans*-THF product (Fig. 7, bottom). In this case, due to the absence of a coordinating OH group, the path depicted for rhenium (VII) in Figure 6 (steric control, trans-selectivity) would be followed.

In conclusion, the first cyclization step of the RuO_4-involving process appears to be under chelation control, if species **31** is involved, or under bond control (C(2)O–Ru bond), if species **28** is involved. On the other hand, when formation of a *trans*-THF is observed, as in related RuO_4-mediated monocyclization of polyenes,[8a] a steric control should be operative via an intermediate of the type **32**.

2.3. Model for the cis-selective second cyclization

As for the second cyclization step, once again it can be speculated that the C(2)O–Ru bond could either be unbroken or already cleaved. The observed cis-selectivity for this step would be explained by either arrangements **35** (C(2)O–Ru intact) or **36** (C(2)O–Ru cleaved) (Fig. 8). As far as arrangement **35** is concerned, the C(2)O–Ru bond imposes the closure of a *cis*-THF ring, irrespective of the fact that the

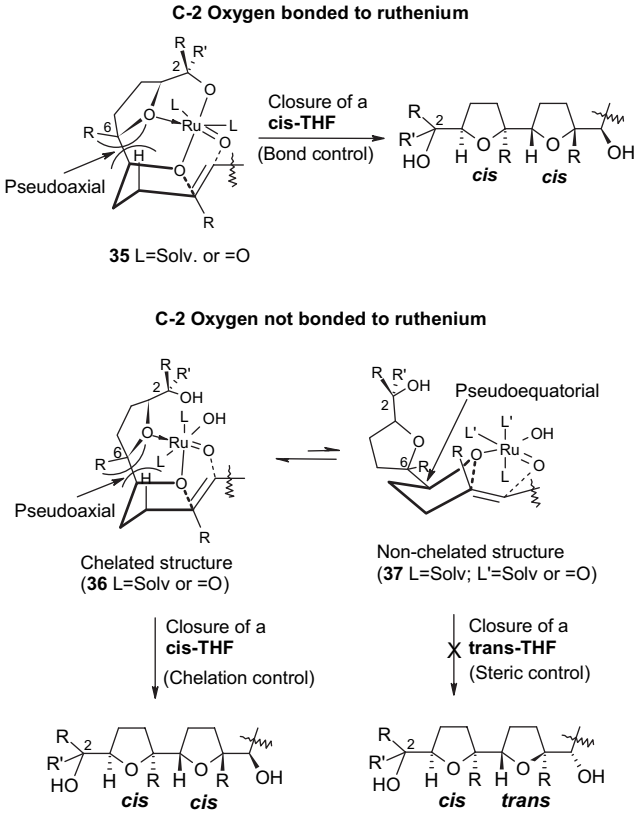


Figure 8. Chelation versus steric control in the second cyclization step of RuO_4-mediated OP process.

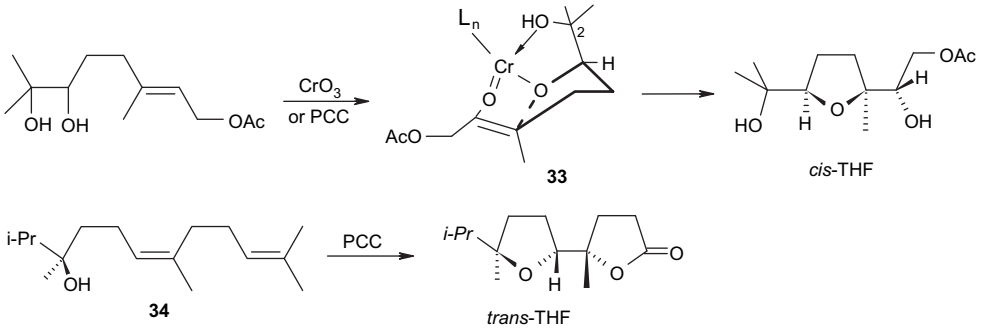


Figure 7. McDonald's model for the *cis*-selective monocyclization of the 6,7-dihydroxyalkene from geranyl acetate (top) and trans-selectivity for a monodentate hydroxydiene (bottom).

first-formed THF ring be or not coordinated to the metal, though this seems possible as molecular models of **35** show. In fact, in this case, the alignment of the alkene for the reaction to take place is incompatible with the closure of a *trans*-THF. In the case the C(2)O–Ru bond be broken, to explain the closure of the *cis*-THF, one should assume that the chelated structure **36** (THF coordinated to Ru), where the angular carbon (C-6) of the coordinated THF is positioned in a sterically demanding pseudoaxial position, should be energetically preferred over the non-chelated structure **37**, where the THF ring is pseudoequatorial, since the latter would lead to a *trans*-THF (not observed) in accord with the steric control model (Fig. 5). This is just what hypothesized by Sinha et al. to explain the observed cis selectivity in the second cyclization step of 4,8-dien-1-ols with $CF_3CO_2ReO_3$ when a *trans–threo* substructure is formed in the first cyclization step.[19b]

On the other hand, it is also to be said that arrangement **36** could be further stabilized by the coordination of the C-2 hydroxyl group to ruthenium as seen for structure **31** (Fig. 5). Therefore, the observed cis selectivity for the second cyclization step would be explained, as seen in the first cyclization step, by a chelation control or by a bond control depending on whether the species **35** or **36** is involved.

2.4. Model for the trans-selective third cyclization in GGA and squalene

Let us refer now to the third cyclization step in GGA and squalene, both proceeding with a trans-selectivity (Scheme 1). A chelated structure **38**, stabilised by coordination of both A and B THF rings, appears in principle possible, as models show, that would impose a cis-selective cyclization. However, a very disfavoured transition state, suffering severe steric repulsions, would be required for a correct alignment of the alkene to take place. In particular, the methyl-carrying carbon (C-10) of the B THF ring is pseudoaxially disposed and, in addition, the R′ group and the methyl at C-10 would be very close in the space during the cycloaddition step. On the other hand, alternative arrangements where the C(2)O is still bonded to ruthenium, or coordinated to it, and one or both the A/B rings coordinated as well (not shown), are also possible but overall these would substantially fix the reacting portions in a reciprocal position as in **38** and the THF closure would suffer similar steric repulsions. A much more favourable spatial arrangement, **39**, leading to a *trans*-THF, is shown in the right side of Figure 9,

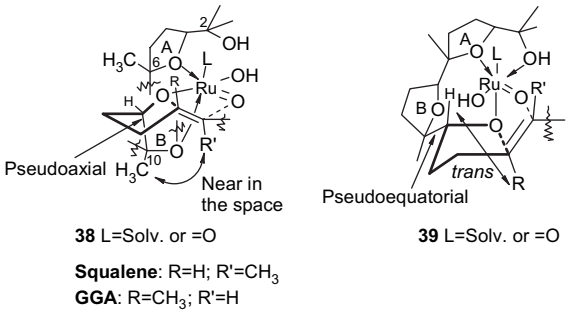


Figure 9. Left: possible chelated structure for the third cyclization step in squalene, leading to a *cis*-THF; the part of the molecule joining the two THF is omitted for sake of clarity. Right: arrangement leading to a *trans*-THF.

where the B THF is pushed away from the metal, and hence non-coordinated to it, due to its pseudoequatorial disposition. This arrangement is, however, compatible with the coordination of both the A THF and the C(2)OH group to ruthenium. Therefore, the trans-selectivity for the third cyclization step both in squalene and GGA appears to be under steric control though a chelation stabilization of the involved arrangement could also exist.

2.5. Model for the trans-selective fourth and fifth cyclizations in the OP of squalene

The trans-selectivity for the fourth ring-closing step in squalene can be explained through the steric control model (arrangement **40**, Fig. 10). In fact, the trans configuration of the third (C) THF ring pushes the metal away from both B and C rings; nor the A ring (not shown) appears to be able to reach a distance suitable for coordination. This is true for the fifth cyclization step as well. On the other hand, an arrangement with C ring chelated to the metal (not shown), that would lead to the closure of a *cis*-THF, would be possible but disfavoured by steric interactions such as those observed in the third cyclization (Fig. 9), though less severe due to the lack of the angular methyl on C THF. Therefore, the formation of *the first trans-THF (the C-THF) in the growing poly-THF chain appears to impose a trans-selectivity to all the successive cyclization steps in an all*-trans *isoprenoid polyene such as squalene*. Further experimental support to this deduction should be given by studying, for example, the oxidative cyclization of analogues of squalene with more than six isoprene units.

2.6. Explaining the failure of the second cyclization in the (*E*,*Z*)-FA and (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester (21), and formation of bis-THF 25

To explain the failure of the second cyclization step in both (*E*,*Z*)-FA and (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester (**21**) the same type of reasoning above seen for the second cyclization step of all-*E* polyenes can be applied; that is after the formation of the first THF, the molecule adopts a spatial arrangement of the type **35/36** (Fig. 8) where the C(2)–O oxygen is in some way linked to the metal (chelated or bonded) (Fig. 11, left). In fact, if so, the *erythro* relationship arising from the *syn* addition of two oxygens to the cis double bond during the first cyclization would impose a sterically disfavoured *endo* transition state, leading to a *cis*-THF, for the second cyclization step to take place. On the other hand, this chelated arrangement is incompatible with the closure of a *trans*-THF since the alignment of the alkene cannot take place at all. As Sinha et al.[19b] pointed out referring to the second cyclization step of the strictly related 4,8-dien-1-ols, the presence of this *erythro* relationship

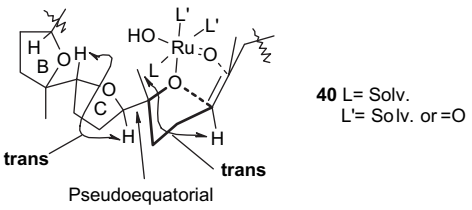


Figure 10. Arrangement explaining the trans-selective fourth cyclization in squalene; only B and C THF's and the cyclizing portion are shown.

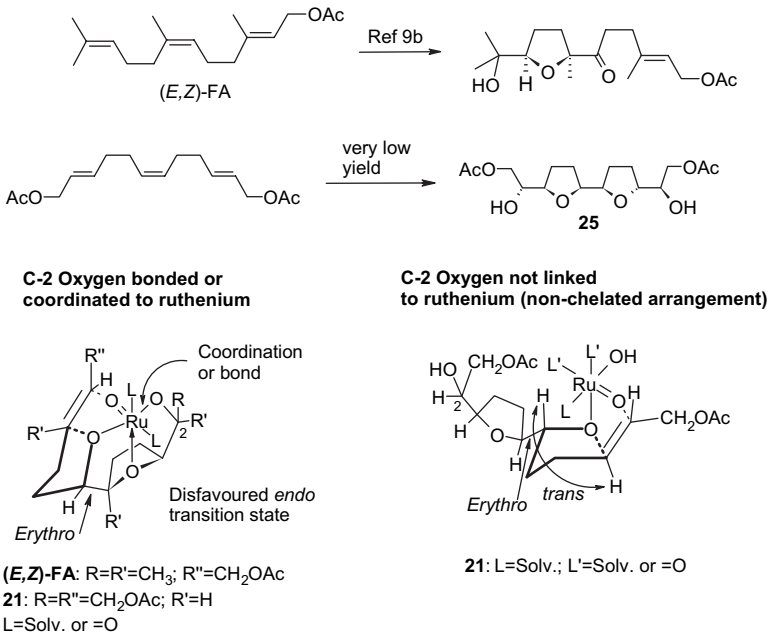


Figure 11. Model explaining the failure of the second cyclization in the (*E*,*Z*)-FA and **21**, and formation of *cis–trans* bis-THF **25**.

would render the non-chelated structure, energetically more favourable leading to a *trans*-THF through a steric control. In our case, however, this non-chelated structure cannot form at all due to the C(2)O vinculum. This explanation well agrees with, and is a further support of, the model above proposed for the cis selectivity of the second cyclization step of an all *E* polyene. On the other hand, formation of the *cis–trans* bis-THF **25** can be explained assuming that the molecule could assume, in a little extent, an arrangement (Fig. 11, right) where both the THF and C(2)–O are not linked to the metal so that a steric control is operative, that leads to a *trans*-THF in the second cyclization step, according to the Sinha's hypothesis.[19b]

2.7. Model explaining the failure of the third cyclization in the all-*trans* tetraene (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester (16)

Finally we have to explain why the OP of the all-*trans* tetraene **16** (Scheme 8) stops at the bis-THF level. A tentative explanation can be given by referring to the reasoning developed for the third cyclization of GGA and squalene (Fig. 9). The absence of methyl groups in **16** along the polyenic chain could render the chelated structure of the type **38** (Fig. 9, left) more stable, a fact that would preclude the further cyclization since this arrangement, only compatible with the formation of a *cis*-THF, would however require a disfavoured transition state, as pointed out above for GGA and squalene.

