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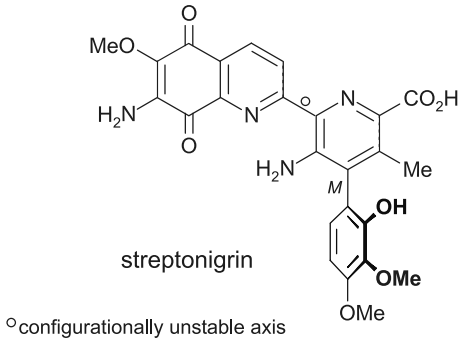
Tetrahedron

Tetrahedron Vol. 60, No. 16, 2004

Contents

REPORT



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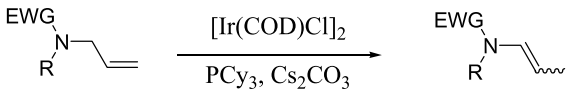
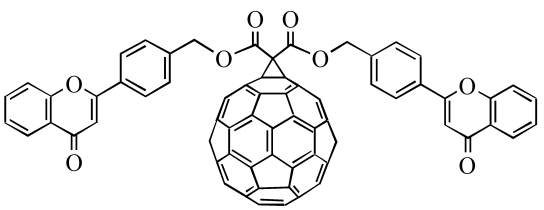
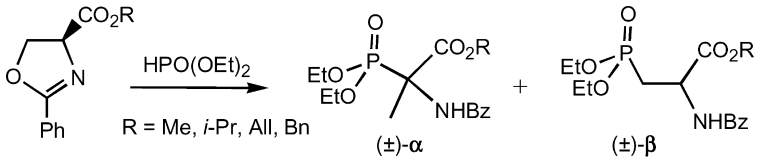
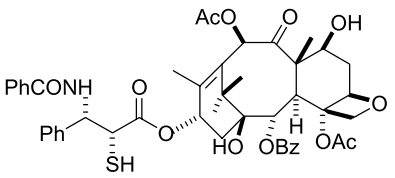
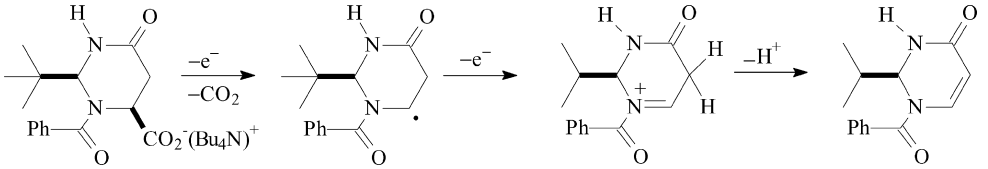


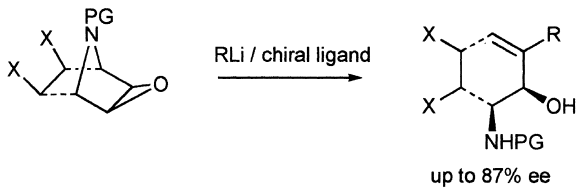


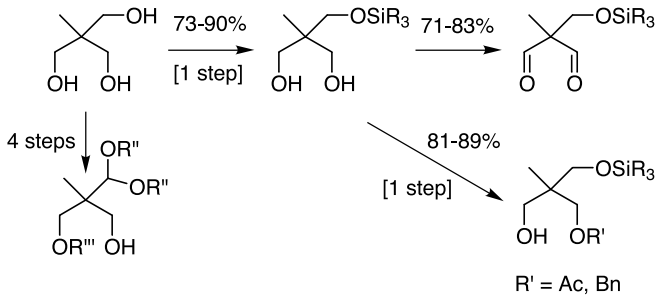


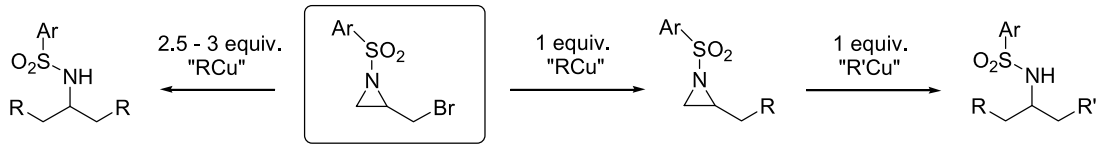
The reaction of oxazolines derived from L-serine with diethylphosphite, leads to a mixture of racemic α- and β-phosphono alanines in about 1:2 ratio, and with isolated yields up to 77%. This new reaction, which proceeds in neutral conditions and without the use of any halogenated intermediate, offers a simple route for various phosphono amino acids bearing suitable protecting groups.



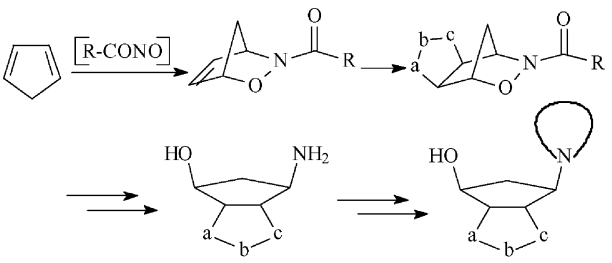


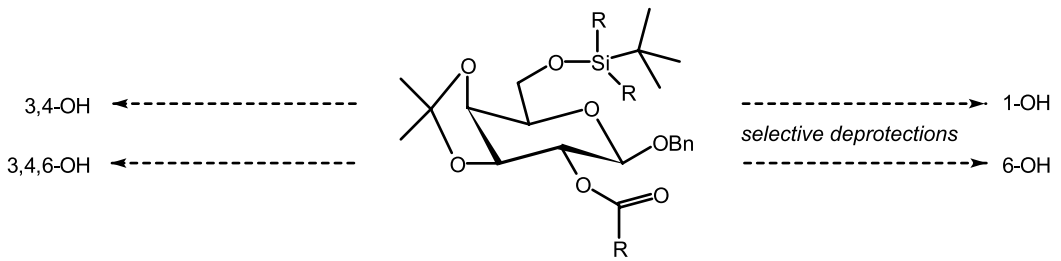


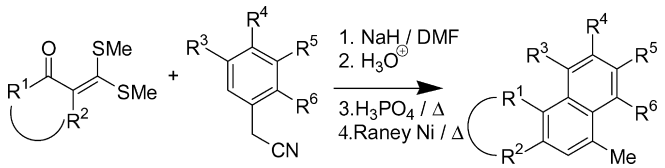


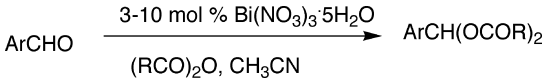


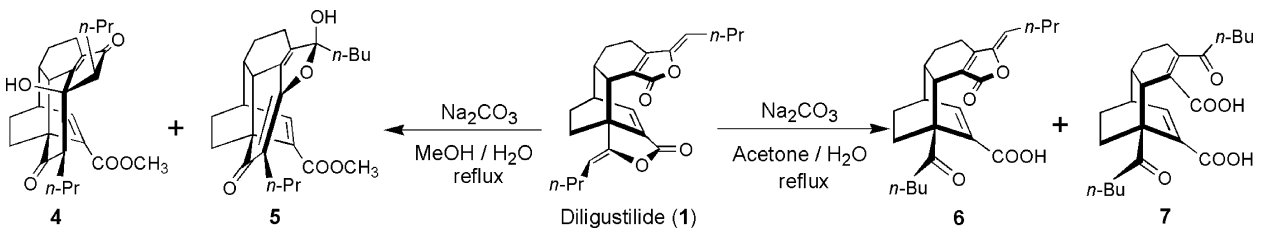
Isoxazoline–carbocyclic nucleosides are obtained through a convenient route involving an hetero Diels–Alder cycloaddition followed by a 1,3-dipolar cycloaddition, cleavage of the N–O tether and elaboration of the heterocyclic aminols into carbocyclic nucleosides via linear construction of purine and pyrimidine rings.

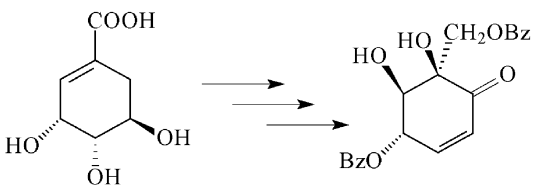


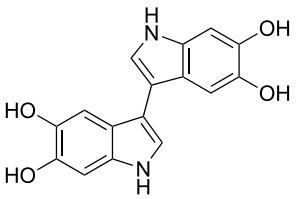


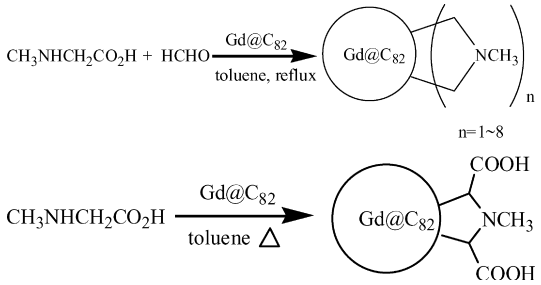


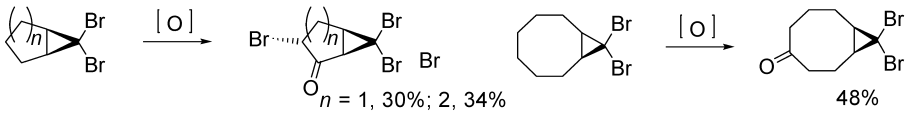












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ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 3539–3574

Tetrahedron report number 677

The total synthesis of streptonigrin and related antitumor antibiotic natural products

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Received 27 November 2003

Dedicated to Professor Helmut Werner on the occasion of his 70th birthday

Contents

1. Introduction

The remarkable capability of *Streptomyces* and *Actinomyces* species to produce a wide variety of structurally diverse natural products with biological activity[1] has received considerable attention from the chemical community, especially from biochemists and synthetic organic chemists who are concerned with human and animal health problems. The chemistry of streptonigrin (**1**, Fig. 1) dates back to 1959. Rao and Cullen[2] disclosed the isolation of an initially un-named dark-brown metabolite of *Streptomyces flocculus* that exhibited striking activity against several animal tumors.[3–7] Subsequently, the same crystalline compound was isolated from *S. rufochromogenes* and *S. echinatus*, here named rufochromomycin,[8] and from *Actinomyces albus var. bruneomycini*, now called bruneomycin.[9,10] The active agent common to all these *Streptomyces* and *Actinomyces* species came to be called streptonigrin (**1**).[10] Since then, intense efforts have been undertaken towards the isolation of bioactive compounds with variations on the same molecular framework.[11–14] In the course of this work, two closely related further antibiotics, streptonigrone (**2**)[15,16] and lavendamycin (**3**), were also isolated.[17]

The use of streptonigrin (**1**) as an anticancer drug, its synthesis and biosynthesis, and its cytotoxic mechanism of action have been studied in depth.[18–21] The stereochemistry of streptonigrin (**1**) has also been investigated.[22,23] Due to the presence of a rotationally hindered biaryl linkage between rings C and D, natural streptonigrin is axially chiral and optically active. Its configuration has initially

Keywords: Streptonigrin; Total synthesis; Antibiotic compounds; Antitumor compounds.

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doi:10.1016/j.tet.2004.02.060

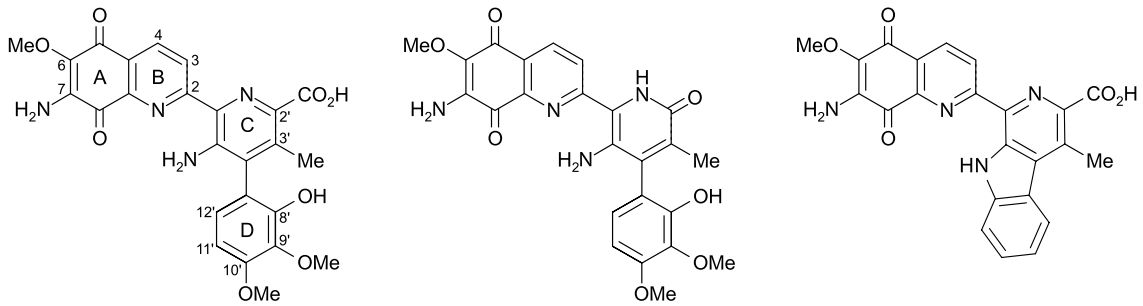


Figure 1.

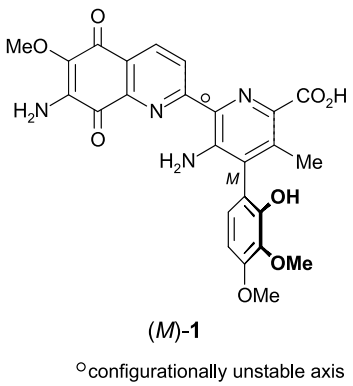


Figure 2.

been reported as *P*,[22] but more recent work has deduced the absolute stereostructure of streptonigrin to be (*M*)-**1** (Fig. 2).[23]

In addition to their biological activity, streptonigrin (**1**) and related analogs are also of interest because of their unique structural and biosynthetic features. The synthetic chemistry of these natural products has been extensively studied and discussed in two reviews[24,25] and two chapters in antibiotic books,[26,27] but no surveys have been published during the past 13 years. Despite the removal of streptonigrin from clinical trials,[28] newer aspects of its chemistry continue to emerge. Our aim in this review is to provide a comprehensive summary covering the years 1960 through November 2003, with special emphasis on methods for the synthesis of streptonigrin (**1**), streptonigrone (**2**), and lavendamycin (**3**).

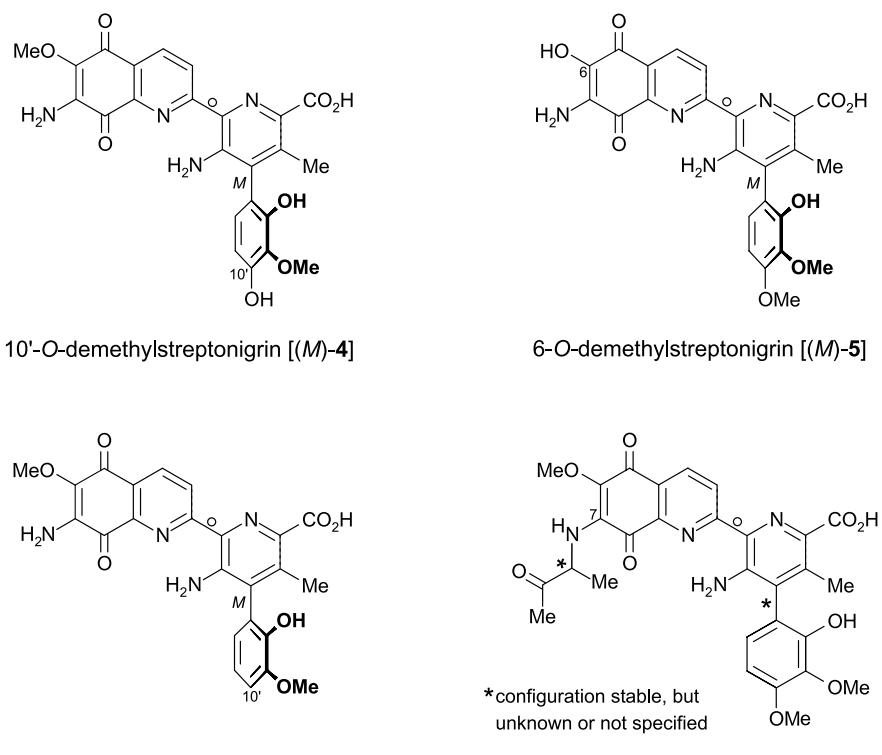


Figure 3.

Biosynthetic features, modes of action, and structure–activity relationships will be dealt with briefly, but will not be exhaustively reviewed.

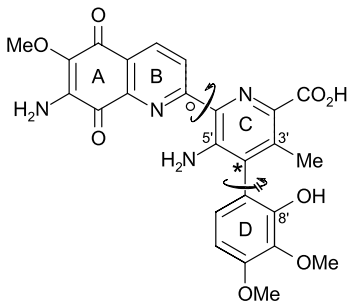
2. Isolation and structural elucidation of streptonigrin and related compounds

Rao and Cullen[2] isolated streptonigrin (**1**) from *S. flocculus* utilizing countercurrent distribution chromatography (ethyl acetate–aqueous 3% phosphate buffer, pH 7.5). The progress of the distribution was monitored by UV measurement at 370 nm, with subsequent crystallization of the isolated material, but, unfortunately, no yields were given. Although countercurrent distribution has more recently been replaced by fast centrifugal partitioning chromatography (FCPC),[29] no report has appeared on the use of FCPC to screen other *Streptomyces* species for streptonigrin (**1**) or for closely related streptonigrins that might be more potent, but less toxic. Extraction of **1** from the culture filtrate (3 l) from a fermentation of a *Streptomyces* species (IA-CAS isolate No. 144), followed by chromatography on a Sephadex column, gave reasonable quantities (110 mg) of streptonigrin, making this simple procedure much more straightforward for isolation.[15,23] Degradative and spectral studies established the unique phenylpyridylquinolinequinone structure **1** for streptonigrin in 1963,[30] without consideration of the phenomenon of axial chirality (see below). In 1975, Chiu and Lipscomb[31] confirmed this constitution by X-ray diffraction analysis. When Lown and Begleiter[32] reported ^{13}C NMR data in pyridine-d_5 in 1974, progress in analytical instrumentation had significantly improved since the original isolation of streptonigrin in the late 1950s. Their assignments were, however, revised by Gould in an independent study in DMSO-d_6 in 1982.[25] Due to the presence of two amino groups (in rings A and C) and two pyridine portions (rings B and C), there are four nitrogen atoms in streptonigrin (**1**), the resonances of which were, however, not attributed unambiguously.[25] Using modern HMBC, HMQC, NOESY, and NOE techniques, Harding and co-workers succeeded in assigning all carbon, hydrogen, and nitrogen resonances to substantiate the structure of streptonigrin as **1**.[33,34] This group also conducted variable temperature studies to assign the four nitrogen resonances, and similar experiments proved to be most useful in analyzing metal complexes of streptonigrin.[35] Their efforts paved the way for the attribution of the signals in streptonigrone (**2**) and lavendamycin (**3**).

Streptomyces species are most prolific producers of drug molecules, and it is therefore no coincidence that numerous streptonigrin-related antibiotics have since been isolated from different subspecies. As an example, four further fascinating structures, **4**-**7**, are shown in Figure 3.

3. Absolute configuration of streptonigrin

Streptonigrin (**1**) has numerous rotatable bonds, of which only two are stereochemically significant (see Fig. 4). These are the two biaryl axes, one of which connects ring B with ring C and the other joins the CD rings. For the axis between



1

Figure 4.

the B and C rings, relatively free rotation may be expected, since there is only one substituent next to the axis, viz. the amino group at C-5′. The CD-ring linkage, by contrast, is flanked by three *ortho* substituents, namely the same that amino function at C-5′, together with a methyl group at C-3′ (both on pyridine ring C), and a phenolic hydroxyl (at C-8′, on ring D). This results in restricted rotation and accounts for the observed optical activity of streptonigrin (**1**),[24,32] which therefore arises from atropisomerism about the pyridyl–phenyl C–D linkage. Curiously, however, there have been no reports to date in the literature on the concrete optical rotation of streptonigrin (**1**), that is, no α_D in any solvent or at any wavelength has ever been given.[36]

In the course of their X-ray study of streptonigrin (**1**, as its solvate with ethyl acetate), Chiu and Lipscomb[31] discovered that the rings A, B, and C are oriented essentially coplanar with each other, while the phenolic ring D is nearly perpendicular to that plane. The co-planarity of the pyridyl ring C with the AB–quinolinequinone system is a consequence of hydrogen bonding between the amino group of ring C and the quinoline nitrogen in ring B. Harding and Long[37] probed the conformation of streptonigrin (**1**) in solution by using variable temperature NMR spectroscopy and confirmed this finding.

An important aspect of the structural work in natural product chemistry is the assignment of the absolute stereostructure of chiral compounds.[38] During the past three decades, several such methods have been applied in order to attribute the absolute axial configuration of streptonigrin (**1**). An X-ray structure analysis of **1** was carried out,[31] but without the benefit of a heavy atom such as bromine, iodine, or silicon in the molecule, so that the absolute configuration could not be determined by this procedure. Atropisomerism in streptonigrin (**1**) and closely related compounds are the only known examples within the numerous axially chiral biarylic natural products[39] in which a pyridine ring is involved. Although naturally occurring biaryls and the phenomenon of atropisomerism have been extensively treated in the literature,[39] newly isolated, apparently likewise axially chiral, biaryl natural products, including closely related streptonigrins, have more recently been published without taking into consideration the phenomenon of hindered rotation,[14] with the exception of Dholakia and Gillard,[22] who, as early as 1981, investigated the stereochemistry of streptonigrin (**1**). From their circular

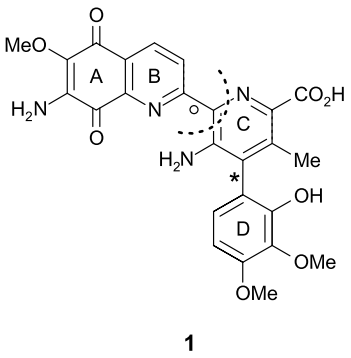
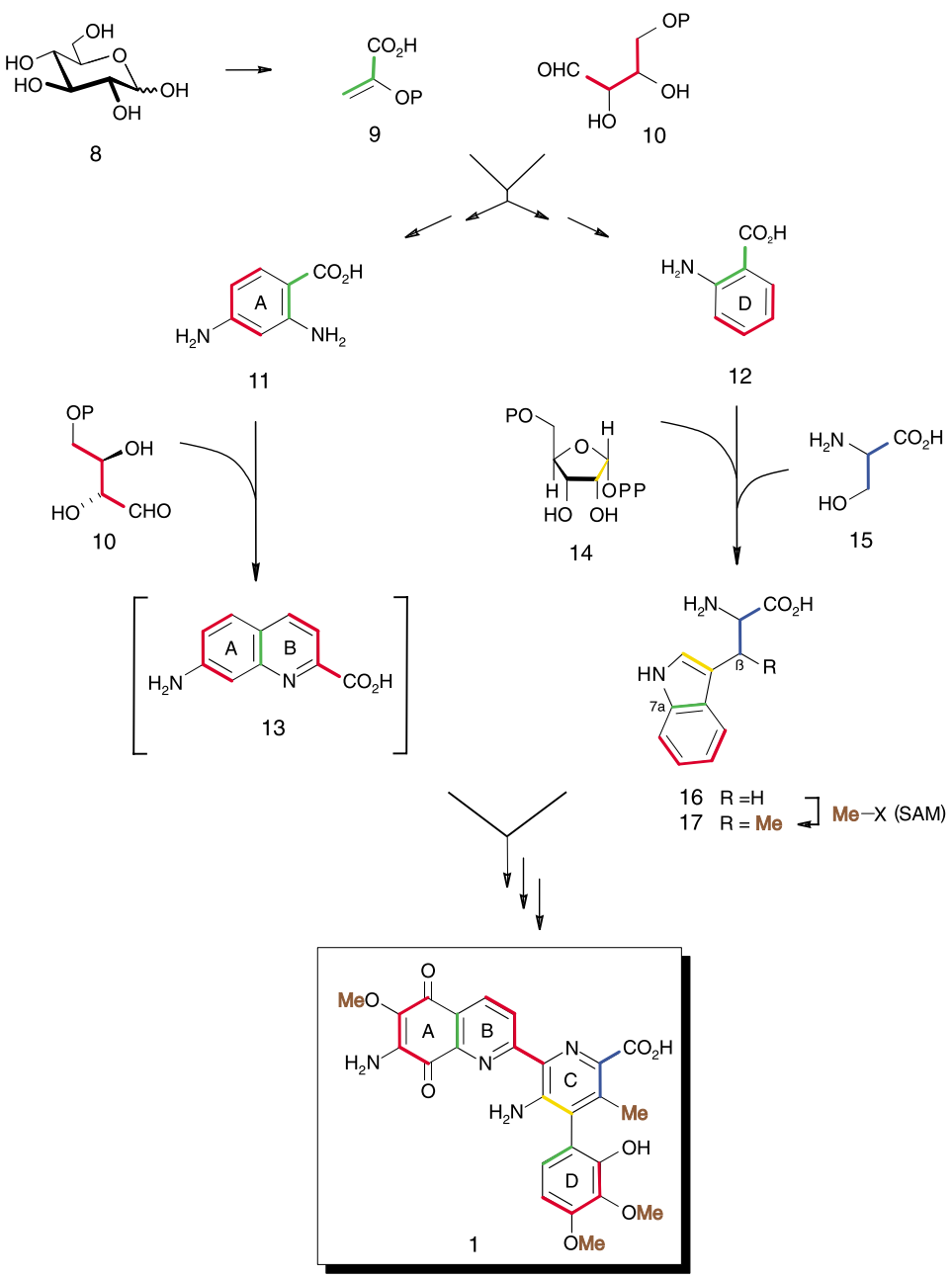
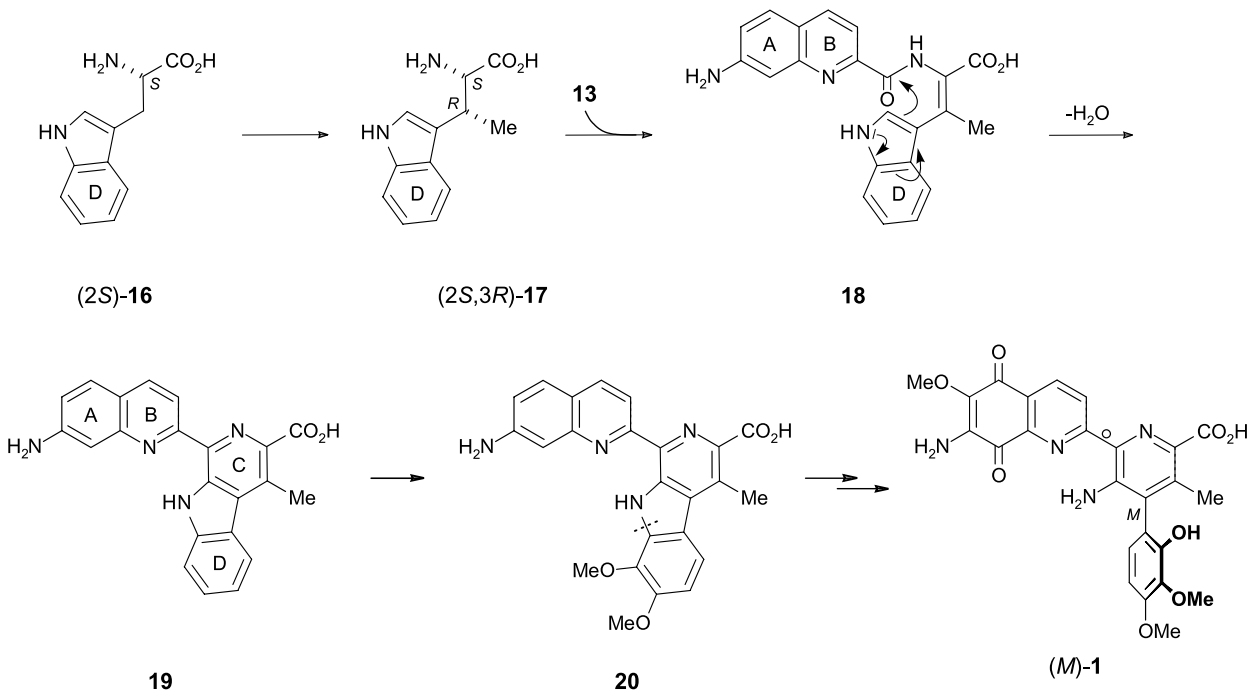


Figure 5.

dichroism (CD) measurements in ethanol, they reached the conclusion that **1** has a *P*-configuration. This assignment was based on the shorter wavelength Cotton effect in the CD spectrum of **1**. On the basis of the CD spectra of a number of derivatives and that of streptonigrin (**1**), Tennent and Rickards, by contrast, have more recently established an *M*-configuration[23]—a conclusion opposite to that of Dholakia and Gillard,[22] although both groups used the same solvent in the CD measurements. The CD spectra are indeed different, particularly in the long-wavelength region, which might possibly be due to different experimental details (presence of metal cations?). An additional complication might be varying enantiomeric ratios of the natural products, as also found in other studies.[39] In addition,



Scheme 1.



Scheme 2.

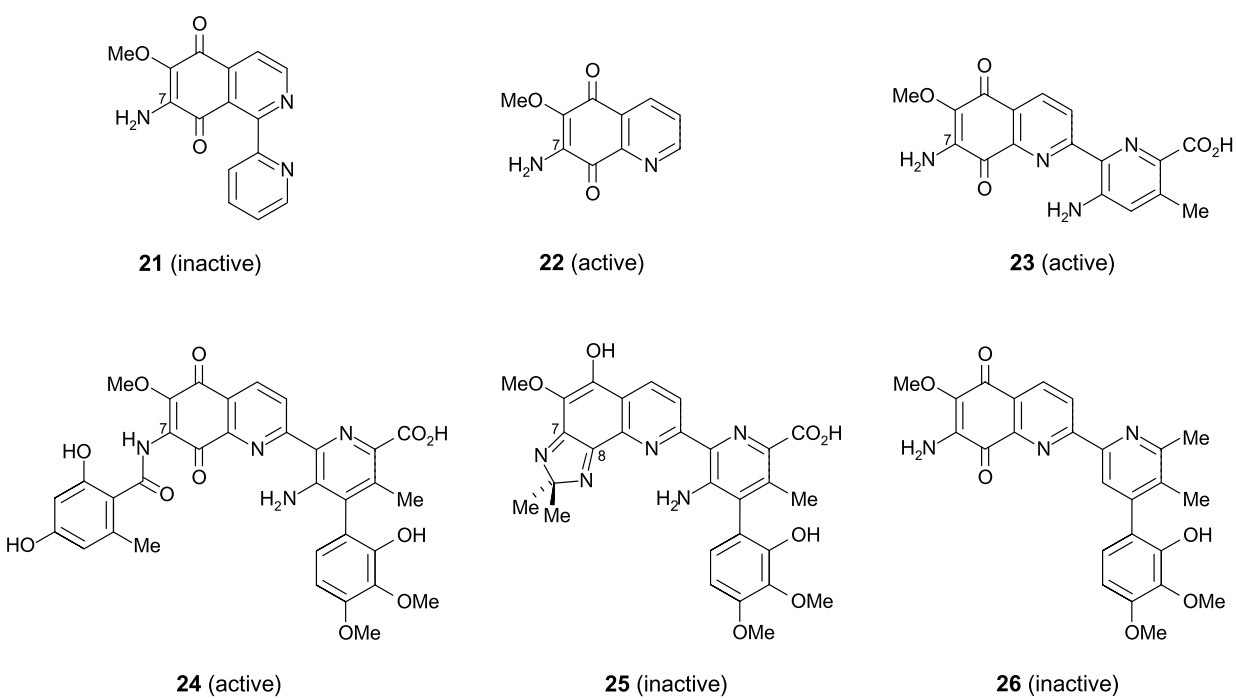
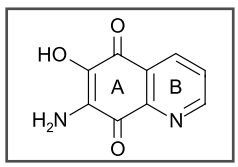
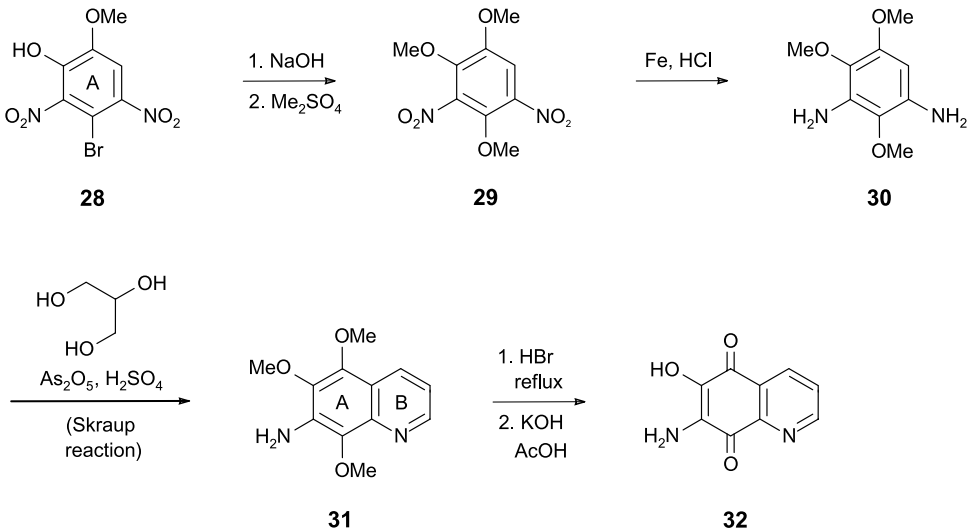


Figure 6.

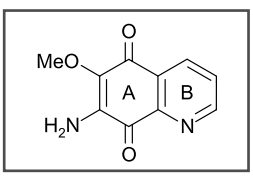


Kametani's first AB-ring model system

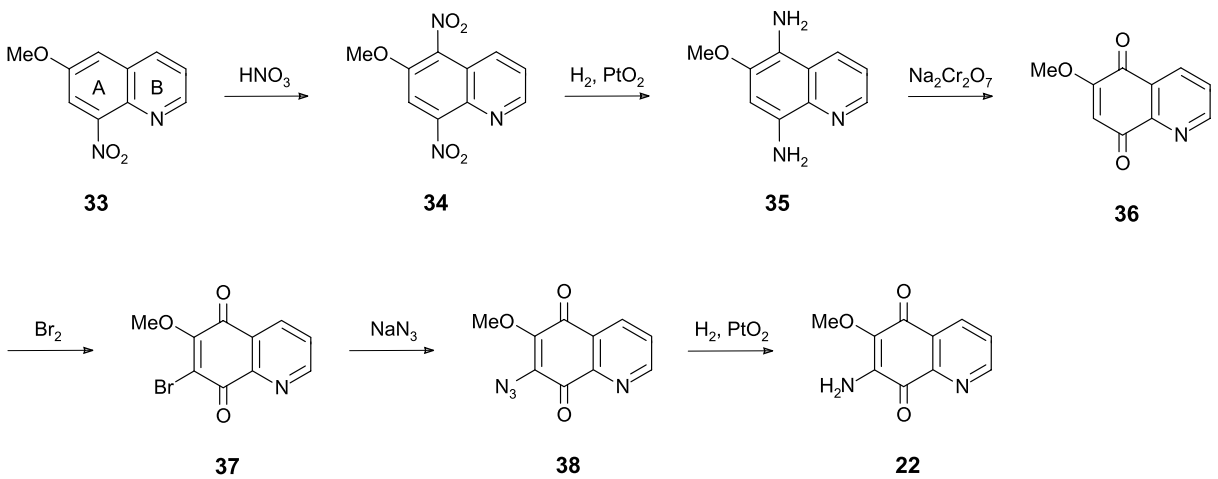


Scheme 3.

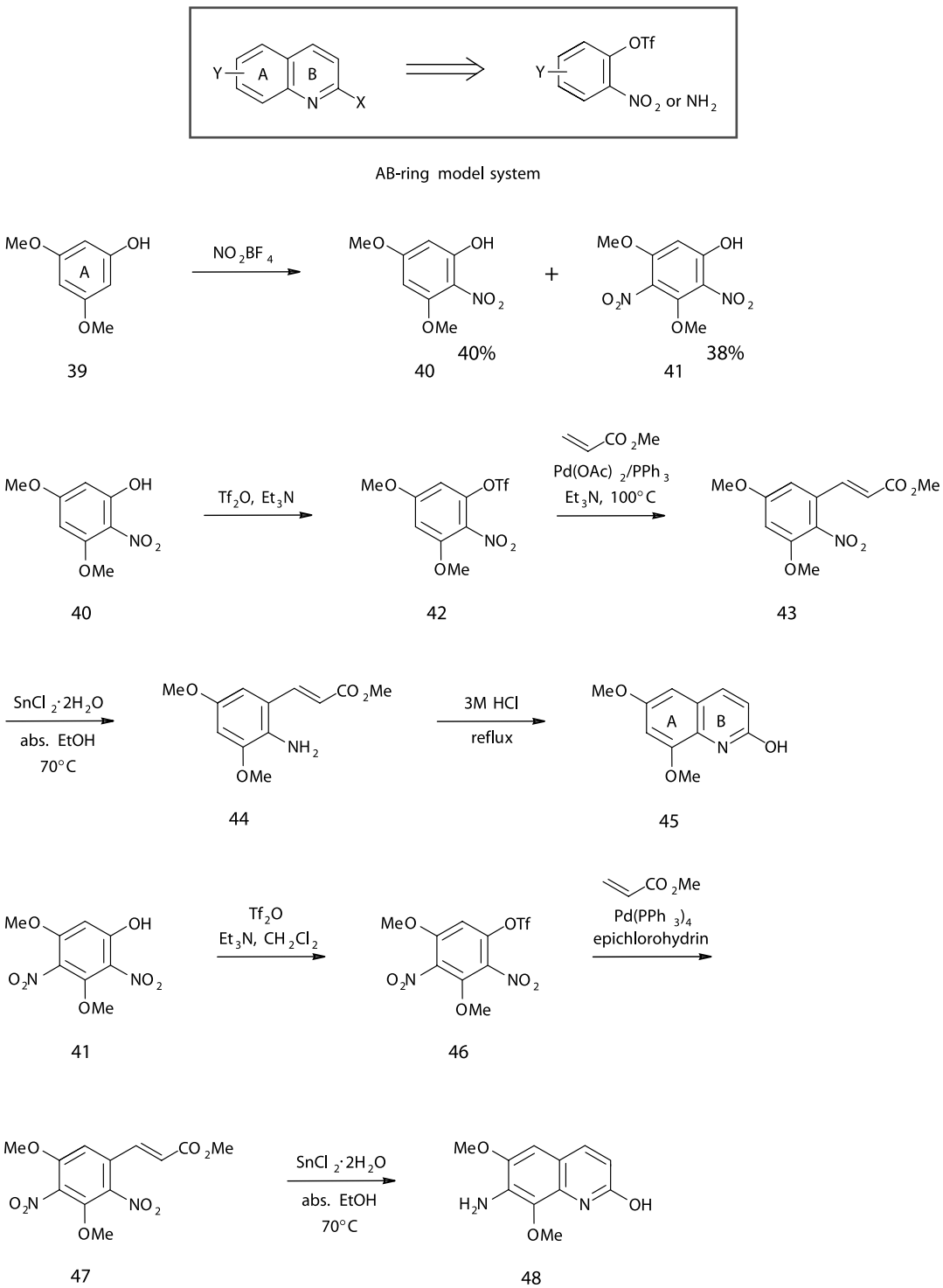
natural 10′-*O*-demethylstreptonigrin (**4**, Fig. 3) has been assigned as being *M*-configured by comparison of its chiroptical properties with those of streptonigrin (**1**).[23] On biogenetic grounds, it might be assumed that 6-*O*-demethylstreptonigrin (**5**) and 10′-demethoxystreptonigrin (**6**) also probably have an *M*-configured absolute stereostructure,[23] but this remains to be proven. No stereochemical assignment has been carried out for of 7-*N*-(1-methyl-2-oxopropyl)streptonigrin (**7**),[14] either for the axis or for the additional stereogenic center in the side



AB-ring model system



Scheme 4.



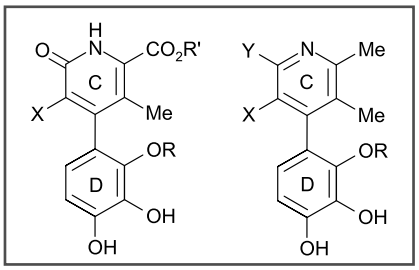
Scheme 5.

chain. The recent appearance of new methods for the determination of absolute configurations by quantum chemical CD calculations[40] might help to firmly establish the absolute configuration of streptonigrin (**1**), but this remains to be pursued.

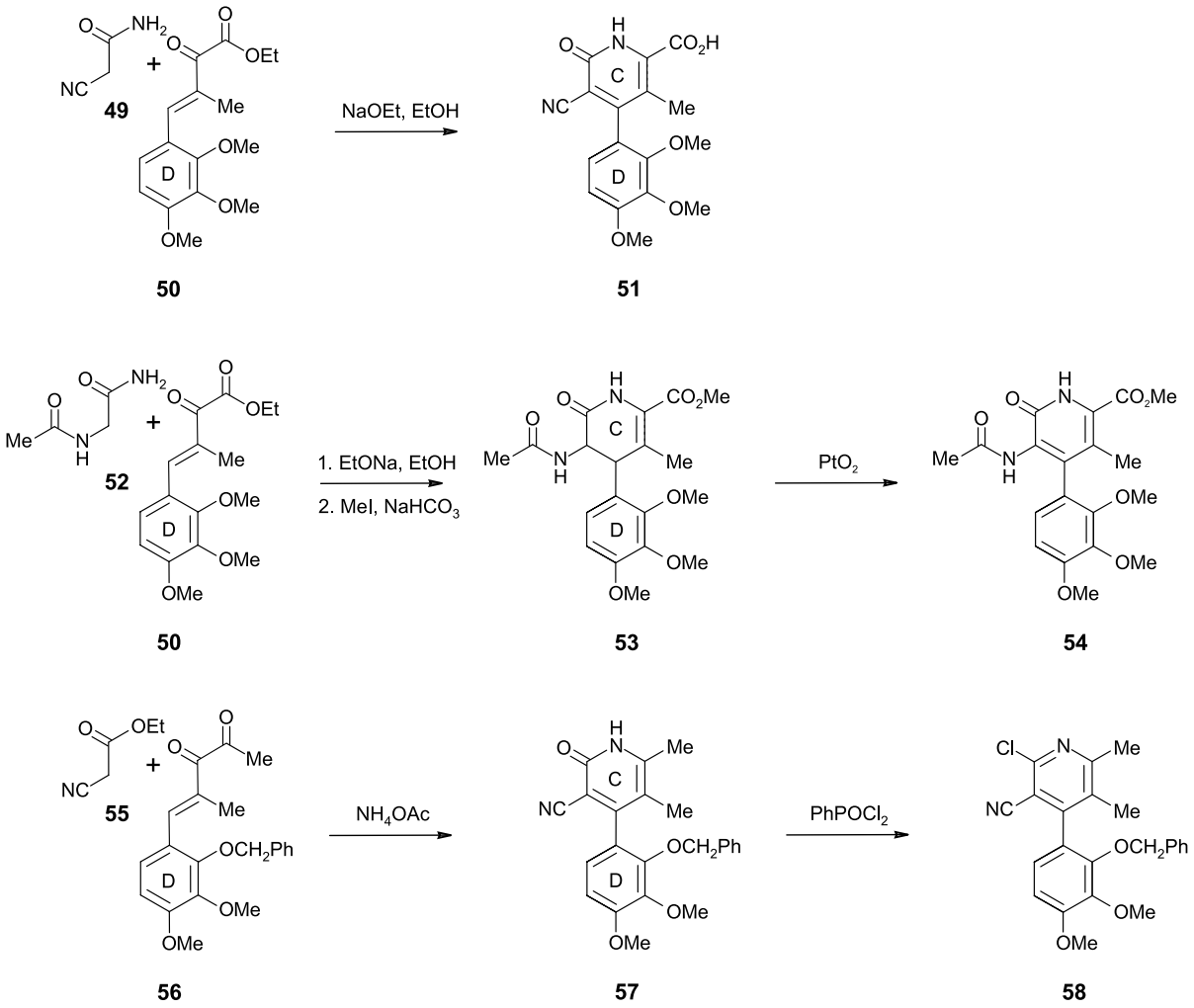
4. Biosynthetic origin

The biosynthesis of streptonigrin (**1**) is now well established, thanks to the detailed studies by Gould and co-workers that have appeared in a series of elegant publications.[25,41–47] Accordingly, streptonigrin (**1**) arises through a convergent pathway involving the assembly of two major units (shown by dotted lines in Fig. 5), possibly linked together in a key Pictet–Spengler condensation step via an intermediate β-carboline (see below).

Gould's group discovered that the quinoline and pyridine subunits of streptonigrin are formed by previously unknown

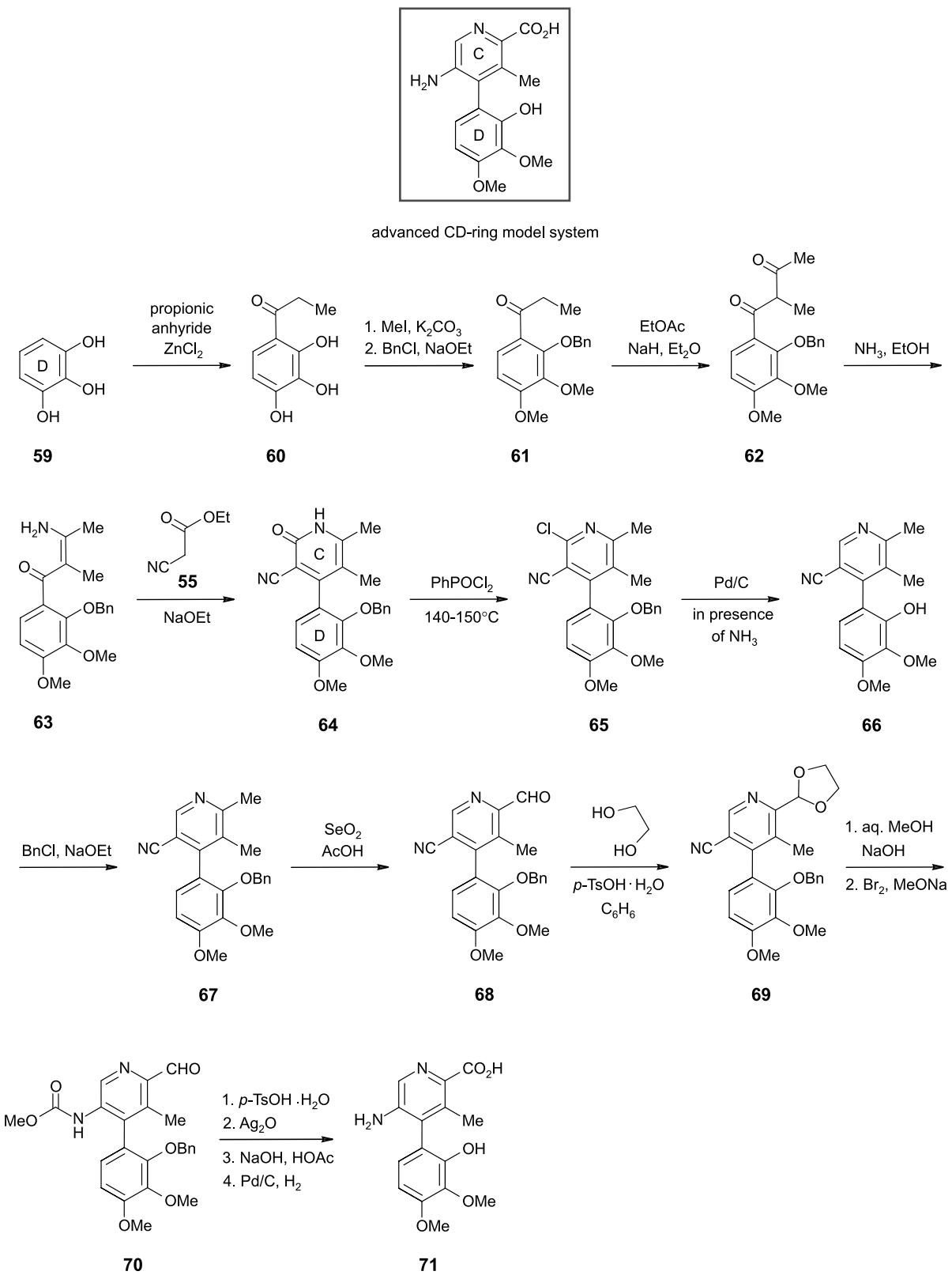


first simple CD-ring models



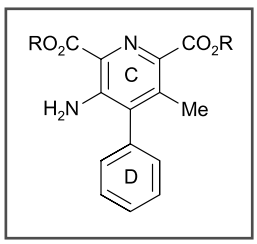
Scheme 6.

pathways (see Scheme 1).[41,43,46] Feeding the labeled precursors, [β-^{14}C, 7a-^{14}C]-tryptophan, [^{14}COOH]-anthranilic acid, [U-^{14}C]-shikimic acid, [2-^{14}C]-pyruvic acid, [β-^{14}C]-tyrosine, [β-^{14}C]-phenylalanine, [2-^{14}C]-acetate, [1,2-$^{13}C_2$]-acetate, [4-^{14}C]-aspartate, [1-^{14}C]-fumarate, [3,4-^{14}C]-glutamate, and [1,4-^{14}C]-succinate, failed to give significant incorporation rates into the quinoline portion of **1**,[43] clearly indicating that none of the known pathways for the formation of this part of **1** is involved. Incorporation experiments with [U-$^{13}C_6$]-**8**, that is, with uniformly ^{13}C-labeled D-glucose, into *S. flocculus* established that all carbon atoms can be traced back to this precursor molecule. The labeling pattern of the non-tryptophan portion of **1** is mostly explained by involving a modified shikimate pathway, which, via phosphoenolpyruvate (**9**) and D-erythrose-4-phosphate (**10**), leads to the amino-substituted anthranilic acid **11**. This condenses with a third molecule of D-erythrose-4-phosphate (**10**) as an equivalent four-carbon source. The carboxy group of the aminoanthranilate **11** is presumably lost in the cyclization and aromatization with the formation of the quinoline AB **13** portion of **1**.[43] The introduction of the three oxygen substituents of the A-ring occurs at a later stage.[46]

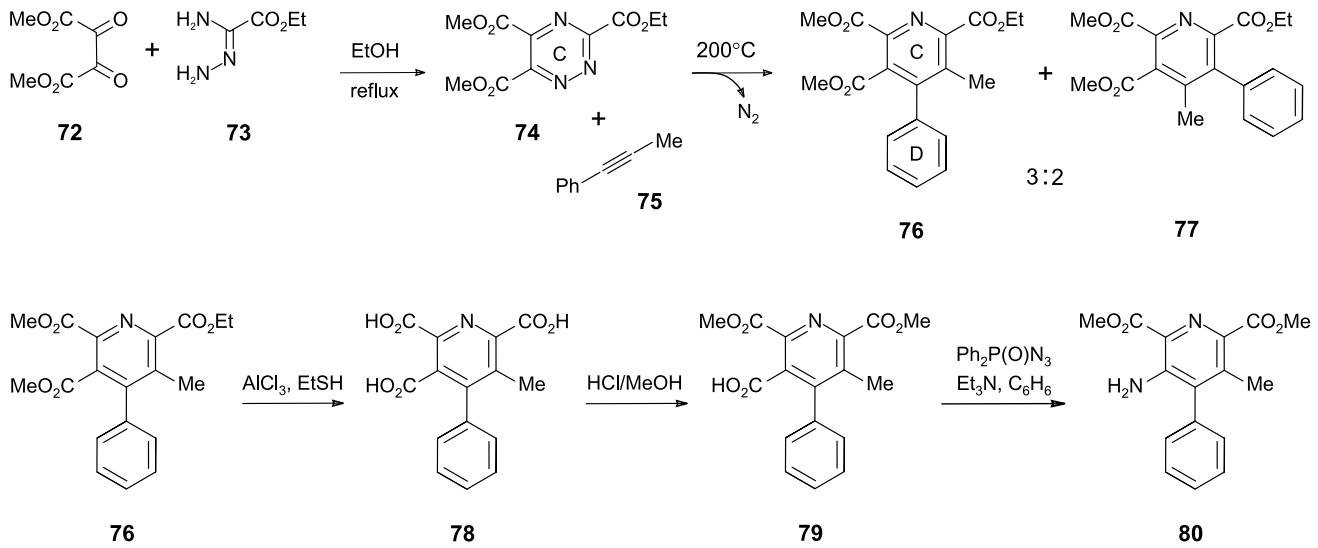


Scheme 7.

L-Tryptophan (**16**) and β-methyl-L-tryptophan (**17**), as formed from the assumed starting materials **12**, **14**, and **15**, are precursors for the C- and D-rings, as proven by feeding these compounds in a ^{13}C-labeled form to *S. flocculus* (see Scheme 2).[41–43] The highly substituted pyridine C-ring, with five substituents, is derived from the β-carboline **19**, this being formed from the quinolinecarboxylic acid AB-ring precursor **13** and β-methyl-L-tryptophan



CD-ring model system

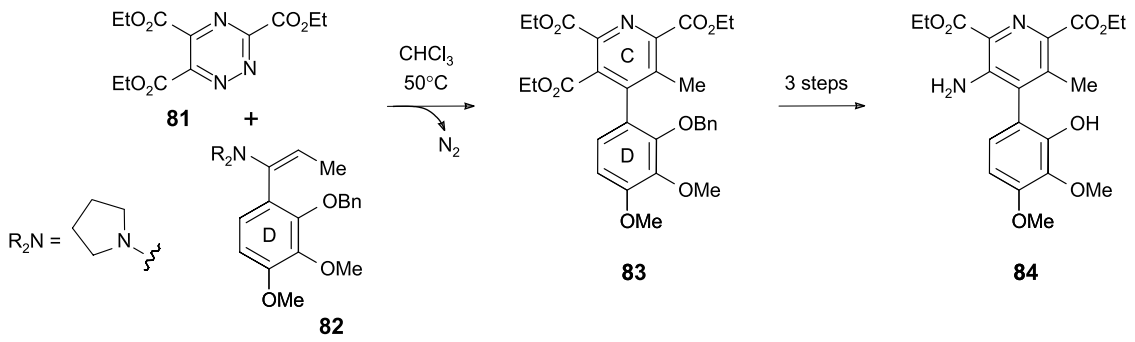


Scheme 8.

(**17**), possibly via **18** or by a Pictet–Spengler reaction with the aldehyde related to **13**. From the feeding experiment, Gould and co-workers also isolated lavendamycin (**3**),[17] which has a β-carboline unit, as in **19**. Possibly, atropo-enantioselective cleavage of the C8′–N bond of the pentacyclic intermediate **20** leads to the axially chiral 4-phenylpyridine CD-ring system of steptonigrin (**1**). This type of cleavage of an indole or a β-carboline is unprecedented to date in synthetic chemistry. An as yet unresolved issue in the biosynthesis of **1** is the role of lavendamycin (**3**) as a real intermediate or as a shunt metabolite.

5. Structure–activity relationships and mode of action

Most of the research into the mode of action and structure–activity of **1** and its analogs was reported after cessation of the clinical trials in 1977. Although streptonigrin (**1**) was extremely effective in the treatment of cancer, the main reason for the discontinuation was its high toxicity, which caused severe side effects, therefore decreasing its potential clinical use.[48–51] Since then, three review articles have appeared on this subject, the first by Gould and Weinreb[25] in 1982, the second by Hajdu in 1985,[18] and the third by Harding and Long in 1997.[37] Studies on the structure–activity relationships of **1** involved ascertaining the key functional groups and/or ring systems essential for its biological activity. Several teams have synthesized streptonigrin analogs[52–55] (see Fig. 6) by changing the functional groups and the rings, one example being the simplified pyridyl isoquinoline–quinone analog **21**, which was found to be inactive. The potency of the analogs **22** and **23** indicates the importance of the quinoline–quinone system equipped with a 7-amino group (even if acylated, as in **24**; see below!), and this was further confirmed by replacement of this amino function by OH or OMe, which provided inactive compounds.[56] The analog **25**, in which an amino group and part of the quinone moiety are blocked by an isopropylidene unit, that is, as a 2*H*-imidazole, proved to be inactive. Rosazza[57] prepared the amide **24** of streptonigrin (**1**) and orsellinic acid, by using a strain of *Streptomyces griseus*. This compound showed significant in vivo activity, but further studies of its toxicity have not yet been reported. Kende[55] described the synthesis of the analog **26**, which was inactive, underscoring the importance of the COOH and NH_2 groups in the C-ring. The substituted D-ring in streptonigrin (**1**) is obviously important in adding a structural element orthogonal to the flat (see above) ABC ring system and therefore also conferring chirality to the molecule. The role of the D-ring unit (e.g., with respect to the element of axial chirality) in the biological activity of **1** is, however, not yet fully understood. On the basis of the finding that **22** and **23** are bioactive, although lacking ring D, Harding and Long proposed that this phenyl ring is not essential for bioactivity.[37] Further support for this assumption was provided by Inouye and co-workers,[58] who derivatized semisynthetic racemic streptonigrin (**1**) at the

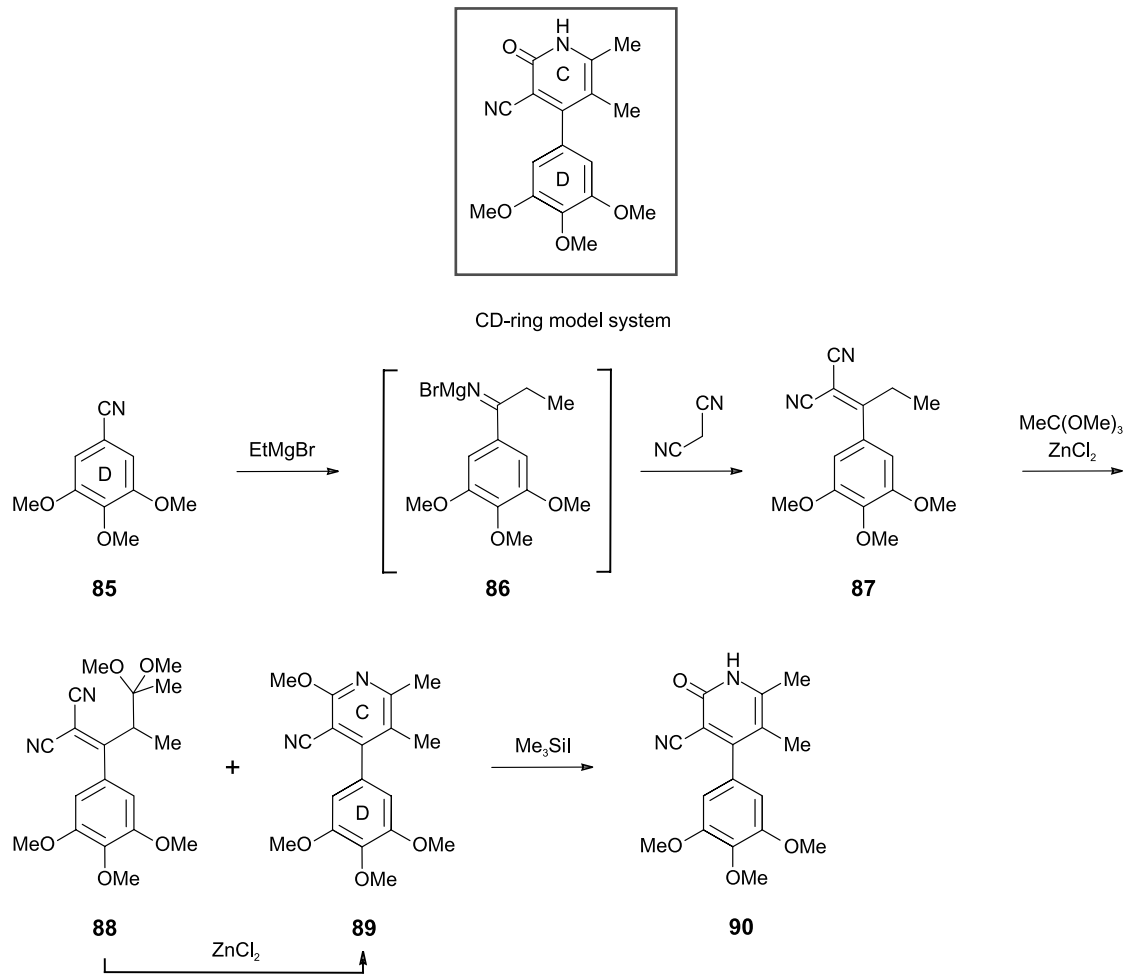


Scheme 9.

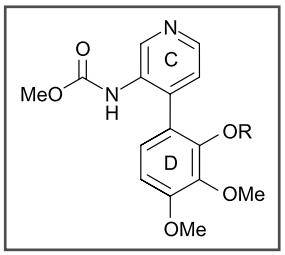
carboxy group in ring C with a chiral, non-racemic amino acid. The resulting two atropo-diastereomeric derivatives were resolved and were tested separately, yet they showed identical biological activities. Rao[56] examined various published studies of the biological properties and biochemical effects of **1**. The extensive data acquired suggested the partial structure **27** (Fig. 6) as a minimal requirement for the biological activity of streptonigrin (**1**). Of particular significance is the finding that this subunit **27** contains the fundamental metal-coordinating groups in **1**.

6. Synthetic efforts towards the AB-rings (quinolinequinone) of streptonigrin

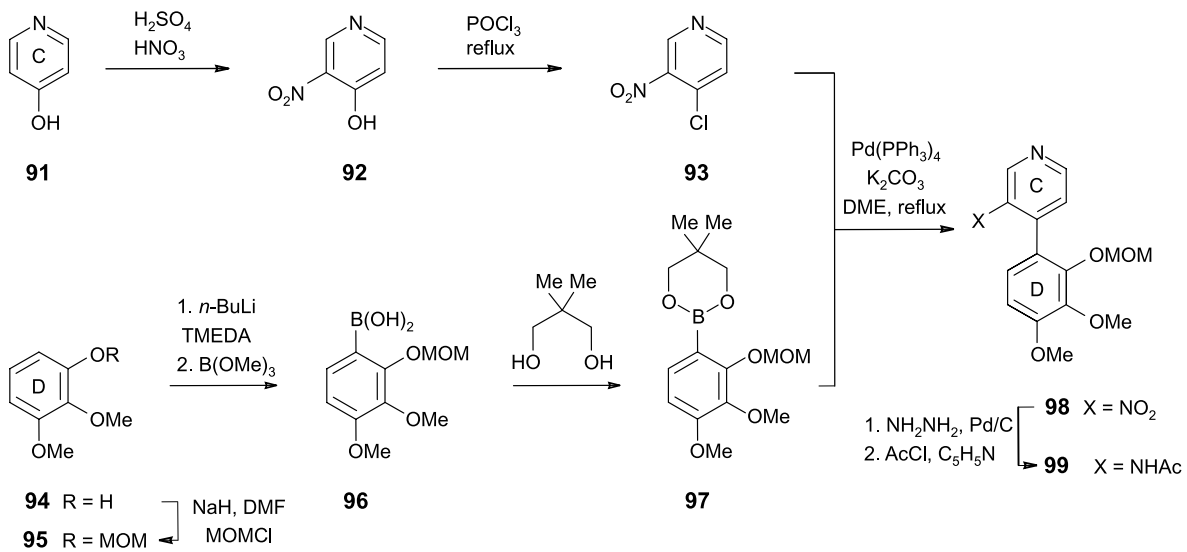
When Woodward and co-workers[30] disclosed the constitution of streptonigrin (**1**), an antitumor antibiotic metabolite of *S. flocculus* of unprecedented structure in 1963, its total synthesis presented a huge challenge to the synthetic chemist. Preliminary approaches dealt with developing methods for constructing a quinolinequinone, viz. the AB-ring system of streptonigrin (**1**) having the



Scheme 10.



CD-ring model system by Suzuki reaction



Scheme 11.

proper substitution in ring A. A route to 7-amino-6-hydoxyquinolinequinone (**32**) had already been developed earlier by Kametani,[59,60] using a classical Skraup synthesis for the formation of the intermediate quinoline **31**, as prepared from the bromodinitrophenol **28**, via the trimethoxy derivative **29** and the *m*-phenylenediamine **30** (see Scheme 3).

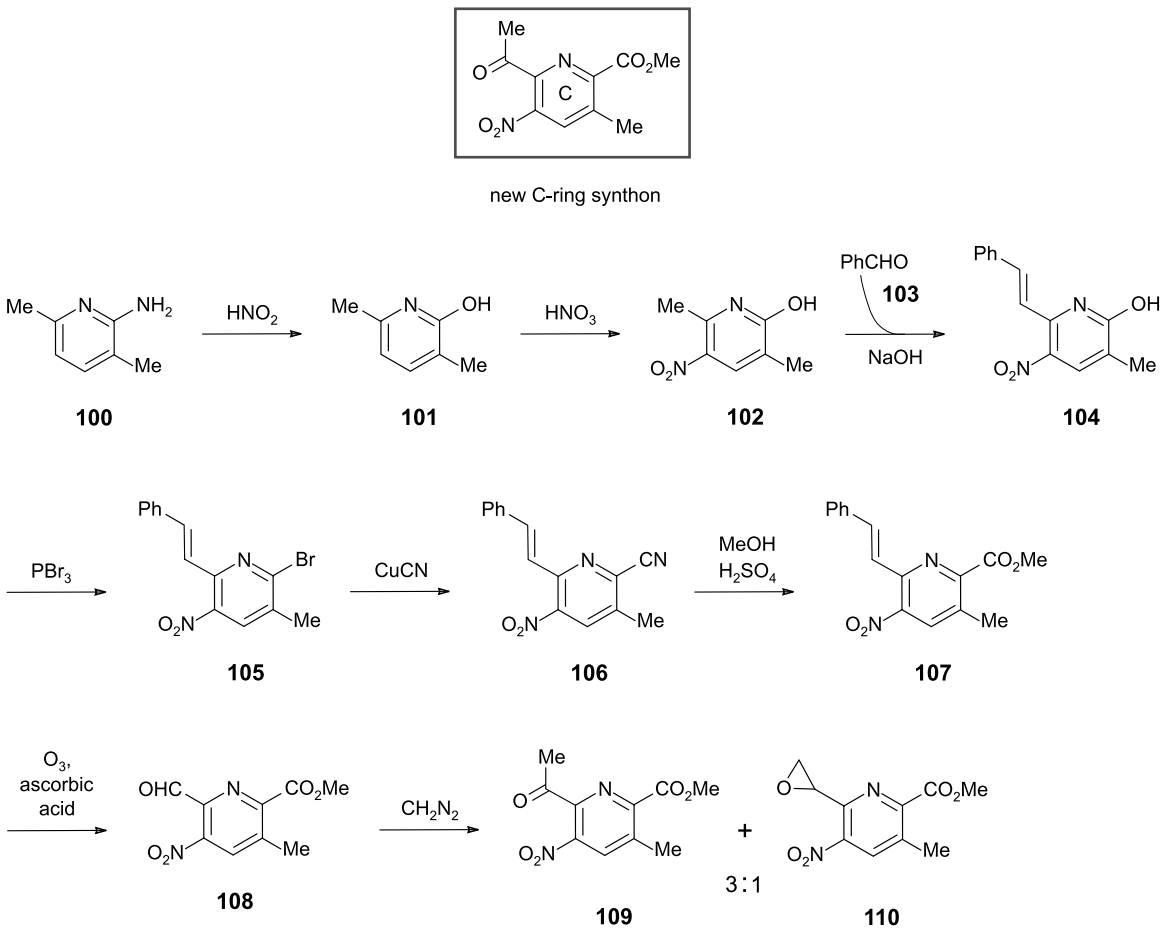
A potentially attractive route to the properly substituted AB system of streptonigrin was reported by Liao, Nyberg, and Cheng[54] (see Scheme 4). The quinoline **33**, previously prepared from 2-nitro-*p*-anisidine via a Skraup reaction,[61] was further nitrated to give **34**. This dinitro compound was subsequently reduced to the diamine **35** and then oxidized to the methoxyquinone **36**, which was cleanly brominated to deliver the bromoquinone **37**. The bromine substituent was then replaced to give the azidoquinone **38**, which, on reduction, gave the amino-quinolinequinone. The strategy shown in Scheme 4 for the conversion of **36** to **22** was later utilized by others and therefore became an important constituent of both subsequent total syntheses of streptonigrin.

In the course of their work on the synthesis of streptonigrin (**1**), Holzapfel and Dwyer[62] used the Heck reaction to assemble the AB quinolinequinone moiety (see Scheme 5). The 2-hydroxy-7-amino-6,8-dimethoxyquinoline as a potential precursor to the quinolinequinone structure might be generated by a simple Fremy's salt oxidation of **48**, which, however, had not been reported previously. Nitration of 3,5-dimethoxyphenol (**39**) with nitronium tetrafluoroborate provided a separable 1:1 mixture of the mono- and dinitro products **40** and **42**. Upon triflation, the mononitro compound **40** gave **42**, and a subsequent Heck reaction of **42** with methyl acrylate produced the cinnamic ester **43**. Reduction of **43** with tin(II) chloride dehydrate to **44**, followed by acid-catalyzed cyclization, afforded the 2-hydroxyquinoline **45** (overall yield of 25% from **39**). A similar sequence on the dinitro compound **41**, via the *O*-triflate **46** and the cinnamic acid derivative **47**, led to the aminoquinolinequinone **48**, a potential precursor to 2-hydroxy-7-amino-6-methoxyquinolinequinone. Although some difficulties were encountered in the Heck reaction, these were overcome by the use of epichlorohydrin and excess palladium catalyst. This route therefore provided a convenient synthetic equivalent of the AB-ring system.

Prior to this work, Quéguiner and his group[63] had also reported a potential streptonigrin AB-ring precursor via a similar approach.

7. Formation of the CD-rings in streptonigrin

The challenge to synthesize the CD-rings of streptonigrin (**1**) was taken up by several groups. In a series of publications beginning as early as 1966, Kametani and

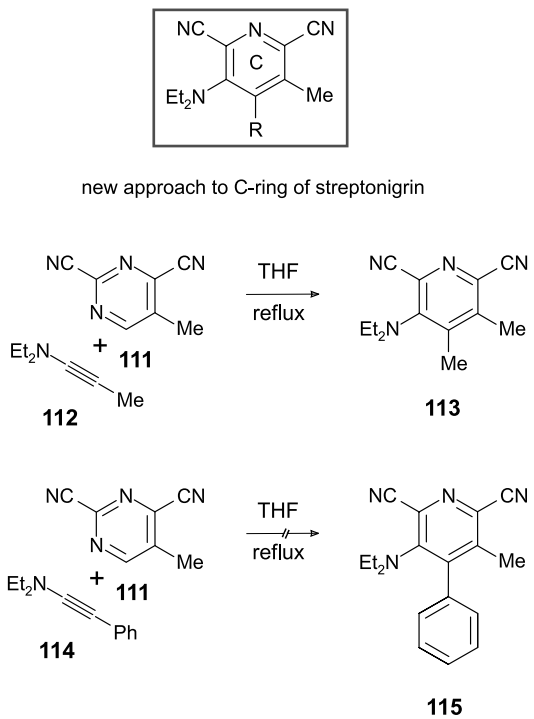


Scheme 12.

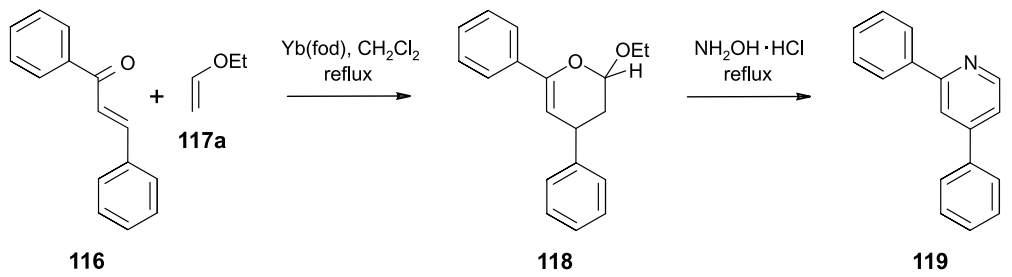
co-workers[64–71] reported several approaches. A few of the successful routes that resulted in the 2-pyridones **51** (from **49** and **50**), **54** (from **52** and **50** via **53**), and **57** (from **55** and **56**) are outlined in Scheme 6. The compound **57** was converted to the respective 2-chloropyridine **58**.

Cheng and his group[72,73] (see Scheme 7) described the synthesis of the CD-ring model system **71** from the commercially available pyrogallol (**59**). This was converted to **71** in a series of steps via the mono- and bicyclic intermediates **60**-**70**, with an overall yield of 15–18%. This synthesis of the CD-ring model system in 1976 paved the way for several further total syntheses of other CD-ring models, each reflecting to some extent the state of the art at the respective time.

It had been well known from the work of Sauer[74,75] and of Boger[76] that the reaction of ynamines and enamines with electron-deficient 1,2,4-triazines, with the subsequent extrusion of dinitrogen, gives substituted pyridines. Such a reaction of an arylpropyne had, however, not been known, nor was the regiochemical outcome anticipated. Using this concept, Martin[77] investigated the synthesis of the CD-rings of streptonigrin (**1**). Condensation of the dioxosuccinate **72** with the amidrazone **73** produced the appropriate triazine **74** (see Scheme 8), the reaction of which with 1-phenylpropyne (**75**) gave a mixture of the pyridines **76** and **77**, which were separated and structurally assigned by NMR. The desired



Scheme 13.



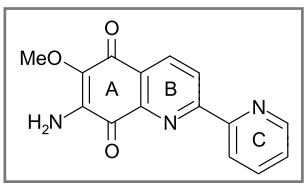
Scheme 14.

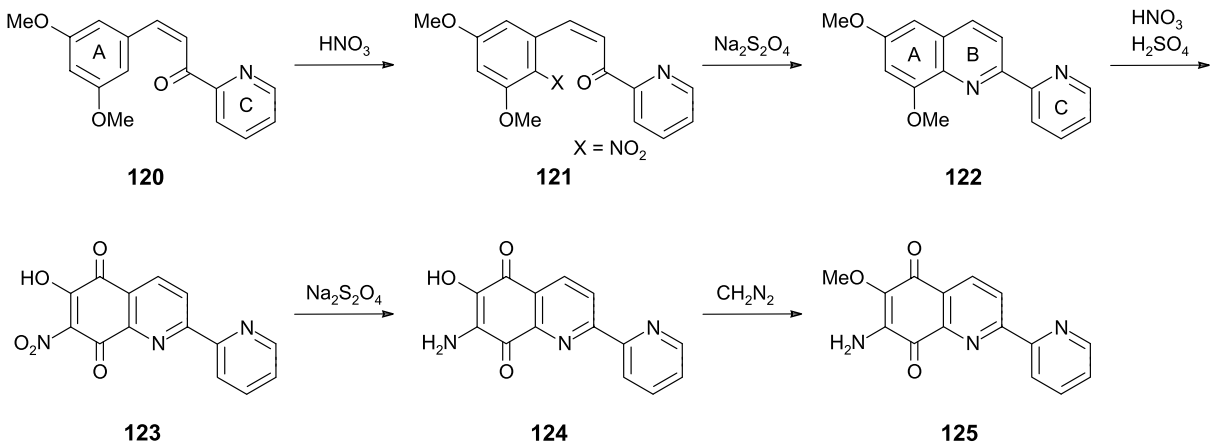
isomer **76** was converted to the highly substituted pyridine **80** via the triacid **78** and the acid **79**. The need for harsh reaction conditions, as well as the formation of a mixture of regioisomeric pyridines, however, precluded further progress.

In a related approach, Boger and Panek[78] employed 1,2,4-triazines and pyrrolidine-derived enamines for the construction of pyridylbiaryl CD-ring model systems of streptonigrin. Their starting enamine **82** was readily prepared, while the triazine **81** was a known compound.[79] Importantly, they found that this cycloaddition to give **83** is highly regioselective (see Scheme 9). The simplicity of these reactions, ultimately leading to **84**, is a hallmark of Boger's work.

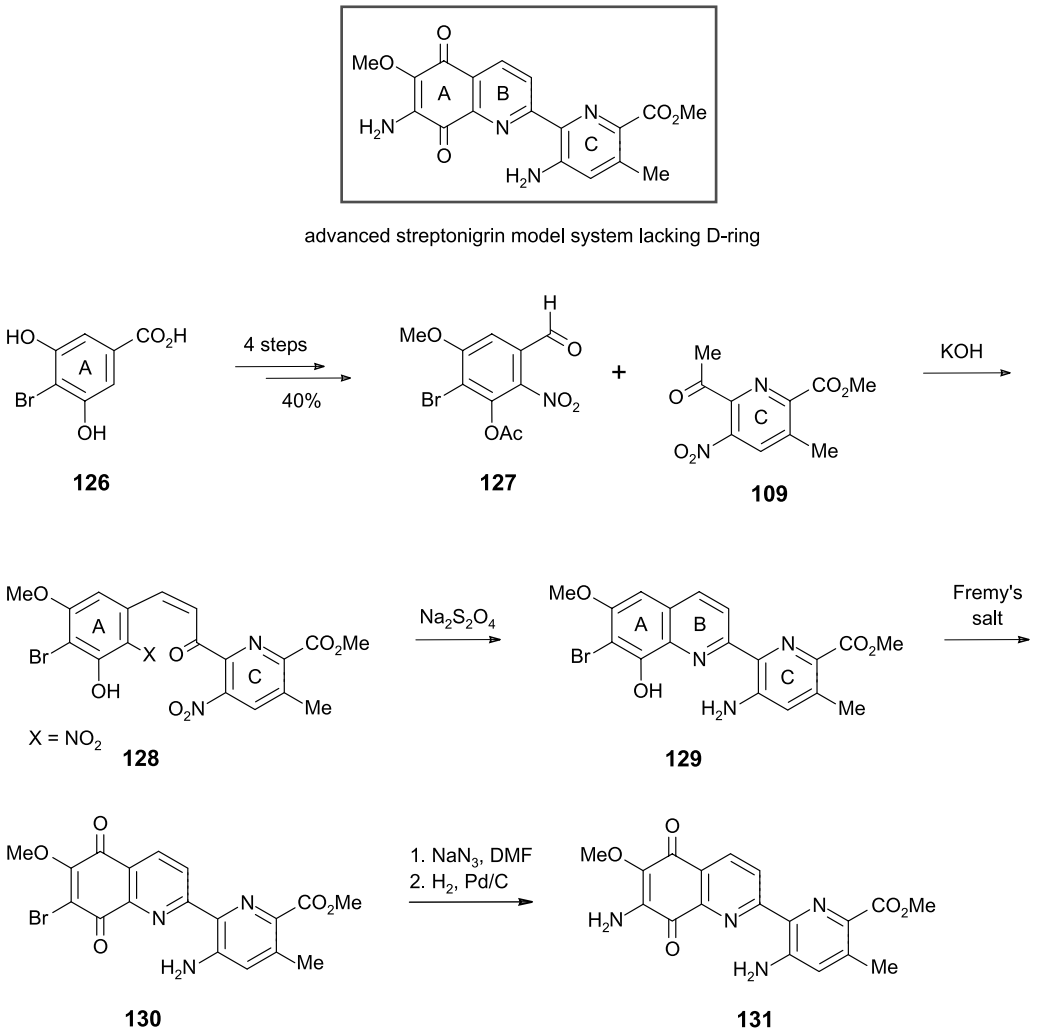
Kilama, Remers and their colleagues[80] successfully prepared the closely related analog **90** (see Scheme 10). This structure was chosen because the starting material, 3,4,5-trimethoxybenzonitrile (**85**), was commercially available and inexpensive. The reaction of **85** with ethylmagnesium bromide in THF, followed by treatment of the intermediate Grignard product **86** with an excess of malonodinitrile, provided **87** in 91% yield. Condensation of **87** with trimethyl orthoacetate in the presence of zinc chloride gave **88** (40% yield) and **89** (45% yield). A significant improvement of the procedure resulted from the fact that **88** can be converted to **89** in 51% yield by further treatment with zinc chloride in trimethyl orthoformate, which raised the final yield of **89** to 66%. Cleavage of the methyl ether with iodotrimethylsilane[81] gave **90** in 85% yield. This method has considerable potential and merits further exploration.

Holzapfel[82] used his cross-coupling strategy for the formation of a model system of the streptonigrin CD rings from the commercially available 4-hydroxypyridine (**91**) and 2,3-dimethoxyphenol (**94**) (see Scheme 11). The first coupling partner, 4-chloro-3-nitropyridine (**93**), was prepared in two steps from 4-hydroxypyridine (**91**) via the compound **92**. Treatment of the D-ring starting material, **94**, with sodium hydride and methoxymethyl chloride in DMF gave the derivative **95**, the MOM group of which was used as an *ortho*-directing group[83,84] to introduce the borate ester.





Scheme 15.



Scheme 16.

Due to incomplete metallation, which complicated the isolation of the boronic acid **96**, this intermediate was then converted to the cyclic 2,2-dimethylpropylidene ester **97**. Suzuki coupling of **93** with **97** gave the desired product **98** in 71% yield. Selective reduction of the nitro group to the amine was achieved using hydrazine and Pd/C and the amine was characterized as its acetamide derivative **99**.

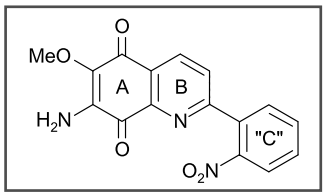
As an alternative to the Suzuki coupling reaction for the formation of the carbon–carbon bond between rings C and D, silicon-derived reagents have more recently been used.[85]

8. New pyridine syntheses for the construction of ring C

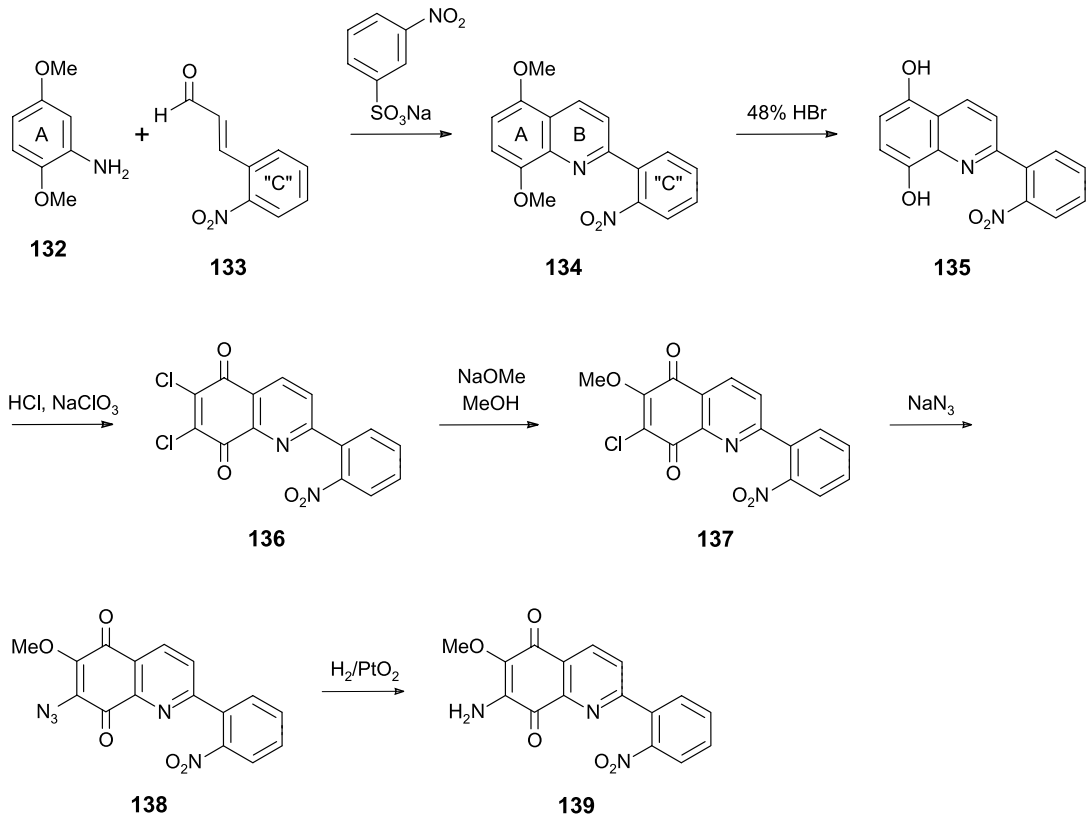
For the construction of the highly substituted pyridine C-ring of streptonigrin (**1**), several research groups have focussed on designing new pyridine ring syntheses. Rao and co-workers[86] have, for example, described the synthesis of the pyridine **109** (see Scheme 12), which still lacks the D-ring. Starting from the aminopyridine **100**, this monocycle was prepared in a straightforward sequence, requiring only eight steps: the conversion into the 2-pyridinol **101**, the nitration to obtain **102**, Knoevenagel reaction with benzaldehyde (**103**) to give **104**, its conversion to the ester **107**, via the bromide **105** and the cyanide **106**, and ozonolysis of **107** to give the aldehyde **108**. Only the last step, which gave a mixture of the desired building block **109** and the epoxide **110**, needs further improvement.

A noteworthy strategy for the synthesis of streptonigrin-related pyridines was described by Martin (Scheme 13).[87] The key step of this approach was a Diels–Alder cycloaddition of pyrimidines, such as **111**, with ynamines, such as **112**, with in situ cyclo-reversion, to afford the respective pentasubstituted pyridine, in this example, the derivative **113**. Unfortunately, no reaction was observed for the phenylynamine **114** with the same pyrimidine **111**, and the desired 4-phenylpyridine **115** was not obtained. Possibly, high-pressure cycloaddition conditions[88–90] might be a solution to force the reaction, but this has not yet been attempted.

Ciufolini and Byrne[91] have developed a modified Knoevenagel–Stobbe condensation for the preparation of substituted pyridines. They found that the required 1,5-dicarbonyl compounds could be obtained in a dihydropyran-protected form, such as **118** (see Scheme 14), by a



AB-ring model system, with C replaced by a nitro-substituted phenyl ring



Scheme 17.

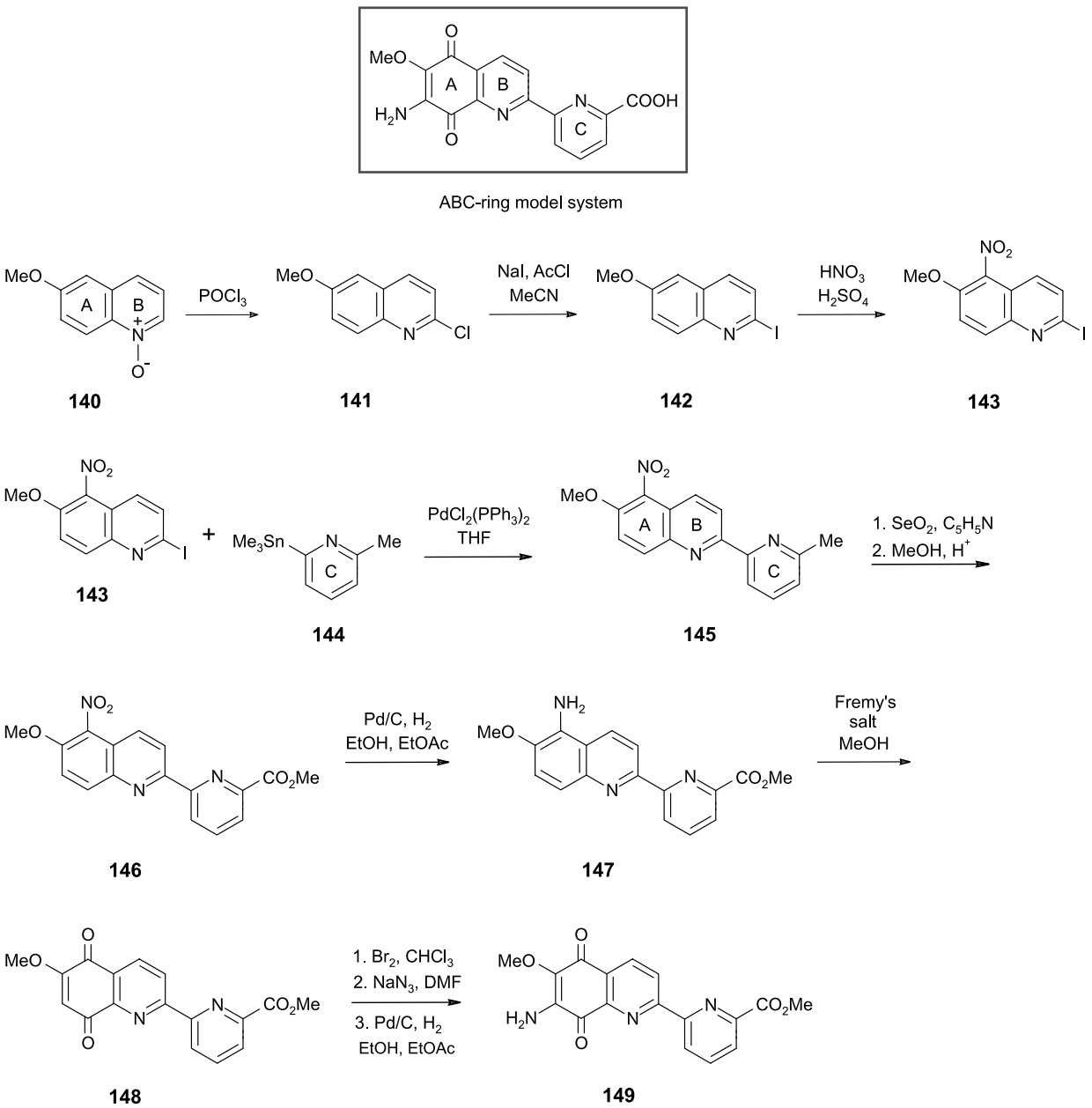
cycloaddition of enones (here **116**) with vinyl ethers (here **117a**) according to the methodology of Danishefsky and Bednarski.[92] On treatment with hydroxylamine hydrochloride,[93] the dihydropyrans provided the corresponding pyridines, for example, **119**. The cycloaddition step has, however, some limitations, the enones failing to react with cyclic vinyl ethers and at least one aryl group in conjugation with the enone carbonyl also being required for the cycloaddition with the vinyl ether.

9. ABC-rings (quinolinequinone) fused to a pyridine ring

Four different routes were developed for the assembly of the ABC-rings of streptonigrin. Rao reported a five-step synthesis of the tricyclic system **125** (Scheme 15).[94] Upon nitration, the chalcone **120** gave the mononitro derivative **121**, which, on reduction with sodium hydrosulfite (sodium dithionite), produced the pyridylquinoline **122**. Nitration of **122** with a 1:1 mixture of sulfuric acid and nitric acid gave 6-hydroxy-7-nitro-2-(2-pyridinyl)-5,8-quinolinedione (**123**), which was then reduced with sodium hydrosulfite to generate **124**. Finally, O-methylation with diazomethane gave the 6-methoxy derivative **125**.

Kuo and Rao[95] synthesized the advanced streptonigrin ABC-ring analog **131**, which still lacks the D-ring (Scheme 16), utilizing an intermediate **109** previously prepared (see Scheme 12) in their own laboratories. Their route to **131** started with the commercially available bromoacid **126**, which was readily converted to the nitroaldehyde **127**. Condensation of **127** with the acetylpyridine **109** gave the dinitrochalcone **128**, and its subsequent reduction with sodium hydrosulfite resulted in the quinoline **129**. Fremy's salt oxidation afforded the quinolinequinone **130**. The A-ring of streptonigrin was elaborated through the established methodology and gave the desired tricyclic compound **131**.

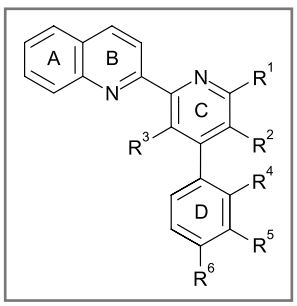
For their structure–activity relationship investigations, Lown and Sim[96] prepared several streptonigrin analogs. Their approach encompassed the formation of **134** by a



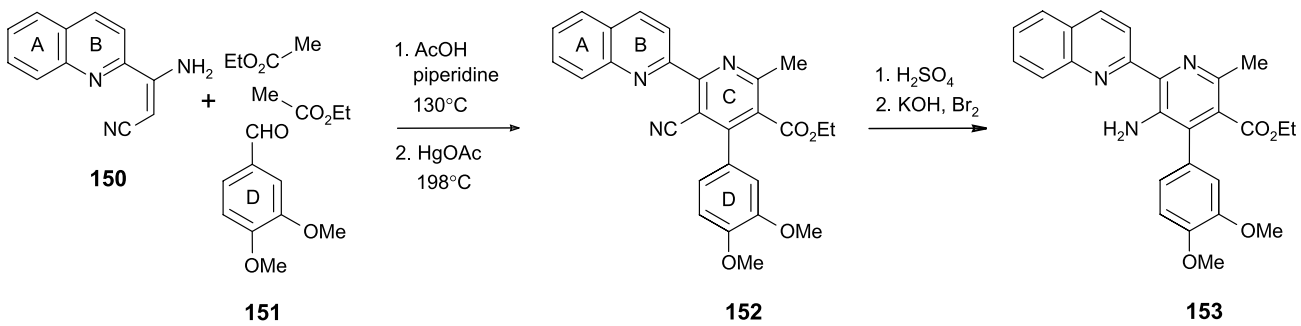
Scheme 18.

modified Skraup reaction of the commercially available dimethoxyaniline **132** and the α,β-unsaturated aldehyde **133** (see Scheme 17). The quinoline **134** was O-demethylated to **135** and further converted to the dichloroquinolinequinone **136**. Stepwise displacement of the chlorine substituents, the first by methoxide to give **137**, and the second by azide, delivered the methoxyazidoquinone **138**, which was catalytically reduced with PtO_2 and H_2 to furnish the aminoquinone **139**.

Harding and co-workers[97] described the synthesis of a tricyclic analog that contained the redox active quinone group with a 7-amino-6-methoxy-substitution pattern, as well as the pyridine-2-carboxylic acid present in streptonigrin (see Scheme 18). The key step was a Stille coupling of the properly substituted 2-iodoquinoline **143** with 2-trimethylstannyl-6-methylpyridine (**144**). Their starting material for **143** was the known[98] 2-chloro-6-methoxyquinoline (**141**), as obtained by reaction of the *N*-oxide **140** with phosphoryl chloride. On treatment with sodium iodide and acetyl chloride, **141** yielded the 2-iodo analog **142**. Nitration of **142** gave 2-iodo-6-methoxy-5-nitroquinoline (**143**, 81% yield), which was coupled to 2-(trimethylstannyl)-6-methylpyridine (**144**) with Pd catalysis to afford the required ABC-ring system **145**. Oxidation of the C-ring methyl group with selenium dioxide, followed by esterification, provided the ester **146**. Reduction to the amine **147**, followed by Fremy's salt oxidation, gave **148**. Following the method developed by Liao (cf. Scheme 4, compounds **36→22**),[60] this quinolinequinone was converted to the final 7-amino derivative **149**.

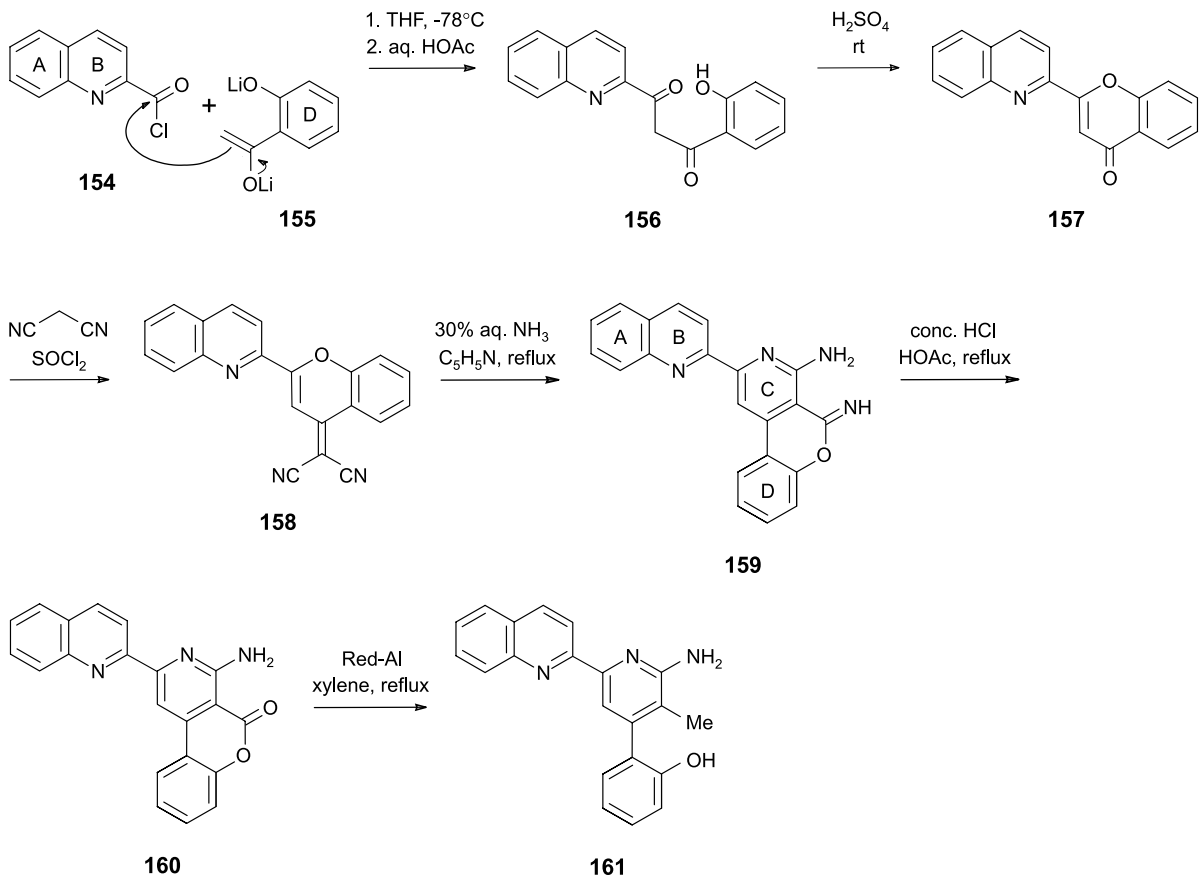


first, largely simplified ABCD-ring model system



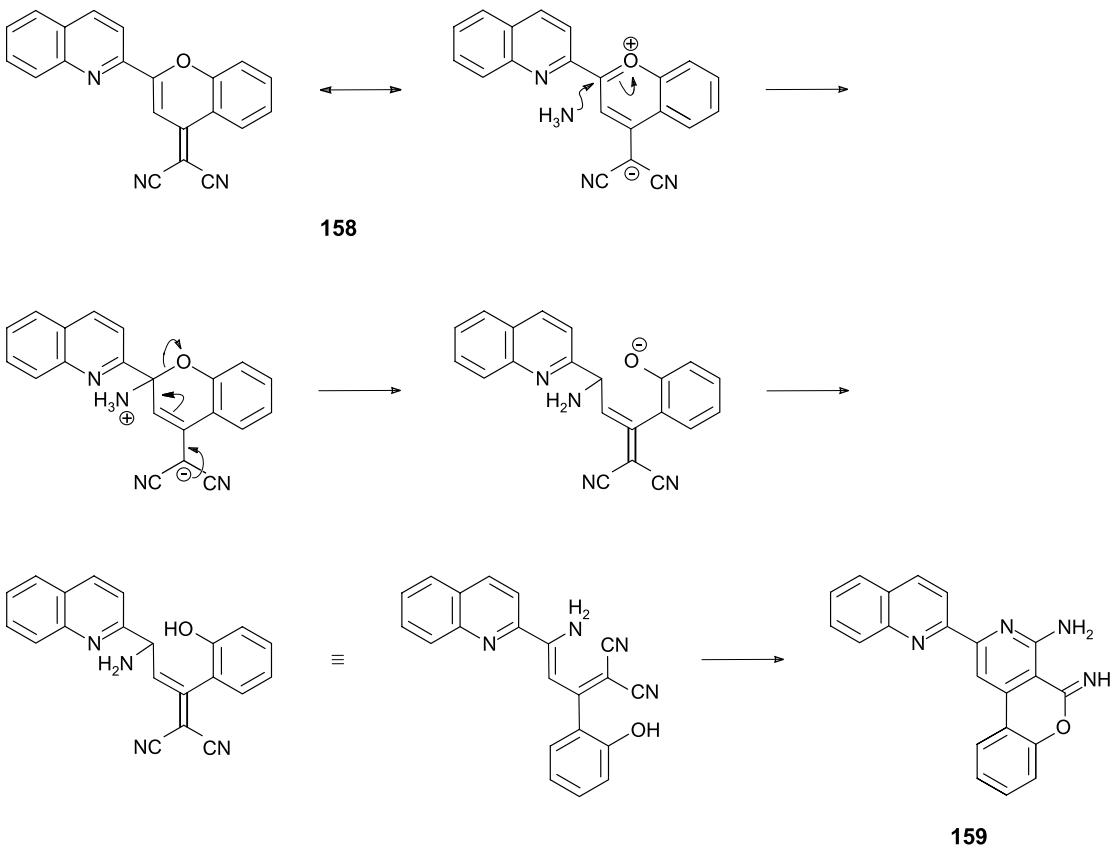
150 **151** **152** **153**

Scheme 19.



154 **155** **156** **157** **158** **159** **160** **161**

Scheme 20.



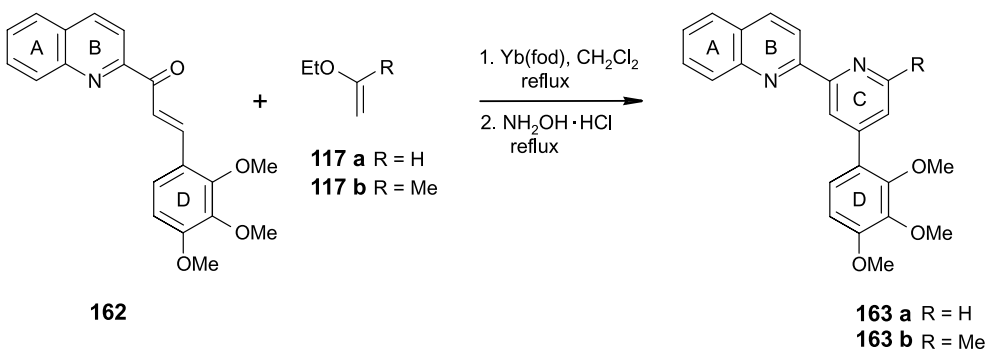
Scheme 21.

10. ABCD-ring model systems

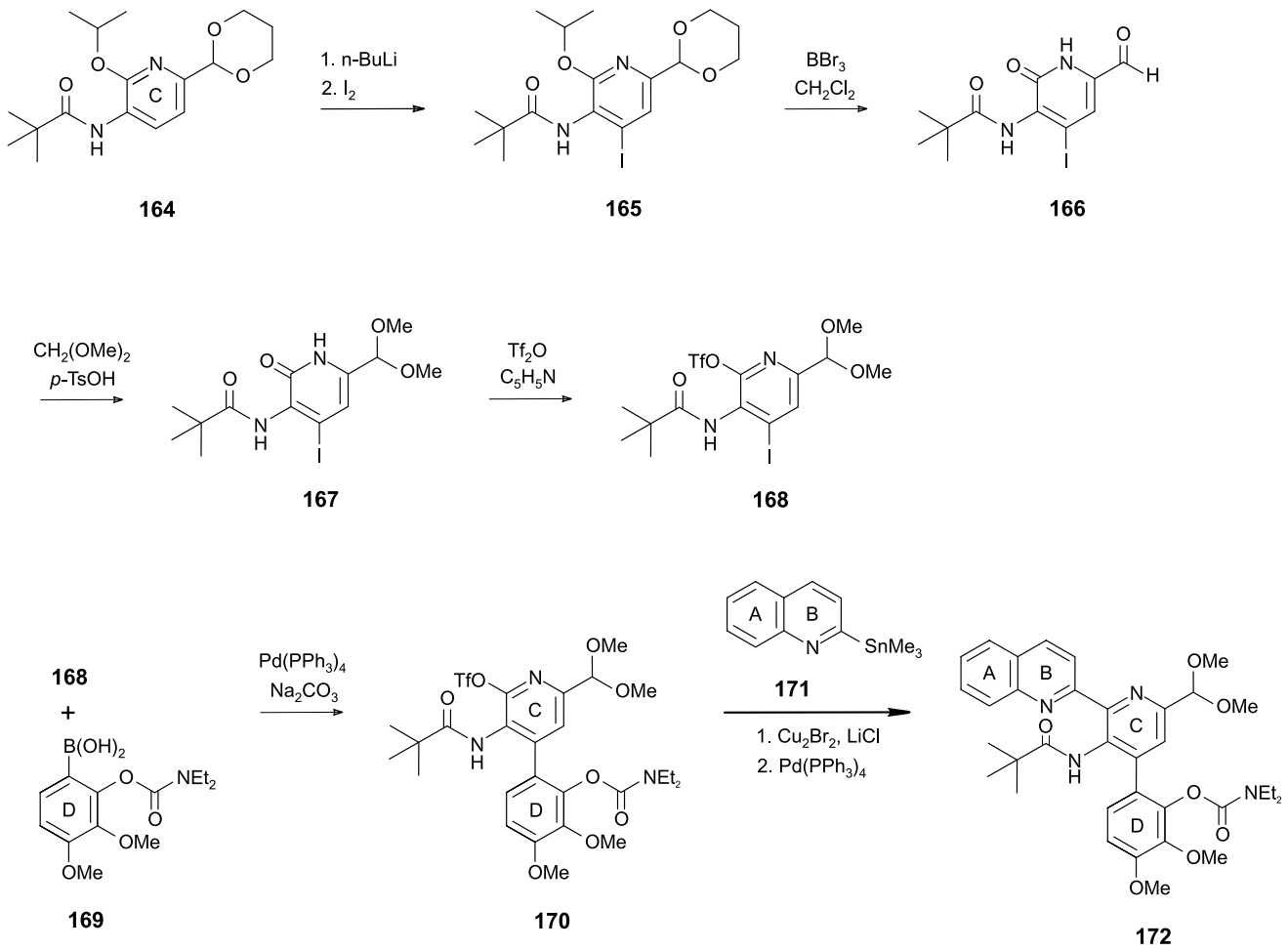
Four syntheses have appeared for model systems of the ABCD-rings, each of which has its own merits. The first tetracyclic model related to streptonigrin (**1**) was published by Kametani, Ogasawara, and Kozuka[65] in 1966 (see Scheme 19). The enamino-nitrile **150**, on heating with ethyl acetate and the aldehyde **151** (the latter supposedly giving the respective benzalacetone), resulted in a dihydropyridine, which was oxidized to the tetracyclic pyridine **152**. The nitrile unit in **152** was converted to the amide, which, on Hoffmann rearrangement with potassium hydroxide and bromine, gave the desired amine **153**.

A novel and completely different approach to the tetracyclic ring system of streptonigrin was reported by Cushman and Mathew (Scheme 20).[99] The dilithium dianion **155** derived from *o*-hydroxyacetophenone was treated with quinaldic acid chloride (**154**) to give the β-diketone **156**, which, on cyclodehydration, afforded the chromone **157** and then, on further treatment with malonodinitrile in thionyl chloride, the dinitrile **158**. By a reaction of the dinitrile **158** with ammonium hydroxide in hot pyridine, the pyridine imino-lactone **159** was obtained. Acid hydrolysis yielded **160**, the oxolactone function of which was reduced down to the methyl group present in the model compound **161** by using sodium bis(2-methoxyethoxy)aluminum hydride (‘Red-Al’)—a novel and intriguing approach to the synthesis of either biologically active analogs of streptonigrin or to the natural product itself!

The conversion of the dicyanomethylene dinitrile **158**



Scheme 22.



Scheme 23.

to the substituted pyridine iminolactone **159** is of mechanistic interest and a likely sequence of steps as suggested by the work of Reynolds[100] is outlined in Scheme 21.

Earlier in this report (Scheme 14), we outlined a new synthesis of substituted pyridines developed by Ciufolini and Byrne,[91] who subsequently used their method to prepare an ABCD-ring model system (see Scheme 22). The enone **162** prepared from 2-acetylquinoline and 2,3,4-trimethoxybenzaldehyde was subjected to cyclocondensation with ethyl vinyl ether (**117a**). The derived primary cycloadduct was converted to **163a** by the use of hydroxylamine hydrochloride. In related work, the same authors synthesized the additionally *C*-methylated analog **163b**, demonstrating an easy entry into the streptonigrin skeleton.[89]

Quéguiner and co-workers[63] have pursued several model systems in the streptonigrin area. Their work on the ABCD-ring system,[101–104] which has considerable potential in total synthesis, is outlined in Scheme 23. These researchers focused on two key reactions, namely *ortho* metallation[84] and Pd-catalyzed cross-coupling under Suzuki conditions. The 1,3-dioxan-2-yl-, *O*-isopropyl-, and 3-*N*-pivaloyl-protected aminopyridine derivative **164** was converted to the iodotriflate **168** in five steps, via the iodide **165**, the 6-formyl-2-pyranone **166** and the acetal **167**. Cross-coupling of **168** with the phenylboronic acid **169** afforded the 2-*O*-triflate-activated 4-phenylpyridine **170** with high selectivity. Coupling of **170** with 2-(trimethylstannyl)quinoline (**171**, prepared from 2-chloroquinoline and chlorotrimethylstannane in the presence of sodium in 1,2-dimethoxyethane as a solvent) gave the tetracycle **172**. If elaborated with a properly substituted A-ring, this would be a candidate for a short and efficient route to streptonigrin (**1**).

11. Total synthesis: general comments

Natural products provide outstanding opportunities for synthetic organic chemists to display creativity in the construction of complex molecules. For streptonigrin and its congeners, several new methods and reagents have evolved and these have helped to advance the organic synthetic methodology. In 1960, the total synthesis of streptonigrin (**1**) was considered to be a monumental—if not impossible—task, owing to its high degree of functionality coupled with an intricate arrangement of aromatic rings. Only after 20 years of careful and extensive preliminary studies did Weinreb complete the first total synthesis of

streptonigrin.[105–107] The extraordinary approaches by Kende's[55,108,109] and Boger's[76,110,111] laboratories soon followed. In the next three sections, we will highlight the synthetic strategies adopted by the respective groups rather than concentrating on the reactions and reagents. Weinreb's pathway is the longest of the three, but he deserves accolades for reaching the target first and at a time when the artistry of synthesis was not as mature as it is now.

12. Weinreb's approach

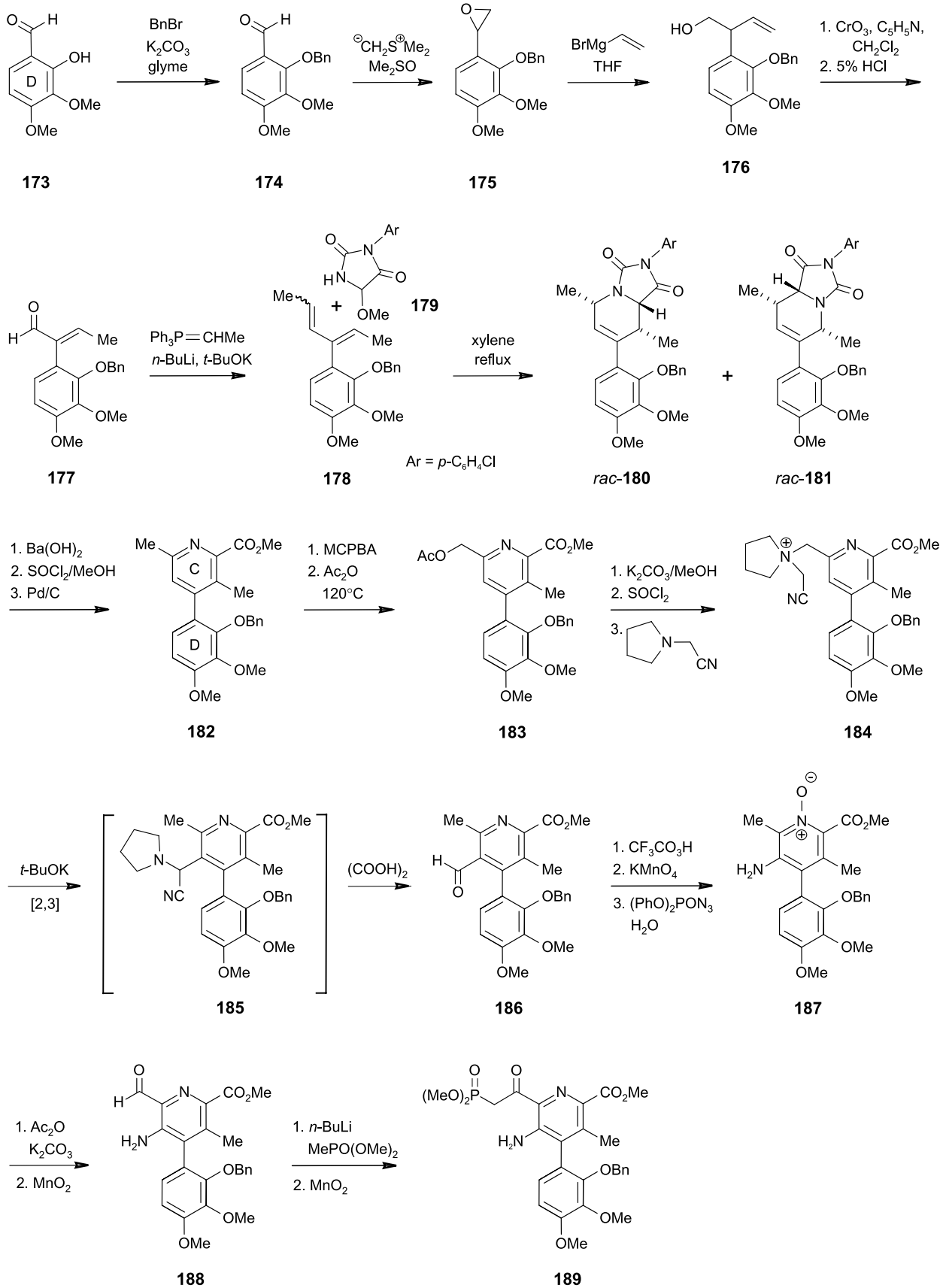
Weinreb adopted a modified Friedländer reaction to form the quinoline portion, that is, the AB-rings (see Scheme 24a).[106] The central strategy involved an imino Diels–Alder reaction for the construction of the CD-rings. The easily available aldehyde **173**[112] was converted in three straightforward steps to the 2-arylated α,β-unsaturated aldehyde **177**, by O-benzylation to **174**, conversion of the formyl function into the oxirane **175**, and its subsequent ring cleavage using vinyl magnesium bromide to give **176**, and eventual oxidation of the primary alcohol to an aldehyde function. Treatment with ethylidene triphenylphosphorane at low temperature, followed by *n*-butyllithium and then potassium *t*-butoxide in *t*-butanol,[113] afforded **178**. The reaction between this diene **178** and the methoxyhydantoin **179** generated the dienophile by elimination of methanol and led to a 3:1 mixture of the regioisomeric adducts **180** and **181**. Without separation, this mixture was transformed to the key tetrasubstituted pyridine **182** in three steps. The next task was the introduction of the amino group as the fifth substituent on the pyridine ring of **182**. This required excellent planning and its execution in 10 steps was a major achievement. It included three key reactions, namely the rearrangement of the *N*-oxide of **182** under Polonovski reaction conditions[114] to the acetoxy compound **183**, another [2,3]-sigmatropic (Sommelet–Hauser-type) rearrangement of **184** to functionalize the 3-position of the pyridine, and the Yamada modification[115] of the Curtius rearrangement, to provide the amine **187**. The final stages involved the renewed functionalization of the 2-methyl group of the pyridine by another Polonovski-type rearrangement and the stepwise formation of the chalcone derivative **191**, via a Wordsworth–Emmons–Horner reaction of **189** with **190** (see Scheme 24b),[116] followed by reduction with sodium hydrosulfite, which proceeded smoothly to give **192**. Cleavage of the *O*-sulfonyl group with sodium methoxide yielded the tetracyclic phenol quinoline-5-ol derivative, which was oxidized to the quinone **193** using Fremy's salt. Final elaboration of **193** to the aminoquinone **194** and further to streptonigrin (**1**) used known procedures developed by Weinreb[25,117] and others.[55]

13. Kende's approach

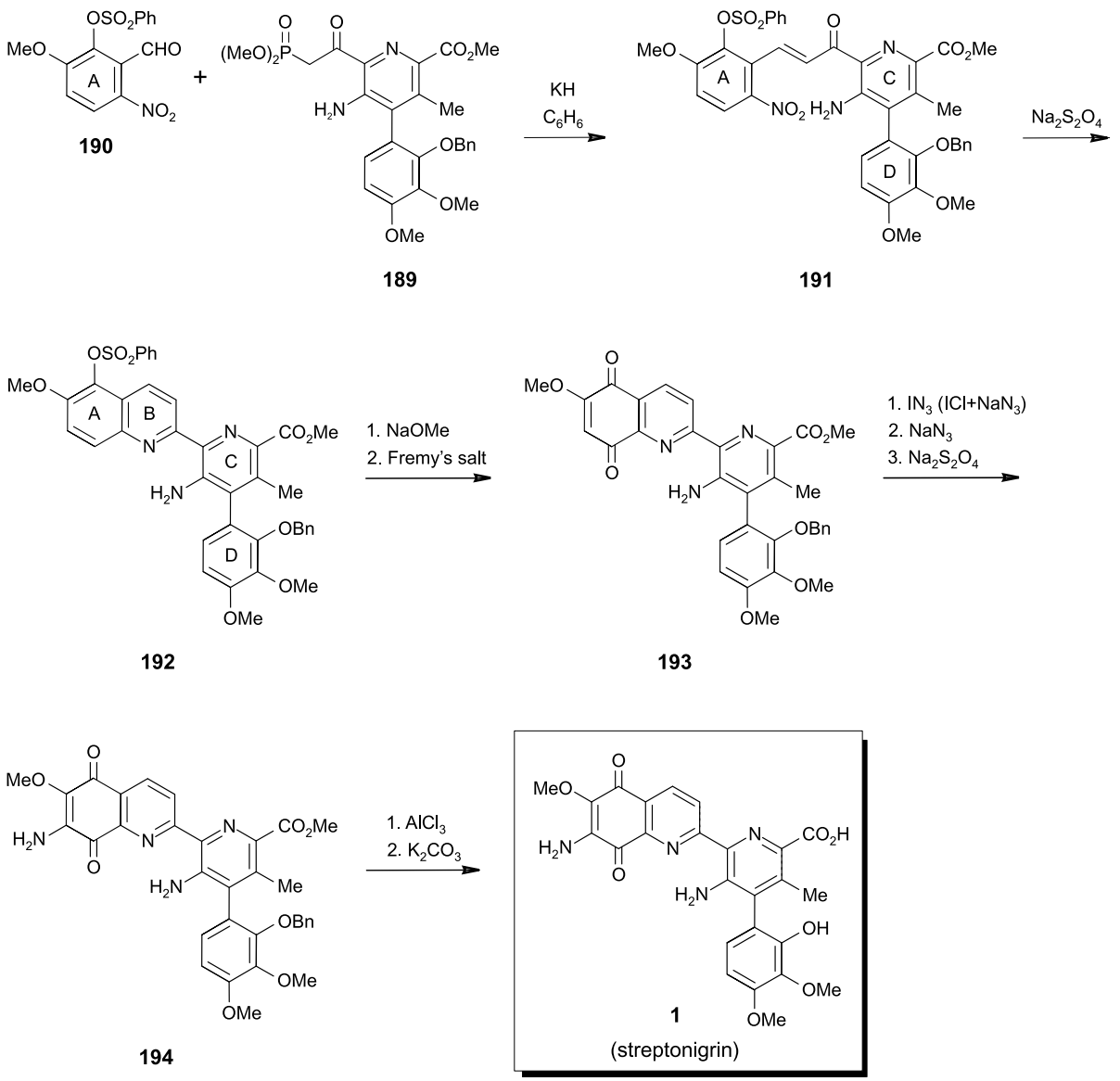
The basic strategy developed by Kende and co-workers[55,108,109] was to concentrate on the regiocontrolled synthesis of the CD-ring portion and then utilize a Friedländer synthesis for the attachment of the AB-ring system (see Scheme 25a or Scheme 25b). The known ketoenamine intermediate **63**, as prepared earlier by Liao, Wittek, and Cheng (see also Scheme 7),[73] was condensed with methyl acetoacetate to form the 3-acetyl-4-arylpyridone **195**. The acetyl group was reduced to the alcohol **196** (possibly a diastereomeric mixture, due to the presence of both central and axial chirality, but not specified) and further converted to the 2-chloro-3-vinylpyridine **197** by using phenylphosphoryl dichloride. On treatment with cuprous cyanide, this compound gave the respective nitrile, which was *C*-methyl-ated to yield the 2-acetylpyridine **198**. The A-ring precursor was prepared in three steps from the known[118] aldehyde **199**, which, upon imination with *p*-toluidine and O-benzyl-ation of the phenolic function with *p*-methoxybenzyl bromide, afforded the nitroimine **200**. This, when reduced with disodium sulfide in methanol, gave the iminoaniline **201**. Reaction of this second building block **201** with the ketone **198** led to the intact phenylpyridylquinoline **202**. Selective cleavage of its A-ring protecting group to give **203** allowed the introduction of the nitro group, followed by O-methylation with dimethyl sulfate, to give the nitro tetracyclic methyl ether **204**, the vinyl unit of which was then oxidatively degraded to deliver a carboxylic group on the pyridine ring.[119,120] Selenium dioxide[72] was found to oxidize the 2-methyl group of the pyridine to give the respective aldehyde, which, on sodium chlorite oxidation, gave the diacid, the selective methylation of which yielded the monoester **205**. Application of the Yamada modification[115] of the Curtius rearrangement produced the aminopyridine **206**. The A-ring nitro group was reduced to the amine with sodium hydrosulfite, followed by Fremy's salt oxidation to the quinolinequinone **193**, which had also been prepared by the Weinreb group (cf. Scheme 24b).[105–107] In this pathway by Kende, the A-ring amino function of **1** was introduced in four steps from **193**, by taking advantage of Weinreb's method developed previously.[25,117] The decision to use the vinyl group at C-5′ in the C-ring to serve as a precursor to the amino group[115,119,120] was a keen insight, and became an elegant feature in Kende's approach, simultaneously resulting in a shorter synthesis.

14. Boger's approach

Boger[76,110,111] reported a convergent seven-step synthesis of the tetracycle **215** (see Scheme 26), with the benefit of a considerable amount of preliminary work first conducted on model systems. Two consecutive Diels–Alder reactions with inverse electron demand and subsequent in situ cycloreversion formed the basis of their approach. The key starting material was the thioimidate **210**, which was prepared from the commercially available 6-methoxyquinoline (**207**). Treatment of **207** with *p*-toluenesulfonyl chloride and then with potassium cyanide gave the 2-cyanoquinoline **208**. Nitration yielded **209**, which, on further reaction with hydrogen sulfide in diethylamine, generated the thioamide, which was converted to the desired *S*-methylthioimidate **210** with methyl iodide. A Diels–Alder reaction of **210** with the 1,2,4,5-tetrazine-3,6-dicarboxylate (**211**)[121] with N_2 extrusion provided the 1,2,4-triazine **212** in 82% yield. Subsequent treatment of **212** with the morpholino enamine **213** of 2-(benzyloxy)-3,4-dimethoxypropiophenone afforded a 1:1 mixture of the Diels–Alder adducts **214** and **215**. Four further steps transformed **215** into **206**,[110] which had previously been converted (Scheme 25a or


BnBr
K2CO3
glyme
CH2SMe2
Me2SO
BrMg
THF
1. CrO3, C5H5N,
CH2Cl2
2. 5% HCl
Ph3P=CHMe
n-BuLi, t-BuOK
xylene
reflux
Ar = p-C6H4Cl
1. Ba(OH)2
2. SOCl2/MeOH
3. Pd/C
1. MCPBA
2. Ac2O
120°C
1. K2CO3/MeOH
2. SOCl2
3.
t-BuOK
[2,3]
(COOH)2
1. CF3CO3H
2. KMnO4
3. (PhO)2PON3
H2O
1. Ac2O
K2CO3
2. MnO2
1. n-BuLi
MePO(OMe)2
2. MnO2
173
174
175
176
177
178
179
rac-180
rac-181
182
183
184
185
186
187
188
189

Scheme 24a.

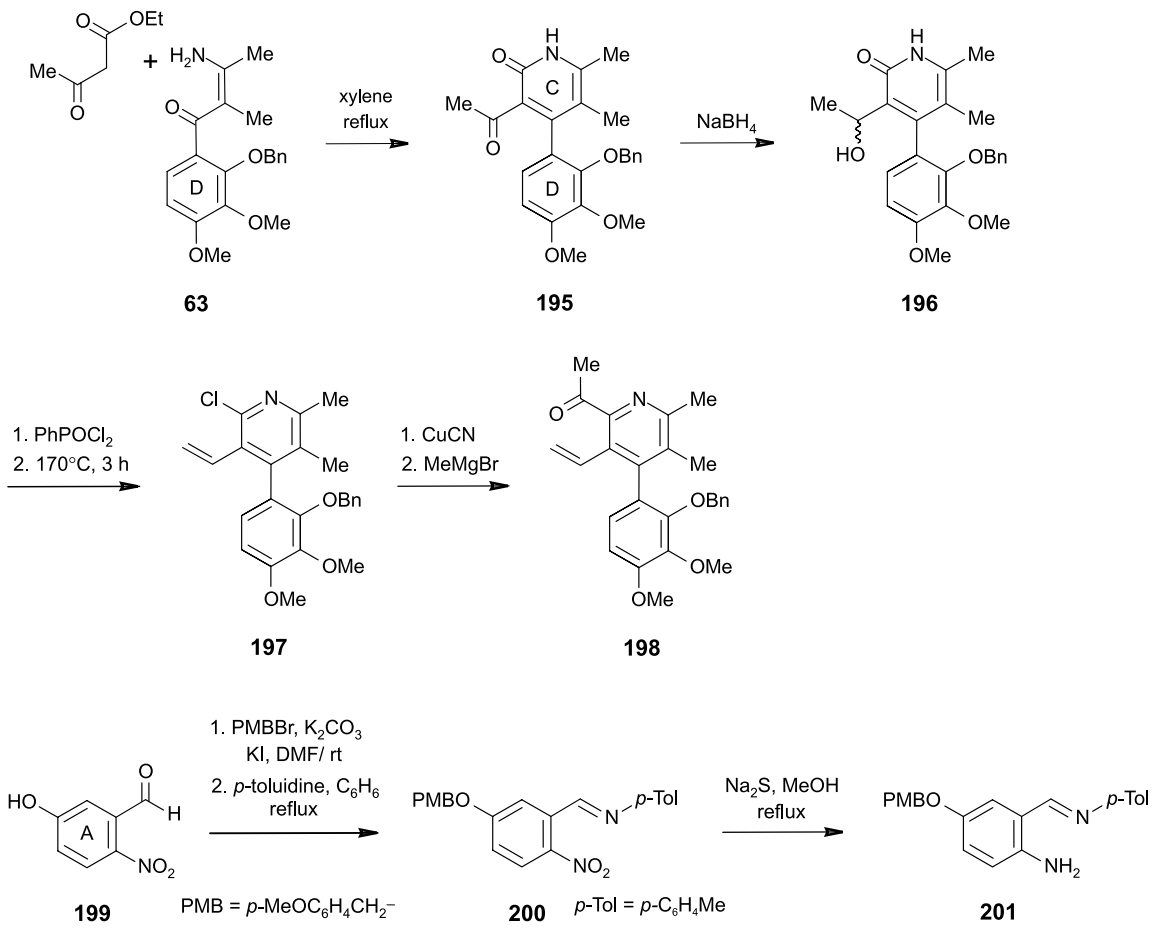


Scheme 24b.

Scheme 25b) to streptonigrin (**1**).[102] Boger's approach therefore corresponds formally to another total synthesis of streptonigrin.

15. Structure and synthesis of streptonigrone

Streptonigrone (**2**) was isolated, along with streptonigrin (**1**), from an unidentified *Streptomyces* species (IA-CAS isolate No. 114) by Rickards and his colleagues,[15] and, additionally, a Russian team isolated **2** from *Streptomyces albus* var. *bruneomycini* as a minor component from both of the species.[16] Streptonigrone (**2**) has a mp of 268–269 °C and the molecular formula $C_{24}H_{22}N_4O_7$, which differs from that of streptonigrin **1** ($C_{25}H_{22}N_4O_8$) by the lack of one C and one O atom. The assigned structure is based mainly on the ^1H and ^{13}C NMR spectra, the characteristics of which are very similar to those of streptonigrin (**1**). In contrast to **1**, however, the lack of any circular dichroism effect[23] demonstrates that streptonigrone (**2**) is a racemate, either due to a non-enantioselective formation or because it is possibly configurationally unstable. Again in contrast to streptonigrin (**1**), **2** showed no antimicrobial activity in disc assays at 50 μg/ml against strains of *Streptomyces aureofaciens*. The only synthesis of streptonigrone (**2**) so far reported was developed by Boger and his group[122] and is outlined in Scheme 27. Their strategy was to use an inverse electron demand Diels–Alder reaction[121,123] of the *N*-sulfonyl-1-aza-1,3-butadiene **221** with the ketene acetal **222** to generate ring C. A Friedländer condensation of pyruvic acid (**217**) with 2-amino-3-benzyloxy-4-bromobenzaldehyde (**216**) and esterification gave the quinoline **218**, which, on treatment with the lithium enolate of ethyl acetate, provided the β-keto ester **219**. A piperidine-catalyzed condensation of **219** with 3,4-dimethoxy-2-hydroxybenzaldehyde[112] (**173**) afforded the benzopyranyl ketone **220**. This ketone was converted to the desired azadiene **221** in two steps by the action of hydroxylamine hydrochloride and methanesulfinyl chloride. A hetero-Diels–Alder reaction of **221** with 1,1-dimethoxypropene (**222**) led to the respective



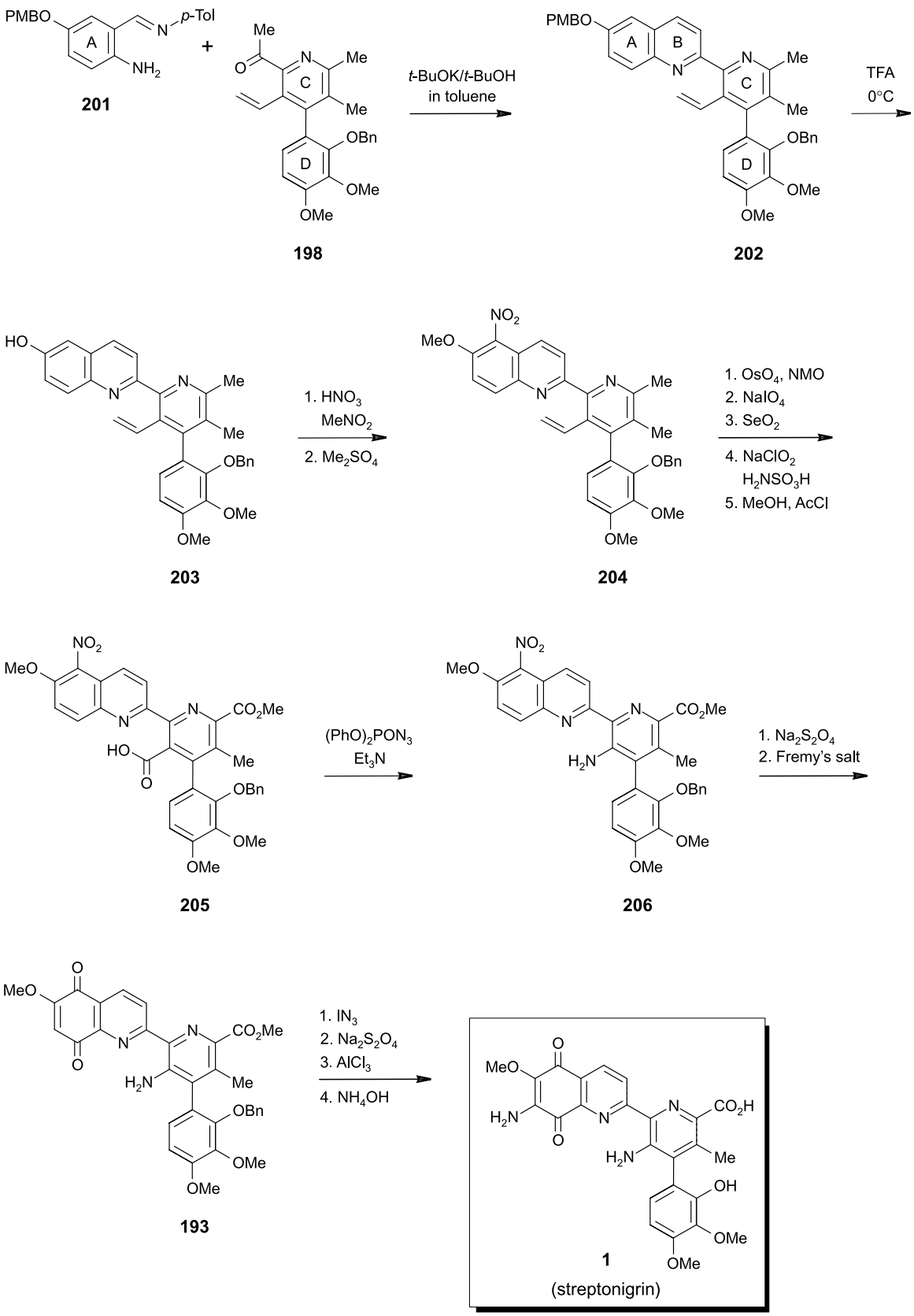
Scheme 25a.

[4+2]-cycloadduct which, on treatment with potassium *t*-butoxide followed by dichlorodicyanoquinone, provided the pyridine lactone **223**. Methanolysis opened the lactone ring and the resulting phenol function was protected as a methoxymethyl (MOM) ether, hydrolysis of the methyl ester with lithium hydroxide giving the nicotinic acid derivative **224**. This intermediate was converted to the benzyl ether of **225** and then further to streptonigrone (**2**) by standard reactions, most of which have already been previously discussed (see Scheme 25a) in connection with the synthesis of streptonigrin (**1**). Two aspects of the Boger synthesis of streptonigrone (**2**) are worthy of note, namely his prediction of a high regioselectivity in the Diels–Alder reaction (**221**+**222**→**223**), which proved to be correct, and the development and application of an improved Lewis acid-catalyzed nucleophilic substitution reaction at C-6 with sodium methoxide (**226**→**227**).

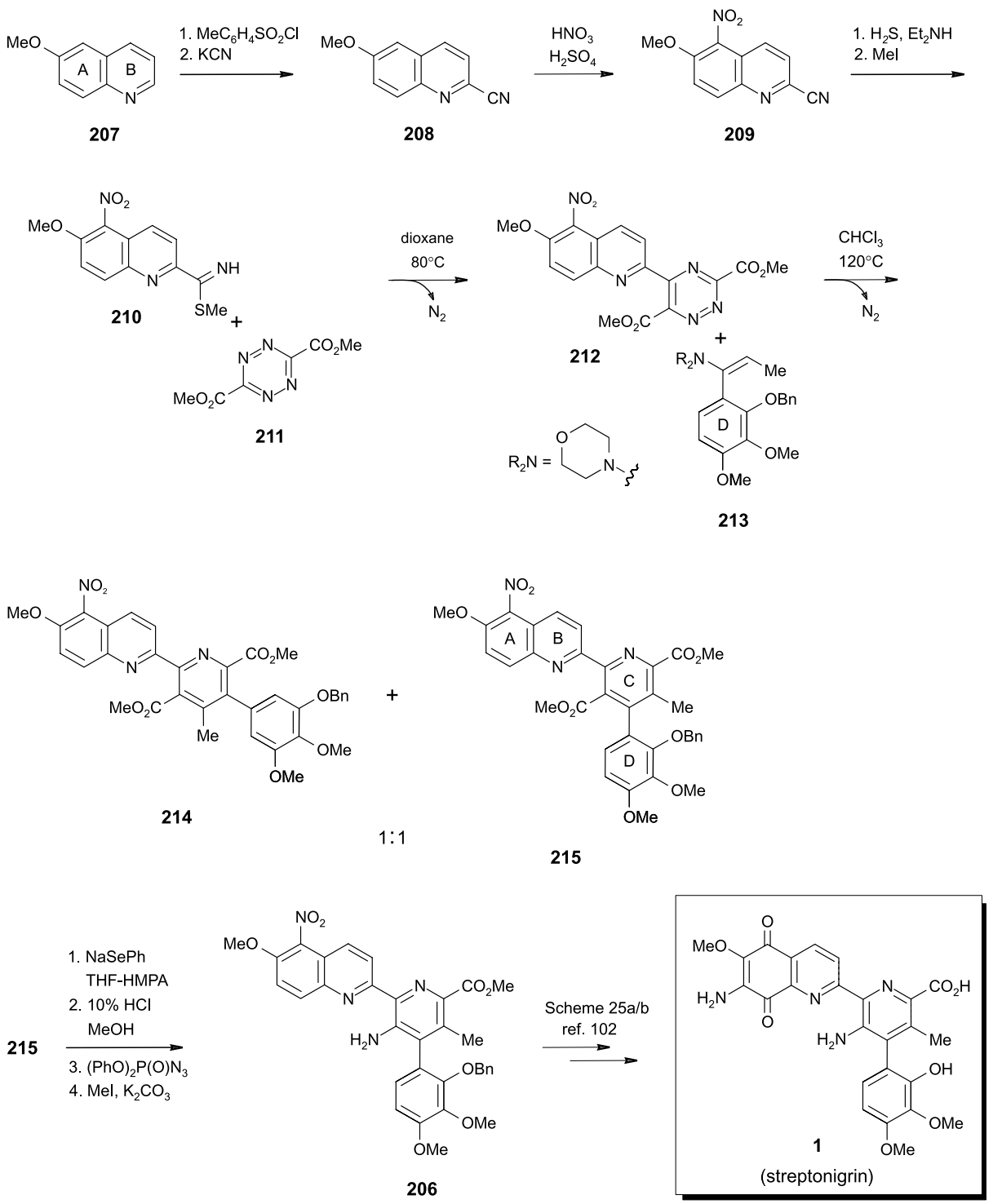
16. Structure and total syntheses of lavendamycin and an analog

While investigating the fermentation broth of *Streptomyces lavendulae* strain C22030, Doyle and his group[17] isolated an antibiotic that was named lavendamycin, a red solid, mp >300 °C, with the molecular formula $C_{22}H_{14}N_4O_4$. Lavendamycin was found to possess a limited solubility in organic solvents, which precluded efforts to grow crystals suitable for an X-ray structure analysis. Only minute quantities of the natural product were available and chemical degradation was therefore not feasible. The NMR, IR, UV, and high resolution mass spectral studies, together with biogenetic consideration, were used to assign structure **3** to lavendamycin. It has antibiotic activity comparable to that of streptonigrin (**1**) and, most importantly, antitumor activity against P-388 and L-1210 cell lines. The biological activity, coupled with novel structural features such as a tricyclic β-carboline subunit attached to a 7-amino-quinolinequinone, were challenging enough for organic chemists to undertake its synthesis. Since the structural assignment of lavendamycin (**3**) by Doyle, Gould, and their collaborators in 1981,[17] four research groups have synthesized its methyl ester between 1984 and 1986.

The first total synthesis was achieved by Kende and Ebetino[124] and their route is outlined in Scheme 28. The key intermediate **231** was prepared in three steps from 2-amino-3-methoxybenzaldehyde (**228**) and pyruvic acid (**217**). A Friedländer condensation[106] gave the 8-methoxyquinaldic acid (**229**), which was nitrated to deliver the 5-nitro derivative **230**. Bromination in the presence of silver trifluoroacetate gave the desired key intermediate **231** in 45% overall yield for the three steps. Reaction of this acid with the methyl ester **232** of β-methyltryptophan


PMBO
p-Tol
A
NH2
201
Me
O
N
Me
C
Me
OBn
D
OMe
OMe
198
t-BuOK/t-BuOH
in toluene
PMBO
A
B
N
Me
C
Me
OBn
D
OMe
OMe
202
TFA
0°C
HO
N
Me
Me
OBn
OMe
OMe
203
1. HNO3
MeNO2
2. Me2SO4
NO2
MeO
204
1. OsO4, NMO
2. NaIO4
3. SeO2
4. NaClO2
H2NSO3H
5. MeOH, AcCl
CO2Me
HO
O
205
(PhO)2PON3
Et3N
H2N
206
1. Na2S2O4
2. Fremy's salt
O
1. IN3
2. Na2S2O4
3. AlCl3
4. NH4OH
CO2H
OH
1
(streptonigrin)

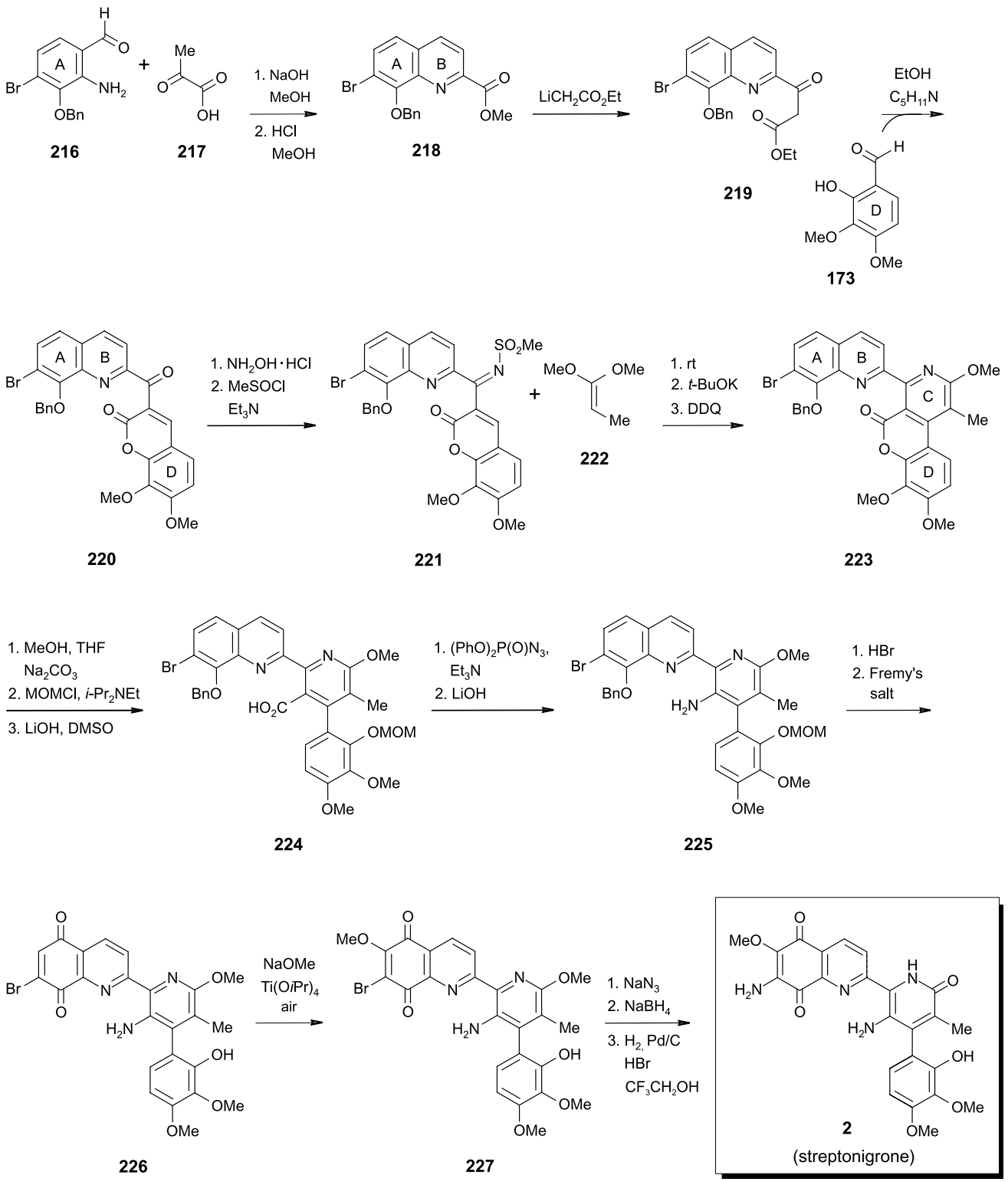
Scheme 25b.



Scheme 26.

(stereoisomeric mixture)[125] in the presence of a carbodiimide gave the amide **233**, which was condensed to the pentacyclic β-carboline ester **234** with polyphosphate esters (PPE)[126] by using a Bischler–Napieralski-type cyclocondensation with a concomitant dehydrogenation reaction. In a straightforward sequence of four steps, this pentacyclic product was converted to the amine **235** and the quinolinequinone **236** and eventually to lavendamycin methyl ester (**237**), which was identical with the methyl ester prepared directly from lavendamycin (**3**).

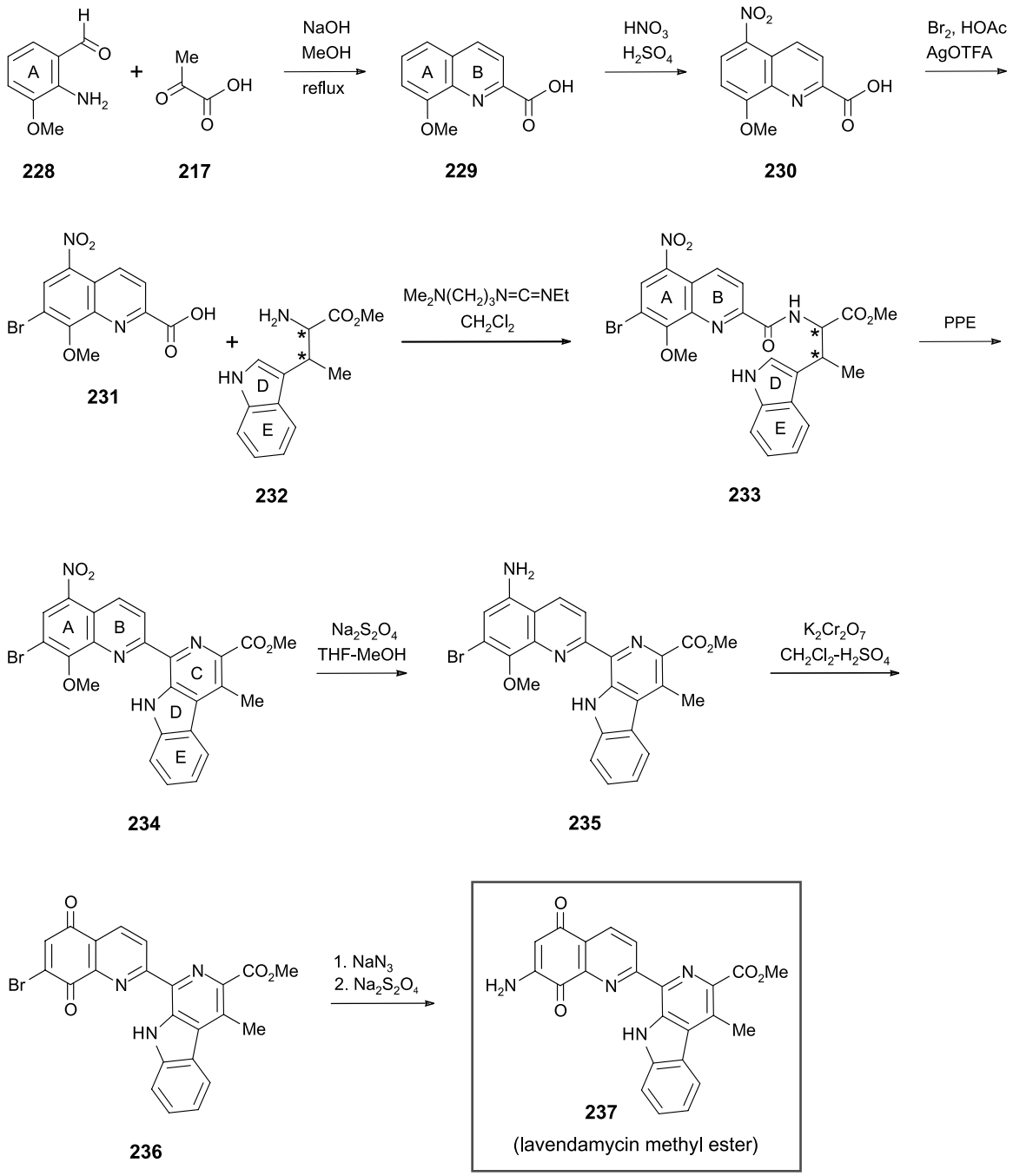
Hibino's[127,128] and Rao's[129,130] groups have independently reported regiospecific formal total syntheses of lavendamycin methyl ester (**237**) in eight and 16 steps, respectively, the first starting from the 2-formylquinoline **238** and β-methyltryptophane ethyl ester (**239**), via the pentacyclic compounds **240**, **241**, **242**, **243**, and **236**, and the second from quinoline-8-ol (**244**), via **245**-**253**. The latter compound, after amidation with the tryptophan derivative **232** to give **254**, was submitted to a Bischler–Napieralski cyclization to give **255**, which was converted to **237** via the



Scheme 27.

bromoquinone **236**. Although both approaches were similar to that of Kende, different starting materials and reagents were used. This does not detract from the value of the ideas presented in these two syntheses, which are outlined in Schemes 29 and 30. It is of interest to note the probably biomimetic-type Pictet–Spengler-based approach by Hibino (see Scheme 29).

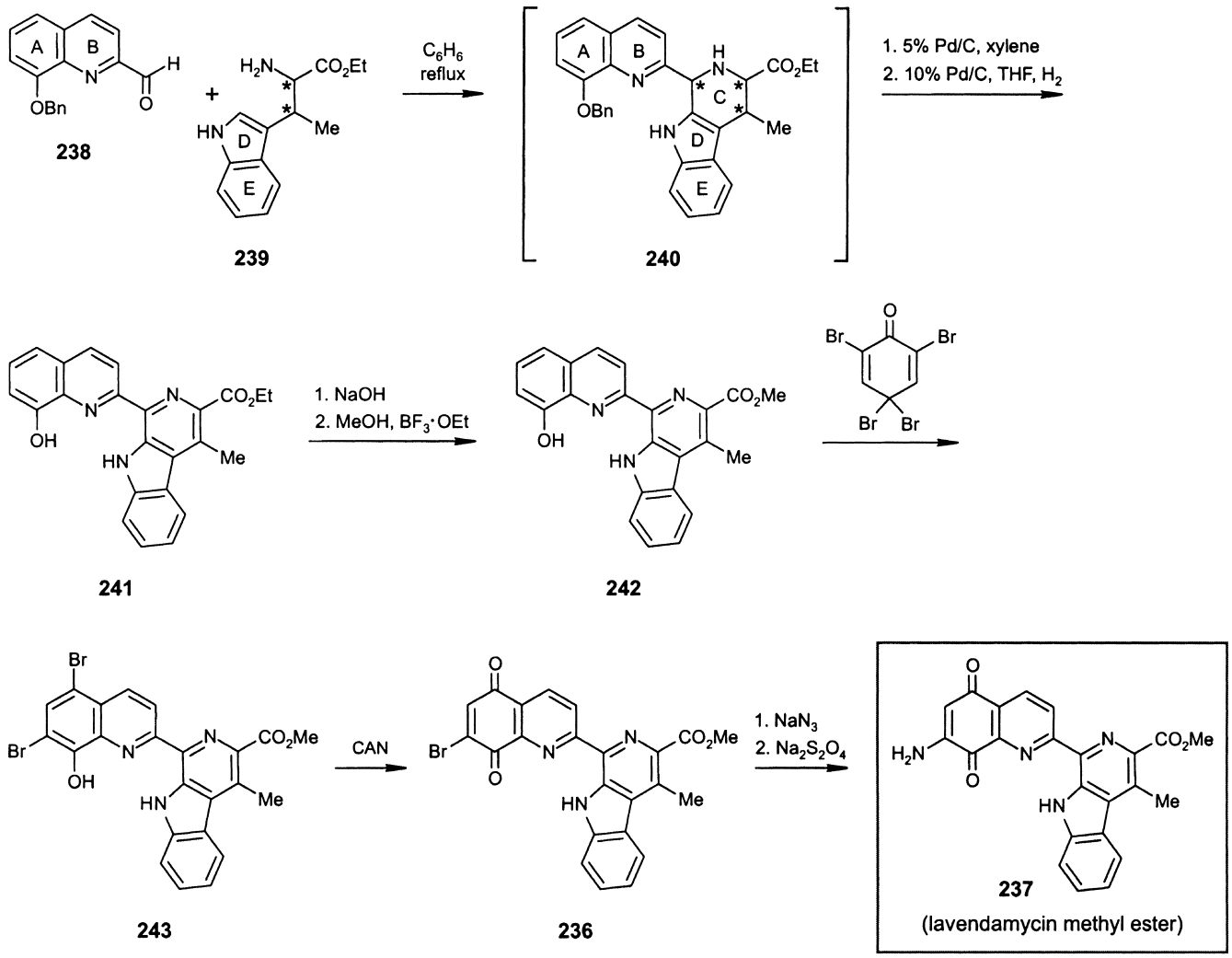
Boger and co-workers[131] succeeded in applying their inverse electron demand [4+2]-cycloaddition of an electron-deficient 1,2,4-triazine with an α-aryl enamine to form the CE-rings as the basis of a synthesis of lavendamycin methyl ester (**237**). Another notable feature was the formation of a D-ring of a β-carboline unit by the oxidative insertion of an aryl halide in the presence of palladium(0). In



Scheme 28.

addition, a Friedländer condensation between a suitable aryl aldehyde and a properly-substituted β-carboline unit was used to form the ABCDE-rings of lavendamycin methyl ester. These three key reactions contributed to the success of Boger's synthesis, which is outlined in Scheme 31. The oxazinone **261** was prepared in a six-step sequence from 3,5,6-tris(ethoxycarbonyl)-1,2,4-triazine (**81**), by a regioselective inverse-electron demand [4+2]-cycloaddition with the pyrrolidine enamine **257** of 2-bromopropiophenone, as prepared from the aldehyde **256**, with concomitant N_2 extrusion. Standard steps completed the conversion of the cycloadduct **258** to **261**, via the monoacid **259** and the acetamido compound **260**. Another four steps were required to convert **261** to the free 2-acetyl-3-aminopyridine **262** and then to **263**. This 2-acetyl-β-carboline, which was condensed with 2-amino-3-benzyloxy-4-bromobenzaldehyde (**264**) to give 1-(8-benzyloxy-7-bromo-2-quinolinyl)-3-(methoxycarbonyl)-4-methyl-β-carboline (**265**). From **265**, the synthesis of the pentacyclic carboline molecule of lavendamycin methyl ester (**237**) was accomplished employing standard reaction conditions.

In 1996, Behforouz[132] reported a short and practical approach for the total synthesis of lavendamycin methyl ester (**237**), attaining a high overall yield of as much as 32%! The novel bis-acetamide **268** was prepared from the



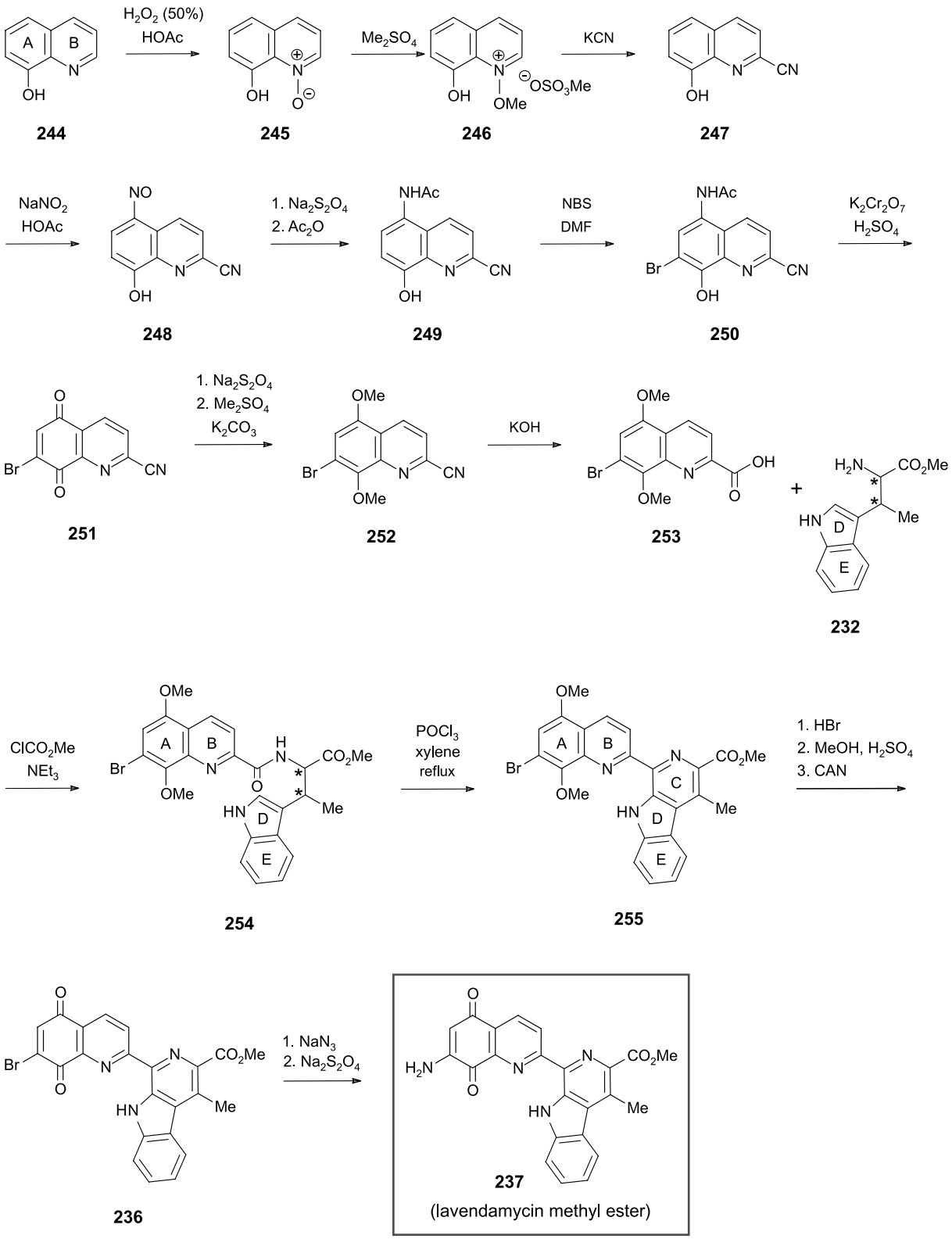
Scheme 29.

commercially available 8-hydroxy-2-methylquinoline (**266**) in three steps via the dinitro compound **267** (see Scheme 32). It was then converted into the pentacyclic product **237** by the selective oxidative cleavage of the 5-acetamide function to give the quinone **269**, followed by the oxidation to the aldehyde **270**, which underwent a Pictet–Spengler reaction with the methyl ester **232** of β-methyltryptophan to give directly the dehydrogenated β-carboline **271**, the treatment of which with aqueous sulfuric acid gave **237**[133] (see also Schemes 28–30).

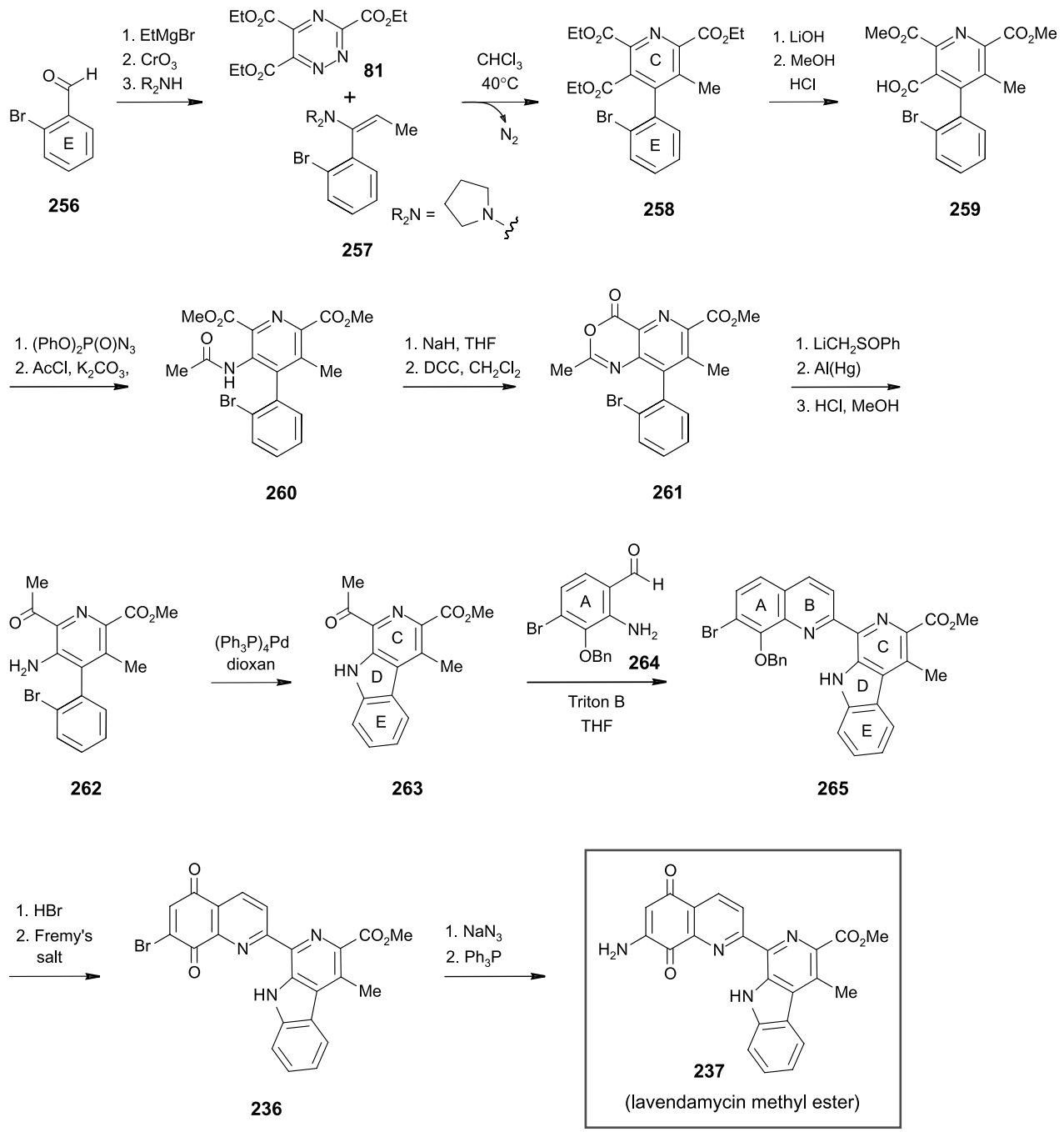
In order to study the structure–activity relationships of lavendamycin (**3**) and its analogs, Godard, Quéguiner and co-workers[104] in 1993 reported a convergent synthesis of a model system. A retrosynthetic analysis suggested that lavendamycin analogs could be obtained in four steps including a cross-coupling involving heterocycles, an indole cyclization by nucleophilic substitution of fluoride, and a final oxidation of the 5,8-dioxyquinoline unit (see Scheme 33). The reaction of the arylstannane **272** with the 2-chloropyridine **273** in the presence of $Pd(PPh_3)_4$ as the catalyst[134] gave the tetracyclic product **274**, the treatment of which with pyridinium chloride afforded **275**. Finally, oxidation with Fremy's salt gave the lavendamycin analog **276** (24% overall yield for these four steps). No biological activity has yet been reported, however, for this analog.

17. Conclusions and outlook

The story of streptonigrin is extremely captivating. It began in 1960 in an industrial environment and ended up in an academic institution world renowned for its structure elucidation, which was reported in 1963 by Rao, Biemann, and Woodward. The structure of streptonigrin is unique and challenging. The last four decades have witnessed considerable progress in the area of its total synthesis, its likewise unprecedented biosynthesis, its structure–activity relationships, its mode of action, and its absolute configuration. The aim of this review has been to describe on the strategies for the synthesis of streptonigrin, streptonigrone, and lavendamycin in a more detailed manner than other reports. The schemes included show a high degree of creativity at the time when applied to the synthesis of these antibiotics. The fascination with streptonigrin and related compounds exhibited especially by organic and medicinal chemists will continue for years to come, with a strong


H2O2 (50%)
HOAc
Me2SO4
KCN
244
245
246
247
NaNO2
HOAc
1. Na2S2O4
2. Ac2O
NBS
DMF
K2Cr2O7
H2SO4
248
249
250
1. Na2S2O4
2. Me2SO4
K2CO3
KOH
251
252
253
232
ClCO2Me
NEt3
POCl3
xylene
reflux
1. HBr
2. MeOH, H2SO4
3. CAN
254
255
1. NaN3
2. Na2S2O4
236
237
(lavendamycin methyl ester)

Scheme 30.



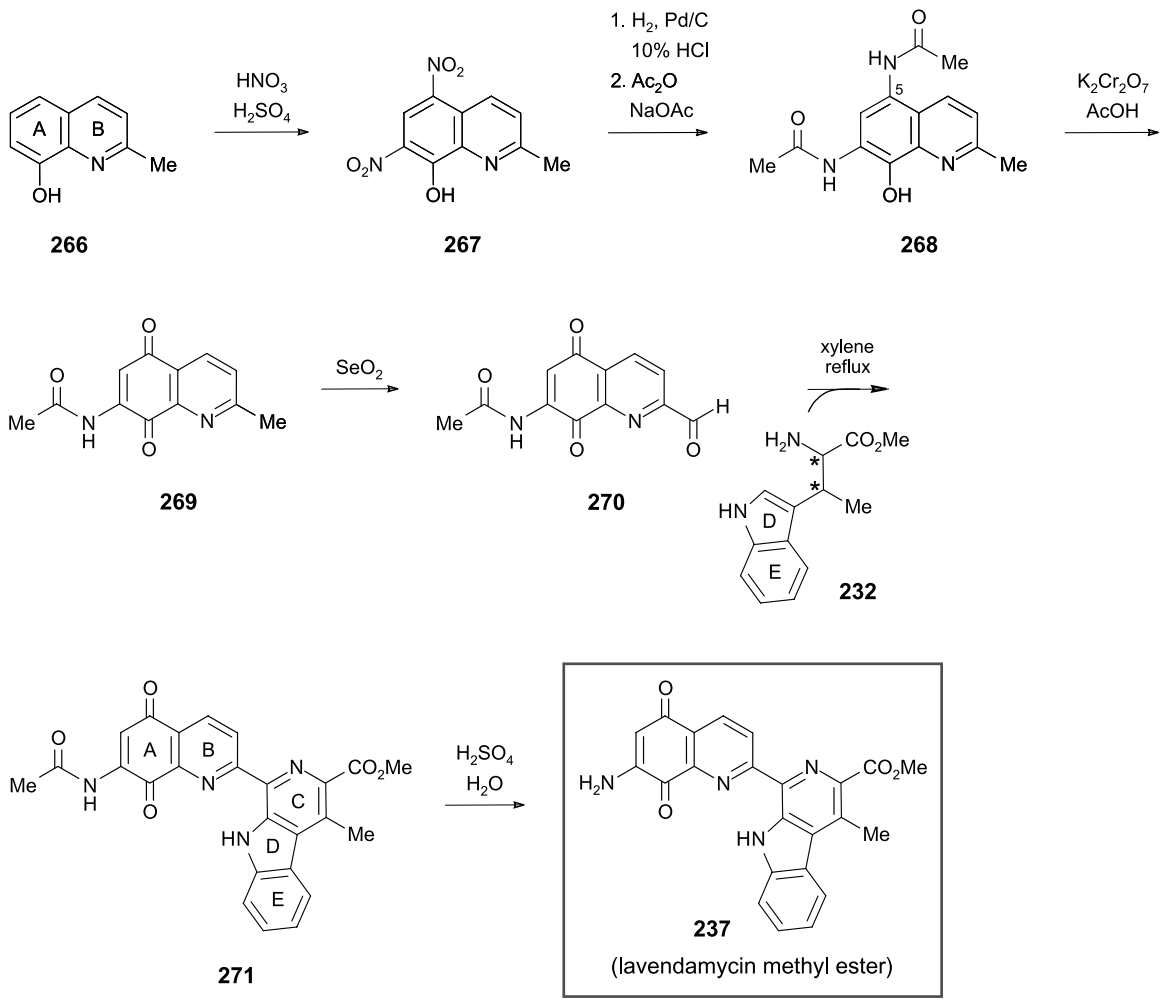
Scheme 31.

emphasis on improved methods and on shorter, more practicable syntheses that will also take into consideration the chirality of the molecule due to the rotationally-hindered biaryl axis.

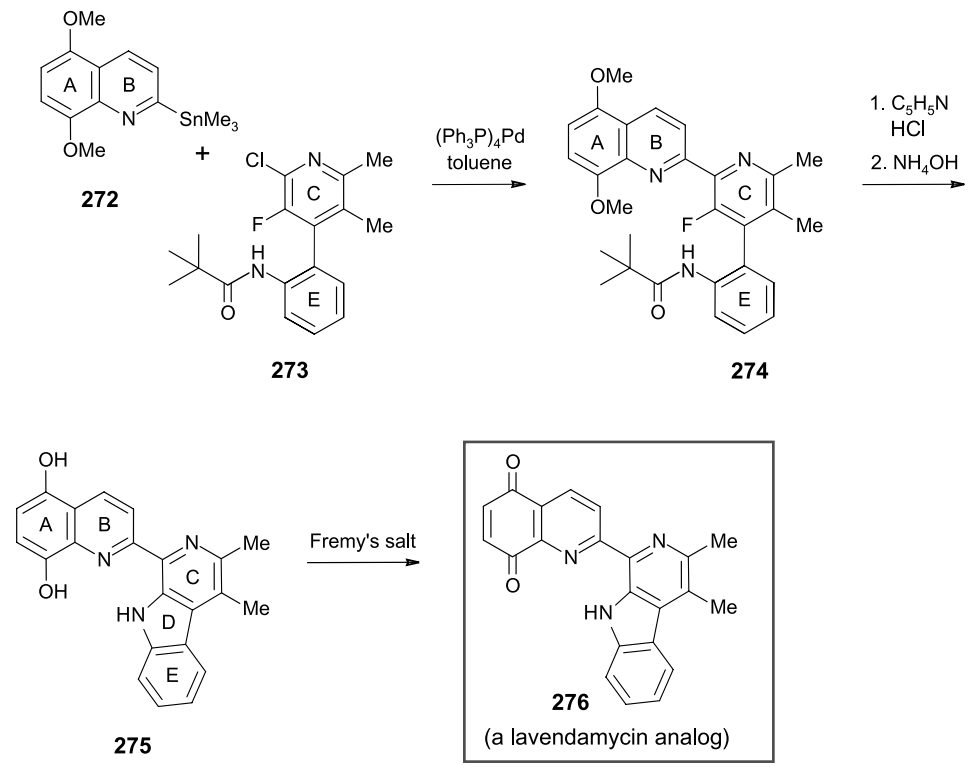
There are several areas for future investigation, one being to target the metal complexes of streptonigrin (**1**) and related compounds as potential therapeutical agents. These metal complexes of **1** have never been assayed in clinical trials, but might develop into second-generation anticancer compounds based on the streptonigrin skeleton. It would be interesting to evaluate if any of the metabolites of streptonigrin (**1**)[135] are more active and/or less toxic than the parent compound **1**. One of the main goals, however, will be that synthetic organic chemistry will in the near future have to provide analogs of streptonigrin (**1**), streptonigrone (**2**), and lavendamycin (**3**) with hopefully higher antitumor activity and lower toxicity. We hope that this review will stimulate interest in the streptonigrin family of antibiotics in the future.

Acknowledgements

Financial support by the Fonds der Chemischen der Industrie and the Deutsche Forschungsgemeinschaft (SFB 630 'Neue Wirkstoffe gegen Infektionskrankheiten') is gratefully acknowledged. We thank Dr. D. Feineis



Scheme 32.



Scheme 33.

for providing difficult-to-access literature and for fruitful discussions, P. Leckert and M. Reichert for assistance in preparing the manuscript and the members of the Würzburg group for stimulating comments and helpful suggestions. V.V.K. thanks Professor Kenneth J. Shea, University of California, Irvine (UCI), for his interest and encouragement.

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Biographical sketch

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Tetrahedron 60 (2004) 3575–3579
Tetrahedron

A new highly chemoselective isomerization of allylamides

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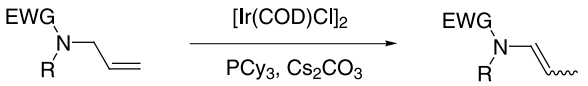
Received 6 November 2003; revised 13 February 2004; accepted 3 March 2004

Abstract—This work describes the first iridium-catalyzed isomerization of *N*-allylamides into enamides. This strategy allows the chemoselective preparation of (*E*)-*N*-(1-propenyl)-enamides and can be applied for the selective deprotection of *N*-allylamides.

1. Introduction

Enamines are versatile intermediates in organic synthesis and are starting substrates for various synthetic transformations.[1] Their preparation procedures usually give mixtures of isomers and low yields.[2] An improvement is provided by the use of enamides instead of enamines since the electron-withdrawing group enhances the stability of these compounds. A short and efficient approach to *N*-vinyl amides is well known but is limited to this class of compounds (unsubstituted enamines).[3] A method of choice would be the isomerization of allylamines since these compounds are easily available. We found numerous methods in the literature to convert allylamines into enamines. Among these methods one can cite the use of strong bases such as *n*BuLi,[4] *t*BuLi,[5] LDA,[4,6] *t*BuOK[7a] or NaH.[7b] Milder conditions have been found to achieve this reaction mainly based on the use of ruthenium,[8] rhodium,[9] iron,[10] chromium,[11] molybdenum,[12] cobalt[13] or titanium complexes.[14] Similar methodologies were applied to the isomerization of *N*-allylamides to enamides using ruthenium,[15] rhodium,[16] iron[17] or cobalt complexes.[13a] In addition, the iron methodology also catalyzes the long-distance migration of a double bond to yield enamides.[18] The synthesis of *N*-(1-propenyl)imides via isomerization of *N*-allylimides is also known, catalyzed by complexes of ruthenium[8b,15a,b] or iron.[19] It has also been recently shown that a commercially available iridium(I) complex could convert allyl ethers into enol ethers[20] and we were intrigued to see whether we could apply this methodology to convert allylamides to enamides (Scheme 1).



Scheme 1. Isomerization of *N*-allyl amides, imides and carbamates to corresponding *N*-(1-propenyl) derivatives.

2. Results and discussion

We synthesized *N*-allylamides via metallation of amides using KHMDS in DMF and subsequent trapping of the resulting anion with allylbromide. The *N*-allylamides thus obtained were then subjected to the commercially available $[Ir(COD)Cl]_2$ in the presence of tricyclohexylphosphine and cesium carbonate. The results are summarized in Table 1.

From the results described below it is clear that the isomerization can be run in the presence of various electron-withdrawing groups linked to the nitrogen atom. In all runs, conversion was greater than 95% as estimated by ^{1}H NMR of the crude reaction mixture, except for entry 11 (vide infra). Sulfonamides (entries 1 and 2), amides (entries 3–5), carbamates (entries 6 and 9) and imides (entries 7 and 8) are prone to isomerization. On the other hand, the second nitrogen substituent can be either aliphatic (entries 2, 4–6) or benzylic (entries 1, 3 and 9). In all cases, a strong preference for the *E* isomer is observed and fair to excellent yields of pure *E* isomers were obtained after column chromatography. All attempts to isomerize a substituted double bond of compound **10** failed (entry 10) and the starting material was recovered unchanged even if 50% isomerization could be observed with the oxazolidinone *N*-methallyl amine derivative **11** (entry 11). Nevertheless, we were not able to isolate the enamide **11** from the starting material. It is worth noting that the use of a catalytic amount of Cs_2CO_3 slightly improves the reaction rate since in 48 h a 2/1 ratio (product/starting material) was observed without base, whereas a 3/1 ratio was obtained with 5 mol% of Cs_2CO_3 when the reaction was run with *N*-allyl, *N*-benzyl

Keywords: Enamide; Iridium; Isomerization.
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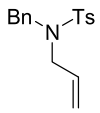
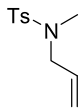
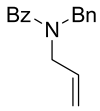
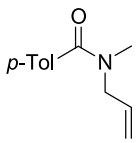
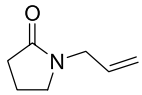
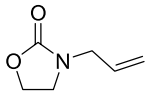
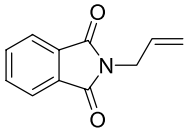
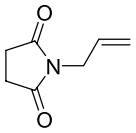
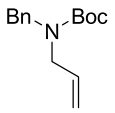
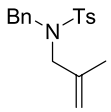
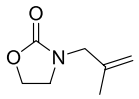
doi:10.1016/j.tet.2004.03.004

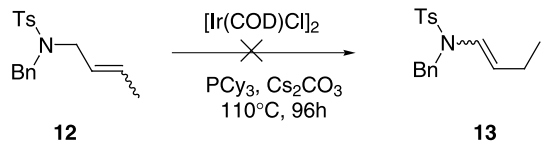
Table 1. Synthesis of *N*-(1-propenyl) amides, imides and carbamates via isomerization of corresponding *N*-allyl derivatives

Entry	Substrate	Compound	*E*/*Z*[a]	Yield (%)[b]
1		**1**	97/3	56
2		**2**	91/9	64
3		**3**	92/8	65
4		**4**	98/2	95
5		**5**	98/2	77
6		**6**	98/2	88
7		**7**	91/9	71
8		**8**	90/10	68
9		**9**	97/3	96
10		**10**	—	—
11		**11**	—	50[c]

[a] Assigned on ^{1}H NMR spectrum of the crude reaction mixture.
[b] Isolated yield after column chromatography.
[c] Conversion estimated by ^{1}H NMR.

4-methylbenzenesulfonamide (entry 1). When the reaction was performed with $[Ir(COD)Cl]_2$ in the absence of PCy_3, a complex mixture of products was obtained and only a small quantity of the expected product could be detected. In addition, a control experiment was run in boiling toluene alone starting from compounds **4** and **9**, but in this case the starting material was recovered unchanged ruling out a possible thermal isomerization. It is also worthy to note that this reaction can be applied to allylamines, for instance when *N*,*N*-diphenyl allylamine or *N*-benzyl, *N*-methyl allylamine were submitted to the previously described conditions the corresponding enamines were obtained in a *E*/*Z*=3/1 ratio but these compounds appeared much more difficult to purify on silica gel resulting in extensive degradation. This last results also confirm the role of an electron-withdrawing group borne by the nitrogen atom on the *E*/*Z* stereoselectivity during isomerization of allylamides.[8b,15b,21]

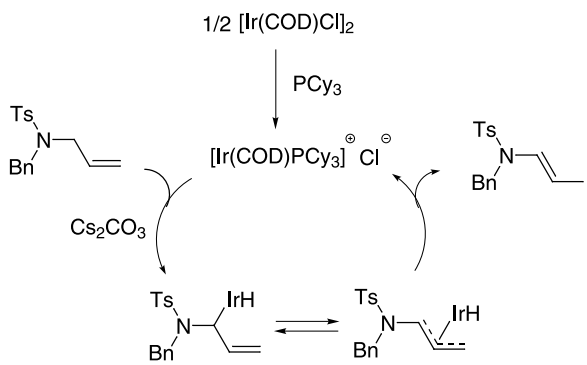
To check whether this method is also chemoselective when using γ-substituted enamides such as *N*-crotylamine derivatives, the reaction was tested with compound **12** (Scheme 2).



Scheme 2. Attempted isomerization of a *N*-crotylamide.

When compound **12** (80/20 *E*/*Z* mixture) was subjected to the previously described experimental conditions using $[Ir(COD)Cl]_2$, PCy_3 and Cs_2CO_3 even after 96 h at 110 °C no change was observed in the ^{1}H NMR spectrum of the crude reaction mixture. This last result, as well as the previous difficulties encountered with methallylamides (Table 1, entries 10 and 11), clearly shows that the isomerization described here is very sensitive to steric hindrance and thus provides a chemoselective entry to the synthesis of enamides.

Although the exact nature of the catalyst involved in this reaction remains unclear, we can rule out an hydridoiridium species.[22] The first step may involve insertion of an Ir(I)–PCy_3 catalyst in the allylic CH bond with the help of Cs_2CO_3 rapidly equilibrating to a η^3-allyl hydride giving the enamine moiety via reductive elimination (Scheme 3). The η-allyl hydride intermediate is consistent with the almost exclusive formation of *trans*-enamine since in this case only hydrogen atoms occupy the '*endo*' positions. This also explains the low reactivity of 2-methyl allylamines due to steric hindrance (Table 1, entries 10 and 11).



Scheme 3. Proposed mechanism for the isomerization.

3. Conclusion

In summary, we describe here an efficient access to enamides starting from easily available *N*-allylamides based on mild experimental conditions. Iridium(I)-catalyzed isomerization affords enamides in good to excellent yields, with a very strong preference for the *E* isomer. Whilst few methods are known for the iridium-catalyzed isomerization of allylethers to enol ethers,[20,23] this report is, to the best of our knowledge, the first example of iridium(I)-catalyzed isomerization of N-protected allylamines to enamides in a chemoselective fashion since only allylamides are prone to isomerization. In addition, this method could also be very useful for the selective deprotection of *N*-allyl amines.[8c,24]

4. Experimental

All reactions were performed in dried glassware under an inert (nitrogen) atmosphere. Standard reagents were purchased from Aldrich and used without further purification, unless otherwise stated. Thin layer chromatography (TLC) was performed on silica gel plates, Merck 60 F_{254}. Flash column chromatography purifications were performed on silica gel 60 (Merck). ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ (unless otherwise stated) on a Bruker AC 300 instrument at 300.132 and 75 MHz, respectively. Low-resolution mass spectra were obtained by positive electrospray ionization (ESI^+) or by electron impact (EI).

4.1. Preparation of allylamides

All starting allylamines were prepared according to a standard protocol.

To a stirred solution of amine (5 mmol) in anhydrous DMF (20 mL), KHMDS (1.1 equiv., 0.5 M in toluene) was slowly added at 0 °C over 10 min. The resulting mixture was stirred for 2 h at 0 °C and allylbromide (6 mmol, 524 μL) was added dropwise. The resulting suspension was warmed to room temperature and stirred overnight. The mixture was quenched by a saturated NH_4Cl solution (30 mL), the aqueous phase was extracted three times with 40 mL of EtOAc. The organic phases were combined, dried over Na_2SO_4, filtered and the solvents were taken off by rotary evaporation. The crude material was then purified by column chromatography using a mixture of pentane/diethyl ether.

4.2. Isomerization of allylamides into enamides

Synthesis of (*E*)-*N*-(1-propenyl)-amides (general method): The amide (250 μmol), anhydrous toluene (500 μL), Cs_2CO_3 (5 mol%, 4 mg), tricyclohexylphosphine (10 mol%, 7 mg) and $[Ir(COD)Cl]_2$ (5 mol%, 9 mg) were placed in a 1 mL vial. The resulting orange mixture was degassed, placed under a positive pressure of nitrogen, sealed and warmed at 110 °C for 72 h. The mixture was then cooled to room temperature and the toluene was taken off by rotary evaporation and the crude mixture was analyzed by ^{1}H NMR ($CDCl_3$ solution). The crude material was then purified by column chromatography using a mixture of pentane/diethyl ether. Data are given for *E* compounds only.

4.2.1. *N*-Benzyl-*N*-(*E*)-propenyl 4-methylbenzenesulfonamide. R_f=0.53 (pentane/Et_2O 80/20). ^{1}H NMR (δ, ppm): 7.68 (d, 2H, $^3J_{1H}$=8.5 Hz); 7.32–7.2 (m, 7H); 6.6 (qd, 1H, $^4J_{3H}$=1.8 Hz, $^3J_{1H}$=14 Hz); 4.71 (qd, 1H, $^3J_{3H}$=6.7 Hz, $^3J_{1H}$=14 Hz); 4.46 (s, 2H); 2.42 (s, 3H); 1.55 (dd, 3H, dd, $^3J_{1H}$=6.7 Hz, $^4J_{1H}$=1.8 Hz). ^{13}C NMR (δ, ppm): 15.49; 21.69; 49.85; 108.71; 126.55; 127.12; 127.46; 128.64; 129.94; 136.09; 136.31; 143.78. MS (ESI/TOF): 626 (23); 625 (58); 340 (13); 325 (21); 324 (100). IR: 1658; 1595; 1494; 1449; 1349; 1162.