3. Conclusion

In conclusion, the OP of some linear polyenes with the RuO_2(cat.)/$NaIO_4$ oxidizing system has been studied and its ability to induce the oxidative bis-cyclization of two all-trans linear polyenes has been established. A plausible explanation of the observed stereoselectivity of each ring-closing step, either in linear or isoprenoid polyenes, has been given based on steric or chelation control models. However, further studies need to be accomplished both to support the above models, by using suitable substrates and theoretical calculations, and to employ the chemistry developed in the present study for the synthesis of selected annonaceous acetogenin targets. In particular, the unique feature of the RuO_4-mediated OP of inducing the formation of the first two THF rings in the poly-THF product with cis selectivity renders the process useful for the synthesis of ACGs such as rollinistatin-1 and rollimembrin, two of the most active ACGs known, both possessing a *threo–cis–threo–cis–erythro* relative configuration, and/or their non-natural analogues. Further studies in this field are currently ongoing.

4. Experimental

4.1. General methods

All reagents and anhydrous solvents were purchased (Aldrich and Fluka) at the highest commercial quality and used without further purification. Where necessary, flame-dried and argon-charged glassware was used. Reactions were monitored by thin-layer chromatography carried out on precoated silica gel plates (Merck 60, F_{254}, 0.25 mm thick). Merck silica gel (Kieselgel 40, particle size 0.063–0.200 mm) was used for column chromatography. Na_2SO_4 was used as drying agent in all the extractive work-up. HPLC separations were carried out on a Varian 2510 apparatus equipped with a Waters R403 dual cell differential refractometer using phenomenex 250×10 mm and 250×4.6 mm (both 5 μm) columns. NMR experiments were performed on Bruker DRX-600, Bruker WM 400, Varian 300, and Gemini 200 spectrometers in $CDCl_3$ unless otherwise mentioned. All the 2D-NMR spectra were acquired at 600 MHz in the phase-sensitive mode with the transmitter set at the solvent resonance and TPPI (time proportional phase increment) used to achieve frequency discrimination in the ω_1 dimension.

Standard pulse sequence and phase cycling were used for DQF-COSY, 2D-TOCSY, HSQC, 2D-HSQC-TOCSY, HMBC, 2D-INEPT-INADEQUATE, 2D-INEDAQUATE and ROESY spectra. The NMR data were processed on a Silicon Graphic Indigo2 Workstation using UXNMR software. Proton chemical shifts were referenced to the residual $CHCl_3$ signal (7.26 ppm); ^{13}C NMR chemical shifts were referenced to the solvent (77.0 ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. *J* values are given in Hertz. IR spectra were collected on a Jasco FT-IR-430 spectrometer. ESI mass spectrometric analyses were recorded on a Waters Micromass ZQ mass spectrometer equipped with an electrospray source used in the positive mode. HRMS spectra were recorded on a Voyager DE-PRO mass spectrometer using MALDI-TOF ionization.

4.1.1. Synthesis of (2*E*,6*E*,10*E*)-acetic acid henicosa-2,6,10-trienyl ester (7).

4.1.1.1. (*E*)-Pentadec-4-enoic acid ethyl ester 4. To a solution of undecylic aldehyde (7.0 g, 41.1 mmol) in dry THF (5 mL), at 0 °C, was added vinylmagnesium bromide (1 M in THF, 49.3 mL, 49.3 mmol) and the mixture was stirred for 30 min. Then, a saturated NH_4Cl solution (20 mL) was added and the mixture stirred for 10 min. The phases were separated and the aqueous phase was extracted with ether (3×20 mL). The combined ether layer was dried and concentrated to yield tridec-1-en-3-ol[26] (8.0 g, 98%) as an oil that was used without further purification in the next step of the synthesis. ^1H NMR: (200 MHz) δ 5.87 (1H, ddd, *J*=17.2, 10.8, 6.6, H-2), 5.21 (1H, dt, *J*=17.2, 1.4, H_a-1), 5.09 (1H, dt, *J*=10.8, 1.4, H_b-1), 4.09 (2H, q, *J*=6.4, H-3), 1.86 (2H, m), 1.52 (2H, m), 1.25 (14H, br s), 0.87 (3H, t, *J*=7.2, Me).

A solution of the crude allyl alcohol (8.0 g, 40.3 mmol), triethyl orthoacetate (2.1 equiv, 84.6 mmol, 15.5 mL) and propionic acid (2%, 80 mmol, 82 μL) in xylene (15 mL) was refluxed for 4 h. Removal of the solvent followed by purification by column chromatography (petroleum ether→petroleum ether–ethyl ether, 9:1) afforded 6.81 g (63%) of (*E*)-pentadec-4-enoic acid ethyl ester[27] **4** as an oil.

Compound **4**: IR (neat): ν_{max} 1738 cm^{-1}. ^1H NMR: (300 MHz) δ 5.42 (2H, m, olefinic protons), 4.11 (2H, q, *J*=7.5, $CO_2CH_2CH_3$), 2.33 (4H, m), 1.95 (2H, m), 1.23 (3H, t, *J*=7.2, $CO_2CH_2CH_3$), 1.25 (16H, m), 0.87 (3H, t, *J*=7.2, Me).

4.1.1.2. Nonadeca-4,8-dienoic acid ethyl ester 5. $LiAlH_4$ (2.03 g, 53.3 mmol) was slowly added to a solution of ester **4** (6.81 g, 25.4 mmol) in dry ether (70 mL) at 0 °C. The mixture was allowed to warm to room temperature over 1 h, then wet ether was added (10 mL) followed by dropwise addition of water (10 mL). The phases were separated and the aqueous phase was extracted with ether (3×20 mL). The combined ether layer was dried and concentrated to give 5.2 g (90%) of (*E*)-pentadec-4-en-1-ol[5b] as an oil that was taken to the next step without further purification. ^1H NMR: (300 MHz) δ 5.41 (2H, m, olefinic protons), 3.65 (2H, q, *J*=5.4, H_2-1), 2.07 (2H, q, *J*=7.4), 1.96 (2H, q, *J*=6.6), 1.63 (2H, m), 1.39–1.20 (16H, m and br s), 0.87 (3H, t, *J*=7.2, Me).

Celite (9.7 g, 0.42 g/mmol) and PCC (10.4 g, 48.3 mmol) were added to a solution of the crude alcohol (5.2 g, 23.0 mmol) in CH_2Cl_2 (100 mL) and the mixture was stirred for 1.5 h. Filtration on a short pad of silica gel gave (*E*)-pentadec-4-enal (4.38 g, 85%)[5b,28] as an oil. ^1H NMR: (200 MHz) δ 9.76 (1H, t, *J*=1.6, C*H*O), 5.43 (2H, m, olefinic protons), 2.47 (2H, q, *J*=7.2), 2.33 (2H, m), 1.96 (2H, br q, 6.2), 1.38–1.17 (16H, br s), 0.88 (3H, t, *J*=7.2, Me). ^{13}C NMR: (50 MHz) δ 201.8, 131.8, 127.5, 43.4, 32.3, 31.7, 29.5 (2C), 29.4, 29.3, 29.2, 29.0, 25.0, 22.5, 13.9.

Vinylmagnesium bromide (1 M in THF, 23.5 mL, 23.5 mmol) was added to a solution of the above crude aldehyde (4.38 g, 19.5 mmol) in dry THF (10 mL) at 0 °C. Work-up with saturated aqueous NH_4Cl and ether, as reported above for the preparation of ester **4**, gave allyl alcohol (*E*)-heptadeca-1,6-dien-3-ol[5b] (3.71 g, 76%) as an oil that was used in the next step without further purification. ^1H NMR: (200 MHz) δ 5.87 (1H, ddd, *J*=17.0, 10.8, 6.4, H-2), 5.43 (2H, m, H-6, H-7), 5.22 (1H, br d, *J*=17.2, H_a-1), 5.10 (1H, br d, *J*=10.8, H_b-1) 4.12 (1H, q, *J*=6.0, H-3), 2.08 (2H, m) 1.96 (2H, m), 1.59 (2H, m), 1.40–1.10 (16H, br s), 0.87 (3H, t, *J*=7.2, Me). ^{13}C NMR: (50 MHz) δ 141.1, 130.8, 129.3, 114.0, 72.2, 36.6, 32.4, 31.8, 29.5 (3C), 29.4, 29.2, 29.1, 28.3, 22.5, 13.9.

A solution of the crude allyl alcohol (3.71 g, 14.7 mmol), triethyl orthoacetate (2.1 equiv, 30.9 mmol, 5.7 mL) and propionic acid (2%, 0.3 mmol, 22 μL) in xylene (10 mL) was refluxed for 2 h. Removal of the solvent followed by purification by column chromatography (petroleum ether→petroleum ether–ethyl ether, 95:5) afforded 2.84 g (60%) of (*E*,*E*)-nonadeca-4,8-dienoic acid ethyl ester **5**[5b] as an oil.

Compound **5**: IR (neat): ν_{max} 1738 cm^{-1}. ^1H NMR: ($CDCl_3$) δ 5.50–5.30 (4H, m, olefinic protons), 4.12 (2H, q, *J*=7.2, $CO_2CH_2CH_3$), 2.37–2.23 (4H, m), 2.08–1.87 (6H, m), 1.38–1.18 (16H, br s), 1.22 (3H, t, *J*=7.2, $CO_2CH_2CH_3$), 0.87 (3H, t, *J*=7.2, Me). ^{13}C NMR: (50 MHz) δ 172.5, 130.8, 130.5, 129.2, 128.1, 59.7, 34.1, 32.4, 31.7, 29.5, 29.4, 29.2, 29.0, 27.7, 22.5, 14.0, 13.8.

4.1.1.3. (*E*,*E*,*E*)-Henicosa-2,6,10-trienoic acid ethyl ester 6. Ester **5** (2.84 g, 8.8 mmol) in dry ethyl ether (20 mL) was reduced with $LiAlH_4$ (702 mg, 18.5 mmol) as reported for ester **4** to give 2.15 g (87%) of (*E*,*E*)-nonadeca-4,8-dien-1-ol as an oil that was subjected to the next step without further purification. A 200 mg amount of this material was subjected to a further HPLC purification on an RP-18 column (MeOH–H_2O, 97:3) to obtain a pure sample for spectral characterization. IR (neat): ν_{max} 3339 cm^{-1}. ^1H NMR: (200 MHz) δ 5.30–5.45 (4H, m, olefinic protons), 3.62 (2H, t, *J*=7.3, H_2-1), 2.10–1.90 (8H, m), 1.61 (2H, quintet, *J*=7.0), 1.38–1.15 (16H, br s), 0.87 (3H, t, *J*=7.2, Me). ^{13}C NMR: (50 MHz) δ 130.7, 130.3, 129.6, 129.4, 62.1, 32.6, 32.5, 32.3, 31.8, 29.5, 29.4, 29.2, 29.1, 28.8, 22.6, 14.0.

A solution of the crude alcohol (2.15 g, 7.6 mmol) in CH_2Cl_2 was oxidized with PCC (3.45 g, 16.0 mmol) and Celite (3.2 g) as reported for the synthesis of ester **5** giving 1.79 g (85%) of (*E*,*E*)-nonadeca-4,8-dienal, as an oil, that was used in the next step. IR (neat): ν_{max} 1728 cm^{-1}. ^1H NMR: (200 MHz) δ 9.76 (1H, t, *J*=1.6, C*H*O), 5.50–5.32 (4H, m,

olefinic protons), 2.48 (2H, br t, J=7.3, H-2), 2.34 (2H, br q, J=6.4, H-3), 2.07–1.88 (6H, m), 1.37–1.17 (16H, br s), 0.88 (3H, t, J=6.7, Me). ^{13}C NMR: (50 MHz) δ 201.1, 131.0, 130.6, 129.1, 127.8, 43.2, 32.34, 32.27, 31.7, 29.46, 29.41, 29.3, 29.2, 29.0, 24.9, 22.4, 13.8. MS m/z 317 (89, M+K)$^+$, 301 (28, M+Na)$^+$. HRMS: calcd for $C_{19}H_{34}ONa$ 301.2499, found 301.2506.

To a mixture of NaH (60% in mineral oil, 113.6 mg, 2.84 mmol) in dry THF (5 mL) triethyl phosphonoacetate (563 μL, 2.84 mmol) was added dropwise at room temperature and the mixture stirred for 1 h. To the light orange solution was dropwise added a solution of the aldehyde (790 mg, 2.84 mmol), obtained as above, in dry THF (2 mL), within a 20 min period. After 1.5 h the mixture was extracted with ether (3×10 mL) and the organic phase dried and concentrated. Purification by column chromatography (gradient from 2% to 10% ethyl ether in hexanes) afforded 740 mg (75%) of pure (*E*,*E*,*E*)-henicosa-2,6,10-trienoic acid ethyl ester **6** as an oil.

Compound **6**: IR (neat): ν_{max} 1725, 1655 cm^{-1}. ^{1}H NMR: (200 MHz) δ 6.95 (1H, dt, J=15.6, 6.4, H-3), 5.81 (1H, dt, J=15.6, 1.6, H-2), 5.47–5.37 (4H, m, olefinic protons), 4.18 (2H, q, J=7.0, $CO_2CH_2CH_3$), 2.27–1.94 (10H, overlapped m's), 1.28 (3H, t, J=7.2, $CO_2CH_2CH_3$), 1.27 (16H, br s), 0.87 (3H, t, J=7.2, Me). ^{13}C NMR: (100 MHz) δ 166.6, 148.5, 131.1, 130.8, 129.4, 128.6, 121.5, 60.0, 32.6, 32.5, 32.22, 32.18, 31.9, 30.9, 29.6, 29.5, 29.3, 29.1, 22.6, 14.2, 14.0. MS m/z 387 (56, M+K)$^+$, 371 (80, M+Na)$^+$. HRMS: calcd for $C_{23}H_{40}O_2Na$ 371.2916, found 371.2910.