4.2.2. *N*-Methyl-*N*-(*E*)-propenyl 4-methylbenzenesulfonamide. R_f=0.48 (pentane/Et_2O 80/20). ^{1}H NMR (δ, ppm): 7.63 (d, 2H, $^3J_{1H}$=8 Hz); 7.3 (d, 2H, $^3J_{1H}$=8 Hz); 6.7 (qd, 1H, $^4J_{3H}$=1.8 Hz, $^3J_{1H}$=14 Hz); 4.7 (qd, 1H, $^4J_{3H}$=6.7 Hz, $^3J_{1H}$=14 Hz); 2.81 (s, 3H); 2.4 (s, 3H); 1.6 (dd, 3H, $^4J_{1H}$=1.8 Hz, $^3J_{1H}$=6.7 Hz). ^{13}C NMR (δ, ppm): 143.31; 134.38; 129.4; 128; 126.78; 106.11; 32.03; 21.25; 14.91. MS (ESI/TOF): 248 (100); 264 (48); 473 (27). IR: 3070; 1930; 1661; 1595; 1456; 1351.

4.2.3. *N*-Benzyl-*N*-(*E*)-propenyl benzamide. R_f=0.39 (pentane/Et_2O 80/20). ^{1}H NMR (C_6D_6, 333 K, δ, ppm): 7.48–7.41 (m, 2H); 7.25–7 (m, 8H); 6.72 (bd, 1H, $^3J_{1H}$=13.4 Hz); 4.86 (s, 2H); 4.82 (qd, 1H, $^3J_{3H}$=6.7 Hz, $^3J_{1H}$=13.4 Hz); 1.27 (d, 3H, $^3J_{1H}$=6.7 Hz). ^{13}C NMR (C_6D_6, 323 K, δ, ppm): 169.7; 138.15; 136.69; 129.96; 128.8; 128.4; 128.22; 127.15; 106.99; 48.34; 15.09. MS (ESI/TOF): 252 (100); 197 (45). IR: 3062; 3032; 2927; 1642; 1495; 1446; 1401; 1373; 1324; 1286.

4.2.4. *N*-Methyl-*N*-(*E*)-propenyl 4-methylbenzamide. R_f=0.5 (pentane/Et_2O 70/30). ^{1}H NMR for major rotamer 72% (δ, ppm): 7.25.7.1 (m, 4H); 6.2 (qd, 1H, $^3J_{1H}$=14 Hz, $^4J_{3H}$=1.8 Hz); 5 (qd, 1H, $^3J_{1H}$=14 Hz, $^3J_{3H}$=6.7 Hz); 3.21 (s, 3H); 2.11 (s, 3H); 1.55 (bd, 3H, $^3J_{1H}$=6.7 Hz); for minor rotamer 28%: 7.5 (bd, 1H, $^3J_{1H}$=14 Hz); 7.35–7.25 (m, 4H); 5.12 (qd, 1H, $^3J_{3H}$=6.7 Hz, $^3J_{1H}$=14.7 Hz); 2.88 (s, 3H); 2.25 (s, 3H); 1.8 (bd, 3H, $^3J_{1H}$=6.7 Hz). ^{13}C NMR (δ, ppm): major isomer 169.9; 135.74; 134.22; 130.14; 129.53; 125.68; 105.59; 29.05;18.73; 15.01; for minor rotamer 169.25; 136.1; 133.96; 128.91; 127.1; 126.26; 107.17; 33.51; 18.73; 15.17. MS (ESI/TOF): 401 (64); 212 (100); 190 (13). IR: 3072; 2924; 1644; 1453; 1371; 1321; 1283.

4.2.5. (*E*)-1-Propenyl-pyrrolidin-2-one. R_f=0.36 (pentane/Et_2O 20/80). ^{1}H NMR (δ, ppm): 6.83 (qd, 1H, $^4J_{3H}$=1.8 Hz, $^3J_{1H}$=14 Hz); 4.9 (qd, 1H, $^3J_{3H}$=6.7 Hz, $^3J_{1H}$=14 Hz); 3.45 (t, 2H, $^3J_{2H}$=7.3 Hz); 2.43 (t, 2H, $^3J_{2H}$=7.9 Hz); 2.04 (m, 2H); 1.68 (dd, 3H, $^4J_{1H}$=1.8 Hz, $^3J_{1H}$=6.7 Hz). ^{13}C NMR (δ, ppm): 172.36; 124.22; 106.56; 45; 30.99; 17.21; 14.91. MS (EI): 125 (75); 110 (15); 96 (7); 82 (19); 70 (100); 54 (9). IR: 2924; 2857; 1697; 1670; 1409.

4.2.6. (*E*)-3-Propenyl-oxazolidin-2-one. R_f=0.43 (pentane/Et_2O 20/80). ^{1}H NMR (δ, ppm): 6.61 (qd, 1H, $^4J_{3H}$=1.7 Hz, $^3J_{1H}$=14 Hz); 4.79 (qd, 1H, $^3J_{3H}$=6.7 Hz, $^3J_{1H}$=14 Hz); 4.4 (t, 1H, $^3J_{2H}$=7.9 Hz); 4.39 (dd, 1H, $^3J_{1H}$=6.7, 9.7 Hz); 3.66 (dd, 1H, $^3J_{1H}$=7.9 Hz, 9.7 Hz); 3.65 (dd, 1H, $^3J_{1H}$=7.9 Hz, 6.7 Hz); 1.69 (dd, 3H, $^4J_{1H}$=1.7 Hz, $^3J_{1H}$=6.7 Hz). ^{13}C NMR (δ, ppm): 155.12; 124.32; 105.46; 61.85; 42.38; 14.62. MS (EI): 127 (71); 82 (29); 68 (100); 55 (35). IR: 2928; 1740; 1674; 1495; 1426; 1245; 1075.

4.2.7. (*E*)-2-Propenyl-isoindole-1,3-dione. R_f=0.55 (pentane/Et_2O 80/20). ^1H NMR (δ, ppm): 7.88–7.81 (m, 2H); 7.75–7.69 (m, 2H); 6.64–6.5 (m, 2H); 1.84 (m, 3H). ^{13}C NMR (δ, ppm): 166.41; 133.96; 131.47; 123.16; 118.11; 117.75; 16.01. MS (EI): 187 (100); 169 (60); 158 (12). IR: 1706; 1606; 1462; 1376; 1321.

4.2.8. (*E*)-1-Propenyl-pyrrolidine-2,5-dione. R_f=0.18 (pentane/Et_2O 30/70). ^1H NMR (δ, ppm): 6.57 (qd, 1H, $^3J_{3H}$=6.7 Hz, $^3J_{1H}$=14.6 Hz); 6.42 (qd, 1H, $^4J_{3H}$=1.8 Hz, $^3J_{1H}$=14.6 Hz); 2.72 (s, 4H); 1.78 (dd, 3H, $^4J_{1H}$=1.8 Hz, $^3J_{1H}$=6.7 Hz). ^{13}C NMR (δ, ppm): 175.64; 120.16; 118.96; 27.93; 16.31. MS (EI): 139 (100); 110 (15); 96 (22); 82 (26); 68 (30); 55 (70). IR: 2944; 1717; 1377; 1188.

4.2.9. *N*-Benzyl (*E*)-propenyl-carbamic acid tertiobutyl ester. R_f=0.6 (pentane/Et_2O 95/5). ^1H NMR (in C_7D_8 at 343 K, δ, ppm): 7.15–7 (m, 5H); 6.93 (bd, 1H, $^3J_{1H}$=13.5 Hz); 4.62 (qd, 1H, $^3J_{1H}$=13.5 Hz, $^3J_{3H}$=6.7 Hz); 4.51 (s, 2H); 1.4 (bd, 3H, $^3J_{1H}$=6.7 Hz); 1.3 (s, 9H). ^{13}C NMR (in C_6D_6 at 323 K, δ, ppm): 153.29; 138.63; 128.8; 128.64; 126.95; 126.70; 103.79; 80.53; 48.08; 30.65; 28.22; 15.25. MS (ESI/TOF): 270 (100); 517 (23). IR: 2975; 2929; 1705; 1665; 1451; 1399; 1371; 1326; 1280; 1231; 1165.

4.2.10. 2-(2-Methyl-propenyl)-isoxazolidin-3-one. Not separated from starting material. ^1H NMR (δ, ppm): 5.89 (bs, 1H); 4.4 (dd, 1H, $^3J_{1H}$=7.9 Hz, 9.2 Hz); 4.39 (dd, 1H, $^3J_{1H}$=6.8 Hz, 7.9 Hz); 3.79 (dd, 1H, $^3J_{1H}$=6.8 Hz, 9.2 Hz); 3.78 (t, 1H, $^3J_{2H}$=7.9 Hz); 1.8 (bs, 3H); 1.78 (bs, 3H).

Acknowledgements

We would like to thank Professor Crabtree (Yale university) and Professor Krompiec (Silesian university) for helpful discussions about the mechanism involved in this isomerization.

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Tetrahedron 60 (2004) 3581–3592

[60]Fullerene–flavonoid dyads

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Received 15 December 2003; revised 13 February 2004; accepted 2 March 2004

Abstract—A range of fullerene–chalcone, fullerene–flavone, and fullerene–chromone dyads, including a bis(flavonyl)-fullerene dyad, were prepared by 1,3-dipolar cycloaddition reactions of azomethine ylides to C_{60} and by cyclopropanation of C_{60} with flavonyl malonates. Synthetic and natural flavonoid derivatives were used as starting materials.

Studies with fullerene derivatives have shown that they exhibit several types of biological activities, both in vitro and in vivo, that can be exploited for medicinal purposes.[1,2] As an example, the ability of C_{60} and its derivatives to scavenge a large number of radicals per molecule[3,4] makes them potentially useful drugs in the prevention or treatment of pathologies in which oxidative damage is involved, namely cardiovascular[5,6] and neurodegenerative diseases.[7,8] The results already published are encouraging and new optimized molecules are being designed, synthesized and evaluated.[9]

Recently, we reported the synthesis of new fullerene derivatives having flavonoid moieties of synthetic and natural origin.[10,11] The idea of preparing fullerene–flavonoid dyads arised from the fact that flavonoids, a widely distributed class of phytochemicals, also possess significant antioxidant activity[12,13] and, eventually, the resulting dyads could show increased radical scavenging activities. Beyond acting as antioxidants, natural flavonoids also act as anticarcinogens,[14,15] and they express beneficial effects in inflammatory and immunomodulatory systems.[16,17]

In this paper, we give full account of our work related with the synthesis of fullerene–flavonoid dyads. The new compounds were obtained by 1,3-dipolar cycloaddition reactions of azomethine ylides[18] to C_{60} and by cyclopropanation[19] of C_{60} with flavonyl malonates. Synthetic chalcones and flavones, a chromone and a natural flavonol were used as reagents.

The novel [60]fullerene-flavonoid dyads **3** and **4** were synthesized from formylchalcones **1** and formylflavones **2** via 1,3-dipolar cycloaddition reactions of the corresponding azomethine ylides (generated in situ from the reaction of the formyl group with *N*-methylglycine) to [60]fullerene (Scheme 1). These cycloaddition reactions were carried out in refluxing toluene, under nitrogen atmosphere, using an excess of C_{60} (1.4 equiv.) and *N*-methylglycine (5 equiv.). The reaction mixtures were separated by flash chromatography using gradients of toluene/ethyl acetate as eluent. The isolated yields are in the range of 31–67%. All adducts **3** and **4** are stable compounds.

The starting compounds **1a**, **2a** and **2b** were prepared according to the literature procedures.[20] The chalcone **1b** and the flavone **2c** were prepared as indicated in Scheme 2. Benzylation of 2′,3′,4′-trihydroxyacetophenone **5a** with benzyl chloride in the presence of potassium carbonate afforded the corresponding 2′,3′,4′-tribenzyloxy-acetophenone **5b** in 90% yield. This compound was condensed with terephthalaldehyde mono(diethyl acetal) to give chalcone **6**. Hydrolysis of the acetal group furnished the formylchalcone **1b**. Selective debenzylation of the 2-benzyloxy group was achieved by the treatment of **1b** with a mixture of acetic acid and concentrated hydrochloric acid (10:1) for 1 h at 40 °C. Finally, formylflavone **2c** was obtained by oxidative cyclization of **1c** in refluxing dimethylsulfoxide with a catalytic amount of iodine.[21]

Compound **8** was obtained from the commercially available 3-formylchromone **7** (Scheme 3) in a similar way as dyads **3** and **4**. This new compound was also purified by flash chromatography using toluene/ethyl acetate (9:1) as eluent.

Keywords: Fullerenes; Flavonoids.
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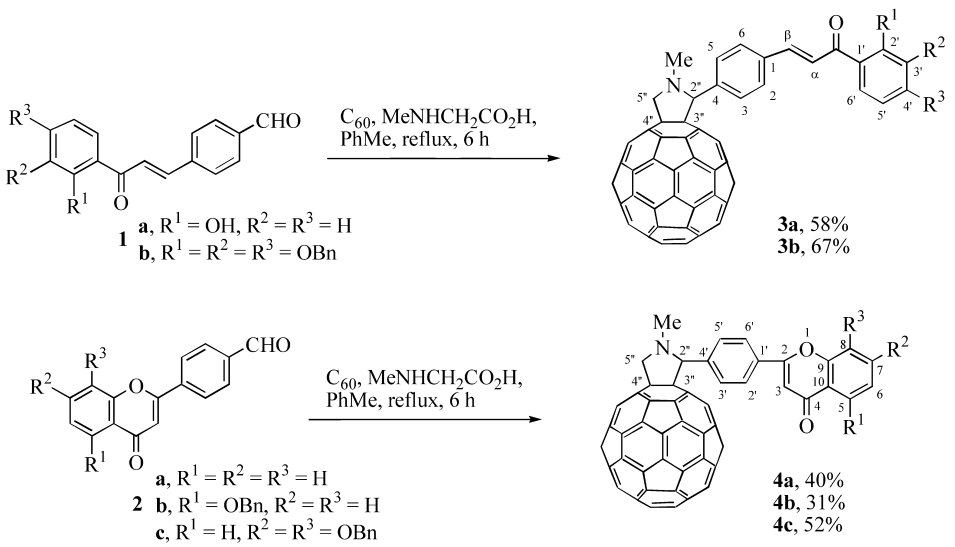
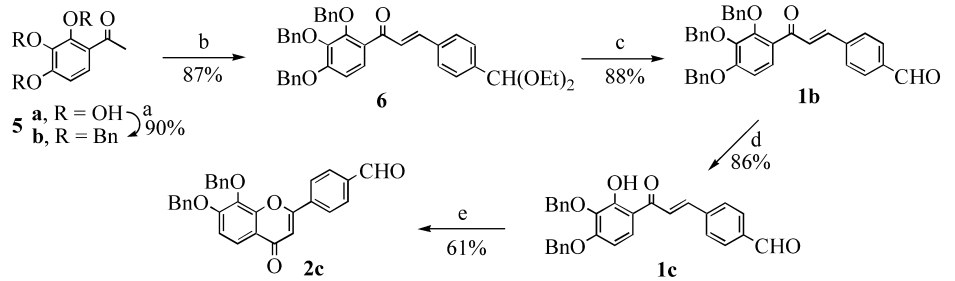
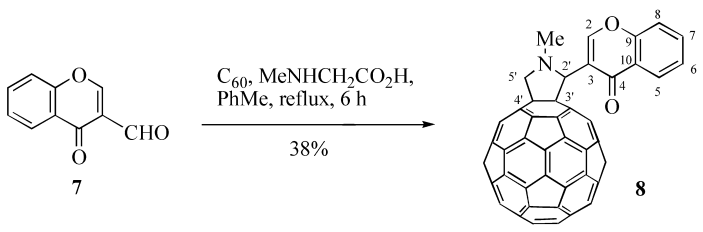
doi:10.1016/j.tet.2004.03.003



Scheme 1.



Scheme 2. (a) BnCl, K_2CO_3, DMF, 150 °C, 3 h. (b) NaOH, $(EtO)_2CHC_6H_4CHO$, MeOH, 60 °C, 2 h. (c) HCl (10%), rt, 3 h. (d) $MeCO_2H$/HCl (10:1), 40 °C, 1 h. (e) I_2 (cat.), DMSO, reflux, 20 min.

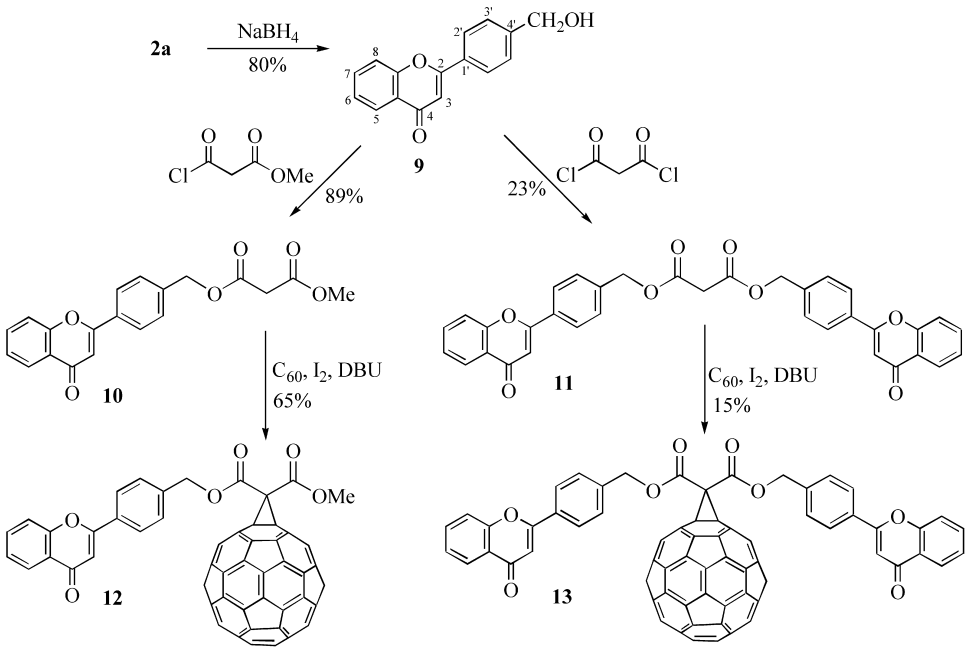


Scheme 3.

3-Formylchromone has been extensively used in the synthesis of heterocyclic systems since their convenient synthesis has been reported in the 1970s.[22] Much of the synthetic utility of this compound derives from the reactivity of its electron-deficient centres at C-2, C-4 and formyl group.

Reduction of 4′-formylflavone **2a** with sodium borohydride afforded alcohol **9** in 80% yield (Scheme 4). This compound was allowed to react with methyl malonyl chloride and malonyl dichloride, in the presence of triethylamine, to give, respectively, the malonate derivatives **10** and **11**. These two compounds were then reacted with C_{60}, following a modification of Bingel's procedure,[19] to afford dyads **12** and **13** in moderate yields.

We decided then to extend our studies to the synthesis of fullerene derivatives having 'natural' flavonoid moieties. Quercetin (3,3′,4′,5,7-pentahydroxyflavone), a natural flavonol, was our first choice because of its high antioxidant activity. The antioxidant activity of quercetin is higher than other pentahydroxyflavonoids (catechin, for instance) due to the presence of a 2,3-double bond and to the 4-oxo function in ring C which allows electron delocalization across the molecule; this increases the stability of the aryloxyl radical after hydrogen donation.[13] The presence of a



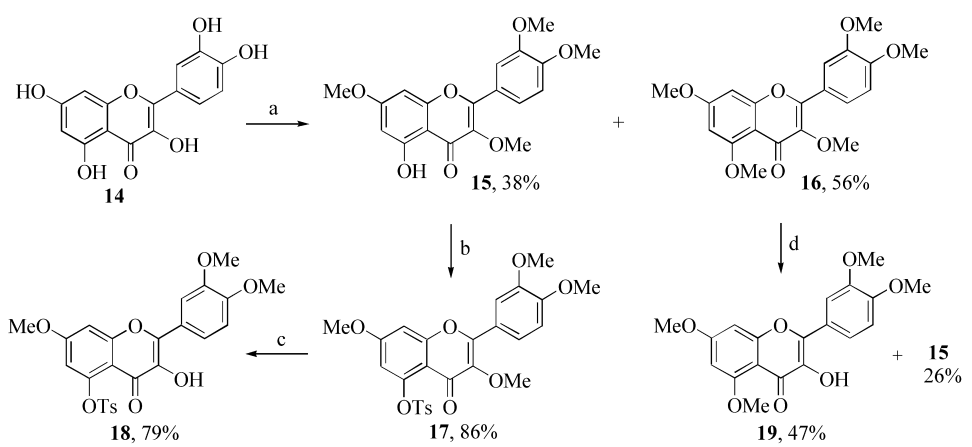
Scheme 4.

3′,4′-dihydroxyphenyl system and a 3-hydroxyl group also contributes to the high antioxidant activity of this compound.[13]

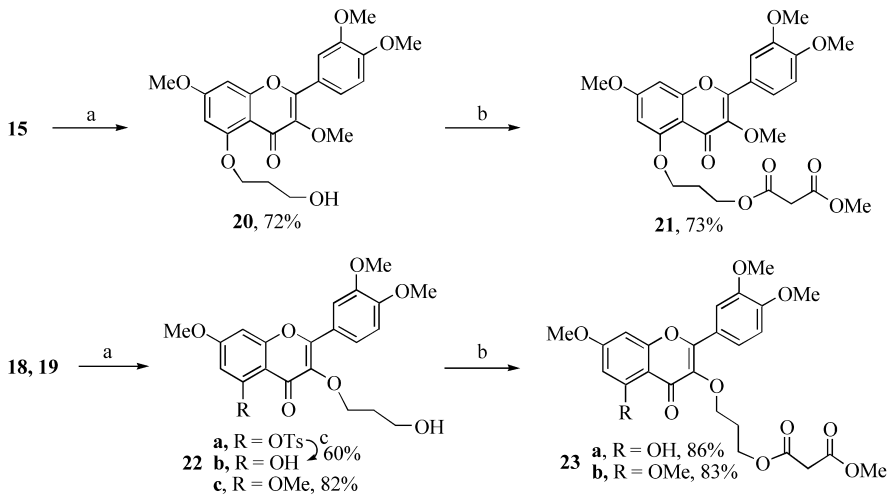
The use of quercetin as starting reagent presented to us the interesting challenge of linking quercetin to C_{60} selectively through one of the five-hydroxyl groups. As shown in Schemes 5–7 we were able to do it in two different positions.

Our initial idea was to methylate all hydroxyl groups and then, using different reaction conditions, demethylate selectively the 3- and 5-methoxy groups, taking advantage of their higher reactivities.[23] O-Methylation of quercetin with methyl iodide afforded a mixture of two compounds which, after separation by flash chromatography and crystallization, were identified as the expected pentamethylated derivative **16** and the tetramethylated compound **15** (Scheme 5). In that way, unexpectedly, we obtained in one step the desired compound having the free 5-hydroxyl group. Demethylation of compound **16** with anhydrous aluminum bromide,[24] at 0 °C, gave the 3-OH derivative **19** and an additional amount of **15** (26%). Tosylation of compound **15** followed by demethylation led exclusively to the 3-OH derivative **18** (Scheme 5).

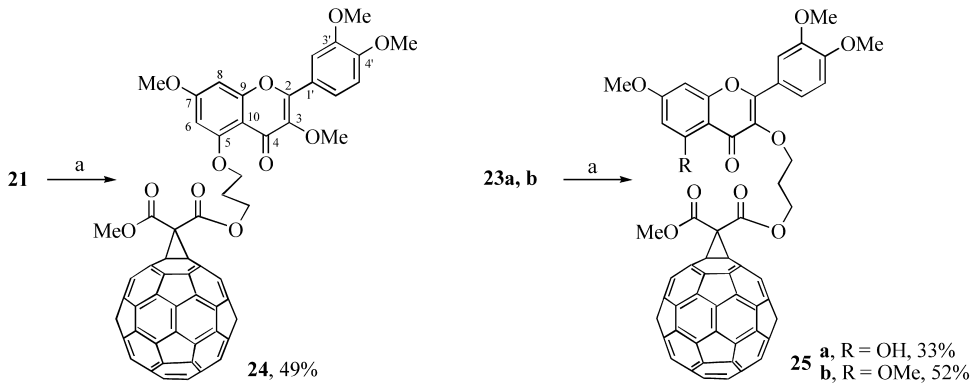
The alkylation of the three mono-hydroxy quercetin derivatives (**15**, **18** and **19**) with 3-iodopropan-1-ol afforded the propanol derivatives **20**, **22a** and **22c** in good yields (Scheme 6). Derivative **22a** was then detosylated to derivative **22b** by treatment with K_2CO_3 in refluxing methanol.[25] Compounds **20**, **22b** and **22c** were converted into the corresponding malonates **21** and **23** by esterification with methyl malonyl chloride in the presence of triethylamine (Scheme 6). Finally, cyclopropanation (Bingel reaction)[19] of C_{60} with malonates **21** or **23** afforded the final dyads **24** or **25** in moderate yields (Scheme 7).



Scheme 5. (a) MeI, K_2CO_3, MeCN/MeOH, 60 °C, 10 h. (b) *p*-TsCl, K_2CO_3, MeCN, 60 °C, 1 h. (c) $AlBr_3$, MeCN, 0 °C, 1 h. (d) $AlBr_3$, MeCN, 0 °C, 1 h.



Scheme 6. (a) 3-Iodopropan-1-ol, K_2CO_3, DMF, 60 °C, 3 h. (b) Methyl malonyl chloride, NEt_3, CH_2Cl_2, 0 °C to rt, 3 h. (c) K_2CO_3, MeOH, reflux, 0.5 h.



Scheme 7. (a) C_{60}, I_2, DBU, PhMe, rt, 1 h.

1. Characterization of the compounds

All new compounds were characterized by ^1H and ^{13}C NMR, MS and elemental analysis or high-resolution MS. In the ^1H NMR spectra of dyads **3**, **4** and **8** the resonance of the *N*-methyl group appears typically at δ 2.82–2.87 ppm and the proton 2″ (2′ for **8**) appears as a singlet at ca. 5.0 ppm (5.6 ppm for H-2′ in **8**). The two non-equivalent protons 5″ (5′ for **8**) appear as two doublets: one centered at ca. 4.3 and the other at ca. 5.0 ppm. The geminal-coupling constant for these protons is in the range of 9.3–9.5 Hz. It is interesting to note that, both in compounds **3** and **4**, the signals corresponding to the protons of the phenyl group directly attached to the pyrrolidine ring are broadened. This indicates restricted rotation of the phenyl substituent on the pyrrolidine ring, as previously described for similar systems.[26,27] In the ^{13}C NMR spectra of dyads **3** and **4** the signals corresponding to C-2″ and C-5″ appear at ca. 83 and 70 ppm, respectively, while the signals corresponding to the *N*-methyl group, C-3″ (C_{60} sp^3 carbons) and C-4″ appear at ca. 40, 69 and 77 ppm, respectively. The corresponding carbons in compound **8** show very similar resonances, except carbon C-2′ which appears at 72 ppm.

The proton and carbon resonances of the chalcone and flavone moieties of dyads **3** and **4** and those of the starting compounds **1** and **2** are very similar and were assigned by using their 2D COSY, HSQC and HMBC spectra and also by comparison with our previous work.[20,28–30] The most important features of these spectra are the resonances of: (i) the proton resonance of hydroxyl groups (12–13 ppm) involved in an intramolecular hydrogen bond with the carbonyl group of compounds **1c** and **3a**; (b) the benzylic groups (δ_H 5.1–5.3 ppm; δ_C 71–77 ppm) of the benzylated compounds; (iii) the formyl groups (δ_H~10 ppm, δ_C 191–192 ppm) of **1b**, **1c** and **2c**; and (iv) the acetal group (δ_H 5.51 ppm, δ_C 101.1 ppm) of chalcone **6**. The connectivities found in the HMBC spectra of compounds **1**-**4** allowed the assignment of the quaternary carbon resonances; some of the most important ones for dyad **3a** are shown in Figure 1.

The proton and carbon resonances of the flavone moieties of compounds **9**-**13** are similar to those of 4′-formylflavone **2a**.[20] The main features of the ^1H and ^{13}C NMR spectra of the substituents of these flavones are the resonances of the benzylic group (δ_H 4.8–5.6 ppm; δ_C 65–68 ppm) and the methylenic group (δ_H~3.5 ppm; δ_C~41 ppm) of the malonyl moieties. The assignment of the resonances of the quaternary carbons of these malonyl moieties were based on the connectivities found in their HMBC spectra; some of the most important ones for compound **10** are shown in Figure 1. The resonance of the methano bridge and

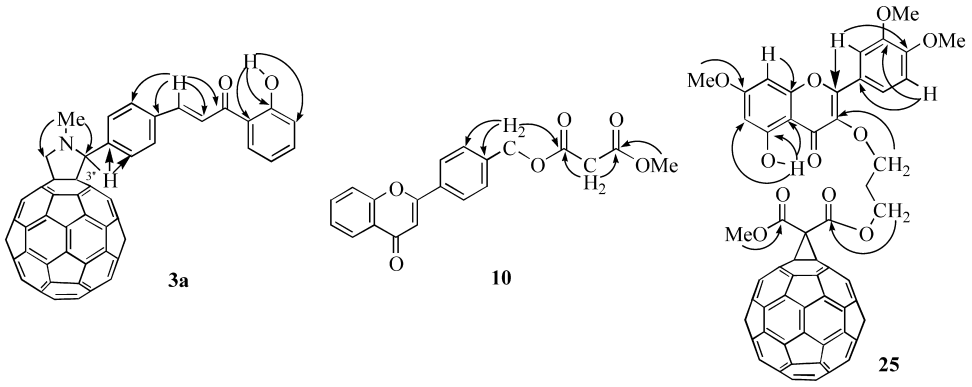


Figure 1. Some of the most important connectivities found in the HMBC spectra of compounds **3a**, **10** and **25**.

of the C_{60}-sp^3 carbons of compounds **12** and **13** appear in its ^{13}C NMR spectra at 53–54 and 71 ppm, respectively.

The assignment of the proton and carbon resonances of the quercetin moiety of compounds **15**-**25** were based in the literature data,[31,32] and on the detailed analysis of the 2D COSY, HSQC and HMBC spectra of final products **21**, **23**-**25**. In Figure 1 it is shown the most important connectivities for dyad **25**; similar connectivities where found in the other compounds. The proton and carbon resonances of the malonyl moiety are similar to those of **10**-**13**. The assignment of the proton and carbon resonances of the remaining propyl moiety was also based on the connectivities found in the HMBC spectra of compounds **20**-**25**. The main NMR features of these chains are the carbon resonance of the CH_2OH group appearing at ca. 69 ppm in compounds **20** and **22** which, after esterification, appear at ca. 62 ppm in compounds **21** and **23**. These assignments were also corroborated by DEPT experiments. In the ^{13}C NMR spectra of fullerene derivatives **24** and **25** the signals appearing at ca. 52 and 71.5 ppm correspond, respectively, to the methano bridge and to the C_{60}-sp^3 carbons.

2. Experimental

2.1. General remarks

Melting points were measured on a Reichert Thermovar apparatus fitted with a microscope and are uncorrected. ^1H and ^{13}C solution NMR spectra were recorded in $CDCl_3$ solutions (unless otherwise stated), on a Bruker DRX 300 spectrometer (except **3b**, which were recorded on a Bruker DRX 500). TMS was used as internal reference and the solvent is indicated on each case; the chemical shifts are expressed in δ (ppm) and the coupling constants (J) in Hertz (Hz). ^{13}C assignments were made on the basis of 2D *g*HSQC and *g*HMBC experiments (delay for long-range J C/H couplings were optimized for 7 Hz). Mass spectra and HRMS were recorded on VG AutoSpec Q and M mass spectrometers using $CHCl_3$ as solvent and NBA as matrix. Elemental analyses were performed in a Leco 932 CHNS analyser. Column chromatography was carried out using silica gel (Merck, 35-70 mesh). Analytical TLC was carried out on precoated sheets with silica gel (Merck 60, 0.2 mm thick).

2.2. General procedure for the synthesis of [60]fullerene derivatives 3, 4 and 8

A solution of C_{60} (100 mg, 0.14 mmol), *N*-methylglycine (45 mg, 0.5 mmol) and the appropriate formyl compound **1**, **2** or **7** (0.1 mmol) in toluene (150 mL), was heated at reflux under N_2 for 6 h. Part of the solvent was removed in vacuo and the mixture was purified by flash chromatography using a gradient of toluene to toluene/ethyl acetate (8:2) as eluent. The first fraction was the unchanged C_{60} and the next one was the mono-adduct **3**, **4** or **8**. Products with higher polarity, probably bis-adducts, were discharged.

2.2.1. 2′-Hydroxy-4-(*N*-methyltetrahydro[60]fullero[*c*]-pyrrol-2-yl)chalcone (3a). Compound **3a** (58 mg, 58%). ^1H NMR ($CDCl_3/CS_2$) δ: 12.74 (s, 1H, 2′-O*H*), 7.92 (d, J=15.5 Hz, 1H, H-β), 7.90 (m, 3H, H-3′, H-2,6), 7.74 (d, J=8.4 Hz, 2H, H-3,5), 7.67 (d, J=15.5 Hz, 1H, H-α), 7.45 (ddd, J=7.8, 7.6, 1.2 Hz, 1H, H-4′), 6.99 (dd, J=8.5, 1.2 Hz, 1H, H-6′), 6.92 (ddd, J=8.5, 7.6, 1.1 Hz, 1H, H-5′), 5.00 (s, 1H, H-2″), 5.02 (d, J=9.3 Hz, 1H, H-5″), 4.31 (d, J=9.3 Hz, 1H, H-5″), 2.86 (s, 3H, N-C*H*$_3$); ^{13}C NMR ($CDCl_3/CS_2$) δ: 192.4 (C=O), 163.5 (C-2′), 153.6, 152.8, 152.5, 147.1, 146.3, 146.2, 146.12, 146.06, 146.04, 145.98, 145.95, 145.8, 145.7, 145.5, 145.4, 145.4, 145.3, 145.22, 145.17, 145.10, 145.06, 145.0, 144.5 (C-β), 144.4, 144.24, 144.17, 143.0, 142.9, 142.56, 142.47, 142.45, 142.4, 142.1, 142.00, 141.98, 141.9, 141.88, 141.80, 141.70, 141.66, 141.5, 141.4, 140.09, 140.07 (C-4), 140.0, 139.8, 139.4, 136.8, 136.3, 136.2 (C-4′), 135.8, 135.5, 134.7, 129.8 (C-3,5), 129.4 (C-6′), 128.9 (C-2,6), 120.2 (C-α), 119.8 (C-1′), 118.6 (C-3′ and C-5′), 83.0 (C-2″), 76.9 (C-4″), 69.9 (C-5″), 68.8 (C-3″), 39.9 (N-*C*H$_3$). HRMS (FAB) m/z calculated for $C_{78}H_{18}NO_2$ $(M+H)^+$ 1000.1338, found 1000.1373.

2.2.2. 2′,3′,4′-Tribenzyloxy-4-(*N*-methyltetrahydro[60]-fullero[*c*]pyrrol-2-yl)chalcone (3b). Compound **3b** (87 mg, 67%). ^1H NMR (500.13 MHz) δ: 7.64 (d, J=15.7 Hz, 1H, H-β), 7.54 (d, J=8.9 Hz, 1H, H-6′), 7.55 (d, J=15.7 Hz, 1H, H-α), 7.48–7.29 and 7.18–7.09 (2 m, 17H, H-2,3 and 3×OCH$_2$C$_6$*H*$_5$), 6.85 (d, J=8.9 Hz, 1H, H-5′), 5.18, 5.10, 5.05 (s, 6H, 3×OC*H*$_2$C$_6$H$_5$), 5.01 (d, J=9.5 Hz, 1H, H-5″), 4.97 (s, 1H, H-2″), 4.28 (d, J=9.5 Hz, 1H, H-5″), 2.82 (s, 3H, N-C*H*$_3$); ^{13}C NMR (125.77 MHz) δ: 190.3 (C=O), 156.6 (C-4′), 156.2 (C-2′), 154.0, 153.3, 153.1, 153.0, 147.4, 146.7, 146.45, 146.36, 146.28, 146.25,

146.20, 146.17, 146.08, 146.0, 145.8, 145.6, 145.5, 145.4, 145.34, 145.29, 145.2, 144.8, 144.6, 144.5, 144.4, 143.2, 143.1, 142.8, 142.7, 142.4, 142.3, 142.22, 142.19, 142.15, 142.11, 142.03, 141.95, 141.90, 141.86, 141.76, 141.6, 140.3, 139.9 (C-4), 139.6, 139.3, 137.3, 137.0, 136.7, 136.5, 136.3, 136.0, 135.7, 135.3, 129.7, 128.9, 128.8, 128.70, 128.66, 128.40, 128.35, 128.23, 128.20, 128.1, 127.5, 127.1 (C-α), 126.2 (C-6′), 109.3 (C-5′), 83.4 (C-2″), 77.6 (C-4″), 76.9 ($OCH_2C_6H_5$), 75.1 ($OCH_2C_6H_5$), 71.0 ($OCH_2C_6H_5$), 70.1 (C-5″), 69.2 (C-3″), 40.0 (N-CH_3). HRMS (FAB) *m/z* calculated for $C_{99}H_{36}NO_4$ $(M+H)^+$ 1302.2644, found 1302.2676.

2.2.3. 4′-(*N*-Methyltetrahydro[60]fullero[*c*]pyrrol-2-yl)flavone (4a). Compound **4a** (39 mg, 40%). ^{1}H NMR ($CDCl_3/CS_2$) δ: 8.80 (dd, *J*=7.8, 1.5 Hz, 1H, H-5), 8.03 (br s, 4H, H-2′,3′,5′,6′), 7.79 (ddd, *J*=8.0, 7.6, 1.5 Hz, 1H, H-7), 7.57 (dd, *J*=8.0, 0.9 Hz, 1H, H-8), 7.45 (ddd, *J*=7.8, 7.6, 0.9 Hz, 1H, H-6), 6.83 (s, 1H, H-3), 5.06 (s, 1H, H-2″), 5.04 (d, *J*=9.4 Hz, 1H, H-5″), 4.28 (d, *J*=9.4 Hz, 1H, H-5″), 2.87 (s, 3H, N−CH_3); ^{13}C NMR ($CDCl_3/CS_2$) δ: 177.5 (C-4), 162.4 (C-2), 155.9, 155.7 (C-9), 153.5, 152.6, 152.3, 147.7, 147.1, 146.2, 146.1, 146.02, 145.96, 145.8, 145.6, 145.5, 145.4, 145.3, 145.2, 145.13, 145.10, 145.04, 145.00, 144.5, 144.4, 144.2, 144.1, 143.0, 142.91, 142.86, 142.5, 142.44, 142.39, 142.04, 141.96, 141.87, 141.8, 141.6, 141.5, 141.44, 141.39, 141.2, 140.9 (C-4′), 140.1, 139.8, 139.4, 136.8, 136.2, 135.8, 135.5, 133.5, 131.7 (C-1′), 129.7 (C-3′,5′), 126.5 (C-2′,6′), 125.7 (C-5), 125.1 (C-6), 123.8 (C-10), 117.8 (C-8), 107.6 (C-3), 82.9 (C-2″), 76.6 (C-4″), 69.9 (C-5″), 68.8 (C-3″), 39.9 (N−CH_3). HRMS (FAB) *m/z* calculated for $C_{78}H_{16}NO_2$ $(M+H)^+$ 998.1181, found 998.1194.

2.2.4. 5-Benzyloxy-4′-(*N*-methyltetrahydro[60]fullero[*c*]-pyrrol-2-yl)flavone (4b). Compound **4b** (33 mg, 31%). ^{1}H NMR ($CDCl_3/CS_2$) δ: 7.98 (br s, 4H, H-2′,3′,5′,6′), 7.62 (d, *J*=7.6 Hz, 1H, H-2,6 of 5-$OCH_2C_6H_5$), 7.52 (t, *J*=8.3 Hz, 1H, H-7) 7.41 (t, *J*=7.6 Hz, 2H, H-3,5 of 5-$OCH_2C_6H_5$), 7.31 (t, *J*=7.6 Hz, 1H, H-4 of 5-$OCH_2C_6H_5$), 7.15 (dd, *J*=8.3, 0.6 Hz, 1H, H-8), 6.85 (d, *J*=8.3 Hz, 1H, H-6), 6.77 (s, 1H, H-3), 5.29 (s, 2H, 5-$OCH_2C_6H_5$), 5.03 (s, 1H, H-2″), 5.03 (d, *J*=9.5 Hz, 1H, H-5″), 4.31 (d, *J*=9.5 Hz, 1H, H-5″), 2.84 (s, 3H, N−CH_3); ^{13}C NMR ($CDCl_3/CS_2$) δ: 178.1 (C-4), 160.6 (C-2), 158.5 (C-5), 158.2 (C-9), 153.8, 152.9, 152.7, 148.2, 147.3, 146.5, 146.4, 146.3, 146.2, 146.1, 145.9, 145.8, 145.55, 145.50, 145.4, 145.3, 145.22, 145.18, 144.7, 144.5, 144.4, 143.4, 143.0, 142.7, 142.6, 142.5, 142.2, 142.1, 142.02, 141.95, 141.8, 141.7, 141.5, 141.4, 140.8, 140.2 (C-4′), 139.6, 137.0 (C-1 of 5-$OCH_2C_6H_5$), 136.5, 136.4, 136.0, 135.6, 133.7 (C-7), 131.5, 129.93 (C-1′), 129.89, 129.8, 128.6 (C-2′,6′) 127.6, 126.6, 126.4, 115.1 (C-10), 110.4 (C-8), 109.2 (C-3), 108.5 (C-6), 83.1 (C-2″), 76.6 (C-4″), 70.8 (5-$OCH_2C_6H_5$), 70.0 (C-5″), 69.1 (C-3″), 40.0 (N-CH_3). HRMS (FAB) *m/z* calculated for $C_{85}H_{22}NO_3$ $(M+H)^+$ 1104.1600, found 1104.1644.

2.2.5. 7,8-Dibenzyloxy-4′-(*N*-methyltetrahydro[60]fullero[*c*]pyrrol-2-yl)flavone (4c). Compound **4c** (62 mg, 52%). ^{1}H NMR δ: 7.92 (d, *J*=8.9 Hz, 1H, H-5),) 7.92 (br s, 4H, H-2′,3′,5′,6′), 7.47–7.12 (m, 10H, 2×$OCH_2C_6H_5$), 7.11 (d, *J*=8.9 Hz, 1H, H-6), 6.77 (s, 1H, H-3), 5.27, 5.19 (2s, 4H, $OCH_2C_6H_5$), 5.02 (s, 1H, H-2″), 5.03 (d, *J*=9.3 Hz, 1H, H-5″), 4.31 (d, *J*=9.3 Hz, 1H, H-5″), 2.84 (s, 3H, N−CH_3); ^{13}C NMR δ: 178.0 (C-4), 162.5 (C-2), 156.0 (C-7), 153.8, 152.9, 152.7, 150.8 (C-9), 147.3, 146.5, 146.35, 146.31, 146.2, 146.14, 146.11, 145.9, 145.8, 145.7, 145.54, 145.50, 145.37, 145.35, 145.30, 145.27, 145.21, 145.17, 144.7, 144.5, 144.4, 143.2, 143.0, 142.7, 142.6, 142.5, 142.23, 142.15, 142.12, 142.07, 142.03, 141.9, 141.8, 141.7, 141.6, 140.9, 140.2 (C-4′), 139.9, 139.5, 136.99, 136.97 (C-8), 136.4, 136.3, 136.0, 131.7 (C-1′), 129.8, 129.6, 129.0 (C-2′,6′), 128.7, 128.6, 128.40, 128.35, 128.2, 127.4, 126.6 (C-3′,5′), 125.3, 121.0 (C-5), 118.9 (C-10), 111.6 (C-6), 106.9 (C-3), 83.1 (C-2″), 76.6 (C-4″), 76.1 and 71.2 (2×$OCH_2C_6H_5$), 70.0 (C-5″), 69.1 (C-3″), 40.1 (N−CH_3). HRMS (FAB) *m/z* calculated for $C_{92}H_{28}NO_4$ $(M+H)^+$ 1210.2018, found 1210.2071.

2.2.6. 2′,3′,4′-Tribenzyloxyacetophenone (5b). A mixture of 2′,3′,4′-trihydroxyacetophenone **5a** (1.73 g, 10 mmol), benzyl chloride (6.39 mL, 50 mmol) and anhydrous K_2CO_3 (5.58 g, 40 mmol) in DMF (10 mL) was refluxed under N_2 for 3 h. The solution was then poured into ice and the resulting precipitate was collected by filtration. It was then purified by column chromatography ($CHCl_3$/acetone 100:2) and crystallized from EtOH; yield: 90%, mp 70–72 °C. ^{1}H NMR δ: 7.51 (d, *J*=8.9 Hz, 1H, H-6′), 7.43–7.30 (m, 15H, $OCH_2C_6H_5$), 6.82 (d, *J*=8.9 Hz, 1H, H-5′), 5.05, 5.15, 5.16 (3s, 6H, $OCH_2C_6H_5$), 2.53 (s, 3H, H-2); ^{13}C NMR δ: 198.4 (C-1), 156.7 (C-4′), 153.2 (C-2′), 141.6 (C-3′), 137.0, 136.8 and 136.1 (C-1 of 3×$OCH_2C_6H_5$), 128.7, 128.6, 128.52, 128.49, 128.3, 128.2, 128.1 and 127.5 (3×$OCH_2C_6H_5$), 126.9 (C-1′), 125.7 (C-6), 108.7 (C-5), 76.3 and 75.6 (2×$OCH_2C_6H_5$), 70.8 (4′-$OCH_2C_6H_5$), 31.1 (C-2). MS (EI) *m/z* (%): 438 ($M^{+\cdot}$, 7), 347 (11), 181 (11), 91 (100), 65 (11). Anal. Calcd for $C_{29}H_{26}O_4$·1/4 H_2O: C, 78.62; H, 6.02. Found: C, 78.92; H, 6.18.

2.2.7. 2′,3′,4′-Tribenzyloxy-4-(diethoxymethyl)chalcone (6). A mixture of 2′,3′,4′-tribenzyloxyacetophenone **5b** (0.68 g, 1.56 mmol) and terephtalaldehyde mono(diethyl acetal) (0.5 mL, 2.43 mmol) in a methanolic solution of NaOH (0.37 mmol/mL) was stirred at 60 °C for 2 h. A precipitate was formed. It was collected by filtration and the mother liquor was evaporated to dryness. It was then purified by column chromatography (hexane/acetone, first 4:1 then 3:2) giving a pale yellow solid by addition of acetone. Yield: 74%, mp 155–156 °C. ^{1}H NMR δ: 7.65 (d, *J*=15.5 Hz, 1H, H-β), 7.55 (d, *J*=15.5 Hz, 1H, H-α), 7.50–7.20 (m, 20H, H-6′, H-2,3,5,6 and 3×$OCH_2C_6H_5$), 6.89 (d, *J*=8.9 Hz, 1H, H-5′), 5.51 [s, 1H, $CH(OCH_2CH_3)_2$], 5.20, 5.12, 5.09 (3s, 6H, 3×$OCH_2C_6H_5$), 3.57 [q, *J*=7.0 Hz, 4H, $CH(OCH_2CH_3)_2$], 1.26 [t, *J*=7.0 Hz, 3H, $CH(OCH_2CH_3)_2$]; ^{13}C NMR δ: 190.1 (C=O), 156.7 (C-4′), 153.1 (C-2′), 142.6 (C-4), 141.76 and 141.73 (C-3′ and C-β), 137.2, 136.7, 136.5, 136.1 (C-1 and 3×C-1 of $OCH_2C_6H_5$), 128.79, 128.76, 128.71, 128.6, 128.4, 128.35, 128.32, 128.23, 128.20, 128.15, 128.11, 127.6, 127.5, 127.3, 127.1 (C-2,6, C-3,5, C-α and 3×$OCH_2C_6H_5$), 126.9 (C-1′), 126.3 (C-6′), 109.2 (C-5′), 101.1 [$CH(OCH_2CH_3)_2$], 76.6 and 75.7 (2×$OCH_2C_6H_5$), 70.9 (4′-$OCH_2C_6H_5$), 61.1 (OCH_2CH_3), 15.2 (OCH_2CH_3). MS (EI) *m/z* (%): 628 ($M^{+\cdot}$, 19), 583 (23), 537 (31), 509 (11), 492 (31), 438 (12), 401 (100), 347 (24), 251 (25), 241 (36), 223 (13), 181 (52), 159 (26), 131 (25), 115 (15). Anal. Calcd for $C_{41}H_{40}O_6$: C, 78.32; H, 6.41. Found: C, 78.66; H, 6.25.

2.2.8. 2′,3′,4′-Tribenzyloxychalcone-4-carbaldehyde (1b). HCl (10%, 2 mL) was added to a solution of 2′,3′,4′-tribenzyloxy-4-(diethoxymethyl)chalcone **6** (0.70 g, mmol) in EtOH (10 mL) and the mixture was stirred for 3 h. A precipitate was formed; it was collected by filtration and washed with EtOH. Recrystallization from EtOH afforded **1b** as a pure compound. Yield: 88%, mp 136–138 °C. ^{1}H NMR δ: 10.03 (s, 1H, C*H*O), 7.82 (d, *J*=8.3 Hz, 2H, H-2,6), 7.63 (s, 2H, H-α and H-β), 7.59 (d, *J*=8.8 Hz, 1H, H-6′), 7.52 (d, *J*=8.3 Hz, 2H, H-3,5), 7.50–7.10 (m, 15H, 3×OCH$_2$C$_6$*H*$_5$), 6.89 (d, *J*=8.8 Hz, 1H, H-5′), 5.20, 5.12 and 5.09 (3s, 6H, OC*H*$_2$C$_6$H$_5$); ^{13}C NMR δ: 191.8 (CHO) 191.6 (C=O), 157.3 (C-4′), 153.4 (C-2′), 141.7 (C-β), 140.5 (C-3′), 137.0, 136.7, 136.2 and 136.0 (C-1 and C-1 of OCH$_2$*C*$_6$H$_5$), 132.7 (C-4), 130.0, 129.8, 129.5, 128.8, 128.7, 128.66, 128.5, 128.41, 128.38, 128.33, 128.28, 128.19, 127.52, 127.50, (C-2,6, C-3,5, C-α and 3×OCH$_2$*C*$_6$H$_5$), 126.5 (C-6′), 109.0 (C-5′), 76.5 and 75.6 (2×OCH$_2$*C*$_6$H$_5$), 70.9 (4′-OCH$_2$*C*$_6$H$_5$). MS (EI) *m*/*z* (%): 554 (M$^{+\cdot}$, 37), 463 (43), 357 (9), 241 (29), 221 (14), 181 (61), 159 (100), 131 (12), 115 (6). Anal. Calcd for C$_{37}$H$_{30}$O$_5$: C, 80.12; H, 5.45. Found: C, 80.14; H, 5.57.

2.2.9. 3′,4′-Dibenzyloxy-2′-hydroxychalcone-4-carbaldehyde (1c). A solution of 2′,3′,4′-tribenzyloxychalcone-4-carbaldehyde **1b** (0.32 g, 0.58 mmol) in AcOH/concd HCl (10:1, 27.5 mL) was stirred at 40 °C for 1 h. Then H$_2$O (25 mL) was added and a precipitate was formed. It was collected by filtration, washed with H$_2$O, and dried under vacuum. Yield: 89%, mp 113–115 °C; ^{1}H NMR δ: 13.09 (s, 1H, 2′-O*H*), 10.06 (s, 1H, C*H*O), 7.95 (d, *J*=8.2 Hz, 2H, H-2′,6′), 7.90 (d, *J*=15.5 Hz, 1H, H-β), 7.79 (d, *J*=8.2 Hz, 2H, H-3′,5′), 7.67 (d, *J*=15.5 Hz, 1H, H-α), 7.65 (d, *J*=9.1, 1H, H-6′), 7.52–7.28 (m, 10H, 2×OCH$_2$C$_6$*H*$_5$), 6.56 (d, *J*=9.1 Hz, 1H, H-5′), 5.21 and 5.15 (2 s, 4H, 2×OC*H*$_2$C$_6$H$_5$); ^{13}C NMR δ: 191.9 (CHO), 191.5 (C=O), 158.8 (C-4′), 158.3 (C-2′), 142.6 (C-β), 140.4 (C-3′), 137.5, 137.3, 136.04 and 135.98 (C-1 and C-1 of OCH$_2$*C*$_6$H$_5$), 130.2, 128.9 128.7, 128.6, 128.2, 128.0 and 127.2 (C-2,6, C-3,5, and 2×OCH$_2$*C*$_6$H$_5$), 126.1 (C-6′), 123.2 (C-α), 115.5 (C-1′), 104.6 (C-5′), 74.8 and 70.8 (2×OCH$_2$*C*$_6$H$_5$). MS (EI) *m*/*z* (%): 464 (M$^{+\cdot}$, 100), 373 (90), 241 (13), 198 (12), 181 (26), 159 (48), 149 (30), 131 (12), 115 (9), 103 (17). Anal. Calcd for C$_{29}$H$_{26}$O$_4$·1/3 H$_2$O: C, 76.63; H, 5.28. Found: C, 76.95; H, 5.48.

2.2.10. 7,8-Dibenzyloxyflavone-4′-carbaldehyde (2c). Iodine (14 mg, 0.055 mmol) was added to a solution of 3′,4′-dibenzyloxy-2′-hydroxy-4-formylchalcone **1c** (0.81 mmol) in DMSO (1.6 mL). The mixture was heated under reflux for 20 min. After cooling to rt, the resulting mixture was poured into ice to precipitate the product. The solid was removed by filtration, dissolved in $CHCl_3$ and washed with a saturated solution of $Na_2S_2O_3$. The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography (CH_2Cl_2/MeOH, 100:3). After evaporation of the solvent, the residue was recrystallized from EtOH. Yield: 58%, mp 160–162 °C. ^{1}H NMR δ: 10.11 (s, 1H, CHO), 7.97 (br s, 4H, H-2′,3′,5′,6′), 7.94 (d, *J*=9.0 Hz, 1H, H-5), 7.50–7.31 (m, 10H, 2×-OCH$_2$C$_6$*H*$_5$), 7.15 (d, *J*=9.0 Hz, 1H, H-6), 6.82 (s, 1H, H-3), 5.30 and 5.22 (2 s, 4H, 2×OC*H*$_2$C$_6$H$_5$); ^{13}C NMR δ: 191.4 (CHO), 177.8 (C-4), 161.3 (C-2), 156.2 (C-7), 150.8 (C-9), 137.9 (C-4′), 137.1 and 137.0 (C-1 of OC*H*$_2$C$_6$H$_5$), 135.8 (C-1′), 130.1 (C-3′,5′), 129.1, 128.8, 128.54, 128.47, 128.4 and 127.4 (2×OCH$_2$*C*$_6$H$_5$), 126.8 (C-2′,6′), 121.1 (C-5), 118.8 (C-10), 111.8 (C-6), 108.4 (C-3), 76.6 and 71.3 (2×O*C*H$_2$C$_6$H$_5$). MS (EI) *m*/*z* (%): 462 (M$^{+\cdot}$, 40), 371 (100), 354 (15), 343 (30), 293 (13), 282 (30), 241 (19), 224 (38), 198 (22), 181 (79), 167 (48), 159 (14), 152 (51), 139 (55), 129 (69), 105 (67). Anal. Calcd for C$_{29}$H$_{26}$O$_4$·3/2 H$_2$O: C, 73.61; H, 5.14. Found: C, 73.47; H, 4.92.

2.2.11. 3-(*N*-Methyltetrahydro[60]fullero[*c*]pyrrol-2-yl)chromone (8). Compound **8** (42 mg, 38%) was obtained from **7** (21 mg) as described above in the general procedure. Mp >300 °C. ^{1}H NMR ($CDCl_3$/CS_2) δ: 8.53 (s, 1H, H-2), 8.19 (dd, *J*=7.9, 1.6 Hz, 1H, H-5), 7.68 (ddd, *J*=8.2, 7.3, 1.6 Hz, 1H, H-7), 7.49 (d, *J*=8.2 Hz, 1H, H-8), 7.41 (ddd, *J*=7.9, 7.3, 1.0 Hz, 1H, H-6), 5.61 (s, 1H, H-2′), 4.93 (d, *J*=9.5 Hz, 1H, H-5′), 4.31 (d, *J*=9.5 Hz, 1H, H-5′), 2.85 (s, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$/CS_2) δ: 176.5 (C-4), 157.1 (C-2), 155.9 (C-9), 156.2 153.9, 153.1, 152.8, 147.13, 147.11, 146.5, 146.3, 146.1, 146.0, 145.90, 145.86, 145.8, 145.6, 145.43, 145.38, 145.36, 145.3, 145.2, 145.1, 145.0, 144.9, 144.4, 144.33, 144.27, 144.2, 142.9, 142.8, 142.52, 142.48, 142.39, 142.36, 142.19, 142.17, 142.1, 141.98, 141.95, 141.9, 141.83, 141.79, 141.7, 141.58, 141.56, 141.3, 140.1, 139.7, 139.6, 136.3, 136.1, 135.2, 133.7 (C-7), 126.2 (C-5), 125.4 (C-6), 123.7 (C-10), 120.7 (C-3), 118.1 (C-8), 75.8 (C-4′), 72.0 (C-2′), 69.7 (C-5′), 68.7 (C-3′), 39.7 (*C*H$_3$). HRMS (FAB) *m*/*z* calculated for C$_{72}$H$_{12}$NO$_2$ (M+H)$^+$ 922.0868, found 922.0883.

2.2.12. (Flavon-4′-yl)methanol (9). Flavone-4′-carbaldehyde **2a** (0.2 g, 0.8 mmol) was dissolved in dry THF (50 mL) and $NaBH_4$ (15 mg; 0.4 mmol) was added. The reaction mixture was stirred for 8 h at rt under N_2. H$_2$O (10 mL) was added to the reaction mixture and then 10% HCl was added carefully and slowly until H_2 liberation was ceased. Flavone **9** was then extracted with $CHCl_3$ (3×20 mL), the solvent was dried (Na_2SO_4), evaporated under vacuo and the residue was recrystallized from hot EtOH. Yield: 0.16 g (80%), mp 150–152 °C. ^{1}H NMR δ: 8.24 (dd, *J*=7.7, 1.7 Hz, 1H, H-5), 7.94 (d, *J*=8.4 Hz, 2H, H-2′,6′), 7.72 (ddd, *J*=7.7, 7.6, 1.7 Hz, 1H, H-7), 7.59 (dd, *J*=7.7 Hz, 1H, H-8), 7.54 (d, *J*=8.4 Hz, 2H, H-3′,5′), 7.44 (ddd, *J*=7.7, 7.6, 1.1 Hz, 1H, H-6), 6.83 (s, 1H, H-3), 4.82 (d, *J*=5.3 Hz, 2H, C*H*$_2$OH), 1.87 (t, *J*=5.3 Hz, 1H, CH$_2$O*H*); ^{13}C NMR δ: 178.5 (C-4), 163.2 (C-2), 156.2 (C-9), 144.7 (C-4′), 133.8 (C-7), 131.0 (C-1′), 127.2 (C-3′,5′), 126.5 (C-2′,6′), 125.7 (C-5), 125.3 (C-6), 124.0 (C-10), 118.1 (C-8), 107.5 (C-3), 64.6 (*C*H$_2$OH). MS (EI) *m*/*z*(%): 252 (M$^{+\cdot}$, 100), 223 (35), 165 (17), 146 (10), 131 (15), 120 (52), 121 (52), 115 (15), 107 (10), 103 (22), 92 (57), 77 (26), 63 (28). Anal. Calcd for C$_{16}$H$_{12}$O$_3$·1/2 H$_2$O: C, 73.55; H, 5.02. Found: C, 73.77; H, 4.74.

2.3. General procedure for the reactions with methyl malonyl chloride

To a cold solution of the flavones **9**, **20**, **22b** or **22c** (0.9 mmol) in CH_2Cl_2 (2–10 mL), triethylamine (0.26 mL, 1.86 mmol), methyl malonyl chloride (0.48 mL, 4 mmol) was added dropwise with stirring; the mixture was allowed to stand at 0 °C to rt until all starting material disappeared

(about 2 h). Then it was poured onto ice and extracted with CH_2Cl_2, the organic layer was dried (Na_2SO_4) and evaporated to dryness. An oily residue was obtained, which was purified by flash chromatography using CH_2Cl_2/acetone 19:1 as eluent.

2.3.1. Methyl 4′-flavonylmethyl malonate (10). Compound **10** (62 mg, 89%) was obtained from flavone **9** (50 mg, 0,2 mmol). Crystallization from $CHCl_3$/hexane, mp 106–107 °C. ^{1}H NMR (500.13 MHz) δ: 8.24 (d, J=7.8 Hz, 1H, H-5), 7.95 (d, J=8.2 Hz, 2H, H-2′,6′), 7.73 (dd, J=8.1, 7.3 Hz, 1H, H-7), 7.59 (d, J=8.1 Hz, 1H, H-8), 7.53 (d, J=8.2 Hz, 2H, H-3′,5′), 7.44 (dd, J=7.8, 7.3 Hz, 1H, H-6), 6.84 (s, 1H, H-3), 5.28 (s, 2H, CO_2CH_2R), 3.77 (s, 3H, CO_2CH_3), 3.49 (s, 2H, malonate CH_2); ^{13}C NMR (125.77 MHz) δ: 178.4 (C-4), 166.8 (CO_2CH_3), 166.2 (CO_2CH_2R), 162.8 (C-2), 156.2 (C-9), 138.9 (C-4′), 133.9 (C-7), 131.8 (C-1′), 128.5 (C-3′,5′), 126.5 (C-2′,6′), 125.7 (C-5), 125.3 (C-6), 123.9 (C-10), 118.1 (C-8), 107.8 (C-3), 66.4 (OCH_2Ph), 52.6 (OCH_3), 41.2 (malonate CH_2). MS (EI) m/z(%): 352 ($M^{+\cdot}$, 78), 251 (100); 235 (47), 223 (11), 207 (29), 178 (13), 121 (25), 104 (11), 92 (26), 74 (20). Anal. Calcd for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 68.49; H, 4.55.

2.3.2. Bis(4′-flavonylmethyl) malonate (11). Malonyl dichloride (9.2 μL, 0.1 mmol) was added dropwise to a cold solution of flavone **9** (50 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) and triethylamine (52 μL, 0.4 mmol); the mixture was stirred at 0 °C for 15 min and then 2 h at rt. Since the TLC of the reaction mixture showed some starting flavone, another portion of malonyl dichloride (9.2 μL, 0.1 mmol) was added and stirring was continued for 2 h. Diluted HCl (0.5%, 10 mL) was added to the reaction mixture and the two phases were separated. The organic phase was washed successively with HCl (0.5%, 10 mL), $NaHCO_3$ (10%, 2×5 mL), and H_2O (10 mL) and then it was dried (Na_2SO_4). After concentration under vacuum, the reaction mixture was purified by preparative TLC using a 4:1 mixture of CH_2Cl_2/AcOEt as eluent. Yield: 13.6 mg (23%), mp 204–205 °C. ^{1}H NMR δ: 8.15 (dd, J=7.7, 1.7 Hz, 2H, H-5), 7.86 (d, J=8.4 Hz, 4H, H-2′,6′), 7.66 (ddd, J=8.0, 7.6, 1.7 Hz, 2H, H-7), 7.50 (d, J=8.0 Hz, 2H, H-8), 7.46 (d, J=8.4 Hz, 4H, H-3′,5′), 7.37 (ddd, J=7.7, 7.6, 1.1 Hz, 2H, H-6), 6.77 (s, 2H, H-3), 5.25 (s, 4H, CH_2OR), 3.55 (s, 2H, malonate CH_2); ^{13}C NMR δ: 178.3 (C-4), 166.0 (CO_2R), 162.6 (C-2), 156.1 (C-9), 138.8 (C-4′), 133.9 (C-7), 131.8 (C-1′), 128.5 (C-3′,5′), 126.5 (C-2′,6′), 125.7 (C-5), 125.3 (C-6), 123.9 (C-10), 118.0 (C-8), 107.7 (C-3), 66.4 (CH_2OR), 41.5 (malonate CH_2). MS (FAB) m/z: 573 $(M+H)^+$. Anal. Calcd for $C_{35}H_{24}O_8$: C, 73.42; H, 4.22. Found: C, 73.68; H, 4.04.

2.4. General procedure for the synthesis of [60]fullerene-flavone dyads 12 and 13

A mixture of malonate **10** (20 mg, 0.057 mmol), C_{60} (41 mg, 0.057 mmol), iodine (14.4 mg, 0.057 mmol) and DBU (17 μL, 0.11 mmol) in toluene (25 mL) was stirred at rt under N_2 until the starting malonate disappeared (about 1 h). Then the crude mixture was concentrated and separated by flash chromatography using toluene and toluene/AcOEt (7:3) as eluent. The first fraction was the unchanged C_{60} and the second one the dyad **12** (39.5 mg, 65%) which was crystallized from $CHCl_3$/hexane. Dyad **13** was prepared in a similar way using **11** (20 mg, 0.035 mmol), C_{60} (25 mg, 0.035 mmol), iodine (9 mg, 0.035 mmol) and DBU (11 μL, 0.07 mmol) in toluene (25 mL). It was crystallized from $CHCl_3$/hexane yielding 6.6 mg (15%).

2.4.1. Dyad 12. Mp >300 °C. ^{1}H NMR (500.13 MHz) δ: 8.25 (dd, J=7.7, 1.5 Hz, 1H, H-5), 7.98 (d, J=8.2 Hz, 2H, H-2′,6′), 7.73 (ddd, J=8.0, 7.5, 1.5 Hz, 1H, H-7), 7.67 (d, J=8.3 Hz, 2H, H-3′,5′), 7.59 (d, J=8.0 Hz, 1H, H-8), 7.45 (dd, J=7.7, 7.5 Hz, 1H, H-6), 6.85 (s, 1H, H-3), 5.61 (s, 2H, CO_2CH_2R), 4.07 (s, 1H, OCH_3); ^{13}C NMR (125.77 MHz) δ: 178.4 (C-4), 163.9 (CO_2CH_3), 163.4 (CO_2R), 162.7 (C-2), 156.2 (C-9), 145.28, 145.27, 145.2, 145.11, 145.00, 144.97, 144.9, 144.74, 144.69, 144.58, 144.4, 143.89, 143.83, 143.1, 143.03, 142.95, 142.2, 141.9, 141.8, 141.00, 140.97, 139.4, 138.6, 138.2 (C-4′), 133.9 (C-7), 132.4 (C-1′), 129.5 (C-3′,5′), 126.7 (C-2′,6′), 125.8 (C-5), 125.4 (C-6), 124.0 (C-10), 118.1 (C-8), 108.0 (C-3), 71.3 (C_{60}-sp^3), 68.1 (CH_2OR), 54.1 (CO_2CH_3), 51.6 (methano bridge). HRMS (FAB) m/z calculated for $C_{80}H_{15}O_6$ $(M+H)^+$ 1071.0869, found 1071.0837.

2.4.2. Dyad 13. Mp >300 °C. ^{1}H NMR δ: 8.13 (dd, J=7.7, 1.7 Hz, 2H, H-5), 7.88 (d, J=8.4 Hz, 4H, H-2′,6′), 7.66 (ddd, J=7.8, 7.7, 1.7 Hz, 2H, H-7), 7.58 (d, J=8.4 Hz, 4H, H-3′,5′), 7.50 (d, J=7.8 Hz, 2H, H-8), 7.37 (dt, J=7.7, 0.9 Hz, 2H, H-6), 6.77 (s, 2H, H-3), 5.57 (s, 4H, CH_2OR); ^{13}C NMR δ: 178.2 (C-4), 163.2 (CO_2R), 162.4 (C-2), 156.0 (C-9), 145.3, 145.2, 145.0, 144.9, 144.7, 144.6, 144.4, 143.8, 143.1, 143.05, 143.00, 142.2, 141.8, 141.0, 139.1, 138.0 (C-4′), 133.9 (C-7), 132.2 (C-1′), 129.1 (C-3′,5′), 126.5 (C-2′,6′), 125.6 (C-5), 125.3 (C-6), 123.7 (C-10), 118.0 (C-8), 107.8 (C-3), 71.2 (C_{60}-sp^3), 68.0 (CH_2OR), 53.2 (methano bridge). HRMS (FAB) m/z calculated for $C_{95}H_{23}O_8$ $(M+H)^+$ 1291.1393, found 1291.1345.

2.5. Methylation of quercetin

A mixture of quercetin hydrate (1.01 g, 3 mmol), methyl iodide (0.16 mL, 30 mmol) and anhydrous K_2CO_3 (3.17 g, 22.5 mmol) in MeCN/MeOH (2:1, 150 mL) was stirred at 60 °C until all starting material disappeared (about 10 h). The TLC (in $CHCl_3$/MeOH, 10:2) of the reaction mixture showed two spots (R_f=0.91 and 0.70). The two products were separated by flash chromatography using mixtures of CH_2Cl_2/acetone (9:1 to 7:3) as eluent. The first fraction was identified as 5-hydroxy-3,3′,4′,7-tetramethoxyflavone **15** and the second one as 3,3′,4′,5,7-pentamethoxyflavone **16**.

2.5.1. 5-Hydroxy-3,3′,4′,7-tetramethoxyflavone (15). Yield: 0.42 g (39%), mp 148–150 °C. ^{1}H NMR δ: 12.65 (s, 1H, 5-O*H*), 7.74 (dd, J=8.6, 2.0 Hz, 1H, H-6′), 6.69 (d, J=2.0 Hz, 1H, H-2′), 7.00 (d, J=8.6 Hz, 1H, H-5′), 6.46 (d, J=2.2 Hz, 1H, H-8), 6.37 (d, J=2.2 Hz, 1H, H-6), 3.98, 3.97, 3.89 and 3.87 (4 s, 12H, 4×OCH_3). MS (EI) m/z (%): 358 ($M^{+\cdot}$, 100), 343 (50), 329 (25), 315 (43), 270 (7), 239 (10), 211 (63), 196 (20), 149 (30), 136 (14), 107 (14), 97 (21), 83 (80). Anal. Calcd for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06. Found: C, 63.39; H, 4.96.

2.5.2. 3,3′,4′,5,7-Pentamethoxyflavone (16). Yield: 0.63 g (60%), mp 137–139 °C. ^{1}H NMR δ: 7.73–7.69 (m, 2H,

H-2′, H-6′), 6.98 (d, *J*=9.2 Hz, 1H, H-5′), 6.50 (d, *J*=2.2 Hz, 1H, H-8), 6.34 (d, *J*=2.2 Hz, 1H, H-6), 3.97, 3.96, 3.91 and 3.87 (4 s, 15H, 5×OC*H*$_3$). MS (EI) *m*/*z* (%): 372 ($M^{+\cdot}$, 100), 357 (60), 341 (18), 329 (14), 311 (14), 283 (7), 181 (7), 172 (14), 165 (8), 149 (10), 137 (5), 119 (5), 106 (4). Anal. Calcd for $C_{20}H_{20}O_7 \cdot 1/2\ H_2O$: C, 62.99; H, 5.55. Found: C, 62.65; H, 5.36.

2.5.3. 3,3′,4′,7-Tetramethoxy-5-(4-methylbenzenesulfonyloxy)flavone (17). A mixture of 5-hydroxy-3,3′,4′,7-tetramethoxyflavone **15** (0.81 g, 2.3 mmol), 4-Me$C_6H_4SO_2$-Cl (1.77 g, 9.1 mmol), and anhydrous K_2CO_3 (2.56 g, 18 mmol) in MeCN (15 mL) was heated at 60 °C, with stirring, until the starting flavone disappeared (about 3 h). The remaining K_2CO_3 was filtered off and the filtrate was evaporated until dryness. The solid residue was dissolved in hot mixture of CH_2Cl_2 (2 mL) and MeOH (4 mL), the mixture was cooled in an ice bath, and the resulting solid was filtered off; yield: 1.00 g (86%), mp 158–160 °C. ^{1}H NMR *δ*: 8.00 (d, *J*=8.3 Hz, 2H, H-2,6 of 5-OTs), 7.70–7.67 (m, 2H, H-2′, H-6′), 7.34 (d, *J*=8.3 Hz, 2H, H-3,5 of 5-OTs), 7.97 (d, *J*=9.0 Hz, 1H, H-5′), 6.85 (d, *J*=2.5 Hz, 1H, H-8), 6.86 (d, *J*=2.5 Hz, 2H, H-6), 3.98, 3.96, 3.90 and 3.77 (4 s, 12H, 4×OC*H*$_3$), 2.43 (s, 3H, C*H*$_3$ of 5-OTs); ^{13}C NMR *δ*: 172.1 (C-4), 162.6 (C-7), 157.6 (C-9), 153.6 (C-5), 151.0 (C-2), 148.6 (C-4′), 147.7 (C-3′), 145.0 (C-4 of 5-OTs), 141.0 (C-3), 132.7 (C-1 of 5-OTs), 129.6 and 129.1 (C-2,6 and C-3,5 of 5-OTs), 122.9 (C-1′), 121.8 (C-6′), 112.3 (C-10), 111.1 (C-2′), 110.7 (C-5′), 108.8 (C-6), 99.8 (C-8), 59.9 (3-OC*H*$_3$), 56.1, 56.02 and 55.95 (3×OC*H*$_3$), 21.7 (C*H*$_3$ of 5-OTs). MS (EI) *m*/*z* (%): 512 ($M^{+\cdot}$, 20), 371 (100), 357 (70), 343 (15), 329 (19), 165 (12), 91 (38), 65 (14). Anal. Calcd for $C_{26}H_{24}O_9S$: C, 60.93; H, 4.72. Found: C, 60.66; H, 4.91.

2.6. General procedure for the demethylation reactions

$AlBr_3$ (0.29 g, 1.1 mmol) was added to a stirred ice-cold solution of 3,3′,4′,5,7-pentamethoxyflavone **16** (0.37 g, 1 mmol) in MeCN (4 mL). The mixture was kept at that temperature for 90 min, then it was diluted with 10% HCl and warmed at 75 °C for 30 min. The mixture was concentrated until a solid has started to appear. The solid was filtered off and washed with H_2O and MeOH. The TLC (CH_2Cl_2/acetone 9:1) showed two spots (R_f=0.64 and 0.35) corresponding, respectively, to 5-hydroxy-3,3′,4′,7-tetramethoxyflavone **15** and 3-hydroxy-3′,4′,5,7-tetramethoxyflavone **19**. The two isomers were separated by flash chromatography using mixtures of CH_2Cl_2/acetone (95:5 to 80:20) as eluent. Yields: **15**, 93 mg (26%); **19**, 170 mg (47%). In a similar way, 3,3′,4′,7-tetramethoxy-5-(4-methylbenzenesulfonyloxy)flavone **17** (0,51 g, 1 mmol) in MeCN (22 mL) was reacted with $AlBr_3$ (0,83 g, 3.1 mmol) to give 3-hydroxy-3′,4′,7-trimethoxy-5-(4-methylbenzenesulfonyloxy)flavone **18** (0.39 g, 79%).

2.6.1. 3-Hydroxy-3′,4′,7-trimethoxy-5-(4-methylbenzenesulfonyloxy)flavone (18). Crystallized from EtOH, mp 176–178 °C. ^{1}H NMR *δ*: 7.95 (d, *J*=8.35 Hz, 2H, H-2,6 of 5-OTs), 7.81–7.77 (m, 2H, H-2′ and H-6′), 7.35 (d, *J*=9.0 Hz, 2H, H-3,5 of 5-OTs), 7.18 (br s, 1H, 3-OH), 6.99 (d, *J*=9.0 Hz, 1H, H-5′), 6.87 (d, *J*=2.3 Hz, 1H, H-8), 6.75 (d, *J*=2.3 Hz, 1H, H-6), 3.98, 3.96 and 3.91 (3 s, 9H, 3×O–C*H*$_3$), 2.46 (s, 3H, 5-OTs); ^{13}C NMR *δ*: 170.4 (C-4), 162.9 (C-7), 157.6 (C-9), 150.5 (C-2 and C-5), 148.8 (C-4′), 147.5 (C-3′), 145.5 (C-4 of 5-OTs), 137.8 (C-3), 132.7 (C-1 of 5-OTs), 129.6 and 128.9 (C-2,6 and C-3,5 of 5-OTs), 123.3 (C-1′), 120.9 (C-6′), 112.4 (C-10), 110.9 (C-2′), 110.4 (C-5′), 108.9 (C-6), 99.6 (C-8), 56.1, 56.0 and 55.9 (3×OC*H*$_3$), 21.8 (C*H*$_3$ of 5-OTs). MS (EI) *m*/*z* (%): 498 ($M^{+\cdot}$, 20), 358 (9), 344 (100), 329 (12), 315 (57), 301 (7), 165 (7), 91 (14), 65 (7). Anal. Calcd for $C_{25}H_{22}O_9S$: C, 60.23; H, 4.45. Found: C, 60.40; H, 4.52.

2.6.2. 3-Hydroxy-3′,4′,5,7-tetramethoxyflavone (19). Crystallized from EtOH, mp 184–186 °C. ^{1}H NMR *δ*: 7.83–7.80 (m, 2H, H-2′ and H-6′), 7.42 (br s, 1H, 3-OH), 7.00 (d, *J*=9.1 Hz, 1H, H-5′), 6.56 (d, *J*=1.8 Hz, 1H, H-8), 6.36 (d, *J*=1.8 Hz, 1H, H-6), 3.99, 3.97 and 3.93 (3 s, 12H, 5×OC*H*$_3$); ^{13}C NMR *δ*: 171.9 (C-4), 164.3 (C-7), 160.5 (C-5), 158.1 (C-9), 150.2 (C-2), 148.8 (C-3′ and C-4′), 137.5 (C-3), 123.7 (C-1′), 120.6 (C-6′), 110.8 (C-2′), 110.3 (C-5′), 106.2 (C-10), 95.6 (C-6), 92.4 (C-8), 56.4, 56.0, 55.9 and 55.8 (4×OC*H*$_3$). MS (EI) *m*/*z* (%): 358 ($M^{+\cdot}$, 100), 343 (8), 329 (10), 312 (37), 179 (8), 165 (6), 136 (4). Anal. Calcd for $C_{19}H_{18}O_7 \cdot 1/2H_2O$: C, 62.12; H, 5.21. Found: C, 62.07; H, 4.91.

2.7. General procedure for the reactions with 3-iodopropan-1-ol

A mixture of flavones **15**, **18** or **19** (1.3 mmol), 3-iodopropan-1-ol (0.26 mL, 2.6 mmol), and anhydrous K_2CO_3 (0.73 g, 5.2 mmol) in DMF (4 mL) was heated with stirring at 60 °C until all starting material disappeared (about 2 h). Then H_2O (20 mL) was added and the resulting mixture was extracted with AcOEt/Et_2O (3:2, 4×25 mL). The organic layer was dried (Na_2SO_4), evaporated to dryness, and the resulting residue was purified by flash chromatography using CH_2Cl_2/acetone (8:2) as eluent.

2.7.1. 3-(3,3′,4′,7-Tetramethoxyflavonyl-5-oxy)propan-1-ol (20). Compound **20** (0.39 g, 72%) was obtained from **15** (0.47 g); crystallization from EtOH; mp 92–94 °C. ^{1}H NMR *δ*: 7.73–7.70 (m, 2H, H-2′ and H-6′), 6.83 (d, *J*=8.4 Hz, 1H, H-5′), 6.52 (d, *J*=2.1 Hz, 1H, H-8), 6.33 (d, *J*=2.1 Hz, 1H, H-6), 5.42 (t, *J*=6.4 Hz, 1H, O*H*), 4.21 (t, *J*=5.6 Hz, 2H, C*H*$_2$O), 3.97, 3.91 and 3.85 (3 s, 14H, 3×OC*H*$_3$ and C*H*$_2$OH overlapped with the first singlet), 2.18 (qui, *J*=5.5 Hz, 2H, C*H*$_2$); ^{13}C NMR *δ*: 174.1 (C-4), 164.0 (C-7), 159.7 (C-5), 158.6 (C-9), 153.9 (C-2), 150.8 (C-4′), 148.6 (C-3′), 141.0 (C-3), 123.3 (C-1′), 121.3 (C-6′), 111.1 (C-2′), 110.7 (C-5′), 109.0 (C-10), 96.8 (C-6), 92.5 (C-8), 69.6 (HO*C*H$_2$), 61.8 (O*C*H$_2$), 59.9 (3-OC*H*$_3$), 56.0, 55.9 and 55.8 (3×OC*H*$_3$), 31.8 (*C*H$_2$). MS (EI) *m*/*z* (%): 416 ($M^{+\cdot}$, 100), 401 (30), 371 (53), 358 (21), 341 (14), 315 (14), 299 (10), 269 (6), 255 (5), 165 (10), 149 (6). Anal. Calcd for $C_{22}H_{24}O_8 \cdot H_2O$: C, 60.82; H, 6.03. Found: C, 60.62; H, 6.07.

2.7.2. 3-(5-Hydroxy-3′,4′,7-trimethoxyflavonyl-3-oxy)-propan-1-ol (22b). 3-[5-(4-Methylbenzenesulfonyloxy)-3′,4′,7-trimethoxyflavonyl-3-oxy)propan-1-ol **22a** was obtained as an oily residue from **18** (0.65 g). It was dissolved in MeOH (30 mL), K_2CO_3 (0.36 g, 2.6 mmol) was added, and the mixture was heated at 60 °C for 30 min. The reaction mixture was acidified with 10% HCl,

concentrated under reduced pressure, and then cooled. The resulting solid was filtered off and recrystallized from EtOH to afford **22b** (0.32 g, 60%), mp 135–137 °C. ^{1}H NMR δ: 12.35 (s, 1H, 5-O*H*), 7.78–7.74 (m, 2H, H-2′ and H-6′), 7.00 (d, *J*=8.3 Hz, 1H, H-5′), 6.48 (d, *J*=2.2 Hz, 1H, H-8), 6.38 (d, *J*=2.2 Hz, 1H, H-6), 4.32 (br s, 1H, O*H*), 4.05 (t, *J*=5.6 Hz, 2H, CH_2O), 3.98, 3.97 and 3.89 (3 s, 11H, 3×OCH_3 and CH_2OH overlapped with the first two singlets), 1.93 (qui, *J*=5.6 Hz, 2H, CH_2); ^{13}C NMR δ: 178.9 (C-4), 165.7 (C-7), 161.9 (C-5), 156.8 (C-9), 156.5 (C-2), 151.5 (C-4′), 148.8 (C-3′), 137.8 (C-3), 122.7 (C-1′), 122.1 (C-6′), 111.1 (C-2′), 110.9 (C-5′), 105.9 (C-10), 98.0 (C-6), 92.4 (C-8), 69.2 (CH_2OH), 59.1 (OCH_2), 56.0 and 55.9 (3×OCH$_3$), 32.2 (CH_2). MS (EI) *m*/*z* (%): 402 ($M^{+\cdot}$, 93), 371 (15), 357 (22), 344 (100), 329 (15), 315 (63), 301 (10), 285 (7), 167 (15), 149 (7). Anal. Calcd for $C_{21}H_{22}O_8\cdot$ 1/2 H_2O: C, 61.31; H, 5.64. Found: C, 61.21; H, 5.59.

2.7.3. 3-(3′,4′,5,7-Tetramethoxyflavonyl-3-oxy)propan-1-ol (22c). Compound **22c** (0.44 g, 82%) was obtained from **19** (0.47 g); crystallization from EtOH, mp 130–132 °C. ^{1}H NMR δ: 7.77 (d, *J*=2.1 Hz, H-2′), 7.75 (dd, *J*=8.5, 2.1 Hz, 1H, H-6′), 6.99 (d, *J*=8.5 Hz, 1H, H-5′), 6.53 (d, *J*=2.3 Hz, 1H, H-8), 6.37 (d, *J*=2.3 Hz, 1H, H-6), 4.67 (br s, 1H, O*H*), 4.02 (t, *J*=5.5 Hz, 2H, CH_2O), 3.97 and 3.92 (2 s, 14H, 4×OCH_3 and CH_2OH overlapped with the first singlet), 1.91 (qui, *J*=5.5 Hz, 2H, CH_2); ^{13}C NMR δ: 174.7 (C-4), 164.2 (C-7), 161.0 (C-5), 158.9 (C-9), 153.5 (C-2), 151.0 (C-4′), 148.7 (C-3′), 139.9 (C-3), 123.1 (C-1′), 121.6 (C-6′), 111.0 (C-2′), 110.8 (C-5′), 109.1 (C-10), 95.9 (C-6), 92.5 (C-8), 69.1 (HOCH_2), 59.6 (CH_2O), 56.5, 56.04, 55.98 and 55.8 (4×OCH_3), 32.3 (CH_2). MS (EI) *m*/*z* (%): 416 ($M^{+\cdot}$, 100), 401 (20), 385 (31), 371 (75), 358 (23), 341 (31), 329 (15), 312 (12), 269 (23), 234 (23), 181 (70), 165 (60), 149 (27). Anal. Calcd for $C_{22}H_{24}O_8\cdot$1/2 H_2O: C, 62.11; H, 5.92. Found: C, 61.99; H, 5.89.

2.7.4. Malonate derivatives of quercetin. Compounds **21** and **23** were prepared as indicated above in the general procedure for the reactions with methyl malonyl chloride.

2.7.5. Methyl 3-(3,3′,4′,7-tetramethoxyflavonyl-5-oxy)-propyl malonate (21). Compound **21** (0.34 g, 73%) was obtained as an oil from **20** (0.37 g). ^{1}H NMR δ: 7.73–7.69 (m, 2H, H-2′ and H-6′), 6.98 (d, *J*=9.8 Hz, 1H, H-5′), 6.51 (d, *J*=2.2 Hz, 1H, H-8), 6.34 (d, *J*=2.2 Hz, 1H, H-6), 4.53 (t, *J*=6.1 Hz, 2H, OCH$_2$CH$_2$CH_2OCO), 4.15 (t, *J*=6.1 Hz, 2H, OCH_2CH$_2$CH$_2$OCO), 3.97, 3.90 and 3.84 (3s, 12H, 4×OCH_3), 3.73 (s, 3H, CO$_2$CH_3), 3.41 (s, 2H, malonate CH_2), 2.29 (qui, *J*=6.1 Hz, 2H, CH_2); ^{13}C NMR δ: 173.8 (C-4), 167.0 (*C*O$_2$CH$_3$), 166.4 (*C*OCH$_2$CO$_2$CH$_3$), 163.7 (C-7), 160.0 (C-5), 158.7 (C-9), 152.6 (C-2), 150.7 (C-4′), 148.6 (C-3′), 141.1 (C-3), 123.3 (C-1′), 121.6 (C-6′), 111.1 (C-2′), 110.7 (C-5′), 109.6 (C-10), 96.7 (C-6), 92.6 (C-8), 65.5 (OCH_2CH$_2$CH$_2$OCO), 62.4 (OCH$_2$CH$_2$*C*H$_2$OCO), 59.9 (3-OCH_3), 56.0, 55.9 and 55.7 (3×OCH$_3$), 52.5 (CO$_2$CH_3), 41.3 (malonate *C*H$_2$), 28.3 (OCH$_2$*C*H$_2$CH$_2$O). MS (EI) *m*/*z* (%): 516 ($M^{+\cdot}$, 100), 501 (12), 486 (11), 415 (15), 397 (17), 385 (33), 371 (65), 357 (23), 341 (19), 315 (15), 159 (27), 101 (41), 91 (40), 69 (23). Anal. Calcd for $C_{26}H_{28}O_{11}\cdot$1/2 H_2O: C, 59.43; H, 5.56. Found: C, 59.69; H, 5.45.

2.7.6. Methyl 3-(5-hydroxy-3′,4′,7-trimethoxyflavonyl-3-oxy)propyl malonate (23a). Compound **23a** (0.39 g, 86%) was obtained as an oil from **22b** (0.36 g). ^{1}H NMR δ: 12.64 (s, 1H, 5-O*H*), 7.69 (dd, *J*=8.5, 2.1 Hz, 1H, H-6′), 7.60 (d, *J*=2.1 Hz, 1H, H-2′), 7.50 (d, *J*=8.5 Hz, 1H, H-5′), 6.45 (d, *J*=2.2 Hz, 1H, H-8), 6.37 (d, *J*=2.2 Hz, 1H, H-6), 4.30 (t, *J*=6.3 Hz, 2H, OCH$_2$CH$_2$CH_2OCO), 4.07 (t, *J*=6.3 Hz, 2H, OCH_2CH$_2$CH$_2$OCO), 3.98, 3.97 and 3.88 (3s, 9H, 3×OCH_3), 3.71 (s, 3H, CO$_2$CH_3), 3.36 (s, 2H, malonate CH_2), 2.08 (qui, *J*=6.3 Hz, 2H, CH_2); ^{13}C NMR δ: 178.6 (C-4), 166.9 (*C*O$_2$CH$_3$), 166.4 (*C*OCH$_2$CO$_2$CH$_3$), 165.4 (C-7), 162.0 (C-5), 156.7 (C-9), 156.3 (C-2), 151.3 (C-4′), 148.7 (C-3′), 137.8 (C-3), 122.8 (C-1′), 122.4 (C-6′), 111.2 (C-2′), 110.8 (C-5′), 106.0 (C-10), 97.9 (C-6), 92.2 (C-8), 69.1 (OCH_2CH$_2$CH$_2$OCO), 62.3 (OCH$_2$CH$_2$*C*H$_2$OCO), 56.1, 56.0 and 55.8 (3×OCH$_3$), 52.5 (CO$_2$CH_3), 41.2 (malonate *C*H$_2$), 29.2 (OCH$_2$*C*H$_2$CH$_2$OCO). HRMS (FAB) *m*/*z* calculated for $C_{25}H_{27}O_{11}$ $(M+H)^+$ 503.1553, found 503.1562.

2.7.7. Methyl 3-(3′,4′,5,7-tetramethoxyflavonyl-3-oxy)-propyl malonate (23b). Compound **23b** (0.38 g, 83%) was obtained as an oil from **22c** (0.37 g). ^{1}H NMR δ: 7.67 (dd, *J*=8.5, 1.9 Hz, 1H, H-6′), 7.63 (d, *J*=1.9 Hz, 1H, H-2′), 6.98 (d, *J*=8.5 Hz, 1H, H-5′), 6.50 (d, *J*=1.7 Hz, 1H, H-8), 6.33 (d, *J*=1.7 Hz, 1H, H-6), 4.31 (t, *J*=6.4 Hz, 2H, OCH$_2$CH$_2$CH_2OCO), 4.08 (t, *J*=6.4 Hz, 2H, OCH_2CH$_2$-CH$_2$OCO), 3.97, 3.95 and 3.90 (3s, 12H, 4×OCH_3), 3.71 (s, 3H, CO$_2$CH_3), 3.35 (s, 2H, malonate CH_2), 2.10 (q, 2H); ^{13}C NMR δ: 173.7 (C-4), 166.8 (*C*O$_2$CH$_3$), 166.2 (*C*OCH$_2$CO$_2$-CH$_3$), 163.7 (C-7), 160.7 (C-5), 158.6 (C-9), 152.7 (C-2), 150.6 (C-4′), 148.4 (C-3′), 139.8 (C-3), 123.0 (C-1′), 121.7 (C-6′), 111.0 (C-2′), 110.5 (C-5′), 109.1 (C-10), 95.6 (C-6), 92.2 (C-8), 68.4 (OCH_2CH$_2$CH$_2$OCO), 62.6 (OCH$_2$CH$_2$-*C*H$_2$OCO), 56.2, 55.9, 55.8 and 55.6 (4×OCH_3), 52.3 (COOCH_3), 41.1 (malonate *C*H$_2$), 29.7 (OCH$_2$CH_2CH$_2$O). HRMS (FAB) *m*/*z* calculated for $C_{26}H_{29}O_{11}$ $(M+H)^+$ 517.1710, found 517.1721.

2.8. General procedure for the synthesis of [60]fullerene-quercetin derivatives

A mixture of flavone **21**, **23a** or **23b** (0.16 mmol), C_{60} (280 mg, 0.39 mmol), iodine (40 mg, 0.16 mmol) and DBU (84 μL, 0.55 mmol) in toluene (100 mL) was stirred at rt under N_2 until the starting flavone disappeared (about 1 h). Then the crude mixture was concentrated, and separated by flash chromatography using toluene and toluene/AcOEt (6:4) as eluent. The first fraction was the unchanged C_{60} and the second one the dyads **24**, **25a** or **25b**.

2.8.1. Dyad 24. Compound **24** (80 mg, 49%) was obtained from **21** (82 mg). ^{1}H NMR δ: 7.67–7.64 (m, 2H, H-2′ and H-6′), 6.98 (d, *J*=8.4 Hz, 1H, H-5′), 6.45 (d, *J*=2.2 Hz, 1H, H-8), 6.25 (d, *J*=2.2 Hz, 1H, H-6), 4.96 (t, *J*=5.7 Hz, 2H, OCH$_2$CH$_2$CH_2OCO), 4.19 (t, *J*=5.7 Hz, 2H, OCH_2CH$_2$-CH$_2$OCO), 4.08 (s, 3H, CO$_2$CH_3), 3.97 and 3.96 (2 s, 6H, 3′- and 4′-OCH_3), 3.86 (s, 3H, 7-OCH_3), and 3.81 (s, 3H, 3-OCH_3), 2.48 (qui, *J*=5.7 Hz, 2H, CH_2); ^{13}C NMR δ: 173.7 (C-4), 163.8 (*C*O$_2$CH$_3$), 163.7 (C-7), 163.4 (*C*O$_2$R), 160.0 (C-5), 158.8 (C-9), 152.9 (C-2), 150.8 (C-4′), 148.6 (C-3′), 145.4, 145.2, 145.14, 145.12, 145.06, 145.02, 144.83, 144.80, 144.7, 144.60, 144.55, 144.3, 144.2,

143.8, 143.6, 143.0, 142.93, 142.90, 142.8, 142.5, 142.13, 142.07, 141.8, 141.6, 141.2, 140.8, 140.7 (C-3), 139.5, 138.3, 129.0, 128.2, 125.3, 123.2 (C-1′), 121.6 (C-6′), 111.1 (C-2′), 110.7 (C-5′), 109.8 (C-10), 96.8 (C-6), 92.8 (C-8), 71.5 (C_{60}-sp^3), 64.9 ($OCH_2CH_2CH_2OCO$), 63.9 (OCH_2-CH_2CH_2OCO), 60.0 (3-OCH_3), 56.1, 55.9 and 55.8 (3×OCH_3), 54.1 (CO_2CH_3), 52.3 (methano bridge), 28.0 ($OCH_2CH_2CH_2O$). HRMS (FAB) *m/z* calculated for $C_{86}H_{27}O_{11}$ $(M+H)^+$ 1235.1553, found 1235.1599.

2.8.2. Dyad 25a. Compound **25a** (64 mg, 33%) was obtained from **23a** (80 mg). ^{1}H NMR δ: 12.60 (s, 1H, 5-O*H*), 7.73 (dd, *J*=8.5, 1.9 Hz, 1H, H-6′), 7.60 (d, *J*=1.9 Hz, 1H, H-2′), 7.01 (d, *J*=8.5 Hz, 1H, H-5′), 6.43 (d, *J*=2.1 Hz, 1H, H-8), 6.34 (d, *J*=2.1 Hz, 1H, H-6), 4.65 (t, *J*=6.2 Hz, 2H, $OCH_2CH_2CH_2OCO$), 4.16 (t, *J*=6.2 Hz, 2H, $OCH_2CH_2CH_2OCO$), 4.07 (s, 3H, CO_2CH_3), 3.97 and 3.96 (2 s, 6H, 3′- and 4′-OCH_3), 3.86 (s, 3H, 7-OCH_3), 2.27 (qui, *J*=6.2 Hz, 2H, CH_2); ^{13}C NMR δ: 178.5 (C-4), 165.5 (C-7), 164.0 (CO_2CH_3), 163.5 (COR), 162.0 (C-5), 156.7 (C-9), 156.1 (C-2), 151.4 (C-4′), 148.7 (C-3′), 145.3, 145.18, 145.16, 145.1, 144.99, 144.96, 144.9, 144.67, 144.65, 144.6, 144.54, 144.47, 143.9, 143.8, 143.1, 143.0, 142.93, 142.89, 142.2, 142.1, 141.9, 141.7, 140.91, 140.87, 139.2, 138.6, 138.0 (C-3), 129.0, 128.2, 125.3, 122.8 (C-1′), 122.5 (C-6′), 111.2 (C-2′), 110.8 (C-5′), 106.1 (C-10), 98.0 (C-6), 92.3 (C-8), 71.4 (C_{60}-sp^3), 69.5 ($OCH_2CH_2CH_2OCO$), 64.3 ($OCH_2CH_2CH_2OCO$), 56.1 (7-OCH_3), 56.0 and 55.9 (3′- and 4′-OCH_3), 54.1 (CO_2CH_3), 52.0 (methano bridge), 29.5 ($OCH_2CH_2CH_2O$). HRMS (FAB) *m/z* calculated for $C_{85}H_{25}O_{11}$ $(M+H)^+$ 1221.1397, found 1221.1399.

2.8.3. Dyad 25b. Compound **25b** (102 mg, 52%) was obtained from **23b** (80 mg). ^{1}H NMR δ: 7.71 (dd, *J*=8.5, 1.9 Hz, 1H, H-6′), 7.64 (d, *J*=1.9 Hz, 1H, H-2′), 7.00 (d, *J*=8.5 Hz, 1H, H-5′), 6.50 (d, *J*=2.1 Hz, 1H, H-8), 6.35 (d, *J*=2.1 Hz, 1H, H-6), 4.65 (t, *J*=6.2 Hz, 2H, $OCH_2CH_2CH_2OCO$), 4.17 (t, *J*=6.2 Hz, 2H, $OCH_2CH_2CH_2OCO$), 4.04 (s, 3H, CO_2CH_3), 3.98, 3.96 and 3.90 (3 s, 4×3H, 4×OCH_3), 2.28 (qui, *J*=6.2 Hz, 2H, CH_2); ^{13}C NMR δ: 173.8 (C-4), 164.01 (CO_2CH_3), 163.96 (C-7), 163.4 (CO_2R), 161.0 (C-5), 158.8 (C-9), 152.9 (C-2), 150.9 (C-4′), 148.6 (C-3′), 145.4, 145.22, 145.15, 145.13, 144.99, 144.97, 144.9, 144.63, 144.58, 144.5, 143.9, 143.8, 143.02, 142.96, 142.87, 142.2, 142.1, 141.9, 141.7, 140.9, 140.2 (C-3), 139.3, 138.5, 137.9, 125.3, 123.2 (C-1′), 122.0 (C-6′), 111.2 (C-2′), 110.8 (C-5′), 109.5 (C-10), 95.9 (C-6), 92.5 (C-8), 71.5 (C_{60}-sp^3), 69.0 ($OCH_2CH_2CH_2OCO$), 64.7 ($OCH_2CH_2CH_2OCO$), 56.4, 56.1, 56.0 and 55.8 (4×OCH_3), 54.0 (CO_2CH_3), 52.1 (methano bridge), 29.6 ($OCH_2CH_2CH_2O$). HRMS (FAB) *m/z* calculated for $C_{86}H_{27}O_{11}$ $(M+H)^+$ 1235.1553, found 1235.1542

Acknowledgements

Thanks are due to the Fundação para a Ciência e a Tecnologia (Portugal) and FEDER for funding the Organic Chemistry Research Unit and to the European Community for funding the Research Network FMRX-CT98-0192 (TMR Program).

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Tetrahedron 60 (2004) 3593–3597
Tetrahedron

A novel phosphorus–carbon bond formation by ring opening with diethyl phosphite of oxazolines derived from serine

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Received 24 November 2003; revised 7 February 2004; accepted 1 March 2004

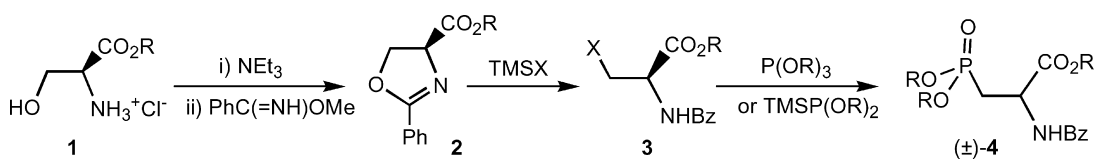
Abstract—A new reaction of oxazolines derived from serine with diethyl phosphite leading to ring opening products with P–C bond formation is reported. This reaction, which proceeds under neutral conditions and without the use of any halogenated intermediate, results in a mixture of racemic α- and β-phosphono alanines in an approximate 1:2 ratio, with isolated yields up to 77%. The mechanism involves the rearrangement of the oxazoline into the corresponding α-benzamido acrylate, followed by addition of the diethyl phosphite to the double bond. Since no significant transesterification is observed, this method constitutes a simple route for α- and β-phosphono amino acids bearing suitable protecting groups.

1. Introduction

β-Phosphono alanine (AP3) and its derivatives are the P-analogues of aspartic acid and are biologically important compounds, due to their antagonist activity on the central nervous system[1] and their use in the synthesis of numerous enzyme inhibitors[2] or modified peptides[3] involved in viral maturation, cell development or infectivity. Recently, the AP3 was also used as a multifunctional ligand to build a chiral hybrid inorganic-organic framework by coordination with a zinc salt.[4] The synthesis of this class of amino acids remains of great interest, particularly in order to obtain suitably protected intermediates, which are useful in peptide chemistry. Several methods[5–11] with phosphorus-, nitrogen- or carbon–carbon bond formation have been described to date for the AP3 synthesis. Thus, addition of phosphite to β-halogeno aminoester or α,β-dehydroalanine,[6] amination of phosphonopyruvates,[7] or even the Strecker reaction with 2-phosphonopropanal,[8] all afford racemic AP3 or its derivatives in good yields. On the other hand, the enantioselective synthesis of AP3 was realized by alkylation of the nickel (II) complex of a chiral Schiff base derived from glycine,[9] by reaction of phosphite with the lactone derived from serine,[10] or by enzymatic resolution of a prochiral phosphonalkyldiol precursor.[11]

In our continuing work on the stereoselective synthesis of protected β-halogeno alanine **3** from oxazoline **2**,[12] we investigated the synthesis of the β-phosphono derivatives **4** by reaction with a trialkyl phosphite or a dialkylsilyl phosphite (Scheme 1). However, despite our efforts, under Michaelis–Arbuzov reaction conditions with or without a solvent, the racemic phosphonate[13] **4** was obtained in only moderate yields (<50%) as a mixture with by-products that were difficult to remove (Scheme 1).

Since the oxazoline **2** reacts with acidic or electrophilic reagents[12,14] to afford the ring opening stereospecifically, we thought that this strategy might be realized by an organophosphorus derivative in order to afford the ring



1 2 3 (±)-4

Scheme 1.

Keywords: Amino acids and derivatives; Phosphonic acids and derivatives; Oxazolines.
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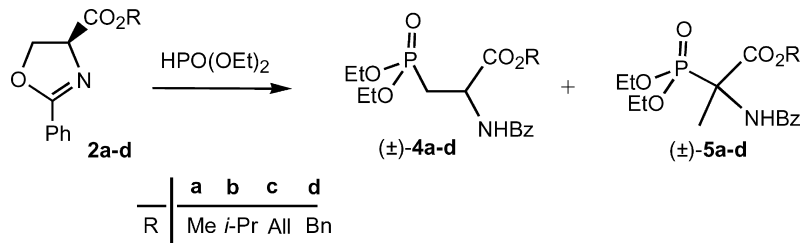
doi:10.1016/j.tet.2004.03.001



Scheme 2.

opening product with P–C bond formation. To date, few examples of an aza heterocycle ring opening with an organophosphorus derivative are known[15] and, to the best of our knowledge, only the reaction of an oxazoline with dibenzyl phosphate leading to the corresponding β-amino-phosphate[15b] has been described. While investigating the reaction of 2-phenyl oxazoline **2** with diethyl phosphite, we succeeded in obtaining the α- and β-phosphono α-benzamido esters (Scheme 2). We wish to report here this new method of P–C bond formation.

2. Results and discussion

The oxazolines **2** were easily prepared in high yields according to the classical condensation[12c] of the phenyl imino ether with the appropriate L-serine ester hydrochloride **1** using triethylamine as a base (Scheme 1). Treatment of the 2-phenyl oxazolines **2a-d** with neat diethyl phosphite at 140 °C led to a mixture of racemic phosphono benzamido esters **4** and **5** in 40–77% isolated yields (Scheme 2, Table 1).

Table 1. Formation of the phosphono α-benzamido esters **4** and **5**

Entry	Oxazoline	Phosphono α-benzamido ester				
	R	**2**	**4**	**5**	Ratio **4/5**	Yield (%)[a]
1	Me	**2a**	**4a**	**5a**	1.7:1	55
2	*i*Pr	**2b**	**4b**	**5b**	1.9:1	46
3	Allyl	**2c**	**4c**	**5c**	2.5:1	77
4	Bn	**2d**	**4d**	**5d**	2.3:1	50

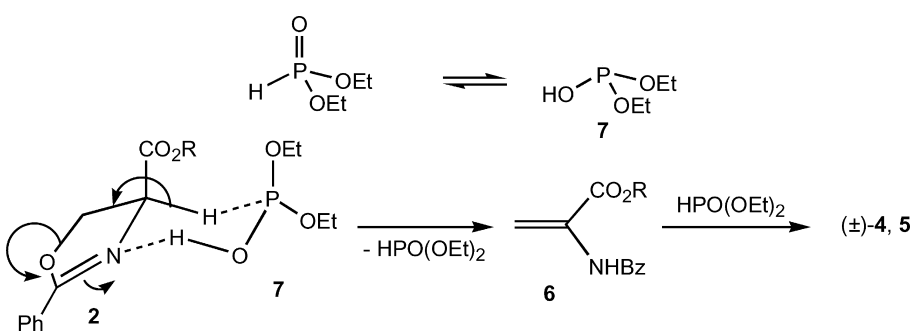
[a] Isolated yield.

The reaction is dependent on the nature of the oxazoline **2** used. Thus, with the methyl ester **2a**, the reaction afforded the phosphonates **4a** and **5a** in a 1.7:1 ratio and 55% yield (entry 1). In the case of the isopropyl, the allyl, and the benzyl derivatives **2b-d**, the corresponding regioisomers **4** and **5** were formed in ratios of 1.9:1 to 2.5:1 (entries 2–4). The best chemical yield was obtained with the allyl ester oxazoline **4c**, to afford the mixture of **4c** and **5c** in 77% yield (entry 3). Despite the low yields for the isolated α-regioisomers **5** (<22%), very few examples of such unusual amino acids bearing a chiral quaternary carbon center have been described until now.[16] In addition, since heating with diethyl phosphite did not produce any significant transesterification, various phosphono amino acid derivatives could be obtained easily with suitable protecting groups on the carboxylic acid function.

The formation of the regioisomers **4** and **5** is in good agreement with a tandem reaction mechanism involving first the rearrangement of the oxazoline **2** into the corresponding α-benzamido acrylate **6** and then addition of the diethyl phosphite to the carbon–carbon double bond (Scheme 3). In fact, formation of the unsaturated compound **6** was detected in the reaction medium, and we demonstrated that heating the α-benzamido acrylate **6a** (R=Me) with diethyl phosphite afforded the mixture of **4a** and **5a** in a 1.7:1 ratio (Scheme 3). It should be noted that in presence of a base, the diethyl phosphite reacts with α-amido acrylate to carry out the regioisomer **4**,[17] when no reaction with the oxazoline **2** occurs under these conditions. In addition, under prolonged heating, the phosphonate **4a** does not isomerize into its regioisomer **5a**. As a consequence of the mechanism involving the diethyl phosphite reagent, the oxazoline **2** affords the phosphonates **4a-d** and **5a-d** as racemic compounds.[18]

3. Conclusion

In conclusion, a new ring opening reaction of oxazolines derived from serine with diethyl phosphite leading to P–C bond formation has been found. This reaction, which proceeds under neutral conditions and without the use of



Scheme 3.

any halogenated precursor, affords a mixture of racemic α- and β-phosphono alanine derivatives in an approximate 1:2 ratio, with isolated yields up to 77%. The formation of the two regioisomers is explained by the rearrangement of the oxazoline into the corresponding α-benzamido acrylate, which then reacts with the diethyl phosphite. Since no significant transesterification occurs during the reaction, the amino acid derivatives obtained bear different protecting groups on the phosphonic and carboxylic acid functions, which is of particular interest for synthesis. Further studies are in progress in our group on the development of this strategy to the ω-phosphono amino acid derivatives.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere in dried glassware. Solvents were dried and freshly distilled under a nitrogen atmosphere. THF, diethyl ether, toluene and benzene, were distilled over sodium/benzophenone, CH_2Cl_2 over P_2O_5, hexane over calcium hydride, and methanol, ethanol and isopropanol over the sodium alcoholate. Commercially available diethyl phosphite, allyl and benzyl alcohols were distilled before use, whereas L-serine and L-serine benzyl ester hydrochloride **1d** were used without further purification. The L-serine ester hydrochlorides were prepared by the addition of acetyl chloride to a solution of L-serine in the corresponding alcohol for **1a**-**b**,[19] or by bubbling HCl gas for **1c**.[20] The phenyl imino ethyl ether hydrochloride[20] was prepared by bubbling HCl gas into a solution of benzonitrile with ethanol. The oxazolines **2a**-**d**[12c] were prepared by condensation of the phenyl imino ether, with the appropriate L-serine ester hydrochloride **1a**-**d**, using triethylamine as the base. The methyl 2-benzamido acrylate **6a**[21] was prepared from the methyl 2-benzamido-3-iodopropanoate,[12c] by reaction with triethylamine in CH_2Cl_2 at room temperature.

Thin-layer chromatography was performed on silica chromagel (60 F_{254}) and visualized by UV, iodine or permanganate treatment. Flash chromatography was performed on silica gel (60ACC, 6–35 μm and 35–70 μm). NMR spectra were obtained on Bruker DPX 250 and Avance 300–500 spectrometers, using TMS as the internal reference for ^1H and ^{13}C NMR and 85% phosphoric acid as the external reference for ^{31}P NMR. Melting points were measured on a Büchi 530 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Bruker Equinox 55 and a Vector 22. Mass spectral analyses were performed on NERMAG R10-10C, JEOL MS 700 and KRATOS Concept S, at the ENSCP (Paris), ENS (Paris) and Burgundy University (Dijon), respectively. Elemental analyses were measured with a precision >0.3% at the Microanalysis Laboratories of P. & M. Curie (Paris) and Burgundy Universities (Dijon).

4.2. Typical procedure for the reaction of oxazolines 2 with diethyl phosphite

Under an inert atmosphere, oxazoline **2** (3.46 mmol) and diethyl phosphite (17.31 mmol, 2.23 mL) were stirred at 140 °C for 48 h. After distillation of the excess diethyl phosphite, the residue was purified by chromatography on silica gel with a mixture of *c*-Hex/AcOEt (1:4) as eluent.

4.2.1. (±)-Methyl 2-benzamido-3-diethoxyphosphonopropanoate 4a. Colorless oil; 40% yield; R_f: 0.14 (*c*-Hex/AcOEt, 1:1); IR (cm^{-1}): 3300, 2984, 1743, 1654, 1236, 713; ^1H NMR (250 MHz, $CDCl_3$) δ 7.79 (3H, m, N*H*, *H* arom.), 7.48–7.30 (3H, m, *H* arom.), 5.03 (1H, dddd, *J*=5.8, 6.1, 7.3, 27.7 Hz, C*H*CH_2P), 4.07 (2H, q, *J*=7.1 Hz, P(OC*H*$_2$CH$_3$)$_2$), 4.02 (2H, q, *J*=7.1 Hz, P(OC*H*$_2$CH$_3$)$_2$), 3.69 (3H, s, C*H*$_3$), 2.46 (1H, ddd, *J*=6.3, 15.6, 17.4 Hz, C*H*HP), 2.40 (1H, ddd, *J*=5.4, 15.5, 17.1 Hz, CH*H*P), 1.20 (6H, t, *J*=7.1 Hz, P(OCH$_2$C*H*$_3$)$_2$); ^{13}C NMR (62.5 MHz $CDCl_3$) δ 170.8 (d, *J*=9.6 Hz, *C*O_2Me), 166.8 (*C*OPh), 133.2, 131.6, 128.3, 127.0 (*C* arom.), 62.1 (P(O*C*H$_2$CH$_3$)$_2$), 62.0 (P(O*C*H$_2$CH$_3$)$_2$), 52.5 (*C*H$_3$), 47.9 (d, *J*=6.4 Hz, *C*HCH$_2$P), 26.9 (d, *J*=141.9 Hz, *C*H$_2$P), 16.1 (d, *J*=2.5 Hz, P(OCH$_2$*C*H$_3$)$_2$), 16.0 (d, *J*=2.5 Hz, P(OCH$_2$*C*H$_3$)$_2$); ^{31}P NMR (101 MHz $CDCl_3$) δ +27.95. Anal. Calcd for $C_{15}H_{22}NO_6P$: C, 52.46; H, 6.46; N, 4.08. Found: C, 52.37; H, 6.26; N, 4.28.

4.2.2. (±)-Methyl 2-benzamido-2-diethoxyphosphonopropanoate 5a. Colorless oil; R_f: 0.22 (*c*-Hex/AcOEt, 1:1); ^1H NMR (250 MHz $CDCl_3$) δ 7.77 (2H, m, *H* arom.), 7.50–7.38 (3H, m, *H* arom.), 7.07 (1H, d, *J*=9.1 Hz, NH), 4.21 (4H, m, P(OC*H*$_2$CH$_3$)$_2$), 3.77 (3H, s, CO_2C*H*$_3$), 1.94 (3H, d, *J*=15.8 Hz, C*H*$_3$C), 1.31 (6H, m, P(OCH$_2$C*H*$_3$)$_2$); ^{13}C NMR (62.5 MHz $CDCl_3$) δ 169.3 (d, *J*=3.0 Hz, *C*O_2Me), 166.8 (d, *J*=11.1 Hz, *C*OPh), 133.5, 131.8, 128.5, 127.0 (*C* arom.), 64.3 (d, *J*=5.6 Hz, P(O*C*H$_2$CH$_3$)$_2$), 64.2 (d, *J*=6.7 Hz, P(O*C*H$_2$CH$_3$)$_2$), 60.1 (d, *J*=141.8 Hz, *C*CH$_3$), 53.1 (CO_2*C*H$_3$), 19.2 (d, *J*=3.3 Hz, C*C*H$_3$), 16.3 (P(OCH$_2$*C*H$_3$)$_2$), 16.2 (P(OCH$_2$*C*H$_3$)$_2$); ^{31}P NMR (101 MHz $CDCl_3$) δ +20.93.

4.2.3. (±)-Isopropyl 2-benzamido-3-diethoxyphosphonopropanoate 4b. White solid; 30% yield; mp <40 °C; R_f: 0.26 (*c*-Hex/AcOEt, 1:4); IR (KBr, cm^{-1}): 3308, 2982, 1734, 1652, 1489, 1240, 742; ^1H NMR (250 MHz $CDCl_3$) δ 7.84 (2H, m, *H* arom.), 7.67 (1H, d, *J*=7.2 Hz, N*H*), 7.47–7.37 (3H, m, *H* arom.), 5.05 (1H, spt, *J*=6.3 Hz, C*H*(CH$_3$)$_2$), 4.89 (1H, tdd, *J*=5.9, 7.3, 28.6 Hz, C*H*CH$_2$P), 4.05 (4H, m, P(OC*H*$_2$CH$_3$)$_2$), 2.44 (1H, ddd, *J*=6, 15.5, 17.5 Hz, C*H*HP), 2.32 (1H, ddd, *J*=5.7, 15.6, 17.3 Hz, CH*H*P), 1.24 (12H, m, CH(C*H*$_3$)$_2$, P(OCH$_2$C*H*$_3$)$_2$); ^{13}C NMR (62.5 MHz $CDCl_3$) δ 169.8 (d, *J*=8.8 Hz, CO_2*i*Pr), 166.8 (COPh), 133.5, 131.6, 128.4, 127.0 (C arom.), 69.5 (*C*H(CH$_3$)$_2$), 62.1 (P(O*C*H$_2$CH$_3$)$_2$), 48.2 (d, *J*=6.6 Hz, *C*HCH$_2$P), 27.0 (d, *J*=141.8 Hz, *C*H$_2$P), 21.6 (*C*H$_3$), 21.5 (*C*H$_3$), 16.2 (P(OCH$_2$*C*H$_3$)$_2$), 16.1 (P(OCH$_2$*C*H$_3$)$_2$); ^{31}P NMR (101 MHz $CDCl_3$) δ +28.13. Anal. Calcd for $C_{17}H_{26}NO_6P$: C, 54.98; H, 7.00; N, 3.77. Found: C, 54.95; H, 7.16; N 3.66; HRMS (DCI, CH_4) anal. calcd for $C_{17}H_{27}NO_6P$ ($M+H^+$): 372.1576. Found: 372.1573.

4.2.4. (±)-Isopropyl 2-benzamido-2-diethoxyphosphonopropanoate 5b. White solid; 16% yield; mp <40 °C; R_f: 0.3 (*c*-Hex /AcOEt, 1:4); IR (KBr, cm^{-1}): 3297, 2981, 1733, 1663, 1489, 1256, 715; ^1H NMR (250 MHz $CDCl_3$) δ 7.73 (2H, d, *J*=7 Hz, *H* arom.), 7.48–7.29 (3H, m, *H* arom.), 7.09 (1H, d, *J*=9.3 Hz, N*H*), 5.04 (1H, spt, *J*=6.2 Hz,

C*H*(CH_3)$_2$), 4.23 (2H, q, *J*=6.5 Hz, P(OC*H*$_2$CH$_3$)$_2$), 4.16 (2H, q, *J*=6.5 Hz, P(OC*H*$_2$CH$_3$)$_2$), 1.94 (3H, d, *J*=16.0 Hz, C*H*$_3$C), 1.31 (3H, t, *J*=6.5 Hz, P(OCH$_2$C*H*$_3$)$_2$), 1.30 (3H, t, *J*=6.5 Hz, P(OCH$_2$C*H*$_3$)$_2$), 1.23 (3H, d, *J*=6.2 Hz, CH(C*H*$_3$)$_2$), 1.21 (3H, d, *J*=6.2 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (62.5 MHz $CDCl_3$) δ 168.0 (d, *J*=2.8 Hz, CO_2*i*Pr), 166.7 (d, *J*=10.7 Hz, *C*OPh), 133.9, 131.5, 128.0, 126.8 (*C* arom.), 69.7 (*C*H(CH_3)$_2$), 64.2 (d, *J*=2 Hz, P(O*C*H$_2$CH$_3$)$_2$), 63.9 (d, *J*=2 Hz, P(O*C*H$_2$CH$_3$)$_2$), 60.5 (d, *J*=141.7 Hz, *C*CH_3), 21.4 (CH(*C*H$_3$)$_2$), 21.3 (CH(*C*H$_3$)$_2$), 19.1 (d, *J*=3.3 Hz, C*C*H$_3$), 16.2 (P(OCH$_2$*C*H$_3$)$_2$), 16.1 (P(OCH$_2$*C*H$_3$)$_2$); ^{31}P NMR (101 MHz $CDCl_3$) δ +21.24; HRMS (DCI, CH_4) anal. calcd for $C_{17}H_{27}NO_6P$ (M+H$^+$): 372.1576. Found: 372.1584.

4.2.5. (±)-Allyl 2-benzamido-3-diethoxyphosphonopropanoate 4c. Colorless oil; 55% yield; R_f: 0.16 (*c*-Hex/AcOEt, 1:1); IR (cm^{-1}): 3392, 3035, 2992, 1750, 1657, 1490, 713; ^{1}H NMR (250 MHz $CDCl_3$) δ 7.85 (2H, m, *H* arom.), 7.77 (1H, d, *J*=7.4 Hz, NH), 7.51–7.36 (3H, m, H arom.), 5.90 (1H, m, C*H*=CH$_2$), 5.32 (1H, ddd, *J*=1.5, 3.0, 17.2 Hz, CH=C*H*H), 5.14 (1H, ddd, *J*=1.2, 2.5, 10.5 Hz, CH=CH*H*), 5.03 (1H, dddd, *J*=5.7, 5.8, 7.3, 28.7 Hz, C*H*CH$_2$P), 4.65 (1H, ddd, *J*=1.3, 2.6, 5.7 Hz, C*H*$_2$–CH=CH$_2$), 4.08 (2H, q, *J*=7.1 Hz, P(O*C*H$_2$CH$_3$)$_2$), 4.04 (2H, q, *J*=7.1 Hz, P(OC*H*$_2$CH$_3$)$_2$), 2.52 (1H, ddd, *J*=6.1, 15.6, 17.4 Hz, C*H*HP), 2.40 (1H, ddd, *J*=5.5, 15.6, 17.1 Hz, CH*H*P), 1.25 (6H, t, *J*=7.1 Hz, P(OCH$_2$C*H*$_3$)$_2$); ^{13}C NMR (62.5 MHz $CDCl_3$) δ 170.0 (d, *J*=9.1 Hz, *C*O$_2$Allyl), 166.7 (*C*OPh), 133.3, 131.6 (*C* arom.), 131.3 (*C*H=CH$_2$), 128.3, 127.0 (*C* arom.), 118.5 (CH=*C*H$_2$), 66.1 (*C*H$_2$–C=CH$_2$), 62.1 (P(O*C*H$_2$CH$_3$)$_2$), 62.0 (P(OC*H*$_2$CH$_3$)$_2$), 48.0 (d, *J*=6.6 Hz, *C*HCH$_2$P), 27.0 (d, *J*=141.7 Hz, *C*H$_2$P), 16.2 (d, *J*=1.2 Hz, (P(OCH$_2$*C*H$_3$)$_2$)), 16.1 (d, *J*=1.2 Hz, P(OCH$_2$*C*H$_3$)$_2$); ^{31}P NMR (101 MHz $CDCl_3$) δ +27.84. Anal. Calcd for $C_{17}H_{24}NO_6P$: C, 55.28; H, 6.55; N, 3.79. Found: C, 55.13, H, 6.88, N, 3.52; HRMS (DCI, CH_4) anal. calcd for $C_{17}H_{25}NO_6P$ (M+H$^+$): 370.1419. Found: 370.1418.

4.2.6. (±)-Allyl 2-benzamido-2-diethoxyphosphonopropanoate 5c. White solid; 22% yield; mp <40 °C; R_f: 0.22 (*c*-Hex/AcOEt, 1:1); IR (KBr, cm^{-1}): 3296, 2979, 1738, 1662, 1490, 1240; ^{1}H NMR (250 MHz $CDCl_3$) δ 7.75 (2H, m, *H* arom.), 7.48–7.37 (3H, m, *H* arom.), 7.08 (1H, d, *J*=9.7 Hz, N*H*), 5.90 (1H, m, C*H*=CH$_2$), 5.32 (1H, ddd, *J*=1.5, 3.0, 17.2 Hz, CH=C*H*H), 5.14 (1H, ddd, *J*=1.2, 2.6, 10.5 Hz, CH=CH*H*), 5.03 (1H, ddd, *J*=1.3, 2.6, 5.7 Hz, C*H*$_2$–CH=CH$_2$), 4.65 (1H, dd, *J*=1.1, 5.6 Hz, C*H*$_2$–CH=CH$_2$), 4.18 (4H, m, P(OC*H*$_2$CH$_3$)$_2$), 1.94 (3H, d, *J*=15.8 Hz, C*H*$_3$C), 1.31 (6H, m, P(OCH$_2$C*H*$_3$)$_2$); ^{13}C NMR (62.5 MHz $CDCl_3$) δ 168.4 (d, *J*=3 Hz, *C*O$_2$Allyl), 166.7 (d, *J*=11.4 Hz, *C*OPh), 133.7, 131.7 (*C* arom.), 131.5 (*C*H=CH$_2$), 128.4, 127.3 (*C* arom.), 118.3 (CH=*C*H$_2$), 66.6 (*C*H$_2$–C=CH$_2$), 64.2 (d, *J*=7.5 Hz, P(O*C*H$_2$CH$_3$)$_2$), 64.1 (d, *J*=7.5 Hz, P(O*C*H$_2$CH$_3$)$_2$), 60.1 (d, *J*=141.1 Hz, *C*CH_3), 19.1 (d, *J*=3.5 Hz, *C*CH_3), 16.3 (d, *J*=1.8 Hz, P(OCH$_2$*C*H$_3$)$_2$), 16.2 (d, *J*=1.8 Hz, P(OCH$_2$*C*H$_3$)$_2$); ^{31}P NMR (101 MHz $CDCl_3$) δ +20.93. Anal. Calcd for $C_{17}H_{24}NO_6P$: C, 55.28; H, 6.55, N, 3.79. Found: C, 55.49; H 6.75; N, 3.56; HRMS (DCI, CH_4) anal. calcd for $C_{17}H_{25}NO_6P$ (M+H$^+$): 370.1419. Found: 370.1417.

4.2.7. (±)-Benzyl 2-benzamido-3-diethoxyphosphonopropanoate 4d. Colorless oil; 35% yield; R_f: 0.4 (*c*-Hex/AcOEt, 1:2); IR (cm^{-1}): 3299, 2926, 1733, 1652, 1506, 713; ^{1}H NMR (250 MHz $CDCl_3$) δ 7.80 (2H, d, *J*=8.3 Hz, *H* arom.), 7.71 (1H, d, *J*=7.8 Hz, N*H*), 7.51–7.34 (8H, m, *H* arom.), 5.20 (2H, s, C*H*$_2$Ph), 5.03 (1H, dddd, *J*=5.7, 5.8, 7.2, 28.7 Hz, C*H*CH$_2$P), 4.07 (4H, m, P(OC*H*$_2$CH$_3$)$_2$), 2.52 (1H, ddd, *J*=6.1, 15.6, 17.4 Hz, C*H*HP), 2.40 (1H, ddd, *J*=5.5, 15.6, 17.1 Hz, CH*H*P), 1.25 (6H, m, P(OCH$_2$C*H*$_3$)$_2$); ^{13}C NMR (62.5 MHz $CDCl_3$) δ 170.3 (d, *J*=8.9 Hz, *C*O$_2$Bn), 166.9 (*C*OPh), 135.1, 133.3, 131.7, 128.4, 128.3, 128.1 (*C* arom.), 67.4 (*C*H$_2$Ph), 62.2 (P(O*C*H$_2$CH$_3$)$_2$), 62.1 (P(O*C*H$_2$CH$_3$)$_2$), 48.1 (d, *J*=6.7 Hz, *C*HCH$_2$P), 27.0 (d, *J*=141.9 Hz, *C*H$_2$P), 16.25 (P(OCH$_2$*C*H$_3$)$_2$), 16.20 (P(OCH$_2$*C*H$_3$)$_2$); ^{31}P NMR (101 MHz $CDCl_3$) δ +28.00. Anal. Calcd for $C_{21}H_{26}NO_6P$: C, 60.14; H, 6.25; N, 3.34. Found: C, 60.36, N, 6.63, N, 3.12; HRMS (DCI, CH_4) anal. calcd for $C_{21}H_{27}NO_6P$ (M+H$^+$): 420.1576. Found: 420.1574.

4.2.8. (±)-Benzyl 2-*N*-benzamido-2-diethoxyphosphonopropanoate 5d. White solid; 15% yield; mp <40 °C; R_f: 0.3 (*c*-Hex/AcOEt, 1:4); ^{1}H NMR (250 MHz $CDCl_3$) δ 7.68 (2H, m, *H* arom.), 7.42–7.14 (4H, m, *H* arom., N*H*), 5.13 (2H, s, C*H*$_2$Ph), 4.04 (4H, m, P(OC*H*$_2$CH$_3$)$_2$), 1.86 (3H, d, *J*=15.8 Hz, C*H*$_3$C), 1.16 (6H, m, P(OCH$_2$C*H*$_3$)$_2$); ^{13}C NMR (62.5 MHz $CDCl_3$) δ 168.5 (d, *J*=2.5 Hz, *C*O$_2$Bn), 166.8 (d, *J*=10.9 Hz, *C*OPh), 135.1, 133.5, 131.6, 131.4, 128.4, 128.3, 128.1, 128.0, 127.2, 126.9 (*C* arom.), 67.6 (*C*H$_2$Ph), 64.0 (d, *J*=6.6 Hz, P(O*C*H$_2$CH$_3$)$_2$), 63.9 (d, *J*=6.6 Hz, P(O*C*H$_2$CH$_3$)$_2$), 60.5 (d, *J*=142.2 Hz, *C*CH_3), 19.1 (d, *J*=3.3 Hz, C*C*H$_3$), 16.1 (d, *J*=5.5 Hz, P(OCH$_2$*C*H$_3$)$_2$), 16.0 (d, *J*=5.5 Hz, P(OCH$_2$*C*H$_3$)$_2$); ^{31}P NMR (101 MHz $CDCl_3$) δ +20.85; HRMS (DCI, CH_4) anal. calcd for $C_{21}H_{27}NO_6P$ (M+H$^+$): 420.1576. Found: 420.1570.

4.3. Reaction of methyl 2-benzamidoacrylate 6a with diethylphosphite

Under an inert atmosphere, methyl benzamidoacrylate **6a** (1.7 mmol) and diethyl phosphite (8.5 mmol) were stirred at 140 °C for 20 h. After distillation of the excess diethyl phosphite, the residue was chromatographed on silica gel with *c*-Hex/AcOEt 1:1 as eluent, giving a mixture of the α- and β-phosphonates **4a** and **5a** in a 1.7:1 ratio and 46% yield.

Acknowledgements

We thank the Ministry of research, the CNRS and the Sté SYNTHELOR for financial support, N. Morin for obtaining HRMS and Dr. A. Meddour (Université Paris Sud-Orsay) for attempting enantiomeric separation using chiral liquid crystal media.

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Tetrahedron 60 (2004) 3599–3603
Tetrahedron

Synthesis of novel thiol surrogate of Taxol®: 2′-deoxy-2′-mercaptopaclitaxel

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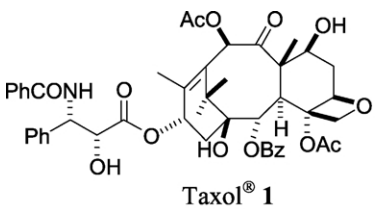
Received 12 February 2004; revised 24 February 2004; accepted 25 February 2004

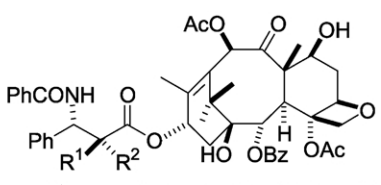
Abstract—Paclitaxel analogues with a thiol group in place of the hydroxyl group on the C-13 side chain constitute an interesting avenue of research for the study of new taxoid compounds. A synthetic route for the preparation of the exact thiol surrogate product of Taxol® by coupling (4*S*, 5*S*)-2,4-diphenyloxazoline-5-carboxylic acid with 7-triethylsilyl baccatin III, followed by ring-opening of the oxazoline intermediate with thiolacetic acid is described.

1. Introduction

The complex natural paclitaxel (Taxol®) **1**, originally isolated from *Taxus brevifolia*, is a powerful therapeutic drug for cancer chemotherapy.[1] Paclitaxel has excellent clinical activity against ovarian and breast cancers, and shows encouraging results for other types of cancers.[2] In contrast to other common anticancer drugs, paclitaxel elicits its biological activity through a unique mechanism, i.e. it inhibits cell replication in the mitotic phase of the cell cycle by promoting tubulin assembly and stabilizing the microtubules formed, which induces cell death.[3] Extensive studies on the structure activity relationship of paclitaxel have been performed for the purpose of elucidating its unique mechanism and designing better analogues, which exert even more effective bioactivity. Although the mechanism of action on the molecular level is still uncertain, it is already well known that the free hydroxyl group at the 2′ position on the C-13 side chain is crucial for microtubule binding[4] and may act as a hydrogen bond donor.[5] In light of this hypothesis, the introduction of thiol functionality, which is more acidic than the hydroxyl group, onto the C-13 side chain **2a** or **2b**, would be of great interest for obtaining information about the taxoid binding site on the microtubules and for the development of new compounds having more desirable properties than paclitaxel. In our earlier report,[6] we demonstrated the first synthetic way of introducing a free thiol functional group onto the C-13 side chain instead of the hydroxyl group, via an oxazoline ring opening procedure with thiolacetic acid. However, only the 2′-epi-mercaptopaclitaxel **2b** had been obtained since the inversion of the configuration at the C-5 position (5*R* to 2′*S*) of the *trans*-oxazoline ring during the ring-opening process. Herein, we report the synthesis of the exact thiol surrogate product of Taxol® by coupling (4*S*, 5*S*)-2,4-diphenyloxazoline-5-carboxylic acid with 7-triethylsilyl baccatin III, followed by ring-opening of the oxazoline intermediate with thiolacetic acid.



Taxol® **1**



2'-deoxy-2'-mercaptotaxol $R_1 = H, R_2 = SH$ **2a**
2'-deoxy-2'-epi-mercaptotaxol $R_1 = SH, R_2 = H$ **2b**

Keywords: Taxol; Mercaptopaclitaxel; Oxazoline.
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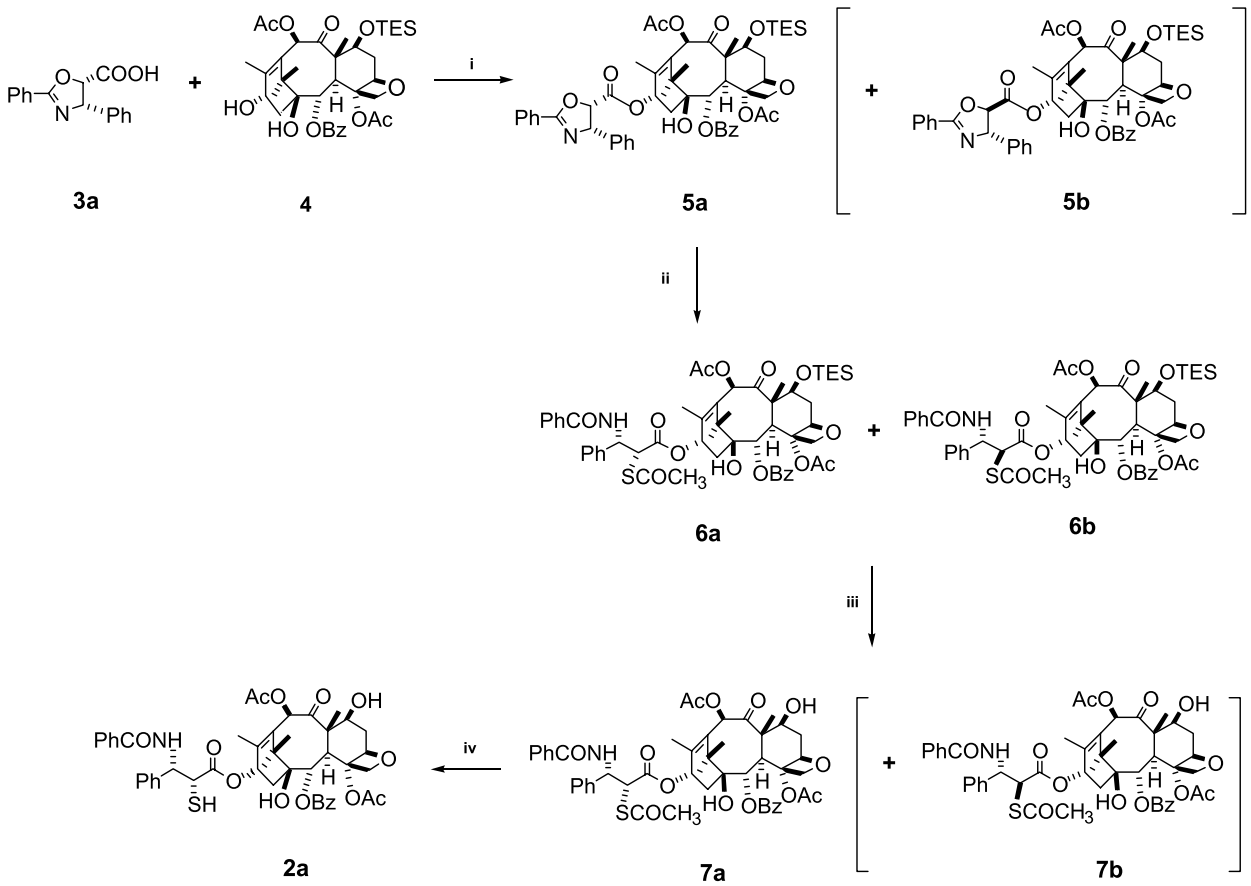
doi:10.1016/j.tet.2004.02.047



Scheme 1. (i) DCC, 4-Pyrrolidinopyridine, toluene, rt, 2 h, 42% (**5a**) and 50% (**5b**). (ii) Thiolacetic acid, dioxane, 70 °C, 12 h, 80 °C, 12 h, 95 °C, 12 h, 71%. (iii) HF/pyridine (70:30), THF, rt, 5 h, 82%. (iv) LiOH, MeOH–H_2O, rt, 2 h, 65%.

2. Results and discussion

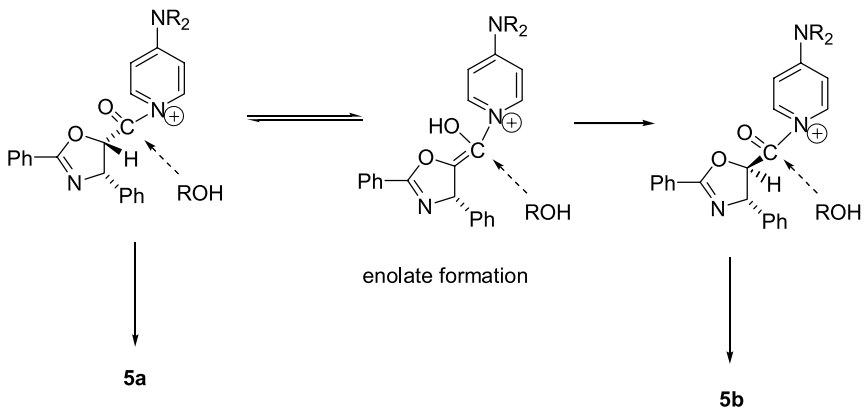
The (4*S*, 5*S*)-2,4-diphenyloxazoline-5-carboxylic acid **3a** was prepared by the literature method.[7] Although the general procedure applied to the synthesis of **2a** involved a similar methodology to that of its counterpart **2b**, as shown in Scheme 1, epimerization occurred during the coupling and ring-opening process of the *cis* structure, which has never happened in the *trans* case,[6] nor in those cases where the simple oxazoline derivatives (both *cis* and *trans*) were involved.[7] Therefore, more attention should be paid to the control of the reaction conditions and the separation procedure.

Thus, when the enantiomerically pure **3a** was coupled to 7-TES-baccatin III **4**,[8] less than half (42% yield) of the *cis*-oxazoline configuration **5a** remained, and nearly half (50% yield) underwent configuration inversion at C5′ leading to the formation of **5b**. Both of the two products were fully characterized. While the ^{1}H NMR spectrum of **5b** was exactly the same as that of the authentic sample, the peaks at 5.78 and 5.41 ppm with a coupling constant of 10.6 Hz corresponding to **5a** were consistent with the corresponding *cis*-oxazoline feature.[9]

This important difference between the coupling products is thought to arise from the repulsions that the *cis* and *trans* structures received from the baccatin skeleton when coupling occurred. For the *cis*-oxazoline carboxylic acid **3a**, the C4 phenyl group lies on the same side as the carboxylic acid group, which directly faces the baccatin skeleton as the C5 carbonyl approaches the C-13 hydroxyl group, which is hidden in the concavity of the baccatin backbone.[10] In this case, the phenyl group has to overcome the steric hindrance and, to some extent, squeeze into a restricted space, which leads to a strong repulsion force being created, which assists portion of the activated reaction species to bring about C5 configuration inversion to afford the formation of **5b**. From the chemical point of view, we believed that the formation of an enol structure (Scheme 2) might be the transitional process for these over-activated reactive species. After the back-migration of the proton to form a more stable configuration (*trans*), the coupling with the C13 hydroxyl of the baccatin afforded **5b**. On the other hand, the C4 phenyl of the *trans* oxazoline acid **3b** likely encounters little counteraction from the baccatin motif, since the phenyl group is facing the opposite direction to the C-5 carboxylic group and is stretched out and away from the concavity of the baccatin backbone during the course of the coupling reaction.

Furthermore, the conformation adopted by the 4′-phenyl group within the *cis* derivative **5a** led to a different, i.e. higher energy ground state of this coupling product. This instability is demonstrated once again in the subsequent ring opening reaction with thiolacetic acid.

The ring-opening product was always a mixture of **6a** and



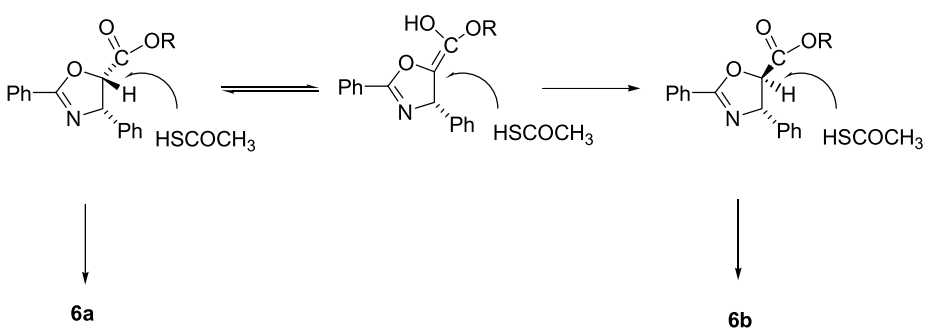
Scheme 2. The possible enol formation during the coupling reaction.

6b. When the reaction temperature was set to 95 °C from the outset, serious epimerization occurred leading to a 1/2.4 ratio of **6a/6b**. As different carefully controlled temperatures were applied, the ratio varied, and the best result was achieved when a stepwise heating model of 70, 80 and finally 95 °C was used and the **6a/6b** ratio in this case was 35:1 (all confirmed by ^{1}H NMR). In our early work with simple alcohol derivatives such as *para*-methoxybenzyl alcohol (PMB), no epimerization occurred, even if the reaction mixture was heated directly to 95 °C and held there for 1.5 days. Therefore, the steric repulsion within the **5a** structure must again account for the various degrees of inversion observed. The pressure acting in the outward direction on the 4′-phenyl group (vide infra) caused the *cis* configuration to be unstable, namely to have a relatively higher energy ground state compared to the simple alcohol derivatives as well as its isomer **5b**. Therefore, the total energy barrier including both energy from ground state to the normal active transition state and from the latter to the crest, which must be surpassed for configuration inversion from the unstable *cis* to the stable *trans* configuration, is relatively lower and easier to reach for activated molecules. Here, the enolation at C5 occurred again (Scheme 3). Once a high reaction temperature is applied, a large portion of the activated molecules will possess enough energy to overcome the above-mentioned lowered energy barrier, thus enabling them to directly follow the inversion pathway and to afford the stable product **5b**. In this case, the key factor is to control the temperature during the reaction procedure, in order to restrict the activated species to within the proper energetic state range, which theoretically lies between the crest and the normal energy barrier.

^{1}H NMR revealed the *cis* structure of **6a** with the amide peak at 6.88 ppm. Fortunately, the diastereoisomeric mixture could easily be separated when the 7-triethylsilyl group were removed by HF/py (70:30), to obtain the pure **7a** and a small amount of **7b**. The basic deprotection approach of the *S*-acetyl group was utilized again to afford the final **2a**, which, similar to its diastereoisomer **7b**, was always formed accompanied by a small amount of **2b**. However, the basicity of potassium bicarbonate was insufficient to fulfil this task, as it did in the case of **7b**. Lithium hydroxide proved to be suitable and an equal number of equivalent of base was used.

With the aid of 2D NMR experiments, the complete assignments of **7a**, the precursor of **2a**, were able to be made. The peak at 6.82 ppm corresponding to the amide group, along with the well-separated peaks as 6.22 ppm (H10) and 6.03 ppm (H3′), 4.36 ppm (H7) and 4.26 ppm (H20α), confirmed the *syn* C-13 side chain, which was distinct from the data of the *anti* **7b**. The two cross peaks due to the vicinal coupling of $H_2$14 with H13 (t, 6.04 ppm) proved that the two protons at around 1.85 ppm must belong to H6β and one of the H14, respectively, which was confirmed by the cross peak from the geminal coupling between the two protons of H6.

The cytotoxicity of the two mercapto taxoids was evaluated using the sulphorhodamine B assay (SRB), unfortunately, both compounds were essentially inactive. We assume that this unexpected result may have come from the formation of the disulfide in situ during the routine assay process when DMSO was used as the solvent. It is well known that



Scheme 3. The possible enol formation during the ring opening reaction.

dimethyl sulfoxide (DMSO) is a good oxidant for the formation of disulfide from thiol functionality at ambient temperature and under a wide range of pH values.[11] Therefore, considering the anticipated role of the free thiol in the cytotoxicity of paclitaxel, the result mentioned above was understandable. The addition of dithiothreitol (DDT) revealed no effect, and further attempts to overcome this problem are currently in progress.

3. Conclusions

In conclusion, we described the synthesis of the exact thiol surrogate product of Taxol® by coupling (4*S*, 5*S*)-2,4-diphenyloxazoline-5-carboxylic acid with 7-triethylsilyl baccatin III, followed by ring-opening of the oxazoline intermediate with thiolacetic acid, which allows the introduction of the sulfur-containing group onto the side chain. Since we have shown the ring-opening reactions of the oxazoline intermediates,[9] our approach can be used for the syntheses of taxol derivatives bearing various C-13 side chains.

4. Experimental

4.1. General methods

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. (4*S*, 5*S*)-2,4-Diphenyloxazoline-5-carboxylic acid **3a** was synthesized by the literature procedure.[7] 7-Triethylsilylbaccatin III **4** was prepared by the literature method from 10-deacetylbaccatin III.[8] THF, toluene and dioxane were freshly distilled over sodium-benzophenone ketyl. Solvents for re-crystallization were purified by standard methods before use. Flash chromatography was carried out on silica gel 60 (230–400 mesh ASTM; Merck). Thin layer chromatography (TLC) was carried out using Merck 60 F_{254} plates with a 0.25 mm thickness. Preparative TLC was performed with Merck 60 F_{254} plates with a 1 mm thickness.

Melting points were measured with Büchi 530 melting point apparatus, and are uncorrected. ^{1}H NMR spectra were recorded using JEOL JNM-LA 300 or Bruker Avance 500 spectrometers with TMS as internal standard. Chemical shifts were expressed in ppm and coupling constants (*J*) in Hz. ^{13}C NMR were recorded using JEOL JNM-LA 300, Bruker Avance 300 or 500 spectrometers. Infrared spectra were recorded on JASCO FTIR-200 Spectrometer. Mass spectra were obtained using JEOL JMS AX505WA or JMS-700 Mstation spectrometers. Elemental analyses were performed using EA 1110 (CHNS-O) (Thermo Finnigan, Italy). Optical rotations were measured using JASCO 3100 polarimeter.

4.1.1. Compound 5a. A solution of DCC (620 mg, 3.00 mmol) in dry toluene (20 mL) was added to a suspension of 7-TES-baccatin III **4** (500 mg, 0.71 mmol), *cis*-carboxylic acid **3a** (792 mg, 2.96 mmol) and catalytic amount of 4-pyrrolidinopyridine in 30 mL of dry toluene at 0 °C under N_2 while stirring. After 10 min at 0 °C, the reaction mixture was stirred for another 2 h at room temperature. (The reaction was monitored by TLC, EtOAc/hexane, 1:2) The reaction mixture was then passed through a short silica gel plug (~5 g) and further eluted with 100 mL of EtOAc. The combined eluent was concentrated to dry under reduced pressure. A 1:1 mixture of EtOAc and hexane (40 mL) was added to the residue and the suspension was filtered through a cotton plug. The filtration was concentrated again. Careful purification of the residue by flash chromatography twice (EtOAc/hexane, 1:3) afforded oxazoline ring inversion product **5b** (which was proved by ^{1}H NMR) as a white solid (337 mg, 0.354 mmol, 50%) and the desired product **5a** as a white solid (283 mg, 0.30 mmol, 42%). An analytical sample of **5a** was obtained by re-crystallization (distilled EtOAc/hexane) as white needles: mp 210–211 °C; $[\alpha]_D^{15}=-71.7°$ (c=0.547, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.55 (m, 6H), 0.91 (t, J=7.9 Hz, 9H), 1.01 (s, 3H), 1.15 (s, 3H), 1.48 (s, 3H), 1.65 (s, 3H), 1.83–1.83 (m, 1H), 2.01–2.04 (m, 2H), 2.16 (s, 3H), 2.28 (s, 3H), 2.47–2.57 (m, 1H), 3.65 (d, J=7.1 Hz, 1H), 4.11 (d, J=8.4 Hz, 1H), 4.26 (d, J=8.2 Hz, 1H), 4.50 (dd, J=6.8, 10.6 Hz, 1H), 4.91 (d, J=8.2 Hz, 1H), 5.41 (d, J=10.6 Hz, 1H), 5.53–5.56 (m, 1H), 5.60 (d, J=7.0 Hz, 1H), 5.78 (d, J=10.4 Hz, 1H), 6.32 (s, 1H), 7.21–7.65 (m, 11H), 8.04–8.12 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.17, 6.66, 9.88, 13.72, 20.72, 20.81, 22.02, 22.39, 26.27, 27.62, 35.78, 37.07, 42.87, 46.62, 58.26, 68.34, 71.86, 72.09, 73.61, 74.62, 74.83, 76.29, 78.60, 80.92, 81.18, 83.97, 126.40, 128.24, 128.65, 129.17, 129.91, 132.08, 133.22, 133.54, 136.18, 139.54, 164.31, 166.71, 167.93, 168.98, 169.28, 201.59; HRMS (FAB) m/z=950.4147 $[M+H]^+$, calcd for $C_{53}H_{64}NO_{13}Si$=950.4129. Anal. calcd for $C_{53}H_{63}NO_{13}Si$: C, 67.00; H, 6.68; N, 1.47; found: C, 67.08; H, 6.74; N, 1.50.

4.1.2. 2′-Deoxy-2′-thioacetoxy-7-triethylsilylpaclitaxel 6a. Compound **5a** (220 mg, 0.231 mmol), thiolacetic acid (1.5 mL) and dioxane (4.5 mL) were added in an 8 mL pressure vial at room temperature. The vial was then closed tightly with a Teflon disk lid, and was heated stepwise at 70 °C for 12 h, 80 °C for 12 h and then 95 °C for 12 h. After concentration under reduced pressure, the sticky yellowish oil was purified twice by flash chromatography (EtOAc/hexane, 1:3) to get **6a** as a white solid (168 mg, 0.164 mmol, 71%), which proved to be a mixture with **6b** by ^{1}H NMR. An analytical sample of **6a** was obtained by re-crystallization (distilled EtOAc/hexane) as white flakes: mp 160–162 °C; $[\alpha]_D^{28}=-3.84°$ (c=0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.52–0.59 (m, 6H), 0.90 (t, J=7.8 Hz, 9H), 1.11 (s, 3H), 1.17 (s, 3H), 1.65 (s, 3H), 1.69–1.74 (m, 1H), 1.82–1.93 (m, 2H), 1.86 (s, 3H), 2.16 (s, 3H), 2.30 (s, 3H), 2.45 (s, 3H), 2.45–2.55 (m, 1H), 3.70 (d, J=7.0 Hz, 1H), 4.09 (m, 1H), 4.25 (d, J=8.4 Hz, 1H), 4.38–4.43 (dd, J=10.6, 6.8 Hz, 1H), 4.73 (d, J=12.4 Hz, 1H), 4.90 (d, J=8.1 Hz, 1H), 5.59 (d, J=7.1 Hz, 1H), 5.74 (m, 1H), 6.02 (m, 1H), 6.37 (s, 1H), 6.88 (d, J=9.0 Hz, 1H), 7.22–7.74 (m, 13H), 8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.23, 6.71, 10.01, 14.02, 20.81, 21.06, 22.57, 26.44, 30.49, 34.82, 37.14, 43.12, 46.63, 51.15, 55.33, 58.36, 71.16, 72.10, 74.81, 78.83, 80.86, 84.15, 126.14, 126.91, 127.09, 127.28, 128.54, 128.68, 128.89, 129.28, 130.06, 131.87, 133.56, 133.74, 138.78, 140.02, 166.42, 166.92, 168.74, 169.14, 169.76, 196.17, 201.61; HRMS (FAB) m/z=1048.3943

$[M+Na]^+$, calcd for $C_{55}H_{67}NO_{14}SSi\,Na$=1048.3931. Anal. calcd for $C_{55}H_{67}NO_{14}SSi$: C, 64.37; H, 6.58; N, 1.36; S, 3.12; found: C, 64.22; H, 6.63; N, 1.34; S, 3.12.

4.1.3. 2′-Deoxy-2′-thioacetoxypaclitaxel 7a. To a vigorous stirred solution of compound **6a** accompanied by **6b** (140 mg, 0.136 mmol) in dry THF (10 mL) was added 1.4 mL of hydrogen fluoride–pyridine (70:30) at 0 °C under N_2. After 10 min stirring at 0 °C, the reaction mixture was then stirred for another 5 h at room temperature. Water (10 mL) was added to quench the reaction and the mixture was extracted with ethyl acetate (4×20 mL). The combined organic layer was washed subsequently with dilute aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude product by flash chromatography (EtOAc/hexane, 1:1) afforded small amount of **7b** and the corresponding product **7a** as a white solid (100 mg, 0.11 mmol, 82%). An analytical sample was obtained by re-crystallization (distilled EtOAc/hexane) as white crystalline: mp 181–183 °C; $[\alpha]_D^{13}=-10.7°$ (c=0.77, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (s, 3H), 1.17 (s, 3H), 1.58 (s, 1H), 1.59 (s, 1H), 1.64 (s, 3H), 1.70–1.76 (m, 3H), 1.76 (s, 1H), 1.83–1.94 (m, 2H), 2.22 (s, 3H), 2.31 (s, 3H), 2.44 (s, 3H), 2.50–2.56 (m, 1H), 3.70 (d, J=7.0 Hz, 1H), 4.12 (d, J=8.5 Hz, 1H), 4.26 (d, J=8.4 Hz, 1H), 4.36–4.40 (m, 1H), 4.75 (d, J=10.7 Hz, 1H), 4.93 (m, 1H), 5.58 (d, J=7.1 Hz, 1H), 5.73 (dd, J=9.0, 10.5 Hz, 1H), 6.03 (dd, J=7.9, 9.0 Hz, 1H), 6.21 (s, 1H), 6.82 (d, J=8.8 Hz, 1H), 7.23 (m, 2H), 7.36 (t, J=7.6 Hz, 2H), 7.42–7.46 (m, 4H), 7.50–7.55 (m, 2H), 7.65 (t, J=7.5 Hz, 1H), 7.72 (d, J=7.2 Hz, 2H), 8.03 (d, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.92, 15.17, 21.22, 22.22, 22.97, 30.91, 35.47, 35.88, 43.44, 45.93, 51.59, 55.61, 58.89, 71.51, 72.52, 75.36, 75.83, 76.73, 79.56, 81.29, 84.81, 127.33, 127.66, 129.02, 129.14, 129.36, 129.62, 130.49, 132.35, 133.25, 133.95, 134.24, 139.16, 142.79, 166.88, 167.32, 169.19, 170.28, 171.67, 196.38, 204.03; HRMS (FAB) m/z=934.3083 $[M+Na]^+$, calcd for $C_{49}H_{53}NO_{14}SNa$=934.3070. Anal. calcd for $C_{49}H_{53}NO_{14}S$: C, 64.53; H, 5.86; N, 1.54; S, 3.52; found: C, 64.51; H, 5.99; N, 1.49; S, 3.45.

4.1.4. 2′-Deoxy-2′-mercaptopaclitaxel 2a. To a solution of **7a** (40 mg, 0.044 mmol) in MeOH (2 mL, degassed) was added dropwise a solution of $LiOH{\cdot}H_2O$ (1.85 mg, 0.044 mmol) in H_2O (0.2 mL, degassed) during 0.5 h at room temperature under N_2 with vigorous stirring. After another 30 min, the reaction mixture was poured into a mixture of $CHCl_3$–H_2O (15:15 mL), and was acidified with two or three drops of 1 N HCl to pH 1–2. The water layer was extracted with $CHCl_3$ (3×10 mL), and the combined organic layer was washed with water (15 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC (2% MeOH/$CHCl_3$) in dark place to afford final product **2a** as a white solid (25 mg, 0.029 mmol, 65%); mp 214–216 °C (dec.); $[\alpha]_D^{15}=-17.6°$ (c=1.00, MeOH); IR (KBr) 3463, 2984, 2937, 2552, 1721, 1642, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11 (s, 3H), 1.18 (s, 3H), 1.65 (s, 3H), 1.74 (s, 1H), 1.85 (m, 1H), 1.88 (s, 3H), 2.03–2.09 (m, 3H), 2.20 (s, 3H), 2.22 (s, 3H), 2.50–2.55 (m, 2H), 3.74 (d, J=7.0 Hz, 1H), 4.05–4.11 (m, 1H), 4.13 (d, J=8.4 Hz, 1H), 4.24 (d, J=8.4 Hz, 1H), 4.39 (m, 1H), 4.91 (d, J=8.0 Hz, 1H), 5.62 (d, J=7.1 Hz, 1H), 5.66 (t, J=7.8 Hz, 1H), 6.13 (t, J=8.7 Hz, 1H), 6.26 (s, 1H), 7.05 (d, J=8.0 Hz, 1H), 7.31–7.63 (m, 11H), 7.79 (d, J=7.7 Hz, 2H), 8.02 (d, J=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.95, 15.32, 21.23, 22.27, 22.95, 27.15, 35.90, 43.50, 46.00, 47.48, 56.20, 58.91, 71.80, 72.54, 75.37, 75.89, 79.59, 81.39, 84.76, 127.45, 127.51, 128.86, 129.06, 129.14, 129.38, 129.51, 130.50, 132.36, 133.24, 134.17, 134.38, 138.99, 142.91, 167.32, 167.62, 170.26, 171.36, 171.65, 204.06; HRMS (FAB) m/z=892.2986 $[M+Na]^+$, calcd for $C_{47}H_{51}NO_{13}SNa$=892.2965.

Acknowledgements

We thank Hanmi Pharmaceutical Co., Ltd for the generous donation of 10-deacetylbaccatin III. This work was supported by Korea Science and Engineering Foundation (R14-2003-014-01001-0) and the Brain Korea 21 Program.

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Tetrahedron 60 (2004) 3605–3610
Tetrahedron

An electrochemical interpretation of the mechanism of the chemical decarboxylation of 6-carboxyperhydropyrimidin-4-ones

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Received 26 January 2004; revised 25 February 2004; accepted 25 February 2004

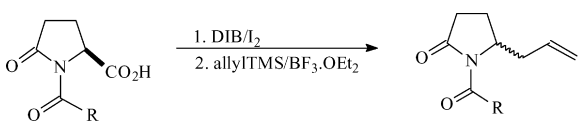
Abstract—The present work analyzes the anodic oxidation of the tetrabutylammonium salt of 1-benzoyl-2(*S*)-*tert*-butyl-6(*S*)-carboxyperhydropyrimidin-4-one, which is a useful starting material in the synthesis of enantiopure α-substituted β-amino acids. It was demonstrated that in CH_2Cl_2 solvent, the anodic oxidation reaction results in fast and complete decarboxylation, followed by proton elimination thereby leading to the same product of chemical (diacetoxyiodobenzene) oxidative decarboxylation. The electrochemical mechanism involves two electron transfer steps, but appears as a monoelectronic process owing to the release of one proton from the key acyliminium carbocation intermediate. The relative stability of this intermediate and the suppression of any solvolysis reaction in CH_2Cl_2 allow for the detection of the acyliminium intermediate by means of cyclic voltammetry experiments. By contrast, in the presence of a nucleophilic solvent such as acetonitrile, the acyliminium intermediate is trapped in a typical Ritter reaction.

1. Introduction

Diacetoxyiodobenzene (DIB) is now a well recognized reagent with numerous applications in synthetic organic chemistry.[1] Particularly useful is the employment of diacetoxyiodobenzene/iodine as an effective mixture of reagents in the oxidative decarboxylation of carboxylic acids (Eq. 1).[2]

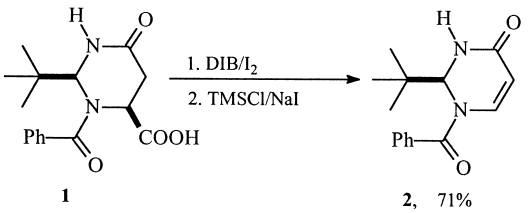
$$\text{R-CO}_2\text{H} \xrightarrow{\text{DIB/I}} \text{R-CO}_2\text{I} \xrightarrow{-\text{CO}_2} \text{R-I} \quad (1)$$

In this context, Suárez and co-workers have recently demonstrated that DIB-mediated radical decarboxylation–oxidation of α-amino acids can be successfully complemented by nucleophilic trapping of the generated iminium ion (Eq. 2).[3]



(2)

By contrast, when 1-benzoyl-2(*S*)-*tert*-butyl-6(*S*)-carboxyperhydropyrimidin-4-one, **1**, a useful intermediate for the enantioselective synthesis of α-substituted β-amino acids,[4,5] was treated with the DIB/I_2/TMSCl/NaI reagent mixture, heterocyclic enone **2** was formed in good yield (Eq. 3).[6,7]



(3)

The formation of enone **2** was accounted for in terms of a three-step radical decarboxylation–oxidation–β-elimination sequence, as outlined in Scheme 1.[6]

The proposal advanced in Scheme 1 is based on reasonable mechanistic considerations,[2,3] and it is supported by recent reports concerning the anodic oxidation of benzylic and aliphatic carboxylic acid salts,[8–11] indicating the intervention of both radical and carbocation intermediates (Scheme 2).

The present report describes the results of a voltammetric study of the decarboxylation process for the tetrabutylammonium salt of the carboxylic acid **1**. The main goal in this study was to establish the participation of radical **3** and/or iminium ion **4** as intermediates in the formation of enone **2**.

Keywords: Oxidative decarboxylation; Non-Kolbe electrochemical reaction; Ritter reaction; Pyrimidinone carboxylic acid.
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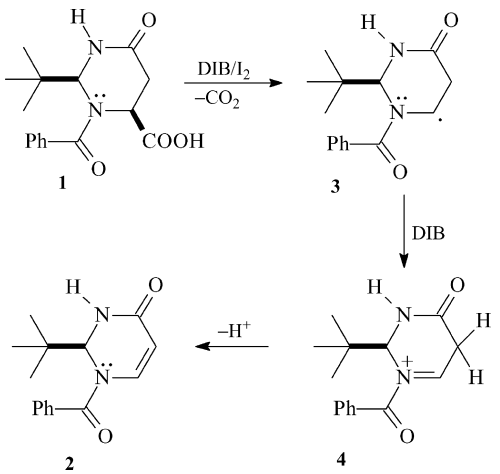
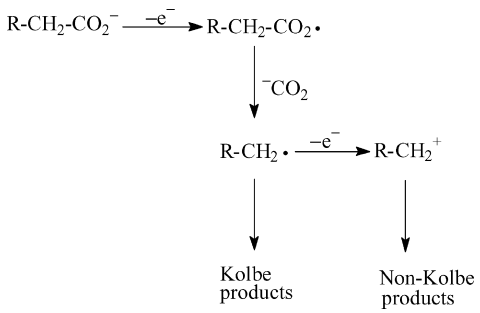
doi:10.1016/j.tet.2004.02.052



Scheme 1. Proposed mechanism for the DIB-induced decarboxylation of **1**.[6]

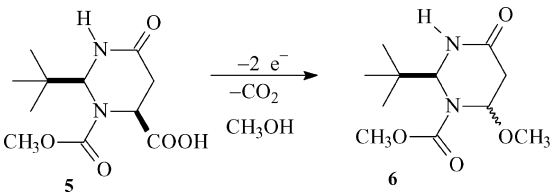


Scheme 2. Electrochemical decarboxylation of carboxylate salts.[8–11]

2. Results and discussion

2.1. Electrochemical oxidation of the tetrabutylammonium salt of carboxylic acid 1 in CH_2Cl_2

Several years ago, Konopelski and co-workers[12] reported the electrolysis of pyrimidinone carboxylic acid **5** in methanol, at very high potential conditions. The non-Kolbe type product **6** obtained, was the result of nucleophilic solvent (methanol) addition to the intermediate[13] (Eq. 4).



(4)

Nevertheless, recent developments in the electrochemical oxidative decarboxylation protocol have demonstrated that carboxylic acid salts decarboxylate under milder electrolytic conditions, relative to those required with the corresponding carboxylic acids. The use of tetrabutylammonium carboxylate salts has proven particularly convenient.[8–11]

Figure 1(a) shows the voltammetric behavior of the oxidative electrochemical process of the tetrabutylammonium carboxylate **7** in CH_2Cl_2, using glassy carbon

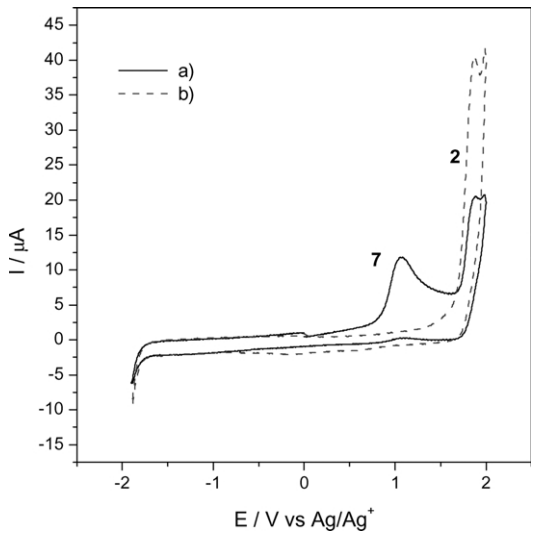
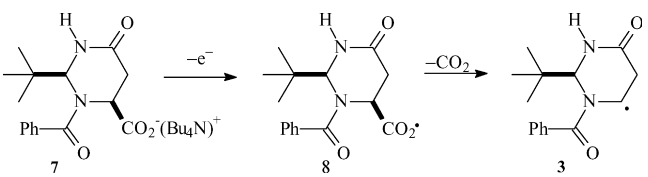


Figure 1. Cyclic voltammetry of (a) 0.82 mM of tetrabutylammonium carboxylate **7** and (b) 1.63 mM of compound **2** in CH_2Cl_2+0.2 M n-Bu_4NPF_6 on glassy carbon electrode (3 mm ϕ) at 0.1 V s^{-1}.

electrodes. Two chemically irreversible waves are observed, corresponding to the oxidation of the starting salt at E_p=1.07 V/Ag/Ag^+ and to the oxidation of the electrolysis product at E_p=1.88 V/Ag/Ag^+. That the product of the initial anodic oxidation corresponds to enone **2** was demonstrated by separate electrochemical oxidation of this previously reported[4b,h,6] heterocyclic enone (Fig. 1(b)).

Based on literature precedent,[8,9a] it can be proposed that one-electron anodic oxidation of carboxylate **7** affords the *O*-radical **8** that immediately loses CO_2[14,15] to give the *C*-radical **3** (Scheme 3).[9b]



Scheme 3. Mechanistic pathway for the one-electron oxidative decarboxylation of carboxylate **7** to give *C*-radical **3**.

Owing to the anticipated lability of the resulting aminoketal **9**, no attempts to trap this intermediate were made.

2.2. Electrochemical oxidation of tetrabutylammonium carboxylate 7 in CH_2Cl_2 and CH_3CN

By comparison with data reported for the oxidation potentials of common radicals,[16,17] the one assigned to the oxidation peak potential of carboxylate **7** is substantially higher (>500 mV), and this observation can be interpreted in terms of a rapid oxidation of radical **3** to delocalized carbocation **4**. Indeed, the reversible wave observed at 0.227 V/Ag/Ag^+ in Figure 2(a), which shows the voltammetric behavior of **7** at the more rapid scan rate of 10 V s^{-1}, may correspond to the redox couple $R^{\cdot}/R^+$. Generally, the reactivity of such intermediates is so high that their voltammetric detection is difficult even at higher scan rates. However, the participation of the electron pair of the vicinal nitrogen contributes to the greater stability of

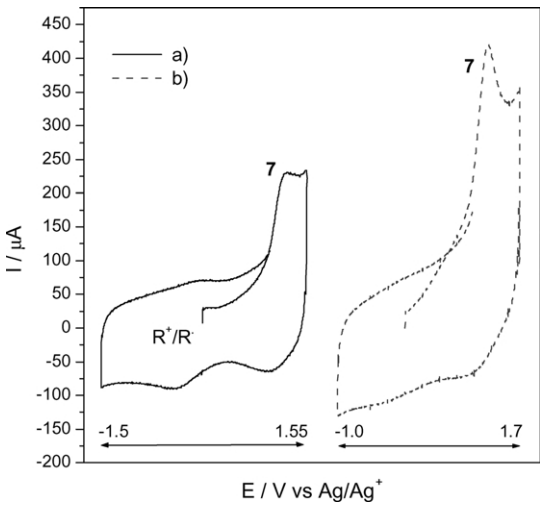
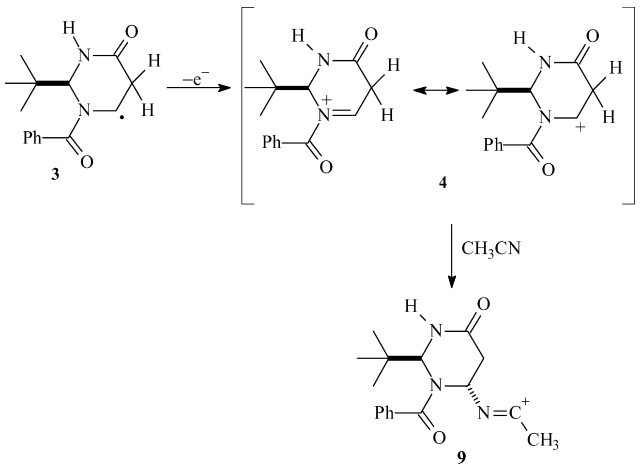


Figure 2. Cyclic voltammetry of carboxylate **7** on glassy carbon electrode (3 mm ϕ) at 10 V s^{-1}. (a) 1.13 mM in CH_2Cl_2+0.2 M *n*-Bu_4NPF_6. (b) 1.69 mM in CH_3CN+0.2 M *n*-Bu_4NPF_6.

acyliminium cation **4**, allowing for its detection. The fact that the addition of acetonitrile causes the disappearance of this reversible signal (Fig. 2(b)), suggests that this acyliminium carbocation is trapped in a Ritter type solvolytic reaction[18] to give intermediate **9** (Scheme 4).



Scheme 4. Radical oxidation and carbocation nucleophilic trapping.

Furthermore, cyclic voltammograms in CH_2Cl_2 conducted in the presence of increasing amounts of acetonitrile (Fig. 3(a)–(c)) show that the concentration of the reaction product decreases with the increase of the concentration of acetonitrile, suggesting that the product of the electrolysis of the carboxylate salt **7** in CH_2Cl_2 is indeed a substrate amenable to nucleophilic trapping.

2.3. Constant potential electrolysis experiment

The previous experiments indicate that in pure CH_2Cl_2 the solvolysis of the cation **4** is precluded. Therefore, the efficient formation of enone **2** in these conditions (Section 2.1) may be interpreted in terms of intermolecular transfer of a proton at C(5) in iminium ion **4** to carboxylate **7** (Scheme 5).

The mechanistic proposal advanced in Scheme 5, and in

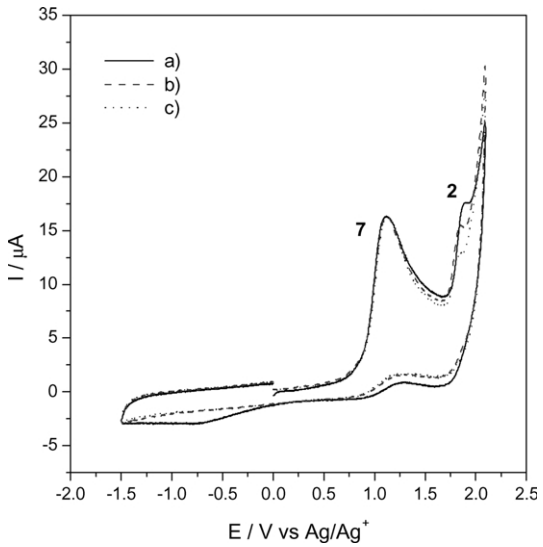


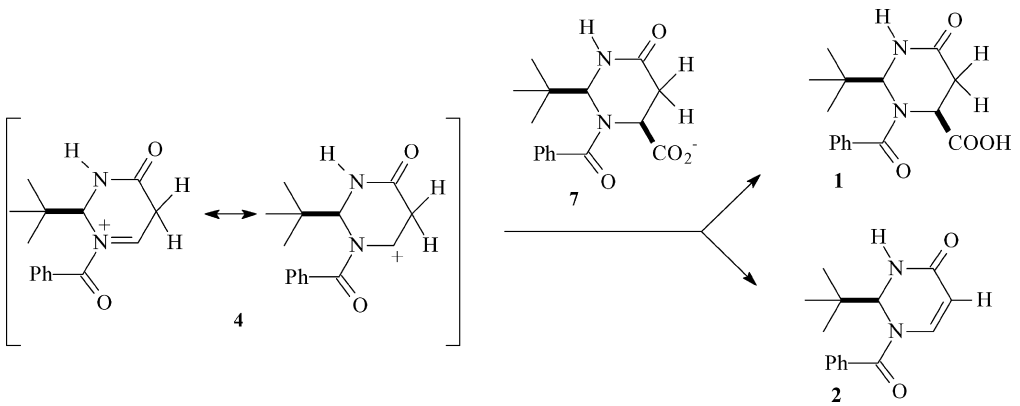
Figure 3. Cyclic voltammetry of 1.13 mM of carboxylate salt **7** in CH_2Cl_2+0.2 M *n*-Bu_4NPF_6 on glassy carbon electrode (3 mm ϕ) at 0.1 V s^{-1} at different concentrations of CH_3CN (a) 0 mM, (b) 1.9 mM, (c) 3.8 mM.

particular the formation of carboxylic acid **1** during the proton-elimination step (**4**→**2**) are supported by the results of a constant potential electrolysis experiment. The imposed potential of electrolysis was selected to be 150 mV more anodic than the peak potential value measured at 0.1 V s^{-1}. Figure 4(a) shows the voltammogram of **7** before the constant potential electrolysis. Following complete electrolysis (Fig. 4(b)), the signal corresponding to the oxidation of enone **2** is the only one observed. Addition of tetrabutylammonium hydroxide produces the recovery of the oxidation signal of the carboxylate **7** now with half of the initial current intensity (Fig. 4(c)). The value of the total charge consumed in the electrolysis corresponds to an apparent electron number close to one (n_{app}=0.96 e^-), which indicates that the mechanism is globally mono-electronic. This is consistent with the global stoichiometry derived from the sequence of reactions proposed here; although the mechanism comprises the transference of two electrons, it appears monoelectronic due to the proton elimination step, which results in the neutralization of half the initial concentration of carboxylate **7**.

2.4. Electrochemical evidence for intermolecular hydrogen bonding

As it can be noticed in Figure 4(b), following complete electrolysis, the signal corresponding to the enone **2** is slightly shifted toward more anodic potential, taking as reference the corresponding signal obtained before the electrolysis (Fig. 4(a)). Furthermore, the peak potential of the regenerated carboxylate **7** shows the same tendency.

In order to explain both peak displacements, additional experiments were carried out. Considering that after the total electrolysis of carboxylate **7** both the carboxylic acid **1** and enone **2** coexist, the oxidation process of **2** in the presence of the carboxylic acid **1** was conducted. Consistent with the electrolysis experiment, it is observed that the oxidation wave of **2** is displaced toward more anodic



Scheme 5. Mechanistic hypothesis for the in situ formation of enone **2** during anodic oxidation of carboxylate salt **7**.

potentials. This result can be explained in terms of intermolecular association between both products of reaction, through hydrogen bond formation. Consideration of the structures of **1** and **2**, suggests that an interaction could be established between the carbonyl oxygen of ring amide **2** and the hydroxyl group of **1** (see Scheme 6(a)). In this interaction, it is expected that a decrease of the partial negative charge on the carbonyl of **2** results in its more difficult oxidation.

By the same token, the neutralization of the carboxylic acid **1** obtained in the electrolysis experiment (Fig. 4(c)) results in the coexistence of the carboxylate **7** and the enone **2**. Thus, the oxidation process of **7** in the presence of the enone **2** was carried out. The shift of the oxidation signal of the carboxylate **7** toward more anodic potentials (35 mV), can be attributed to hydrogen bond interaction between the NH group of **2** and the negative oxygen of **7**. Accordingly, the negative charge of the carboxylate **7** is stabilized with the NH group of **2** (see Scheme 6(b)), resulting in its more difficult oxidation.

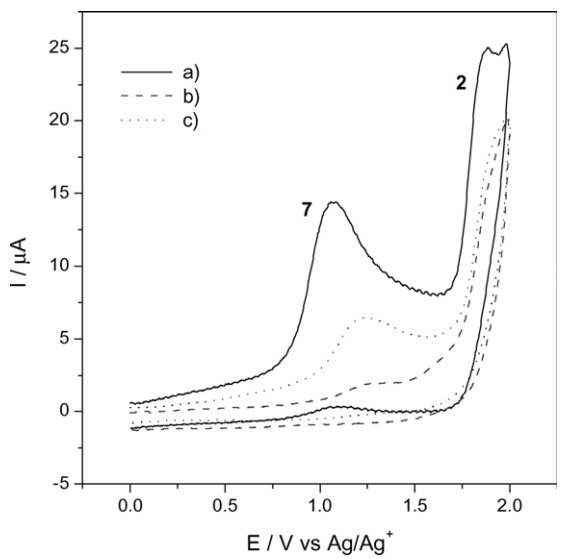


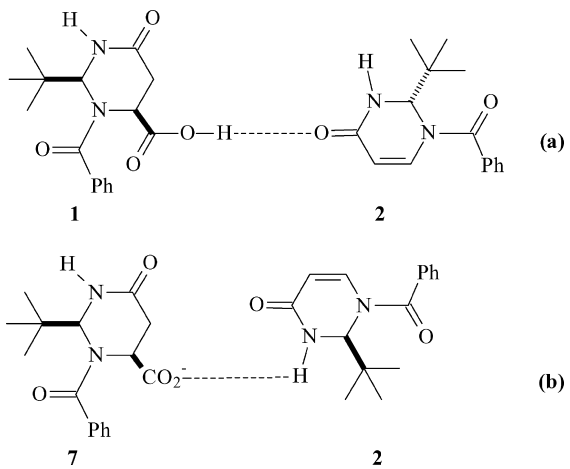
Figure 4. Cyclic voltammetry of 1.0 mM of tetrabutylammonium carboxylate **7** in CH_2Cl_2+0.2 M *n*-Bu_4NPF_6 on glassy carbon electrode (3 mm ϕ) at 0.1 V s^{-1}. (a) Before the electrolysis. (b) After complete electrolysis. (c) After complete electrolysis and following addition of 0.5 mM *n*-Bu_4NOH.

3. Conclusions

The efficient decarboxylation of pyrimidinone carboxylic acid **1** was achieved under mild oxidative electrolytic conditions via the tetrabutylammonium carboxylate **7**, in the non-nucleophilic solvent CH_2Cl_2.

The accumulated evidence supports an initial one-electron loss, followed by rapid decarboxylation, so that carboxylate **7** is converted to radical **3**. A second electron transfer produces the nitrogen-stabilized cationic species **4** that eliminates a β-proton by intermolecular proton transfer to the available carboxylate **7**. Thus, enone **2** is produced in a process that involves two electron-transfer steps that appears, nevertheless, monoelectronic owing to such release of a proton from acyliminium cation **4**.

The suppression of any solvolysis reaction in CH_2Cl_2 solvent allows for the detection of cationic intermediate **4** in the cyclic voltammetry experiments, at 10 V s^{-1}. By contrast, in the presence of a nucleophilic solvent such as



Scheme 6. Intermolecular hydrogen bond associations (a) between **1** and enone **2** and (b) between carboxylate **7** and enone **2**.

acetonitrile, intermediate **4** is trapped in a typical Ritter reaction.

The present report shows the great potential that electrochemical techniques have in the study or verification of organic reaction mechanisms.

4. Experimental

CH_2Cl_2 and CH_3CN (spectrophotometric grade) were used as solvents. Tetrabutylammonium hexafluorophosphate (99%) was the supporting electrolyte. The tetrabutylammonium pyrimidine-carboxylate **7** was prepared by mixing stoichiometric amounts of the corresponding carboxylic acid and tetrabutylammonium hydroxide in anhydrous methanol, which was then removed under reduced pressure. The obtained glassy solid was dried in a vacuum pump for several hours to provide the solid salt. An authentic sample of the expected decarboxylation product, enone **2**, was obtained following our recently reported tandem chemical decarboxylation protocol.[6,7]

The electrochemical apparatus consisted of a potentiostat DEA-332 (Radiometer, Copenhagen) with positive feedback compensation. A conventional three-electrode cell was used to carry out the voltammetric experiments. The work electrode was a 3 mm diameter glassy carbon disk. This electrode was carefully polished with 1 μm alumina powder and ultrasonically rinsed with ethanol before each run. The counter electrode was a platinum screen and the reference electrode was an aqueous saturated Ag/Ag^+ electrode. A salt bridge, containing 0.2 M n-Bu_4NPF_6+CH_2Cl_2, connected the cell with the reference electrode.

4.1. Voltammetric and electrolysis experiments

Cyclic voltammetry experiments were carried out by using a carboxylate solution which was deoxygenated by dry argon bubbling. After this, an argon atmosphere was maintained over the solutions during each experimental run. All electrochemical experiments were performed at room temperature. The electrolysis of the carboxylate **7** (20 mM), was carried out in a 10 mL divided cell. The working electrode was a 5 mm diameter glassy carbon rod. The electrolysis potential was selected to be 150 mV more positive than the peak potential of the carboxylate **7**.

Acknowledgements

We are indebted to Conacyt, México, for financial support via grants 33023-E and G23710-E, and for the Cátedra Patrimonial de Excelencia granted to MAIA. We are also grateful to María Luisa Kaiser for technical assistance, and to the referees for useful comments and suggestions.

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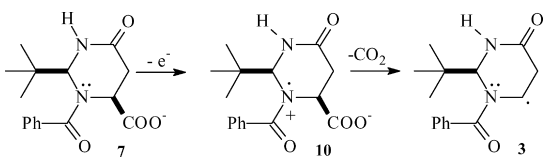
9. (a) Andrieux, C. P.; González, F.; Saveant, J.-M. *J. Electroanal. Chem.* **2001**, *498*, 171. (b) An alternative mechanism for electron transfer and bond breaking involves the formation of a zwitterionic radical **10**, which after an intramolecular dissociative electron transfer (Ref. 9a) would afford the C-radical **3**.



This alternative mechanism may be discarded owing to the fact that the parent amide moiety in enone **2** is more difficult to oxidize than the carboxylate group in substrate **7**, that is approximately 800 mV more anodic. Furthermore, the transfer coefficient (α=0.501) obtained from the variation of the peak potential with the scan rate ($\partial E_P/\partial \log \nu$=58.1 mV/dec) indicates that the electron transfer is not intrinsically slow and it should be followed by a very fast chemical step as the

decarboxylation of the acyloxy radical here proposed. Contrasting with this, in pathways involving zwitterionic radicals, the variation of the peak potential with the scan rate ($\partial E_P/\partial \log \nu$) is expected to be smaller than the observed value, which approaches those reported for an electrochemical–chemical mechanism where the chemical step corresponds totally or partially to the rate determining step (Ref. 9a).