4.1.1.4. (*E*,*E*,*E*)-Acetic acid henicosa-2,6,10-trienyl ester 7. To a solution of the ester **6** (740 mg, 2.1 mmol) in dry THF (3 mL) was added dropwise DIBAL-H (1 M in THF, 6.4 mL, 6.4 mmol) at −78 °C. The mixture was stirred at this temperature for 1 h and then quenched by dropwise addition of a saturated NH_4Cl solution (3 mL). The phases were separated and the aqueous phase was extracted with ether (3×5 mL). The combined ether layer was dried and concentrated to give 610 mg (94%) of crude (*E*,*E*,*E*)-henicosa-2,6,10-trien-1-ol. IR (neat): ν_{max} 3393 cm^{-1}. ^{1}H NMR: (200 MHz) δ 5.66 (2H, m, olefinic protons), 5.40 (4H, m, olefinic protons), 4.08 (2H, d, J=4.4, H_2-1), 3.65 (1H, t, J=6.8, OH), 2.18–1.90 (10H, m), 1.40–1.10 (16H, m), 0.87 (3H, t, J=7.2, Me). ^{13}C NMR: (150 MHz) δ 132.8, 131.1, 130.8, 130.5, 129.5 (2C), 129.2, 63.8, 32.7, 32.6, 32.4, 32.3, 32.1, 29.6 (2C), 29.5, 29.3, 29.2, 28.9, 22.7, 14.1. MS m/z 345 (45, M+K)$^+$, 329 (75, M+Na)$^+$. HRMS: calcd for $C_{21}H_{38}ONa$ 329.2811, found 329.2830.

Acetic anhydride (3 mL) and pyridine (3 mL) were added to 610 mg (2.0 mmol) of the above alcohol and the solution was left at room temperature overnight. Then, the mixture was partitioned between EtOAc and HCl 0.1 M, and the organic layer was washed with a saturated $NaHCO_3$ solution and water, dried (Na_2SO_4), filtered and concentrated. HPLC purification (hexane–EtOAc, 98:2, flow 2.5 mL/min) gave 505 mg (73%) of pure triene **7** (t_R=15.0 min) as an oil.

Compound **7**: IR (neat): ν_{max} 1738, 1229 cm^{-1}. ^{1}H NMR: (200 MHz) δ 5.78 (1H, dt, J=15.5, 6.0, olefinic proton), 5.56 (1H, dt, J=15.5, 6.6, olefinic proton), 5.45–5.34 (4H, m, olefinic protons), 4.50 (2H, d, J=6.4, CH_2OAc), 2.14–1.89 (overall 13H, m overlapped with the 3H-singlet acetate at 2.05), 1.33–1.19 (16H, m), 0.87 (3H, t, J=6.9, Me). ^{13}C NMR: (100 MHz) δ 170.8, 135.9, 130.8, 130.5, 129.5, 129.3, 124.0, 65.2, 32.6, 32.2, 31.9, 29.6, 29.3, 29.1, 22.6, 20.9, 14.1. MS m/z 387 (55, M+K)$^+$, 371 (77, M+Na)$^+$. HRMS: calcd for $C_{23}H_{40}O_2Na$ 371.2916, found 371.2923.

4.1.2. Oxidation of triene 7 with $RuO_{4(cat.)}$/$NaIO_4$. To a solution of triene **7** (50 mg, 0.14 mmol) in the biphasic mixture EtOAc–CH_3CN–H_2O (3:3:1) (17.5 mL) were added in sequence $NaIO_4$ (4 equiv, 118 mg, 0.55 mmol) and $RuO_2\cdot 2H_2O$ (20 mol %, 3.6 mg) under vigorous stirring at 0 °C. TLC monitoring (hexane–EtOAc, 3:7) indicated that the reaction to be completed after 30 min. The process was quenched by the addition of excess of a saturated $Na_2S_2O_3\cdot 5H_2O$ solution (2 mL) until the yellowish mixture turned to black (RuO_2 precipitation). Then the mixture was filtered and extracted with EtOAc (3×10 mL), and the combined organic phase was dried and evaporated to give 60 mg of an oil. HPLC separation (hexane–EtOAc, 3:7, flow 2.5 mL/min) afforded bis-THF diol **8** (12.5 mg, 24%, t_R=15.3 min), ketol **10** (4.5 mg, 8.5%, t_R=9.2 min) and **9** (7.5 mg, 14%, t_R=11.7 min) as oils.

4.1.2.1. Acetic acid 2-hydroxy-2-[5′-(1-hydroxy-undecyl)-octahydro-[2,2′]bifuranyl-5-yl]-ethyl ester 8. IR (neat): ν_{max} 3419, 1742 cm^{-1}. ^{1}H NMR (600 MHz, attributions by 2D-NMR): δ 4.17, 4.14 (1H each, AB system further coupled, J_{AB}=11.5, J_{AX}=7.0, J_{BX}=4.8, H_2-1), 4.02, 3.94, 3.91, 3.81 (1H each, m's, H-3, H-6, H-7, H-10, respectively), 3.70 (1H, dt, J=7.0, 4.8, H-2), 3.43 (1H, dt, J=7.8, 4.7, H-11), 2.09 (3H, s, acetate), 2.01, 1.97 (1H each, m's, H_2-4), 1.96 (2H, m, H_2-5) 1.96, 1.88 (1H each, m's, H_2-8), 1.96, 1.81 (1H each, m's, H_2-9), 1.45 (2H, m, H_2-12), 1.27 (16H, br s, H_2-13/H_2-20), 0.88 (3H, t, J=6.8, H_3-21).

^{1}H NMR (DMSO-d_6, 600 MHz, attributions by 2D-NMR): δ 4.88, 4.26 (1H each, d's, J=6.3 and 6.1, respectively, 2×OH), 3.99, 3.96 (1H each, AB system further coupled, J_{AB}=11.1, J_{AX}=6.9, J_{BX}=4.8, H_2-1), 3.83 (1H, m, H-3), 3.73 (2H, m, H-6 and H-7), 3.68 (1H, q, J=6.0, H-10), 3.58 (1H, ddd, J=6.9, 6.3, 4.8, H-2), 3.28 (1H, m, H-11), 2.09 (3H, s, acetate), 1.80, 1.72 (1H each, m's, H_2-4), 1.73, 1.62 (1H each, m's, H_2-9), 1.21-1.31 (2H, m, H_2-12), 1.26 (16H, br s, H_2-13/H_2-20), 0.86 (3H, t, J=6.8, H_3-21).

^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 171.1 (carbonyl), 83.2 (CH-10), 81.4 (CH-6), 81.2 (CH-7), 79.6 (CH-3), 74.1 (CH-11), 72.2 (CH-2), 66.5 (CH_2-1) 34.6 (CH_2-12), 29.9 (8×CH_2, C-13/C-20) 28.6 (CH_2-9), 28.4 (CH_2-8, CH_2-5), 28.3 (CH_2-4), 21.2 (CH_3 acetate), 14.3 (CH_3-21).

^{13}C NMR (DMSO-d_6, 150 MHz, attributions by 2D-NMR): δ 171.1 (carbonyl), 83.0 (CH-10), 81.7 (CH-6, CH-7), 79.7 (CH-3), 72.8 (CH-11), 70.7 (CH-2), 66.6 (CH_2-1) 33.5 (CH_2-12), 29.9, 29.8 (8×CH_2, C-13/C-20), 28.3 (CH_2-5, CH_2-8), 27.6 (CH_2-9), 27.4 (CH_2-4), 21.1 (CH_3 acetate), 14.6 (CH_3-21). MS m/z 453 (100, M+K)$^+$, 437 (17, M+Na)$^+$. MS m/z 453 (100, M+K)$^+$, 437 (27, M+Na)$^+$. HRMS: calcd for $C_{23}H_{42}O_6Na$ 437.2868, found 437.2874.

4.1.2.2. Acetic acid 2-hydroxy-2-(5′-undecanoyl-octahydro-[2,2′]bifuranyl-5-yl)-ethyl ester 9. IR (neat): ν_{max} 3444, 1734, 1716 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 4.40 (1H, dd, J=8.7, 6.0, H-10), 4.15 (2H, d, J=6.0, H_2-1), 4.07–3.89 (3H, m, H-3, H-6, H-7), 3.69 (1H, br q, J=6.0, H-2), 2.50 (2H, dt, J=7.2, 2.1, H_2-12), 2.09 (3H, s, acetate), 1.37–1.18 (16H, br s, H_2-13/H_2-20), 0.88 (3H, t, J=6.9, H_3-21). ^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 211.6 (C-11), 170.6 (carbonyl acetate), 82.7 (CH-7), 80.9 (CH-6), 80.8 (CH-10), 80.1 (CH-3), 71.9 (CH-2), 66.7 (CH_2-1), 33.6 (CH_2-12), 29.4 (CH_2-13/CH_2-20), 27.5, 28.3 (CH_2-4, CH_2-5, CH_2-8, CH_2-9), 20.9 (CH_3 acetate), 13.9 (CH_3-21). MS m/z 451 (100, M+K)$^+$, 435 (78, M+Na)$^+$, 413 (16, M+H)$^+$. HRMS: calcd for $C_{23}H_{40}O_6Na$ 435.2712, found 435.2719.

4.1.2.3. Acetic acid 2-[5′-(1-hydroxy-undecyl)-octahydro-[2,2′]bifuranyl-5-yl]-2-oxo-ethyl ester 10. IR (neat): ν_{max} 3400, 1734, 1716 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 5.16, 4.91 (1H each, AB system, J_{AB}=17.7, H_2-1), 4.48 (1H, dd, J=7.6, 6.4, H-3), 3.98 (1H, br q, J=6.8, H-6), 3.92 (1H, br q, J=6.8, H-7), 3.81 (1H, br q, J=6.4, H-10), 3.43 (1H, m, H-11), 2.18 (3H, s, acetate), 2.05–1.85 (H_2-4, H_2-5, H_2-8, H_2-9), 1.45 (2H, m, H_2-12), 1.27 (16H, br s, H_2-13/H_2-20), 0.88 (3H, t, J=6.9, H_3-21). ^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 204.9 (C-2), 170.2 (carbonyl acetate), 83.2 (CH-3), 82.8 (CH-10), 82.7 (CH-6), 80.9 (CH-7), 74.1 (CH-11), 66.5 (CH_2-1) 33.6 (CH_2-12), 29.9 (CH_2-13/CH_2-20), 27.5, 29.0 (CH_2-4, CH_2-5, CH_2-8, CH_2-9), 20.2 (CH_3 acetate), 14.0 (CH_3-21). MS m/z 451 (83, M+K)$^+$, 435 (63, M+Na)$^+$, 413 (18, M+H)$^+$. HRMS: calcd for $C_{23}H_{40}O_6Na$ 435.2712, found 435.2705.

4.1.2.4. Acetic acid 6-hydroxy-6-[5-(1-hydroxy-undecyl)-tetrahydro-furan-2-yl]-hex-2-enyl ester 11. IR (neat): ν_{max} 3412, 1741, 1235 cm^{-1}. ^1H NMR (200 MHz): δ 5.80 (1H, dt, J=15.7, 6.6, olefinic proton), 5.59 (1H, dt, J=15.7, 5.9, olefinic proton), 4.51 (2H, d, J=6.4, H_2-1), 3.82 (2H, m, H-7, H-10), 3.42 (2H, m, H-6, H-11), 2.05 (3H, s, acetate), 1.42–1.18 (br s, H_2-13/H_2-20), 0.87 (3H, t, J=6.3, H_3-21). MS m/z 437 (65, M+K)$^+$, 421 (87, M+Na)$^+$. HRMS: calcd for $C_{23}H_{42}O_5Na$ 421.2919, found 421.2926.

4.1.3. Oxidation of bis-THF diol 9 with TPAP/NMO. To a solution of **8** (4.0 mg, 0.01 mmol) in CH_2Cl_2 (400 μL) were sequentially added *N*-methylmorpholine *N*-oxide monohydrate (NMO) (2.0 mg, 1.5 equiv), powdered 4 Å molecular sieves (5 mg) and TPAP (10 mol %, 0.4 mg) under stirring at room temperature. After 1 h the mixture was concentrated, filtered on silica gel ($CHCl_3$–CH_3OH, 9:1) to give 3.5 mg of a crude material. ^1H NMR analysis revealed the presence of a mixture of ketols **9** and **10** (together ca. 50%) in a ca. 2:1 ratio along with a 20–25% amount of a product tentatively identified as the corresponding diketone (δ 5.10, 4.90, AB system, J=17.7).