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Tetrahedron 60 (2004) 3611–3624
Tetrahedron

Organolithium-induced enantioselective alkylative double ring-opening of epoxides: synthesis of enantioenriched unsaturated amino alcohols☆

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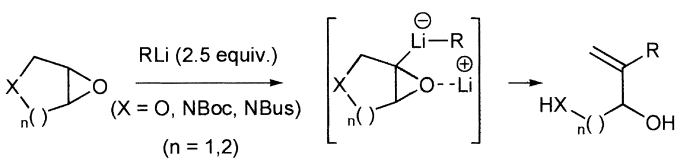
Received 13 January 2004; revised 11 February 2004; accepted 25 February 2004

Abstract—The use of (−)-sparteine as an external chiral ligand in enantioselective organolithium-induced alkylative double ring-opening of dihydropyrrole epoxides and 7-azanorbornene-type epoxides gives unsaturated acyclic amino alcohols, and amino cyclohexenols in up to 87% ee.

1. Introduction

Enantioselective desymmetrisation of achiral materials is an attractive and powerful concept in asymmetric synthesis.[1] *meso*-Epoxides represent an important class of substrates for new desymmetrisation methodologies,[1,2] and base-induced enantioselective transformations of such epoxides by β-elimination[3] or α-deprotonation[4] are a focus of current interest. We recently reported the organolithium-induced alkylative deoxygenation of epoxides of dihydrofuran (Scheme 1, n=1, X=O) and dihydropyran (n=2, X=O),[5] as well as epoxides of dihydropyrrole [n=1, X=NBus (Bus=Bu^{t}SO$_2$)] and tetrahydropyridine (n=2, X=NBus)[6] to generate acyclic unsaturated diols and amino alcohols, respectively. These processes most likely proceed via α-deprotonation and insertion (possibly by a 1,2-metallate shift)[7] of a second equivalent of organolithium into the initially formed lithiated epoxide, followed by elimination.

Due to the widespread occurrence of the 1,2-amino alcohol motif in bioactive natural products, many pharmaceutical agents and in useful synthetic intermediates, auxiliaries, and ligands in catalysis, considerable importance is attached to new methods to access this moiety.[8] In conjunction with our studies into chiral ligand-assisted organolithium-induced enantioselective α-deprotonations of cycloalkene- and heterocycloalkene-derived epoxides,[4] we sought to develop the above alkylative desymmetrisation reaction of epoxides into an enantioselective entry to acyclic unsaturated 1,2-amino alcohols, as well as cyclic (2-aminocyclohex-5-en-1-ol) systems, and detail our results in these areas in the current paper.[9]



Scheme 1.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.02.055

Keywords: Epoxides; Organolithiums; Amino alcohols; Eliminations and alkenes.
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doi:10.1016/j.tet.2004.02.055

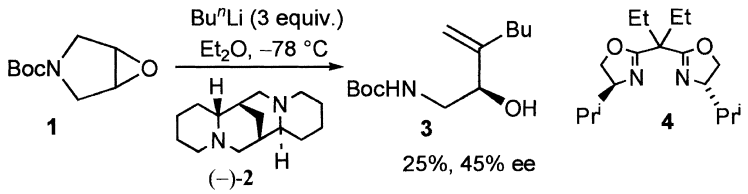
2. Results and discussion

Our initial investigations focused on the alkylative desymmetrisation of the simplest available achiral epoxides derived from dihydropyrrole (Scheme 2). The product distribution arising from the alkylative double ring-opening of such 3,4-epoxytetrahydropyrroles was previously found to be dependent on the nitrogen protecting group.[6] In the current study, the use of the Bus protecting group[10] was again found to result in superior yields of amino alcohol (in comparison to using Boc protection) in the ligand-assisted process. Thus, reaction of NBoc epoxide **1** under typical enantioselective desymmetrisation conditions [addition of epoxide to Bu^{n}Li and (−)-sparteine **2** (3 equiv. each) in Et_2O at −78 °C, followed after 1 h at −78 °C by warming to 0 °C (1 h)] gave amino alcohol (+)-**3** in only 25% yield, and 45% ee; the corresponding non-ligand mediated reaction with Bu^{n}Li in Et_2O had previously given **3** in 46% yield.[6] Switching to valine-derived bisoxazoline **4** as ligand with NBoc epoxide **1** returned mainly starting epoxide (90%), along with traces of NBoc pyrrole (7%). The sense of asymmetric induction observed in amino alcohol (+)-**3** using Bu^{n}Li/**2** with epoxide **1** is tentatively assigned as shown in Scheme 2. This assignment is by analogy with all our previous observations on organolithium-induced enantioselective α-deprotonation of epoxides[4] [medium-sized (8, 9 and 10-membered) cycloalkene epoxides,[11] silyloxysubstituted cyclooctene epoxides,[12] norbornene epoxide,[11] (*N*-Boc)-7-azanorbornene epoxide[13] and 3,4-epoxytetrahydrofuran[14]] using sparteine **2**, where proton removal at the *R*-epoxide stereocentre is consistently seen. Products from similar α-deprotonation–alkylation of related epoxides discussed later in this paper are similarly assigned by analogy as being derived from proton removal at the *R*-epoxide stereocentre when using sparteine **2**.

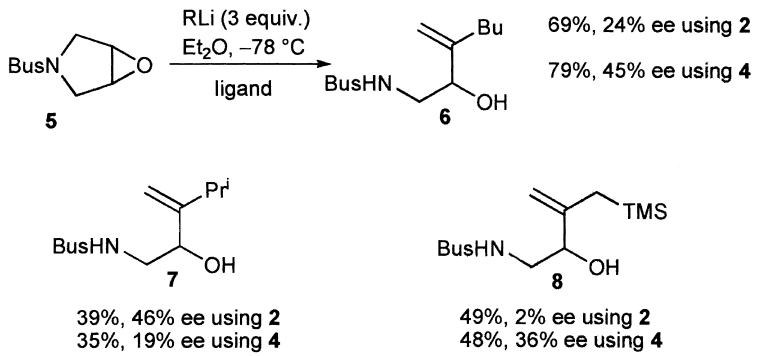
Using NBus epoxide **5** under the typical desymmetrisation conditions with (−)-sparteine **2** gave amino alcohol (+)-**6** in 69% yield, but in only 24% ee (Scheme 3); NBus pyrrole [confirmed by independent synthesis (88%) from Bu^tSO_2-NH_2[15] and 2,5-dimethoxytetrahydrofuran using P_2O_5[16]] was observed as a minor byproduct (18%).

Some variations to the standard reaction conditions with sparteine **2** were examined in an attempt to improve yields and/or asymmetric induction with NBus epoxide **5**. However, reducing the quantity of sparteine to one equivalent,[14] or initiating the reaction at −100 °C, or maintaining the reaction for a longer period (5 h) at −78 °C, or slowly warming up from a longer period (5 h) at −78 °C had little effect (52–64% yields, 16–27% ees). Several alternative ligands to sparteine were also investigated (Fig. 1).[17] No reaction was observed using diamine ligand **9**,[18] or using the amino alkoxide of **10**[19] (4 equiv. of Bu^{n}Li were used in this latter case), whereas with diether **11**[20] the desired amino alcohol (+)-**6** was observed (65% yield), but in only 6% ee. More encouraging was the use of bisoxazoline **4**, which gave (−)-**6** in 79% yield and 45% ee; 11% of NBus pyrrole was also isolated. The corresponding alanine- and *tert*-leucine-derived bisoxazolines were also studied, however these led to no improvement (33% yield, 43% ee, and 53% yield, 14% ee, respectively) compared with the use of bisoxazoline **4**. Maintaining the valine-derived bisoxazoline unit, but varying the linking *gem*-dialkyl group from diethyl to diisobutyl was also detrimental to yield (52%) and asymmetric induction (29% ee).

With NBus epoxide **5** two other organolithiums (Pr^{i}Li and $TMSCH_2Li$) were also investigated using sparteine **2** and bisoxazoline **4** as ligands (Scheme 3), so as to provide a comparison with the reactions of Bu^{n}Li. As observed in previous reactions with sparteine,[4] Pr^{i}Li provided higher asymmetric induction compared with Bu^{n}Li: isopropyl-substituted amino alcohol (+)-**7** was formed in 46% ee, compared with butyl-substituted (+)-**6** in 24% ee. In contrast, the secondary organolithium was less effective when using bisoxazoline **4** as ligand [(−)-**7**, 19% ee; (−)-**6**,



Scheme 2.



Scheme 3.

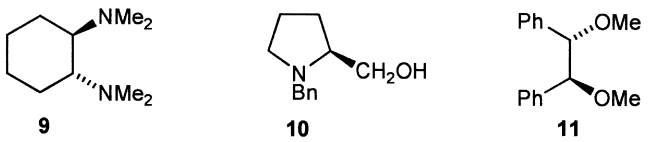


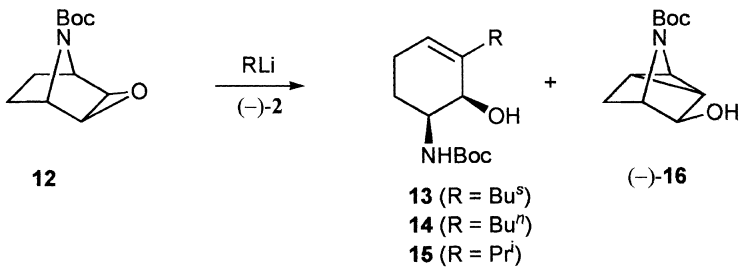
Figure 1. Ligands **9**–**11**.

45% ee]. Allylsilane **8** was formed essentially as the racemate when using sparteine **2**, and in 36% ee using bisoxazoline **4**.

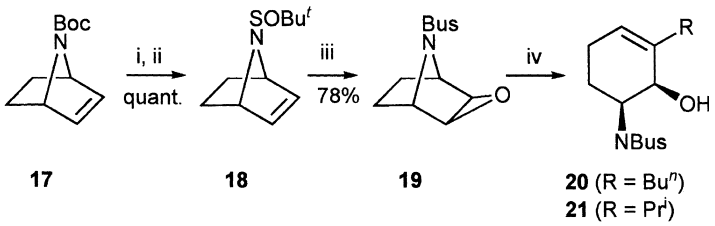
In seeking to extend the enantioselective alkylative desymmetrisation process to generate amino cyclohexenols we focused on NBoc azanorbornene epoxide **12** (Scheme 4). Previously, we had established that rearrangement of epoxide **12** by enantioselective deprotonation transannular C–H insertion was possible using substituted *aryl*lithiums in combination with (−)-sparteine **2**, or bisoxazoline ligands such as **4**, to give azanortricyclanol **16** in up to 60% yield and 87% ee; amino cyclohexenols (cf, **13**–**15**, but R=aryl) were not observed in these reactions.[13] Reaction of epoxide **12** with Bu^{s}Li in the presence of bisoxazoline **4** in Et_2O was also known to only give azanortricyclanol **16** [37%, 51% based on recovered starting material (brsm), 63% ee].[13] However, with epoxide **12**, the use of Bu^{s}Li in combination with sparteine **2** (3 equiv. each) in Et_2O at −78 °C for 5 h followed by warming to room temperature gave amino alcohol **13** as the major product (56%), along with a lesser quantity of the azanortricyclanol **16** (20%, 59% ee) and some recovered epoxide **12** (16%). The amino alcohol **13** obtained in this reaction was optically active, but the presence of diastereomers (due to the stereocentre in the Bu^s substituent) made the enantiomeric excess determination problematic. Nevertheless, this result suggested that reactions of alkyllithiums with azanorbornene oxide **12** could be an interesting avenue for further investigations.

Initial screenings with NBoc azanorbornene epoxide **12**[21] using Bu^{n}Li (3 equiv.) in the absence of an added ligand in THF, Et_2O or toluene at −78 °C established that Et_2O was the preferred solvent to preferentially generate the amino cyclohexenol **14** [42% isolated yield, 26% of **16**[21] also isolated; **14**:**16**, 1:0.5 (THF), 1:0.6 (Et_2O), 1:1 (toluene)]. Pleasingly, with Bu^{n}Li in the presence of sparteine **2** (3 equiv. each) in Et_2O the proportion of amino cyclohexenol **14** increased (**14**:**16**, 1:0.25) and (−)-**14** was isolated in 55% yield and 67% ee; the azanortricyclanol (−)-**16** was also isolated in 14% yield and 35% ee. The determination of absolute configuration of azanortricyclanol (−)-**16** has previously been communicated,[13] and the absolute configuration of (−)-**16** is as shown in Scheme 4. With Pr^{i}Li the amino cyclohexenol (−)-**15** was obtained in 51% yield and 87% ee [(−)-**16** was also isolated: 24%, 46% ee), demonstrating once again the higher enantiodiscrimination possible using this secondary organolithium with sparteine. Using slightly more Pr^{i}Li (3.5 equiv.) led to a significant improvement in isolated yield of the amino cyclohexenol (−)-**15** (78%, 87% ee), and in this case no azanortricyclanol **16** was detected; using 3.5 equiv. of Bu^{s}Li with epoxide **12** also led to a higher yield of amino alcohol **13** (74%, cf. 56% with 3 equiv.) along with some azanortricyclanol (−)-**16** (12%, 65% ee). Use of $TMSCH_2Li$ however, returned mainly unreacted starting epoxide **12** (68%). Remarkably, if the reaction of NBoc azanorbornene epoxide **12** with Pr^{i}Li in the presence of sparteine **2** was carried out in toluene instead of Et_2O, amino cyclohexenol **15** was not observed, and only azanortricyclanol (−)-**16** was isolated (50% yield, 75% ee). This last reaction underlines the strong influence of solvent on product profile with this substrate. In the reactions of azanorbornene epoxide **12** with Bu^{n}Li and Pr^{i}Li in Et_2O, the observations of different ees for the amino cyclohexenol **14**/**15** and the NBoc azanortricyclanol **16** provide further examples of enantiomeric partitioning:[12,14] in the presence of the chiral ligand sparteine, the relative proportions of the enantiomeric α-lithiated epoxides of **12** proceeding to **14**/**15** and **16** are different.

Given the earlier dependence on the nitrogen protecting group of reaction efficiency (both in terms of yield and asymmetric induction) in the desymmetrisations of 3,4-epoxytetrahydropyrroles, it was of interest to examine the corresponding NBus azanorbornene epoxide **19** (Scheme 5).



Scheme 4.



Scheme 5. Reagents and conditions: (i) TFA, CH_2Cl_2, 25 °C, 4 h; (ii) Et_3N, 25 °C, CH_2Cl_2, 1 h, then Bu^{t}SOCl, CH_2Cl_2, 0 °C, 1 h; (iii) CF_3COCH_3, Na_2EDTA, $NaHCO_3$, oxone, MeCN, 0 °C, 1.5 h; (iv) Bu^{n}Li or Pr^{i}Li, (−)-sparteine, Et_2O, −78 °C (5 h) to 25 °C (15 h).

The latter was prepared from the known NBoc azanorbornene **17**[21] via protecting group interchange. Thus, deprotection of NBoc azanorbornene **17** with TFA, followed by reaction of the TFA salt with Et_3N and Bu^{t}SOCl,[10] then oxidation of the resulting sulfinamide **18** using methyl(trifluoromethyl)dioxirane generated in situ[22] gave the desired NBus epoxide **19**. However, reaction of NBus epoxide **19** with Bu^{n}Li or Pr^{i}Li in the presence of sparteine in Et_2O gave lower yields and ees of amino cyclohexenols (−)-**20** (53%, 40% ee) and (−)-**21** (42%, 64% ee) respectively, compared to the corresponding NBoc systems (−)-**14** (55%, 67% ee) and (−)-**15** (78%, 87% ee). In Et_2O for NBus azanorbornene epoxide **19** (as with NBoc azanorbornene epoxide **12**), the corresponding NBus azanortricyclanol **16** (Bus=Boc) side-product was only detected (3%, 35% ee) when using Bu^{n}Li. We conclude that Boc protection is preferred to Bus protection for alkylative desymmetrisations in the aza bridged system (where bridgehead deprotonation is unlikely).

To study the substrate scope of the alkylative ring-opening process of 7-azabicyclo[2.2.1]heptyl systems we selected three other substrates for examination (Fig. 2). Potentially competing transannular C–H insertion was considered to be unlikely for acetal epoxide **22**, due to the additional strain that would arise from the presence of the acetal, and would not be possible for systems **23** and **24**. Also, alkylative desymmetrisation of substrates such as acetal epoxide **22** could potentially result in a new strategy to substituted aminocyclitols, which are an important group of bioactive compounds.[23]

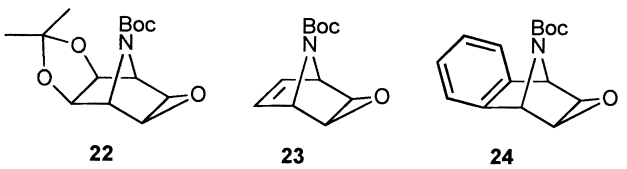
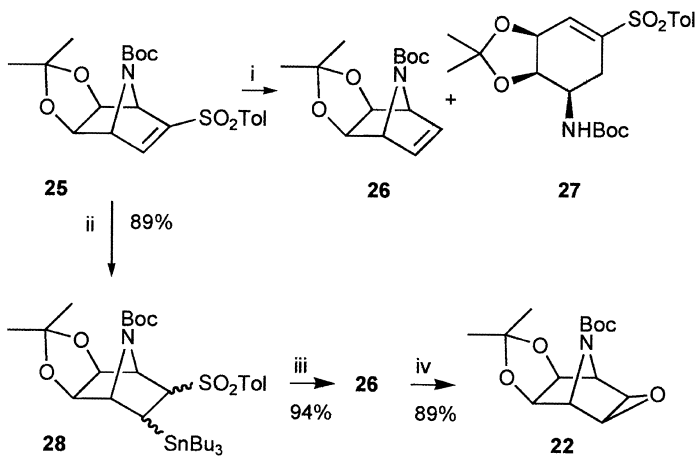


Figure 2. Desymmetrisation substrates **22**–**24**.

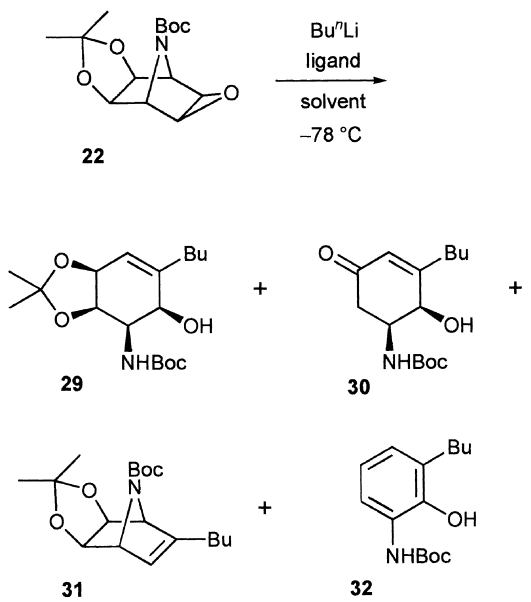
The synthesis of acetal-substituted epoxide **22** commenced with known sulfone **25** (Scheme 6), which is readily prepared in 3 steps via cycloaddition of commercially available NBoc pyrrole and tosyl ethyne.[24] Direct desulfonylation of sulfone **25** to give alkene **26**, the immediate precursor to epoxide **22**, was initially attempted using sodium amalgam. However, examination of typical desulfonylation conditions using 6% Na–Hg, with or without buffer [MeOH–THF (1:1), −20 °C (18 h);[25] NaH_2PO_4/Na_2HPO_4, MeOH, −10 °C (1 h) to 0 °C (5 h)[26]] led to inseparable mixtures of the desired alkene **9** together with the known[24] cyclohexene sulfone **27** (**26**:**27**, 1:0.6 and 1:3.6, respectively); **27** likely arises from electron transfer to the double bond in sulfone **25**, followed by aza-bridge opening. When boric acid was used as an additive[27] (MeOH, 25 °C, 5 h), very little of the unwanted cyclohexene sulfone **27** was observed; however, the desired alkene **26** was contaminated with substantial aromatic impurities.

We therefore applied a two-step procedure which has been successfully used to desulfonylate the corresponding 7-azabicyclo[2.2.1]heptene system lacking the acetal.[28] Pleasingly, addition of Bu_3SnH to sulfone **25** followed by fluoride-induced elimination in the resulting stannane **28** efficiently delivered alkene **26** (84% over two steps). Epoxidation of alkene **26** using MCPBA was very slow, and the epoxidation was best effected using in situ generated methyl(trifluoromethyl)dioxirane[22] to give the desired epoxide **22** in excellent yield (89%). The *exo*-selectivity in the epoxidation was assigned by analogy with epoxide **12**.[21]

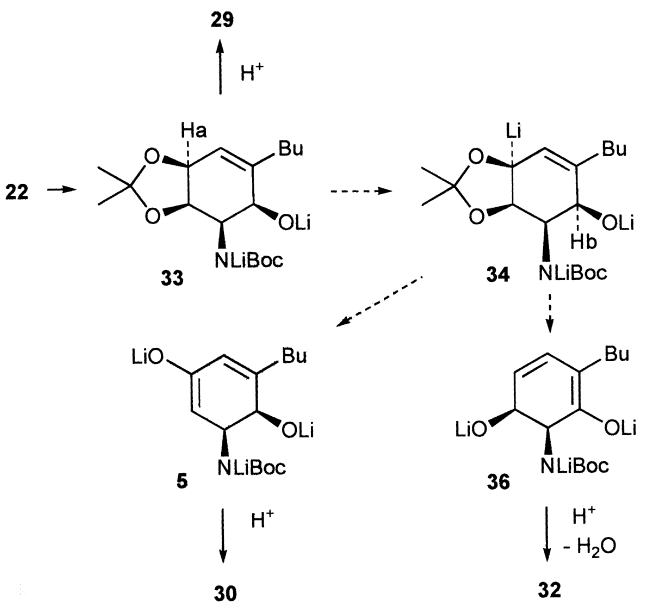
With an efficient route to epoxide **22** developed, we initiated desymmetrisation studies (Scheme 7, Table 1). Surprisingly, addition of epoxide **22** to Bu^{n}Li (3.5 equiv.) in THF at −78 °C, followed after 5 h at −78 °C by warming to 0 °C (1 h), led to one major product, aminophenol **32** [41%, Table 1, entry 1, **32** displays ^{1}H NMR spectral data (δ and J values) in the 8.2–6.5 region which are essentially identical to that reported[29] for the analogous aminophenol bearing a methyl instead of a butyl substituent; possible reaction pathways leading to **32** are discussed below]. In contrast, under otherwise identical reaction conditions but using Et_2O as solvent gave only a low recovery of starting epoxide **22** (19%, entry 2). With toluene as solvent the sought-after amino alcohol **29** was isolated, but only in low yield (11%, 30% brsm, entry 3). Also isolated from the reactions in THF and toluene was alkene **31** (5 and 17%, respectively).



Scheme 6. Reagents and conditions: (i) 6% Na–Hg; (ii) Bu_3SnH, AIBN, toluene, 80 °C, 1 h; (iii) TBAF, THF, reflux, 2 h; (iv) CF_3COCH_3, Na_2EDTA, $NaHCO_3$, oxone, MeCN, 0 °C, 2.5 h.



Scheme 7.



Scheme 8.

Table 1. Reaction of epoxide **22** with Bu^{n}Li (3.5 equiv.) at −78 °C

Entry	Ligand	Solvent	Recovered **22** (%)	**29** (%)	**30** (%)	**31** (%)	**32** (%)
1	—	THF	7	—	—	5	41
2	—	Et_2O	19	—	—	—	—
3	—	Toluene	37	11	—	17	—
4	**2**	Et_2O	7	16	16	7	10
5[a]	**2**	Et_2O	66	20[b]	—	—	—
6	**4**	Et_2O	24	—	—	—	52
7	**2**	Toluene	15	45[c]	9	—	—
8[a]	**2**	Toluene	36	41[d]	—	—	—
9	**4**	Toluene	37	11[e]	—	13	19
10	**2**	Cumene	5	35[f]	27	3	—

[a] Reaction quenched after 5 h at −78 °C.
[b] 70% ee.
[c] 72% ee.
[d] 76% ee.
[e] −67% ee.
[f] 71% ee.

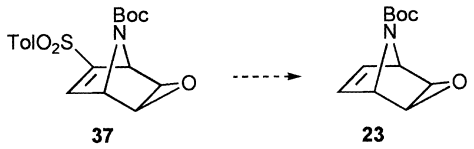
Alkene **31** is likely derived from the common α-lithiated epoxide intermediate (cf. Scheme 1) which also leads to the desired amino alcohol **29**; however, following intermolecular trapping by BuLi, elimination of Li_2O occurs. Although this latter process is a well-known reaction pathway for simple epoxides with organolithiums,[4] elimination of the uncharged NBoc group (with concomitant relief of ring strain) is normally strongly preferred in substrates structurally related to epoxide **22**, such as **12**.

In organolithium-mediated desymmetrisation reactions of achiral epoxides, the presence of a chiral ligand often exerts a significant influence on product profile, as well as inducing enantioselectivity.[4] Reaction under the above conditions in Et_2O but with (−)-sparteine **2** present (3.5 equiv.) led to a mixture of the desired amino alcohol **29** (16%), enone **30** (16%), bicyclic alkene **31** (7%) and aminophenol **32** (10%) (Table 1, entry 4). Enone **30** likely originates from the intermediate **33** which leads on protonation to **29** (Scheme 8). Deprotonation at the activated allylic acetal position (loss of Ha) in intermediate **33** leads to lithiated acetal **34**. Cycloelimination[30] (loss of acetone) from lithiated acetal **34** would give cross-conjugated enolate **35**, which generates enone **30** on work-up. When an otherwise identical reaction was carried out, but quenched after 5 h at −78 °C (rather than allowing it to warm-up), then only the desired amino alcohol (−)-**29** was isolated, albeit in low yield (20, 59% brsm, entry 5); this suggests that the undesired products derive from less selective reactions during the warm-up period. The ee of (−)-**29** from this latter reaction was determined to be 70%, which encouraged further studies. Intriguingly, under otherwise standard conditions but using bisoxazoline **4** as ligand in Et_2O led only to isolation of aminophenol **32** (52, 69% brsm, entry 6). Aminophenol **32** could potentially also arise from lithiated acetal **34** via an alternative (α-elimination) pathway which reveals its carbenoid[31] character; an ensuing (alkoxide-assisted) 1,4-hydride shift of Hb generates extended enolate **36** which leads to aminophenol **32** following loss of water on work-up. In an attempt to probe if **33** could be a potential intermediate en route to enone **30** and/or aminophenol **32**, amino alcohol **29** was treated with Bu^{n}Li (3.5 equiv., THF) which, however, led to an unidentifiable mixture of products.

Previous studies on enantioselective alkylative double ring-opening of epoxides derived from 8-oxabicyclo[3.2.1]-octenes indicated that switching from Et_2O to aromatic hydrocarbon solvents resulted in improved yields of cycloheptene diols.[14] In the present case under standard conditions with (−)-sparteine **2** present and using toluene as solvent led to a significant improvement in yield of the desired amino alcohol (−)-**29** (45% yield, 53% brsm, 72% ee; Table 1, entry 7), compared to the corresponding reaction in Et_2O (16% of **29**, entry 4). The desired reaction was clearly more rapid in toluene than Et_2O, as evidenced by quenching a sparteine-assisted reaction in toluene after 5 h at −78 °C: this resulted in formation of amino alcohol (−)-**29** (41%, 64% brsm, entry 8) in better conversion than the corresponding reaction in Et_2O (20%, 59% brsm, entry

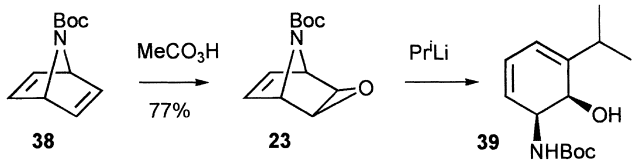
5). The ee of **29** was also slightly improved in toluene (76%) compared to Et_2O (70%). The conversion of epoxide **22** to amino alcohol **29** in toluene was not improved by extending the reaction time (17 h at −78 °C). Use of bisoxazoline **4** as ligand in toluene gave small amounts of (+)-**29** and alkene **31** (13%), along with the aminophenol **32** (19%, entry 9) which was also observed using **4** in Et_2O but to a greater extent (53%, entry 6). Cumene was briefly examined as an alternative solvent with (−)-sparteine **2** (entry 10); however, under otherwise standard conditions this led to a slightly lower yield of **29** with essentially the same ee to that seen in toluene (entry 7), and in cumene the enone **30** was a significant byproduct (27%). Attempted reaction of acetal epoxide **22** with Pr^{i}Li/sparteine **2** in toluene led to a mixture of unidentifiable products; whereas, similarly to epoxide **12**, no reaction was observed between acetal epoxide **22** and $TMSCH_2Li$/sparteine **2** in toluene.

In order to examine unsaturated epoxide **23**, its preparation was attempted by desulfonylation of known epoxide **37**[32] using sodium amalgam, and also by the Bu_3SnH-TBAF protocol [Bu_3SnH (1.5 equiv.), AIBN, toluene, 90 °C, 2 h followed by TBAF (12 equiv.), THF][28] (Scheme 9). However, these procedures gave the impure unsaturated epoxide **23** in low yield; moreover **23** could not be purified further by repeated column chromatography.



Scheme 9.

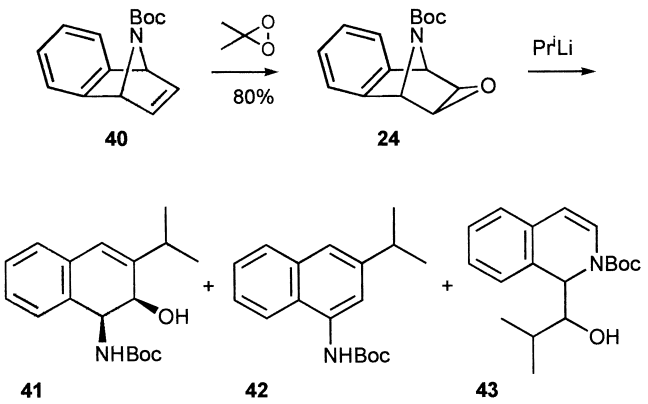
A more successful approach to unsaturated epoxide **23** involved monoepoxidation of the known diene **38**[33] (Scheme 10). Whilst epoxidation of diene **38** using peracetic acid was slow (36 h), it gave pure unsaturated epoxide **23** in 77% yield, without any evidence for di-epoxidation.



Scheme 10.

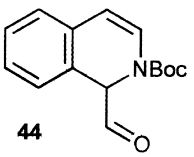
Reaction of unsaturated epoxide **23** with Pr^{i}Li in Et_2O gave the desired amino alcohol **39**, albeit in low yield (22%) along with a number of other products which were not identified; in the presence of sparteine **2**, the yield of amino alcohol **39** increased slightly to 32% and **39** was generated in good ee (79%). Due to the low yields of **39** obtained, however, further investigation of this substrate was not pursued and efforts focused on the more available benzo-epoxide **24** (Scheme 11).

Benzo-epoxide **24** was synthesised from the cycloadduct **40** of NBoc pyrrole and benzyne[34] by epoxidation using dimethyldioxirane generated in situ (80%).[35] Reaction of benzo-epoxide **24** with Pr^{i}Li in Et_2O was examined in the

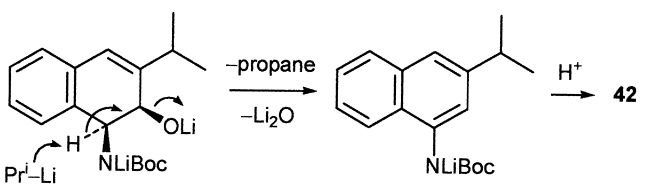


Scheme 11.

absence of a ligand, and with added TMEDA and sparteine, and provided another example of significant ligand affects on product profile. For Pr^{i}Li (2 equiv.) in the absence of a ligand, the desired amino alcohol **41** was obtained in 32% yield. The reaction also yielded several other products, among which the naphthylamine **42** (6%) and the dihydro-isoquinolinol **43** (17%) were isolated; possible reaction pathways leading to **42** and **43** are discussed below. Use of Pr^{i}Li/TMEDA (3 equiv. each) was found to give exclusively naphthylamine **42** (65%), whereas with Pr^{i}Li/sparteine **2** (3 equiv. each), a mixture of the amino alcohol **41** (44%, 71% ee) and naphthylamine **42** (41%) were obtained. On reducing the equivalents of organolithium/(−)-sparteine used (from **3** to **2**), amino alcohol **41** was formed in slightly lower yield (30%), and the amount of naphthylamine **42** formed was reduced more significantly (from 41 to 14%), but an additional product was also isolated, aldehyde **44** (33%).



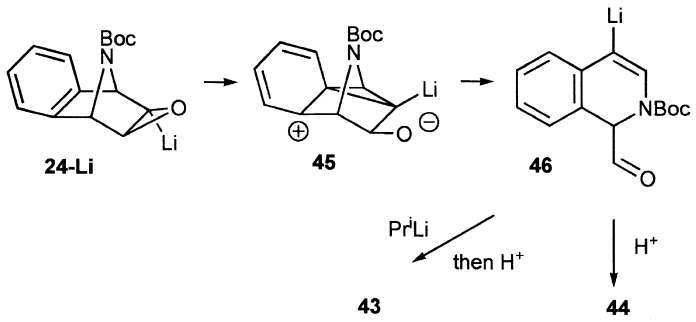
The naphthylamine **42** is likely derived from the amino alcohol **41** by elimination/dehydration. The amino alcohol **41** was shown to be stable to the acidic conditions used for work-up, but when **41** was treated with Pr^{i}Li (3 equiv., Et_2O, −78 °C), a quantitative yield of the naphthylamine **42** was obtained. These observations suggest aromatisation to **42** occurs with concomitant formation of Li_2O (*eg.* Scheme 12).



Scheme 12.

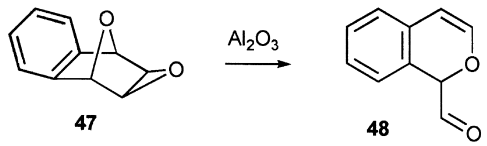
Suggested reaction pathways for the formation of dihydro-isoquinolinol **43** and aldehyde **44** are more speculative (Scheme 13).

π-Participation from the aromatic ring may assist C–O



Scheme 13.

cleavage of the electrophilic[31] lithiated epoxide **24**-Li to give **45**; fragmentation of **45** could then lead to lithiated aldehyde **46** from which aldehyde **44** arises on protonation, and dihydroisoquinolinol **43** (as a 1:1 mixture of rotational isomers or diastereoisomers) via addition of Pr^{i}Li. French and Charlton have reported a related rearrangement of the benzyne–furan cycloadduct-derived epoxide **47** to aldehyde **48** using acidic alumina (Scheme 14).[36]



Scheme 14.

3. Conclusion

Enantioselective nucleophilic ring-opening of unsaturated oxa- and (to a lesser extent) aza-bicyclic compounds, principally being developed by Lautens,[37] results in cycloalkenes bearing the nucleophile in an allylic position. Proceeding via double ring-opening, the chemistry described herein comprises an intermolecular C–C single bond forming reaction with cogeneration of unsaturation and two functional group reorganizations, leading to nucleophile incorporation at a vinylic position and synthetically valuable 1,2-amino alcohol functionality. It provides a new and enantioselective access to sought-after cyclic unsaturated amino alcohols[8] in a regio-, stereo- and enantiocontrolled fashion, and thus has the potential to be a powerful method for organic synthesis. Extensions of the current process to other epoxides, organolithiums and manipulations of the adducts towards targets of biological interest are under investigation.

4. Experimental

4.1. General

All reactions requiring anhydrous conditions were conducted in flame- or oven-dried apparatus under an atmosphere of argon. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl under argon; CH_2Cl_2, pentane, hexane and toluene from CaH_2 under argon. External reaction temperatures are reported unless stated otherwise. Reactions were monitored by TLC using commercially available aluminium-backed plates, pre-coated with a 0.25 mm layer of silica containing fluorescent indicator (Merck). Column chromatography was carried out on Kieselgel 60 (40–63 mm). Petrol refers to the fraction with bp 40–60 °C. Melting points were determined using a Leica VMTG apparatus and are uncorrected. Elemental analyses were performed by Elemental Microanalysis Limited, Okehampton, Devon, UK. $[\alpha]_D$ Values are given in 10^{-1} deg. cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise stated with Bruker JEOL EX400 or Bruker AM500 spectrometers. Chemical shifts are reported relative to $CDCl_3$ [δ_H 7.26, δ_C (central line of triplet) 77.0]. Coupling constants (J) are given in Hz, to the nearest 0.5 Hz. Mass spectra were obtained by the EPSRC National Mass Spectrometry Service Centre at the University of Swansea, using a Micromass Quattro II low resolution triple quadrupole mass spectrometer or, for accurate masses, using a Finnigan MAT 900 XLT high resolution double focusing mass spectrometer with tandem Ion Trap. Chiral stationary phase HPLC was performed using a Daicel Chiralcel OD column (4.6 mm×250 mm) or Daicel Chiralpak AD column (4.6 mm×250 mm) on a Gilson System with 712 Controller Software and a 118 UV–vis detector set at 254 nm. Retention times for major (t_R mj) and minor (t_R mn) enantiomers are given in minutes.

4.1.1. 1,1-Dimethylethyl (2-hydroxy-3-methyleneheptyl)-carbamate 3.[6] To a solution of (−)-sparteine **2** (0.19 cm^3, 0.81 mmol) in Et_2O (1 cm^3) at −78 °C was added Bu^{n}Li (2.3 mol dm^{-3} in pentane; 0.35 cm^3, 0.81 mmol). After 1 h at −78 °C a solution of NBoc epoxide **1** (50 mg, 0.27 mmol) in Et_2O (8 cm^3) was added dropwise. After 1 h at −78 °C the reaction was warmed to 25 °C over 1 h and then sat. aq. NH_4Cl (5 cm^3) was added. The reaction mixture was extracted with Et_2O (3×10 cm^3) and the combined organic extracts were washed with sat. aq. $NaHCO_3$ (15 cm^3), brine (15 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (gradient elution, 30–60% Et_2O–petrol) gave amino alcohol **3** (17 mg, 25%) as a white solid; $[\alpha]_D^{23}$=+2.8 (c 1.0 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate (see Supporting information) was determined to be 45% by chiral HPLC (OD column, 10% Pr^{i}OH in heptane, 0.5 cm^3 min^{-1}, t_R mj, 44.2; t_R mn, 53.9).

4.1.2. *N*-(2-Hydroxy-3-methyleneheptyl)-2-methyl-2-propanesulfonamide 6.[6] Following the above procedure for **3**, but using (−)-sparteine **2** (0.34 cm^3, 1.46 mmol),

Bu^nLi (2.5 mol dm^{-3} in hexanes; 0.59 cm^3, 0.15 mmol) and NBus epoxide **5** (100 mg, 0.49 mmol) gave amino alcohol **6** (89 mg, 69%) as a white solid; $[\alpha]_D^{23}=+4.4$ (*c* 1.0 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate (see Supporting information) was determined to be 24% by chiral HPLC (OD column, 10% Pr^iOH in heptane, 0.5 cm^3 min^{-1}, t_R mj, 56.9; t_R mn, 75.1).

4.1.3. 1-[(1,1-Dimethylethyl)sulfonyl]-1*H*-pyrrole. 2,5-Dimethoxytetrahydrofuran (0.062 cm^3, 0.48 mmol) was added to a stirred suspension of P_2O_5 (91 mg, 0.32 mmol) and $Bu^tSO_2NH_2$[15] (45 mg, 0.32 mmol) in toluene (40 cm^3) at 25 °C. The mixture was then heated to 110 °C for 15 min (the time required for the reaction mixture to change colour from yellow to black). Aq. KOH (2 mol dm^{-3}; 1.25 cm^3) was then added and the organic layer was extracted with Et_2O (3×5 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (gradient elution, 0–2.5% Et_2O–petrol) gave NBus pyrrole (53 mg, 88%) as a white crystalline solid; R_f 0.75 (40% Et_2O–petrol); mp 107–108 °C (Found: C, 51.8; H, 7.0; N, 7.1. $C_8H_{13}NSO_2$ requires C, 51.3; H, 7.0; N, 7.5%); ν_{max}(KBr)/cm^{-1} 2986, 1636, 1479, 1451, 1346, 1180, 1140, 1064 and 1035; δ_H (400 MHz) 7.08–7.07 (2H, m, NCH), 6.34–6.32 (2H, m, CH=) and 1.38 (9H, s, $C(CH_3)_3$); δ_C (100 MHz) 129.7 (NCH), 119.3 (CH=), 69.4 ($C(CH_3)_3$) and 31.5 ($C(CH_3)_3$); *m*/*z* [CI+(NH_3)] 205 ($M+NH_4^+$, 100%), 188 ($M+H^+$, 17), 118 (21) and 68 (45) (Found: $M+H^+$, 188.0749. $C_8H_{14}NSO_2$ requires 188.0745).

4.1.4. *N*-(2-Hydroxy-4-methyl-3-methylenepentyl)-2-methyl-2-propanesulfonamide 7.[6] Following the above procedure for **3**, but using (−)-sparteine **2** (0.34 cm^3, 1.46 mmol), Pr^iLi[38] (2.0 mol dm^{-3} in petrol; 0.73 cm^3, 1.46 mmol) and NBus epoxide **5** (100 mg, 0.49 mmol) gave amino alcohol **7** (48 mg, 39%) as a white solid; $[\alpha]_D^{23}=+3.6$ (*c* 1.0 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate was determined to be 46% by chiral HPLC (OD column, 10% Pr^iOH in heptane, 0.5 cm^3 min^{-1}, t_R mj, 58.4; t_R mn, 72.2).

4.1.5. *N*-[2-Hydroxy-3-[(trimethylsilyl)methyl]-3-butenyl]-2-methyl-2-propanesulfonamide 8.[6] Following the above procedure for **3**, but using (−)-sparteine **2** (0.34 cm^3, 1.46 mmol), $TMSCH_2Li$ (1.00 mol dm^{-3} in pentane; 1.46 cm^3, 1.46 mmol) and NBus epoxide **5** (100 mg, 0.49 mmol) gave amino alcohol **8** (70 mg, 49%) as a white solid; $[\alpha]_D^{23}=+1.8$ (*c* 1.0 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate was determined to be 2% by chiral HPLC (OD column, 10% Pr^iOH in heptane, 0.5 cm^3 min^{-1}, t_R mj, 40.7; t_R mn, 59.7).

4.1.6. 1,1-Dimethylethyl [(1*R,2*S**)-2-hydroxy-(1-methylpropyl)-3-cyclohexen-1-yl]carbamate 13.** (−)-Sparteine **2** (1.14 cm^3, 5 mmol, 3.5 equiv.) was added dropwise to a stirred solution of Bu^sLi (1.3 mol dm^{-3} in cyclohexane; 3.8 cm^3, 5 mmol, 3.5 equiv.) in Et_2O (10 cm^3) at −78 °C. After 1 h, epoxide **12** (300 mg, 1.42 mmol) in Et_2O (4 cm^3) was added. The reaction mixture was stirred at −78 °C for 5 h and then slowly warmed to 25 °C over 10 h. 1 M HCl (5 cm^3) was added and the aqueous layer was extracted with Et_2O (3×20 cm^3). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (5 cm^3) and brine (5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (50% Et_2O–petrol) gave amino cyclohexenol **13** (283 mg, 74%) as a colourless oil; R_f 0.36 (50% Et_2O–petrol); $[\alpha]_D^{24}=-52.8$ (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3438s, 2963s, 1690s, 1500s and 1360s; δ_H (500 MHz) 5.57–5.54 (1H, m, C=CH), 5.14 (1H, br s, NH), 4.01–3.98 (1H, m, C*H*OH), 3.62–3.60 (1H, m, C*H*NHBoc), 2.21–2.16 (2H, m, $=CH_2$), 2.08 (1H, ap. sxt, *J*=7.0, CH), 1.78–1.73 (1H, m, H of CH_2), 1.63–1.49 (2H, m, 2×H of CH_2), 1.47 (9H, s, Bu^t), 1.45–1.31 (1H, m, H of CH_2), 1.07 (1H, d, *J*=7.0 Hz, Me), 1.06 (2H, d, *J*=7.0 Hz, Me) and 0.86 (3H, t, *J*=7.5 Hz, Me); δ_C (125 MHz, 2:1 mixture of rotational isomers observed) 155.4 (C=O), 142.9 and 142.5 (*C*=CH, quat.), 124.5 and 124.1 (C=*C*H), 79.2 (CMe_3), 67.5 and 66.8 (CHOH), 50.9 (CHNH), 40.5 and 38.9 (CH of Bu^s), 29.2 and 28.2 (CH_2), 28.4 (3×Me), 24.8 ($=CH_2$), 23.0 and 22.9 (CH_2), 20.8 and 19.0 (Me) and 12.3 and 11.6 (Me); *m*/*z* (CI) 270 ($M+H^+$, 65%), 213(100) and 196 (65) (Found: $M+H^+$, 270.2069. $C_{15}H_{28}NO_3$ requires 270.2069).

Also isolated was NBoc azanortricyclanol **16**[21] (35 mg, 12%); $[\alpha]_D^{23}=-10.0$ (*c* 1.0 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate of **16** (see Supporting information) was determined to be 65% by chiral HPLC (OD column, 50% EtOH in hexane, 0.5 cm^3 min^{-1}, t_R mj, 18.9; t_R mn, 21.2).

4.1.7. 1,1-Dimethylethyl [(1*R,2*S**)-3-butyl-2-hydroxy-3-cyclohexen-1-yl]carbamate 14.** Following the above procedure for **13**, but using (−)-sparteine **2** (0.16 cm^3, 3 equiv.), Bu^nLi (2.5 mol dm^{-3} in hexanes; 0.28 cm^3, 0.72 mmol, 3 equiv.) and epoxide **12** (50 mg, 0.237 mmol) gave amino cyclohexenol **14** (35 mg, 55%) as a colourless oil; R_f 0.43 (50% Et_2O–petrol); $[\alpha]_D^{24}=-52.2$ (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3436br s, 2957s, 2931s, 1716s, 1691s, 1503s, 1367s and 1169s; δ_H (400 MHz) 5.55 (1H, br s, C=CH), 5.12–5.10 (1H, br d, *J*=7.5 Hz, NH), 3.96 (1H, br s, C*H*OH), 3.66–3.61 (1H, m, C*H*NHBoc), 2.17–2.05 (4H, m, 2×CH_2), 1.75–1.51 (4H, m, 2×CH_2), 1.46 (9H, s, Bu^t), 1.43–1.25 (2H, m, CH_2) and 0.90 (3H, t, *J*=7.0 Hz, Me); δ_C (100 MHz) 155.5 (C=O), 138.3 (HC=*C*, quat.), 125.0 (*C*H=C), 79.2 (CMe_3), 67.8 (CHOH), 50.7 (CHNH), 34.1 (CH_2 of Bu^n), 30.3 (CH_2), 28.4 (3×Me), 24.7 (CH_2), 23.0 (CH_2 of Bu^n), 22.5 (CH_2 of Bu^n) and 14.0 (Me of Bu^n); *m*/*z* (CI) 270 ($M+H^+$, 5%), 214 (10), 196 (55), 170 (M−Boc, 15) and 152 (100) (Found: $M+H^+$, 270.2064. $C_{15}H_{28}NO_3$ requires 270.2069). The ee of the 3,5-dinitrobenzoate of **14** (see Supporting information) was determined to be 67% by chiral HPLC (OD column, 15% EtOH in hexane, 0.5 cm^3 min^{-1}, t_R mj, 14.1; t_R mn, 22.4).

Also isolated was NBoc azanortricyclanol **16**[21] (7 mg, 14%, 35% ee); $[\alpha]_D^{24}=-3.0$ (*c* 1.0 in $CHCl_3$).

4.1.8. 1,1-Dimethylethyl [(1*R,2*S**)-2-hydroxy-3-(1-methylethyl)-3-cyclohexen-1-yl]carbamate 15.** Following the above procedure for **13**, but using (−)-sparteine **2** (0.95 cm^3, 4.1 mmol, 3.5 equiv.), Pr^iLi[38] (1.4 mol dm^{-3} in petrol; 3.0 cm^3, 4.2 mmol, 3.5 equiv.) and epoxide **12** (250 mg, 1.2 mmol) gave amino cyclohexenol **15** (240 mg, 78%) as a white solid; R_f 0.55 (50% Et_2O–petrol); $[\alpha]_D^{24}=-65.0$ (*c* 1.0 in $CHCl_3$); mp 77.5–80.5 °C (from Et_2O–petrol) (Found: C, 65.8; H, 9.8; N, 5.5.

$C_{14}H_{25}NO_3$ requires C, 65.85; H, 9.9; N, 5.5%); ν_{max}(KBr)/cm^{-1} 3437br s, 2960s, 1691s, 1501s and 1367s; δ_H (500 MHz) 5.56 (1H, t, J=3.5 Hz, C=CH), 5.15 (1H, d, J=8.0 Hz, NH), 4.03 (1H, d, J=2.5 Hz, C*H*OH), 3.62–3.58 (1H, m, C*H*NHBoc), 2.38 (1H, septet, J=7 Hz, CH of Pr^i), 2.19–2.08 (2H, m, =CH_2), 1.81–1.69 (1H, m, H of CH_2), 1.60–1.51 (1H, m, H of CH_2), 1.45 (9H, s, Bu^t), 1.06 (3H, d, J=7.0 Hz, Me) and 1.03 (3H, d, J=7.0 Hz, Me); δ_C (125 MHz) 155.5 (C=O), 144.1 (HC=*C*, quat.), 122.9 (H*C*=C), 79.2 (*C*Me_3), 67.0 (CHOH), 50.8 (CHNH), 32.1 (CH of Pr^i), 28.4 (3×Me), 24.7 (=CH_2), 22.9 (Me), 22.6 (Me) and 21.6 (CH_2); m/z (CI) 256 ($M+H^+$, 5%), 156 (5) and 138 (100) (Found: $M+H^+$, 256.1911. $C_{14}H_{26}NO_3$ requires 256.1912). The ee of the 2,4-dinitrobenzoate (see Supporting information) was determined to be 87% by chiral HPLC (AD Column, 50% EtOH in hexane, 1.0 cm^3 min^{-1}, t_R mj, 4.0; t_R mn, 10.0).

4.1.9. 7-(2-Methylpropane-2-sulfinyl)-7-azabicyclo-[2.2.1]hept-2-ene 18. TFA (0.75 cm^3, 9.7 mmol) was added to a solution of alkene **17**[21] (100 mg, 0.51 mmol) in CH_2Cl_2 (7 cm^3) at 0 °C. The reaction mixture was stirred at 25 °C for 4 h. The solvent was removed under reduced pressure and the residue azeotroped with toluene (3×15 cm^3) to give the TFA salt as a dark coloured oil (150 mg, >100%); ν_{max}(film)/cm^{-1} (very broad peaks) 3420 m, 2967 s, 1780 s and 1672 s; δ_H (200 MHz) 8.50 (1H, br s, NH.TFA), 8.20 (1H, br s, NH.TFA), 6.28 (2H, s, HC=CH), 4.63 (2H, s, 2×CH), 2.15 (2H, br d, J=8.5 Hz, 2×H of CH_2) and 1.38 (2H, br d, J=8.5 Hz, 2×H of CH_2). To a solution of the above TFA salt (0.10 g, 0.48 mmol) in CH_2Cl_2 (3 cm^3) at 25 °C was added Et_3N (0.670 cm^3, 4.80 mmol) dropwise. After 1 h, the reaction was cooled to 0 °C and a solution of ice-cold Bu^tSOCl[10] (0.135 g, 0.96 mmol) in CH_2Cl_2 (2 cm^3) was added. After a further 1 h, the mixture was diluted with sat. aq. $NaHCO_3$ (3 cm^3). The aqueous layer was extracted with CH_2Cl_2 (3×5 cm^3) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography (gradient elution, 0–30% Et_2O–petrol) gave the sulfinamide **18** (95 mg, quant.) as a clear colourless oil; R_f 0.25 (30% Et_2O–petrol); ν_{max}(film)/cm^{-1} 2949, 2866, 1589, 1476, 1457, 1360, 1311, 1187, 1077 and 981; δ_H (200 MHz) 7.28 (1H, dd, J=6.0, 2.0 Hz, CH=), 6.16 (1H, dd, J=6.0, 2.0 Hz, CH=), 4.45 (1H, br, s, NCH), 4.33 (1H, br, s, NCH), 2.05–1.80 (2H, m, 2×CH of CH_2), 1.30–1.13 (11H, m, 2×CH of CH_2, $C(CH_3)_3$); δ_C (50 MHz) 136.8 (CH=), 132.9 (CH=), 64.4 (NCH), 61.6 (NCH), 57.5 ($C(CH_3)_3$), 25.3 (CH_2), 23.7 (CH_2) and 22.7 ($C(CH_3)_3$); m/z[CI+(NH_3)] 202 (20%), 200 ($M+H^+$, 100), 184 (17), 112 (22), 100 (22), 98 (55), 96 (87) and 72 (22) (Found: $M+H^+$, 200.1109. $C_{10}H_{18}NOS$ requires 200.1109).

4.1.10. 8-(2-Methylpropane-2-sulfonyl)-8-aza-3-oxatricyclo[3.2.1.0^{2,4}]octane 19. To a solution of sulfinamide **18** (0.42 g, 2.11 mmol) and Na_2EDTA (4×10^{-4} mol dm^{-3} in H_2O; 10.6 cm^3, 0.004 mmol) in MeCN (15 cm^3) at 0 °C was added trifluoroacetone (2.10 cm^3, 23.4 mmol) dropwise. A mixture of $NaHCO_3$ (1.36 g, 16.2 mmol) and oxone (6.43 g, 10.1 mmol) was then added portionwise over 1 h. After 1.5 h the reaction mixture was filtered, the filtrate was diluted with H_2O (50 cm^3) and extracted with CH_2Cl_2 (3×30 cm^3). The combined organic layers were washed with sat. aq. sodium bisulfite, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by column chromatography (gradient elution, 0–100% Et_2O–petrol) gave NBus azanorbornene epoxide **19** (0.38 g, 78%) as a white crystalline solid; R_f 0.33 (30% Et_2O–petrol); mp 104.5–105 °C; (Found: C, 51.7; H, 7.0; N, 7.1. $C_{10}H_{17}NO_3S$ requires C, 51.3; H, 7.0; N, 7.5%); ν_{max}(KBr)/cm^{-1} 3435, 2982, 2875, 1591, 1478, 1319, 1215, 1147, 1122 and 1050; δ_H (400 MHz) 4.16–4.15 (2H, m, 2×NCH), 3.27 (2H, s, 2×OCH), 1.88 (2H, d, J=5.0 Hz, 2×CH_{exo} of CH_2), 1.51 (2H, dd, J=5.0, 13.0 Hz, 2×CH_{endo} of CH_2) and 1.35 (9H, s, $C(CH_3)_3$); δ_C (100 MHz) 60.4 (NCH), 60.1 ($C(CH_3)_3$), 26.4 (CH_2), and 23.9 ($C(CH_3)_3$); m/z [CI+(NH_3)] 249 ($M+NH_4^+$, 100), 233 (23), 216 (20), 112 (28), 100 (20), 96 (24) and 74 (17) (Found: $M+NH_4^+$, 249.1273. $C_{10}H_{21}N_2O_3S$ requires 249.1273).

4.1.11. *N*-[(1*R* *,2*S* *)-3-Butyl-2-hydroxy-3-cyclohexen-1-yl]-2-methyl-2-propanesulfonamide 20. To a stirred solution of (−)-sparteine **2** (0.15 cm^3, 0.65 mmol) in Et_2O (1 cm^3) at −78 °C was added Bu^nLi (2.3 mol dm^{-3} in hexanes; 0.28 cm^3, 0.65 mmol). After 1 h at −78 °C a solution of NBus azanorbornene epoxide **19** (50 mg, 0.22 mmol) in Et_2O (2.5 cm^3) was added and after 5 h at −78 °C the reaction was warmed to 25 °C overnight. Sat. aq. NH_4Cl (5 cm^3) was added to the reaction mixture which was then extracted with Et_2O (3×10 cm^3) and the combined organic layers washed with sat. aq. $NaHCO_3$ (15 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (gradient elution, 30–60% Et_2O–petrol) gave amino alcohol **20** (32 mg, 53%) as a white solid; R_f 0.30 (50% Et_2O–petrol); mp 97–98.5 °C; $[\alpha]_D^{23}$=−22.3 (c 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3484, 3011, 2995, 2991, 2852, 1736, 1735, 1631, 1594, 1583, 1642, 1408, 1400, 1374, 1271, 1122, 1100, 1068 and 977; δ_H (400 MHz) 6.56–6.52 (1H, m, =CH), 4.65 (1H, br, d, J=10.0 Hz, NH), 4.04–4.00 (1H, m, CHO), 3.47–3.39 (1H, m, CHN), 2.16–2.04 (4H, m, =CHCH_2, CH_2C=), 1.83–1.66 (2H, m, CH_2CHN), 1.66–1.27 (13H, m, $CH_3CH_2CH_2$, CH_3CH_2, $C(CH_3)_3$) and 0.90 (3H, t, J=7.0 Hz, CH_2CH_3); δ_C (100 MHz) 138.3 (C=), 124.6 (=CH), 68.7 (CHO), 59.6 ($C(CH_3)_3$), 55.3 (CHN), 34.1 (CH_2C=), 30.2 ($CH_3CH_2CH_2$), 25.0 (=CHCH_2), 24.3 (CH_2CHN), 24.2 ($C(CH_3)_3$), 22.5 (CH_3CH_2) and 14.2 ($CH_3(CH_2)_3$); m/z [CI+(NH_3)] 307 ($M+NH_4^+$, 100%), 291 (28), 272 (32), 249 (30), 170(25), 155 (56), 137 (25) and 52 (27) (Found: $M+NH_4^+$, 307.2058. $C_{14}H_{31}N_2O_3S$ requires 307.2055). The ee of the 3,5-dinitrobenzoate (see Supporting information) was determined to be 40% by chiral HPLC (OD column, 15% EtOH in hexane, 0.5 cm^3 min^{-1}, $t_R$mn, 15.6; $t_R$mj, 25.2).

Also isolated was NBus azanortricyclanol **16** (Bus=Boc) (1.5 mg, 3%): R_f 0.20 (50% Et_2O in petrol); $[\alpha]_D^{23}$=−7.7 (c 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3463, 3010, 2982, 1463, 1420, 1402, 1371, 1206, 1111, 1006 and 964; δ_H (500 MHz) 3.98 (1H, s, CHO), 3.75 (1H, s, NC*H*CH_2), 3.49 (1H, dd, J=4.5, 4.5 Hz, NC*H*CHCH_2), 1.66 (2H, s, CH_2), 1.64–1.60 (2H, m, NHCHC*H*CH_2, OH), 1.54–1.49 (1H, m, OCHC*H*CH) and 1.46 (9H, s, $C(CH_3)_3$); δ_C (100 MHz) 77.0 ($C(CH_3)_3$), 75.7 (CHO), 60.5 (N*C*HCH_2), 35.8 (N*C*HCH), 30.8 (CH_2), 24.2 (($CH_3)_3$C), 17.8 (OCH*C*HCH)

and 14.6 (NHCH*C*HCH$_2$); *m*/*z*[CI+(NH$_3$)] 249 (M+NH$_4^+$, 64%), 232 (M+H$^+$, 100), 192 (19), 190 (57), 173 (41), 155 (25), 152 (12), 112 (49), 110 (84), 108 (16), 96 (11), 94 (22), 86 (17) and 80 (16) (Found: M+H$^+$, 232.1006. $C_{10}H_{18}NO_3S$ requires 232.1007). The ee of the 3,5-dinitrobenzoate derivative (see Supporting information) was determined to be 35% by chiral HPLC (OD column 50% EtOH in hexane, 0.5 cm^3 min^{-1}, $t_R$mj, 26.4; $t_R$mn, 32.9).

4.1.12. *N*-[(1*R* *,2*S* *)-2-hydroxy-3-(1-methylethyl)-3-cyclohexen-1-yl]-2-methyl-2-propanesulfonamide 21. Following the procedure for amino alcohol **20** above, but using (−)-sparteine **2** (0.13 cm^3, 0.57 mmol), Pr^{i}Li[38] (1.1 mol dm^{-3} in petrol; 0.53 cm^3, 0.58 mmol) and NBus azanorbornene epoxide **19** (44 mg, 0.19 mmol) gave amino alcohol **21** (21 mg, 42%) as a white solid; R_f 0.13 (50% Et$_2$O–petrol); mp 95–95.5 °C; $[\alpha]_D^{23}=-56$ (*c* 1.0 in CHCl$_3$); ν_{max}(KBr)/cm^{-1} 3460, 3277, 2957, 2872, 2839, 1457, 1395, 1365, 1300, 1212, 1187, 1167, 1126, 1081, 1064, 1032 and 992; δ_H (400 MHz) 5.58 (1H, t, *J*=3.0 Hz, =CH), 4.75–4.63 (1H, m, NH), 4.13–4.06 (1H, m, CHO), 3.45–3.37 (1H, m, CHN), 2.36 (1H, septet, *J*=6 Hz, C*H*(CH$_3$)$_2$), 2.34–2.08 (2H, m, =CHC*H*$_2$), 1.86–1.67 (2H, m, NHCHC*H*$_2$), 1.39 (9H, s, C(C*H*$_3$)$_3$), 1.06 (3H, d, *J*=7.0 Hz, CHC*H*$_3$) and 0.85 (3H, dd, *J*=7.0, 14.5 Hz, CHC*H*$_3$); δ_C (100 MHz) 144.1 (C=), 122.6 (=CH), 67.9 (CHO), 65.8 (*C*(CH$_3$)$_3$), 55.5 (CHN), 32.2 (*C*H(CH$_3$)$_2$), 24.8 (*C*H$_2$CHN), 24.2 (*C*H$_2$C=), 22.6 ((*C*H$_3$)$_3$C) and 21.7 (*C*H$_3$)$_2$CH); *m*/*z* [CI+(NH$_3$)] 293 (M+NH$_4^+$, 91%), 275 (14), 258 (100), 155 (23), 138 (39) and 123 (31) (Found: M+NH$_4^+$, 293.1900. $C_{13}H_{29}N_2O_3S$ requires 293.1899). The ee of the 3,5-dinitrobenzoate derivative (see Supporting information) was determined to be 64% by chiral HPLC (OD column, 15% EtOH in hexane, 0.5 cm^3 min^{-1}, $t_R$mn, 21.4; $t_R$mj, 25.4).

4.1.13. 1,1-Dimethylethyl (3aα,4β,7β,7aα)-5-tributylstannyl-3a,4,5,6,7,7a-octahydro-2,2-dimethyl-5-[(4-methylphenyl)sulfonyl]-1,3-benzodioxol-4,7-imine-8-carboxylate 28. BuSn$_3$H (2.604 g, 8.9 mmol) and AIBN (0.04 g, 0.24 mmol) were added to a solution of alkene **25**[24] (1.523 g, 3.6 mmol) in toluene (16 cm^3) and the mixture heated to 80 °C. After 1 h the reaction mixture was cooled, adsorbed onto SiO$_2$ and purified by column chromatography (20% EtOAc–petrol) to give a mixture of stannanes **28** (2.281 g, 89%) as a colourless oil; R_f 0.61 (20% EtOAc–petrol); ν_{max}/cm^{-1} 3438br, m, 2958s, 2928s, 2872m, 1704s, 1597w, 1403s, 1323m, 1261m, 1210m, 1148s, 1107m, 1088 m, 1064 m, 901m, 813m, 733m, 668s and 584s; δ_H (200 MHz) 7.75 (2H, d, *J*=8 Hz, Ar), 7.35 (2H, d, *J*=8 Hz, Ar), 5.20 (1H, ap. d, *J*=5.5 Hz, 6-H), 4.35 (1H, ap. d, *J*=5.5 Hz,), 4.30–4.18 (2H, m), 3.63–3.45 (1H, m), 2.45 (3H, s, Ar*Me*), 1.43 (9H, s, OCMe$_3$), 1.70–1.15 (25H, m) and 0.89 (9H, t, *J*=7 Hz, 3×CH$_2$*Me*); δ_C (100 MHz) 145.2, 130.3, 127.9, 110.0, 83.3, 80.2, 77.6, 63.3, 60.1, 28.9, 28.4, 27.4, 25.5, 21.6, 13.7 and 9.0; *m*/*z* [CI+(NH$_3$)] 714 (M+H$^+$, 100%), 713 (M$^+$, 50), 712 (70) and 710 (35) (Found: M+H$^+$, 714.2862. $C_{33}H_{56}NO_6S^{120}Sn$ requires 714.2850).

4.1.14. 1,1-Dimethylethyl (3aα,4β,7β,7aα)-3a,4,7,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxol-4,7-imine-8-carboxylate 26. TBAF (1 mol dm^{-3} in THF; 10 cm^3, 0.01 mol) was added to a solution of **28** (3.0 g, 4.2 mmol) in THF (25 cm^3) and the mixture then heated under reflux. After 2 h the reaction mixture was cooled and evaporated under reduced pressure. Purification of the residue by column chromatography (20% EtOAc–petrol) gave alkene **26** (1.057 g, 94%) as a white solid; R_f 0.3 (20% EtOAc–petrol); mp 63–65 °C; ν_{max}/cm^{-1} 2797m, 2936m, 1704s, 1369m, 1209m, 1159s, 1112m, 1089w, 1060m, 882w and 857w; δ_H (400 MHz, 2 rotamers observed) 6.34 and 6.29 (2H, two m, 5,6-H), 4.72 and 4.63 (2H, two m, 4,7-H), 4.28 (2H, s, 3a,7a-H), 1.48 (3H, s, Me), 1.46 (9H, s, OCMe$_3$) and 1.31 (3H, s, Me); δ_C (100 MHz) 154.4 (C=O), 136.7 and 135.5 (C5, C6), 115.8 (Me$_2$*C*O$_2$), 79.8 (O*C*Me$_3$), 79.8 and 79.4 (C3a, C7a), 62.8 and 62.1 (C4, C7), 28.3 (OC*Me*$_3$), 25.2 (Me) and 23.3 (Me); *m*/*z* [Cl$^+$] 268 (M+H$^+$, 25%), 169 (100), 100 (40) and 85 (18) (Found: M+H$^+$, 268.1553. $C_{14}H_{22}NO_4$ requires 268.1549).

4.1.15. 1,1-Dimethylethyl (3aα,4β,7β,7aα)-3a,4,7,7a-octahydro-2,2-dimethyl-1,3-benzodioxol-5,6-oxiren-4,7-imine-8-carboxylate 22. Na$_2$EDTA (4×10^{-4} mol dm^{-3} in H$_2$O; 20 cm^3, 0.008 mmol) was added to a solution of alkene **26** (1.057 g, 3.96 mmol) in MeCN (29 cm^3). The resulting homogeneous solution was cooled to 0 °C, followed by addition of trifluoroacetone (4 cm^3, 45 mmol). To this solution a mixture of NaHCO$_3$ (2.4 g, 29 mmol) and oxone (11.2 g, 18 mmol) was added in portions. After 2.5 h the mixture was poured into H$_2$O (200 cm^3) and extracted with CH$_2$Cl$_2$ (3×80 cm^3). The combined organic extracts were dried (MgSO$_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (50% EtOAc–petrol) gave epoxide **22** (0.993 g, 89%) as a white solid; R_f 0.45 (50% EtOAc–petrol); mp 116–118 °C; ν_{max}/cm^{-1} 2980s, 2935m, 1705s, 1371s, 1299m, 1248m, 1211m, 1169s, 1112m, 1079m, 992m, 861m, 783w and 687m; δ_H (400 MHz, 2 rotamers observed) 4.43 and 4.28 (2H, two s, 3a,7a-H), 4.27 (2H, m, 4,7-H), 3.22 and 3.19 (2H, two d, *J*=3, 5,6-H),1.46 (12H, two s, OCMe$_3$ and MeCO$_2$) and 1.29 (3H, s, MeCO$_2$); δ_C (100 MHz) 157.2 (C=O), 113.0 (Me$_2$*C*O$_2$), 80.2 (O*C*Me$_3$), 80.0 and 79.3 (C3a, C7a), 60.9 and 60.3 (C5, C6), 48.0 and 47.4 (C4, C7), 28.2 (OC*Me*$_3$), 26.0 (Me), and 25.1 (Me); *m*/*z*[CI+(NH$_3$)] 284 (M+H$^+$, 10%), 245 (35), 184 (100), and 168 (20) (Found: M+H$^+$, 284.1496. $C_{14}H_{22}NO_5$ requires 284.1498).

4.2. Reaction of epoxide 22 with Bu^{n}Li

(a, Table 1, entry 4) Epoxide **22** (100 mg, 0.353 mmol) was added to a solution of Bu^{n}Li (1.5 mol dm^{-3} in hexanes; 0.80 cm^3, 1.24 mmol, 3.5 equiv.) and sparteine **2** (0.28 cm^3, 1.24 mmol, 3.5 equiv.) in Et$_2$O (3.5 cm^3) at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (14 h), and gave, following standard work-up and purification of the residue by column chromatography (50% EtOAc–petrol), four new compounds described below and recovered epoxide **22** (7 mg).

4.2.1. 1,1-Dimethylethyl (3aα,4β,5β,7aα)-[6-butyl-3a,4,5,7a-tetrahydro-5-hydroxy-2,2-dimethyl-1,3-benzodioxol-4-yl]carbamate 29. (19 mg, 16%) as a colourless liquid; R_f 0.50 (20% EtOAc–petrol), 0.75 (50% EtOAc–petrol); ν_{max}(neat)/cm^{-1} 3524w, 3448w, 2959m, 2931s,

2873w, 1715s, 1505s, 1368s, 1229m, 1167s, 1047s and 876m; δ_H (400 MHz) 5.61 (1H, d, J=9 Hz, NH), 5.40 (1H, m, =CH), 4.61 (1H, m, 7a-H), 4.25 (1H, m, 3a-H), 3.92–3.80 (2H, m, 4-H and 5-H), 2.82 (1H, d, J=11 Hz, OH), 2.20 (2H, t, J=8 Hz, =CCH_2), 1.47 (9H, s, $OCMe_3$), 1.52–1.34 (4H, m, 2×CH_2), 1.41 (3H, s, $MeCO_2$), 1.34 (3H, s, $MeCO_2$) and 0.91 (3H, t, J=7 Hz, Me); δ_C (100 MHz) 155.5 (C=O), 141.4 (=C), 121.3 (=CH), 110.1 (O_2CMe), 79.8 ($OCMe_3$), 76.0 (C3a), 73.7 (C7a), 68.5 (C5), 49.3 (C4), 34.1 (CH_2), 29.6 (CH_2), 28.4 ($OCMe_3$), 28.2 ($MeCO_2$), 26.5 ($MeCO_2$), 22.4 (CH_2) and 13.9 (CH_2Me); m/z [CI+(NH_3)] 342 ($M+H^+$, 55%), 284 (100), 245(20), 228 (61) and 224 (35) (Found: $M+H^+$, 342.2280. $C_{18}H_{32}NO_5$ requires 342.2280).

4.2.2. 1,1-Dimethylethyl [(1*R,2*S**)-3-butyl-2-hydroxy-5-oxo-3-cyclohexen-1-yl]carbamate 30.** (16 mg, 16%) as a colourless liquid; R_f 0.50 (50% EtOAc–petrol); $[\alpha]_D^{23}=-16$ (c 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3364br s, 2960s, 2932s, 2873m, 1674s, 1504m, 1367m, 1283m, 1250m, 1164s, 1061w and 1017w; δ_H (400 MHz) 5.90 (1H, s, =CH), 5.00 (1H, d, J=8 Hz, NH), 4.35 (1H, br s, C*H*OH), 4.20 (1H, m, C*H*NHBoc), 2.65–2.52 (2H, m, CH_2C=O), 2.38 (2H, t, J=7 Hz, =CCH_2), 1.62–1.26 (4H, m, CH_2CH_2), 1.46 (9H, s, $OCMe_3$) and 0.94 (3H, t, J=7 Hz, Me); δ_C (125 MHz) 196.8 (C=O), 165.0 (=C), 155.0 (CO_2), 126.2 (=CH), 80.0 ($OCMe_3$), 68.6 (CHOH), 50.2 (CHNH), 39.0 (CH_2C=O), 34.5 (=CCH_2), 29.0 (CH_2), 28.3 ($OCMe_3$), 22.3 (CH_2) and 13.7 (Me); m/z [CI+(NH_3)] 301 ($M+NH_4^+$, 18%), 284 ($M+H^+$, 42), 268 (30), 245 (100), 229 (70), 212 (35), 150 (40), 135 (60) and 79 (32).

4.2.3. 1,1-Dimethylethyl (3aα,4β,7β,7aα)-5-butyl-3a,4,7,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxol-4,7-imine-8-carboxylate 31. (7.5 mg, 7%) as a colourless oil; R_f 0.41 (20% EtOAc–petrol); ν_{max}(neat)/cm^{-1} 2959s, 2933s, 2874w, 1709s, 1624w, 1368s, 1300m, 1160s, 1102m, 1063s and 859w; δ_H (400 MHz, 2 rotamers observed) 5.82 and 5.75 (1H, two m, =CH), 4.62 and 4.55 (1H, two m, CHN), 4.48 and 4.36 (1H, two m, CHN), 4.27 (2H, dd, J=15, 5 Hz, 3a,7a-H), 2.20–2.05 (2H, m, =CCH_2), 1.47 (3H, s, $MeCO_2$), 1.45 (9H, s, Me_3CO), 1.29 (3H, s, $MeCO_2$), 1.50–1.25 (4H, m, CH_2CH_2), 1.29 (3H, s, $MeCO_2$) and 0.88 (3H, br t, J=7 Hz, Me); m/z [CI+(NH_3)] 324 ($M+H^+$, 55), 224 (100), 123 (35), 100 (28) and 90 (80) (Found: $M+H^+$, 324.2176. $C_{18}H_{30}NO_4$ requires 324.2175).

4.2.4. 1,1-Dimethylethyl (3-butyl-2-hydroxyphenyl)carbamate 32. (9 mg, 10%) as a colourless oil; R_f 0.54 (20% EtOAc–petrol); ν_{max}(neat)/cm^{-1} 3322br m, 2957s, 2930s, 2871w, 1683s, 1526s, 1480s, 1368m, 1283m, 1246m, 1159s, 1067m, 866w and 770w; δ_H (400 MHz) 8.2 (1H, br s, OH), 6.96 (1H, dd, J=7, 2 Hz, 4-H), 6.85 (1H, dd, J=8, 2 Hz, 6-H), 6.79 (1H, dd, J=8, 7 Hz, 5-H), 6.62 (1H, br s, NH), 2.67 (2H, t, J=8 Hz, CH_2), 1.64–1.56 (2H, m, CH_2), 1.54 (9H, s, $OCMe_3$), 1.38 (2H, sxt, J=7 Hz, CH_2) and 0.94 (3H, t, J=7 Hz, Me); δ_C (100 MHz) 155.3 (C=O), 146.1 (=COH), 132.8 (=CCH_2), 126.6 (C4), 125.3 (=CNH), 120.1 (C6), 119.6 (C5), 82.1 ($OCMe_3$), 32.1 (CH_2), 30.2 (CH_2), 28.2 ($OCMe_3$), 22.7 (CH_2) and 14.0 (CH_2); m/z (EI) 266 ($M+H^+$, 20%), 265 (M^+, 100), 238 (15) and 225 (22); m/z [CI+(NH_3)] 283 ($M+NH_4^+$, 48%), 266 ($M+H^+$, 100), 227 (75), 165 (37), 214 (100), 198 (95) and 170 (35) (Found: $M+H^+$, 266.1752. $C_{15}H_{24}NO_3$ requires 266.1756).

(b, Table 1, entry 6) Epoxide **22** (100 mg, 0.353 mmol) was added to a solution of Bu^{n}Li (1.4 mol dm^{-3} in hexanes; 0.90 cm^3, 1.24 mmol, 3.5 equiv.) and bisoxazoline **4** (0.36 g, 1.24 mmol, 3.5 equiv.) in Et_2O (3.5 cm^3) at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (14 h), and gave, following standard work-up and purification of the residue by column chromatography (50% EtOAc–petrol), aminophenol **32** (49 mg, 52%, 69% based on recovered epoxide **22**).

(c, Table 1, entry 8) Epoxide **22** (100 mg, 0.353 mmol) was added to a solution of Bu^{n}Li (1.5 mol dm^{-3} in hexanes; 0.80 cm^3, 1.24 mmol, 3.5 equiv.) and sparteine **2** (0.28 cm^3, 1.24 mmol, 3.5 equiv.) in toluene (3.5 cm^3) at −78 °C. After 5 h at 78 °C the reaction was quenched to give, following standard work-up and purification of the residue by column chromatography (50% EtOAc–petrol), amino alcohol **29** (49 mg, 41%, 64% based on recovered epoxide **22**). $[\alpha]_D^{23}=-9$ (c 1.0 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate derivative (see Supporting information) was determined to be 76% by chiral HPLC (OD column, 10% EtOH in heptane, 1.0 cm^3 min^{-1}, $t_R$mj, 10.5; $t_R$mn, 14.2).

4.2.5. 1,1-Dimethylethyl (1*R,2*R**,4*S**,5*S**)-8-aza-3-oxatricyclo[3.2.1.0^{2,4}]-6-octene-8-carboxylate 23.** Peracetic acid (38% w/v in acetic acid; 1.38 cm^3, 7.77 mmol) was added to a mixture of diene **38**[33] (1.0 g, 5.2 mmol), NaOAc (20 mg) and Na_2CO_3 (1.6 g) in CH_2Cl_2 (20 cm^3) at 0 °C. The reaction mixture was stirred for a total of 36 h, with further peracetic acid (1.38 cm^3) added over this period. CH_2Cl_2 (10 cm^3) and 1 M HCl (5 cm^3) were then added and the aqueous layer was extracted with CH_2Cl_2 (3×20 cm^3). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ (10 cm^3) and brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Purification of the residue by column chromatography (75% Et_2O–petrol) gave epoxide **23** (0.83 g, 77%) as a white solid; R_f 0.28 (50% Et_2O–petrol); mp 108–109 °C (from Et_2O) (Found: C, 63.1; H, 7.25; N, 6.5. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.25; N, 6.7%); ν_{max}(KBr)/cm^{-1} 1698s, 1380s, 1258s, 1172s, 1101s and 906m; δ_H (400 MHz) 6.56–6.51 (2H, m, HC=CH), 4.71 (1H, d, J=2.0 Hz, CH), 4.58 (1H, dd, J=2.0, 0.5 Hz, CH), 3.48 (2H, 2×d, J=3.5 Hz, 2×CH–O) and 1.47 (9H, s, Bu^t); δ_C (100 MHz) 156.1 (C=O), 138.2 and 138.0 (C=C), 80.1 (CMe_3), 61.0 and 60.7 (2×CH–O), 57.1 and 56.7 (2×CH) and 28.2 and 28.1 (3×Me); m/z (CI) 210 ($M+H^+$, 15%), 155 (12), 110 (15) and 80 (100) (Found: $M+H^+$, 210.1131. $C_{11}H_{16}NO_3$ requires 210.1130).

4.2.6. 1,1-Dimethylethyl [(1*R,2*S**)-2-hydroxy-3-(1-methylethyl)-3,5-cyclohexadien-1-yl]carbamate 39.** (a) Epoxide **23** (70 mg, 0.34 mmol) was added to a solution of Pr^{i}Li (1.4 mol dm^{-3} in petrol; 0.50 cm^3, 0.70 mmol) in Et_2O at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (1 h), and gave, following standard work-up and purification of the residue by column chromatography (gradient elution, 30–50% Et_2O–petrol) diene **39** (19 mg, 22%) as a clear colourless oil; R_f 0.40 (50% Et_2O–petrol); ν_{max}(film)/cm^{-1} 3430br m, 2965s, 1694s, 1499s, 1367s, and 1167s; δ_H (500 MHz) 6.01–5.97 (1H, m, *H*C=CH), 5.75 (1H, d, J=5.5 Hz, HC=C*H*), 5.56 (1H, dd, J=9.5,

2.0 Hz, C═CH), 5.23–5.21 (1H, m, NH), 4.45 (1H, s, C*H*NHBoc), 3.94 (1H, d, *J*=4.0 Hz, C*H*OH), 2.49 (1H, septet, *J*=7.0 Hz, CH of Pr^i), 1.68 (1H, br s, OH), 1.47 (9H, s, Bu^t), 1.12 (3H, d, *J*=7.0 Hz, Me) and 1.11 (3H, d, *J*=7.0 Hz, Me); δ_C (100 MHz) 155.9 (C═O), 147.5 (HC═*C*, quat.), 127.1 (H*C*═C), 124.7 (H*C*═CH), 117.5 (HC═*C*H), 79.6 (*C*Me$_3$), 67.8 (CHOH), 52.4 (CHNH), 32.4 (CH of Pr^i), 28.4 (3×Me), 22.0 (Me) and 21.3 (Me); *m*/*z* (CI) 196 (10%), 180 (15), 154 (M−Boc, 50) and 136 (M−NHBoc, 100) (Found: M+H$^+$, 254.1756. $C_{14}H_{24}NO_3$ requires 254.1756).

(b) Epoxide **23** (70 mg, 0.34 mmol) was added to a solution of Pr^{i}Li (1.4 mol dm^{-3} in petrol; 0.50 cm^3, 0.70 mmol) and (−)-sparteine **2** (0.16 cm^3, 0.70 mmol) in Et$_2$O at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (1 h), and gave, following standard work-up and purification of the residue by column chromatography (gradient elution, 30–0% Et$_2$O–petrol) gave diene **39** (27 mg, 32%) as a clear colourless oil; $[\alpha]_D^{24}$=−40.4 (*c* 1.0 in CHCl$_3$). The ee was determined to be 79% by chiral HPLC (AD Column, 10% EtOH in hexane, 0.4 cm^3 min^{-1}, t_R mj, 12.0; t_R mn, 15.5).

4.2.7. 1,1-Dimethylethyl (1a*R,2*R**,7*S**,7a*S**)-1a,2,7,7a-tetrahydronaphth[2,3-b]oxiren-2,7-imine-8-carboxylate 24.** Oxone (5.1 g, 8.3 mmol) and Na$_2$EDTA (16 mg, 0.04 mmol) in H$_2$O (21 cm^3) was added slowly (over 1 h) to a vigorously stirred mixture of alkene **40**[34] (200 mg, 0.82 mmol), NaHCO$_3$ (1.4 g, 17 mmol) and Bu$_4$NHSO$_3$ (56 mg, 0.19 mmol) in acetone (0.7 cm^3) and CH$_2$Cl$_2$ (10 cm^3). The pH was maintained at 7.8–8.0 by the addition of NaHCO$_3$. The reaction mixture was stirred vigorously for a total of 3 days with further addition of oxone (5 g, 8.1 mmol). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3×30 cm^3). The organic layers were combined, dried (MgSO$_4$) and evaporated under reduced pressure to yield a cream solid. Purification of the residue by column chromatography (gradient elution, 20–50% Et$_2$O–petrol) gave epoxide **24** (170 mg, 80%) as a white solid; R_f 0.47 (50% Et$_2$O–petrol); mp (Et$_2$O–petrol) 123.5–124.5 °C (Found: C, 69.5; H, 6.5; N, 5.4. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%); ν_{max}(KBr)/cm^{-1} 2977m, 1709s, 1371s, 1253s and 1169s; δ_H (400 MHz) 7.34–7.29 (2H, m, 2×CH of Ar), 7.18–7.13 (2H, m, 2×CH of Ar), 5.16 (1H, s, CH), 5.04 (1H, s, CH), 3.47 (1H, d, *J*=3.5 Hz, CH–O), 3.45 (1H, d, *J*=3.5 Hz, CH–O) and 1.50 (9H, s, Bu^t); δ_C (100 MHz) 156.6 (C═O), 144.0 and 143.5 (2×C of Ar, quat.), 126.9 and 126.8 (2×CH of Ar), 121.7 and 121.5 (2×CH of Ar), 80.3 (*C*Me$_3$), 62.3 and 61.4 (2×CH), 55.2 and 54.7 (2×CH–O) and 28.2 (3×Me); *m*/*z* (CI) 260 (M+H$^+$, 5%), 160 (M−Boc, 15) and 130 (100) (Found: M+H$^+$, 260.1289. $C_{15}H_{18}NO_3$ requires 260.1286).

4.2.8. Reaction of epoxide 24 with Pr^{i}Li. (a) Epoxide **24** (80 mg, 0.31 mmol) was added to a solution of Pr^{i}Li (1.4 mol dm^{-3} in petrol; 0.44 cm^3, 0.62 mmol) in Et$_2$O at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (1 h), and following standard work-up the residue by was purified by column chromatography (20% Et$_2$O–petrol).

First to elute was 1,1-dimethylethyl [3-(1-methylethyl)-naphthalen-2-yl]carbamate **42** (5 mg, 6%) isolated as a white solid; R_f 0.64 (50% Et$_2$O–petrol); mp 110–112 °C; ν_{max}(film)/cm^{-1} 3336br s, 2963m, 1696s, 1534s, 1367s and 1159s; δ_H (400 MHz) 7.85–7.80 (3H, m, 3×CH of Ar), 7.47–7.45 (3H, m, 3×CH of Ar), 6.85 (1H, br s, NH), 3.07 (1H, septet, *J*=7.0 Hz, CH of Pr^i), 1.58 (9H, s, Bu^t) and 1.36 (6H, d, *J*=7.0 Hz, 2×Me); δ_C (100 MHz) 153.4 (C═O), 146.6 (2×C of Ar, quat.), 134.2 (C of Ar, quat.), 132.8 (C of Ar, quat.), 128.4 (CH of Ar), 125.8 (CH of Ar), 125.2 (CH of Ar), 120.5 (CH of Ar), 120.2 (CH of Ar), 118.4 (CH of Ar), 80.5 (*C*Me$_3$), 34.3 (CH of Pr^i), 28.4 (3×Me of Boc) and 23.8 (2×Me); *m*/*z* (EI) 285 (M$^+$, 10%), 229 (M−CMe$_3$, 75), 185 (M−Boc, 40), 170 (50) and 57 (100) (Found: M$^+$, 285.1729. $C_{18}H_{23}NO_2$ requires 285.1729).

Second to elute was 1,1-dimethylethyl 1-(1-hydroxy-2-methylpropyl)-1*H*-isoquinoline-2-carboxylate **43** (16 mg, 17%) isolated as a clear colourless oil; R_f 0.55 (50% Et$_2$O–petrol); ν_{max}(film)/cm^{-1} 3483br w, 2975m, 1707s, 1629m, 1353s and 1166s; δ_H (400 MHz) (1:1 mixture of rotational isomers or diastereoisomers observed) 7.27–7.08 (4H, m, 4×CH of Ar), 7.01 and 6.85 (1H, 2×d, *J*=8.0, *H*C═CH), 5.92 and 5.79 (1H, 2×d, *J*=8.0 Hz, HC═C*H*), 5.39 and 5.17 (1H, 2×d, *J*=6.5 Hz, C(1)H), 3.52–3.49 (1H, m, C*H*OH), 1.73 (1H, septet, *J*=6.5 Hz, CH of Pr^i), 1.55 and 1.52 (9H, 2×s, Bu^t), 1.46–1.45 and 1.26–1.24 (1H, 2×m, OH), 1.06 (3H, d, *J*=7.0 Hz, Me) and 1.01 (3H, d, *J*=7.0 Hz, Me); δ_C (100 MHz) (4:3 mixture of rotational isomers or diastereoisomers observed) 152.3 and 152.0 (C═O), 131.7 and 131.4 (C of Ar, quat.), 128.9 and 128.6 (C of Ar, quat.), 128.3, 128.1, 127.9, 127.8 and 126.6 (3×CH of Ar), 126.4 and 126.3 (*C*═C), 124.8 and 124.6 (3×CH of Ar), 109.1 and 108.2 (C═*C*), 82.1 and 81.7 (*C*Me$_3$), 77.8 and 77.1 (CHOH), 57.4 and 56.5 (C2), 28.8 (CH of Pr^i), 28.4, 28.3 and 28.2 (3×Me), 20.6 (Me) and 16.6 and 16.4 (Me); *m*/*z* (EI) 303 (M$^+$, 80%) and 247 (M−CMe$_3$, 100) (Found: M$^+$, 303.1829. $C_{18}H_{25}NO_3$ requires 303.1834).

Third to elute was 1,1-dimethylethyl [(1*R**,2*S**)-1,2-dihydro-2-hydroxy-3-(1-methylethyl)naphthalen-1-yl]-carbamate **41** (30 mg, 32%) isolated as a clear colourless oil; R_f 0.45 (50% Et$_2$O–petrol); ν_{max}(film)/cm^{-1} 3432br w, 2965m, 1716s, 1498s, 1367m and 1170s; δ_H (400 MHz) 7.32–7.30 (1H, m, CH of Ar), 7.25–7.23 (2H, m, 2×CH of Ar), 7.11–7.09 (1H, m, CH of Ar), 6.30 (1H, br s, C═CH), 5.40–5.38 (1H, m, NH), 4.93–4.90 (1H, m, C*H*NHBoc), 4.08 (1H, d, *J*=4.0 Hz, C*H*OH), 2.59 (1H, septet, *J*=7.0 Hz, CH of Pr^i), 1.53 (9H, s, Bu^t), 1.21 (3H, d, *J*=7.0 Hz, Me) and 1.19 (3H, d, *J*=7.0 Hz, Me); δ_C (100 MHz) 156.3 (C═O), 147.4 (C of Ar, quat.), 133.0 (C of Ar, quat.), 132.8 (CH═*C*, quat.), 127.7 (CH of Ar), 127.6 (CH of Ar), 126.7 (CH of Ar), 125.7 (H*C*═C), 122.1 (CH of Ar), 79.7 (*C*Me$_3$), 68.7 (CHOH), 54.0 (*C*HNHBoc), 32.8 (CH of Pr^i), 28.4 (3×Me), 21.8 (Me) and 21.5 (Me); *m*/*z* (EI) 303 (M$^+$, 30%), 285 (35) and 247 (M−CMe$_3$, 100) (Found: M$^+$, 303.1835. $C_{18}H_{25}NO_3$ requires 303.1834).

(b) Epoxide **24** (70 mg, 0.27 mmol) was added to a solution of Pr^{i}Li (1.0 mol dm^{-3} in petrol; 0.81 cm^3, 0.81 mmol) and TMEDA (0.13 cm^3, 0.86 mmol) in Et$_2$O at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (1 h), and gave, following standard work-up and purification of the residue by column chromatography (20% Et$_2$O–petrol) naphthylamine **42** (50 mg, 65%).

(c) Epoxide **24** (80 mg, 0.31 mmol) was added to a solution of Pr^{i}Li (1.0 mol dm^{-3} in petrol; 0.62 cm^3, 0.62 mmol) and (−)-sparteine **2** (0.15 cm^3, 0.65 mmol) in Et_2O at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (1 h), and following standard work-up the residue by was purified by column chromatography (20% Et_2O–petrol).

First to elute was naphthylamine **42** (12 mg, 14%). Second to elute was 1,1-dimethylethyl 1-formyl-1*H*-isoquinoline-2-carboxylate **44** (26 mg, 33%) isolated as a clear colourless oil; R_f 0.55 (50% Et_2O–petrol); ν_{max}(film)/cm^{-1} 3397br s, 2978m, 1715s, 1630m, 1369s and 1160s; δ_H (400 MHz) (2:1 mixture of rotational isomers observed) 9.46 and 9.42 (1H, 2×s, H–C═O), 7.31–7.22 (3H, m, 3×CH of Ar), 7.13 and 6.97 (1H, 2×d, J=8.0 Hz, *H*C═CH), 7.06 (1H, d, J=7.0 Hz, CH of Ar), 5.79 and 5.59 (1H, 2×s, C(1)H), 5.71 and 5.65 (1H, 2×d, J=8.0 Hz, HC═C*H*), and 1.55 and 1.52 (9H, 2×s, Bu^t); δ_C (100 MHz) (2:1 mixture of rotational isomers observed) 194.7 and 194.4 (C═O of aldehyde), 151.9 (C═O), 131.3 (C of Ar, quat.), 129.2 and 129.0 (CH of Ar), 127.4 and 127.3 (C═*C*), 127.1 and 126.9 (CH of Ar), 126.2 and 126.0 (CH of Ar), 125.2 and 125.0 (CH of Ar), 124.0 (C of Ar, quat.), 106.1 (*C*═C), 82.6 and 82.5 (*C*Me$_3$), 65.6 and 64.4 (CHOH) and 28.4, 28.1 and 28.0 (3×Me); *m/z* (CI) 188 (M−OMe$_3$, 5%), 158 (M−Boc, 5) and 130 [M−(Boc, formyl), 100] (too unstable for accurate mass measurement).

Third to elute was amino alcohol **41** (28 mg, 30%); $[\alpha]_D^{23}$=−45.2 (*c* 1.0 in $CHCl_3$). The ee was determined to be 71% by chiral HPLC (OD Column, 10% EtOH in hexane, 0.25 cm^3 min^{-1}, t_R mj, 19.0; t_R mn, 35.0).

4.3. Supporting information

Electronic supporting information available: determination of the absolute configuration of (−)-**16** and the preparation and characterisation of representative derivatives for ee determinations.

Acknowledgements

We thank the EPSRC for a research grant (GR/M72340), Syngenta (C.R.M.) and GlaxoSmithKline (T.J.M.) for CASE awards, and the European Community for a Marie Curie Fellowship (E.P.; program TMR under contract number HPMF-CT-2000-00560). We also thank the EPSRC National Mass Spectrometry Service Centre for mass spectra.

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Full and partial differentiation of tris-1,1,1-(hydroxymethyl)ethane via direct and indirect methodology

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Received 12 December 2003; revised 2 February 2004; accepted 25 February 2004

Abstract—Tris-1,1,1-(hydroxymethyl)ethane **1** was converted to a series of mono- and disubstituted derivatives. An indirect protocol for the differentiation of the alcohol groups was employed for the synthesis of partially and fully differentiated **1** containing a protected aldehyde unit. Complete differentiation of the alcohol groups was also achieved using a direct strategy (two steps from **1**). The first synthesis of 1,3-dialdehydes derived from **1** is reported in two steps.

1. Introduction

Tris-1,1,1-(hydroxymethyl)ethane $CH_3C(CH_2OH)_3$ **1** and pentaerythritol $C(CH_2OH)_4$ are very cheap bulk chemicals. They are obtained on industrial scale via a mixed aldol reaction of formaldehyde with, propanal and ethanal, respectively, followed by a Cannizzarro reaction.[1] Due to the polyfunctional, symmetrical nature of these small molecules, they are interesting and useful starting materials/precursors for a range of applications, for example, as low-molecular weight scaffolds for combinatorial chemistry purposes,[2] as building blocks for dendrimer synthesis,[3] as initiators for polymerisation reactions,[4] or for a range of other purposes.[5] In most cases, a chemical differentiation of the alcohol groups needs to be achieved prior to use in the aforementioned applications.

Three typical differentiation levels, labelled A–C, that are commonly found in the literature for **1** are shown in Figure 1. In type A, two hydroxyl groups are protected as an acetal group, leaving one hydroxyl group available for reaction. In type B, only one hydroxyl group is functionalised, leaving two hydroxyl groups available for further conversion. Type C differs from type A in that different substituents were introduced on two alcohol groups, resulting in the presence of a chiral quaternary carbon atom.

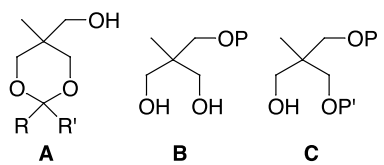

Figure 1. Differentiation levels of tris-1,1,1-(hydroxymethyl)ethane.

The traditional synthetic approach to obtain these three differentiated forms of **1** is shown in Scheme 1. Acetal formation of **1** leads directly to type A differentiated molecules. Functionalisation of the remaining hydroxyl group is now possible, leading to **2**. Removal of the acetal group then gives rise to type B differentiation. Following this three-step method, monosilylated product **3** has been obtained.[4] This differentiation method also has been applied for the construction of dendrimers with **1** as a building block (where, in this context, P represents the attachment to the dendrimer core in **2**).[3]Alternatively, type B monobenzylated product **4** was directly obtained from type A benzylidene acetal **5** by a reductive acetal-opening reaction with $LiAlH_4$–BF_3.[5f]

When **2** is subjected to reductive acetal cleavage, then the fully differentiated type C can be obtained in a three-step sequence. Following this process, Gardiner reported the synthesis of type C products **6** and **7** via cleavage of the corresponding benzylidene or *para*-methoxy benzylidene acetals.[6]

In an alternative indirect differentiation strategy, **1** was converted to the oxetane-containing product **8** via a two-step procedure.[5e,7] Acid-catalysed opening of the oxetane ring with an alcohol leads to type B differentiated substrates in

Keywords: Scaffold; Building block; Alcohol differentiation; Chemoselective acetal cleavage.
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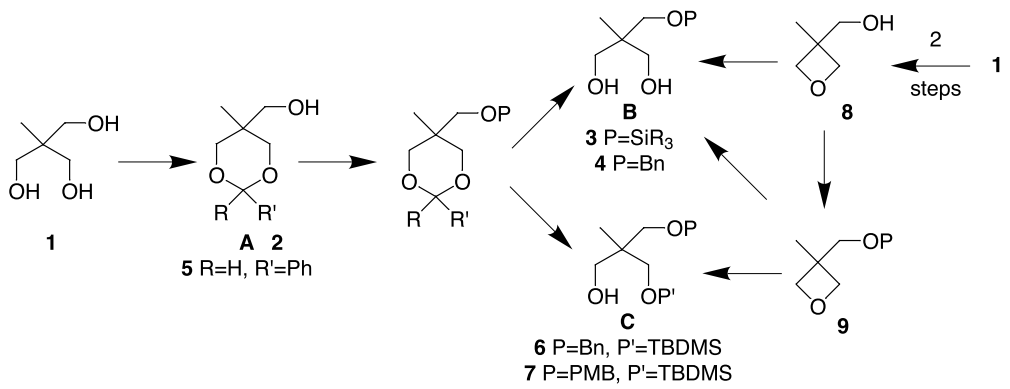
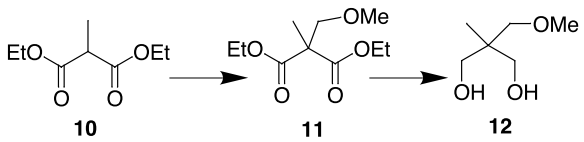
doi:10.1016/j.tet.2004.02.056



Scheme 1. Indirect differentiation methods for tris-1,1,1-(hydroxymethyl)ethane.

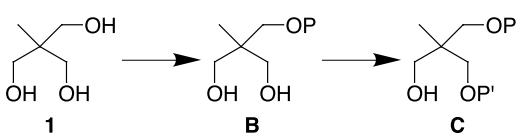
three steps. Alternatively, the free alcohol group in **8** can be functionalised to give **9**. Acid-catalysed alcoholysis at this stage gives rise to type C functionalisation in four steps. A disadvantage of this method is that the alcohol is used as a solvent in the oxetane opening reaction, which has obvious implications to its scope. Hydrolysis of **9** leads to the type B differentiated products.

Another method for the synthesis of (alkylated) type B differentiation products was achieved starting from diethyl methyl malonate **10** (Scheme 2). Alkylation with chloromethyl methyl ether gives rise to **11**, which subsequently is reduced to give **12**.[5a]



Scheme 2. Formation of type B molecule from diethyl methyl malonate.

A shorter, more efficient synthesis of type B and type C differentiated tris-1,1,1-(hydroxymethyl)ethane could be achieved via direct monofunctionalisation which, surprisingly, has been only scarcely explored (Scheme 3). This approach relies twice on a monofunctionalisation reaction, of the triol and a diol, respectively. Type B structures were obtained via monotritylation using 5.5 equiv. of **1**, in 68% yield.[8] Monoalkylation of **1** via a Williamson alkylation was reported in good yield as well (80%).[9] With a weak base (K_2CO_3) and a reactive alkylating agent (allyl bromide), a 6:1 ratio of mono- to diallylation product was achieved in 85% combined yield.[10] Surprisingly, to the best of our knowledge, no direct monosilylation of **1** has yet been reported.



Scheme 3. Direct differentiation of tris-1,1,1-(hydroxymethyl)ethane.

Following this methodology, type C differentiation can be obtained in two steps from **1**. Type B structures have been monoalkylated (allyl, benzyl) in moderate to good yields (56 and 76%, respectively).[4a,10] Monoesterification (Ac, $C(O)CMe_2Br$) was achieved in good yields (77–78%).[4b,10]

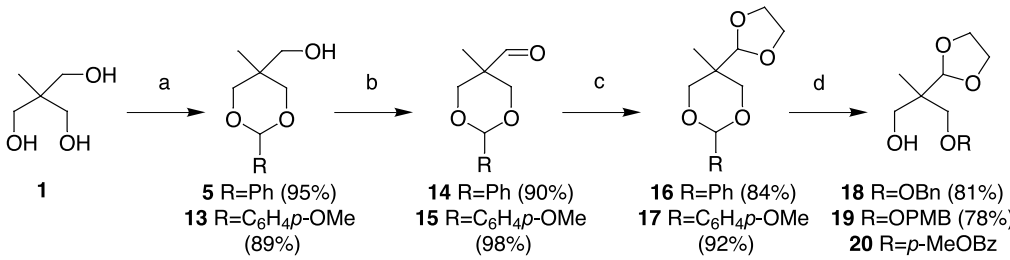
The direct differentiation strategy is more appealing than the indirect strategy in terms of number of steps. In addition, the acetal formation of **1** is often reported to proceed in rather moderate yield. Though the yield of this transformation is of less importance due to the low cost of the starting materials, it could complicate purification and isolation of the desired acetals. In addition, lower yields generate additional waste, which could be important on large scale. Nevertheless, the indirect differentiation method remains important for applications where initial monofunctionalisation is not possible.

In this paper, we wish to describe an improved procedure for the initial acetal protection in the synthesis of type A compounds, leading to an efficient indirect differentiation protocol to type B and type C products of tris-1,1,1-(hydroxymethyl)ethane **1** that contain a protected aldehyde group. This synthesis includes investigations concerning selective reactions between two different acetal groups. We report the first direct silyl monoprotection of **1** (TBDMS, TBDPS, TIPS), leading to an efficient direct differentiation protocol for type B and type C compounds containing orthogonal protecting groups. The first type B 1,3-dialdehyde structures derived from **1** in two steps are described as well. Their straightforward synthesis of all these derivatives should make these compounds readily available as interesting building blocks for a range of applications.

2. Results and discussion

2.1. Indirect differentiation of tris-1,1,1-(hydroxymethyl)ethane

Our indirect differentiation protocol conventionally started with reaction of tris-1,1,1-(hydroxymethyl)ethane **1** with benzaldehyde (Scheme 4). Several conditions have been described in the literature for this reaction (Table 1). However, for large scale purposes, the use of large quantities of $ZnCl_2$ (entry 4) in conjunction with a workup which was described as difficult,[5f] was deemed impractical. Benzaldehyde dimethyl acetal (entry 3), though still cheap, is five times as expensive as benzaldehyde itself. When the reaction was performed in aqueous medium (entry 1), the acetal product was reported to precipitate from the reaction mixture, albeit with a yield of only 60%.



Scheme 4. Reagents and conditions: (a) ArCHO, PPTS, toluene, reflux (Dean and Stark), 1 h. (b) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0 °C, 3–6 h. (c) $TMSOCH_2CH_2OTMS$, TMSOTf, CH_2Cl_2, 0 °C, 1 h. (d) BH_3·SMe_2, TMSOTf, CH_2Cl_2, −78 °C, 3 h.

Table 1. Reaction of tris-1,1,1-(hydroxymethyl)ethane with benzaldehyde

Entry	PhCHO (equiv.)	Conditions	Yield (%)	*c*/*t* ratio	Reference
1	1.0	HCl (cat), H_2O, 70–80 °C, 3 h	60	[a]	11
2	2.2	Toluene, *p*TSA (cat), Dean and Stark, 6 h	66	[a]	12
3	1.05[b]	THF, *p*TSA (cat), room temperature, 3 h	74	[a]	4
4	5.9	$ZnCl_2$ (0.9 equiv.), room temperature, 12 h	81	7:1	5f
5	0.83	Toluene, PPTS (cat), Dean and Stark, 1 h	95	3.8:1	This work

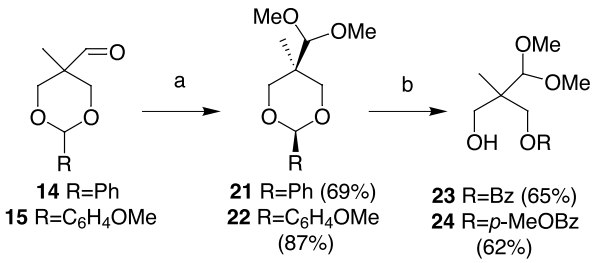
[a] Not determined.
[b] Benzaldehyde dimethyl acetal was used.

Hence, it was decided to optimise the acetal formation reaction. Refluxing **1** and benzaldehyde (1.5 equiv.) in toluene with PPTS as catalyst and $MgSO_4$ to bind the liberated water[13] only returned 43% of **5**. When these conditions were used in conjunction with a Dean and Stark trap, a mixture of *cis* and *trans* **5** was formed. However, the remaining primary alcohol subsequently reacted with excess benzaldehyde to form the corresponding acyclic acetal 'dimer' as a mixture of isomers, which could be separated by preparative HPLC (see Section 4). Hence, when a limiting amount of benzaldehyde was used, subsequent acetal formation involving the free alcohol in **5** did not take place, and a 95% yield of **5** was obtained, with a 3.8:1 ratio of *cis*/*trans* isomers. Structural assignment of the isomers was easily achieved based on the characteristic downfield shift of the equatorial methyl group of the major isomer compared to the upfield shift of the axial methyl group of the minor isomer.[14]

Reaction of **1** with anisaldehyde under identical conditions gave **13** as a mixture of *cis*/*trans* isomers in good yield as well. The acetals **5** and **13** were subsequently oxidised under Parikh–Doering[15] conditions, leading to the corresponding aldehydes **14** and **15** in excellent yield. The subsequent protection of the aldehyde as 1,3-dioxolane proved difficult. Reaction of **14** with 1,2-ethanediol in toluene or cyclohexane with a range of acid-catalysts under Dean and Stark conditions did not provide the desired product **16**. However, reaction of **14** with 1,2-ethanediol in toluene with *p*TSA at room temperature gave **16** in 69% yield. In the event, the very mild Noyori-conditions[16] using 1,2-bis-(trimethylsilyloxy)ethane and trimethylsilyltriflate as catalyst were found to give the highest yield for the protection reaction (84%). The protection of **15**, which contains a more acid-sensitive *para*-methoxybenzylidene acetal group, was also successfully achieved under Noyori conditions, leading to **17** in 92% yield.

With the acetals **16** and **17** in hand, the final transformation to type C differentiated products was attempted, which would rely on selective acetal cleavage reactions. Treatment of **16** with trimethylsilyl trifluoromethane sulfonate and borane dimethyl sulfide complex[17] resulted in selective reduction of the benzylidene acetal to give the corresponding benzyl ether **18** in 81% yield. Similarly, selective reductive cleavage of the *para*-methoxybenzylidene acetal **17** under the same conditions gave **19** in 78% yield. It has been reported, based on competition experiments, that 1,3-dioxane based acetals are more reactive towards reductive ringopening than 1,3-dioxolane based acetals. However, there are very few synthetic examples in the literature that exploit this selectivity. While the selective reductive cleavage of a *para*-methoxybenzylidene acetal in the presence of a dimethyl acetal has been reported, to the best of our knowledge no such selective reaction has been reported involving the less reactive benzylidene acetal.[18]

Unfortunately, in our hands, an attempted selective oxidation of the *para*-methoxybenzylidene acetal **17** with DDQ did not give a significant yield of the type C **20**. As it is known that cyclic acetals oxidise faster than acyclic acetals,[19a] it was decided to change the 1,3-dioxolane protecting group to an acyclic dimethyl acetal (Scheme 5). Aldehyde **14** was subjected to Noyori conditions at −78 °C with triflic acid as the catalyst. Surprisingly, this provided the dimethyl acetal **21** as a single isomer, even though the



Scheme 5. Reagents and conditions: (a) $TMSOCH_3$, CF_3SO_3H (cat), CH_2Cl_2, −78 °C, 3 h. (b) O_3, EtOAc, −78 °C, 1 h.

starting material was a mixture of *cis*/*trans* isomers. A similar result was achieved with **15** as starting material. The structure of both **21** and **22** were elucidated by X-ray crystallography,[20] and determined to be the *cis*-isomer in both cases.

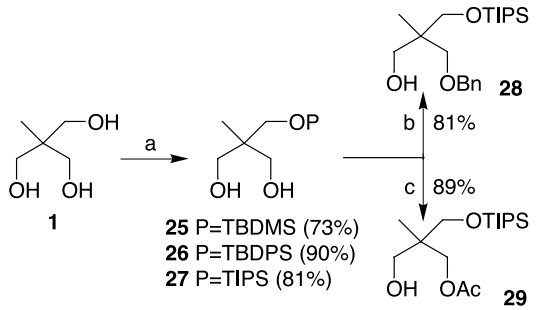
Finally, ozone treatment[19] of the diacetals **21** and **22** was chemoselective, with the acyclic acetal left untouched. The corresponding benzoate and *para*-methoxybenzoate esters **23** and **24** were obtained in 65 and 62% yield, respectively. To the best of our knowledge, this is the first example of such a selective oxidative cleavage between these two types of acetals.

It can be noted that the selective acetal cleavage of the benzylidene acetal occurs in similar yield compared to the *para*-methoxybenzylidene acetal, which adds to the versatility of the described indirect differentiation process, as a range of protecting groups are made accessible.

Hence, the fully differentiated compounds **18**, **19**, **23**, and **24** are accessible from **1** in four steps.

2.2. Synthesis of type C structures by direct differentiation of tris-1,1,1-(hydroxymethyl)ethane

The first direct preparation of monosilylated tris-1,1,1-(hydroxymethyl)ethane was successfully accomplished, based on a similar protocol as reported for pentaerythritol.[21] An excess of **1** was used (Scheme 6), not only to reduce polysilylation, but also for economic reasons, as **1** is vastly cheaper than any silylating agent. By using a 5-fold excess of **1**, yields of the corresponding silyl ethers **25**–**27** ranged from 73 to 90%.[22] Any residual starting material was easily removed during aqueous workup, and the small amounts of disilylated compounds were separated in a straightforward manner by column chromatography.



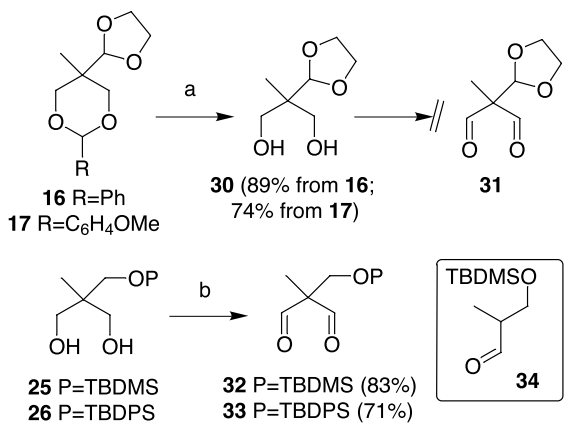
Scheme 6. Reagents and conditions: (a) R_3SiCl, imidazole, DMF, room temperature, 24 h. (b) NaH, BnBr, THF, reflux, 22 h. (c) Ac_2O, $CeCl_3$, room temperature, 5 h.

With the monosilyl ethers in hand, further direct differentiation was investigated. The selective monofunctionalisation of *meso* and C_2-symmetric 1,3-diols, including 2-substituted propanediols, has been the subject of extensive research,[23] yet is scarcely exploited for the synthesis of type-B differentiated tris-1,1,1-(hydroxymethyl)ethane.[4,10] As shown in Scheme 6, deprotonation with 1 equiv. of NaH in THF,[23d] followed by benzyl bromide addition at reflux temperature led to the formation of type C product **28** in 81% yield, together with 8% of recovered starting material. Attempted monobenzylation using silver oxide[23c] was not successful. Monoacetylation was successfully achieved with Clarke's $CeCl_3$-catalysed process[23a] using 10 equiv. of acetic anhydride. Though stirring the reaction mixture for 24 h as described mainly returned diacetylated product (69%, with 29% of **29**), close monitoring of the reaction by TLC revealed an optimum reaction time of 5 h, after which 89% of **29** was obtained. Hence, the synthesis of fully differentiated tris-1,1,1-(hydroxymethyl)ethane possessing orthogonal protecting groups is easily obtained in a high-yielding two-step operation.

2.3. Synthesis of type B 1,3-dialdehydes derived from tris-1,1,1-(hydroxymethyl)ethane

Finally the synthesis towards type B 1,3-dialdehydes was undertaken. To our surprise, there were only a handful reported examples for the synthesis of 1,3-dialdehydes from the corresponding 2,2-disubstituted 1,3-propanediol starting materials, mostly from 2,2-dimethyl-1,3-propanediol. PCC was used as oxidant, though without mention of yields.[24] Under Swern conditions, very divergent results were reported, ranging from very low to good yields.[25] However, Frigerio obtained a high yield for the oxidation of a 1,1-bis(hydroxymethyl)cyclohexene derivative to the corresponding 1,3-dialdehyde using *o*-iodoxybenzoic acid (IBX) as oxidant.[26]

The 1,3-diol precursor, type B diol **30**, was obtained in good yields from the acetals **16** and **17** via hydrogenolysis (Scheme 7). It is clear that **30** would be difficult to synthesise in a direct differentiation protocol from **1**. Unfortunately, though a range of oxidants was explored, we were not able to obtain **31** in good yields. IBX, Dess–Martin periodinane (DMP) and TPAP/NMO, all returned complex reaction mixtures, while with silver(I)carbonate only starting material was recovered. Oxidation with PCC and PDC gave complex reaction mixtures, though the use of 1 equiv. of PDC cleanly led to the corresponding monoaldehyde.[27] Under Swern conditions, the monoaldehyde was also isolated after a reaction time of 1 h, but when longer reaction times were applied, again a complex mixture was obtained.



Scheme 7. Reagents and conditions: (a) $Pd(OH)_2/C$, MeOH, room temperature, 18 h. (b) IBX, EtOAc, room temperature, 3.5 h.

In the event, the oxidation was more successful starting from the type B monosilyl ethers **25** and **26**. Though most of the oxidation methods mentioned before gave complex reaction mixtures as well, encouraging results were obtained with PDC/AcOH(cat) and Dess–Martin periodinane as oxidants, where, starting from **25**, a mixture of **32** and **34** was obtained in 52 and 20% yield, respectively. The side-product **34** is likely to arise from a retro-aldol reaction at the intermediate mono-aldehyde stage. When IBX was used, **32** was obtained in 58% yield after chromatography. However, the procedure that was used could not be scaled up. The reaction is conducted in DMSO as solvent under dilute conditions in order to dissolve the oxidant, and the workup procedure simply consists of evaporating the solvent under vacuum, followed by chromatography of the residue. Since **32** is quite volatile, loss of material during evaporation of large quantities of DMSO reduced the yield to 39% on 4 mmol scale. A solution was found by using the higher-boiling sulpholane as solvent. As IBX is not very soluble in sulpholane, the reagent was used as a suspension. Distillation of the 1,3-dialdehyde product from the reaction mixture was now possible, leading to an isolated yield of 69%. The yield could be raised to 76% when DMSO was used as a co-solvent to obtain a homogeneous reaction mixture. Finally, the best procedure was found to use excess IBX reagent under heterogeneous conditions using ethyl acetate as solvent.[28] This method allowed simple filtration of excess IBX and its byproducts, followed by evaporation of the solvent and isolation after column chromatography. Hence, reaction of **25** or **26** in EtOAc at 80 °C for 3.5 h, followed by the aforementioned workup protocol gave the corresponding dialdehydes **32** and **33** in 83 and 71% isolated yields, respectively.

3. Conclusion

We have established a short, high-yielding, direct differentiation strategy for the synthesis of fully differentiated derivatives of tris-1,1,1-(hydroxymethyl)ethane **1**, possessing orthogonal functional groups. An indirect differentiation strategy, based on the initial protection of **1** as a benzylidene acetal, was used to prepare fully differentiated derivatives of **1** where one hydroxyl group was converted to an acetal-protected aldehyde. A key aspect in this synthesis was the selective oxidative or reductive ring-opening of the benzylidene and *para*-methoxybenzylidene acetal groups in the presence of, respectively, a cyclic 1,3-dioxolane type acetal and an acyclic dimethylacetal. These investigations resulted in an extension of the scope of selective transformations between different acetal groups which should be of use in general synthetic organic chemistry. In addition, an improved preparation of the benzylidene acetal of **1** is reported. Finally, the first synthesis of a 1,3-dialdehyde building block from **1** is reported in two high yielding steps. The reactions involved are very straightforward and this work should further extend the usefulness of the very cheap building block **1** for a range of applications in organic, combinatorial and polymer chemistry.

4. Experimental

4.1. General

1,1,1-Tris(hydroxymethyl)ethane **1** was obtained from commercial sources and used without further purification. Reaction solvents were dried immediately prior to use as follows: Et_3N and CH_2Cl_2 were distilled from CaH_2. EtOAc was distilled from $CaCl_2$. MeOH was dried with Mg/I_2, followed by distillation. THF was distilled from Na/benzophenone. Toluene was distilled from Na. DMSO was distilled from CaH_2 under reduced pressure and stored over molecular sieves. Anhydrous DMF was purchased from commercial sources and stored in a Schlenk flask. All non-aqueous reactions were carried out under an atmosphere of nitrogen. Chromatography refers to column chromatography and was performed on 230–400 mesh silica gel. Reactions were monitored by TLC (Merck) with detection by UV illumination or through alkaline $KMnO_4$ oxidation. The melting points are reported uncorrected. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker DPX400 spectrometer at 300K in either d^6-acetone or $CDCl_3$ referenced to residual solvent peaks; chemical shifts are quoted in ppm. IR spectra were recorded on a Nicolet Impact 400 spectrometer. The MS were run on a Thermoquest 2000 spectrometer.

4.1.1. (1-Methyl-4-phenyl-3,5-dioxanyl) methanol (5). To a stirred solution of 1,1,1-tris(hydroxymethyl)ethane **1** (4.32 g, 36.0 mmol) in toluene (125 mL) was added PPTS (86 mg). Benzaldehyde (3.1 mL, 30.0 mmol) was added dropwise and the mixture was refluxed for 1 h using a Dean and Stark apparatus. A 5% $NaHCO_3$ (100 mL) solution was added and the reaction was allowed to cool to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The organic phases were combined, dried (Na_2SO_4), and after filtration the solvents were removed in vacuo. The crude product was purified by chromatography (hexanes/acetone 8:2) to yield **5** as a white solid (5.95 g, 95%, 3.8:1 *cis*/*trans*). The isomers were separated for identification purposes by preparative HPLC (hexane/acetone 8:2).

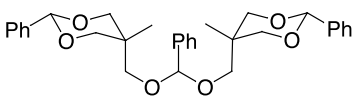
Compound cis-**5**. Mp 100–102 °C; IR (CH_2Cl_2-solution ca. 10 mg mL^{-1}): 3054 (m), 2978 (w), 2959 (w), 2850 (w), 1460 (m), 1420 (m), 1379 (m), 1195 (s), 1043 (s), 888 (m) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 7.51–7.49 (2H, m, Ar*H*); 7.38–7.36 (3H, m, Ar*H*); 5.46 (1H, s, ArC*H*); 4.02 (2H, br d, J=11.5 Hz, 2×C*H*HOCHAr); 3.93 (1H, t, J=5.3 Hz, OH); 3.84 (2H, d, J=4.8 Hz, CH_2OH); 3.62 (2H, dd, J=10.3, 1.3 Hz, 2×C*H*HOCHAr); 0.79 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 140.8 (C), 129.4 (CH), 129.3 (2×CH), 127.8 (2×CH), 102.8 (CH) 74.2 (2×CH_2), 65.6 (CH_2), 36.2 (C), 18.0 (CH_3); CIMS: *m*/*z* (%): 209 ($(M+H)^+$, 100).

Compound trans-**5**. Mp 60–62 °C; IR (solution CH_2Cl_2 ca. 10 mg mL^{-1}): 339 (m), 2950 (w), 2860 (w), 1451 (m), 1100 (s), 1039 (s), 741 (m) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 7.52–7.49 (2H, m, Ar*H*); 7.37–7.34 (3H, m, Ar*H*); 5.42 (1H, s, ArC*H*); 3.94 (2H, m, 2×C*H*HOCHAr); 3.87 (1H, m, O*H*); 3.78 (2H, m, 2×CH*H*OCHAr); 3.35 (2H, m, CH_2OH); 1.25 (3H, m, CH_3); ^{13}C NMR+DEPT

(100 MHz, d^6-acetone): δ 141.0 (C), 130.0 (CH), 129.5 (2×CH), 127.9 (2×CH), 103.0 (CH) 75.4 (2×CH_2), 67.5 (CH_2), 36.7 (C), 19.9 (CH_3); CIMS: *m/z* (%): 209 ($(M+H)^+$, 100), 105 (10).

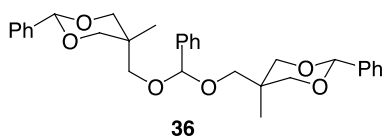
Anal. (mixture of isomers) for $C_{12}H_{16}O_3$ calcd C=69.21; H=7.74. Found C=69.26; H=7.80.

4.1.2. Synthesis of the 'dimeric' acetal isomers. To a stirred solution of 1,1,1-tris(hydroxymethyl)ethane **1** (8.93 g, 74.5 mmol) in toluene (250 mL) was added PPTS (86 mg) and $MgSO_4$ (13.4 g). Benzaldehyde (11.3 mL, 111.7 mmol) was added dropwise and the mixture was refluxed overnight using a Dean and Stark trap. 5% $NaHCO_3$ (100 mL) solution was added and the reaction was allowed to cool to room temperature. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2×100 mL). The organic phases were combined and dried (Na_2SO_4). After filtration the solvents were removed in vacuo. The crude product was purified by column chromatography (95:5 hexanes/ethyl acetate) to yield the acyclic acetals as a mixture of three ring isomers as a white solid (7.30 g, 14.5 mmol, 39%, ratio **35/36/37** 4.6:2.3:1). The isomers were separated by HPLC (hexanes/ethyl acetate 95:5).



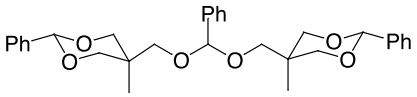
35

Compound **35**. Mp 110–111 °C; IR 2950 (w), 2868 (w), 1454 (w), 1393 (m), 1205 (m), 1095 (s), 1045 (s), 1025 (s), 967 (m) 756 (s) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 7.57–7.55 (2H, m, Ar*H*); 7.45–7.39 (4H, m, Ar*H*); 7.38–7.37 (2H, m, Ar*H*); 7.35–7.32 (7H, m, Ar*H*); 5.72 (1H, s, C*H*Ph); 5.46 (2H, s, 2×ring C*H*Ph); 4.07–4.02 (4H, m, 4×ring C*H*HOCHPh); 3.89 (2H, d, *J*=9.0 Hz, 2×C*H*HOCHPh); 3.80 (2H, d, *J*=8.9 Hz, 2×CH*H*OCHPh); 3.65 (4H, d, *J*=12.5 Hz, 4×ring CH*H*OCHPh); 0.95 (6H, s, 2×CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 140.8 (2×C), 140.5 (C), 130.1 (2×CH), 129.7 (2×CH), 129.67 (2×CH), 129.4 (2×CH), 128.3 (2×CH), 127.9 (5×CH), 103.3 (CH), 103.0 (CH), 74.8 (2×CH_2), 74.4 (2×CH_2), 69.0 (2×CH_2), 35.6 (2×C), 18.6 (2×CH_3); ESMS: *m/z* (%) 543 ($(M+K)^+$, 30), 527 ($(M+Na)^+$, 35), 225 (100); HRMS (ES^+) calcd for $C_{31}H_{36}O_6Na$ $(M+Na)^+$ 527.2404, found 527.2399.



36

Compound **36**. Mp 96–98 °C; IR 2950 (w), 2868 (w), 1454 (w), 1393 (m), 1205 (m), 1095 (s), 1045 (s), 1025 (s), 968 (m), 756 (s) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 7.47–7.31 (15H, m, Ar*H*); 5.66 (1H, s, C*H*Ph); 5.49 (1H, s, C*H*Ph); 5.30 (1H, s, C*H*Ph); 4.09 (1H, dd, *J*=6.0, 2.5 Hz, ring C*H*HOCHPh); 4.07 (1H, dd, *J*=6.0, 2.5 Hz, ring C*H*HOCHPh); 3.92 (1H, d, *J*=10.8 Hz, ring CH*H*OCHPh); 3.89 (1H, d, *J*=10.5 Hz, ring CH*H*OCHPh); 3.86 (1H, d, *J*=9.0 Hz, CH*H*OCHPh); 3.80 (1H, dd, *J*=7.3, 2.5 Hz, ring C*H*HOCHPh); 3.78 (1H, dd, *J*=7.0, 2.3 Hz, ring C*H*HOCHPh); 3.76 (1H, d, *J*=9.0 Hz, C*H*HOCHPh); 3.69 (2H, d, *J*=11.3 Hz, 2×ring CH*H*OCHPh); 3.34 (1H, d, *J*=9.5 Hz, CH*H*OCHPh); 3.28 (1H, d, *J*=9.5 Hz, C*H*HOCHPh); 1.29 (3H, s, CH_3); 0.89 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 140.9 (C), 140.7 (C), 140.3 (C), 130.1 (CH), 130.0 (CH), 129.9 (CH), 129.8 (2×CH), 129.5 (3×CH), 128.5 (2×CH), 127.9 (2×CH), 127.8 (3×CH), 103.02 (CH), 130.00 (CH), 102.9 (CH), 75.48 (CH_2), 75.45 (CH_2), 74.56 (CH_2), 74.54 (CH_2), 70.1 (CH_2), 68.8 (CH_2), 35.8 (C), 35.7 (C), 20.3 (CH_3), 18.6 (CH_3); ESMS: *m/z* (%) 543 ($(M+K)^+$, 8), 527 ($(M+Na)^+$, 5), 225 (100); HRMS (ES^+) calcd for $C_{31}H_{36}O_6Na$ $(M+Na)^+$ 527.2404, found 527.2409.



37

Compound **37**. Mp 104–106 °C; IR 2992 (w), 2972 (w), 2907 (w), 2869 (w), 1453 (m), 1382 (m), 1100 (s), 1038 (s), 1025 (s), 994 (s), 980 (s), 745 (s) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 7.52–7.48 (6H, m, Ar*H*); 7.46–7.42 (2H, m, Ar*H*); 7.39–7.34 (7H, m, Ar*H*); 5.58 (1H, s, C*H*Ph); 5.46 (2H, s, 2×ring C*H*Ph); 4.00 (2H, d, *J*=10.8 Hz, 2×ring C*H*HOCHPh); 3.97 (2H, d, *J*=9.5 Hz, 2×ring C*H*HOCHPh); 3.86 (2H, dd, *J*=7.0, 2.5 Hz, 2×ring CH*H*OCHPh); 3.84 (2H, dd, *J*=7.0, 2.3 Hz, 2×ring CH*H*OCHPh); 3.36 (2H, d, *J*=9.5 Hz, 2×C*H*HOCHPh); 3.29 (2H, d, *J*=9.5 Hz, 2×CH*H*OCHPh); 1.34 (6H, s, 2×CH_3); ^{13}C NMR+DEPT (100M Hz, d^6-acetone): δ 140.95 (2×C), 140.0 (C), 130.1 (2×CH), 129.9 (2×CH), 129.5 (5×CH), 128.3 (2×CH), 127.9 (4×CH), 103.3 (2×CH), 103.2 (CH), 75.5 (2×CH_2), 75.4 (2×CH_2), 70.6 (2×CH_2), 35.9 (2×C), 20.4 (2×CH_3); ESMS: *m/z* (%) 527 ($(M+Na)^+$, 100), 522 ($(M+NH_4)^+$, 40); HRMS (ES^+) calcd for $C_{31}H_{36}O_6Na$ $(M+Na)^+$ 527.2404, found 527.2399.

4.1.3. [2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-5yl]methanol (13). An identical procedure was followed as for the preparation of **5** (same scale). The crude product was recrystallised (hexane/ethyl acetate 9:2) and the residue purified by chromatography (hexanes/acetone 8:2) to yield **13** as a white solid (6.36 g, 89%, 2.9:1 *cis*/*trans*). The isomers were separated for identification purposes by preparative HPLC (hexanes/acetone 8:2).

Compound cis-**13**. Mp 82–84 °C; IR (solution CH_2Cl_2 ca. 10 mg mL^{-1}): 3290 (m), 2968 (m), 2935 (m), 2864 (m), 1620 (w), 1502 (w), 1379 (m), 1247 (s), 1006 (s), 816 (m) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 7.39 (2H, d, *J*=8.5 Hz, ArH); 6.90 (2H, d, *J*=8.7 Hz, ArH); 5.39 (1H, s, ArC*H*); 3.89 (2H, m, 2×CH*H*OCHAr); 3.87 (1H, br s, O*H*); 3.81 (2H, s, CH_2OH); 3.77 (3H, s, OCH_3); 3.59 (2H, m, 2×C*H*HOCHAr); 0.77 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 161.4 (C), 133.2 (C), 129.0 (2×CH), 114.7 (2×CH) 102.8 (CH), 74.2 (2×CH_2), 65.6 (CH_2), 56.2 (CH_3), 36.1 (C), 18.0 (CH_3); CIMS: *m/z* (%): 239 ($(M+H)^+$, 100), 137 (27), 121, (82).

Compound trans-**13**. Mp 122–123° C; IR (solution CH_2Cl_2 ca. 10 mg mL^{-1}): 3465 (m), 2968 (w), 2907 (w), 2850 (w),

1611 (m), 1516 (m), 1266 (s), 1062 (s), 987 (m), 835 (s) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 7.41 (2H, d, J=8.8 Hz, ArH); 6.91 (2H, d, J=8.8 Hz, ArH); 5.35 (1H, s, ArC*H*); 3.91 (2H, br d, J=10.8 Hz, 2×CH*H*OCHAr); 3.83 (1H, t, J=5.3 Hz, O*H*); 3.78 (3H, s, ArOCH_3); 3.75 (2H, dd, J=10.0, 1.0 Hz, 2×C*H*HOCHAr); 3.34 (2H, d, J=5.3 Hz, CH_2OH); 1.24 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 161.5 (C), 133.5 (C), 129.2 (2×CH), 114.8 (2×CH) 103.0 (CH), 75.4 (2×CH_2), 67.5 (CH_2), 56.3 (CH_3), 36.6 (C), 19.9 (CH_3); CIMS: *m*/*z* (%): 239 ((M+H)$^+$, 20), 137 (52), 121, (100).

Anal. (mixture of isomers) for $C_{13}H_{18}O_4$ calcd. C=65.53; H=7.61. Found C=65.69; H=7.79.

4.1.4. 2-Phenyl-5-methyl-1,3-dioxane-5-carbaldehyde (14). A suspension of SO_3·pyridine (10.06 g, 63.3 mmol) in CH_2Cl_2 (50 mL) was dissolved in a mixture of DMSO (50 mL) and Et_3N (10.6 mL, 76.5 mmol). This solution was immediately added dropwise to a stirred solution of **5** (6.01 g, 28.8 mmol) in CH_2Cl_2 (62 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was poured into a mixture of saturated aqueous NH_4Cl/water/Et_2O/pentane (1:1:1:1, 300 mL), and the aqueous phase extracted with an Et_2O/pentane mixture (1:1, 3×100 mL). The combined organic phases were dried over anhydrous Na_2SO_4. After removing the solvent in vacuo, the pale yellow oil was purified by chromatography (hexane/ethyl acetate 9:1) to yield a white solid (5.34 g, 90%). The isomers were separated for identification purposes by preparative HPLC (hexane/ethyl acetate 9:1).

Major isomer. Mp 58–60 °C; IR (solution CH_2Cl_2 ca. 10 mg mL^{-1}): 2968 (w), 2860 (w),1725 (s), 1460 (m), 1375 (m), 1095 (s), 1015 (w) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 9.89 (1H, s, C*H*O); 7.44–7.41 (2H, m, Ar*H*); 7.37–7.32 (3H, m, Ar*H*); 5.55 (1H, s, ArC*H*); 4.50 (2H, d, J=12.0 Hz, 2×C*H*HOCHAr); 3.86 (2H, d, J=11.3 Hz, 2×CH*H*OCHAr); 0.84 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 205.8 (CH), 140.2 (C), 130.2 (CH), 129.5 (2×CH); 127.8 (2×CH), 102.7 (CH), 73.3 (2×CH_2), 46.7 (C), 15.1 (CH_3); CIMS: *m*/*z* (%): 205 (M−H$^+$, 15), 123 (25), 105 (100), 77 (53).

Minor isomer. Mp 56–58 °C; IR (solution CH_2Cl_2 ca. 10 mg mL^{-1}): 2954 (w), 2850 (w), 2727 (w), 1715 (s), 1455 (m), 1379 (m), 1105 (w), 987 (m) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 9.56 (1H, s, C*H*O); 7.51–7.48 (2H, m, Ar*H*); 7.39–7.36 (3H, m, Ar*H*); 5.52 (1H, s, ArC*H*); 4.19 (2H, m, 2×C*H*HOCHAr); 3.97 (2H, m, 2×CH*H*OCHAr); 1.48 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 204.5 (CH), 140.0 (C), 130.4 (CH), 129.6 (2×CH); 127.9 (2×CH), 103.0 (CH), 72.2 (2×CH_2), 47.6 (C), 17.4 (CH_3); EIMS: *m*/*z* (%): 206 (M$^+$, 34), 205 (70), 123 (51), 105 (100), 77 (78).

Anal. (mixture of isomers) for $C_{12}H_{14}O_3$ calcd C=69.89; H=6.84. Found C=69.77; H=6.89.

4.1.5. 2-(4-Methoxyphenyl)-5-methyl-1,3dioxane-5-carbaldehyde (15). An identical procedure was followed as for the preparation of **14** (2.50 mmol scale). The crude product (pale yellow oil) was purified by chromatography (8:2 hexane/acetone) to yield a white solid (0.58 g, 98%). The isomers were separated for identification purposes by preparative HPLC (hexane/ethyl acetate 9:1).

Major isomer. Mp 102–104 °C; IR (solution CH_2Cl_2 ca. 10 mg mL^{-1}): 2973 (m), 2940 (m), 2874 (m), 2836 (m), 1715 (s), 1611 (s), 1524 (s), 1393 (s), 1242 (s), 1001 (s), 821 (s) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 9.89 (1H, s, C*H*O); 7.33 (2H, d, J=8.3 Hz, Ar*H*); 6.89 (2H, d, J=9.0 Hz, Ar*H*); 5.48 (1H, s, ArC*H*); 4.47 (2H, d, J=11.8 Hz, 2×C*H*HOCHAr); 3.83 (2H, dd, J=11.8, 1.0 Hz, 2×CH*H*OCHAr); 3.77 (3H, s, OCH_3); 0.83 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 205.9 (CH), 161.6 (C), 132.6 (C), 129.1 (2×CH), 114.8 (2×CH), 102.6 (CH), 73.3 (2×CH_2), 56.2 (CH_3), 46.6 (C), 15.1 (CH_3); EIMS: *m*/*z* (%): 236 (M$^+$, 7), 235 (M−H$^+$, 12), 135 (100).

Minor isomer. Mp 108–110 °C; IR (solution CH_2Cl_2 ca. 10 mg mL^{-1}): 3049 (w), 2959 (w), 2831 (w), 1720 (m), 1621 (m), 1516 (m), 1270 (w), 1171 (m), 736 (s) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 9.59 (1H, s, C*H*O); 7.41 (2H, d, J=8.8 Hz, Ar*H*); 6.92 (2H, d, J=8.8 Hz, Ar*H*); 5.46 (1H, s, ArC*H*); 4.15 (2H, m, 2×C*H*HOCHAr); 3.94 (2H, m, 2×CH*H*OCHAr); 3.80 (3H, s, OCH_3); 1.47 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 204.5 (CH), 161.8 (C), 132.7 (C), 129.2 (2×CH), 114.9 (2×CH), 102.9 (CH), 72.1 (2×CH_2), 56.3 (CH_3), 47.5 (C), 17.4 (CH_3); EIMS: *m*/*z* (%): 235 (M−H$^+$, 13), 152 (20), 135 (100).

Anal. (mixture of isomers) for $C_{13}H_{16}O_4$ calcd C=66.09; H=6.83. Found C=66.17; H=6.89.

4.1.6. 5-(1,3-Dioxalan-2-yl)-2-phenyl-5-methyl-1,3-dioxane (16). A solution of aldehyde **14** (0.78 g, 3.78 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. 1,2-Bis-(trimethylsilyloxy) ethane (1.4 mL, 5.7 mmol) was added and trimethylsilyl trifluoromethane sulphonate (0.3 mL, 1.9 mmol) was added dropwise. The solution was stirred at 0 °C for 1 h. Pyridine (3 mL) was added and the mixture was poured into saturated aqueous $NaHCO_3$ solution (75 mL). The aqueous layer was extracted with CH_2Cl_2 (2×90 mL) and the combined organic phases dried (Na_2SO_4). After filtration the CH_2Cl_2 was removed in vacuo. The crude product was subjected to chromatography (hexane/acetone 85:15) to yield the product as a mixture of ring isomers (0.79 g, 3.18 mmol, 84%). The isomers were separated for identification purposes by preparative HPLC, both were isolated as white solids (hexanes/acetone 9.5:0.5).

Major isomer. Mp 104–106 °C; IR (CH_2Cl_2 soln ca. 10 mg mL^{-1}) 3054 (w), 2988 (w), 2889 (w) 2865 (w), 1451 (w), 1385 (w), 1266 (s), 1214 (m), 1105 (m), 1015 (w), 722 (s) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 7.47–7.44 (2H, m, Ar*H*); 7.35–7.34 (3H, m, Ar*H*); 5.50 (1H, s, ArC*H*); 5.47 (1H, s, C*H*(OCH$_2$)$_2$); 4.20 (2H, m, 2×CH*H*OCHAr); 3.93 (4H, m, CH(OCH_2)$_2$); 3.72 (2H, m, 2×CH*H*OCHAr); 0.67 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 138.9 (C), 130.7 (CH), 129.5 (2×CH) 127.9 (2×CH), 104.8 (CH), 103.0 (CH), 74.9 (2×CH_2), 66.9 (2×CH_2), 38.1 (C), 13.1 (CH_3); CIMS: *m*/*z* (%): 251 ((M+H)$^+$, 38), 105 (30), 73 (100).

Minor isomer. Mp 68–70 °C; IR (CH_2Cl_2 soln ca.

10 mg mL^{-1}) 2964 (w), 2893 (w), 2845 (w), 1445 (m), 1384 (s), 1328 (m), 1162 (w), 1082 (s), 1034 (m), 935 (m), 750 (m) cm^{-1}; ^{1}H NMR (400 MHz, d^6-acetone): δ 7.53–7.51 (2H, m, Ar*H*); 7.40–7.37 (3H, m, Ar*H*); 5.54 (1H, s, ArC*H*); 4.58 (1H, s, C*H*(OCH$_2$)$_2$); 4.03–3.96 (4H, m, 2× C*H*HOCHAr, CH(OC*H*H)$_2$); 3.89–3.83 (4H, m, 2× CH*H*OCHAr, CH(OCH*H*)$_2$); 1.31 (3H, s, C*H*$_3$); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 140.9 (C), 130.1 (CH), 129.5 (2×CH), 127.9 (2×CH), 107.1 (CH), 103.2 (CH), 73.7 (2×CH$_2$), 66.6 (2×CH$_2$), 38.6 (C), 17.3 (CH$_3$); CIMS: *m*/*z* (%): 251 ((M+H)$^+$, 100), 105 (20), 73 (80).

Anal. (mixture of isomers) for $C_{14}H_{18}O_4$ calcd C=67.18; H=7.25. Found C=67.38; H=7.36.

4.1.7. 5-(1,3-Dioxalan-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane (17). An identical procedure was followed as for the preparation of **16** (8.47 mmol scale). The crude product was subjected to chromatography (hexane/acetone 85:15) to yield the product as a mixture of ring isomers (2.18 g, 92%). The isomers were separated for identification purposes by preparative HPLC, both were isolated as white solids (hexane/acetone 95:5).

Major isomer. Mp 126–128 °C; IR (CH_2Cl_2 soln ca. 10 mg mL^{-1}) 3054 (w), 2974 (m), 2889 (m), 2846 (m), 1621 (m), 1512 (s), 1470 (m), 1389 (s), 1262 (s), 1186 (s), 1087 (s), 826 (m), 727 (s) cm^{-1}; ^{1}H NMR (400 MHz, d^6-acetone): δ 7.37 (2H, d, *J*=7.8 Hz, Ar*H*); 6.89 (2H, d, *J*=8.7 Hz, Ar*H*); 5.47 (1H, s, ArC*H*); 5.44 (1H, s, C*H*(CH$_2$)$_2$); 4.17 (2H, m, 2×C*H*HOCHAr); 3.87 (4H, m, CH(C*H*$_2$)$_2$); 3.71 (3H, s, OC*H*$_3$); 3.69 (2H, m, 2× CH*H*OCHAr); 0.66 (3H, s, CH$_3$); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 161.6 (C), 133.1 (C), 129.1 (2×CH), 114.8 (2×CH), 104.9 (CH), 102.9 (CH), 74.9 (2×CH$_2$), 66.9 (2×CH$_2$), 56.3 (CH$_3$), 38.0 (C), 13.1 (CH$_3$); CIMS: *m*/*z* (%): 281 (M+H)$^+$, 29), 151 (10), 133 (100).

Minor isomer. Mp 116–118 °C; IR (CH_2Cl_2 soln ca. 10 mg mL^{-1}) 3045 (m), 2978 (m), 2931 (m), 2832 (m), 1620 (m), 1522 (s), 1465 (m), 1389 (s), 1270 (s), 1176 (s), 1086 (s), 1034 (m), 822 (m), 736 (s) cm^{-1}; ^{1}H NMR (400 MHz, d^6-acetone): δ 7.39 (2H, m, Ar*H*); 6.91 (2H, m, Ar*H*); 5.36 (1H, s, ArC*H*); 4.53 (1H, s, C*H*(CH$_2$)$_2$); 3.96–3.91 (4H, m, CH(C*H*$_2$)$_2$); 3.83–3.77 (7H, m, OC*H*$_3$+2× C*H*HOCHAr); 1.27 (3H, s, C*H*$_3$); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 161.8 (C), 133.5 (C), 129.4 (2×CH), 115.0 (2×CH), 107.3 (CH), 103.3 (CH), 73.8 (2×CH$_2$), 66.7 (2×CH$_2$), 56.5 (CH$_3$), 38.7 (C), 17.5 (CH$_3$); CIMS: *m*/*z* (%): 281 (M+H)$^+$, 64), 136 (78), 73 (100).

Anal. (mixture of isomers) for $C_{15}H_{20}O_5$ calcd C=64.27; H=7.19. Found C=64.43; H=7.31.

4.1.8. 3-Benzyloxy-2-[1,3]dioxolan-2-yl-2-methyl-propan-1-ol (18). A solution of diacetal **16** (0.25 g, 1 mmol) in CH_2Cl_2 (5 mL) was cooled to −78 °C. Borane dimethyl sulfide complex (0.19 mL, 2 mmol) was added followed by dropwise addition of trimethylsilyl trifluoromethane sulfonate (0.36 mL, 2 mmol). The reaction mixture was stirred at −78 °C for 3 h. After this time NaOMe (0.5 M solution in MeOH, 16 mL) was added, followed by saturated aqueous $NaHCO_3$ solution (5 mL). When the reaction mixture had warmed to room temperature it was poured into a saturated aqueous $NaHCO_3$ solution (15 mL) and water (15 mL) and was extracted with CH_2Cl_2 (3×30 mL). The organic phases were combined and dried ($MgSO_4$). After filtration the CH_2Cl_2 was removed in vacuo. The crude product was subjected to chromatography (hexane/ethyl acetate 6:4) to yield the product as a colourless oil (0.202 g, 81%).

IR (film) 3494 (m), 2983 (m), 2936 (m), 2874 (s), 1503 (w), 1451 (s), 1366 (m), 1101 (s), 1034 (s), 945 (s), 741 (s), 703 (s) cm^{-1}; ^{1}H NMR (400 MHz, d^6-acetone): δ 7.39–7.35 (4H, m, Ar*H*); 7.32 (1H, m, Ar*H*); 4.88 (1H, s, C*H*(OCH$_2$)$_2$); 4.55 (2H, s, CHHOC*H*$_2$Ar); 3.95–3.81 (4H, m, CH(OC*H*$_2$)$_2$); 3.68 (1H, dd, *J*=10.8, 4.5 Hz, C*H*HOH); 3.64 (1H, m, CH*H*OH); 3.60 (1H, d, *J*=8.7 Hz, C*H*HOCH$_2$-Ar); 3.52 (1H, d, *J*=8.8 Hz, C*H*HOCH$_2$Ar); 3.35 (1H, br s, CHHO*H*); 0.95 (3H, s, C*H*$_3$); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 140.7 (C), 129.8 (CH), 128.8 (4×CH), 107.1 (CH), 74.7 (CH$_2$), 74.0 (CH$_2$), 66.42 (CH$_2$), 66.36 (CH$_2$), 65.8 (CH$_2$), 44.9 (C), 15.1 (CH$_3$); CIMS: *m*/*z* (%): 253 ((M+H)$^+$, 28), 205 (12), 115 (40), 73 (100): HRMS (EI) calcd for $C_{14}H_{19}O_4$ (M−H)$^+$ 251.1283, found 251.1279.

4.1.9. 2-[1,3]Dioxolan-2-yl-3-(4-methoxy-benzyloxy)-2-methyl-propan-1-ol (19). Starting from **17**, an identical procedure was followed as for the preparation of **18** (same scale). The crude product was subjected to chromatography (hexane/ethyl acetate 6:4) to give the product as a colourless oil (0.221 g, 78%).

IR (film) 3489 (m), 2936 (s), 2988 (s), 2841 (s), 1621 (s), 1516 (s), 1465 (s), 1304 (s), 1034 (m), 1252 (s), 1105 (s), 1025 (s) cm^{-1}; ^{1}H NMR (400 MHz, d^6-acetone): δ 7.31 (2H, m, Ar*H*); 6.93 (2H, m, Ar*H*); 4.86 (1H, s, C*H*(OCH$_2$)$_2$); 4.47 (2H, s, CHHOC*H*$_2$Ar); 3.94–3.81 (4H, m, CH(OC*H*$_2$)$_2$); 3.82 (3H, s, ArOC*H*$_3$); 3.64 (1H, dd, *J*=10.8, 5.5 Hz, C*H*HOH); 3.58 (1H, m, CH*H*OH); 3.55 (1H, d, *J*=8.8 Hz, C*H*HOCH$_2$Ar); 3.47 (1H, d, *J*=9.0 Hz, CH*H*OCH$_2$Ar); 3.29 (1H, t, *J*=5.5 Hz, CHHO*H*); 0.93 (3H, s, C*H*$_3$); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 160.8 (C), 132.6 (C), 130.5 (2×CH), 115.2 (2×CH), 107.2 (CH), 74.4 (CH$_2$), 73.8 (CH$_2$), 66.43 (CH$_2$), 66.37 (CH$_2$), 65.9 (CH$_2$), 56.2 (CH$_3$), 44.8 (C), 15.1 (CH$_3$); EIMS: *m*/*z* (%): 281 ((M−H)$^+$, 4), 220 (12), 189 (27), 121 (100): HRMS (EI) calcd for $C_{15}H_{22}O_5$ (M)$^+$ 282.1467, found 282.1460.

4.1.10. *cis*-5-Dimethoxymethyl-5-methyl-2-phenyl-[1,3]-dioxane (21). A solution of aldehyde **14** (2.99 g, 14.5 mmol) in CH_2Cl_2 (58 mL) was cooled to −78 °C. Methoxytrimethylsilane (6.0 mL, 43.5 mmol) was added followed by dropwise addition of triflic acid (0.76 mL, 4.2 mmol). The solution was stirred at −78 °C for 3 h. Pyridine (7 mL) was added and the mixture poured on to satd $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×100 mL) and the organic phases were combined and dried (Na_2SO_4). After filtration, the CH_2Cl_2 was removed in vacuo. The crude product was subjected to chromatography (hexane/acetone 9:1) to yield a single isomer as a white solid (2.53 g, 69%).

Mp 108–112 °C; IR (CH_2Cl_2 soln ca. 10 mg mL^{-1}) 3054 (m), 2978 (m), 1393 (w), 1209 (w), 1167 (w), 1101 (m),

1072 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51–7.49 (2H, m, Ar*H*); 7.42–7.37 (3H, m, Ar*H*); 5.47 (1H, s, ArC*H*); 4.89 (1H, s, C*H*$(OCH_3)_2$); 4.24 (2H, m, 2×C*H*HOCHAr); 3.62 (6H, s, CH$(OCH_3)_2$); 3.59 (2H, m, 2×CH*H*OCHAr); 0.74 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, $CDCl_3$): δ 138.4 (C), 128.9 (CH), 128.3 (2×CH), 126.1 (2×CH), 107.1 (CH), 102.0 (CH), 74.1 (2×CH_2), 58.8 (2×CH_3), 39.0 (C), 12.2 (CH_3); CIMS: *m/z* (%): 221 ($(M-OMe)^+$, 30), 105 (35), 75 (100). Anal. for $C_{14}H_{20}O_4$ calcd C=66.65; H=7.99. Found C=66.64; H=8.03.

4.1.11. *cis*-5-Dimethoxymethyl-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxane (22). Starting from **15**, an identical procedure was followed as for the preparation of **21** (2.45 mmol scale). The crude product was subjected to chromatography (hexane/acetone 9:1) to give a single isomer as a white solid (0.601 g, 87%).

Mp 118–119 °C; IR (CH_2Cl_2 soln ca. 10 mg mL^{-1}) 2964 (m), 2860 (m), 2827 (m), 1616, (m), 1497 (s), 1384 (s), 1261 (s), 1152 (s), 1053 (s), 816 (m) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 7.43 (2H, d, *J*=8.6 Hz, Ar*H*); 6.94 (2H, d, *J*=8.8 Hz, Ar*H*); 5.48 (1H, s, ArC*H*); 4.90 (1H, s, C*H*$(OCH_3)_2$); 4.13 (2H, m, 2×C*H*HOCHAr); 3.82 (3H, s, ArOCH_3); 3.61 (2H, m, 2×CH*H*OCHAr); 3.59 (6H, s, CH$(OCH_3)_2$); 0.68 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 161.7 (C), 133.3 (C), 129.1 (2×CH), 114.9 (2×CH), 108.5 (CH), 103.2 (CH), 75.1 (2×CH_2), 59.4 (2×CH_3), 56.3 (CH_3), 40.3 (C), 13.3 (CH_3); CIMS: *m/z* (%): 283 ($(M+H)^+$, 4), 251 (6), 133 (100). Anal. for $C_{15}H_{22}O_5$ calcd C=63.81; H=7.85. Found C=64.06; H=8.11.

4.1.12. Benzoic acid 2-hydroxymethyl-3,3-dimethoxy-2-methyl-propyl ester (23). A solution of diacetal **21** (0.126 g, 0.5 mmol) in ethyl acetate (40 mL) was cooled to −78 °C. Ozone was passed through the solution for 1 h. After this time nitrogen was passed through the solution until the blue colouration disappeared. The ethyl acetate was removed in vacuo and the residue subjected to chromatography (hexane/acetone 8:2). The product **23** was obtained as a colourless oil (0.087 g, 65%).

IR (film) 3503 (br s), 2936 (s), 2837 (s), 1725 (s), 1592 (s), 1469 (w), 1445 (s), 1271 (s), 1176 (s), 1105 (s), 1067 (s), 703 (s) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 8.09 (2H, m, Ar*H*); 7.66 (1H, m, Ar*H*); 7.55 (2H, m, Ar*H*); 4.47 (1H, s, C*H*$(OCH_3)_2$); 4.33 (2H, s, CH_2OCOAr); 3.66 (3H, m, CH_2O*H*); 3.57 (3H, s, 1×CHOCH_3); 3.55 (3H, s, 1×CHOCH_3); 1.03 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): 167.5 (C), 134.6 (CH), 132.3 (C), 130.9 (2×CH), 130.2 (2×CH), 110.7 (CH), 67.8 (CH_2), 65.2 (CH_2), 59.5 (CH_3), 59.2 (CH_3), 46.6 (C), 15.4 (CH_3); CIMS: *m/z* (%): 237 ($(M-OCH_3)^+$, 54), 105 (62), 85 (72), 75 (100); HRMS (ES^+) calcd for $C_{14}H_{20}O_5Na$ $(M+Na)^+$ 291.1203, found 291.1204.

4.1.13. 4-Methoxy-benzoic acid 2-hydroxymethyl-3,3-dimethoxy-2-methyl-propyl ester (24). Starting from **22**, an identical procedure was followed as for the preparation of **23** (0.47 mmol scale). The crude product was subjected to chromatography (hexane/acetone 8:2) to give the product as a colourless oil (0.092 g, 62%).

IR (film) 3522 (br m), 2936 (m), 2841 (m), 1706 (s), 1606 (s), 1507 (s), 1469 (s), 1261 (s), 1167 (s), 1072 (s), 845 (m), 765 (m), 689 (m) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 8.03 (2H, d, *J*=9.0 Hz, Ar*H*); 7.06 (2H, d, *J*=8.8 Hz, Ar*H*); 4.45 (1H, s, C*H*$(OCH_3)_2$); 4.29 (2H, s, CH_2OCOAr); 3.92 (3H, s, ArOCH_3); 3.67–3.63 (3H, m, CH_2O*H*); 3.56 (3H, s, CHOCH_3); 3.54 (3H, s, CHOCH_3); 1.01 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 167.3 (C), 165.2 (C), 133.0 (2×CH), 124.5 (C), 115.4 (2×CH), 110.7 (CH), 67.5 (CH_2), 65.2 (CH_2), 59.6 (CH_3), 59.3 (CH_3), 56.7 (CH_3), 46.7 (C), 15.4 (CH_3); CIMS: *m/z* (%): 268 (M^+, 6), 267 (28), 135 (40), 85 (100); HRMS (ES^+) calcd for $C_{15}H_{22}O_6Na$ $(M+Na)^+$ 321.1308, found 321.1311.

4.1.14. 2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-propane-1,3-diol (25). To 1,1,1-tris(hydroxymethyl)ethane **1** (2.39 g, 19.9 mmol) and imidazole (0.903 g, 13.26 mmol) was added DMF (20 mL) and the reaction was stirred until complete dissolution occurred. TBDMSCl (1.00 g, 6.63 mmol) was added dropwise and the reaction mixture stirred at room temperature for 24 h. The reaction was poured into water (10 mL) and the resultant solution extracted with EtOAc (3×100 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated in vacuo. Chromatography (hexane/acetone 4:1) gave **25** as a colourless oil (1.13 g, 73%).

IR 3354 (w), 2952 (m), 2927 (m), 2881 (m), 2855 (m), 1470 (m), 1252 (m), 1092 (s), 1035 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.70 (2H, dd, *J*=11.0, 4.8 Hz, 2×CH*H*OH); 3.59 (2H, s, CH_2OSi); 3.56 (2H, dd, *J*=11.0, 6.6 Hz, 2×C*H*HOH); 2.83 (2H, dd, *J*=7.0, 4.8 Hz, 2×CH_2O*H*); 0.89 (9H, s, C$(CH_3)_3$); 0.79 (3H, s, CH_3); 0.07 (6H, s, Si$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.8 (CH_2), 67.7 (2×CH_2), 41.0 (C), 25.8 (3×CH_3), 18.1 (C), 16.8 (CH_3), −5.7 (2×CH_3); CIMS *m/z* (%) 235 ($(M+H)^+$, 100), 217 (6), 159 (57), 129 (9), 92 (26); HRMS (EI) calcd for $C_7H_{17}O_2Si$ $(M-{}^tBu)^+$ 177.0947, found 177.0943.

4.1.15. 2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-2-methyl-propane-1,3-diol (26). To a stirred solution of 1,1,1-tris(hydroxymethyl)ethane **1** (1.31 g, 10.91 mmol) and imidazole (0.49 g, 7.2 mmol) in dry DMF (20 mL), TBDPSCl (1.0 g, 3.64 mmol) was added dropwise over 90 min. The reaction was then stirred at ambient temperature for 24 h. The reaction was poured into water (60 mL) and the aqueous solution extracted with Et_2O (2×50 mL). The organic phases were combined, washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant colourless oil was purified by chromatography (hexane/acetone 75:25) to yield **26** as a colourless oil (1.18 g, 90%).

IR 3394 (s), 3069 (m), 3049 (m), 2958 (s), 2929 (s), 2857 (s), 1589 (m), 1470 (s), 1427 (s),1049 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71–7.69 (4H, m, Ar*H*); 7.49–7.40 (6H, m, Ar*H*); 3.75 (2H, d, *J*=10.5 Hz, 2×C*H*HOH); 3.65 (2H, s, CH_2OSi); 3.60 (2H, d, *J*=11.0 Hz, 2×CH*H*OH); 2.84 (2H, br s, 2×CH_2O*H*); 1.11 (9H, s, C$(CH_3)_3$); 0.84 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (4×CH), 132.9 (2×C), 129.8 (2×CH), 127.8 (4×CH), 68.4 (CH_2), 67.6 (2×CH_2), 41.5 (C), 26.8 (3×CH_3), 19.2 (C), 16.7 (CH_3); ES *m/z* (%) 739 ($(2M+Na)^+$, 100), 717 (53), 696 (12), 619 (21),

460 (58), 381 (33), 127 (50); HRMS (ES^+) calcd for $C_{21}H_{30}O_2SiNa$ $(M+Na)^+$ 381.1856, found 381.1857.

4.1.16. 2-Methyl-2-triisopropylsilanyloxymethyl-propane-1,3-diol (27). To a stirred solution of 1,1,1-tris(hydroxymethyl)ethane **1** (5.61 g, 46.7 mmol) and imidazole (1.27 g, 18.7 mmol) in dry DMF (25 mL), TIPSCl (2.0 mL, 9.34 mmol) was added dropwise. The reaction was stirred overnight at room temperature before pouring into water (50 mL). The resultant solution was extracted with EtOAc (3×20 mL), the organic phases were combined, washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and then concentrated in vacuo. Chromatography of the crude product (hexane/acetone 4:1) yielded **27** as a colourless oil (1.44 g, 81%).

IR 3385 (s), 2943 (s), 2893 (s), 2867 (s), 1464 (m), 1384 (m), 1104 (s), 1105 (s), 882 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.74 (2H, br d, J=10.8 Hz, 2×C*H*HOH); 3.71 (2H, s, CH_2OSi); 3.60 (2H, dd, J=10.8, 5.0 Hz, 2×CH*H*OH); 2.68 (2H, br s, 2×CH_2O*H*); 1.15–1.06 (21H, m, Si(C*H*(CH_3)$_2$)$_3$); 0.82 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.5 (CH_2), 67.8 (2×CH_2), 41.3 (C), 17.9 (6×CH_3), 16.9 (CH_3), 11.8 (3×CH); CIMS *m*/*z* (%) 277 ($(M+H)^+$, 76), 259 (12), 233 (16), 215 (30), 173 (98), 119 (34), 75 (100); HRMS (EI) calcd for $C_{11}H_{25}O_3Si$ $(M-C_3H_7)^+$ 233.1573, found 233.1575.

4.1.17. 3-Benzyloxy-2-methyl-2-triisopropylsilanyloxy-methyl-propan-1-ol (28). To a suspension of sodium hydride (0.22 g, 5.58 mmol, 60% dispersion in mineral oil) in THF (8 mL) was added dropwise a solution of **27** (1.50 g, 5.42 mmol) in THF (5 mL) over a period of 10 min. The reaction mixture was then heated under reflux for 1 h and then allowed to cool to room temperature. Benzyl bromide (0.70 mL, 5.91 mmol) was then added dropwise over a period of 10 min. The reaction mixture was then heated under reflux for 22 h and then allowed to cool to room temperature. Water (20 mL) was then added and the layers separated. The aqueous layer was then extracted with Et_2O (3×25 mL). The organic phases were then combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was subjected to chromatography (hexane/acetone 6:1) to give **28** as a colourless oil (1.599 g, 81%).

IR 3447 (br m), 3089 (vw), 3065 (w), 3031 (w), 2943 (s), 2891 (m), 2866 (s), 1714 (w), 1497 (w), 1463 (s), 1455 (s), 1384 (m), 1363 (m), 1248 (w), 1207 (w), 1098 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.28 (5H, m, Ar*H*); 4.52 (2H, s, ArCH_2O); 3.76 (1H, d, J=9.5 Hz, C*H*HOCH_2Ar); 3.72 (1H, d, J=9.0 Hz, CH*H*OCH_2Ar); 3.63 (2H, s, CH_2OSi); 3.53 (1H, d, J=8.5 Hz, C*H*HOH); 3.48 (1H, d, J=8.5 Hz, CH*H*OH); 2.99 (1H, br s, CH_2O*H*); 1.15–1.05 (21H, m, Si(C*H*(CH_3)$_2$)$_3$); 0.89 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, $CDCl_3$): δ 138.3 (C), 128.3 (CH), 127.52 (2×CH), 127.48 (2×CH), 74.4 (CH_2), 73.5 (CH_2), 69.6 (CH_2), 68.1 (CH_2), 41.3 (C), 18.0 (6×CH_3), 17.3 (CH_3), 11.8 (3×CH); ES^+MS: *m*/*z* (%) 389 ($(M+Na)^+$, 100); HRMS (ES^+) calcd for $C_{21}H_{38}O_3SiNa$ $(M+Na)^+$ 389.2482, found 389.2485.

4.1.18. 3-Acetyl-2-methyl-2-triisopropylsilanyloxy-methyl-propan-1-ol (29). To $CeCl_3$ (88 mg, 0.36 mmol) was added a solution of **27** (1.00 g, 3.62 mmol) in THF (15 mL) and the mixture was stirred for 5 min. Acetic anhydride (3.4 mL, 36.2 mmol) was added and the reaction mixture was stirred at ambient temperature for 5 h. The mixture was diluted with Et_2O (25 mL) and was then washed with satd aq. $NaHCO_3$ solution (2×20 mL), and brine (20 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent removed in vacuo. The residue was subjected to chromatography (ethyl acetate/hexane 80:20) to give **29** as a colourless oil (1.032 g, 89%).

IR 3469 (br w), 2943 (s), 2892 (m), 2867 (s), 1743 (s), 1725 (s), 1464 (m), 1382 (m), 1242 (s), 1103 (s), 1039 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.12 (2H, s, CH_2OAc); 3.69 (1H, d, J=9.5 Hz, C*H*HOSi); 3.65 (1H, d, J=9.5 Hz, CH*H*OSi); 3.56 (1H, dd, J=11.0, 5.5 Hz, C*H*HOH); 3.52 (1H, dd, J=11.0, 7.0 Hz, CH*H*OH); 2.73 (1H, dd, J=6.5, 5.5 Hz, CH_2O*H*); 2.07 (3H, s, OCOCH_3); 1.11–1.05 (21H, m, Si(C*H*(CH_3)$_2$)$_3$); 0.87 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, $CDCl_3$): δ 171.3 (C), 68.2 (CH_2), 67.6 (CH_2), 66.3 (CH_2), 40.8 (C), 20.8 (CH_3), 17.9 (6×CH_3), 16.8 (CH_3), 11.8 (3×CH); CIMS: *m*/*z* (%) 319 ($(M+H)^+$, 79), 301 ($(M-H_2O)^+$, 100), 275 ($(M-{}^iPr)^+$, 34), 173 (87), 145 ($(M-OTIPS)^+$, 47); HRMS (ES^+) calcd for $C_{32}H_{68}O_8Si_2$-Na $(2M+Na)^+$ 659.4344, found 659.4348.

4.1.19. 2-(1,3-Dioxolan-2yl)-2methyl-1,3-propanediol (30). To a stirred solution of **16** (0.76 g, 3.04 mmol) in methanol (20 mL) was added 20% palladium hydroxide on carbon (201 mg). The flask was evacuated and filled with hydrogen gas three times and was then left under an atmosphere of hydrogen (balloon) at room temperature for 18 h. The reaction mixture was then filtered through a plug of Celite and was washed with methanol (2×25 mL). The solvent was removed in vacuo and the residue chromatographed on silica (hexane/acetone 6:4) to give the product **30** as a white solid (0.437 g, 89%).

Starting from **17**, using an identical procedure (3.57 mmol scale) **30** was obtained (0.427 g, 74%) after a reaction time of 48 h.

Mp 48–52 °C; IR (CH_2Cl_2 10 mg mL^{-1}) 3380 (br s), 2959 (m), 2889 (s), 1696 (m), 1649 (m), 1394 (m), 1091 (s), 1044 (s), 727 (s) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 4.83 (1H, s, $(CH_2O)_2$C*H*); 3.96–3.82 (4H, m, (CH_2O)$_2$CH); 3.66 (2H, d, J=10.0 Hz, 2×C*H*HOH); 3.57 (2H, d, J=11.0 Hz, 2×CH*H*OH); 3.54 (2H, br s, CHHO*H*); 0.89 (3H, s, CH_3); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 107.7 (CH), 66.4 (2×CH_2), 66.3 (2×CH_2), 44.8 (C), 14.9 (CH_3); CIMS: *m*/*z* (%) 163 ($(M+H)^+$, 12), 115 (18), 73 (100). Anal. for $C_7H_{14}O_4$ calcd C=51.84; H=8.70. Found C=51.40; H=8.63.

4.1.20. 2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-malonaldehyde (32). To a solution of diol **25** (0.23 g, 1 mmol) in ethyl acetate (7 mL) was added iodoxybenzoic acid (1.66 g, 6 mmol). The suspension was then warmed in an oil bath at 80 °C for 3.5 h. After this time, the reaction was cooled to room temperature and the IBX removed by filtration. The filtrate was concentrated and subjected to chromatography (hexane/ethyl acetate 95:5) to give the product as a colourless oil (0.189 g, 83%).

IR (film) 2954 (s), 2931 (s), 2860 (s), 2728 (w), 1706 (s), 1474 (m), 1379 (w), 1256 (m), 1096 (s), 1011 (w), 831 (s), 779 (s) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 9.82 (2H, s, 2×C*H*O); 4.16 (2H, s, CH_2); 1.27 (3H, s, CH_3); 0.92 (9H, s, SiC(CH_3)$_3$); 0.13 (6H, s, Si(CH_3)$_2$); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 202.2 (2×CH), 66.0 (CH_2), 65.5 (C), 26.8 (CH_3), 19.5 (C),13.4 (3×CH_3), −4.8 (2×CH_3); EIMS: *m/z* (%) 201 ((M−CHO)$^+$, 4), 143 (M−^{t}Bu−2CH_3)$^+$, 100), 57 (19). HRMS (ES$^+$) calcd for $C_{12}H_{26}O_4$-SiNa (M+Na+MeOH)$^+$ 285.1493, found 285.1496.

4.1.21. 2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-2-methyl-malonaldehyde (33). Starting from **26**, an identical procedure was followed as for the preparation of **32** (same scale). The crude product was subjected to chromatography (hexane/ethyl acetate 95:5) to give the product as a colourless oil (0.248 g, 71%).

IR (film) 3078 (w), 2955 (s), 2931 (s), 2869 (s), 2718 (w), 1715 (s), 1474 (m), 1422 (s), 1384 (w), 1110 (s), 816 (s), 689 (s) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone): δ 9.90 (2H, s, 2×C*H*O); 7.75–7.73 (4H, m, Ar*H*); 7.50–7.47 (6H, m, Ar*H*); 4.21 (2H, s, CH_2); 1.33 (3H, s, CH_3); 1.09 (9H, s, C(CH_3)$_3$); ^{13}C NMR+DEPT (100 MHz, d^6-acetone): δ 201.9 (2×CH), 137.1 (4×CH), 134.1 (2×C), 131.6 (2×CH), 129.5 (4×CH), 66.6 (CH_2), 66.0 (C), 27.8 (3×CH_3), 20.5 (C), 13.6 (CH_3); EIMS: *m/z* (%) 297 ((M−^{t}Bu)$^+$, 40), 267 ((M−^{t}Bu−CHO)$^+$, 67), 199 (100). HRMS (ES$^+$) calcd for $C_{22}H_{30}O_4SiNa$ (M+Na+MeOH)$^+$ 409.1806, found 409.1809.

Acknowledgements

We thank the University of Southampton, the EPSRC, Pfizer, and the Royal Society for support. We are indebted to Joan Street and Dr. Neil Wells for NMR support, and to Dr. John Langley and Julie Herniman for MS support. We wish to acknowledge the use of the EPSRC's Chemical database service at Daresbury.[29]

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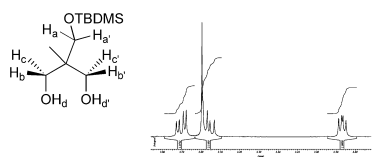

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Tetrahedron 60 (2004) 3637–3641
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Ring opening reactions of 1-arenesulfonyl-2-(bromomethyl)aziridines

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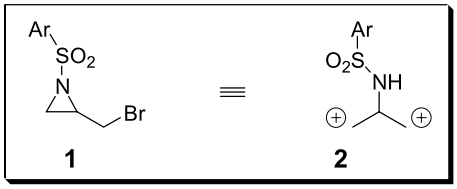
Received 9 December 2003; revised 24 February 2004; accepted 25 February 2004

Abstract—The reactivity of 1-arenesulfonyl-2-(bromomethyl)aziridines with respect to lithium dialkylcyanocuprates and lithium dialkylcuprates (Gilman reagents) has been evaluated for the first time, pointing to the conclusion that these substrates can be applied successfully as synthetic equivalents for the 2-aminopropane dication synthon towards 2-alkylaziridines and α-branched *N*-tosylamides in good yields.

1. Introduction

In the past decade, many efforts have been devoted to the implementation of aziridines in synthetic organic chemistry, complementary to the yet well-established epoxide chemistry. An interesting feature of these constrained heterocycles concerns ring opening towards a large variety of functionalized amines, depending on the choice of the appropriate nucleophile.[1] It has been generally acknowledged that N-activation of aziridines augments the facility for ring opening by nucleophilic attack and, consequently, a variety of N-activated aziridines have been studied in the literature. Among others,[2] the arenesulfonyl group has proven to be a very suitable activating group, hence the interest in *N*-(arenesulfonyl)aziridines for a variety of synthetic protocols.[3] 1-Arenesulfonyl-2-(bromomethyl)-aziridines **1**[4] constitute a peculiar subclass of these activated aziridines due to the presence of three electrophilic centres, namely the two carbon atoms of the aziridine moiety and the exocyclic methylene group. In this report, the applicability of these hitherto scarcely reported 2-(bromomethyl)aziridines in ring opening reactions with lithium cuprate reagents is disclosed, allowing selective synthesis of 2-alkylaziridines and α-branched *N*-tosylamides depending on the amount of reagent used. In this way, these substrates can be seen as useful synthetic equivalents for the 2-aminopropane dication synthon **2**, in close relationship with the very recently published dication equivalence of *N*,*O*-bis(diphenylphosphinyl)hydroxymethylaziridine in ring opening reactions with copper(I)-modified Grignard reagents.[2d]



1 **2**

2. Results and discussion

1-Arenesulfonyl-2-(bromomethyl)aziridines **1** are very easily accessible, and thus very attractive, starting materials for organic synthesis.[4] 1-Tosyl-2-(bromomethyl)aziridine **1a** and 1-benzenesulfonyl-2-(bromomethyl)aziridine **1b** were prepared from allylamine in a very efficient two-step procedure adapted from the literature (Scheme 1).[5] First, allylamine **3** was treated with 1.1 equiv. of hydrobromic acid and subsequently with 1.5 equiv. of bromine in water, resulting in 1-amino-2,3-dibromopropane hydrobromide **4** in 86% yield after stirring for 4 h at room temperature. Second, treatment of this ammonium salt with 1.05 equiv. of arenesulfonyl chloride in aqueous sodium hydroxide (2.5 M) afforded the desired 2-(bromomethyl)aziridines **1** after 1 h stirring at room temperature.

In the next stage, the reactivity of these 1-arenesulfonyl-2-(bromomethyl)aziridines **1** with respect to lithium cuprate reagents was evaluated. The synthetic potential of these organocuprates explains the general interest in these sources of carbon-centered nucleophiles as alternatives for conventional organometallic reagents.[6] Treatment of 1-tosyl-2-(bromomethyl)aziridine **1a** with 1.05 equiv. of a lithium dialkylcyanocuprate in THF or diethyl ether furnished the

Keywords: 2-(Bromomethyl)aziridines; Ring opening; Organometallics.
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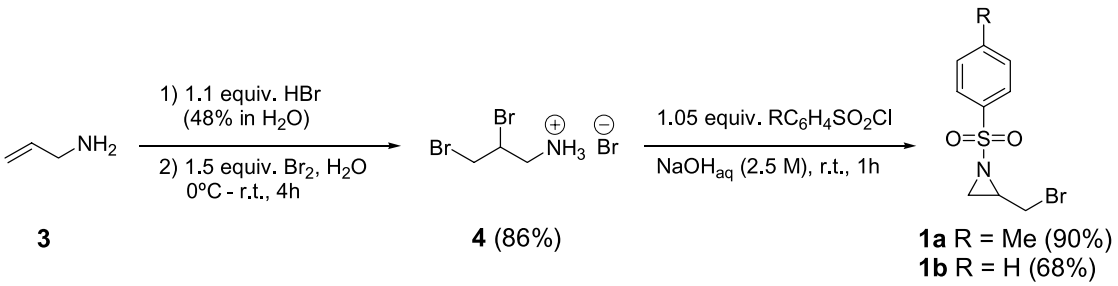
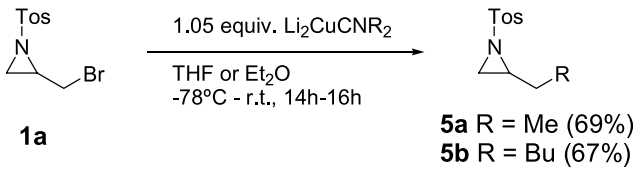
doi:10.1016/j.tet.2004.02.059



Scheme 1.



Scheme 2.

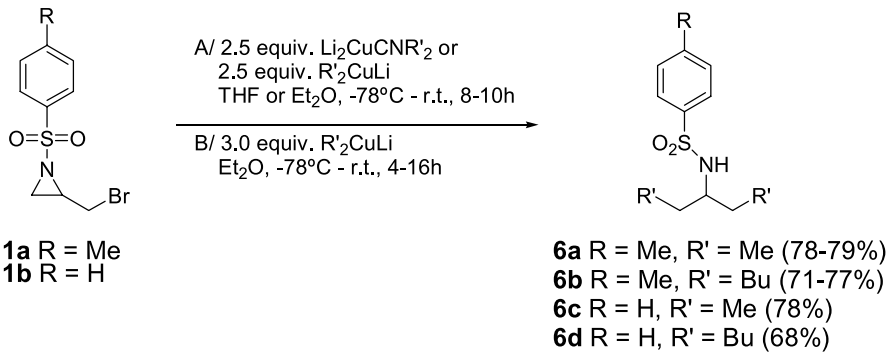
corresponding 2-substituted alkylaziridines **5** in good yield after 14–16 h stirring at room temperature (Scheme 2).

The observation that this transformation was very straightforward allowed to reject the possibility that the nucleophile might react at least as rapidly with the newly formed aziridines as with the starting material. In that case also acyclic amines would be present in the reaction mixture, besides some unreacted starting material.

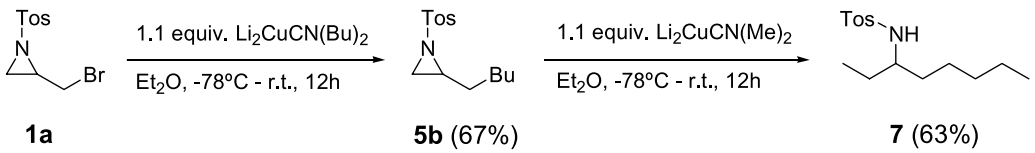
It had already been demonstrated in the literature that the closely related 1-tosyl-2-(tosyloxymethyl)aziridines exhibit a similar reactivity upon treatment with organocuprate reagents.[7] These substrates suffer ring opening by attack at the least hindered carbon atom of the aziridine moiety, immediately followed by ring closure by displacement of the tosylate in a straightforward manner.[7] Also for *N*,*O*-bis(diphenylphosphinyl)-2-(hydroxymethyl)aziridine comparable results were published, although in this case the reaction with some copper(I)-modified Grignard reagents gave rise to the formation of a side product, namely 1-diphenylphosphinyl-2-(bromomethyl)aziridine, up to 25%.[2d]

1-Arenesulfonyl-2-(bromomethyl)aziridines **1** also provide an easy access to symmetrical sulfonamides, simply be increasing the amount of lithium cuprate reagent. When 1-tosyl-2-(bromomethyl)aziridine **1a** was treated with 2.5 equiv. of lithium dialkylcyanocuprate, or alternatively, with 2.5 equiv. of lithium dialkylcuprate (Gilman reagent) in THF or in diethyl ether at room temperature, the corresponding ring opened symmetrical sulfonamides **6a**-**b** were isolated in good yields (Scheme 3). 1-Benzenesulfonyl-2-(bromomethyl)aziridine **1b** was easily converted into the sulfonamides **6c**-**d** in a similar way upon treatment with 3 equiv. of Gilman reagent in diethyl ether after 4 or 16 h stirring at room temperature (Scheme 3). Comparable observations were described for the reaction of *N*,*O*-bis-(diphenylphosphinyl)-2-(hydroxymethyl)aziridine with copper(I)-modified Grignard reagents, that is, different alkyl and aryl magnesium bromides in the presence of 5 mol% $CuBr{\cdot}SMe_2$.[2d]

The different intrinsic reactivity of 1-arenesulfonyl-2-(bromomethyl)aziridines and 1-arenesulfonyl-2-alkylaziridines with respect to organocuprate reagents paved the way for the selective synthesis of an unsymmetrical amine **7** (Scheme 4). When 1-tosyl-2-pentylaziridine **5b**, prepared



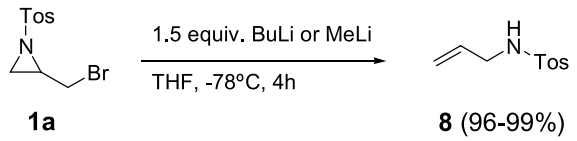
Scheme 3.



Scheme 4.

from 1-tosyl-2-(bromomethyl)aziridine **1a** upon treatment with 1.1 equiv. of lithium dibutylcyanocuprate in Et_2O, was treated with 1.1 equiv. of lithium dimethylcyanocuprate in Et_2O, the desired *N*-(1-ethylhexyl)tosylamide **7** was isolated in 63% yield as a single reaction product (Scheme 4).

Attempts to replace the lithium cuprates by alkyllithium reagents for the delivery of carbon-centered nucleophiles were unsuccessful. Instead, when 1-tosyl-2-(bromomethyl)-aziridine **1a** was treated with 1.5 equiv. of butyllithium or methyllithium in THF at −78 °C for 4 h, metal-halogen exchange resulted in *N*-(allyl)tosylamide **8** due to ring opening of the aziridine (Scheme 5).



Scheme 5.

3. Conclusion

1-Arenesulfonyl-2-(bromomethyl)aziridines are convenient synthetic equivalents for the 2-aminopropane-1,3-dication synthon. Depending on the amount of lithium cuprate used, these aziridines were successfully transformed into 2-alkyl-aziridines and symmetrical α-branched *N*-tosylamides in a good yield, with either 1 or at least 2 equiv. of reagent, respectively. Also an unsymmetrical amine was prepared by consecutive treatment of 1-tosyl-2-(bromomethyl)aziridine with 1 equiv. of two different lithium cuprate reagents. As plentiful methods exist for the N-detosylation of *N*-tosylamides,[8] the presented methodology offers a suitable access to the synthesis of the corresponding amines.

4. Experimental

^{1}H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 68 MHz (JEOL JNM-EX 270) with $CDCl_3$ as solvent. Mass spectra were obtained with a mass spectrometer (VARIAN MAT 112, 70 eV) using a GC–MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). IR spectra were measured with a Perkin–Elmer 1310 spectrophotometer or a Spectrum One FT-IR spectrophotometer. Dichloromethane was distilled over calcium hydride, and diethyl ether and THF were dried by distillation over sodium benzophenone ketyl. Other solvents were used as received from the supplier.

4.1. Synthesis of 1-arenesulfonyl-2-(bromomethyl)-aziridines 1 (Adapted from the literature)[5]

To an ice-cooled, stirred solution of allylamine **3** (8.57 g, 150 mmol) in water (50 mL), hydrobromic acid (27.81 g, 165 mmol, 1.1 equiv., 48% in H_2O) was added dropwise, followed by the addition of a solution of bromine (35.96 g, 225 mmol, 1.5 equiv.) in water (50 mL) at 0 °C, and the mixture was further stirred for 4 h at room temperature. Evaporation of the solvent in vacuo and recrystallisation from methanol afforded 1-amino-2,3-dibromopropane hydrobromide **4** (38.42 g, 86% yield) as white crystals. Subsequently, 1-amino-2,3-dibromopropane hydrobromide **4** (29.78 g, 100 mmol) was dissolved in water (100 mL), followed by the addition of arenesulfonyl chloride (105 mmol, 1.05 equiv.) at room temperature. Finally, a sodium hydroxide solution (100 mL, 5 M in H_2O) was added under vigorous stirring at room temperature, followed by a stirring period of 1 h at room temperature. Extraction with dichloromethane (3×75 mL), washing with brine (1×100 mL), drying ($MgSO_4$), filtration and evaporation of the solvent in vacuo afforded 1-arenesulfonyl-2-(bromomethyl)aziridine **1**.

The spectral data of 1-tosyl-2-(bromomethyl)aziridine **1a** have been reported previously in the literature.[4b] No full spectroscopic data of 1-benzenesulfonyl-2-(bromomethyl)-aziridine **1b** have been reported up to now, therefore they are reported here.

4.1.1. 1-Benzenesulfonyl-2-(bromomethyl)aziridine 1b. Yield 68%, white crystals. Mp 83.4–84.5 °C, recrystallisation from ethanol. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.22 (1H, d, J=5.0 Hz, (H_{trans}CH)N); 2.81 (1H, d, J=6.5 Hz, (HCH_{cis})N); 3.09–3.16 (1H, m, CHN); 3.31 (2H, d, J=7.8 Hz, CH_2Br); 7.41–8.06 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 30.55 (CH_2N); 34.34 (CH_2Br); 39.96 (CHN); 128.19 and 129.11 (2×HC$_{ortho}$ and 2×HC$_{meta}$); 133.92 (HC$_{para}$); 137.37 (C$_{arom,quat}$). IR (NaCl, cm^{-1}): ν= 1583, 1446, 1321, 1174. MS (70 eV) *m*/*z* (%): 275/7 (M^+, 2); 196 (90); 141 (82); 136 (91); 134 (93); 77 (100). Anal. Calcd for $C_9H_{10}BrNO_2S$: C 39.14%; H 3.65%; N 5.07%. Found: C 39.31%; H 3.78%; N 4.91%.