4.1.4. Synthesis of acetic acid 2,3,6-trihydroxy-6-[5-(1-hydroxy-undecyl)-tetrahydro-furan-2-yl]-hexyl esters 12. A solution of triene **7** (15.6 mg, 0.046 mmol) in CH_2Cl_2 (4 mL) was treated with NMO (50 mg, 0.37 mmol) and CSA (127.2 mg, 0.55 mmol) followed by osmium tetroxide (1.2 mg, 0.0046 mmol, 10%) and the solution was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous sodium thiosulfate (1 mL) and $NaHCO_3$ (1 mL) solutions and the biphasic solution was extracted with $CHCl_3$ (3×10 mL), then the organic phase was dried and evaporated. The oily residue was purified by column chromatography (gradient from $CHCl_3$ to $CHCl_3$–MeOH, 98:2) to give in the first-eluted fractions (eluent $CHCl_3$) a brown oil (10 mg) tentatively identified as the osmate ester corresponding to tetrols **12** and then tetrols **12** (2 mg, 10%) as an oil. Compound **12**: ^1H NMR (200 MHz): δ 4.30–4.05 (2H, m), 3.93–3.77 (2H, m), 3.77–3.56 (2H, m), 3.56–3.35 (2H, m), 2.10 (3H, s, acetate), 1.25 (16H, br s), 0.87 (t, J=6.6, Me). MS m/z 471 (62, M+K)$^+$, 455 (100, M+Na)$^+$. HRMS: calcd for $C_{23}H_{44}O_7Na$ 455.2973, found 455.2966.

4.1.4.1. Dihydroxylation of 11 to 12. To a solution of **11** (5 mg, 0.012 mmol) in acetone–water (5:1, 600 μL) was added OsO_4 (0.3 mg, 10%) and NMO (32 mg, 0.24 mmol) and the mixture stirred at room temperature for 1 h. The reaction was quenched by the addition of a saturated solution of sodium thiosulfate (0.5 mL) and $NaHCO_3$ (0.5 mL) and the whole was extracted with $CHCl_3$ (3×3 mL). The organic phase was dried and evaporated and the residue purified by preparative TLC ($CHCl_3$–CH_3OH, 9:1, R_f=0.31) to give 4.3 mg (80%) of tetrols **12**.

4.1.5. Synthesis of acetic acid 2-hydroxy-2-[5′-(1-hydroxy-undecyl)-octahydro-[2,2′]bifuranyl-5-yl]-ethyl esters 13 and 14. To a solution of **11** (5.0 mg, 0.012 mmol) in CH_2Cl_2 (1 mL) was added MCPBA (4.4 mg, 0.026 mmol) at 0 °C and the mixture was stirred at the same temperature for 1.5 h. Then, CSA (0.6 mg, 0.0026 mmol) was added and the solution was stirred for further 45 min. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution (1 mL) and extracted with EtOAc (3×5 mL). The organic phase was dried and evaporated. The residue was purified by HPLC (hexane–EtOAc, 1:1) to give the two diastereomeric bis-THF diols **13** and **14** as oils. Major isomer (t_R=23 min, 1.6 mg, 30%); minor isomer (t_R=24.5 min, 1.4 mg, 26%).

Major isomer. IR (neat): ν_{max} 3440, 1742, 1240 cm^{-1}. ^1H NMR (500 MHz): δ 4.22, 4.05 (1H each, AB system further coupled, J=11.5, 3.0 and 11.5, 7.2, respectively, CH_2OAc), 4.02–3.92 (3H, m, 3×C*H*–O), 3.88 (2H, m, C*H*–O), 3.37 (1H, dt, J=7.5, 4.9, H-11), 2.10 (3H, s, acetate), 1.25 (br s, overlapped with other signals), 0.88 (3H, t, J=6.7, H_3-21). MS m/z 453 (90, M+K)$^+$, 437 (53, M+Na)$^+$. HRMS: calcd for $C_{23}H_{42}O_6Na$ 437.2868, found 437.2875.

Minor isomer. IR (neat): ν_{max} 3450, 1742, 1240 cm^{-1}. ^1H NMR (500 MHz): δ 4.15 (1H, m), 4.05 (2H, m), 3.97 (1H, br ddd, J=7.2, 7.2, 3.3), 3.89 (2H, m), 3.83 (1H, q, J=6.2), 3.41 (1H, ddd, J=7.4, 5.1, 5.1), 2.09 (3H, s, acetate), 1.25 (br s, overlapped with other signals), 0.88 (3H, t, J=7.0, H_3-21). MS m/z 453 (88, M+K)$^+$, 437 (64, M+Na)$^+$. HRMS: calcd for $C_{23}H_{42}O_6Na$ 437.2868, found 437.2861.

4.1.6. Synthesis of (*E*,*E*,*E*,*E*)-acetic acid pentacosa-2,6,10,14-tetraenyl ester (16).

4.1.6.1. (*E*,*E*,*E*)-Tricosa-4,8,12-trienoic acid ethyl ester 15. (*E*,*E*)-Nonadeca-4,8-dienal (2.8 g, 10.07 mmol) in dry THF (5 mL), at 0 °C, was reacted with vinylmagnesium bromide (1 M in THF, 11 mL, 11 mmol) as reported above

for undecylic aldehyde (see synthesis of **4**) and worked-up in the same manner to give (*E*,*E*,*E*)-heneicosa-1,6,10-trien-3-ol (2.8 g, 91%) as an oil that was used without further purification in the next step of the synthesis. IR (neat): ν_{max} 3361 cm^{-1}. ^1H NMR (200 MHz): δ 5.81 (1H, ddd, J=17.2, 10.5, 6.4, H-2), 5.54–5.25 (4H, m, H-6, H-7, H-10, H-11), 5.17 (1H, br d, J=17.2, H_a-1), 5.04 (1H, br d, J=10.5, H_b-1), 4.06 (1H, q, J=6.2, H-3), 2.17–1.84 (8H, m), 1.70–1.45 (2H, m), 1.40–1.13 (16H, m), 0.86 (3H, t, J=6.7, Me). ^{13}C NMR (50 MHz): δ 141.1, 130.6, 130.4, 129.7, 129.4, 114.3, 72.4, 36.6, 32.63, 32.60, 32.5, 31.8, 29.6, 29.5, 29.3, 29.1, 28.4, 22.6, 14.0. MS *m*/*z* 345 (40, M+K)$^+$, 329 (83, M+Na)$^+$. HRMS: calcd for $C_{21}H_{38}ONa$ 329.2811, found 399.2800.

A solution of crude allyl alcohol (2.8 g, 9.1 mmol), triethyl orthoacetate (2.1 equiv, 19.2 mmol, 3.5 mL) and propionic acid (2%, 0.18 mmol, 19 μL) in xylene (3.5 mL) was refluxed for 4 h. Removal of the solvent followed by purification by column chromatography (petroleum ether → petroleum ether–ethyl ether, 9:1) afforded 1.77 g (53%) of (*E*,*E*,*E*)-tricosa-4,8,12-trienoic acid ethyl ester **15** as an oil.

Compound **15**: IR (neat): ν_{max} 1738 cm^{-1}. ^1H NMR (200 MHz): δ 5.49–5.26 (6H, m, olefinic protons), 4.12 (2H, q, J=6.7, $CO_2CH_2CH_3$), 2.42–2.21 (2H, m), 2.15–1.86 (12H, m), 1.41–1.15 (19H, br s including the $CO_2CH_2CH_3$ signal), 0.88 (3H, t, J=6.5, Me). ^{13}C NMR (50 MHz): δ 172.7, 130.9, 130.5, 130.0, 129.6, 129.4, 128.2, 59.9, 34.2, 32.5, 32.43, 32.38, 31.8, 29.5, 29.4, 29.2, 29.0, 27.8, 22.5, 14.0, 13.9. MS *m*/*z* 415 (54, M+K)$^+$, 399 (85, M+Na)$^+$. HRMS: calcd for $C_{25}H_{44}O_2Na$ 399.3228, found 399.3223.

4.1.6.2. (*E*,*E*,*E*,*E*)-Acetic acid pentacosa-2,6,10,14-tetraenyl ester 16. Ester **15** (1.77 g, 4.7 mmol) was reduced with $LiAlH_4$ (178 mg, 4.7 mmol) in dry ethyl ether (15 mL) following the same procedure employed for the synthesis of ester **5** to give 1.74 g of crude (*E*,*E*,*E*)-tricosa-4,8,12-trien-1-ol as an oil that was used without further purification in the next step of the synthesis. IR (neat): ν_{max} 3347 cm^{-1}. ^1H NMR (200 MHz): δ 5.50–5.24 (6H, m, olefinic protons), 3.57 (2H, t, J=7.0, H_2-1), 2.13–1.87 (12H, m), 1.57 (2H, quintet, J=7.0), 1.30 1.17 (16H, br s), 0.85 (3H, t, J=6.7, Me). ^{13}C NMR (50 MHz): δ 130.6, 130.4, 130.1, 129.8, 129.6, 129.5, 62.1, 32.64, 32.61, 32.56, 32.5, 32.3, 31.8, 29.6, 29.4, 29.3, 29.1, 28.8, 22.6, 14.0. MS *m*/*z* 373 (70, M+K)$^+$, 399 (45, M+Na)$^+$. HRMS: calcd for $C_{23}H_{42}ONa$ 357.3123, found 357.3140.

A solution of the crude alcohol (1.74 g, 5.2 mmol) in CH_2Cl_2 (23 mL) was oxidised with PCC (2.25 g, 10.4 mmol) and Celite (2.2 g) as reported for the synthesis of ester **5** to give 1.8 g of (*E*,*E*,*E*)-tricosa-4,8,12-trienal, as an oil, that was used in the next step. IR (neat): ν_{max} 1729 cm^{-1}. ^1H NMR (200 MHz): δ 9.76 (1H, t, J=1.6, C*H*O), 5.53–5.22 (6H, m, olefinic protons), 2.52–2.32 (2H, m), 2.39–2.24 (2H, m), 2.09–1.88 (10H, overlapped m's), 1.42–1.15 (16H, br s), 0.87 (3H, t, J=7.2, Me). ^{13}C NMR (50 MHz): δ 201.9, 131.2, 130.6, 130.1, 129.55, 129.47, 127.9, 43.4, 32.6, 32.5, 32.3, 31.8, 29.5, 29.4, 29.2, 29.0, 25.1, 22.6, 14.0. MS *m*/*z* −371 (45, M+K)$^+$, 355 (90, M+Na)$^+$. HRMS: calcd for $C_{23}H_{40}ONa$ 355.2967, found 355.2961.

The crude aldehyde obtained as above (1.80 g, 5.42 mmol) dissolved in dry THF (2 mL) was added to a solution of triethyl phosphonoacetate (1.07 mL, 5.42 mmol) in dry THF (3 mL), previously mixed with NaH (60% in mineral oil, 216 mg, 5.42 mmol), as described for the synthesis of ester **6**, to give 1.66 g of crude (*E*,*E*,*E*,*E*)-pentacosa-2,6,10,14-tetraenoic acid ethyl ester as an oil. Purification of a 50 mg amount of this material by HPLC (hexane–EtOAc, 98:2, flow: 2.5 mL/min) afforded a pure sample (25 mg, 38%, t_R=14.6 min) for spectral characterization. IR (neat): ν_{max} 1724 cm^{-1}. UV λ_{max} (MeOH)=208 nm (ε=25,300). ^1H NMR (300 MHz): δ 6.95 (1H, dt, J=15.8, 6.7, H-3), 5.81 (1H, dt, J=15.8, 1.2, H-2), 5.50–5.30 (6H, m, olefinic protons), 4.18 (2H, q, J=7.4, $CO_2CH_2CH_3$), 2.31–2.19 (2H, m), 2.19–2.09 (2H, m), 2.09–1.90 (10H, overlapped m's), 1.38–116 (19H, br s partly overlapped with a triplet (J=7.6) attributable to $CO_2CH_2CH_3$), 0.88 (3H, t, J=7.0, Me). ^{13}C NMR (50 MHz): δ 166.6, 148.5, 131.1, 130.7, 130.2, 129.7, 129.6, 128.6, 121.5, 60.0, 32.7, 32.57, 32.55, 32.52, 32.2, 31.9, 30.9, 29.6, 29.5, 29.3, 29.1, 22.6, 14.0. MS *m*/*z* 441 (90, M+K)$^+$, 425 (65, M+Na)$^+$. HRMS: calcd for $C_{27}H_{46}O_2Na$ 425.3384, found 425.3378.

The remaining crude ester (1.60 g, 4.23 mmol) dissolved in dry THF (12 mL) was reduced with DIBAL-H (1 M in THF, 12.7 mL, 12.7 mmol) at −78 °C as described for triene **7** to give 1.26 g of an oily product. HPLC purification (hexane–ethyl acetate, 7:3) gave 410 mg (24% respect to ester **15**; four steps) of (*E*,*E*,*E*,*E*)-pentacosa-2,6,10,14-tetraen-1-ol as an oil. IR (neat): ν_{max} 3348 cm^{-1}. ^1H NMR (200 MHz): δ 5.67 (2H, m, olefinic protons), 5.40 (6H, m, olefinic protons), 4.08 (2H, d, J=4.4, H_2-1), 2.15–1.87 (14H, overlapped m's), 1.35–1.5 (16H, br s), 0.87 (3H, t, J=7.2, Me). ^{13}C NMR (100 MHz): δ 132.7, 130.7, 130.4, 130.1, 129.9, 129.6, 129.5, 129.2, 63.8, 32.65, 32.62, 32.5, 32.2, 32.1, 31.9, 29.6, 29.5, 29.3, 29.1, 22.6, 14.0. MS *m*/*z* 399 (80, M+K)$^+$, 383 (43, M+Na)$^+$. HRMS: calcd for $C_{25}H_{44}ONa$ 383.3279, found 383.3277.

Acetylation of the above alcohol (410 mg, 1.14 mmol) with Ac_2O–pyridine (1:1, 1 mL), as described for the synthesis of triene **7**, gave 495 mg of tetraene **16**. Accurate ^1H NMR analysis revealed it to be still contaminated by other minor products exhibiting very similar chromatographic (HPLC direct-phase) mobility. Pure **16**, an oil, could be obtained after reverse-phase (MeOH) HPLC (250 mg, 55%).

Compound **16**: IR (neat): ν_{max} 1738, 1229 cm^{-1}. ^1H NMR (400 MHz): δ 5.78 (1H, dt, J=15.4, 6.2, olefinic proton), 5.58 (1H, dt, J=15.4, 6.4, olefinic proton), 5.35–5.45 (6H, m, olefinic protons), 4.51 (2H, d, J=6.4, H_2-1), 2.13–1.95 (17H, overlapped m's including a 3H singlet at 2.06 ppm due to the acetate methyl), 1.40–1.20 (16H, br s), 0.90 (3H, t, J=7.2, Me). ^{13}C NMR (100 MHz): δ 170.7, 135.8, 130.7, 130.5, 130.1, 129.8, 129.6, 129.3, 124.1, 65.1, 32.67, 32.65, 32.61, 32.5, 32.2, 31.9, 29.6, 29.5, 29.3, 29.1, 22.6, 20.9, 14.0. MS *m*/*z* 441 (33, M+K)$^+$, 425 (62, M+Na)$^+$. HRMS: calcd for $C_{27}H_{46}O_2Na$ 425.3384, found 425.3377.

4.1.7. Oxidation of tetraene 16 with $RuO_{4(cat.)}$/$NaIO_4$. Tetraene **16** was oxidised as reported above for triene **7**. In particular, to a solution of tetraene **16** (27.3 mg,

0.068 mmol) in the biphasic mixture EtOAc–CH_3CN–H_2O (3:3:1) (10.5 mL) were added in sequence $NaIO_4$ (5 equiv, 75 mg) and $RuO_2\cdot 2H_2O$ (20 mol %, 1.7 mg) under vigorous stirring at 0 °C. After 20 min a saturated $Na_2S_2O_3\cdot 5H_2O$ solution (2 mL) was added and, after a further 10 min stirring, the mixture was filtered and extracted with EtOAc (3×10 mL). The combined organic phase was dried and evaporated to give 35 mg of an oily product. HPLC separation (hexane–EtOAc, 3:7, flow 2.5 mL/min) afforded bis-THF diol **17** (6.2 mg, 21%, t_R=13 min), bis-THF ketol **18** (4.8 mg, 16%, t_R=9.6 min) and bis-THF ketol **19** (1.1 mg, 5%, t_R=9.2 min) as oils.

4.1.7.1. Acetic acid 6-hydroxy-6-[5′-(1-hydroxy-undecyl)-octahydro-[2,2′]bifuranyl-5-yl]-hex-2-enyl ester 17. IR (neat): ν_{max} 3414, 1737 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 5.73 (1H, dt, J=15.2, 6.5, H-3), 5.59 (1H, dt, J=15.2, 6.5, H-2), 4.50 (2H, d, J=6.5, H_2-1), 3.89 (2H, m, H-10 and H-11), 3.83 (2H, m, H-7 and H-14), 3.40 (1H, m, H-6), 3.39 (1H, m, H-15), 2.28, 2.15 (1H each, m's, H_2-4), 2.06 (3H, s, acetate), 1.94, 1.81 (4H each, m's, H_2-8, H_2-9, H_2-12, H_2-13), 1.55, 1.53 (1H each, m's, H_2-5), 1.45 (2H, m, H_2-16), 1.26 (16H, br s, H_2-17/H_2-24), 0.87 (3H, t, J=6.8, H_3-25).

^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 171.4 (carbonyl), 136.2 (CH-3), 124.1 (CH-2), 83.1 (CH-7, CH-14), 81.3 (CH-10, CH-11); 74.1 (CH-15), 73.4 (CH-6), 65.3 (CH_2-1), 34.5 (CH_2-16), 33.9 (CH_2-5), 29.7 (CH_2-17/CH_2-24), 28.5 (CH_2-4, CH_2-8, CH_2-9, CH_2-12, CH_2-13), 21.1 (acetate), 14.0 (CH_3-25). MS m/z 507 (47, M+K)$^+$, 491 (75, M+Na)$^+$. HRMS: calcd for $C_{27}H_{48}O_6Na$ 491.3336, found 491.3343.

4.1.7.2. Acetic acid 6-hydroxy-6-(5′-undecanoyl-octahydro-[2,2′]bifuranyl-5-yl)-hex-2-enyl ester 18. IR (neat): ν_{max} 3414, 1734, 1716 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 5.77 (1H, dt, J=15.4, 6.5, H-3), 5.62 (1H, dt, J=15.4, 6.7, H-2), 4.50 (2H, d, J=6.7, H_2-1), 4.38 (1H, dd, J=8.3, 5.8, H-14), 3.95 (2H, m, H-10 and H-11), 3.83 (1H, dt, J=7.5, 5.6, H-7), 3.40 (1H, m, H-6), 2.57 (2H, dt, J=7.2, 2.6, H_2-16), 2.30, 2.19 (1H each, m's, H_2-4), 2.16, 1.96 (1H each, m's, H_2-13), 2.07 (3H, s, acetate), 2.03, 1.71 (1H each, m's, H_2-12), 1.96, 1.81 (1H each, m's, H_2-9), 1.95, 1.77 (1H each, m's, H_2-8), 1.56, 1.54 (1H each, m's, H_2-5), 1.27 (16H, br s, H_2-17/H_2-24), 0.88 (3H, t, J=6.8, H_3-25).

^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 211.0 (C-15), 171.6 (carbonyl acetate), 136.3 (CH-3), 124.1 (CH-2), 83.4 (CH-14), 82.9 (CH-7), 82.7 (CH-11), 81.1 (CH-10), 73.4 (CH-6), 65.3 (CH_2-1), 39.2 (CH_2-16), 33.5 (CH_2-5), 29.8 (CH_2-17/CH_2-24), 29.1 (CH_2-13), 28.8 (CH_2-4), 28.2 (CH_2-8), 28.1 (CH_2-9), 27.9 (CH_2-12), 21.1 (CH_3 acetate), 14.2 (CH_3-25). MS m/z 505 (45, M+K)$^+$, 489 (71, M+Na)$^+$. HRMS: calcd for $C_{27}H_{46}O_6Na$ 489.3180, found 489.3172.

4.1.7.3. Acetic acid 6-[5′-(1-hydroxy-undecyl)-octahydro-[2,2′]bifuranyl-5-yl]-6-oxo-hex-2-enyl ester 19. IR (neat): ν_{max} 3444, 1739, 1716 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 5.76 (1H, dt, J=15.3, 6.8, H-3), 5.59 (1H, dt, J=15.3, 6.5, H-2), 4.48 (2H, d, J=6.5, H_2-1), 4.37 (1H, dd, J=8.5, 6.0, H-7), 3.94 (1H, m, H-10), 3.92 (1H, m, H-11), 3.83 (1H, m, H-14), 3.37 (1H, br q, J=7.2, H-15), 2.69 (1H, dt, J=7.2, 2.0, H_2-5), 2.33 (2H, br q, J=7.4, H_2-4), 2.15, 1.98 (1H each, m's, H_2-8), 2.05 (3H, s, acetate), 1.92, 1.76 (3H each, m's, H_2-9, H_2-12, H_2-13), 1.26 (16H, br s, H_2-17/H_2-24), 0.87 (3H, t, J=6.8, H_3-25).

^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 213.0 (C-6), 171.6 (carbonyl acetate), 134.5 (CH-3), 124.1 (CH-2), 84.2 (CH-7), 83.1 (CH-10, CH-14), 81.6 (CH-11), 74.2 (CH-15), 65.2 (CH_2-1), 38.1 (CH_2-5), 29.8 (CH_2-17/CH_2-24), 28.8 (CH_2-8), 28.5 (CH_2-9, CH_2-12, CH_2-13), 25.7 (CH_2-4), 21.0 (CH_3 acetate), 14.2 (CH_3-25). MS m/z 505 (60, M+K)$^+$, 489 (82, M+Na)$^+$. HRMS: calcd for $C_{27}H_{46}O_6Na$ 489.3180, found 489.3187.

4.1.8. Oxidation of bis-THF diol 17 with TPAP/NMO. To a solution of **17** (5.0 mg, 0.01 mmol) in CH_2Cl_2 (400 μL) were sequentially added NMO (2.0 mg, 1.5 equiv), powdered 4 Å molecular sieves (5 mg) and TPAP (10 mol %, 0.4 mg) under stirring at room temperature. After 1 h, the mixture was concentrated, filtered on silica gel ($CHCl_3$–CH_3OH, 9:1) to give 4.5 mg of a crude material whose ^1H NMR analysis revealed the presence of a mixture of ketols **18** and **19** in a ca. 1:1 ratio.

4.1.9. Synthesis of (*E*,*Z*,*E*)-acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester (21). Ozone was bubbled through a solution of 12 g (110 mmol) of 1,5-cyclooctadiene (COD) in 120 mL of CH_2Cl_2 at −78 °C as reported in Ref. 18. Then PPh_3 (5.82 g, 22 mmol) was added and the bath removed. After 1 h $Ph_3P{=}CHCO_2Et$ (25 g, 71.8 mmol) was added and the mixture kept at room temperature for 16 h. Then the solvent was evaporated to give a white solid to which was added petroleum ether (40–70). Filtration under vacuum afforded a yellowish oil that was chromatographed on silica gel. The fraction eluted with petroleum ether–ethyl ether (85:15) gave 4.42 g (14.3%) of pure (*E*,*Z*,*E*)-dodeca-2,6,10-trienedioic acid diethyl ester **20** as an oil.[18]

Compound **20**: IR (neat): ν_{max} 1720, 1655 cm^{-1}. ^1H NMR (300 MHz): δ 6.94 (1H, dt, J=15.6, 6.6, H-3), 5.83 (1H, d, J=15.6, H-2), 5.40 (1H, br t, J=4.2, H-6), 4.18 (2H, q, J=6.9, $CO_2CH_2CH_3$), 2.30–2.10 (4H, m, 2×CH_2), 1.28 (3H, t, J=7.2, Me). ^{13}C NMR (75 MHz): δ 165.9, 147.7, 128.8, 121.4, 59.6, 31.5, 25.4, 13.8. MS m/z 319 (55, M+K)$^+$, 303 (90, M+Na)$^+$.

To a solution of diester **20** (1.64 g, 5.86 mmol) in dry THF (10 mL) was dropwise added DIBAL-H (1 M in toluene, 25.8 mL, 25.8 mmol) at −78 °C. The mixture was stirred at this temperature for 1 h and then a saturated NH_4Cl solution (5 mL) was dropwise added. The mixture was extracted with EtOAc (4×20 mL). The combined organic layer was dried and concentrated to give 1.12 g (98%) of (*E*,*Z*,*E*)-dodeca-2,6,10-triene-1,12 diol as an oil. IR (neat): ν_{max} 3330 cm^{-1}. ^1H NMR (200 MHz): δ 5.63 (2H, m, olefinic protons), 5.35 (1H, br t, J=3.8, olefinic proton), 4.03 (2H, d, J=3.8, olefinic proton, H_2-1), 2.20–2.00 (4H, br s, 2×CH_2).[18] ^{13}C NMR (50 MHz): δ 132.0, 129.3, 63.2, 32.0, 26.7. MS m/z 235 (70, M+K)$^+$, 219 (86, M+Na)$^+$.

To 1.12 g (5.7 mmol) of the above diol were added Ac_2O and pyridine (1:1, 5 mL) and the mixture was kept overnight at room temperature. Usual work-up followed by HPLC purification (4:6 hexane–EtOAc) afforded 1.16 g (73%) of pure triene diacetate **21** as an oil.

4.1.9.1. (*E*,*Z*,*E*)-Acetic acid 12-acetoxy-dodeca-2,6,10-trienyl ester 21. IR (neat): ν_{max} 1738, 1234 cm^{-1}. ^1H NMR (300 MHz): δ 5.84–5.65 (1H, m, olefinic proton), 5.57 (1H, dt, J=15.3, 6.0, olefinic proton), 5.42–5.28 (1H, br s, olefinic proton), 4.48 (2H, d, J=6.3, H_2-1), 2.10, 2.03 (overall 7H, br s and s, 2×CH_2 and methyl acetate). ^{13}C NMR (75 MHz): δ 170.8, 135.7, 129.3, 124.2, 65.1, 32.2, 26.6, 21.00. MS *m*/*z* 319 (43, M+K)$^+$, 303 (91, M+Na)$^+$. HRMS: calcd for $C_{16}H_{24}O_4Na$ 303.1566, found 303.1573.