4.2. Synthesis of 1-(4-methylbenzenesulfonyl)-2-alkyl-aziridines 5

As a representative example, the synthesis of 1-tosyl-2-ethylaziridine **5a** is described. To a solution of copper cyanide (0.25 g, 2.7 mmol, 1.05 equiv.) in dry diethyl ether (45 mL), methyllithium (3.4 mL, 5.4 mmol, 2.1 equiv., 1.6 M in ether) was added dropwise via a syringe at −78 °C and under nitrogen atmosphere, and the resulting mixture was stirred for 30 min at −78 °C. Subsequently, a solution of 1-tosyl-2-(bromomethyl)aziridine **1a** (0.74 g, 2.6 mmol) in diethyl ether (10 mL) was added at −78 °C, after which the mixture was stirred for 12 more hours at room temperature. The reaction mixture was then filtered over Celite®, and the filtrate was extracted with a saturated $NaHCO_3$ solution and ether (3×50 mL). Drying ($MgSO_4$), filtration and evaporation in vacuo afforded 1-(4-methyl-benzenesulfonyl)-2-ethylaziridine **5a** (0.40 g, 69%).

4.2.1. 1-(4-Methylbenzenesulfonyl)-2-ethylaziridine 5a. Yield 69%, colorless liquid. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.83 (3H, t, J=7.6 Hz, CH_3CH$_2$); 1.07–1.61 (2H, m, CH$_3$CH_2); 2.07 (1H, d, J=4.3 Hz, (H_{trans}CH)N); 2.44 (3H, s, CH_3Ar); 2.62 (1H, d, J=7.3 Hz, (HCH_{cis})N); 2.63–2.71 (1H, m, CHN); 7.33 and 7.82 (4H, 2×d, J=7.9 Hz, 2×HC$_{ortho}$ and 2×HC$_{meta}$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 10.84 (*C*H$_3$CH$_2$); 21.64 (*C*H$_3$Ar); 24.47 (CH$_3$*C*H$_2$); 33.58 (CH_2N); 41.71 (CHN); 127.98 and 129.63 (2×HC$_{ortho}$ and 2×HC$_{meta}$); 135.16 (CH$_3$*C*$_{arom,quat}$); 144.42 (C$_{arom,quat}$). IR

(NaCl, cm^{-1}): ν=1672, 1591, 1460, 1319, 1228, 1157, 1086, 1026. MS (70 eV) *m/z* (%): 225 (M^+, 0.5); 197 (1); 155 (4); 91 (24); 70 (100); 65 (14); 51 (3). Anal. Calcd for $C_{11}H_{15}NO_2S$: C 58.64%; H 6.71%; N 6.22%. Found: C 58.77%; H 6.85%; N 6.13%.

4.2.2. 1-(4-Methylbenzenesulfonyl)-2-pentylaziridine 5b. Yield 67%, colorless liquid. ^1H NMR (270 MHz, $CDCl_3$): δ 0.81 (3H, t, J=5.9 Hz, CH_3CH_2); 1.11–1.56 (8H, m, $CH_3(CH_2)_4$); 2.05 (1H, d, J=4.3 Hz, (H_{trans}CH)N); 2.42 (3H, s, CH_3Ar); 2.62 (1H, d, J=6.9 Hz, (HCH_{cis})N); 2.65–2.72 (1H, m, CHN); 7.32 and 7.82 (4H, 2×d, J=8.0 Hz, 2×HC_{ortho} and 2×HC_{meta}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.84 (CH_3CH_2); 21.58 (CH_3Ar); 22.43, 26.43, 31.16 and 31.27 ($CH_3(CH_2)_4$); 33.75 (CH_2N); 40.48 (CHN); 127.99 and 129.61 (2×HC_{ortho} and 2×HC_{meta}); 135.20 ($CH_3C_{arom,quat}$); 144.44 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=2931, 2863, 1598, 1465, 1324, 1240, 1154. Anal. Calcd for $C_{14}H_{21}NO_2S$: C 62.89%; H 7.92%; N 5.24%. Found: C 63.04%; H 8.11%; N 5.12%.

4.3. Synthesis of tosylamides 6

As a representative example, the synthesis of *N*-(1-ethylpropyl)-4-methylbenzenesulfonamide **6a** is described. To a solution of copper iodide (0.99 g, 5.2 mmol, 3 equiv.) in dry diethyl ether (35 mL), methyllithium (6.5 mL, 10.4 mmol, 6 equiv., 1.6 M in ether) was added dropwise via a syringe at −78 °C and under nitrogen atmosphere, and the solution was further stirred for 30 min at −78 °C. Subsequently, a solution of 1-(4-methylbenzenesulfonyl)-2-(bromomethyl)-aziridine **1a** (0.50 g, 1.7 mmol) in diethyl ether (5 mL) was added at −78 °C, after which the mixture was stirred for 5 more hours at room temperature. The reaction mixture was then filtered over Celite®, and the filtrate was extracted with water and ether (3×50 mL). Drying ($MgSO_4$), filtration and evaporation in vacuo afforded *N*-(1-ethylpropyl)-4-methylbenzenesulfonamide **6a** (0.32 g, 79%).

4.3.1. *N*-(1-Ethylpropyl)-4-methylbenzenesulfonamide 6a. Yield 79%, colorless liquid. Flash chromatography on silica gel: Acetone/chloroform (1:1), R_f=0.70. ^1H NMR (270 MHz, $CDCl_3$): δ 0.71 (6H, t, J=7.3 Hz, ($CH_3CH_2)_2$); 1.21–1.45 (4H, m, ($CH_3CH_2)_2$); 2.37 (3H, s, CH_3Ar); 3.01–3.09 (1H, m, CHN); 4.94 (1H, br s, NH); 7.24 and 7.74 (4H, 2×d, J=8.2 Hz, 2×HC_{ortho} and 2×HC_{meta}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 9.61 (($CH_3CH_2)_2$); 21.49 (CH_3Ar); 27.15 (($CH_3CH_2)_2$); 56.69 (CHN); 126.99 and 129.52 (2×HC_{ortho} and 2×HC_{meta}); 138.59 ($CH_3C_{arom,quat}$); 142.98 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=3350, 3287, 1596, 1456, 1413, 1327, 1157. MS (70 eV) *m/z* (%): no M^+; 155 (1); 123 (4); 121 (13); 119 (15); 88 (52); 86 (94); 84 (100); 51 (21); 49 (83); 47 (77). Anal. Calcd for $C_{12}H_{19}NO_2S$: C 59.72%; H 7.93%; N 5.80%. Found: C 59.88%; H 8.10%; N 5.74%.

4.3.2. *N*-(1-Pentylhexyl)-4-methylbenzenesulfonamide 6b. Yield 77%, colorless liquid. ^1H NMR (270 MHz, $CDCl_3$): δ 0.81 (6H, t, J=6.6 Hz, 2×CH_3CH_2); 1.05–1.39 (16H, m, 2×($CH_3(CH_2)_4$)); 2.41 (3H, s, CH_3Ar); 3.17–3.19 (1H, m, CHN); 4.57 (1H, br d, J=8.3 Hz, NH); 7.28 and 7.41 (4H, 2×d, J=8.0 Hz, 2×HC_{ortho} and 2×HC_{meta}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.93 (2×CH_3CH_2); 21.46 (CH_3Ar); 22.46, 24.89, 31.55 and 35.02 (2×($CH_3(CH_2)_4$)); 54.14 (CHN); 127.06 and 129.50 (2×HC_{ortho} and 2×HC_{meta}); 138.54 ($CH_3C_{arom,quat}$); 143.03 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=3277, 2936, 2853, 1598, 1457, 1423, 1324, 1153. MS (70 eV) *m/z* (%): 326 (M^+, 1); 255 (74); 184 (5); 171 (8); 155 (62); 147 (5); 139 (4); 107 (5); 91 (100); 77 (3); 65 (24); 56 (28). Anal. Calcd for $C_{18}H_{31}NO_2S$: C 66.42%; H 9.60%; N 4.30%. Found: C 66.58%; H 9.76%; N 4.21%.

4.3.3. *N*-(1-Ethylpropyl)benzenesulfonamide 6c. Yield 78%, colorless liquid. Flash chromatography on silica gel: Acetonitrile/Chloroform (1/1), R_f=0.75. ^1H NMR (270 MHz, $CDCl_3$): δ 0.75 (6H, t, J=7.4 Hz, ($CH_3CH_2)_2$); 1.26–1.56 (4H, m, ($CH_3CH_2)_2$); 3.08–3.16 (1H, m, CHN); 4.82 (1H, br d, J=7.9 Hz, NH); 7.47–7.62 (3H, m, 2×HC_{meta} and HC_{para}); 7.89–7.98 (2H, m, 2×HC_{ortho}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 9.61 (($CH_3CH_2)_2$); 27.19 (($CH_3CH_2)_2$); 56.78 (CHN); 126.90 and 128.95 (2×HC_{ortho} and 2×HC_{meta}); 132.36 (HC_{para}); 141.42 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=3275, 1450, 1312, 1164. MS (70 eV) *m/z* (%): 227 (M^+, 0.2); 198 (100); 141 (48); 77 (41); 51 (9). Anal. Calcd for $C_{11}H_{17}NO_2S$: C 58.12%; H 7.54%; N 6.16%. Found: C 58.20%; H 7.68%; N 6.05%.

4.3.4. *N*-(1-Pentylhexyl)benzenesulfonamide 6d. Yield 68%, colorless liquid. Flash chromatography on silica gel: EtOAc/Hexane (1/1), R_f=0.42. ^1H NMR (270 MHz, $CDCl_3$): δ 0.81 (6H, t, J=6.9 Hz, 2×CH_3); 1.11–1.42 (16H, m, 2×($CH_3(CH_2)_4$)); 3.17–3.25 (1H, m, CHN); 5.02 (1H, br d, J=8.2 Hz, NH); 7.29–7.92 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, ref=$CDCl_3$): δ 13.86 (2×CH_3); 22.36, 24.80, 31.45 and 34.88 (2×($CH_3(CH_2)_4$)); 54.16 (CHN); 126.88 and 128.81 (2×HC_{ortho} and 2×HC_{meta}); 132.18 (HC_{para}); 141.46 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=3282, 1587, 1448, 1325, 1162. MS (70 eV) *m/z* (%): 311 (M^+, 0.1); 240 (100); 170 (9); 141 (33); 77 (36); 51 (4). Anal. Calcd for $C_{17}H_{29}NO_2S$: C 65.55%; H 9.38%; N 4.50%. Found: C 65.75%; H 9.49%; N 4.40%.

4.3.5. Synthesis of *N*-(1-ethylhexyl)-4-methylbenzenesulfonamide 7. This compound was prepared in a two-step procedure starting from 1-(4-methylbenzenesulfonyl)-2-(bromomethyl)aziridine **1a** via 1-(4-methylbenzenesulfonyl)-2-pentylaziridine **5b**, analogous to the procedures described above.

Yield 63%, colorless liquid. ^1H NMR (270 MHz, $CDCl_3$): δ 0.75–0.84 (6H, m, 2×CH_3); 1.12–1.49 (10H, m, (CH_3CH_2-$CH(CH_2)_4CH_3$); 2.42 (3H, s, CH_3Ar); 3.27–3.33 (1H, m, CHN); 4.81 (1H, br s, NH); 7.29 and 7.79 (4H, 2×d, J=7.2, 8.2 Hz, 2×HC_{ortho} and 2×HC_{meta}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.94 (2×CH_3); 21.47 (CH_3Ar); 22.46 (2×CH_3CH_2); 24.89 ($CH_3CH_2CH_2$); 31.55 ($CH_3(CH_2)_2$-CH_2); 34.92 ($CH_3(CH_2)_3CH_2$); 55.35 (CHN); 127.04 and 129.50 (2×HC_{ortho} and 2×HC_{meta}); 138.56 ($CH_3C_{arom,quat}$); 143.00 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν=3282, 1599, 1494, 1455, 1429, 1326, 1157, 1094, 1031. MS (70 eV) *m/z* (%): no M^+; 212 (5); 166 (4); 140 (4); 126 (35); 112 (8); 97 (12); 86 (16); 85 (61); 84 (13); 71 (100); 69 (13); 57 (98); 55 (19). Anal. Calcd for $C_{15}H_{25}NO_2S$: C 63.56%; H 8.89%; N 4.94%. Found: C 63.68%; H 9.02%; N 4.91%.

Acknowledgements

The authors are indebted to the 'Fund for Scientific Research-Flanders (Belgium)' (F.W.O.-Vlaanderen) and Ghent University (GOA) for financial support.

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Tetrahedron 60 (2004) 3643–3651
Tetrahedron

From cyclopentadiene to isoxazoline–carbocyclic nucleosides: a rapid access to biological molecules through nitrosocarbonyl chemistry

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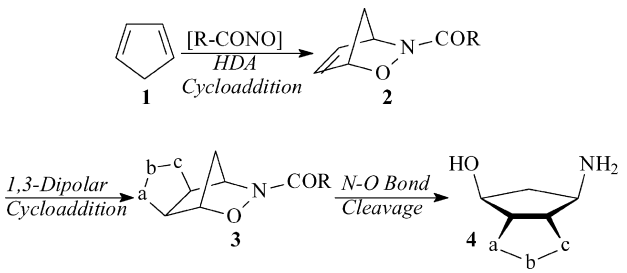
Received 17 November 2003; revised 3 February 2004; accepted 25 February 2004

Abstract—A rapid access to carbocyclic nucleosides containing a fused isoxazoline ring is proposed starting from cyclopentadiene. The route involves an hetero Diels–Alder cycloaddition reaction of nitrosocarbonylbenzene followed by a 1,3-dipolar cycloaddition of nitrile oxides, cleavage of the N–O tether and elaboration of the heterocyclic aminols into nucleosides via linear construction of purine and pyrimidine heterocycles.

1. Introduction

Nucleosides are primary building blocks of biological systems and are processed into nucleic acids.[1–3] Many efforts have been recently addressed in the search for nucleoside analogues as non-toxic, selective inhibitors of kinases and polymerases with increased antiviral power.[4–6] In particular, carbocyclic nucleosides, where the sugar portion of the nucleoside has been replaced with a cyclopentane ring, have been found to be highly resistant to host enzymes.[7] Even though the exact mechanism of these antivirals is not fully understood, new inhibitors of a variety of viral infective agents are extensively proposed by different research groups.[8] The construction of carbocyclic nucleosides can be achieved mainly through two synthetic approaches regarding the attachment of the heterocyclic base: (1) linear construction of the heterocyclic base starting from an amino substituted carbocycle: (2) convergent attachment of an intact heterocyclic base to an appropriately substituted carbocyclic ring via nucleophilic substitution.

We have recently found that the chemistry of nitrosocarbonyls (RCONO) can be applied since these intermediates are highly reactive in hetero Diels–Alder (HDA) reactions.[9] Cyclopentadiene **1** efficiently traps these fleeting intermediates affording the HDA adducts **2** (Scheme 1), which were found to be highly reactive dipolarophiles in the 1,3-dipolar cycloaddition of nitrile oxides.[10] Detachment of the acyl moiety in cycloadducts of type **3** and reductive cleavage of the N–O bond afforded quantitatively the stereodefined *anti* aminols **4**[10] which could serve as the appropriate precursors of nucleosides through assembly of purine and pyrimidine rings.



Scheme 1.

On pursuing our studies on the synthetic potential of the nitrosocarbonyl adducts **2**, we detail the first synthesis of a class of racemic purine- and pyrimidine–carbocyclic nucleosides containing a fused isoxazole ring and lacking a methylene (CH_2) group in the side chain in the carbocyclic unit. Nucleosides lacking a methylene group in the side chain have been reported and in some cases display reduced cytotoxicity.[11] The paper gives a complete account on the purine and pyrimidine rings construction and further functionalization of the purine compounds.

Keywords: Carbocyclic nucleosides; Nitrosocarbonyls; Nitrile oxides; Cycloadditions.
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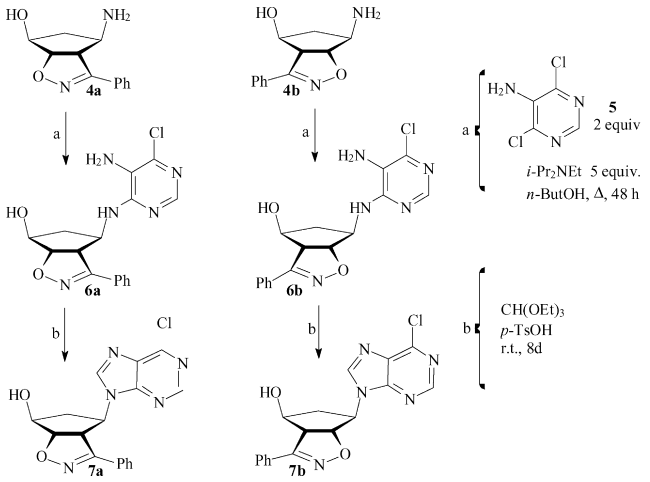
doi:10.1016/j.tet.2004.02.057

2. Results

2.1. Construction of the purine heterocycles

By adapting known procedures for the construction of the purine nucleus,[8b,12] we have converted the stereodefined aminols **4a**,**b** into the pyrimidine derivatives **6a**,**b** by substitution of 5-amino-4,6-dichloropyrimidine **5** and then into the chloropurines **7a**,**b** by condensation with orthoformates (Scheme 2).



Scheme 2.

The pyrimidine derivatives **6a**,**b** were obtained in moderate yields (**6a**, 52%: **6b**, 49%) by refluxing a solution of the aminols **4a**,**b** and 5-amino-4,6-dichloropyrimidine **5** (2 equiv.) in *n*-BuOH (bp 117 °C) in the presence of an excess of *i*-Pr_2NEt (5 equiv.) for 48 h. Yields were less satisfactory in *n*-PrOH (bp 97 °C) leading to the pyrimidine derivatives **6a**,**b** in somewhat lower yields (**6a**, 47%: **6b**, 30%). Duplicate experiments in *n*-BuOH with a larger excess of base (*i*-Pr_2NEt, 10 equiv.) led to a decrease in the reaction yields (**6a**, 35%: **6b**, 32%). From all indications obtained so far, *n*-BuOH is the most appropriate solvent for these reactions while more basic conditions are detrimental presumably because of the sensitivity of the isoxazoline moieties to severe basic conditions, which can often cause ring cleavage.[13]

The structures of **6a**,**b** rely upon analytical and spectroscopic data. While the IR spectra of pyrimidines **6a**,**b** exhibit complex series of bands between 3200 and 3430 cm^{-1} due to the presence of OH, NH and NH_2 groups, the ^{1}H NMR spectra were unambiguously consistent for the assigned structures. The spectrum of **6a** in $CDCl_3$ showed the pyrimidine ring proton as a singlet at δ 8.08, the NH_2 and OH protons as a broad singlet at δ 3.62 and 3.50, the NH proton as a doublet at δ 6.41 (J=8.6 Hz) and the 5- and 4-isoxazoline protons at δ 5.16 (d, J=8.7 Hz) and 4.29 (d, J=8.7 Hz), respectively, while the cyclopentane protons are at δ 4.92 (m, CH–N), 4.62 (d, J=3.2 Hz, CH–O) and 2.00 (m, CH_2). The spectrum of the stereoisomeric **6b** is essentially similar, showing the pyrimidine singlet at δ 8.15, the NH_2 and OH at δ 3.51, the NH at δ 6.10 (d, J=8.8 Hz) and the 5- and 4-isoxazoline protons δ 5.25 (d, J=8.8 Hz) and 4.25 (d, J=8.8 Hz) while the cyclopentane protons are at δ 4.99 (m, CH–N), 4.64 (m, CH–O) and 2.10 (m, CH_2).

The conversion of the stereoisomeric pyrimidine **6a**,**b** into the corresponding chloropurines **7a**,**b** was somewhat problematic. The results obtained under various conditions are collected in Table 1. On applying the frequently reported methods[14] using triethyl orthoformate in the presence of 37% HCl at rt no condensation took place and the starting materials were recovered unchanged after the suggested work-up (entries 1 and 2). Upon replacing the HCl with acetic anhydride or acetic acid and performing the reactions at 100 °C,[15] the desired compounds **7a**,**b** (entries 3 and 4) could be eventually obtained, albeit in poor yields. The use of diethoxymethyl acetate[12a,16] instead of triethyl orthoformate did not improve significantly the yields after heating for 1 h at 100 °C (entries 5 and 6).

The conversion of the stereoisomeric pyrimidines **6a**,**b** into the chloropurines **7a**,**b** could finally be achieved in excellent yield by treatment with triethyl orthoformate in the presence of catalytic *p*-TsOH by keeping the reactions at rt for 8 days (entries 7 and 8). Isolation and purification of **7a**,**b** were secured by evaporation of triethyl orthoformate, addition of Et_3N to the chloroform solution of the residues, washings with water and column chromatography of the organic residues.

The chloropurines **7a**,**b** have been fully characterized spectroscopically. Infrared spectra show a single broad band at 3556 cm^{-1} (**7a**) and 3291 cm^{-1} (**7b**) corresponding to the OH absorptions. In the ^{1}H NMR spectra the two N=*CH* protons of the purine rings occur as singlets at δ 8.77 and 8.49 for **7a** and at δ 8.81 and 8.39 for **7b** while the 5- and 4-isoxazolinic protons appear as doublets at δ 5.40 and 4.59 (J=9 Hz) for **7a** and at δ 5.59 and 4.55 (J=8.7 Hz) for **7b**. In order to have a firm structural assignment, a single

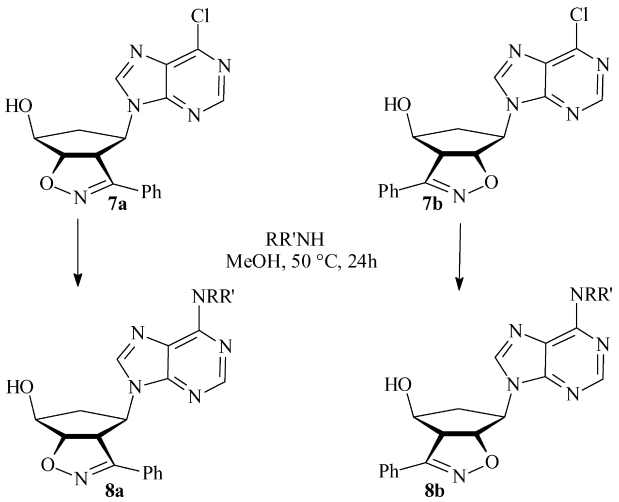
Table 1. Conversion of pyrimidine derivatives **6a**,**b** into chloropurines **7a**,**b** upon various reaction conditions

Entry	Compound	Formate and solvent	Acid	T (°C)	Time	Product (%)
1	**6a**	$CH(OEt)_3$	HCl 37%	25	14 h	**6a**
2	**6b**	$CH(OEt)_3$	HCl 37%	25	14 h	**6b**
3	**6a**	$CH(OEt)_3$	Ac_2O[a]	100	20 h	**7a** (39)
4	**6b**	$CH(OEt)_3$	AcOH cat.	100	20 h	**7b** (20)
5	**6a**	DEMA[b]	/	100	1 h	**7a** (30)
6	**6b**	DEMA[b]	/	100	1 h	**7b** (35)
7	**6a**	$CH(OEt)_3$	*p*-TsOH cat.	25	8 days	**7a** (91)
8	**6b**	$CH(OEt)_3$	*p*-TsOH cat.	25	8 days	**7b** (89)

[a] Ratio 1:1 with respect to triethyl orthoformate.
[b] DEMA, diethoxymethyl acetate.

crystal of **7a** was submitted to X-ray analysis which substantiated the attributed structure.[17]

From the chloro-substituted nucleosides **7a**,**b** a variety of derivatives can be obtained by nucleophilic substitution.[8b,12b,18] On heating MeOH solutions of **7a**,**b** at 50 °C in the presence of an excess of NH_3 or other differently substituted primary and secondary amines, the amino derivatives **8a**,**b**(**A**-**G**) could easily be obtained (Scheme 3).



Scheme 3.

Table 2 reports the chemical yields and physical constants of nucleosides **8a**,**b**(**A**-**G**) which have been fully characterized through their analytical and spectroscopic data.

Table 2. Yields and physical constants of purine derivatives **8a**,**b**

	R	R′	Mp (°C) (Solv.)	Yields (%)
8aA	H	H	129–132 (EtOH)	66
8aB	H	Me	228–230 (MeOH)	99
8aC	H	Et	212–3 (MeOH)	97
8aD	Me	Me	205–8 (MeOH)	98
8aE	H	CH_2Ph	222–6 (MeOH)	93
8aF	H	*c*-Pr	233–4 (AcOEt)	73
8aG	H	*c*-Hept	Thick oil	94
8bA	H	H	223–5 (MeOH)	74
8bB	H	Me	260–2 (MeOH)	98
8bC	H	Et	196–200 (MeOH)	96
8bD	Me	Me	169–170 (MeOH)	100
8bE	H	CH_2Ph	192–4 (MeOH)	94
8bF	H	*c*-Pr	216 dec. (MeOH)	99
8bG	H	*c*-Hept	199–201 (AcOEt)	92

The IR spectra of the adenine derivatives **8aA** and **8bA** showed neat and distictive OH bands (3524 and 3310 cm^{-1}, respectively) and NH_2 bands (3269, 3119 and 3288, 3143 cm^{-1}, respectively). The ^1H NMR spectra showed the characteristic signals of adenine (CH=singlets at δ 7.78, 8.40 and 8.24, 8.36, respectively). Unlike the previous cases, however, the isoxazolinic protons are no longer neat doublets but one or both the isoxazolinic protons occur as double doublets, because of an additional coupling with the adjacent cyclopentane methines, thus indicating a conformational change in the cyclopentane ring. The new coupling constants are sizeable for the isoxazolinic protons adjacent to the *CH*–N methine (J=3–4 Hz) while the coupling of the isoxazolinic protons to the adjacent CHO methines is negligible in **8Aa** and sizeable in **8Ab** (J=3 Hz).

When fused to an isoxazolinic ring or similar rings[19] the cyclopentane moiety usually adopt an envelope conformation with the flap directed toward the isoxazoline ring thus giving a boat-like appearance to the bicyclic system. The conformation of the bicyclic system with the flap directed away from the isoxazoline ring looks like a chair and is higher in energy.

Figure 1 shows the B3LYP/6-31G*[20] optimized structure of the boat-like and chair-like conformations of the parent 2,3-oxaza[3.3.0]bicyclooct-3-ene. The boat-like conformation allows for the relief of non-bonded interactions between the heterocyclic ring and the substituents on the adjacent cyclopentane carbons and causes the dihedral angles between the isoxazoline protons and the adjacent *trans* cyclopentane protons to be near 90°, that is, with a vanishing coupling constant.

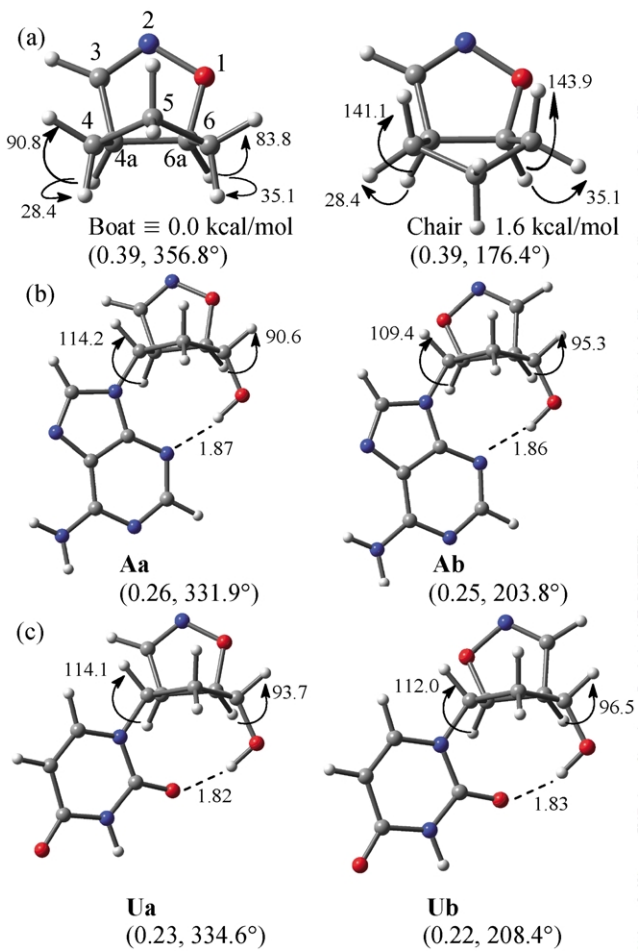


Figure 1. (a) Boat- and chair-like conformations of 2,3-oxaza[3.3.0]bicyclooct-3-ene, whose numbering system is shown in the case of the boat conformer. Relative energies are given near the conformational labels. Curved arrows specify the dihedral angles in degrees between the bridge-head protons and the protons of the adjacent methylenes. Numbers in parentheses are the ring puckering amplitudes Q and phase angles Φ of the cyclopentane moieties along the 5–4–4a–6a–6 perimeter. Structures **Aa**, **Ab** and **Ua**, **Ub** shown in (b) and (c) are simple models lacking the phenyl substituent of the adenine nucleosides **8Aa**, **8Ab** and the uracil nucleosides **11Ua**, **11Ub**, respectively. Dashed lines indicate hydrogen bonds and the distances are given in Å.

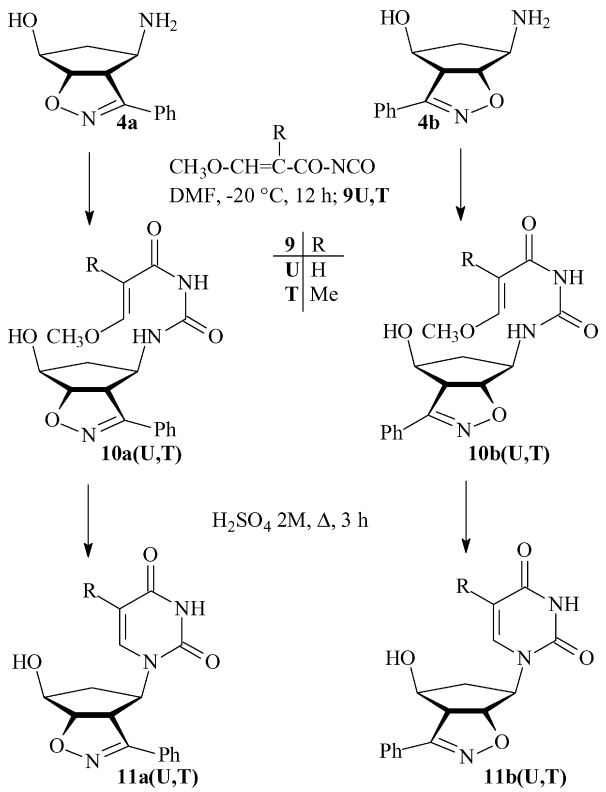
In the adenine derivatives a conformational change ensues in order to accommodate a strong intramolecular hydrogen bond between the OH and the basic adenine N3 nitrogen. This causes a flattening of the cyclopentane envelope as well as some twisting around the fused bond of the bicyclic array toward a half-chair cyclopentane conformation[19c] with the adenine moiety projecting outside. Figure 1b shows the optimized B3LYP/6-31G* structures of models of the adenine derivatives **8aA** and **8bA** lacking the phenyl ring. The relevant dihedral angles around the CH–CHN bonds increase to 109–114° while those around the CH–CHO bonds show only negligible or modest changes to 95°, in agreement with the observed trend in the coupling constants. The distances involved in the intramolecular hydrogen bonding are given in the figure and correspond well to cases of strong hydrogen bonding.[21]

The ring puckering parameters of the cyclopentane moieties (puckering amplitudes Q and phase angle Φ)[22] are also given in Figure 1. The puckering amplitudes Q demonstrate the flattening of the cyclopentane ring in the hydrogen bonded structures while the phase angles indicate their neat distortions to the half-chair conformation having the two carbons of the $CH_2CH(OH)$ moiety out of plane.[23]

The N-substituted derivatives **8a**(**B**-**G**) display spectroscopic patterns essentially similar to the adenine derivatives and consistent with the substituents.

2.2. Construction of the pyrimidine nucleosides

The stereoisomeric aminols **4a**,**b** were also converted into the uracil and thymine nucleosides[24] through the linear construction of these heterocycles.[4,6,25] The synthetic route to uracil and thymine nucleosides involves the steps illustrated in Scheme 4 and started with the preparation of the appropriate isocyanate **9U**,**T**.



Scheme 4.

The 3-methoxy-2-propenoyl isocyanate **9U** was easily obtained starting from the commercially available methyl 3-methoxy-2-propenoate through basic hydrolysis to the acid,[25] conversion to the chloride with thionyl chloride[26] and coupling with silver cyanate in benzene.[25] The 3-methoxy-2-methyl-2-propenoyl isocyanate **9T** was similarly obtained from the corresponding methyl 3-methoxy-2-methyl-2-propenoate. The latter is available from the simple methyl methacrylate according to a convenient reported protocol.[27]

The addition reactions of the aminols **4a**,**b** to isocyanates **9U**,**T** were conducted according to the procedure reported in the literature[25] by performing the reactions at −20 °C in DMF solutions for 12 h. After chromatographic purification, the urea adducts **10a**,**b**(**U**,**T**) were obtained in fair yields (50%). Their structures rely upon the analytical and spectroscopic data. Table 3 reports the yields, the physical constants and the significative spectroscopic data. Neat distinctive bands corresponding to the OH and the two NH groups were evident in the IR spectra. The NMR spectra showed the signals of the methoxy propenoyl and methyl propenoyl chains as well as those of the carbocyclic moiety in the usual ranges.

Table 3. Yields, physical constants and significative spectroscopic data of the ureas **10** and nucleosides **11**

Compounds	Yield (%)	Mp (°C) (EtOH)	IR (cm^{-1})	
			ν_{OH}	ν_{NH}
10Ua	53	245 dec.	3493	3282–3240
10Ta	50	231 dec.	3536	3327–3243
10Ub	52	221–2	3474	3274–3253
10Tb	48	226–7	3485	3237–3343
11Ua	70	143–4	3500	3180
11Ub	65	112–3	3400	3180
11Ta	64	245–6	3461	3153
11Tb	61	218–9	3323	3141

Cyclization of the ureas **10** took place smoothly upon refluxing in 2 M H_2SO_4 solution for 3 h. The uracil nucleosides **11Ua**,**b** and the thymine analogues **11Ta**,**b** were isolated from these solutions after pH adjustment to 7 and extraction with dichloromethane. The yields of the cyclization steps were satisfactory (61–70%) and the structures of the nucleosides **11** rely upon their analytical and spectroscopic data. The IR spectra of nucleosides **11** showed neat and distinct OH and NH bands, which are reported in Table 3. The ^1H NMR spectra of the uracil nucleoside **11Ua**,**b** showed the characteristic coupled vinyl protons of the uracil unit as doublets at δ 5.68 and 7.85 (J=8 Hz) while the thymine nucleosides **11Ta**,**b** display the vinyl proton and the methyl of the thymine unit as singlets at δ 7.7–7.8 and 1.80, respectively.

Both the isoxazolinic protons occur as double doublets owing to a conformational change due to a favorable strong intramolecular hydrogen bond between the OH and the uracil and thymine carbonyl as in the case of the adenine

derivatives. Figure 1c shows the optimized structures of models of the uracil derivatives.

3. Conclusions

The first synthesis of isoxazoline–carbocyclic nucleosides and a variety of analogues was attained starting from the stereodefined heterocyclic aminols **4**, which are readily available through *exo* selective 1,3-dipolar cycloadditions of benzonitrile oxide to *N*-benzoyl-oxazanorbornene **2** (R=Ph) and a simple elaboration of the cycloadducts. The stereodefined heterocyclic aminols **4** afford the carbocyclic skeleton for the linear construction of the purine, uracil and thymine moieties. Functionalization of the chloropurines **7** with a variety of amines extended the synthetic potential of this strategy allowing for a fine tuning of their biological and antiviral activity.[18,28] Owing to the availability of the enantiomerically pure adducts **2**[29] the route described here lends itself to the synthesis of optically pure nucleoside derivatives.

Biological evaluation of the obtained compounds is in progress. Preliminary data show that compound **7a** possesses a good inhibitory activity against Herpes Simplex virus type 1 and 2.

4. Experimental

All melting points are uncorrected. Elemental analyses were done on a C. Erba 1106 elemental analyzer. IR spectra (nujol mulls) were recorded on an FT-IR Perkin–Elmer RX-1. ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 in the specified deuterated solvents. Chemical shifts are expressed in ppm from internal tetramethylsilane (δ). UV–vis spectra were recorded on a UV Perkin–Elmer LAMBDA 16 spectrophotometer using acetonitrile as solvent. HPLC analyses were carried out by means of a WATERS 1525 instrument equipped with an UV 2487 detector (λ=266 nm) both controlled by Breeze™ software and a RP C-18 Intersil ODS-2 column: a mixture of H_2O/CH_3CN 60:40 was used as eluant. Column chromatography and TLC: silica gel 60 (0.063–0.200 mm) (Merck): eluant cyclohexane/ethyl acetate from 9:1 to 5:5. The identification of samples from different experiments was secured by mixed mps and superimposable IR spectra.

Materials. Aminols **4a**,**b** were prepared through NaOH/MeOH hydrolysis and N–O bond hydrogenolysis as previously reported.[10a] Methyl 3-methoxy-2-propenoate and silver cyanate were from ACROS ORGANICS. Methyl methacrilate was from SIGMA-ALDRICH.

4.1. Synthesis of the pyrimidine derivatives 6a,b

To aminols **4a**,**b** (1.70 g, 7.27 mmol) dissolved in *n*-BuOH (75 mL), 5-amino-4,6-dichloropyrimidine **5** (2.55 g, 15.5 mmol) and *i*-Pr_2NEt (4.02 g, 31.1 mmol) were added. The mixtures were refluxed at 117 °C with stirring for 48 h. The cooled solutions were evaporated to dryness, taken up in CH_2Cl_2, washed with water and dried over anhydrous Na_2SO_4. The crude residues were then submitted to column chromatography to separate the excess of amino-pyrimidine **5** from adducts **6a**,**b** which were isolated in 52 and 49% yield, respectively.

4.1.1. Compound 6a. The title compound (1.40 g, 52%) as white crystals from ethanol, mp 215–216 °C: [found C, 55.6: H, 4.7: N, 20.3. $C_{16}H_{16}N_5O_2Cl$ (MW=345.79) requires C, 55.58: H, 4.66: N, 20.25%]: ν_{max} (Nujol) 3424, 3240, 3340, 3200 cm^{-1}: δ_H (300 MHz, $CDCl_3$) 8.10 (2H, m, Ph), 8.08 (1H, s, CH=N), 7.40 (3H, m, Ph), 6.41 (1H, d, *J*=8.6 Hz, NH), 5.16 (1H, d, *J*=8.7 Hz, H5-isoxaz.), 4.92 (1H, m, C*H*–NH), 4.62 (1H, d, *J*=3.2 Hz, C*H*–OH), 4.29 (1H, d, *J*=8.7 Hz, H4-isoxaz.), 3.62 (3H, bs, OH and NH_2), 2.00 (2H, m, CH_2): δ_C (75 MHz, $CDCl_3$) 156.6, 153.3, 149.0, 130.2, 128.6, 128.3, 127.7, 91.5, 79.1, 60.2, 58.3, 56.8, 36.7, 18.3.

4.1.2. Compound 6b. The title compound (1.32 g, 49%) as white crystals from benzene, mp 119–121 °C: [found C, 55.6: H, 4.6: N, 20.2. $C_{16}H_{16}N_5O_2Cl$ (MW=345.79) requires C, 55.58: H, 4.66: N, 20.25%]: ν_{max} (Nujol) 3420, 3230, 3399, 3258 cm^{-1}: δ_H (300 MHz, $CDCl_3$) 8.15 (1H, s, CH=N), 7.76 (2H, m, Ph), 7.45 (3H, m, Ph), 6.10 (1H, d, *J*=8.8 Hz, NH), 5.25 (1H, d, *J*=8.8 Hz, H5-isoxaz.), 4.99 (1H, m, C*H*–NH), 4.64 (1H, m, C*H*–OH), 4.25 (1H, d, *J*=8.8 Hz, H4-isoxaz.), 3.51 (2H, bs, NH_2), 2.10 (2H, m, CH_2), 2.00 (1H, bs, OH): δ_C (75 MHz, $CDCl_3$) 156.6, 153.5, 148.9, 130.2, 126.9, 126.7, 122.0, 90.1, 76.9, 61.8, 60.8, 58.7, 37.4, 18.6.

4.2. Construction of the purine nucleosides 7a,b

To a solution of pyrimidine derivatives **6a**,**b** (0.532 g, 1.54 mmol) in triethyl orthoformate (25 mL), a catalytic amount of *p*-TsOH was added. The reaction was stirred at rt for 8 days. After this period of time, the orthoformate was evaporated and the residue taken up with chloroform and Et_3N was added and stirred for several hours. Then the organic phase was washed with water and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was taken up with ethyl acetate and finally, after a new evaporation to dryness, submitted to column chomatography to purify the purine derivatives **7a**,**b**.

4.2.1. Compound 7a. The title compound (0.50 g, 91%) as white crystals from ethyl acetate, mp 229–230 °C: [found C, 57.4: H, 4.0: N, 19.7. $C_{17}H_{14}N_5O_2Cl$ (MW=355.78) requires C, 57.39: H, 3.97: N, 19.68%]: ν_{max} (Nujol) 3556, 1591, 1561 cm^{-1}: δ_H (300 MHz, $CDCl_3$) 8.77 (1H, s, CH=N), 8.49 (1H, s, CH=N), 7.58 (2H, m, Ph), 7.40 (3H, m, Ph), 5.40 (1H, d, *J*=9 Hz, H5-isoxaz.), 5.23 (1H, d, *J*=9.4 Hz, CH–N), 4.78 (1H, d, *J*=4.7 Hz, C*H*–OH), 4.59 (1H, d, *J*=9 Hz, H4-isoxaz.), 3.50 (1H, bs, OH), 2.3–2.7 (2H, m, CH_2): δ_C (75 MHz, $CDCl_3$) 156.9, 151.7, 150.6, 145.6, 130.8, 129.1, 127.4, 127.0, 93.6, 77.1, 60.7, 58.8, 39.4.

4.2.2. Compound 7b. The title compound (0.49 g, 89%) as white crystals from ethyl acetate, mp 234–236 °C: [found C, 57.4: H, 3.9: N, 19.7. $C_{17}H_{14}N_5O_2Cl$ (MW=355.78) requires C, 57.39: H, 3.97: N, 19.68%]: ν_{max} (Nujol) 3291, 1596, 1588 cm^{-1}: δ_H (300 MHz, $CDCl_3$) 8.81 (1H, s, CH=N), 8.39 (1H, s, CH=N), 7.85 (2H, m, Ph), 7.45 (3H,

m, Ph), 5.59 (1H, d, *J*=8.7 Hz, H5-isoxaz.), 5.26 (1H, m, CH–N), 4.71 (1H, m, C*H*–OH), 4.55 (1H, d, *J*=8.7 Hz, H4-isoxaz.), 3.50 (1H, bs, OH), 2.74 (1H, m, CH_2), 2.44 (1H, m, CH_2): δ_C (75 MHz, $CDCl_3$) 156.9, 155.6, 151.5, 145.4, 130.5, 128.9, 127.7, 127.0, 90.4, 77.0, 63.9, 63.0, 39.5.

4.3. Syntheses of the amino derivatives 8a,b

General method. Solutions of chloro-nucleosides **7a**,**b** (30 mg, 0.08 mmol) in MeOH (2 mL) were saturated with ammonia or other gaseous amines and kept in a sealed tube at 50 °C for 24 h. In the case of liquid amines, an excess (50 equiv.) was added to the solutions. The solutions are then cooled and in most cases the products crystallize from the methanolic solutions. Otherwise, concentration of the solutions allows the amino derivatives to crystallize (with a single exception, **8aG** remains a thick oil). Table 2 reports the physical constants (solvent of crystallization) and yields (determined by HPLC analyses) of the amino nucleosides **8a**,**b**.

4.3.1. Compound 8aA. The title compound (66%) as white crystals from ethanol, mp 129–132 °C: [found C, 60.8: H, 4.9: N, 24.9. $C_{17}H_{16}N_6O_2$ (MW=336.35) requires C, 60.70: H, 4.80: N, 24.99%]: ν_{max} (Nujol) 3524, 3269, 3119 cm^{-1}: δ_H (300 MHz, $CDCl_3$) 8.40 (1H, s, CH=N), 7.78 (1H, s, CH=N), 7.3–7.6 (5H, m, Ph), 5.88 (2H, bs, NH_2), 5.42 (1H, d, *J*=8 Hz, H5-isoxaz.), 4.90 (1H, m, CH–N), 4.71 (1H, m, CH–OH), 4.48 (1H, dd, *J*=8, 3.4 Hz, H4-isoxaz.), 2.88 (1H, m, CH_2), 2.29 (1H, m, CH_2): δ_C (75 MHz, $CDCl_3$) 157.6, 155.4, 151.9, 150.2, 147.5, 140.6, 130.3, 128.8, 127.5, 126.5, 94.9, 76.8, 61.8, 58.1, 40.4.

4.3.2. Compound 8aB. The title compound (99%) as white crystals from methanol, mp 228–230 °C: [found C, 61.7: H, 5.2: N, 24.0. $C_{18}H_{18}N_6O_2$ (MW=350.37) requires C, 61.70: H, 5.18: N, 23.99%]: ν_{max} (Nujol) 3471, 3225 cm^{-1}: δ_H (300 MHz, $CDCl_3$) 8.43 (1H, s, CH=N), 7.76 (1H, s, CH=N), 7.3–7.6 (5H, m, Ph), 5.96 (1H, bs, NH), 5.52 (1H, d, *J*=8 Hz, H5-isoxaz.), 4.85 (1H, m, CH–N), 4.70 (1H, m, C*H*–OH), 4.46 (1H, dd, *J*=8, 4 Hz, H4-isoxaz.), 3.28 (3H, s, C*H*$_3$–NH), 2.89 (1H, m, CH_2), 2.28 (1H, m, CH_2): δ_C (75 MHz, $CDCl_3$) 200.3, 182.7, 152.4, 140.0, 130.5, 129.1, 127.9, 126.8, 95.5, 62.3, 58.4, 50.7, 40.9.

4.3.3. Compound 8aC. The title compound (97%) as white crystals from methanol, mp 212–213 °C: [found C, 62.6: H, 5.6: N, 23.1. $C_{19}H_{20}N_6O_2$ (MW=364.40) requires C, 62.62: H, 5.53: N, 23.06%]: ν_{max} (Nujol) 3310, 3230 cm^{-1}: δ_H (300 MHz, CD_3COCD_3) 8.24 (1H, s, CH=N), 8.20 (1H, s, CH=N), 7.61 (2H, m, Ph), 7.39 (3H, m, Ph), 6.90 (1H, bs, NH), 5.70 (1H, d, *J*=6 Hz, OH), 5.32 (1H, d, *J*=9.4 Hz, H5-isoxaz.), 5.18 (1H, m, C*H*–OH), 4.88 (1H, dd, *J*=9.4, 3 Hz, H4-isoxaz.), 4.53 (1H, m, CH–N), 3.74 (2H, b, CH_2–N), 2.56 (1H, m, CH_2), 2.30 (1H, m, CH_2), 1.32 (3H, t, CH_3): δ_C (75 MHz, CD_3COCD_3) 168.1, 162.8, 150.8, 140.6, 139.8, 139.4, 137.7, 104.7, 87.7, 87.6, 69.9, 68.5, 50.3, 45.5, 25.1.

4.3.4. Compound 8aD. The title compound (98%) as white crystals from methanol, mp 205–208 °C: [found C, 62.5: H, 5.5: N, 23.0. $C_{19}H_{20}N_6O_2$ (MW=364.40) requires C, 62.62: H, 5.53: N, 23.06%]: ν_{max} (Nujol) 3320 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.36 (1H, s, CH=N), 7.66 (1H, s, CH=N), 7.3–7.6 (5H, m, Ph), 5.42 (1H, dd, *J*=9, 1 Hz, H5-isoxaz.), 4.86 (1H, m, CH–N), 4.69 (1H, m, C*H*–OH), 4.46 (1H, dd, *J*=9, 4 Hz, H4-isoxaz.), 3.60 (6H, b, CH_3), 2.87 (1H, m, CH_2), 2.25 (1H, m, CH_2): δ_C (75 MHz, $CDCl_3$) 158.2, 151.2, 147.9, 138.7, 130.5, 129.1, 127.9, 126.8, 95.5, 77.1, 76.6, 62.2, 58.2, 40.9, 39.0.

4.3.5. Compound 8aE. The title compound (93%) as white crystals from methanol, mp 222–226 °C: [found C, 67.5: H, 5.1: N, 19.8. $C_{24}H_{22}N_6O_2$ (MW=426.46) requires C, 67.59: H, 5.20: N, 19.71%]: ν_{max} (Nujol) 3250, 3198 cm^{-1}: δ_H (300 MHz, $CDCl_3$) 8.45 (s, 1H, CH=N), 7.65 (s, 1H, CH=N), 7.2–7.6 (m, 10H, Ph), 6.13 (bs, 1H, NH), 5.42 (d, *J*=9 Hz, 1H, H5-isoxaz.), 4.92 (b, 2H, C*H*$_2$–Ph), 4.80 (m, 1H, CH–N), 4.69 (m, 1H, CH–OH), 4.45 (dd, *J*=9, 4 Hz, 1H, H4-isoxaz.), 2.85 (m, 1H, CH_2), 2.25 (m, 1H, CH_2): δ_C (75 MHz, $CDCl_3$) 157.8, 154.6, 152.1, 139.9, 137.5, 130.2, 128.8, 128.4, 128.2, 128.1, 127.6, 127.4, 127.3, 126.6, 126.5, 126.4, 95.1, 76.8, 76.4, 61.9, 58.1, 46.1, 44.2, 40.5.

4.3.6. Compound 8aF. The title compound (73%) as white crystals from ethyl acetate, mp 233–234 °C: [found C, 63.9: H, 5.4: N, 22.4. $C_{20}H_{20}N_6O_2$ (MW=376.40) requires C, 63.82: H, 5.36: N, 22.33%]: ν_{max} (Nujol) 3230, 3225 cm^{-1}: δ_H (300 MHz, CD_3COCD_3) 8.28 (1H, s, CH=N), 8.23 (1H, s, CH=N), 7.61 (2H, m, Ph), 7.40 (3H, m, Ph), 6.95 (1H, bs, NH), 5.63 (1H, d, *J*=6 Hz, OH), 5.33 (1H, d, *J*=10 Hz, H5-isoxaz.), 5.19 (1H, m, CH–N), 4.90 (1H, dd, *J*=10, 3 Hz, H4-isoxaz.), 4.51 (1H, m, C*H*–OH), 2.51 (1H, m, CH_2), 2.26 (1H, m, CH_2), 2.20 (1H, m, C*H*–NH), 0.75 (4H, m, CH_2–CH_2): δ_C (75 MHz, CD_3COCD_3) 167.0, 166.2, 153.0, 140.2, 129.9, 129.6, 128.7, 127.0, 93.9, 77.0, 59.1, 57.8, 39.5, 29.9, 6.2, 3.2.

4.3.7. Compound 8aG. The title compound (94%) as thick oil: [found C, 66.3: H, 6.4: N, 19.2. $C_{24}H_{28}N_6O_2$ (MW=432.51) requires C, 66.64: H, 6.53: N, 19.43%]: ν_{max} (Neat) 3340, 3339 cm^{-1}: δ_H (300 MHz, CD_3COCD_3) 8.26 (1H, s, CH=N), 8.23 (1H, s, CH=N), 7.60 (2H, m, Ph), 7.32 (3H, m, Ph), 6.68 (1H, d, *J*=8 Hz, NH), 5.70 (1H, d, *J*=6 Hz, OH), 5.30 (1H, d, *J*=9.4 Hz, H5-isoxaz.), 5.20 (1H, m, CH–OH), 4.85 (1H, dd, *J*=9.4, 3 Hz, H4-isoxaz.), 4.49 (1H, m, CH–N), 2.48 (1H, m, CH_2), 2.30 (1H, m, CH_2), 2.15 (4H, m, CH_2), 1.5–2.0 (8H, m, CH_2): δ_C (75 MHz, CD_3COCD_3) 161.1, 157.3, 152.2, 140.0, 129.9, 128.6, 128.5, 127.0, 93.9, 76.7, 60.5, 59.0, 57.9, 39.4, 35.5, 34.6, 28.4, 28.0, 24.3, 23.9.

4.3.8. Compound 8bA. The title compound (74%) as white crystals from methanol, mp 223–225 °C: [found C, 60.7: H, 4.8: N, 25.0. $C_{17}H_{16}N_6O_2$ (MW=336.35) requires C, 60.70: H, 4.80: N, 24.99%]: ν_{max} (Nujol) 3310, 3288, 3143 cm^{-1}: δ_H (300 MHz, CD_3COCD_3) 8.36 (1H, s, CH=N), 8.24 (1H, s, CH=N), 7.92 (2H, m, Ph), 7.49 (3H, m, Ph), 6.59 (2H, bs, NH_2), 5.56 (1H, m, OH), 5.68 (1H, dd, *J*=10, 3 Hz, H5-isoxaz.), 5.11 (1H, m, CH–N), 4.50 (1H, m, C*H*–OH), 4.48 (1H, dd, *J*=10, 3 Hz, H4-isoxaz.), 2.51 (2H, m, CH_2): δ_C (75 MHz, CD_3COCD_3) 158.7, 157.3, 153.8, 152.7, 150.8, 141.8, 131.3, 130.1, 128.6, 128.4, 91.0, 76.2, 62.8, 40.2, 30.4.

4.3.9. Compound 8bB. The title compound (98%) as white

crystals from methanol, mp 260–262 °C: [found C, 61.5: H, 5.1: N, 23.8. $C_{18}H_{18}N_6O_2$ (MW=350.37) requires C, 61.70: H, 5.18: N, 23.99%]: ν_{max} (Nujol) 3220, 3223 cm^{-1}: δ_H (300 MHz, CD_3COCD_3) 8.35 (1H, s, CH=N), 8.20 (1H, s, CH=N), 7.92 (2H, m, Ph), 7.49 (3H, m, Ph), 6.80 (1H, bs, NH), 5.70 (1H, dd, *J*=9, 3.3 Hz, H5-isoxaz.), 5.57 (1H, m, OH), 5.11 (1H, m, CH–N), 4.50 (1H, m, C*H*–OH), 4.48 (1H, dd, *J*=9, 3 Hz, H4-isoxaz.), 2.78 (3H, s, CH_3), 2.51 (2H, m, CH_2): δ_C (75 MHz, CD_3COCD_3) 168.1, 151.1, 139.5, 133.6, 132.4, 131.0, 130.7, 97.3, 65.5, 56.0, 40.1.

4.3.10. Compound 8bC. The title compound (96%) as white crystals from methanol, mp 196–200 °C: [found C, 62.5: H, 5.5: N, 23.0. $C_{19}H_{20}N_6O_2$ (MW=364.40) requires C, 62.62: H, 5.53: N, 23.06%]: ν_{max} (Nujol) 3260, 3220 cm^{-1}: δ_H (300 MHz, CD_3COCD_3) 8.28 (1H, s, CH=N), 8.23 (1H, s, CH=N), 7.92 (2H, m, Ph), 7.50 (3H, m, Ph), 6.80 (1H, bs, NH), 5.71 (1H, dd, *J*=10, 3.4 Hz, H5-isoxaz.), 5.59 (1H, d, *J*=6 Hz, OH), 5.11 (1H, m, CH–N), 4.54 (1H, m, C*H*–OH), 4.46 (1H, dd, *J*=10, 3 Hz, H4-isoxaz.), 3.73 (2H, bs, CH_2–N), 2.81 (2H, m, CH_2), 2.56 (2H, m, CH_3–CH_2), 1.31 (3H, t, CH_3–CH_2): δ_C (75 MHz, CD_3COCD_3) 158.7, 153.7, 141.2, 131.3, 130.4, 130.1, 128.4, 91.3, 76.7, 76.6, 63.2, 63.1, 40.6, 36.2, 15.8.

4.3.11. Compound 8bD. The title compound (100%) as white crystals from methanol, mp 169–170 °C: [found C, 62.5: H, 5.6: N, 23.1. $C_{19}H_{20}N_6O_2$ (MW=364.40) requires C, 62.62: H, 5.53: N, 23.06%]: ν_{max} (Nujol) 3240 cm^{-1}: δ_H (300 MHz, CD_3COCD_3) 8.28 (1H, s, CH=N), 8.26 (1H, s, CH=N), 7.94 (2H, m, Ph), 7.49 (3H, m, Ph), 5.70 (1H, dd, *J*=10, 3 Hz, H5-isoxaz.), 5.62 (1H, bs, OH), 5.14 (1H, m, CH–N), 4.55 (1H, m, C*H*–OH), 4.47 (1H, dd, *J*=10, 3 Hz, H4-isoxaz.), 2.85 (3H, s, CH_3), 2.69 (3H, s, CH_3), 2.51 (2H, m, CH_2): δ_C (75 MHz, CD_3COCD_3) 158.6, 156.1, 152.9, 151.6, 140.0, 131.2, 130.3, 130.0, 128.4, 91.3, 76.6, 63.1, 62.9, 40.4, 38.9, 38.7, 34.9.

4.3.12. Compound 8bE. The title compound (94%) as white crystals from methanol, mp 192–194 °C: [found C, 67.6: H, 5.1: N, 20.0. $C_{24}H_{22}N_6O_2$ (MW=426.46) requires C, 67.59: H, 5.20: N, 19.71%]: ν_{max} (Nujol) 3330, 3380 cm^{-1}: δ_H (300 MHz, CD_3COCD_3) 8.31 (1H, s, CH=N), 8.26 (1H, s, CH=N), 7.90 (2H, m, Ph), 7.2–7.6 (8H, m, Ph), 5.71 (1H, dd, *J*=10, 3.4 Hz, H5-isoxaz.), 5.56 (1H, bs, OH), 5.56 (1H, bs, NH), 5.13 (1H, m, CH–N), 4.92 (2H, b, CH_2–Ph), 4.54 (1H, m, C*H*–OH), 4.45 (1H, dd, *J*=10, 3 Hz, H4-isoxaz.), 2.51 (2H, m, CH_2): δ_C (75 MHz, CD_3COCD_3) 156.1, 151.1, 139.0, 129.8, 128.7, 127.8, 127.5, 127.0, 126.2, 125.9, 125.5, 88.7, 74.1, 74.0, 60.5, 42.1, 38.0.

4.3.13. Compound 8bF. The title compound (99%) as white crystals from methanol, mp 216 °C dec.: [found C, 63.7: H, 5.4: N, 22.2. $C_{20}H_{20}N_6O_2$ (MW=376.40) requires C, 63.82: H, 5.36: N, 22.33%]: ν_{max} (Nujol) 3260, 3250 cm^{-1}: δ_H (300 MHz, CD_3COCD_3) 8.30 (1H, s, CH=N), 8.25 (1H, s, CH=N), 7.90 (2H, m, Ph), 7.50 (3H, m, Ph), 6.90 (1H, bs, NH), 5.74 (1H, dd, *J*=10, 3.3 Hz, H5-isoxaz.), 5.60 (1H, d, *J*=6 Hz, OH), 5.14 (1H, m, CH–N), 4.51 (1H, m, C*H*–OH), 4.47 (1H, dd, *J*=10, 3 Hz, H4-isoxaz.), 2.51 (2H, m, CH_2), 2.25 (1H, m, C*H*–NH), 0.75 (4H, m, CH_2–CH_2): δ_C (75 MHz, CD_3COCD_3) 167.4, 166.2, 152.2, 140.1, 129.9, 129.6, 128.7, 127.1, 89.9, 75.3, 61.8, 61.7, 39.2, 31.1, 6.2, 3.2.

4.3.14. Compound 8bG. The title compound (92%) as white crystals from ethyl acetate, mp 199–201 °C: [found C, 66.5: H, 6.5: N, 19.4. $C_{24}H_{28}N_6O_2$ (MW=432.51) requires C, 66.64: H, 6.53: N, 19.43%]: ν_{max} (Nujol) 3340, 3320 cm^{-1}: δ_H (300 MHz, CD_3COCD_3) 8.26 (1H, s, CH=N), 8.25 (1H, s, CH=N), 7.90 (2H, m, Ph), 7.74 (3H, m, Ph), 6.52 (1H, d, *J*=8 Hz, NH), 5.72 (1H, dd, *J*=10, 3.3 Hz, H5-isoxaz.), 5.15 (1H, m, CH–N), 4.52 (1H, m, C*H*–OH), 4.45 (1H, dd, *J*=10, 3 Hz, H4-isoxaz.), 4.74 (1H, bs, OH), 3.30 (1H, m, C*H*–NH), 2.51 (2H, m, CH_2), 2.15 (4H, m, CH_2), 1.5–2.0 (8H, m, CH_2): δ_C (75 MHz, CD_3COCD_3) 156.0, 151.1, 138.7, 128.7, 127.6, 127.5, 125.9, 88.8, 74.0, 60.6, 60.5, 58.7, 38.0, 33.3, 32.7, 31.3, 26.3, 22.8, 22.7.

4.4. Syntheses of the isocyanate adducts 10a,b(U,T)

General method. To solutions of aminols **4a**,**b** (2.29 mmol) in anhydrous DMF (10 mL) at −20 °C, solutions of isocyanates **9U**,**T** (2.52 mmol) in anhydrous benzene were added dropwise with stirring in a nitrogen atmosphere and in the presence of MS 4 Å. After keeping for one night at rt, the solutions were filtered and solvent removed under reduced pressure. The residues were submitted to column chromatography to isolate the compounds **10a**,**b**(**U**,**T**). Table 3 reports the physical constants (solvent of crystallization) and the yields of the isocyanate adducts **10a**,**b**(**U**,**T**).

4.4.1. Compound 10Ua. The title compound (0.42 g, 53%) as white crystals from ethanol, mp 245 °C dec.: [found C, 59.1: H, 5.6: N, 12.2. $C_{17}H_{19}N_3O_5$ (MW=345.35) requires C, 59.12: H, 5.55: N, 12.17%]: ν_{max} (Nujol) 3493, 3282, 3240, 1700 cm^{-1}: δ_H (300 MHz, DMSO) 10.06 (1H, s, NH), 9.27 (1H, d, *J*=9 Hz, NH), 7.96 (2H, m, Ph), 7.60 (1H, d, *J*=12 Hz, =C*H*–OMe), 7.44 (3H, m, Ph), 5.60 (1H, d, *J*=3 Hz, OH), 5.53 (1H, d, *J*=12 Hz, =CH–CO), 5.00 (1H, d, *J*=9 Hz, H5-isoxaz.), 4.42 (1H, bs, CH–N), 4.26 (1H, s, C*H*–OH), 4.25 (1H, d, *J*=9 Hz, H4-isoxaz.), 3.68 (3H, s, CH_3O), 1.71 (2H, m, CH_2): δ_C (75 MHz, DMSO) 166.9, 162.6, 156.5, 152.8, 130.0, 128.7, 128.5, 127.1, 98.0, 91.5, 66.7, 60.0, 57.9, 54.3, 36.9.

4.4.2. Compound 10Ub. The title compound (0.40 g, 50%) as white crystals from ethanol, mp 231 °C dec.: [found C, 59.2: H, 5.7: N, 12.3. $C_{17}H_{19}N_3O_5$ (MW=345.35) requires C, 59.12: H, 5.55: N, 12.17%]: ν_{max} (Nujol) 3536, 3327, 3243, 1700 cm^{-1}: δ_H (300 MHz, DMSO) 10.11 (1H, s, *NH*), 9.09 (1H, d, *J*=8 Hz, NH), 7.76 (2H, m, Ph), 7.58 (1H, d, *J*=12 Hz, =C*H*–OMe), 7.47 (3H, m, Ph), 5.71 (1H, d, *J*=2 Hz, OH), 5.51 (1H, d, *J*=12 Hz, =CH–CO), 5.02 (1H, d, *J*=9 Hz, H5-isoxaz.), 4.37 (1H, bs, CH–N), 4.24 (1H, s, C*H*–OH), 4.19 (1H, d, *J*=9 Hz, H4-isoxaz.), 3.70 (3H, s, CH_3O), 1.74 (2H, m, CH_2): δ_C (75 MHz, DMSO) 167.0, 162.6, 156.2, 152.9, 130.1, 128.9, 128.7, 126.7, 97.9, 91.4, 75.6, 61.0, 57.9, 56.5, 36.8.

4.4.3. Compound 10Ta. The title compound (0.43 g, 52%) as white crystals from ethanol, mp 221–222 °C: [found C, 60.1: H, 5.9: N, 11.7. $C_{18}H_{21}N_3O_5$ (MW=359.37) requires

C, 60.16: H, 5.89: N, 11.69%]: ν_{max} (Nujol) 3474, 3274, 3243, 1678 cm^{-1}: δ_H (300 MHz, DMSO) 9.73 (1H, s, NH), 9.36 (1H, d, *J*=9 Hz, NH), 7.99 (2H, m, Ph), 7.46 (4H, m, Ph and CH═), 5.61 (1H, d, *J*=2 Hz, OH), 5.00 (1H, d, *J*=9 Hz, H5-isoxaz.), 4.43 (1H, m, C*H*–OH), 4.27 (1H, bs, CH–N), 4.22 (1H, d, *J*=9 Hz, H4-isoxaz.), 3.80 (3H, s, CH_3O), 1.72 (2H, b, CH_2), 1.63 (3H, s, CH_3): δ_C (75 MHz, DMSO) 169.3, 158.3, 156.8, 153.3, 130.3, 129.0, 128.9, 127.5, 107.4, 91.9, 77.0, 61.4, 60.4, 54.7, 37.2, 9.2.

4.4.4. Compound 10Tb. The title compound (0.40 g, 48%) as white crystals from ethanol, mp 226–7 °C: [found C, 60.2: H, 5.8: N, 11.6. $C_{18}H_{21}N_3O_5$ (MW=359.37) requires C, 60.16: H, 5.89: N, 11.69%]: ν_{max} (Nujol) 3485, 3237, 3343, 1689 cm^{-1}: δ_H (300 MHz, DMSO) 9.73 (1H, s, NH), 9.19 (1H, d, *J*=9 Hz, NH), 7.76 (2H, m, Ph), 7.48 (4H, m, Ph and CH═), 5.71 (1H, d, *J*=1 Hz, OH), 5.01 (1H, d, *J*=9 Hz, H5-isoxaz.), 4.38 (1H, m, C*H*–OH), 4.25 (1H, bs, CH–N), 4.18 (1H, d, *J*=9 Hz, H4-isoxaz.), 3.80 (3H, s, CH_3O), 1.73 (2H, m, CH_2), 1.62 (3H, s, CH_3): δ_C (75 MHz, DMSO) 169.4, 158.3, 156.6, 153.4, 130.4, 129.3, 129.1, 127.0, 107.3, 91.8, 76.0, 61.4, 56.9, 37.1, 9.2.

4.5. Construction of the uracil and thymine nucleosides 11a,b(U,T)

General method. 0.14 mmol adducts **10a**,**b**(**U**,**T**) are suspended in 2 M H_2SO_4 (10 mL) solutions and refluxed for 3 h. After cooling, the pH is adjusted to 7 with $NaHCO_3$ and the water phase extracted with dichloromethane. Evaporation of the dried organic phase afforded the uracil or thymine nucleosides which were purified by crystallization.

4.5.1. Compound 11Ua. The title compound (30 mg, 70%) as white crystals from ethanol, mp 143–144 °C: [found C, 61.4: H, 4.9: N, 13.5. $C_{16}H_{15}N_3O_4$ (MW=313.30) requires C, 61.33: H, 4.83: N, 13.41%]: ν_{max} (Nujol) 3500, 3181, 1695 cm^{-1}: δ_H (300 MHz, DMSO) 11.20 (1H, bs, NH), 7.87 (1H, d, *J*=8 Hz, ═*CH*), 7.53 (2H, m, Ph), 7.43 (3H, m, Ph), 5.68 (1H, d, *J*=8 Hz, ═CH–CO), 5.66 (1H, d, *J*=3.7 Hz, OH), 5.07 (1H, dd, *J*=10, 3 Hz, H5-isoxaz.), 4.81 (1H, m, CH–N), 4.62 (1H, dd, *J*=10, 4.4 Hz, H4-isoxaz.), 4.19 (1H, m, CH–O), 2.11 (1H, m, CH_2), 1.90 (1H, m, CH_2): δ_C (75 MHz, DMSO) 163.2, 157.6, 150.7, 143.3, 130.2, 128.9, 128.0, 126.9, 101.5, 92.8, 75.8, 59.0, 55.5, 38.4.

4.5.2. Compound 11Ub. The title compound (28 mg, 65%) as white crystals from benzene/ligroin, mp 112–113 °C: [found C, 61.3: H, 4.8: N, 13.4. $C_{16}H_{15}N_3O_4$ (MW=313.30) requires C, 61.33: H, 4.83: N, 13.41%]: ν_{max} (Nujol) 3400, 3180, 1701 cm^{-1}: δ_H (300 MHz, DMSO) 10.09 (1H, bs, NH), 7.87 (1H, d, *J*=8 Hz, ═CH), 7.54 (2H, m, Ph), 7.44 (3H, m, Ph), 5.67 (1H, d, *J*=8 Hz, ═CH–CO), 5.64 (1H, d, *J*=3.8 Hz, OH), 5.08 (1H, dd, *J*=9, 2.4 Hz, H5-isoxaz.), 4.83 (1H, m, CH–N), 4.62 (1H, dd, *J*=10, 4 Hz, H4-isoxaz.), 4.19 (1H, m, CH–O), 2.15 (1H, m, CH_2), 1.90 (1H, m, CH_2): δ_C (75 MHz, DMSO) 163.1, 157.5, 150.7, 143.3, 130.2, 128.9, 128.0, 126.8, 101.4, 92.8, 75.8, 59.0, 55.4, 38.4.

4.5.3. Compound 11Ta. The title compound (29 mg, 64%) as white crystals from ethanol, mp 245–246 °C: [found C, 62.4: H, 5.2: N, 12.9. $C_{17}H_{17}N_3O_4$ (MW=327.33) requires C, 62.37: H, 5.24: N, 12.84%]: ν_{max} (Nujol) 3461, 3153, 1680 cm^{-1}: δ_H (300 MHz, DMSO) 11.25 (1H, s, NH), 7.75 (1H, s, CH═), 7.48 (2H, m, Ph), 7.32 (3H, m, Ph), 5.63 (1H, d, *J*=3.8 Hz, OH), 5.08 (1H, dd, *J*=10.2, 2.8 Hz, H5-isoxaz.), 4.81 (1H, dt, *J*=11.9, 4.8 Hz, CH–N), 4.58 (1H, dd, *J*=10.2, 4.8 Hz, H4-isoxaz.), 4.18 (1H, m, CH–O), 2.15 (1H, m, CH_2), 1.90 (1H, m, CH_2), 1.81 (3H, s, CH_3): δ_C (75 MHz, DMSO) 163.8, 157.7, 150.7, 138.8, 130.2, 128.9, 128.1, 126.9, 109.2, 92.8, 75.8, 58.3, 55.4, 38.6, 12.4.

4.5.4. Compound 11Tb. The title compound (28 mg, 61%) as white crystals from ethanol, mp 218–219 °C: [found C, 61.9: H, 5.0: N, 12.6. $C_{17}H_{17}N_3O_4$ (MW=327.33) requires C, 62.37: H, 5.24: N, 12.84%]: ν_{max} (Nujol) 3323, 3141, 1695 cm^{-1}: δ_H (300 MHz, DMSO) 11.35 (1H, s, NH), 7.90 (2H, m, Ph), 7.80 (1H, s, CH═), 7.51 (3H, m, Ph), 5.85 (1H, bs, OH), 5.41 (1H, dd, *J*=10.2, 5 Hz, H5-isoxaz.), 4.71 (1H, m, CH–N), 4.15 (2H, m, CH–O and H4-isoxaz.), 2.10 (2H, m, CH_2), 1.80 (3H, s, CH_3): δ_C (75 MHz, DMSO) 163.7, 157.7, 150.9, 139.0, 130.1, 128.9, 128.4, 127.1, 109.1, 87.8, 73.2, 61.4, 60.3, 38.3, 12.1.

Acknowledgements

Financial support by University of Pavia (FAR), MIUR (PRIN 2002 and FIRB 2001) and CNR 2000 is gratefully acknowledged. Thanks are due to Prof. Giovanni Romeo for fruitful discussions on nucleoside chemistry. We also thank Prof. L. Toma for invaluable aid in determining the puckering parameters.

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23. In the ^{1}H NMR spectra of chloropurine **7a** (and **7b**) the coupling constants do not indicate a change in the cyclopentane conformation similar to that observed in the adenine derivatives **8aA** and **8bA**, presumably because of the lower basicity of the N3 nitrogen of **7a** and **7b**. The X-ray structure[17] of **7a** does not show an intramolecular H-bond. The puckering amplitude (Q=0.33) shows intermediate flattening while the phase angle (Φ=338.2°) indicates a distortion to the $^5T_6$ half-chair conformation.
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Selectively protected galactose derivatives for the synthesis of branched oligosaccharides

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Received 14 November 2003; revised 3 February 2004; accepted 25 February 2004

Abstract—Synthesis and characterization of several new anomerically pure galactose derivatives, based on simple and effective protective group manipulations of benzyl β-D-galactopyranoside, are reported. The monosaccharides described contain selectively protected/deprotected hydroxyl functionalities at their 1,2,3,4- and 6-positions rendering them useful as building blocks for construction of branched oligosaccharides.

1. Introduction

Carbohydrates and glycoconjugates play a central role in various biological recognition processes.[1] Recent years have seen a rapid extension of the field of glycobiology with carbohydrate-derived therapeutics now entering clinical trials.[2] The limited availability of pure and structurally defined specific oligosaccharides nevertheless remains a major impediment to the study of carbohydrates in biological applications. Besides the traditional chemical synthesis techniques, enzymatic[3] and automated solid-phase synthetic[4] methods have been successfully applied for constructing stereo- and regiospecific glycosidic linkages in complex oligosaccharide structures. However, both of these methods suffer from limitations in scale-up. An additional concern is the inability of fermentation techniques to produce unnatural branched oligosaccharides. Thus, in many cases, conventional organochemical synthesis remains the method of choice for the preparation of multigram amounts of chemically defined oligosaccharides and the improvement and development of efficient protective group strategies and purification methods remains an important and actively investigated area of carbohydrate chemistry.[5] Of particular significance is the preparation of partially protected carbohydrate building blocks, where the protecting groups can be manipulated such that each can be selectively removed during the course of the synthetic route. In this regard, galactose is a particularly interesting monosaccharide due to its occurrence as a building block in various biological structures. In plants it is one of the main constituents of galactoglucomannans[6] and arabinogalactans.[7] In humans, it is one of the main constituents of human milk oligosaccharides[8] and polylactosamines.[9] The latter structures consisting of *N*-acetyllactosamine units [β-D-galactopyranosyl-(1→4)-*N*-acetyl-D-glucosamine] with galactose residues at their non-reducing ends have been extensively studied as anti-inflammatory agents. Furthermore, the axial 4-OH group of galactose renders it an optimal starting material for exploitation of various protective group strategies. Here, we report the preparation of some new anomerically pure galactose derivatives, obtained by simple and efficient protective group manipulations of benzyl β-D-galactopyranoside (**1**). The present paper continues our recently initiated studies on the synthesis and conformational behavior[10] of galactose-containing mono- and oligosaccharides. The galactose derived monosaccharides described here contain selectively protected hydroxyl functionalities in their 1,2,3,4- and/or 6-positions, thus potentially serving as useful building blocks for the construction of branched oligosaccharide libraries.

2. Results and discussion

Benzyl β-D-galactopyranoside (**1**) was prepared from β-D-galactose pentaacetate in 66% overall yield following a slightly modified literature procedure.[11] Protecting group manipulations of **1** are summarized in Scheme 1. The following strategy was designed in order to create selectively deprotected hydroxyl functionalities on the 1,2,3,4- and 6-positions of a fully protected galactose

Keywords: Galactose; Protecting groups; Monosaccharides; Oligosaccharides.
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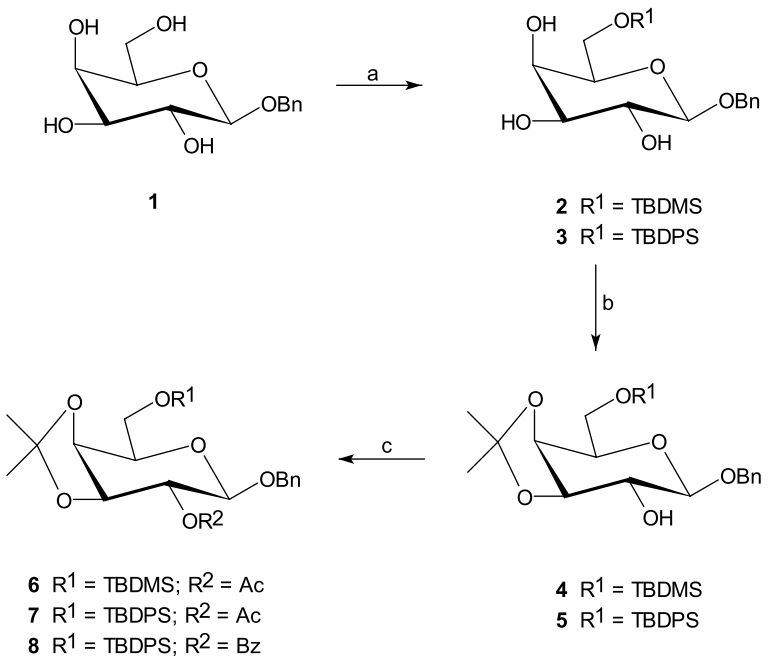
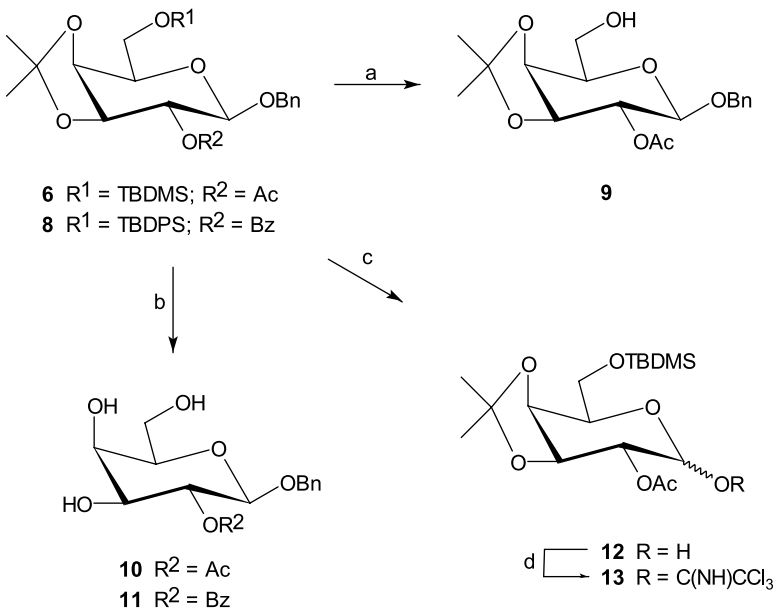
doi:10.1016/j.tet.2004.02.054



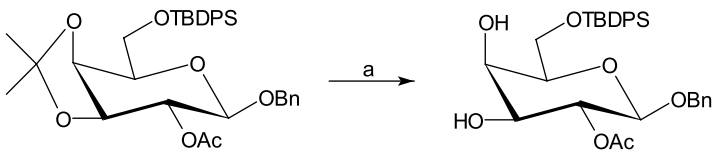
Scheme 1. (a) TBDMSCl, DBU, CH_2Cl_2, 0 °C then rt, 48 h, 98% (**2**); or TBDPSCl, imidazole, DMF, 0 °C then rt, 24 h, 60% (**3**); (b) 2,2-dimethoxypropane, TsOH, rt, 2–3 h, 93% (**4**) or 71% (**5**); (c) acetic anhydride, Et_3N or pyridine, CH_2Cl_2, rt, 12–48 h, 74% (**6**) or 93% (**7**); or BzCl, pyridine, rt, 6 h, 99%.

backbone: in the first step, the 6-*O*-position of **1** was protected as silyl ethers of varying acid lability (TBDMS or TBDPS). Next, the 3- and 4-hydroxyls were protected using the conventional isopropylidene ketal formation. Finally, the 2-hydroxyl group was protected as the base labile acetate or benzoate.

Thus, reaction of **1** with TBDMSCl and DBU in dichloromethane gave the 6-*O*-protected silyl ether, benzyl 6-*O*-(*tert*-butyldimethylsilyl)-β-D-galactopyranoside (**2**) in 98% isolated yield after purification by flash chromatography. The corresponding β-D-glucopyranoside has been described previously.[12,13] The previously reported 6-*O*-TBDPS analogue, benzyl 6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactopyranoside (**3**)[14,15] was prepared as described in the literature and isolated in 60% yield after purification by flash chromatography. Acid catalyzed reactions of **2** and **3** with 2,2-dimethoxypropane gave the corresponding isopropylidene ketals **4** and **5** in 93 and 71% yields, respectively, after purification by flash chromatography. Compound **5** has been prepared and characterized previously by Redlich and co-workers.[14a] Both compounds **4** and **5** were converted into the corresponding benzyl 6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside 2-*O*-acetates **6** and **7** according to standard procedures. Compound **5** was additionally converted



Scheme 2. (a) $Bu_4NF{\cdot}3H_2O$, THF, 0 °C then rt, 1.5 h, 84%; (b) As (a) then Dowex DR-2030, MeOH, 22 h, 65% (**10**) or 55% (**11**); (c) 10% Pd/C, cyclohexene, EtOH, reflux, 72 h, 93%; (d) CCl_3CN, DBU, CH_2Cl_2, 0 °C, 2 h, 78%.



7 14

Scheme 3. (a) 98% CF_3COOH, CH_2Cl_2, 0 °C then rt, 30 min, 76%.

into the corresponding 2-*O*-benzoate **8**. The 6-*O*-TBDMS derivative **6** was isolated as a transparent oil in 74% yield after purification by flash chromatography, while its 6-*O*-TBDPS analogue was conveniently purified by crystallization from pentane to afford **7** as a bright white solid in 93% isolated yield. The benzoate **8** was obtained as a white solid and in quantitative yield after standard work-up procedures. Remaining trace impurities were removed by column chromatography.

Selective deprotection sequences for the new compounds **6**-**8** are summarized in Schemes 2 and 3. In order to obtain a 1,2,3,4-protected galactose derivative with a free hydroxyl group in the 6-position, the TBDMS group of **6** was cleaved with Bu_4NF in THF under standard conditions to yield benzyl 2-*O*-acetyl-3,4-*O*-isopropylidene-*β*-D-galactopyranoside (**9**) in 84% yield after purification by flash chromatography.[16] The 3,4,6-deprotected derivatives benzyl 2-*O*-acetyl-*β*-D-galactopyranoside (**10**) and benzyl 2-*O*-benzoyl-*β*-D-galactopyranoside (**11**)[17] were prepared in 65 and 55% yields, respectively, by treating compounds **6** and **8** first with Bu_4NF in THF to obtain the crude desilylated products, which then were stirred overnight with Dowex DR-2030 acidic ion-exchange resin in order to cleave the 3,4-*O*-isopropylidene protection. Analytically pure **10** and **11** were then conveniently obtained after filtration of the acid catalyst, evaporation of the solvent and crystallization from $CHCl_3$ or pentane/EtOAc. In a simplified approach, both 6-TBDMS and 3,4-*O*-isopropylidene protective groups of **6** were successfully and simultaneously cleaved by stirring **6** with Dowex DR-2030 in MeOH overnight. Monitoring by TLC indicated the formation of one major product after 17 h. Filtration of the catalyst and evaporation of the solvent left an off-white solid that was shown to consist of fairly pure **10** by ^1H NMR analysis. This batch was not purified further. The 2,3,4,6-protected compound 2-*O*-acetyl-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-D-galactopyranose (**12**), containing a free hydroxyl group only in the anomeric position, was prepared from **6** in 93% yield under standard debenzylation conditions using Pd/C and cyclohexene followed by subsequent purification by flash chromatography. Compound **12** was converted to the corresponding trichloroacetimidate **13** in 78% yield following standard procedures.

The TBDPS silyl ether group is considerably (≈100 times) more stable than the TBDMS group toward acid hydrolysis.[18] Thus, the 3,4-*O*-isopropylidene protection of **7** was successfully and selectively cleaved with CF_3COOH in CH_2Cl_2 leaving the protective groups in 1,2- and 6-positions intact (Scheme 3). The desired benzyl 2-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-*β*-D-galactopyranoside (**14**) containing free hydroxyl groups in the 3,4-positions only was conveniently purified by precipitation from pentane to obtain analytically pure product in 76% isolated yield.

In summary, we have prepared several new anomerically pure *β*-D-galactopyranoside derivatives containing selectively protected hydroxyl groups in the 1,2,3,4- and 6 positions of the galactose framework. All new compounds have been fully characterized by elemental analysis, mass spectrometry, polarimetry, as well as by ^1H and ^{13}C NMR spectroscopy. A specific objective of this study was to design a versatile and orthogonal protective group strategy in a simple and efficient manner. First, the anomeric position of galactose was protected as a conventional benzyl ether. This protective group may later be easily removed by hydrogenation under neutral conditions. The free 1-OH can then potentially be further activated using various strategies leaving the protected 2,3,4- and 6-positions intact. For example, imidate,[19] fluoride[20] and thiophenyl[21] activations can be used for further glycosidations.

Next, the 6-OH position was protected as a silyl ether, removable in high yields by tetrabutylammonium fluoride. The acid lability of the silyl ether may be tuned by choosing properly substituted silyl chlorides as silylation reagents. The 3,4-*O*-isopropylidine protection installed in the subsequent step may then be removed in nearly quantitative yields with concomitant removal or retention of the 6-*O*-silyl ether protection. Galactose precursors containing free 3- and 4-hydroxyl groups may be selectively glycosidated in the 3-*O*-position using activated imidate[22] or halogenide[23] donors. Likewise, selective 4-*O*-glycosidations in the presence of free 3-OH groups have been reported.[24,25]

In the final step of the strategy described herein, the 2-OH position is protected as an acetyl or benzoyl ester. Thus, both 2-*O*- and 6-*O*-glycosidations should be accessible with the selectively removable 2-*O*-ester and 6-*O*-silyl ether protection strategies.[26] Compound **10**, described in the present work, containing only 2-*O*-acetyl protection in addition to the 1-*O*-benzyl ether group, is in turn a suitable candidate for either 3,6-*O*-[27] or 4,6-*O*-diglycosidations and, with its free 3,4,6-hydroxyl groups, a particularly interesting model compound for intramolecular acetyl group migration studies.[28] This topic is currently under investigation in the authors' laboratories.

3. Experimental

3.1. General remarks

All operations with air or moisture sensitive reagents and materials were carried out under an argon atmosphere using

standard Schlenk and vacuum techniques. Solvents were dried and distilled under argon prior to use when applicable or purchased from commercial sources NMR spectra were recorded on a JEOL JNM A 500 NMR spectrometer, unless otherwise indicated, and referenced against tetramethylsilane or the solvent signal. The sample temperature was maintained at 30 °C by a Jeol variable temperature unit. The ^{1}H and ^{13}C NMR spectra were recorded at 500.16 and 125.78 MHz, respectively, using a broadband 5 mm probe. All 2D experiments were performed with an inverse 5 mm probe with pulsed field gradient capability. For the complete assignment of the ^{1}H and ^{13}C NMR spectra of compounds **1**-**14**, a combination of two-dimensional COSY, TOCSY, HMBC and HMQC experiments were carried out. Inverse detected $^{1}H-^{13}C$ 2D chemical shift correlation spectra were acquired using the pulsed field gradient versions of HMBC and HMQC. In the cases of severe signal overlapping, the 500.16 MHz ^{1}H NMR spectra were finally analyzed by PERCH software[29] to perform complete spectral analyses. Electron impact high resolution mass spectra (EIMS) were obtained with Fisons ZabSpec mass spectrometer at 70 eV. Polarimetric measurements were carried out using a Perkin Elmer 241 Polarimeter with a cell volume of 1 mL and a cell length of 10 cm. TLC analyses were performed using silica gel F254 precoated aluminum sheets or glass plates and visualized by charring with 25% H_2SO_4 in methanol or methanol/orcinol and/or UV. Column chromatography was performed using silica gel 60 optionally enriched with 0.1% Ca to minimize hydrolysis of acid-labile protecting groups. Microanalyses were conducted at the Department of Microanalytics, University of Groningen, the Netherlands.

3.2. Synthesis and characterization of the monosaccharides

3.2.1. Benzyl β-D-galactopyranoside (1). To a solution of β-D-galactose pentaacetate (29.87 g, 76.52 mmol) in CH_2Cl_2 (300 mL) was added molecular sieves 4 Å (30 g) and benzyl alcohol (10.34 mL, 99.48 mmol). The reaction mixture was cooled on an ice-bath and $BF_3{\cdot}Et_2O$ (19.39 mL, 153.04 mmol) was added dropwise during a period of 15 min. The reaction mixture was slowly warmed up to ambient temperature and stirred for 20 h. The mixture was cooled to 0 °C, neutralized with triethylamine, extracted with CH_2Cl_2 and washed with water (3×200 mL). The organic layer was filtered through paper, the solvents were evaporated and the crude product was dried in vacuo. The obtained benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (42.05 g) was used in the subsequent step without further purification. This product was dissolved in a mixture of MeOH (1000 mL) and 1,4-dioxane (160 mL) and treated with sodium methoxide (4.0 g, 74 mmol). The reaction mixture was stirred at ambient temperature and monitored by TLC indicating completion of the reaction after 22 h ($MeOH/CH_2Cl_2$ 1:5, R_f=0.33 for the product). The reaction mixture was neutralized with Dowex 50 W (H^+ form), filtered and concentrated in a rotary evaporator. Solvents were co-evaporated with toluene and the product obtained was dried in vacuo. Column chromatography (silica gel, $MeOH/CH_2Cl_2$, gradient elution) gave pure **1** (13.53 g, overall yield 66% based on β-D-galactose pentaacetate) as a white solid: $[\alpha]_{22}^{D}=-31.4$ (c=0.14 in MeOH); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.44–7.30 (5H, m, Ph), 4.86, 4.68 (2H, d, J=11.6 Hz, CH_2Ph), 4.38 (1H, d, J=7.7 Hz, H-1), 3.84 (1H, dd, J=0.8, 3.4 Hz, H-4), 3.73 (1H, dd, J=4.5, 11.7 Hz, H_b-6), 3.67 (1H, dd, J=7.8, 11.7 Hz, H_a-6), 3.59 (1H, ddd, J=0.8, 4.5, 7.8 Hz, H-5), 3.53 (1H, dd, J=3.4, 9.9 Hz, H-3), 3.47 (1H, dd, J=9.9, 7.7 Hz, H-2); δ_C (125.78 MHz, $CDCl_3$, 303 K); 139.3, 129.6, 129.6, 129.3 (Ph), 102.7 (C-1), 76.1 (C-3), 73.8 (C-2), 72.3 (C-5), 71.7 (CH_2Ph), 69.6 (C-4), 61.9 (C-6); EIMS calcd for $C_{13}H_{19}O_6$ $[M+H]^+$ 271.1181. Found 271.1200. Anal. Calcd for $C_{13}H_{18}O_6$ (270.3): C, 57.77; H, 6.71. Found C, 56.76; H, 6.81.