4.1.10. Oxidation of triene 21 with $RuO_{4(cat.)}$/$NaIO_4$. Triene **21** was oxidised as reported above for triene **7**. In particular, to a solution of **21** (45 mg, 0.16 mmol) in the biphasic mixture EtOAc–CH_3CN–H_2O (3:3:1) (21 mL) were added in sequence $NaIO_4$ (4 equiv, 137.5 mg) and $RuO_2\cdot 2H_2O$ (20%, 4.2 mg) under vigorous stirring at 0 °C. After 30 min, the process was complete (disappearance of the starting product). A saturated $Na_2S_2O_3\cdot 5H_2O$ solution (2 mL) was added and stirring continued for further 10 min. Then the mixture was filtered and extracted with EtOAc (3×10 mL) and the combined organic phase was dried and evaporated to give 30 mg of an oily product. HPLC separation (hexane–EtOAc, 2:8, flow 2.5 mL/min) afforded mono-THF lactone **22** (5.4 mg, 13%), the corresponding lactol (ca. 1:1 mixture of epimers) **23** (0.8 mg, 2%) and a mixture of diastereomeric tetrols **24** (6.9 mg, 12%).

When the reaction was conducted in the same conditions using a 2.0 equiv amount of $NaIO_4$ (**21**: 30 mg; $NaIO_4$: 45.8 mg; solvent amount 12 mL) a partial cyclization was observed as previously seen for triene **7**. In particular, the starting triene was recovered in a 35% yield while mono-THF diol **26** and mono-THF ketone **27** were obtained in 25% and 11% yields, respectively, after HPLC (EtOAc–hexane, 75:25, flow 2.5 mL/min; **26**: t_R=17.0 min; **27**: t_R=12.5 min).

4.1.10.1. Acetic acid 2-hydroxy-2-(5′-oxo-octahydro-[2,2′]bifuranyl-5-yl)-ethyl ester 22. IR (neat): ν_{max} 3430, 1772, 1733 cm^{-1}; ^1H NMR (300 MHz): δ 4.49 (1H, br q, J=−5.5, H-7), 4.15 (2H, d, J=6.0, H_2-1), 4.02 (1H, br q, J=5.5, H-3 or H-6), 3.97 (1H, br q, J=6.0, H-6 or H-3), 3.74 (1H, br q, J=5.5, H-2), 2.54 (2H, m), 2.32 (2H, m), 2.13–1.95 (overall 5H, multiplet overlapped to a 3H singlet at 2.10 ppm for the acetate methyl), 1.95–1.82 (2H, m). ^{13}C NMR (75 MHz): δ 176.7, 171.1, 80.9, 80.4, 79.8, 71.8, 66.1, 28.1, 27.3, 27.2, 24.0, 20.9. MS *m*/*z* 297 (60, M+K)$^+$, 281 (100, M+Na)$^+$. MS *m*/*z* 297 (36, M+K)$^+$, 281 (77, M+Na)$^+$. HRMS: calcd for $C_{12}H_{18}O_6Na$ 281.0996, found 281.0989.

4.1.10.2. Acetic acid 2-hydroxy-2-(5′-hydroxy-octahydro-[2,2′]bifuranyl-5-yl)-ethyl esters 23. IR (neat): ν_{max} 3396, 1733 cm^{-1}; ^1H NMR (300 MHz): δ 5.50, 5.59 (1H each, br s's, 2×H-10), 4.41, 4.25 (1H each, m's, 2×H-7), 4.20–4.08 (5H, overlapped m's, 2×H_2-1 and 1×C*H*O-THF), 4.08–3.96 (3H, m, 3×C*H*O-THF), 3.66 (2H, m, 2×H-2), 2.22–1.78 (overall 11H, multiplet overlapped with a 3H singlet at 2.09 ppm for the acetate methyl). ^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 170.8 (carbonyl), 81.5, 81.0 (CH-1, CH-4, CH-5), 78.9 (CH-8), 72.0 (CH-9), 66.1 (CH-10), 29.0, 27.5 (CH_2-2, CH_2-3, CH_2-6, CH_2-7), 20.9 (CH_3 acetate). MS *m*/*z* 299 (56, M+K)$^+$, 283 (78, M+Na)$^+$. HRMS: calcd for $C_{12}H_{20}O_6Na$ 283.1152, found 283.1160.

4.1.10.3. Acetic acid 6-[5-(2-acetoxy-1-hydroxy-ethyl)-tetrahydro-furan-2-yl]-2,3,6-trihydroxy-hexyl ester 24. IR (neat): ν_{max} 3390, 1733 cm^{-1}; ^1H NMR (selected values, 200 MHz): δ 4.30–4.10 (4H, m, 2×C*H*$_2$OAc), 4.10–3.84 (2H, br m, 2×H-THF), 3.84–3.55 (4H, br m, H-2, H-3, H-6, H-11), 2.10, 2.09 (3H each, s's, 2×OAc), 2.10–1.40 (8H, m, 4×CH_2). MS *m*/*z* 403 (100, M+K)$^+$, 387 (78, M+Na)$^+$, 365 (30, M+H)$^+$. MS *m*/*z* 403 (88, M+K)$^+$, 387 (43, M+Na)$^+$. HRMS: calcd for $C_{16}H_{28}O_9Na$ 387.1623, found 387.1617.

4.1.10.4. Acetic acid 2-[5′-(2-acetoxy-1-hydroxy-ethyl)-octahydro-[2,2′]bifuranyl-5-yl]-2-hydroxy-ethyl ester 25. IR (neat): ν_{max} 3422, 1739 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 4.28 (1H, A part of an AB system further coupled, J=11.3, 7.7, C(1)H_aHOAc), 4.23 (1H, ddd, J=9.3, 6.0, 4.0, H-7), 4.17, 4.12 (1H each, AB system further coupled, J=11.7, 4.1 and 11.7, 6.8, respectively, C(12)H_2OAc), 4.09, 4.07, 4.05 (overall 3H, overlapped m's, C(1) HH_bOAc, H-3, H-6, respectively), 4.00 (1H, dt, J=8.5, 5.6, H-10), 3.73 (1H, q, J=5.0, H-11), 3.67 (1H, q, J=4.1, H-2), 2.093 (3H, s, acetate), 2.087 (3H, s, acetate), 1.85–2.05 (8H, overlapped m's, H_2-4, H_2-5, H_2-8, H_2-9). ^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 171.1 (acetate carbonyl linked to C-12), 170.8 (acetate carbonyl linked to C-1), 82.0 (CH-6), 81.3 (CH-7), 80.4 (CH-10), 79.2 (CH-3), 72.6 (CH-2), 72.0 (CH-11), 65.9 (CH_2-1), 65.7 (CH_2-12), 28.3, 27.5 (CH_2-4, CH_2-5, CH_2-8, CH_2-9), 21.3 (acetate methyl linked to C-1), 21.2 (acetate methyl linked to C-12). MS *m*/*z* 385 (89, M+K)$^+$, 369 (71, M+Na)$^+$. HRMS: calcd for $C_{16}H_{26}O_8Na$ 369.1518, found 369.1526.

4.1.10.5. Acetic acid 6-[5-(2-acetoxy-1-hydroxy-ethyl)-tetrahydro-furan-2-yl]-6-hydroxy-hex-2-enyl ester 26. IR (neat): ν_{max} 3419, 1739 cm^{-1}. ^1H NMR (600 MHz, attributions by 2D-NMR): δ 5.78 (1H, dt, J=15.6, 6.8, H-3), 5.61 (1H, dt, J=15.6, 6.5, H-2), 4.52 (2H, d, J=6.5, C(1)H_2OAc), 4.19, 4.16 (1H each, AB system further coupled, J=11.7, 6.8 and 11.7, 4.1, respectively, CH_2(12)-OAc), 4.01 (1H, m, H-10), 3.92 (1H, dt, J=7.2, 2.8, H-7), 3.88 (1H, m, H-6), 3.74 (1H, m, H-11), 2.30, 2.16 (1H, each, m's, H_2-4), 2.09, 2.06 (3H each, s's, acetates), 2.05–1.85 (4H, m's, H_2-8, H_2-9), 1.48 (2H, m, H_2-5). ^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 171.6 (2×carbonyl), 135.2 (CH-3), 124.6 (CH-2), 83.2 (CH-7), 78.7 (CH-10), 72.0 (CH-11), 71.9 (CH-6), 66.3 (CH_2-12), 65.0 (CH_2-1), 32.0 (CH_2-5), 28.7 (CH_2-4), 28.2 (CH_2-8, CH_2-9), 21.0 (2×CH_3 acetates). MS=*m*/*z* 369 (40, [M+K]$^+$), 353 (81, [M+Na]$^+$). HRMS: calcd for $C_{16}H_{26}O_7Na$ 353.1569, found 353.1577.

4.1.10.6. Acetic acid 6-[5-(2-acetoxy-1-hydroxy-ethyl)-tetrahydro-furan-2-yl]-6-oxo-hex-2-enyl ester 27. IR (neat): ν_{max} 3403, 1733, 1716 cm^{-1} ^1H NMR (600 MHz,

attributions by 2D-NMR): δ 5.76 (1H, dt, J=20.5, 6.8, H-3), 5.62 (1H, dt, J=20.5, 6.8, H-2), 4.56 (1H, dd, J=8.7, 3.9, H-7), 4.55 (2H, d, J=6.0, C(1)H_2OAc), 4.24 (2H, m, C(12)H_2OAc) 4.18 (1H, m, H-10), 3.74 (1H, m, H-11), 2.61, 2.53 (1H each, m's, H_2-5), 2.37, 2.41 (1H each, m's, H_2-4), 2.09, 2.06 (3H each, s's, acetates), 2.05–1.85 (4H, overlapped m's, H_2-8, H_2-9). ^{13}C NMR (150 MHz, attributions by 2D-NMR): δ 211.4 (C-6), 171.6, 171.0 (2×acetate carbonyls), 133.5 (CH-3), 125.2 (CH-2), 82.6 (CH-7), 80.4 (CH-10), 70.2 (CH-11), 65.1 (CH_2-12), 64.9 (CH_2-1), 38.2 (CH_2-5), 29.0, 27.5 (CH_2-8, CH_2-9), 25.5 (CH_2-4), 21.0, 20.9 (2×acetate methyls). MS m/z 367 (31, M+K)$^+$, 351 (93, M+Na)$^+$. HRMS: calcd for $C_{16}H_{24}O_7Na$ 351.1413, found 351.1406.

4.1.11. Synthesis of mono-THF olefin 26 from triene 21. To a solution of 19.5 mg (0.070 mmol) of triene **21** in CH_2Cl_2 (500 μL) were added TMEDA (1 equiv, 10.5 μL) and OsO_4 (1 equiv, 17.7 mg) under stirring at rt. Immediate TLC analysis ($CHCl_3$–MeOH, 9:1) revealed the formation of two coloured spots (R_f=0.2 and 0.4), likely attributable to the two possible osmate ester, along with a minor amount of unreacted triene. The mixture was taken to dryness after some 2 h and subjected to two successive HPLC runs ($CHCl_3$–MeOH, 9:1 then 95:5). The material eluted after 9 min (6.5 mg) in the second solvent mixture was identified as the osmate ester at one of the terminal double bonds. Starting triene (4.2 mg, 22%) was recovered as well.

3.4 mg of the above material was dissolved in CH_2Cl_2–AcOH (2:1, 700 μL). After 2 h, 10 drops of AcOH were added and the mixture left at 5 °C for two days. Then a saturated $NaHCO_3$ solution was dropwise added, the mixture was diluted with $CHCl_3$ (1 mL) and extracted with the same solvent (3×2 mL). The organic phase was washed with water, dried and taken to dryness to give 1.0 mg (12% from **21**) of a very pure compound that showed to be identical to mono-THF olefin **26** by NMR and chromatographic methods.

4.1.12. Dihydroxylation of 26 to 24. To a solution of **26** (3.0 mg, 0.009 mmol) in acetone–H_2O (5:1) (600 μL) was added OsO_4 1.2 equiv (12 μL from a 1 M stock solution in acetone–H_2O, 5:1). TLC analysis carried out within 10 min revealed the disappearance of the starting product. Excess NMO (3 equiv, 2.7 mg) was then added and the mixture stirred for 15 min. TLC analysis indicated the formation of a single spot at the R_f expected for tetrols **24**. The mixture was dried under a nitrogen flow and $CHCl_3$ was added. The $CHCl_3$ solution was recovered through a small piece of cotton wool, taken to dryness and separated by HPLC (250×4.6 mm column, $CHCl_3$–MeOH, 9:1; flow 0.9 mL/min) to give two partially overlapped peaks eluted at t_R=21.5 and 22.5 min (together 0.5 mg, 15%). This material showed to be identical to tetrols **24** by ^{1}H NMR analysis and co-injection in the same solvent mixture.

4.1.13. Synthesis of lactols 23 from mono-THF olefin 26. To a solution of **26** (2.0 mg, 0.006 mmol) in THF–H_2O (4:1, 500 μL), was added OsO_4 (1.3 equiv, 2.0 mg) under stirring. After 5 min $NaIO_4$ (5 equiv, 6.5 mg) was added and the mixture stirred for 2.5 h. Then a saturated $Na_2S_2O_3\cdot 5H_2O$ solution (500 μL) was added and the mixture, after a further 10 min stirring, was extracted with EtOAc (3×3 mL). The organic phase was dried and evaporated to give 2.4 mg of a crude product that was further purified by HPLC (hexane–EtOAc, 2:8, flow 2.5 mL/min). 1.4 mg (90%) of a pure product was obtained that showed to be identical to the mixture of lactols **23**.

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Stereoselective preparation of 1,2,4-oxadiazole derivatives substituted by pentafluorophenyl by 1,3-dipolar cycloaddition reaction

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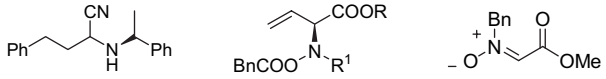
Abstract—1,3-Dipolar cycloaddition reactions of chiral imines obtained from optically active amino acids with nitrile oxides afforded 1,2,4-oxadiazole derivatives in moderate to good yields with good stereoselectivity. Investigation on the effect of bases suggested that triethylamine was prone to afford better stereoselectivity, while $NaHCO_3$ was prone to increase the reaction rates and yields.

1. Introduction

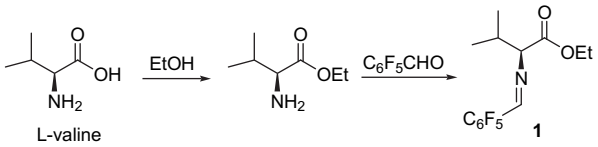
1,3-Diploar cycloaddition (1,3-DC) reaction for the synthesis of five-membered heterocycles is a classic reaction in organic chemistry, due to a high degree of site-, regio-, and stereoselectivity.[1] Therefore, these reactions are widely used for the preparation of molecules with significance for both academia and industry. In recent years, the development of new stereoselective version has been a major challenge. The stereochemistry of the 1,3-DC reaction can be controlled either by the appropriate substrates or choosing a metal complex as a catalyst.[2] Compared with the utilization of a metal catalyst, it is straightforward to employ the chiral substrate in the reaction system. Generally, the most commonly used chiral dipoles or philodipoles were derived from optically active amino acids or their derivatives.[3]



Nitrile oxides are known to be remarkably active dipoles in 1,3-DC reactions, and have been extensively investigated for their synthetic application and for elucidation of the reaction mechanism of 1,3-DC reaction.[4] Generally, the 1,3-DC reaction of nitrile oxides with philodipoles can afford two regioisomers, each as a pair of enantiomers in which the relative configuration between the 4- and 5-substituents is determined by the geometry of the phliodipoles. Due to the potential versatility of this reaction for the construction of chiral compounds,[5] the demand for asymmetric versions of this reaction has increased over the last 20 years. Thus, several publications on asymmetric 1,3-DC reactions of nitrile oxides with alkenes have appeared.[6] However, to the best of our knowledge, only a few applications of imino-1,3-DC reaction were reported;[7] furthermore, no literature has reported the reaction of optically active imine in the reaction. As a continuation of our research interests in chemical transformation of fluorine-containing imine,[8] we report herein the 1,3-DC reaction of chiral imine **1** prepared from perfluorobenzaldehyde and (*S*)-ethyl 2-amino-3-methylbutanoate with nitrile oxides in the presence of triethylamine or $NaHCO_3$. It was favorable that the reaction can afford the corresponding five-membered heterocycles with good stereoselectivity.

2. Results and discussion

Compound **1** can be conveniently prepared by the dehydration reaction of perfluorobenzaldehyde with (*S*)-ethyl 2-amino-3-methylbutanoate (Scheme 1).[9] Compared with unfluorinated imine, pentafluorophenyl reinforced the stability of **1** to react with nitrile oxides.



Scheme 1.

Keywords: 1,3-Dipolar cycloaddition; Nitrile oxides; Pentafluorophenyl-containing imine; Stereoselectivity.
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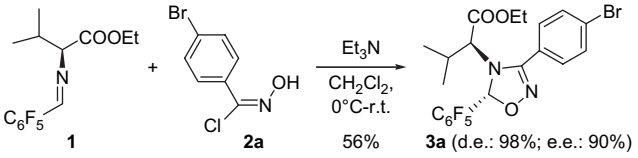
Nitrile oxides are almost always generated in situ in order to avoid dimerization. Generally, triethylamine (TEA) was utilized prevalently to prepare nitrile oxides in situ from benzohydroximinoyl chlorides.[10] On the other hand, $NaHCO_3$ could be employed in some 1,3-DC reactions as an alternative to TEA.[11] In this work, we compared base effects in the 1,3-DC reaction of optically active imine with nitrile oxides. First, we investigated the 1,3-DC reaction of **1** and *p*-bromophenyl nitrile oxide in the presence of TEA and the expected oxadiazole derivative **3a** was isolated in a moderate yield and with good diastereoselectivity and enantioselectivity (Scheme 2). Furthermore, the X-ray single crystal diffraction analysis was carried out to get more stereochemistry information (Fig. 1).



Scheme 2.

Based on the same reaction conditions, a series of structurally diversified nitrile oxides were used in the reaction and all results are summarized in Table 1. Just like **2a**, other substituted-phenyl nitrile oxides reacted with optically active imine in the presence of TEA (Table 1, entries 2–5). The aliphatic nitrile oxide **2f** also afforded the oxadiazole derivative in considerable yield. It showed that all the yields were not satisfactory and it was attributed to the slow and uncontrollable decomposition of the imine, because pentafluorobenzaldehyde and valinoethylate were detected in the reaction mixture. It was worthy to note that no product was isolated when a strong electron-withdrawing group such as NO_2 was present (Table 1, entry 7).

Compared with TEA, $NaHCO_3$ shortened the reaction time obviously from 3 days to 1 day as well as improved the yield (Table 2, entries 1–5). In addition, it was worthy to note that nitrile oxide containing the strong electron-withdrawing group such as nitryl could also afford the 1,2,4-oxadiazole

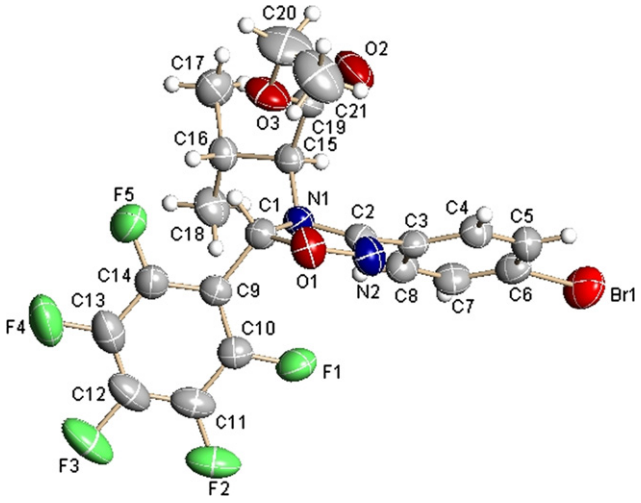
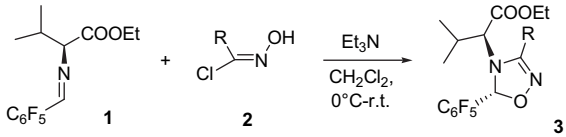


Figure 1. Molecular structure of **3a**.

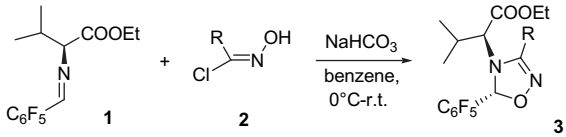
Table 1. Results of 1,3-DC reaction of **1** in the presence of TEA



Entry	**2** (R=)	Time (d)	Yield[a] **3** (%)	de[b] (%)	ee[c] (%)
1	**2a** (*p*-C_6H_4Br)	2	**3a** (56)	98	90
2	**2b** (*o*-C_6H_4Cl)	3	**3b** (44)	95	78
3	**2c** (*p*-C_6H_4F)	3	**3c** (45)	99	78
4	**2d** (*o*-C_6H_4F)	2	**3d** (54)	96	68
5	**2e** (*p*-C_6H_4Me)	2	**3e** (42)	91	86
6	**2f** ($CH{=}CHC_6H_5$)	2	**3f** (57)	90	77
7	**2g** (*m*-$C_6H_4NO_2$)	3	No[d]	—	—

[a] Isolated yield.
[b] ^1H NMR.
[c] Chiral HPLC.
[d] No product was isolated.

Table 2. Results of 1,3-DC reaction of **1** in the presence of $NaHCO_3$



Entry	**2** (R=)	Time (d)	Yield[a] **3** (%)	de[b] (%)	ee[c] (%)
1	**2a** (*p*-C_6H_4Br)	1	**3a** (90)	97	57
2	**2b** (*o*-C_6H_4Cl)	1	**3b** (78)	92	54
3	**2c** (*p*-C_6H_4F)	1	**3c** (84)	97	55
4	**2d** (*o*-C_6H_4F)	1	**3d** (74)	95	55
5	**2e** (*p*-C_6H_4Me)	1	**3e** (54)	99	59
6	**2g** (*m*-$C_6H_4NO_2$)	1	**3g** (69)	89	[d]

[a] Isolated yield.
[b] ^1H NMR.
[c] Chiral HPLC.
[d] Due to the limitation of the apparatus the ee value cannot be detected.

product in the presence of $NaHCO_3$ (Table 2, entry 6). However, lower enantioselectivity was observed in all cases, which could be attributed to the greater racemization of imine in the presence of $NaHCO_3$. On the other hand, the value of de in both tables indicated that the ratio of the diastereoisomers was not influenced by the experimental conditions.

3. Conclusion

We have demonstrated a new version of enantioselective 1,3-DC reaction of pentafluorophenyl-substituted imines and nitrile oxides. When TEA was utilized as the base, the 1,2,4-oxadiazole derivatives were isolated in moderate yields with good enantioselectivity. On the other hand, if $NaHCO_3$ was employed, higher yields were obtained even with nitrile oxides substituted by strong electron-withdrawing group; furthermore, the mild reaction conditions, ease of manipulation, straightforward procedure, and considerable yield of useful products make this transformation potentially useful in organic synthesis.

4. Experimental

4.1. General

Melting points were measured on a Temp-Melt. apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker AM-300 or AM-400 instruments with Me_4Si and $CFCl_3$ as the internal standards, respectively. FTIR spectra were obtained with a Nicolet AV-360 spectrophotometer. Low resolution mass spectra (LRMS) or high resolution mass spectra (HRMS) were obtained on a Finnigan GC–MS 4021 or a Finnigan MAT-8430 instrument, respectively, using the electron impact ionization technique (70 eV). Single crystal X-ray structure analysis was performed on a Bruker P4 instrument.

4.2. Preparation of compound 1

(*S*)-Ethyl 2-amino-3-methylbutanoate (50 mmol) and pentafluorobenzaldehyde (50 mmol) were refluxed in EtOH (10 ml) for 20 h. Then TLC analysis showed that the reaction was over and the product was purified by column chromatography on silica gel to give compound **1** (92%).

4.2.1. (*S*,*E*)-Ethyl 3-methyl-2-(perfluorobenzylideneamino)butanoate 1. Yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.27 (1H, s, CH═), 4.16 (2H, dd, $^3J_{HH}$=14, 7 Hz, CH_2), 3.64 (1H, d, $^3J_{HH}$=7 Hz, CH), 2.37–2.34 (1H, m, CH), 1.22 (3H, t, $^3J_{HH}$=7 Hz, CH_3), 0.90 (6H, t, $^3J_{HH}$=6 Hz, CH_3). ^{19}F NMR ($CDCl_3$): −142.00 to −142.11 (2F, m), −150.61 (1F, t, $^2J_{FF}$=20 Hz), −161.70 to −161.90 (2F, m).

4.3. Experimental procedure

Method a: Et_3N (0.5 mmol) in 1 mL of CH_2Cl_2 was added slowly to the mixture of **1** (0.3 mmol) and nitrile oxide **2a** (0.3 mmol) in 2 mL CH_2Cl_2 at 0 °C. Then the mixture was warmed to room temperature. TLC analysis was used to monitor the reaction. After 2 days, the reaction was completed. After general work-up, the residue was purified by column chromatography on silica gel to give the product **3a** in a yield of 56%. *Method b*: the mixture of **1** (0.3 mmol) and nitrile oxide **2a** (0.3 mmol) in 2 mL of benzene was added slowly into the mixture of $NaHCO_3$ (0.6 mmol) in 1 mL benzene at 0 °C. Then the mixture was warmed to room temperature. TLC analysis was used to monitor the reaction. After 1 day, the reaction was over completely. After general work-up, the residue was purified by column chromatography on silica gel to give the product **3a** in a yield of 90%.

4.3.1. (*S*)-Ethyl-2-((*R*)-3-(4-bromophenyl)-5-(perfluorophenyl)-1,2,4-oxadiazol-4(5*H*)-yl)-3-methylbutanoate 3a. Mp: 56–57 °C. ^{1}H NMR ($CDCl_3$): δ 7.56 (2H, d, $^3J_{HH}$=8 Hz, Ph), 7.40 (2H, d, $^3J_{HH}$=8 Hz, Ph), 7.19 (1H, s, CH), 4.21–4.05 (2H, m, CH_2), 3.42 (1H, d, $^3J_{HH}$=11 Hz, CH), 1.89–1.85 (1H, m, CH), 1.19 (3H, t, $^3J_{HH}$=7 Hz, CH_3), 0.809 (3H, d, $^3J_{HH}$=6 Hz, CH_3), 0.76 (3H, d, $^3J_{HH}$= 6 Hz, CH_3). ^{19}F NMR ($CDCl_3$): −142.72 to −142.82 (2F, m), −151.5 (1F, t, $^2J_{FF}$=20 Hz), −160.42 to −160.61 (2F, m). ^{13}C NMR ($CDCl_3$): δ 169.36 (C═O), 156.53 (C═N), 132.49 (Ph), 129.85 (Ph), 125.64 (Ph), 123.49 (Ph), 85.69, 66.52, 61.52, 29.71 (CH), 19.46 (CH_3), 19.30 (CH_3), 14.22 (CH_3). MS [ESI] (*m*/*z*, %): 521.2 (M^++H). IR (cm^{-1}): 2967, 1734, 1522, 1506, 1153, 1003. HRMS calcd for $C_{21}H_{19}BrN_2O_3F_5$: 521.0499; found: 521.0494.

X-ray data of compound ***3a***: $C_{21}H_{19}BrF_5N_2O_3$: FW=521.28; temperature 293(2) K; monoclinic, *P*2(1)/*c*; wavelength 0.71 Å; a=11.934(3) Å, b=12.730(3) Å, c=15.089(14) Å, α=90.00°, β=108.035(4)°, γ=90.00°; V=2179.7(9) Å; Z=4, Dc=1.589 mg/m^3; absorption coefficient 1.954 mm^{-1}; F (000)=1048; 1.79<θ<27.00; reflections collected 12,234; absorption correction empirical; transmission 1.000_{max}−0.5946_{min}; final R indices R_1=0.0511, wR_2=0.0867. The CCDC number is 612390.

4.3.2. (*S*)-Ethyl-2-((*R*)-3-(2-chlorophenyl)-5-(perfluorophenyl)-1,2,4-oxadiazol-4(5*H*)-yl)-3-methylbutanoate 3b. Mp: 73–75 °C. ^{1}H NMR ($CDCl_3$): δ 7.59 (1H, s, Ph), 7.53–7.40 (3H, m, Ph), 7.29 (1H, s, CH), 4.30–4.14 (2H, m, CH_2), 3.52 (1H, d, $^3J_{HH}$=11 Hz, CH), 1.99–1.92 (1H, m, CH), 1.34 (3H, t, $^3J_{HH}$=7 Hz, CH_3), 0.89 (3H, d, $^3J_{HH}$=7 Hz, CH_3), 0.84 (3H, d, $^3J_{HH}$=7 Hz, CH_3). ^{19}F NMR ($CDCl_3$): −142.6 to −142.79 (2F, m), −151.45 (1F, t, $^2J_{FF}$=20 Hz), −160.35 to −160.54 (2F, m). ^{13}C NMR ($CDCl_3$): δ 169.34 (C═O), 156.22 (C═N), 135.16 (Ph), 131.26 (Ph), 130.45 (Ph), 128.48 (Ph), 126.45 (Ph), 126.34 (Ph), 85.79, 66.44, 61.54, 29.69 (CH), 19.44 (CH_3), 19.28 (CH_3), 14.19 (CH_3). MS [ESI] (*m*/*z*, %): 477.2 (M^++H). IR (cm^{-1}): 2970, 1735, 1653, 1523, 1508, 1004. HRMS calcd for $C_{21}H_{18}ClN_2O_3F_5$: (M^++H) 477.1008; found: 477.0999.

4.3.3. (*S*)-Ethyl-2-((*R*)-3-(4-fluorophenyl)-5-(perfluorophenyl)-1,2,4-oxadiazol-4(5*H*)-yl)-3-methylbutanoate 3c. Mp: 109–111 °C. ^{1}H NMR ($CDCl_3$): δ 7.60 (2H, t, $^3J_{HH}$=6 Hz, Ph), 7.298 (1H, s, CH), 7.19 (2H, d, $^3J_{HH}$=6 Hz, Ph), 4.29–4.14 (2H, m, CH_2), 3.51 (1H, d, $^3J_{HH}$=11 Hz, CH), 1.99–1.92 (1H, m, CH), 1.26 (3H, t, $^3J_{HH}$=7 Hz, CH_3), 0.89 (3H, d, $^3J_{HH}$=7 Hz, CH_3), 0.84 (3H, d, $^3J_{HH}$= 7 Hz, CH_3). ^{19}F NMR ($CDCl_3$): −108.09 (1F), −142.76 to −143.92 (2F, m), −151.73 (1F, t, $^2J_{FF}$=20 Hz), −160.51 to −160.70 (2F, m). ^{13}C NMR ($CDCl_3$): δ 169.43 (C═O), 156.45 (C═N), 130.56 (Ph), 130.47 (Ph), 116.56 (Ph), 116.33 (Ph), 85.57, 66.40, 61.49, 29.72 (CH), 19.46 (CH_3), 19.30 (CH_3), 14.21 (CH_3). MS [ESI] (*m*/*z*, %): 461.2 (M^++H). IR (cm^{-1}): 2973, 1735, 1605, 1523, 1508, 1003. HRMS calcd for $C_{21}H_{18}N_2O_3F_6$: (M^++H) 461.1298; found: 461.1294.

4.3.4. (*S*)-Ethyl-2-((*R*)-3-(2-fluorophenyl)-5-(perfluorophenyl)-1,2,4-oxadiazol-4(5*H*)-yl)-3-methylbutanoate 3d. Oil. ^{1}H NMR ($CDCl_3$): δ 7.56–7.54 (2H, m, Ph), 7.35 (1H, s, CH), 7.29–7.21 (2H, m, Ph), 4.24–4.18 (2H, m, CH_2), 3.38 (1H, d, $^3J_{HH}$=11 Hz, CH), 1.96–1.84 (1H, m, CH), 1.27 (3H, t, $^3J_{HH}$=7 Hz, CH_3), 0.85 (3H, d, $^3J_{HH}$= 7 Hz, CH_3), 0.75 (3H, d, $^3J_{HH}$=7 Hz, CH_3). ^{19}F NMR ($CDCl_3$): −111.16 (1F), −142.59 to −142.66 (2F, m), −151.76 (1F, t, $^2J_{FF}$=20 Hz), −160.69 to −160.91 (2F, m). ^{13}C NMR ($CDCl_3$): δ 169.59 (C═O), 158.99 (C═N), 133.36 (Ph), 133.02 (Ph), 131.25 (Ph), 124.90 (Ph), 116.79 (Ph), 116.58 (Ph), 85.59, 66.22, 61.45, 29.59 (CH), 19.44 (CH_3), 19.01 (CH_3), 14.09 (CH_3). MS [ESI] (*m*/*z*, %): 461.2 (M^++H). IR (cm^{-1}): 2972, 1734, 1522, 1508, 1003.

HRMS calcd for $C_{21}H_{18}N_2O_3F_6$: (M^++H) 461.1302; found: 461.1294.

4.3.5. (*R*)-Ethyl-3-methyl-2-((*R*)-5-(perfluorophenyl)-3-*p*-tolyl-1,2,4-oxadiazol-4(5*H*)-yl)butanoate 3e. Mp: 72–73 °C. ^{1}H NMR ($CDCl_3$): δ 7.42 (2H, d, $^3J_{HH}$=7 Hz, Ph), 7.28 (2H, d, $^3J_{HH}$=7 Hz, Ph), 7.27 (1H, s, CH), 4.26–4.14 (2H, m, CH_2), 3.56 (1H, d, $^3J_{HH}$=10 Hz, CH), 2.42 (3H, s, CH_3), 1.96–1.92 (1H, m, CH), 1.28 (3H, t, $^3J_{HH}$=7 Hz, CH_3), 0.87 (3H, d, $^3J_{HH}$=7 Hz, CH_3), 0.84 (3H, d, $^3J_{HH}$=7 Hz, CH_3). ^{19}F NMR ($CDCl_3$): −142.63 to −142.73 (2F, m), −151.99 (1F, t, $^2J_{FF}$=20 Hz), −160.68 to −160.86 (2F, m). ^{13}C NMR ($CDCl_3$): 169.62 (C=O), 157.30 (C=N), 141.48 (Ph), 129.94 (Ph), 128.37 (Ph), 121.48 (Ph), 85.42, 66.31, 61.39, 29.74 (CH), 21.54 (CH_3), 19.50 (CH_3), 19.31 (CH_3), 14.23 (CH_3). MS [ESI] (*m*/*z*, %): 457.2 (M^++H). IR (cm^{-1}): 2966, 1733, 1522, 1507, 1154. HRMS calcd for $C_{22}H_{21}N_2O_3F_5$: 456.1472; found: 456.1465.

4.3.6. (*S*)-Ethyl-3-methyl-2-((*R*)-5-(perfluorophenyl)-3-((*E*)-styryl)-1,2,4-oxadiazol-4(5*H*)-yl)butanoate 3f. Mp: 59–61 °C. ^{1}H NMR ($CDCl_3$): δ 7.50 (2H, d, $^3J_{HH}$=6 Hz, Ph), 7.42–7.30 (3H, m, Ph), 7.25 (1H, s, CH), 7.24 (1H, d, $^3J_{HH}$=11 Hz, CH=), 6.56 (1H, d, $^3J_{HH}$=11 Hz, CH=), 4.24–4.19 (2H, m, CH_2), 3.69 (1H, d, $^3J_{HH}$=10 Hz, CH), 2.09–1.98 (1H, m, CH), 1.27 (3H, t, $^3J_{HH}$=7 Hz, CH_3), 0.96 (3H, d, $^3J_{HH}$=7 Hz, CH_3), 0.86 (3H, d, $^3J_{HH}$=7 Hz, CH_3). ^{19}F NMR ($CDCl_3$): −142.54 to −142.67 (2F, m), −151.81 (1F, t, $^2J_{FF}$=20 Hz), −160.72 to −160.91 (2F, m). ^{13}C NMR ($CDCl_3$): δ 169.65 (C=O), 155.08 (C=N), 138.75 (Ph), 138.57, 135.13 (Ph), 129.68 (Ph), 129.57 (Ph), 128.88 (Ph), 127.37, 110.04, 86.07, 66.41, 61.48, 29.86 (CH), 19.55 (CH_3), 19.29 (CH_3), 14.15 (CH_3). MS [ESI] (*m*/*z*, %): 469.2 (M^++H). IR (cm^{-1}): 2970, 1735, 1653, 1522, 1508, 1003. HRMS calcd for $C_{23}H_{21}N_2O_3F_5$: (M^++H) 469.1559; found: 469.1545.

4.3.7. (*S*)-Ethyl-3-methyl-2-((*R*)-3-(3-nitrophenyl)-5-(perfluorophenyl)-1,2,4-oxadiazol-4(5*H*)-yl)butanoate 3g. Mp: 87–89 °C. ^{1}H NMR ($CDCl_3$): δ 8.46 (1H, s, Ph), 8.41 (1H, d, $^3J_{HH}$=8 Hz, Ph), 7.98 (1H, d, $^3J_{HH}$=7 Hz, Ph), 7.75 (1H, d, $^3J_{HH}$=7 Hz, Ph), 7.34 (1H, s, CH), 4.32–4.18 (2H, m, CH_2), 3.50 (1H, d, $^3J_{HH}$=11 Hz, CH), 2.02–1.98 (1H, m, CH), 1.27 (3H, t, $^3J_{HH}$=7 Hz, CH_3), 0.96–0.86 (6H, m, CH_3). ^{19}F NMR ($CDCl_3$): −142.75 to −142.85 (2F, m), −151.03 (1F, t, $^2J_{FF}$=20 Hz), −160.08 to −160.26 (2F, m). ^{13}C NMR ($CDCl_3$): δ 169.03 (C=O), 155.59 (C=N), 148.64 (Ph), 133.91 (Ph), 130.44 (Ph), 126.51 (Ph), 125.96 (Ph), 123.25 (Ph), 86.08, 66.67, 61.72, 29.67 (CH), 19.40 (CH_3), 19.26 (CH_3), 14.18 (CH_3). MS [ESI] (*m*/*z*, %): 488 (M^++H). IR (cm^{-1}): 2970, 1736, 1730, 1523, 1508, 1350, 1003. HRMS calcd for $C_{20}H_{18}N_3O_5F_5$: 487.1167; found: 487.1174.

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