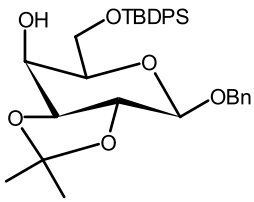
3.2.2. Benzyl 6-*O*-(*tert*-butyldimethylsilyl)-β-D-galactopyranoside (2). To a solution of **1** (2.30 g, 8.52 mmol) in CH_2Cl_2 (60 mL) was added *tert*-butyldimethylchlorosilane (1.41 g, 9.35 mmol). The reaction mixture was stirred for 30 min at ambient temperature and cooled to 0 °C. A solution of DBU (1.40 mL, 9.37 mmol) in CH_2Cl_2 (10 mL) was added during a period of 30 min and the reaction mixture was stirred for 48 h at ambient temperature. Silica gel was added to the reaction mixture and the solvents were removed in vacuo. Flash column chromatography (silica gel containing 0.1% Ca, CH_2Cl_2/MeOH, gradient elution) gave pure **2** (3.22 g, 98%) as a white solid: $[\alpha]_{22}^{D}=-38.6$ (c=0.05 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.28–7.14 (5H, m, Ph), 4.80, 4.50 (2H, d, J=11.6 Hz, CH_2Ph), 4.18 (1H, d, J=7.8 Hz, H-1), 3.85 (1H, ddd, J=1.1, 3.3, 4.0 Hz, H-4), 3.80 (1H, dd, J=5.4, 10.5 Hz, H_b-6), 3.76 (1H, dd, J=6.9, 10.5 Hz, H_a-6), 3.61 (1H, ddd, J=2.7, 7.8, 9.5 Hz, H-2), 3.40 (1H, ddd, J=3.3, 5.9, 9.5 Hz, H-3), 3.32 (1H, ddd, J=1.1, 5.4, 6.9 Hz, H-5), 3.25 (1H, d, J=5.9 Hz, OH-3), 3.06 (1H, d, J=2.7 Hz, OH-2), 2.99 (1H, d, J=4.0 Hz, OH-4), 0.81 (9H, s, CMe_3), 0.00 (6H, s, $SiMe_2$); δ_C (125.78 MHz, $CDCl_3$, 303 K); 137.3, 128.6, 128.5, 128.2 (Ph), 102.1 (C-1), 75.2 (C-5), 73.9 (C-3), 71.7 (C-2), 70.9 (CH_2Ph), 69.1 (C-4), 62.7 (C-6), 26.0 (CMe_3), 18.5 (CMe_3), −5.2, −5.5 ($SiMe_2$); EIMS calcd for $C_{15}H_{23}O_6Si$ $[M-C(CH_3)_3]^+$ 327.1263. Found 327.1240. Anal. Calcd for $C_{19}H_{32}O_6Si$ (384.5): C, 59.34; H, 8.39. Found C, 59.18; H, 8.42.

3.2.3. Benzyl 6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactopyranoside (3). To an ice-cooled solution of **1** (5.10 g, 18.87 mmol) and imidazole (2.57 g, 37.74 mmol) in DMF (50 mL) was added dropwise a solution of *tert*-butyldiphenylchlorosilane (5.19 g, 18.88 mmol) in DMF (25 mL). The reaction mixture was stirred overnight at ambient temperature. Monitoring by TLC indicated the disappearance of nearly all starting material after 23 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (100 mL) and extracted with Et_2O (3×80 mL). The combined organics were washed with H_2O (100 mL) and dried over sodium sulphate. Evaporation of the solvents left a yellowish oily foam (7.87 g) that was analyzed by ^{1}H NMR (250 MHz) in $CDCl_3$ indicating the presence of the desired product and *tert*-butyldiphenylsilanol in a 1:1 mixture. Flash column chromatography (silica gel, dichloromethane/methanol, gradient elution) gave pure **3** (5.75 g, 60%) as confirmed by ^{1}H and ^{13}C NMR analysis. δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.65–7.14 (15H, m, Ph), 4.78, 4.47 (2H, d, J=11.6 Hz, CH_2Ph), 4.18 (1H, d, J=7.8 Hz, H-1), 3.83, (1H, dd, J=0.8, 3.4 Hz, H-4), 3.82, (1H, dd, J=5.7, 10.6 Hz, H_b-6), 3.80 (1H, dd, J=6.0, 10.6 Hz, H_a-6), 3.61 (1H, dd,

J=7.8, 9.5 Hz, H-2), 3.40 (1H, dd, J=3.4, 9.5 Hz, H-3), 3.38 (1H, ddd, J=0.8, 5.7, 6.0 Hz, H-5), 0.99 (9H, s, CMe_3); δ_C (125.78 MHz, $CDCl_3$, 303 K); 137.2–127.9 (Ph), 101.9 (C-1), 74.9 (C-5), 73.8 (C-3), 72.1 (C-2), 70.9 (CH_2Ph), 69.2 (C-4), 63.4 (C-6), 27.0 (CMe_3), 19.4 (CMe_3). The 500.16 MHz NMR spectral data for **3** are consistent with those reported previously for this compound.[14]

3.2.4. Benzyl 6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (4). To a solution of compound **2** (5.20 g, 13.54 mmol) in 2,2-dimethoxypropane (100 ml) was added in one portion *p*-TsOH·H_2O (50 mg, 0.26 mmol). The reaction mixture was stirred at ambient temperature under argon. The reaction was quenched after 3 h by neutralizing the solution with a mixture of Et_3N and dichloromethane (1:1). The solvents were evaporated and the remaining transparent oil was dried in vacuo. Flash column chromatography (silica gel containing 0.1% Ca, EtOAc/toluene 5:100) gave pure **4** (5.34 g, 93%) as a white solid: $[\alpha]_{23}^{D}$=−17.9 (c=0.12 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.34–7.15 (5H, m, Ph), 4.80, 4.49 (2H, d, J=11.6 Hz, CH_2Ph), 4.11 (1H, d, J=8.3 Hz, H-1), 4.05 (1H, dd, J=2.2, 5.4 Hz, H-4), 3.91 (1H, dd, J=5.4, 7.3 Hz, H-3), 3.82 (1H, dd, J=7.2, 9.9 Hz, H_b-6), 3.79 (1H, dd, J=5.8, 9.9 Hz, H_a-6), 3.66 (1H, ddd, J=2.2, 5.8, 7.2 Hz, H-5), 3.49 (1H, dd, J=7.3, 8.3 Hz, H-2), 1.40, 1.21 (6H, s, CMe_2), 0.82 (9H, s, CMe_3), 0.00 (6H, s, $SiMe_2$); δ_C (125.78 MHz, $CDCl_3$, 303 K); 137.0, 128.6, 128.4, 128.0 (Ph), 110.0 (CMe_2), 101.1 (C-1), 78.9 (C-3), 73.9 (C-5), 73.8 (C-2), 73.3 (C-4), 70.6 (CH_2Ph), 62.2 (C-6), 28.3, 26.4 (CMe_2), 26.0 (CMe_3), 18.3 (CMe_3), −5.2, −5.5 ($SiMe_2$); EIMS calcd for $C_{21}H_{33}O_6Si$ $[M-CH_3]^+$ 409.2046. Found 409.2049.

3.2.5. Benzyl 6-*O*-(*tert*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (5). To a solution of **3** (5.65 g, 11.1 mmol) in 2,2-dimethoxypropane (100 mL) was added *p*-TsOH·H_2O (50 mg). The reaction mixture was stirred at ambient temperature. Monitoring by TLC indicated the formation of three products. The reaction was quenched after 2 h by neutralizing with Et_3N in CH_2Cl_2 and evaporated to dryness. The remaining off-white/yellow foamy solid (7.61 g) was flash chromatographed (silica gel, toluene/ethyl acetate, gradient elution) to afford the desired product as a highly viscous colorless oil (4.55 g) in a mixture with toluene, as confirmed by NMR. The residual toluene was removed by co-evaporation with EtOH to leave, after drying in vacuo, pure **5** (4.34 g, 71%) as an off-white solid: $[\alpha]_{24}^{D}$=−12.9 (c=0.14 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.68–7.21 (15H, m, Ph), 4.83, 4.52 (2H, d, J=11.6 Hz, CH_2Ph,), 4.18 (1H, dd, J=2.2, 5.4 Hz, H-4), 4.15 (1H, d, J=8.3 Hz, H-1), 3.97 (1H, dd, J=5.4, 7.4 Hz, H-3), 3.95 (1H, dd, J=5.2, 10.0 Hz, H_b-6), 3.85 (1H, dd, J=6.4, 10.0 Hz, H_a-6), 3.79 (1H, ddd, J=2.2, 5.2, 6.4 Hz, H-5), 3.54 (1H, ddd, J=1.9, 7.4, 8.3 Hz, H-2), 2.25 (1H, d, J=1.9 Hz, OH-2), 1.44, 1.27 (6H, s, CMe_2), 1.00 (9H, s, CMe_3); δ_C (125.78 MHz, $CDCl_3$, 303 K); 137.08–127.8 (Ph), 110.3 (CMe_2), 101.1 (C-1), 78.9 (C-3), 74.1 (C-2), 74.0 (C-5), 73.5 (C-4), 70.9 (CH_2Ph), 63.0 (C-6), 27.0 (CMe_3), 28.4, 26.5 (CMe_2), 19.5 (CMe_3). The NMR spectral data for **5** are consistent with those reported previously for this compound.[14a] EIMS calcd for $C_{31}H_{37}O_6Si$ $[M-CH_3]^+$ 533.2359. Found 533.2359. Anal. Calcd for $C_{32}H_{40}O_6Si$ (548.7): C, 70.04; H, 7.35. Found C, 70.11; H, 7.26. Residual fractions from the flash chromatography were combined, evaporated to dryness and dried in vacuo to leave a viscous off-yellow oil (1.43 g) consisting of three major components as shown by TLC. Refluxing of this mixture for 24 h in MeOH/H_2O (50:5 mL) and monitoring by TLC indicated the conversion of one unidentified compound to **5**. The solvents were evaporated and the residual transparent oil (1.26 g) purified by flash chromatography according to the procedure described for the initial crude product (vide supra) to afford an additional crop of **5** (0.98 g, 16%) containing trace impurities, as confirmed by NMR, and an off-yellow oil (165 mg, 3%) identified as benzyl 6-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-β-D-galactopyranoside by ^1H and ^{13}C NMR analyses: δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.73–7.26 (15H, m, Ph), 4.90, 4.66 (2H, d, J=11.7 Hz, CH_2Ph), 4.67 (1H, d, J=7.9 Hz, H-1), 4.42 (1H, ddd, J=1.2, 2.6, 3.3 Hz, H-4), 3.99 (1H, dd, J=5.4, 10.5 Hz, H_b-6), 3.96 (1H, dd, J=6.5, 10.5 Hz, H_a-6), 3.94 (1H, dd, J=7.9, 9.5 Hz, H-2), 3.56 (1H, ddd, J=1.2, 5.4, 6.5 Hz, H-5), 3.52 (1H, dd, J=2.6, 9.5 Hz, H-3), 2.41 (1H, d, J=3.3 Hz, OH-4), 1.48, 1.46 (6H, s, CMe_2), 1.08 (9H, s, CMe_3); δ_C (125.78 MHz, $CDCl_3$, 303 K); 137.08–127.8 (Ph), 110.3 (CMe_2), 101.1 (C-1), 79.2 (C-3), 76.0 (C-5), 73.1 (C-2), 69.9 (CH_2Ph), 67.2 (C-4), 62.9 (C-6), 26.8 (CMe_3), 26.8, 26.5 (CMe_2), 19.2 (CMe_3).



3.2.6. Benzyl 2-*O*-acetyl-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (6). To a solution of **4** (1.14 g, 2.69 mmol) in CH_2Cl_2 (50 mL) was added acetic anhydride (10 mL, 0.11 mol) and Et_3N (3 mL, 21.6 mmol). The reaction mixture was stirred for 48 h at ambient temperature, cooled to 0 °C and treated with MeOH (100 mL). The solvents were evaporated and the remaining oil was dissolved in CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (2×50 mL) and water (50 mL). The CH_2Cl_2 extracts were dried over $MgSO_4$ and evaporated to dryness. Flash column chromatography (silica gel containing 0.1% Ca, ethyl acetate/toluene, gradient elution) gave pure **6** (0.92 g, 74%) as a transparent oil: $[\alpha]_{23}^{D}$=−16.3 (c=0.12 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.25–7.16 (5H, m, Ph), 4.95 (1H, dd, J=7.6, 8.3 Hz, H-2), 4.77, 4.50 (2H, d, J=12.4 Hz, CH_2Ph), 4.23 (1H, d, J=8.3 Hz, H-1), 4.09 (1H, dd, J=2.1, 5.4 Hz, H-4), 4.01 (1H, dd, J=5.4, 7.6 Hz, H-3), 3.83 (1H, dd, J=7.0, 10.0 Hz, H_b-6), 3.81 (1H, dd, J=6.1, 10.0 Hz, H_a-6), 3.68 (1H, ddd, J=2.1, 6.1, 7.0 Hz, H-5), 1.97 (3H, s, Me), 1.47, 1.22 (6H, s, CMe_2), 0.82 (9H, s, CMe_3), 0.00 (6H, s, $SiMe_2$); δ_C (125.78 MHz, $CDCl_3$, 303 K); 169.8 (C=O), 137.5, 128.6, 128.0, 127.9 (Ph), 110.6 (CMe_2), 99.1 (C-1), 77.3 (C-3), 73.9 (C-5), 73.6 (C-4), 73.5 (C-2), 70.1 (CH_2Ph), 62.3 (C-6), 28.0, 26.6 (CMe_2), 26.0 (CMe_3), 21.2 (Me), 18.5 (CMe_3), −5.1, −5.2 ($SiMe_2$); EIMS calcd for $C_{23}H_{35}O_7Si$ $[M-CH_3]^+$ 451.2152. Found 451.2147.

3.2.7. Benzyl 2-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (7). To a solution of **5** (3.41 g, 6.21 mmol) in pyridine (40 mL) was added acetic anhydride (20 mL) and the reaction mixture was stirred overnight at ambient temperature. Monitoring by TLC indicated the formation of one major product after 2 h. The reaction mixture was cooled using an ice-bath and quenched by addition of MeOH (100 mL). The solvents were evaporated and the remaining oil extracted with CH_2Cl_2 (100 mL), washed with H_2O (100 mL) and evaporated to dryness. The residual pyridine was co-evaporated with toluene after which the remaining toluene traces were co-evaporated with EtOH. The resulting oil (3.73 g) was dried in vacuo and crystallized from pentane at −20 °C to afford pure **7** (3.42 g, 93%) as a bright white solid: $[\alpha]_{24}^{D}=-14.5$ (c=0.05 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.72–7.22 (15H, m, Ph), 5.02 (1H, dd, J=8.0, 8.3 Hz, H-2), 4.83, 4.57 (2H, d, J=12.5 Hz, CH_2Ph), 4.32 (1H, d, J=8.3 Hz, H-1), 4.25 (1H, dd, J=2.1, 5.4 Hz, H-4), 4.11 (1H, dd, J=5.4, 8.0 Hz, H-3), 3.99 (1H, dd, J=7.0, 10.1 Hz, H_b-6), 3.95 (1H, dd, J=6.2, 10.1 Hz, H_a-6), 3.83 (1H, ddd, J=2.1, 6.2, 7.0 Hz, H-5), 2.05 (3H, s, Me), 1.54, 1.32 (6H, s, CMe_2), 1.05 (9H, s, CMe_3); δ_C (125.78 MHz, $CDCl_3$, 303 K); 169.8 (C=O), 137.5–127.9 (Ph), 110.6 (*C*Me_2), 99.1 (C-1), 77.0 (C-3), 73.8 (C-4), 73.7 (C-2), 73.5 (C-5), 70.2 (*C*H_2Ph), 63.0 (C-6), 28.0, 26.8 (C*Me*$_2$), 27.0 (C*Me*$_3$), 21.2 (Me), 19.5 (*C*Me_3); EIMS calcd for $C_{33}H_{39}O_7Si$ $[M-CH_3]^+$ 575.2465. Found 575.2463. Anal. Calcd for $C_{34}H_{42}O_7Si$ (590.8): C, 69.12; H, 7.17. Found C, 69.58; H, 7.19.

3.2.8. Benzyl 2-*O*-benzoyl-6-*O*-(*tert*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (8). To a solution of **5** (0.58 g, 1.06 mmol) in pyridine (10 mL) was added benzoyl chloride (0.18 mL, 1.58 mmol). The reaction mixture was stirred at ambient temperature and monitored by TLC. Quantitative conversion of the starting material to a single product was observed after 6 h. The mixture was cooled using an ice-bath, quenched by addition of MeOH (100 mL) and extracted with CH_2Cl_2 (100 mL). The organic phase was washed with H_2O (100 mL), dried over sodium sulphate and evaporated to dryness. The residual pyridine was co-evaporated with toluene after which the remaining toluene traces were co-evaporated with EtOH. Drying in vacuo afforded **8** as a white solid containing trace impurities as confirmed by ^{1}H NMR. Flash column chromatography (silica gel, MeOH/CH_2Cl_2 1:100) gave after subsequent evaporation and drying 700 mg (99%) of pure **8** as a white solid: $[\alpha]_{24}^{D}=-11.4$ (c=0.05 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 8.04–7.14 (20H, m, Ph), 5.23 (1H, dd, J=7.3, 8.3 Hz, H-2), 4.76, 4.55 (2H, d, J=12.7 Hz, CH_2Ph), 4.39 (1H, d, J=8.3 Hz, H-1), 4.23 (1H, dd, J=5.4, 2.1 Hz, H-4), 4.20 (1H, dd, J=7.3, 5.4, Hz, H-3), 3.97 (1H, dd, J=6.7, 10.1 Hz, H_b-6), 3.94 (1H, dd, J=6.5, 10.1 Hz, H_a-6), 3.83 (1H, ddd, J=2.1, 6.5, 6.7 Hz, H-5), 1.51, 1.34 (6H, s, CMe_2), 1.10 (9H, s, CMe_3); δ_C (125.78 MHz, $CDCl_3$, 303 K); 165.6 (C=O), 137.3–127.9 (Ph), 110.7 (*C*Me_2), 98.9 (C-1), 77.5 (C-3), 74.0 (C-2), 73.9 (C-5), 73.7 (C-4), 69.9 (*C*H_2Ph), 63.0 (C-6), 27.0 (C*Me*$_3$), 28.0, 26.5 (C*Me*$_2$), 19.5 (*C*Me_3); EIMS calcd for $C_{38}H_{41}O_7Si$ $[M-CH_3]^+$ 637.2622. Found 637.2617. Anal. Calcd for $C_{39}H_{44}O_7Si$ (652.8): C, 71.75; H, 6.79. Found C, 71.61; H, 6.77.

3.2.9. Benzyl 2-*O*-acetyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (9). To an ice-cooled solution of **6** (681 mg, 1.46 mmol) in THF (15 mL) was added in one portion a solution of $Bu_4NF{\cdot}3H_2O$ (920 mg, 2.92 mmol) in THF (10 mL). The ice-bath was removed after 15 min and the reaction mixture was stirred at ambient temperature. Monitoring by TLC indicated the formation of one major product. The reaction was quenched after 1 h by the addition of CH_2Cl_2 (50 mL) and subsequent washing with saturated $NaHCO_3$ (50 mL). The aqueous phase was extracted with an additional portion of CH_2Cl_2 (20 mL) and the combined organics washed with brine (2×50 mL) and dried over sodium sulphate. The solvents were evaporated and the remaining off-yellow oil was dried in vacuo to leave 636 mg of fairly pure **9** as an off-white solid (identified by ^{1}H and ^{13}C NMR spectroscopy). Flash column chromatography (silica gel, toluene/ethyl acetate, gradient elution) gave pure **9** (433 mg, 84%): $[\alpha]_{24}^{D}=-0.83$ (c=0.06 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.38–7.05 (5H, m, Ph), 5.05 (1H, dd, J=7.2, 8.2 Hz, H-2), 4.86, 4.66 (2H, d, J=12.5 Hz, CH_2Ph), 4.41 (1H, d, J=8.2 Hz, H-1), 4.17 (1H, dd, J=5.4, 7.2 Hz, H-3), 4.15 (1H, dd, J=2.2, 5.4 Hz, H-4), 3.99 (1H, dd, J=4.3, 11.9 Hz, H_b-6), 3.84 (1H, dd, J=7.4, 11.9 Hz, H_a-6), 3.84 (1H, ddd, J=2.2, 4.3, 7.4 Hz, H-5), 2.07 (3H, s, Me), 1.55, 1.32 (6H, s, CMe_2); δ_C (125.78 MHz, $CDCl_3$, 303 K); 169.8 (C=O), 137.4, 128.6, 128.1, 127.9 (Ph), 111.1 (*C*Me_2), 99.5 (C-1), 77.5 (C-3), 74.2 (C-4), 73.6 (C-5), 73.1 (C-2), 70.9 (*C*H_2Ph), 62.6 (C-6), 27.8, 26.6 (CMe_2), 21.2 (Me). The ^{1}H and ^{13}C NMR data of **9** reported here in $CDCl_3$ solution deviate from those given previously in CD_3CN/D_2O.[16] EIMS calcd for $C_{18}H_{24}O_7$ 352.1522. Found 352.1489. Anal. Calcd for $C_{18}H_{24}O_7$ (352.4): C, 61.35; H, 6.86. Found C, 61.11; H, 6.91.

3.2.10. Benzyl 2-*O*-acetyl-β-D-galactopyranoside (10). To an ice-cooled solution of **6** containing a trace of the α-anomer (171 mg, 0.37 mmol) in THF (10 mL) was added in one portion a solution of $Bu_4NF{\cdot}3H_2O$ (230 mg, 0.74 mmol) in THF (10 mL). An immediate color change to light yellow was observed. TLC analysis after 90 min indicated the formation of one major product in accordance with the earlier observations during the synthesis of **9** (vide supra). The reaction was quenched by the addition of CH_2Cl_2 (50 mL) and subsequent washing with saturated $NaHCO_3$ (50 mL). The aqueous phase was extracted with additional portions of CH_2Cl_2 (2×20 mL) and the combined organics washed with brine (50 mL) and dried over sodium sulphate. Evaporation of the solvents and drying in vacuo left a yellowish oily solid (183 mg) that was dissolved in MeOH (30 mL) and stirred at ambient temperature overnight with Dowex DR-2030 (0.5 g, Fluka, H^+-form). The reaction was monitored by TLC showing the disappearance of all starting material after 21 h. The solid catalyst was removed by filtration, solvents were evaporated and the residue dried in vacuo to leave an off-white/yellowish solid (113 mg). The residue was purified by repeated washing and cooling cycles with $CHCl_3$ to yield pure **10** (75 mg, 65%) as a bright white crystalline solid: $[\alpha]_{23}^{D}=-10.4$ (c=0.02 in MeOH); δ_H (500.16 MHz, CD_3OD, 303 K); 7.34–7.24 (5H, m, Ph), 5.07 (1H, dd, J=8.1, 10.0 Hz, H-2), 4.86, 4.62 (2H, d, J=12.2 Hz, CH_2Ph), 4.46 (1H, d, J=8.1 Hz, H-1), 3.87 (1H, dd, J=0.8, 3.4 Hz, H-4), 3.81 (1H, dd, J=6.9, 11.4 Hz, H_b-6), 3.75 (1H, dd, J=5.2, 11.4 Hz, H_a-6), 3.62 (1H, dd,

J=3.4, 10.0 Hz, H-3), 3.54 (1H, ddd, J=0.8, 5.2, 6.9 Hz, H-5), 2.01 (3H, s, Me); δ_C (125.78 MHz, CD_3OD, 303 K); 172.3 (C=O), 139.3, 129.5, 129.0, 128.9 (Ph), 101.8 (C-1), 77.1 (C-5), 74.1 (C-2), 73.4 (C-3), 71.7 (CH_2Ph), 70.6 (C-4), 62.6 (C-6), 21.2 (Me); EIMS calcd for $C_{14}H_{15}O_5$ $\{[M-H_2O]-CH_2OH\}^+$ 263.0919. Found 263.0913. Anal. Calcd for $C_{15}H_{20}O_7$ (312.3): C, 57.69; H, 6.45. Found C, 57.34; H, 6.22. Alternatively, a solution of **6** (75 mg, 0.16 mmol) in MeOH (15 mL) was stirred at ambient temperature overnight with Dowex DR-2030 (0.31 g). TLC showed the formation of one major product after 17 h. The solid catalyst was removed by filtration, solvents were evaporated and the residue dried in vacuo to leave an off-white solid (50 mg). The crude product was analyzed by ^{1}H NMR (250 MHz) in MeOD showing nearly quantitative cleavage of both isopropylidene and TBDMS protective groups and the high yield formation of **10** evidenced by comparison of the ^{1}H NMR spectrum with that of the pure compound (vide supra). Further purification was not performed.

3.2.11. Benzyl 2-*O*-benzoyl-β-D-galactopyranoside (11). To an ice-cooled solution of **8** (332 mg, 0.51 mmol) in THF (10 mL) was added in one portion a solution of $Bu_4NF\cdot 3H_2O$ (320 mg, 1.0 mmol) in THF (10 mL). TLC analysis after 2 h was consistent with complete conversion of the starting material. The reaction was quenched by addition of CH_2Cl_2 (50 mL) and subsequent washing with saturated $NaHCO_3$ (50 mL). The organic phase was washed with H_2O (2×50 mL) and dried over sodium sulphate. Evaporation of the solvents and drying in vacuo left a viscous yellow oil that was dissolved in MeOH (30 mL) and stirred at ambient temperature overnight with Dowex DR-2030 (0.5 g, Fluka, H^+-form). The solid catalyst was removed by filtration, solvents were evaporated and the residue dried in vacuo to leave an off-yellow/brown solid (300 mg). Washing with pentane and subsequent crystallization from ethyl acetate afforded **11** (105 mg, 55%) as an off white powder: $[\alpha]_{23}^{D}$=−34.0 (c=0.02 in MeOH); δ_H (500.16 MHz, CD_3OD, 303 K); 8.00–7.05 (10H, m, Ph), 5.33 (1H, dd, J=8.0, 9.9 Hz, H-2), 4.83, 4.64 (2H, d, J=12.4 Hz, CH_2Ph), 4.60 (1H, d, J=8.0 Hz, H-1), 3.92 (1H, dd, J=1.1, 3.4 Hz, H-4), 3.85 (1H, dd, J=7.1, 11.4 Hz, H_b-6), 3.79 (1H, dd, J=5.0, 11.4 Hz, H_a-6), 3.79 (1H, dd, J=3.4, 9.9 Hz, H-3), 3.61 (1H, ddd, J=1.1, 5.0, 7.1 Hz, H-5); δ_C (125.78 MHz, CD_3OD, 303 K); 167.6 (C=O), 138.8–128.6 (Ph), 101.6 (C-1), 77.0 (C-5), 74.5 (C-2), 73.2 (C-3), 71.4 (CH_2Ph), 70.7 (C-4), 62.5 (C-6). In the EIMS analysis of the parent compound **11** ($C_{20}H_{22}O_7$) only peaks corresponding to decomposition products were observed. A satisfactory analysis was, however, obtained from the fully silylated 3,4,6-trimethylsiloxy derivative of **11**, benzyl 2-*O*-benzoyl-tris-3,4,6-*O*-(trimethylsilyl)-β-D-galactopyranoside for which EIMS calcd for $C_{28}H_{43}O_7Si_3$ 575.2317 gave the observed 575.2313.

3.2.12. 2-*O*-Acetyl-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-D-galactopyranose (12). To a solution of **6** (1.45 g, 3.11 mmol) in EtOH (100 mL) was added activated 10% Pd/C (250 mg) and cyclohexene (5 mL). The reaction mixture was refluxed for 72 h. The solids were separated by filtration through Celite and subsequent washing with CH_2Cl_2. Evaporation of the solvents and drying in vacuo afforded a dark oil (1.45 g). Analysis of the crude product by ^{1}H NMR (250 MHz) indicated the formation of the desired product as a mixture of the α- and β-anomers. Flash column chromatography (silica gel, toluene/ethyl acetate, gradient elution) gave pure **12** (1.04 g, 93%): (α-form) δ_H (500.16 MHz, $CDCl_3$, 303 K); 5.25 (1H, dd, J=3.5, 4.1 Hz, H-1), 4.83 (1H, ddd, J=1.3, 3.5, 7.7 Hz, H-2), 4.28 (1H, dd, J=5.7, 7.7 Hz, H-3), 4.21 (1H, ddd, J=2.4, 2.6, 6.1 Hz, H-5), 4.20 (1H, dd, J=2.4, 5.7 Hz, H-4), 3.80 (1H, dd, J=6.1, 10.0 Hz, H_b-6), 3.71 (1H, dd, J=2.6, 10.0 Hz, H_a-6), 2.90 (1H, dd, J=1.3, 4.1 Hz, OH-1), 2.02 (3H, s, Me), 1.38, 1.21 (6H, s, CMe_2), 0.82 (9H, s, CMe_3), 0.00 (6H, s, $SiMe_2$); δ_C (125.78 MHz, $CDCl_3$, 303 K); 170.8 (C=O), 109.8 (CMe_2), 90.6 (C-1), 73.2 (C-3), 73.1 (C-5), 72.3 (C-2), 68.3 (C-4), 62.5 (C-6), 28.1, 26.4 (CMe_2), 26.1 (CMe_3), 21.3 (Me), 18.6 (CMe_3), −5.1, −5.2 ($SiMe_2$); (β-form) δ_H (500.16 MHz, $CDCl_3$, 303 K); 4.74 (1H, dd, J=7.3, 7.8 Hz, H-2), 4.46 (1H, dd, J=9.8, 7.8 Hz, H-1), 4.20 (1H, ddd, J=2.0, 4.6, 5.4 Hz, H-5), 4.13 (1H, dd, J=5.4, 7.3 Hz, H-3), 3.79 (1H, dd, J=5.4, 10.3 Hz, H_b-6), 3.77 (1H, dd, J=2.0, 10.3 Hz, H_a-6), 3.77 (1H, dd, J=4.6, 5.4 Hz, H-4), 3.40 (1H, d, J=9.8 Hz, OH-1), 2.02 (3H, s, Me), 1.53, 1.45 (6H, s, CMe_2), 0.81 (9H, s, CMe_3), 0.00 (6H, s, $SiMe_2$); δ_C (125.78 MHz, $CDCl_3$, 303 K); 170.8 (C=O), 109.9 (CMe_2), 95.6 (C-1), 76.1 (C-3), 75.8 (C-2), 73.6 (C-4), 73.2 (C-5), 61.9 (C-6), 28.0, 26.2 (CMe_2), 26.0 (CMe_3), 21.3 (Me), 18.5 (CMe_3), −5.2, −5.2 ($SiMe_2$); EIMS calcd for $C_{16}H_{29}O_7Si$ $[M-CH_3]^+$ 361.1683. Found 361.1691.

3.2.13. 2-*O*-Acetyl-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-D-galactopyranosyl trichloroacetimidate (13). To an ice-cooled solution of **12** (1.04 g, 2.88 mmol) in CH_2Cl_2 (50 mL) was subsequently added trichloroacetonitrile (4.16 g, 2.9 mL, 28.8 mmol) and DBU (0.52 mL, 3.46 mmol). The reaction mixture was monitored by TLC showing consumption of all starting material after 2 h. The solvents were evaporated to leave a thick brown oil that was dissolved in a small amount of a solvent mixture containing toluene, ethyl acetate and CH_2Cl_2. Flash column chromatography (silica gel, with toluene/ethyl acetate/Et_3N, gradient elution) gave **13** in two fractions (1.07+0.1 g, total yield 78%) as a thick yellow oil. ^{1}H NMR (600 MHz) analysis revealed the first fraction to consist of fairly pure **13** enriched in single anomer, whereas the second fraction consisted of the anomeric mixture. (α-form) δ_H (600.13 MHz, $CDCl_3$, 298 K); 8.55 (s, 1H, NH), 6.36 (1H, d, J=3.6 Hz, H-1), 5.09 (1H, dd, J=3.6, 7.6 Hz, H-2), 4.41 (1H, dd, J=5.5, 7.6 Hz, H-3), 4.35 (1H, dd, J=2.3, 5.5 Hz, H-4), 4.22 (1H, ddd, J=2.3, 6.1, 7.3 Hz, H-5), 3.87 (1H, dd, J=7.3, 10.0 Hz, H_b-6), 3.79 (1H, dd, J=6.1, 10.0 Hz, H_a-6), 2.04 (3H, s, Me), 1.51, 1.31 (6H, s, CMe_2), 0.85 (9H, s, CMe_3), 0.00 (6H, s, $SiMe_2$); δ_C (150.90 MHz, $CDCl_3$, 298 K); 170.5 (C=O), 161.0 (C=NH), 110.1 (CMe_2), 93.8 (C-1), 91.2 (CCl_3), 73.0 (C-3), 72.7 (C-4), 70.9 (C-5), 70.6 (C-2), 62.0 (C-6), 28.0, 26.4 (CMe_2), 26.0 (CMe_3), 21.0 (Me), 18.5 (CMe_3), −5.1, −5.2 ($SiMe_2$); EIMS calcd for $C_{18}H_{29}Cl_3NO_7Si$ $[M-CH_3]^+$ 504.0779. Found 504.0792.

3.2.14. Benzyl 2-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-β-D-galactopyranoside (14). To an ice-cooled solution of **7** (105 mg, 0.18 mmol) in freshly distilled CH_2Cl_2 (15 mL) was added via syringe CF_3COOH (1 mL) containing 2%

deionized H_2O. The reaction mixture was stirred for 10 min at 0 °C followed by 20 min at ambient temperature. Next, the reaction mixture was cooled on an ice-bath followed by addition of saturated aqueous $NaHCO_3$ (5 mL) and stirred for 20 min. Ice-cold saturated aqueous $NaHCO_3$ (30 mL) was added and the mixture extracted with CH_2Cl_2 (2×50 mL). The combined organics were washed with $NaHCO_3$ (30 mL), H_2O (50 mL) and dried over sodium sulphate. Evaporation of the solvents and drying in vacuo left an off-yellow solid (122 mg) that was analyzed by ^1H NMR (250 MHz) in $CDCl_3$. The spectral data indicated nearly quantitative conversion of the starting material to the desired product. Precipitation from pentane gave an isolated yield of 75 mg (76%) of pure **14** as a white solid: $[\alpha]_{24}^{D}=-27.9$ (c=0.02 in $CHCl_3$); δ_H (500.16 MHz, $CDCl_3$, 303 K); 7.74–7.24 (15H, m, Ph), 5.07 (1H, dd, J=7.9, 9.7 Hz, H-2), 4.89, 4.62 (2H, d, J=12.4 Hz, CH_2Ph), 4.43 (1H, d, J=7.9 Hz, H-1), 4.09 (1H, ddd, J=1.1, 3.3, 4.4 Hz, H-4), 4.00 (1H, dd, J=5.9, 10.6 Hz, H_b-6), 3.97 (1H, dd, J=5.0, 10.6 Hz, H_a-6), 3.60 (1H, ddd, J=3.3, 8.5, 9.7 Hz, H-3), 3.51 (1H, ddd, J=1.1, 5.0, 5.9 Hz, H-5), 2.92 (1H, d, J=8.5 Hz, OH-3), 2.88 (1H, d, J=4.4 Hz, OH-4), 2.11 (3H, s, Me), 1.10 (9H, s, CMe_3); δ_C (125.78 MHz, $CDCl_3$, 303 K); 171.5 (C=O), 137.4–127.8 (Ph), 99.7 (C-1), 74.3 (C-5), 73.7 (C-2), 73.2 (C-3), 70.3 (*C*H_2Ph), 69.7 (C-4), 63.6 (C-6), 27.0 (C*Me*$_3$), 21.2 (Me), 19.4 (*C*Me_3). Anal. Calcd for $C_{31}H_{38}O_7Si$ (550.7): C, 67.61; H, 6.95. Found C, 67.72; H, 6.86.

Acknowledgements

The authors wish to thank Markku Reunanen for the EIMS-measurements.

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α-Oxoketene dithioacetal mediated aromatic annulation: highly efficient and concise synthetic routes to potentially carcinogenic polycyclic aromatic hydrocarbons

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Received 4 September 2003; revised 2 February 2004; accepted 25 February 2004

Abstract—Highly efficient regiospecific routes to potentially carcinogenic polycyclic aromatic hydrocarbons such as substituted benzo[*c*]phenanthrenes, benzo[*c*]fluorenes, 16,17-dihydro-11-methyl-15[*H*]cyclopenta[*a*]phenanthrene, 5-methyl-7,8,9,10-tetrahydrochrysene and 1,4-dimethylphenanthrene have been developed. The overall strategy involves our aromatic annulation protocol through base induced conjugate addition–elimination on the cyclic and acyclic α-oxoketene dithioacetals with the appropriate arylacetonitriles followed by acid induced cyclodehydration of the resulting conjugate adducts. Subsequent reductive dethiomethylation (Raney Ni) and dehydrogenation (DDQ) of the cyclized products affords the methyl substituted PAHs in high yields.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs), many of which are carcinogenic in animal assays, are widespread environmental contaminants[1] which are introduced into our environment by incomplete combustion of organic matter and fossil fuels.[2] In recent years, there has been a renewed interest in structure-activity relationships of PAHs[3] which is primarily due to the findings that PAHs containing a bay/*fjord* region are exceptionally mutagenic/tumourogenic and their corresponding diol epoxides exhibit a higher DNA adduct formation ability and a greater binding affinity to deoxyadenosine over deoxyguanosine compared to less hindered bay region PAH diol epoxides.[4] It is also well established that increasing steric hindrance in a bay region by substitution of a methyl group in the non-benzo ring position tends to markedly enhance their carcinogenic activity.[5] For example, 7,12-dimethylbenzo[*a*]anthracene (**2**)[6] and 5-methylchrysene (**4**)[7] are among the most potent known carcinogens, whereas benzo[*a*]anthracene (**1**) and chrysene (**3**) exhibit only weakly borderline activity. Similarly in the cyclopenta[*a*]phenanthrene series, the parent hydrocarbon 16,17-dihydro-15*H*-cyclopenta[*a*]-phenanthrene **5a** and its 17-keto analog **6a** are inactive, whereas the 11-methyl-17-keto derivative **6b** is a relatively potent carcinogen in mouse skin assay comparable in activity to benzo[*a*]pyrene.[8] The 11-Me derivative **5b** is intermediate in carcinogenic activity between **5a** and **6b** (Chart 1).[5c] However, the efficient synthesis of these methyl substituted and other carcinogenic PAHs remains a challenging problem and investigation of the mechanism of PAH carcinogenesis at molecular genetic level has been hampered by the lack of efficient methods for the synthesis of PAHs and their oxidized metabolites, most of which were developed several years earlier.[9,10] Therefore the development of efficient and high yielding synthetic routes for this class of PAHs from readily available precursors is highly desirable.

During the course of our aromatic and heteroaromatic annulation studies involving [3+3] cyclocondensation of α-oxoketene dithioacetals (1,3-bielectrophilic components) with various allyl and heteroallyl anions (1,3-binucleophilic components),[11,12] we have developed efficient and highly regiospecific routes for benzo-, naphtho- and phenanthrene annulation of active methylene ketones via these intermediates. Thus we have previously demonstrated that substituted benzyl, 1- and 2-naphthyl Grignard reagents add to various α-oxoketene dithoacetals either in sequential 1,4- and 1,2-or exclusive 1,2-addition fashion to afford the corresponding carbinols in high yields.[13,14] The problem of sequential 1,4- and 1,2-addition of benzyl and 2-naphthyl Grignard reagents was subsequently circumvented by

Keywords: Polycyclic aromatic hydrocarbons; α-Oxoketene dithioacetals; Aromatic annulation; Carcinogenic hydrocarbons; Benzo[*c*]phenanthrene.
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doi:10.1016/j.tet.2004.02.053

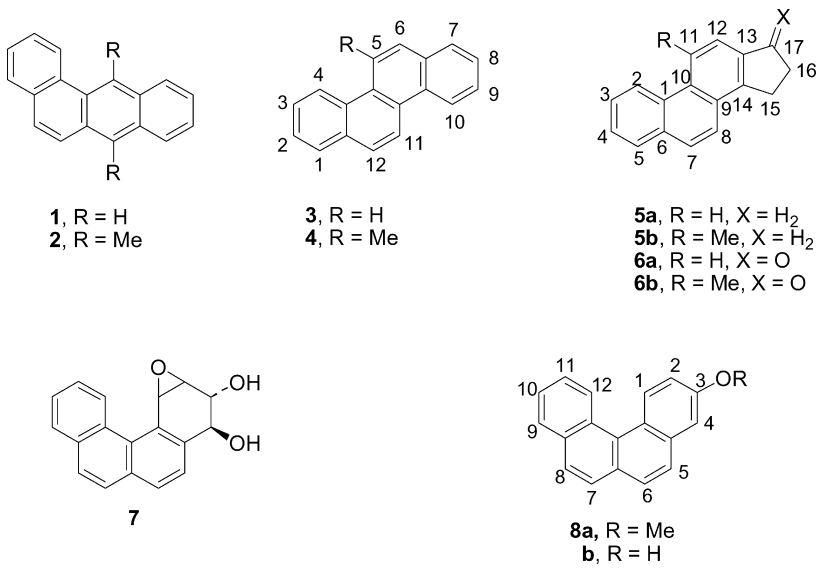


Chart 1.

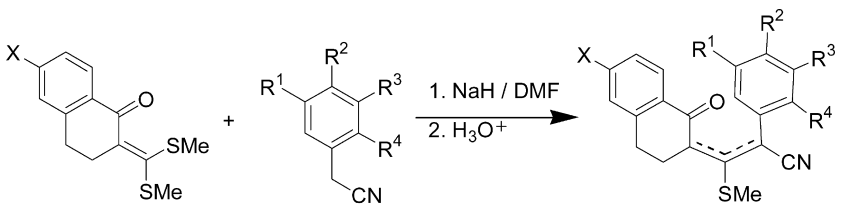
reacting these Grignard reagents with various β-oxodithioacetals[15] to give the corresponding carbinol adducts through exclusive 1,2-addition.[13,14] These carbinols (through 1,2-addition) underwent smooth cycloaromatization in the presence of $BF_3{\cdot}Et_2O$ to afford a series of regiospecifically substituted/annulated polycyclic aromatic hydrocarbons in high yields. Thus making use of these methods, a number of polycyclic aromatic hydrocarbons such as benz[*a*]anthracene, dibenz[*a*,*j*]anthracene and the corresponding dibenz[*a*,*h*]anthracene were synthesized in good yields.[13,14] In subsequent studies, we have further demonstrated that the stabilized carbanions derived from 3-cyanomethylindole, 2-cyanomethylpyrrole and 2/3-cyanomethylthiophenes add to α-oxoketene dithioacetals in exclusive 1,4-addition–elimination fashion to give conjugate adducts which on subsequent acid induced cycloaromatization lead to the formation of angularly substituted/annulated benzoheterocycles such as carbazoles,[16] indoles[17] and benzothiophenes[18] in highly regiospecific fashion. We have now extrapolated this strategy for the synthesis of a few angularly fused polycyclic aromatic hydrocarbons such as benzo[*c*]phenanthrene, benzo[*c*]fluorene, 11-methylcyclopenta[*a*]phenanthrene, 5-methylchrysene and 1,4-dimethylphenanthrene and the results of these studies are presented in the following section.

2. Results and discussion

2.1. Synthesis of substituted benzo[*c*]phenanthrenes

The *fjord*-region diol epoxide derivative **7** of benzo[*c*]-phenanthrene with additional crowding in the bay region exhibits significantly higher levels of carcinogenic activity in comparison to other hydrocarbon diol epoxides[4a] and therefore several approaches have been developed[19,20] for the synthesis of key intermediates, i.e. 3-methoxy/hydroxybenzo[*c*]phenanthrenes **8a–b** which are best obtained in 4–6 steps with 16–31% yields through tedious separation of reaction mixtures. Recently, Kumar has developed an efficient synthesis of 3-hydroxybenzo[*c*]phenanthrene involving palladium catalyzed cross coupling of readily accessible precursors.[4a,21] The general synthetic approach for benzo[*c*]phenanthrene framework adopted by us is shown in Schemes 1 and 2. The α-oxoketene dithioacetal **9** derived from α-tetralone was subjected to base induced addition–elimination with various methoxy substituted arylacetonitriles **11a–d** to afford the conjugate adducts **12a–d** in excellent yields (Scheme 1). Similarly the α-oxoketene dithioacetal **10** from 6-methoxytetralone afforded the conjugate adduct **12e** with 3,4-dimethoxyphenylacetonitrile in high yield under identical conditions. Cyclocondensation of the adducts **12a–e** in the presence of various protic and Lewis acids were next investigated. The adduct **12a** from 4-methoxyphenylacetonitrile failed to yield the desired dihydrobenzo[*c*]phenanthrene derivative **13a** under the influence of various acids (Scheme 2), whereas the cyclocondensation of the corresponding adducts **12b** and **12c** from 3-methoxy- and 3,4-dimethoxy phenylacetonitriles, respectively, proceeded smoothly in the presence of hot H_3PO_4 to furnish the respective methoxy substituted dihydrobenzo[*c*]phenanthrenes **13b–c** in high yields (Scheme 2). Thus the presence of an electron donating group such as methoxy *para* to the site of cyclization in the adducts **12b–c** appears to facilitate the cyclodehydration process. Similarly, the adduct **12e** from 6-methoxytetralone and 3,4-dimethoxyphenylacetonitrile underwent facile cyclization in the presence of hot H_3PO_4 to afford dihydrobenzo[*c*]phenanthrene **13e** in 92% yield (Scheme 2). However, the attempted cyclization of the adduct **12d** from 2,5-dimethoxyphenylacetonitrile did not yield the desired benzo[*c*]phenanthrene derivative **13d** under these cyclization conditions (Scheme 2), which may be due to the steric interference between aromatic ring proton and the methoxy group in the *fjord* region of the cyclization intermediate.

The 7,8-dihydrobenzo[*c*]phenanthrene derivative **13b** was subjected to dehydrogenation in the presence of DDQ to afford the corresponding 3-methoxy-5-cyano-6-methylthiobenzo[*c*]phenanthrene **14b** in 78% yield (Scheme 3). Raney Ni dethiomethylation of **14b** yielded



9, X = H
10, X = OMe

11a-d

12a-e

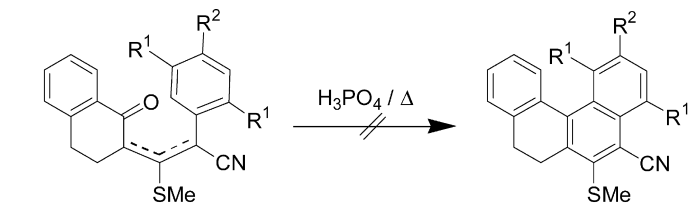
9-10	11	R^1	R^2	R^3	R^4	X	12	% Yield 12
9	**11a**	H	OMe	H	H	H	**12a**	90
9	**11b**	H	H	OMe	H	H	**12b**	90
9	**11c**	H	OMe	OMe	H	H	**12c**	89
9	**11d**	OMe	H	H	OMe	H	**12d**	79
10	**11c**	H	OMe	OMe	H	OMe	**12e**	**87**

Scheme 1.

3-methoxy-5-methylbenzo[*c*]phenanthrene **15b** (77%) with concomitant reduction of the nitrile group. The structures of **14b** and **15b** were established with the help of spectral and analytical data. In particular, the 400 MHz ^{1}H NMR spectrum of **15b** exhibited a pair of low field doublets at δ 8.91 and 8.96 assigned to H-1 and H-12 characteristic of protons in *fjord* region as a consequence of 'edge deshielding'.[22] Alternatively, the 2,3-dimethoxybenzo[*c*]-phenanthrene **13c** was first subjected to Raney Ni reductive dethiomethylation to afford 2,3-dimethoxy-5-methyl-7,8-dihydrobenzo[*c*]phenanthrene **15c** in 78% yield. Subsequent dehydrogenation of **15c** with DDQ afforded the corresponding 2,3-dimethoxybenzo[*c*]phenanthrene-5-aldehyde **16c** in 72% yield, the dehydrogenation being concomitant with oxidation of the methyl group (Scheme 3). When the benzo[*c*]phenanthrene **13b** was subjected to hydrolytic-decarboxylation in H_2SO_4/AcOH medium, 3-hydroxy-6-methylthio-7,8-dihydrobenzo[*c*]-phenanthrene **17b** was obtained in 70% yield (Scheme 3). However, the attempted dethiomethylation or dehydrogenation of **17b** in the presence of various reagents did not meet with much success and yielded only intractable mixture of products.

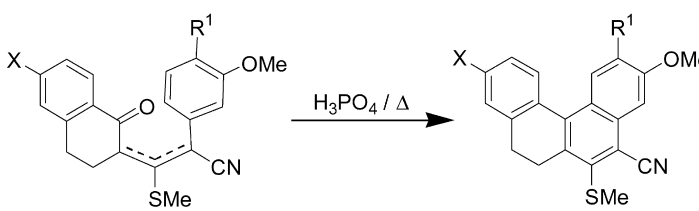
2.2. Synthesis of substituted benzo[*c*]fluorenes

We next extended our conjugate addition–elimination–cyclization protocol for the synthesis of the benzo[*c*]fluorene



12a, R^1 = H; R^2 = OMe
12d, R^1 = OMe; R^2 = H

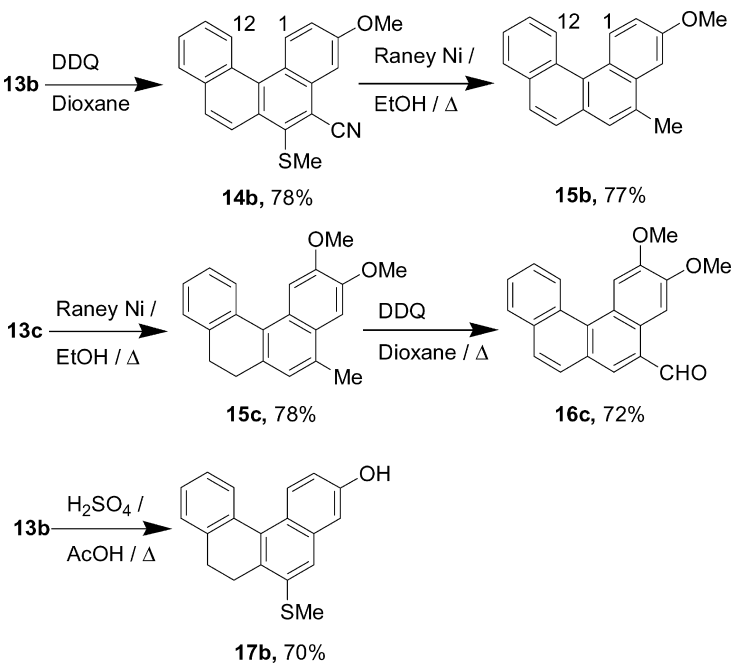
13a, R^1 = H; R^2 = OMe
13d, R^1 = OMe; R^2 = H



12b, X = R^1 = H
12c, X = H; R^1 = OMe
12e, X = R^1 = OMe

13b, X = R^1 = H, 82%
13c, X = H; R^1 = OMe, 90%
13e, X = R^1 = OMe, 92%

Scheme 2.

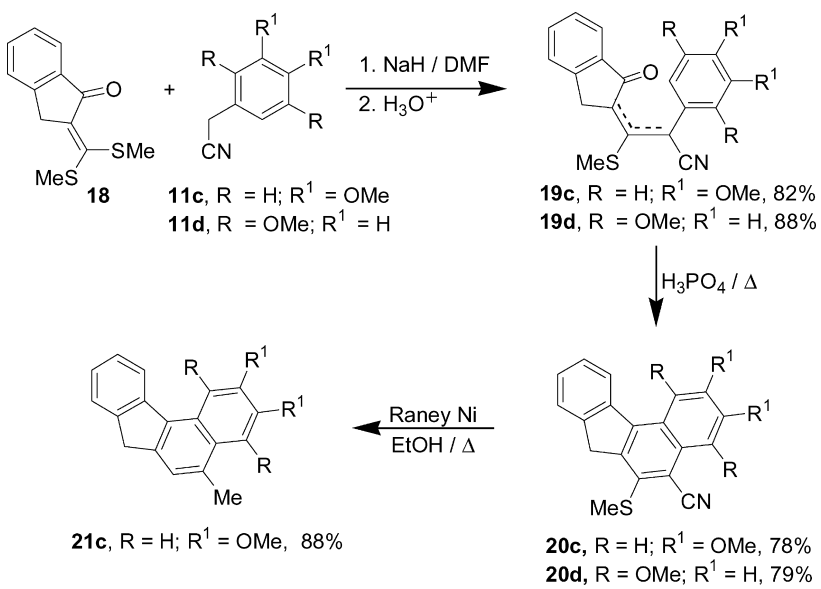


Scheme 3.

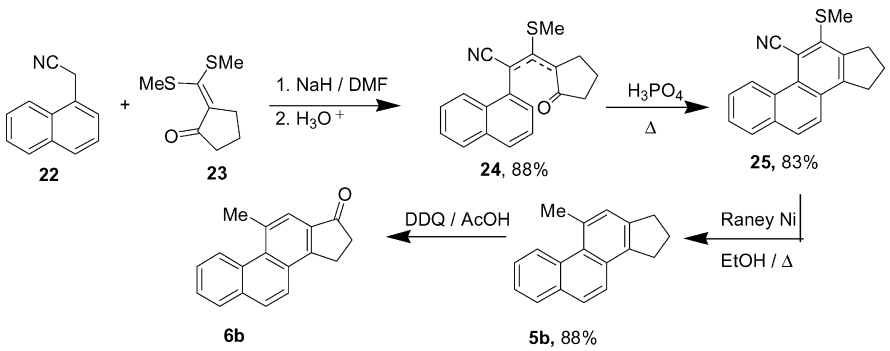
framework as shown in Scheme 4. Only a few syntheses of the benzo[*c*]fluorene derivatives[23,24] are described in the literature and carcinogenic properties of this ring system are not explored. The *S*,*S*-acetal **18** from 1-indanone was reacted with 3,4-dimethoxy- and 2,5-dimethoxyphenylacetonitriles, **11c** and **11d**, respectively, in the presence of NaH under the earlier described conditions to afford the adducts **19c–d** in high yields. The adduct **19c** was smoothly transformed into the benzo[*c*]fluorene derivative **20c** (78%) when subjected to cyclization in the presence of hot H_3PO_4. Raney Ni reduction of benzo[*c*]fluorene **20c** in refluxing ethanol afforded the corresponding 6-dethiomethylated 5-methyl-2,3-dimethoxy benzo[*c*]fluorene **21c** in 88% yield. Interestingly, the adduct **19d** from 2,5-dimethoxyphenylacetonitrile also underwent facile cyclodehydration under identical conditions to afford 1,4-dimethoxybenzo[*c*]fluorene derivative **20d** in 79% yield. Thus, unlike the adduct **12d** from tetralone, the steric hindrance between 1-methoxy group and 11-H is eliminated in the cyclization adduct **19d** which is probably due to the enhanced electrophilicity of the carbonyl group of indanone along with widening of the bay or *fjord* region in this framework thus diffusing the energy barrier towards cyclization.

2.3. Synthesis of 11-methyl-16,17-dihydro-15[*H*]cyclopenta[*a*]phenanthrene

Cyclopenta[*a*]phenanthrenes are of interest because hydrocarbons of this series are widely distributed in petroleum, mineral oils, coal, lake sediments and other natural environment, where they are thought to arise from steroids by microbiological dehydrogenation.[25] The chemistry and



Scheme 4.



Scheme 5.

biological properties of cyclopenta[*a*]phenanthrenes have been extensively reviewed in the excellent monograph by Coombs and Bhatt.[26] One of the principal bottlenecks to investigation of the cyclopenta[*a*]phenanthrenes has been their unavailability except through multistep synthesis.[8,25,27] We have sought to devise a more convenient and concise synthetic approach to potentially carcinogenic 11-methylcyclopenta[*a*]phenanthrene **5b** as shown in Scheme 5. Thus the conjugate adduct **24** was prepared in excellent yield by conjugate addition–elimination of 1-naphthylacetonitrile **22** to cyclopentanone derived *S*,*S*-acetal **23** in the presence of sodium hydride under earlier described reaction conditions. The adduct **24** was directly cyclized in presence of hot H_3PO_4 to afford the corresponding 11-cyano-12-methylthio-16,17-dihydro-15[*H*]cyclopenta[*a*]phenanthrene **25** in excellent yield (83%) (Scheme 5). The compound **25** was then transformed in one step through Raney Ni dethiomethylation-reduction to the corresponding 11-methylcyclopenta[*a*]phenanthrene derivative **5b** in 88% yield. The cyclopenta[*a*]phenanthrene **5b** has been converted to the carcinogenic 17-keto derivative **6b** by oxidation with DDQ in acetic acid.[25]

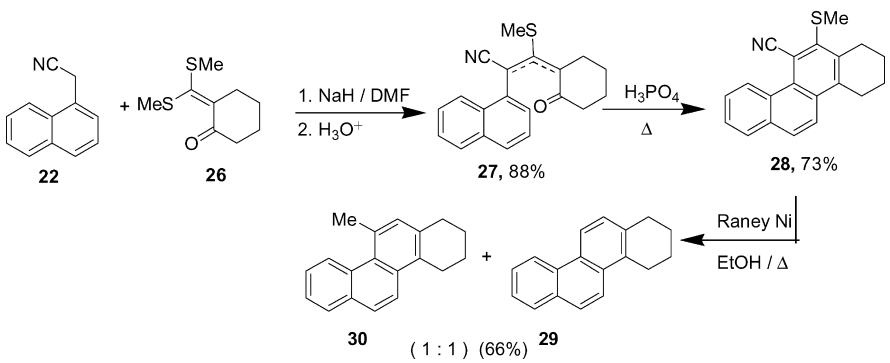
2.4. Synthesis of 7,8,9,10-tetrahydro-5-methylchrysene

5-Methylchrysene (**4**), a potent polycyclic aromatic hydrocarbon carcinogen, is a useful compound for studies in carcinogenesis because it has two dissimilar bay regions, one of which contains a methyl group. The latter feature seems to be a key factor in its high carcinogenic activity.[28] Chrysene (**3**), 5-methylchrysene (**4**) and their diol epoxides have been prepared previously in low yields through multistep synthesis.[7,29] The most versatile synthesis of 5-methylchrysene and its derivative is through photocyclization of the appropriate 2-(1-naphthyl)-1-arylpropenes.[28] However, the yields in the photocyclization steps are usually in the range of 3–30% depending on the substitution pattern[28] and only occasionally have higher yields been obtained. Recently, Kumar[4c,30] has reported synthesis of chrysene (**3**) and 5-methylchrysene (**4**) via Suzuki cross coupling of the appropriate precursors.

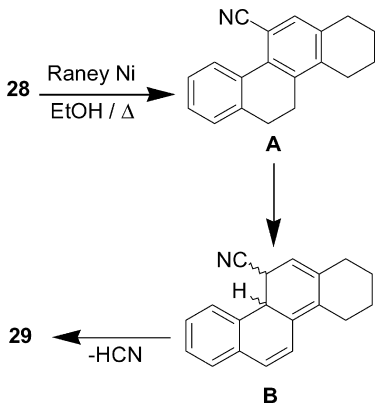
We have extended our aromatic annulation protocol for the synthesis of 5-methylchrysene parallel to the 11-methylcyclopenta[*a*]phenanthrene **5b** (Scheme 6). Thus base induced conjugate addition of 1-naphthylacetonitrile **22** to oxoketene dithioacetal **26** derived from cyclohexanone afforded the adduct **27** in high yield. Subsequent H_3PO_4 induced cyclocondensation of **27** furnished the 5-cyano-6-methylthio-7,8,9,10-tetrahydrochrysene **28** in 73% yield. Interestingly when the 5-cyanochrysene derivative **28** was subjected to Raney Ni assisted dethiomethylation-reduction, the product isolated was found to be 1:1 unseparable mixture of 5-methyltetrahydrochrysene **30** and tetrahydrochrysene **29** which were confirmed by ^1H, ^{13}C NMR and mass spectral data. The tetrahydrochrysene **29** is possibly formed from **28** through facile reduction of 11,12 double bond in the presence of Raney Ni followed by proton isomerization and elimination of HCN via intermediates **A** and **B** (Scheme 7).

2.5. Synthesis of 1,4-dimethylphenanthrene

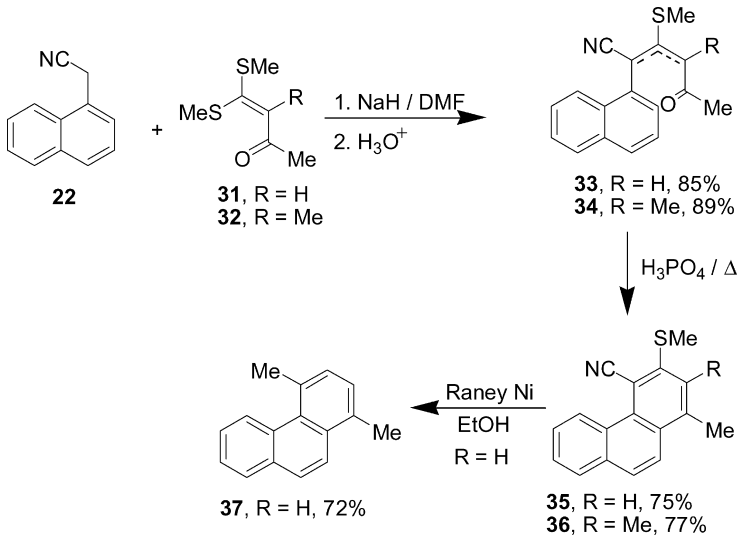
The present methodology was next extended to bay region methyl substituted phenanthrene derivatives (Scheme 8). The 1,4-dimethylphenanthrene **37** is a commonly detected PAH in the environment and its carcinogenic and tumourogenic activities are well established.[31] Thus the anion



Scheme 6.



Scheme 7.



Scheme 8.

derived from 1-naphthylacetonitrile **22** was reacted with acyclic ketene dithioacetals **31** and **32** from acetone and ethyl methyl ketone and the adducts **33** and **34** were directly treated with H_3PO_4 at 80 °C to afford the corresponding 4-cyano-1-methyl (**35**) and 4-cyano-1,2-dimethyl (**36**) phenanthrenes in 75 and 77% yields, respectively. The 4-cyano-1-methyl-3-methylthiophenanthrene **35** was further transformed into the corresponding 1,4-dimethyl derivative **37** in high yield through Raney Ni reductive dethiomethylation. The structures of newly synthesized phenanthrenes **35**–**37** were confirmed with the help of spectral and analytical data.

3. Conclusion

In summary, the present study describes a highly efficient application of our α-oxoketene dithioacetal mediated aromatic annulation strategy[11] for the synthesis of wide range of potent carcinogenic polycyclic aromatic hydrocarbons in overall high yields from readily accessible precursors. This simple conjugate-addition cyclization protocol for polycyclic aromatic hydrocarbons enables relatively fewer steps in comparison to earlier described methods and is readily adaptable for synthesis of these compounds on preparative scale. Also the method holds promise as a potentially general synthetic approach for substituted *peri* condensed PAH ring systems. The nitrile functionality in these compounds serves as a 'latent' methyl group or can be removed through hydrolytic decarboxylation. Our efforts in this direction are in progress.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra are recorded in $CDCl_3$ with TMS as internal standard and chemical shifts are reported in δ (ppm) relative to tetramethylsilane and coupling constants (J) are given in Hertz. The reactions are carried out under argon or nitrogen atmosphere wherever mentioned and in oven dried (120 °C) glassware using syringe septum technique. Low temperature reactions are carried in a bath made of appropriate solvent and liquid nitrogen. All reactions were monitored by TLC on glass plate coated with silica gel (Acme) containing 13% calcium sulfate as binder and visualization was effected with short wavelength UV light (254 nm) or acidic $KMnO_4$ solution. Column chromatography is carried out using Acme's silica gel (60–120 or 100–200 mesh).

NaH is purchased from Lancaster, DMF is distilled over CaH_2 and stored over molecular sieves whereas indanone[32] and tetralone[33] and Raney Ni (W2)[34] were prepared according to the reported procedure. Various α-oxoketene dithioacetals were prepared according to our earlier reported procedure.[35]

4.2. General procedure for the preparation of 1,4-addition–elimination adducts 12a–e, 19c–d, 24, 27, 33 and 34

To a stirred suspension of NaH (0.60 g, 40%, 10 mmol) in

DMF (10 mL) at 0 °C, a solution of arylacetonitrile (5 mmol) in DMF (5 mL) was added dropwise during 15 min and the reaction mixture was further stirred at 0 °C for 45 min. Appropriate α-oxoketene dithioacetal (5 mmol) in DMF (10 mL) was slowly added and the reaction mixture was allowed to warm to room temperature with stirring during 8–10 h. It was then poured into saturated NH_4Cl solution (200 mL) and extracted with chloroform (3×50 mL). The combined organic layer was washed with water (3×50 mL), dried (Na_2SO_4) and evaporated to give the crude 1,4-addition–elimination adducts which were used as such for further cyclization. A few of the adducts were purified by column chromatography and the spectral data of one of the adducts are given below.

4.2.1. 2-(4-Methoxyphenyl)-3-(methylthio)-3-(1-oxo-1,2,3,4-tetrahydronaphth-2-yl)propenenitrile (12a). Yellow crystalline solid (chloroform–hexane); R_f 0.1 (8:2 hexane–EtOAc); Yield 90%; mp 126–127 °C; IR (KBr): 2933, 2370, 2205, 1674, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.04–2.08 (m, 1H, CH_2), 2.58 (s, 3H, SCH_3), 2.56–2.60 (m, 1H, CH_2), 2.91–2.96 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.94 (dd, *J*=13.3, 4.4 Hz, 1H, C*H*), 6.87 (d, *J*=8.5 Hz, 2H, Ar*H*), 7.23 (d, *J*=7.5 Hz, 1H, Ar*H*), 7.33 (d, *J*=8.5 Hz, 2H, Ar*H*), 7.34 (dd, *J*=8.0, 6.6 Hz, 1H, Ar*H*), 7.50 (dd, *J*=8.0, 6.6 Hz, 1H, Ar*H*), 8.07 (d, *J*=7.5 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2 (S*C*H$_3$), 28.3 (*C*H$_2$), 28.8 (*C*H$_2$), 54.7 (*C*H), 55.3 (O*C*H$_3$), 114.4 (*C*H), 118.1 (C), 118.6 (C), 126.2 (C), 127.0 (*C*H), 127.7 (*C*H), 128.7 (*C*H), 129.9 (*C*H), 131.8 (C), 134.0 (*C*H), 143.6 (C), 156.4 (C), 160.2 (C), 195.8 (*C*O); MS (*m*/*z*, %): 347 (M^+-2, 50); Anal. calcd for $C_{21}H_{19}NO_2S$ (349.45): C, 72.17; H, 5.48; N, 4.00%. Found: C, 72.29; H, 5.40; N, 3.96%.

4.3. General procedure for the cyclization of 1,4-adducts with orthophosphoric acid

The crude adducts (~5 mmol) obtained from earlier reaction was dissolved in H_3PO_4 (20 mL, 85%) and the reaction mixture was heated with stirring at 80–100 °C for 3–6 h (monitored by TLC). It was then cooled, poured into ice-cold water (150 mL), extracted with chloroform (3×50 mL). The combined organic phases were washed with water (3×50 mL) and dried over Na_2SO_4. The solvent was distilled out to give crude product, which was purified by column chromatography over silica gel using hexane–ethyl acetate (97:3) as eluent.

4.3.1. 5-Cyano-7,8-dihydro-3-methoxy-6-methylthiobenzo[*c*]phenanthrene (13b). White crystalline solid (chloroform–hexane); R_f 0.5 (8:2 hexane–EtOAc); Yield 82%; mp 115–116 °C; IR (KBr): 2930, 2212, 1613, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 3H, SCH_3), 2.81 (t, *J*=6.8 Hz, 2H, CH_2), 3.18 (brs, 2H, CH_2), 3.99 (s, 3H, OCH_3), 7.20 (dd, *J*=2.4, 9.2 Hz, 1H, Ar*H*), 7.33–7.40 (m, 3H, Ar*H*), 7.53 (d, *J*=2.4 Hz, 1H, Ar*H*), 7.69–7.72 (m, 1H, Ar*H*), 8.33 (d, *J*=9.2 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5 (S*C*H$_3$), 27.5 (*C*H$_2$), 29.1 (*C*H$_2$), 55.5 (O*C*H$_3$), 103.5 (*C*H), 113.4 (C), 117.5 (C), 120.4 (*C*H), 124.8 (C), 126.1 (*C*H), 127.7 (*C*H), 128.4 (*C*H), 128.5 (*C*H), 129.6 (*C*H), 132.9 (C), 135.3 (C), 137.4 (C), 138.0 (C), 140.0 (C), 140.2 (C), 159.1 (C); MS (*m*/*z*, %): 331 (M^+, 100); Anal. calcd for $C_{21}H_{17}NOS$ (331.43): C, 76.10; H, 5.16; N, 4.22%. Found: C, 76.23; H, 5.18; N, 4.16%.

4.3.2. 5-Cyano-7,8-dihydro-2,3-dimethoxy-6-methylthiobenzo[*c*]phenanthrene (13c). White crystalline solid (chloroform–hexane); R_f 0.4 (8:2 hexane–EtOAc); Yield 90%; mp 192–193 °C; IR (KBr): 2941, 2212, 1506, 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H, SCH_3), 2.82 (t, *J*=6.6 Hz, 2H, CH_2), 3.19 (brs, 2H, CH_2), 3.95 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 7.34–7.37 (m, 2H, Ar*H*), 7.40–7.43 (m, 1H, Ar*H*), 7.52 (d, *J*=2 Hz, 1H, Ar*H*), 7.82–7.87 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4 (S*C*H$_3$), 27.7 (*C*H$_2$), 29.2 (*C*H$_2$), 55.8 (O*C*H$_3$), 56.1 (O*C*H$_3$), 104.3 (*C*H), 105.5 (*C*H), 113.4 (C), 117.6 (C), 125.4 (C), 126.0 (*C*H), 127.9 (*C*H), 128.4 (*C*H), 128.5 (*C*H), 130.1 (C), 133.3 (C), 136.5 (C), 136.8 (C), 138.3 (C), 140.4 (C), 150.6 (C), 151.0 (C); MS (*m*/*z*, %): 361 (M^+, 100); Anal. calcd for $C_{22}H_{19}NO_2S$ (361.47): C, 73.10; H, 5.29; N, 3.87%. Found: C, 73.17; H, 5.32; N, 3.82%.

4.3.3. 5-Cyano-7,8-dihydro-6-methylthio-2,3,10-trimethoxybenzo[*c*]phenanthrene (13e). White crystalline solid (chloroform–hexane); R_f 0.5 (8:2 hexane–EtOAc); Yield 92%; mp 236–237 °C; IR (KBr): 2923, 2212, 1604, 1467, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3H, SCH_3), 2.80 (t, *J*=6.7 Hz, 2H, CH_2), 3.18 (brs, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 6.90 (dd, *J*=2.6, 8.8 Hz, 1H, Ar*H*), 6.95 (d, *J*=2.6 Hz, 1H, Ar*H*), 7.51 (s, 1H, Ar*H*), 7.78 (d, *J*=8.5 Hz, 1H, Ar*H*), 7.79 (s, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6 (S*C*H$_3$), 27.6 (*C*H$_2$), 29.7 (*C*H$_2$), 55.3 (O*C*H$_3$), 55.9 (O*C*H$_3$), 56.1 (O*C*H$_3$), 104.3 (*C*H), 105.7 (*C*H), 111.4 (*C*H), 112.5 (C), 113.3 (*C*H), 117.8 (C), 125.2 (C), 126.1 (C), 129.9 (*C*H), 130.2 (C), 136.6 (C), 136.7 (C), 137.3 (C), 142.3 (C), 150.5 (C), 151.0 (C), 159.6 (C); MS (*m*/*z*, %): 391 (M^+, 100); Anal. calcd for $C_{23}H_{21}NO_3S$ (391.50): C, 70.56; H, 5.40; N, 3.57%. Found: C, 70.59; H, 5.45; N, 3.63%.

4.3.4. 5-Cyano-2,3-dimethoxy-6-methylthio-7*H*-benzo[*c*]fluorene (20c). Pale yellow crystals (chloroform–hexane); R_f 0.51 (8:2 hexane–EtOAc); Yield 78%; mp 246–247 °C; IR (KBr): 2968, 2361, 2213, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H, SCH_3), 4.06 (s, 2H, CH_2), 4.07 (s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 7.26 (s, 1H, Ar*H*) 7.43–7.54 (m, 2H, Ar*H*), 7.68 (d, *J*=7.5 Hz, 1H, Ar*H*), 7.91 (s, 1H, Ar*H*), 8.21 (d, *J*=8.0 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2 (S*C*H$_3$), 37.8 (*C*H$_2$), 56.03 (O*C*H$_3$), 56.04 (O*C*H$_3$), 103.0 (*C*H), 104.8 (*C*H), 117.7 (C), 123.2 (*C*H), 124.2 (C), 125.2 (*C*H), 127.2 (*C*H), 127.5 (*C*H), 127.6 (C), 130.8 (C), 134.9 (C), 139.4 (C), 141.2 (C), 142.8 (C), 144.8 (C), 150.7 (C), 150.8 (C); MS (*m*/*z*, %): 347 (M^+, 100); Anal. calcd for $C_{21}H_{17}NO_2S$ (347.43): C, 72.59; H, 4.93; N, 4.03%. Found: C, 72.63; H, 4.87; N, 4.10%.

4.3.5. 5-Cyano-1,4-dimethoxy-6-methylthio-7*H*-benzo[*c*]fluorene (20d). Pale yellow solid (chloroform–hexane); R_f 0.6 (8:2 hexane–EtOAc); Yield 79%; mp 194–195 °C (hexane); IR (KBr): 2923, 2205, 1496, 1420, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.66 (s, 3H, SCH_3), 3.96 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 4.19 (s, 2H, CH_2), 6.96 (2H, s, Ar*H*), 7.36–7.43 (m, 2H, Ar*H*), 7.62 (d, *J*=6.8 Hz, 1H, Ar*H*), 8.38 (d, *J*=7.8 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 18.9 (SCH_3), 39.0 (CH_2), 55.5 (OCH_3), 56.4 (OCH_3), 107.3 (*C*H), 107.5 (*C*H), 109.4 (C), 118.4 (C), 122.2 (C), 124.2 (*C*H), 126.5 (*C*H), 127.4 (*C*H), 127.6 (C), 128.3 (*C*H), 140.5 (C), 140.7 (C), 142.3 (C), 144.8 (C), 146.1 (C), 148.9 (C), 150.3 (C); MS (*m/z*, %): 347 (M^+, 100); Anal. calcd for $C_{21}H_{17}NO_2S$ (347.43): C, 72.59; H, 4.93; N, 4.03%. Found: C, 72.64; H, 4.99; N, 4.11%.

4.3.6. 11-Cyano-12-methylthio-16,17-dihydro-15*H*-cyclopenta[*a*]phenanthrene (25). White crystalline solid (chloroform–hexane); R_f 0.45 (8:2 hexane–EtOAc); Yield 83%; mp 153–154 °C; IR (KBr): 2924, 2206, 1570, 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.90 (m, 2H, CH_2), 2.63 (s, 3H, SCH_3), 3.30 (t, *J*=7.5 Hz, 2H, CH_2), 3.40 (t, *J*=7.5 Hz, 2H, CH_2), 7.64–7.74 (m, 3H, Ar*H*), 7.79 (d, *J*=8.7 Hz, 1H, Ar*H*), 7.89 (dd, *J*=1.7, 7.7 Hz, 1H, Ar*H*), 9.85 (d, *J*=8 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0 (SCH_3), 23.7 (CH_2), 33.1 (CH_2), 34.1 (CH_2), 110.5 (C), 120.4 (C), 122.8 (*C*H), 125.2 (*C*H), 127.1 (*C*H), 127.7 (*C*H), 128.7 (C), 128.8 (*C*H), 129.0 (C), 129.2 (*C*H), 130.7 (C), 132.8 (C), 140.0 (C), 145.6 (C), 146.7 (C); MS (*m/z*, %): 289 (M^+, 100); Anal. calcd for $C_{19}H_{15}NS$ (289.40): C, 78.85; H, 5.22; N, 4.84%. Found: C, 78.89; H, 5.30; N, 4.89%.

4.3.7. 5-Cyano-6-methylthio-7,8,9,10-tetrahydrochrysene (28). White crystalline solid (chloroform–hexane); R_f 0.87 (8:2 hexane–EtOAc); Yield 73%; mp 165–166 °C; IR (KBr): 2931, 2205, 1505, 1424 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.88–1.99 (m, 4H, (CH_2)$_2$), 2.60 (s, 3H, SCH_3), 3.19 (t, *J*=6.6 Hz, 2H, CH_2), 3.24 (t, *J*=6.6 Hz, 2H, CH_2), 7.64–7.74 (m, 2H, Ar*H*), 7.82 (d, *J*=9.2 Hz, 1H, Ar*H*), 7.88–7.95 (m, 2H, Ar*H*), 9.80 (d, *J*=8.5 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 19.6 (SCH_3), 22.5 (CH_2), 22.5 (CH_2), 27.9 (CH_2), 29.6 (CH_2), 111.6 (C), 120.5 (C), 120.9 (C), 121.0 (*C*H), 125.5 (*C*H), 127.0 (*C*H), 127.6 (*C*H), 128.5 (C), 128.6 (*C*H), 129.2 (*C*H), 131.5 (C), 132.4 (C), 139.0 (C), 139.2 (C), 143.7 (C); MS (*m/z*, %): 303 (M^+, 100); Anal. calcd for $C_{20}H_{17}NS$ (303.42): C, 79.17; H, 5.64; N, 4.61%. Found: C, 79.22; H, 5.61; N, 4.55%.

4.3.8. 4-Cyano-1-methyl-3-methylthiophenanthrene (35). White crystalline solid (chloroform–hexane); R_f 0.6 (8:2 hexane–EtOAc); Yield 75%; mp 172–173 °C; IR (KBr): 2197, 1575, 1497, 1424 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H, SCH_3), 2.70 (s, 3H, CH_3), 7.26 (s, 1H, Ar*H*), 7.63–7.70 (m, 3H, Ar*H*), 7.75 (d, *J*=8.8 Hz, 1H, Ar*H*), 7.84–7.86 (m, 1H, Ar*H*), 9.76 (d, *J*=8 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.9 (SCH_3), 21.1 (CH_3), 102.7 (C), 119.3 (C), 121.9 (*C*H), 124.1 (*C*H), 125.2 (*C*H), 126.8 (*C*H), 127.8 (*C*H), 128.0 (*C*H), 128.2 (C), 128.6 (*C*H), 128.8 (C), 130.8 (C), 133.1 (C), 140.6 (C), 146.2 (C); MS (*m/z*, %): 263 (M^+, 100); Anal. calcd for $C_{17}H_{13}NS$ (263.27): C, 77.55; H, 4.94; N, 5.32%. Found: C, 77.62; H, 4.86; N, 5.38%.

4.3.9. 4-Cyano-1,2-dimethyl-3-methylthiophenanthrene (36). White crystalline solid (chloroform–hexane); R_f 0.71 (8:2 hexane–EtOAc); Yield 77%; mp 116–117 °C; IR (KBr): 2920, 2205, 1508, 1446 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.55 (s, 3H, SCH_3), 2.72 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 7.64–7.73 (m, 2H, Ar*H*), 7.79 (d, *J*=9.2 Hz, 1H, Ar*H*), 7.87 (dd, *J*=1.2, 7.6 Hz, 1H, Ar*H*), 7.93 (d, *J*=9.2 Hz, 1H, Ar*H*), 9.77 (d, *J*=8.5 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3 (SCH_3), 19.1 (CH_3), 19.8 (CH_3), 111.8 (C), 120.6 (C), 122.0 (*C*H), 125.6 (*C*H), 126.9 (*C*H), 127.8 (*C*H), 128.3 (*C*H), 128.4 (C), 129.2 (*C*H), 129.7 (C), 131.6 (C), 132.4 (C), 138.3 (C), 139.0 (C), 142.8 (C); MS (*m/z*, %): 277 (M^+, 100); Anal. calcd for $C_{18}H_{15}NS$ (277.39): C, 77.94; H, 5.45; N, 5.05%. Found: C, 77.99; H, 5.40; N, 5.10%.

4.4. General procedure for the dehydrogenation of benzo[*c*]phenanthrenes 13b and 15c with DDQ

To a stirred solution of the compound (5 mmol) in dry dioxane, DDQ (1.6 g, 7 mmol) was added and the reaction mixture was refluxed for 6–8 h. After the completion of the reaction (monitored by TLC), solvent was evaporated and it was poured into water (100 mL) and extracted with chloroform (3×50 mL). The combined organic layer was washed with water (3×50 mL), dried (Na_2SO_4) and evaporated to give the crude product which was purified by silica gel column chromatography using hexane–ethyl acetate (98:2) as eluent.

4.4.1. 5-Cyano-3-methoxy-6-methylthiobenzo[*c*]phenanthrene (14b). Yellow crystalline solid (chloroform–hexane); R_f 0.51 (8:2 hexane–EtOAc); Yield 78%; mp 95–96 °C; IR (KBr): 2920, 2215, 1615, 1401 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.61 (s, 3H, SCH_3), 4.05 (s, 3H, OCH_3), 7.36 (dd, *J*=2.6, 9.5 Hz, 1H, Ar*H*), 7.65–7.72 (m, 3H, ArH), 7.74 (d, *J*=2.6 Hz, 1H, Ar*H*), 7.93 (d, *J*=9 Hz, 1H, ArH), 8.03 (d, *J*=9.0 Hz, 1H, Ar*H*), 8.65 (d, *J*=8.8 Hz, 1H, Ar*H*), 8.86 (d, *J*=9 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4 (SCH_3), 55.6 (OCH_3), 105.0 (*C*H), 115.2 (C), 117.2 (C), 119.2 (*C*H), 124.2 (*C*H), 124.6 (C), 126.5 (*C*H), 127.6 (*C*H), 127.7 (*C*H), 128.2 (*C*H), 128.9 (*C*H), 128.9 (C), 129.2 (C), 130.2 (*C*H), 131.3 (C), 132.9 (C), 134.4 (C), 141.4 (C), 159.1 (C); MS (*m/z*, %): 329 (M^+, 80); Anal. calcd for $C_{21}H_{15}NOS$ (329.42). C, 76.56; H, 4.58; N, 4.22%. Found: C, 76.63; H, 4.51; N, 4.31%.

4.4.2. 2,3-Dimethoxybenzo[*c*]phenanthren-5-carboxaldehyde (16c). Light yellow crystalline solid (chloroform–hexane); R_f 0.43 (8:2 hexane–EtOAc); Yield 72%; mp 188–189 °C; IR (KBr): 2921, 2358, 1706, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.08 (s, 3H, OCH_3), 4.14 (s, 3H, OCH_3), 7.65–7.70 (m, 2H, Ar*H*), 7.85 (t, *J*=8.7 Hz, 2H, Ar*H*), 8.02 (t, *J*=5.5 Hz, 1H, Ar*H*), 8.17 (s, 1H, Ar*H*), 8.47 (s, 1H, Ar*H*), 9.0 (s, 1H, Ar*H*), 9.07 (t, *J*=5.5 Hz, 1H, Ar*H*), 10.36 (s, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8 (OCH_3), 56.0 (OCH_3), 105.4 (*C*H), 108.6 (*C*H), 125.4 (C), 126.3 (*C*H), 126.9 (*C*H), 127.2 (*C*H), 127.3 (*C*H), 127.8 (*C*H), 128.4 (C), 128.7 (C), 128.8 (*C*H), 129.0 (C), 129.5 (C), 131.0 (C), 135.0 (C), 138.8 (*C*H), 149.2 (C), 150.3 (C), 193.8 (*C*H); MS (*m/z*, %): 316 (M^+, 30.4); Anal. calcd for $C_{21}H_{16}O_3$ (316.36): C, 79.72; H, 5.09%. Found: C, 79.64; H, 5.14%.

4.5. General procedure for reductive-dethiomethylation of PAHs with Raney Ni

To a solution of the appropriate PAH (2 mmol) in absolute ethanol (25 mL), Raney Ni (W2, ~0.8 g) was added and the suspension was refluxed with stirring for 6–7 h (monitored

by TLC). The reaction mixture was then cooled, filtered through a sintered funnel and the residue was washed with ethanol. The combined filtrate was evaporated under reduced pressure and the residue was dissolved in chloroform (50 mL), washed with water (2×50 mL), dried (Na_2SO_4) and concentrated to give the crude product which was purified by column chromatography using hexane–ethyl acetate (8:2) as eluent.

4.5.1. 3-Methoxy-5-methylbenzo[*c*]phenanthrene (15b). White crystalline solid (chloroform–hexane); R_f 0.8 (8:2 hexane–EtOAc); Yield 77%; mp 91–92 °C; IR (KBr): 2925, 1608, 1502, 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.67 (s, 3H, C*H*$_3$), 3.93 (s, 3H, OC*H*$_3$), 7.25 (dd, *J*=3.2, 9.2 Hz, 1H, Ar*H*), 7.39 (d, *J*=2.4 Hz, 1H, Ar*H*), 7.47–7.55 (m, 2H, Ar*H*), 7.57 (s, 1H, Ar*H*), 7.64 (d, *J*=8.0 Hz, 1H, Ar*H*), 7.72 (d, *J*=8.0 Hz, 1H, Ar*H*), 7.89 (dd, *J*=1.2, 7.6 Hz, 1H, Ar*H*), 8.91 (d, *J*=8 Hz, 1H, Ar*H*), 8.96 (d, *J*=9.2 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9 (*C*H$_3$), 55.3 (O*C*H$_3$), 104.8 (*C*H), 115.8 (*C*H), 125.0 (C), 125.3 (*C*H), 125.8 (*C*H), 126.0 (C), 126.4 (*C*H), 127.6 (*C*H), 127.7 (*C*H), 127.9 (*C*H), 128.4 (*C*H), 129.4 (C), 129.9 (C), 130.1 (*C*H), 132.1 (C), 133.2 (C), 134.6 (C), 157.4 (C); MS (*m*/*z*, %): 272 (M^+, 100); Anal. calcd for $C_{20}H_{16}O$ (272.35): C, 88.20; H, 5.92%. Found: C, 88.15; H, 5.99%.

4.5.2. 2,3-Dimethoxy-5-methyl-7,8-dihydrobenzo[*c*]phenanthrene (15c). White crystalline solid (chloroform–hexane); R_f 0.53 (8:2 hexane–EtOAc); Yield 78%; mp 147–148 °C; IR (KBr): 2924, 1623, 1515, 1488 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 3H, C*H*$_3$), 2.80 (s, 4H, –(C*H*$_2$)$_2$), 3.96 (s, 3H, OC*H*$_3$), 4.03 (s, 3H, OC*H*$_3$), 7.12 (s, 1H, Ar*H*), 7.23 (d, *J*=8.8 Hz, 1H, Ar*H*), 7.24 (s, 1H, Ar*H*), 7.31–7.36 (m, 2H, Ar*H*), 7.94 (d, *J*=7.5 Hz, 1H, Ar*H*), 7.97 (s, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7 (*C*H$_3$), 29.7 (*C*H$_2$), 30.3 (*C*H$_2$), 55.75 (O*C*H$_3$), 55.77 (O*C*H$_3$), 103.4 (*C*H), 105.5 (*C*H), 125.8 (C), 125.9 (*C*H), 126.0 (*C*H), 126.3 (*C*H), 127.5 (*C*H), 127.8 (*C*H), 128.4 (C), 128.8 (C), 132.1 (C), 134.7 (C), 135.3 (C), 139.7 (C), 148.3 (C), 149.1 (C); MS (*m*/*z*, %): 304 (M^+, 100); Anal. calcd for $C_{21}H_{20}O_2$ (304.39): C, 82.86; H, 6.62%. Found: C, 82.94; H, 6.55%.

4.5.3. 2,3-Dimethoxy-5-methyl-7*H*-benzo[*c*]fluorene (21c). White crystalline solid (chloroform–hexane); R_f 0.83 (8:2 hexane–EtOAc); Yield 88%; mp 204–205 °C; IR (KBr): 2925, 1624, 1518, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.70 (s, 3H, C*H*$_3$), 3.94 (s, 2H, C*H*$_2$), 4.05 (s, 3H, OC*H*$_3$), 4.14 (s, 3H, OC*H*$_3$), 7.31 (s, 1H, Ar*H*), 7.32 (t, *J*=5.3 Hz, 1H, Ar*H*), 7.42 (s, 1H, Ar*H*), 7.46 (dd, *J*=6.8, 7.3 Hz, 1H, Ar*H*), 7.60 (d, *J*=7.6 Hz, 1H, Ar*H*), 8.02 (s, 1H, Ar*H*), 8.19 (d, *J*=7.8 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2 (*C*H$_3$), 37.4 (*C*H$_2$), 55.6 (O*C*H$_3$), 55.8 (O*C*H$_3$), 103.5 (*C*H), 104.1 (*C*H), 121.7 (*C*H), 122.7 (*C*H), 124.8 (*C*H), 125.14 (*C*H), 125.16 (C), 126.6 (*C*H), 127.9 (C), 132.2 (C), 133.4 (C), 140.5 (C), 142.9 (C), 144.0 (C), 148.1 (C), 149.4 (C). MS (*m*/*z*, %): 290 (M^+, 100). Anal. calcd for $C_{20}H_{18}O_2$ (290.36): C, 82.73; H, 6.24%. Found: C, 82.67; H, 6.18%.

4.5.4. 11-Methyl-16,17-dihydro-15*H*-cyclopenta[*a*]phenanthrene (5b). Colorless crystalline solid (chloroform–hexane); R_f 0.9 (8:2 hexane–EtOAc); Yield 88%; mp 80–81 °C; IR (KBr): 2963, 1654, 1513, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.35 (quintet, *J*=7.3 Hz, 2H, C*H*$_2$), 3.22 (t, *J*=7.5 Hz, 2H, C*H*$_2$), 3.23 (s, 3H, C*H*$_3$), 3.39 (t, *J*=7.5 Hz, 2H, C*H*$_2$), 7.50 (s, 1H, Ar*H*), 7.66–7.80 (m, 2H, Ar*H*), 7.85 (t, *J*=5.8 Hz, 2H, Ar*H*), 8.02 (dd, *J*=1.4, 7.5 Hz, 1H, Ar*H*), 9.01 (d, *J*=8.3 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5 (*C*H$_2$), 27.5 (*C*H$_3$), 31.6 (*C*H$_2$), 33.4 (*C*H$_2$), 124.2 (*C*H), 125.1 (*C*H), 125.3 (*C*H), 127.0 (*C*H), 127.2 (*C*H), 127.7 (*C*H), 128.3 (C), 128.6 (*C*H), 129.9 (C), 132.1 (C), 132.9 (C), 133.7 (C), 138.9 (C), 141.2 (C); MS (*m*/*z*, %): 232 (M^+, 100); Anal. calcd for $C_{18}H_{16}$ (232.33): C, 93.05; H, 6.94%. Found: C, 93.01; H, 6.87%.

4.5.5. 1,2,3,4-Tetrahydro-5-methylchrysene: 1,2,3,4-tetrahydrochrysene (30/29). White solid (chloroform–hexane); R_f 0.93 (8:2 hexane–EtOAc); mp 107–113 °C; Yield 66%; IR (KBr): 2964, 1619, 1503, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.85–1.92 (m, 4H, (C*H*$_2$)$_2$), [1.96–2.01 (m, 4H, (C*H*$_2$)$_2$)], 2.93 (t, *J*=6 Hz, 2H, C*H*$_2$), [2.97 (t, *J*=6 Hz, 2H, C*H*$_2$)], 3.08 (s, 3H, C*H*$_3$), 3.18 [quintet, *J*=6 Hz, 4H, (C*H*$_2$)$_2$], 7.24 (s, 1H, Ar*H*), 7.38 (d, *J*=8.5 Hz, 1H, Ar*H*), 7.54–7.64 (m, 4H, Ar*H*), 7.76 (t, *J*=9 Hz, 2H, *Ar*H), 7.89 (t, *J*=9 Hz, 2H, Ar*H*), 7.96 (d, *J*=4.8 Hz, 1H, Ar*H*), 7.97 (d, *J*=4.8 Hz, 1H, Ar*H*), 8.48 (d, *J*=8.5 Hz, 1H, Ar*H*), 8.67 (d, *J*=8.2 Hz, 1H, Ar*H*), 8.85 (d, *J*=8.2 Hz 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4 (*C*H$_2$), 18.7 (*C*H$_2$), 19.7 (*C*H$_2$), 27.3 (*C*H$_3$), 28.0 (*C*H$_2$), 28.8 (*C*H$_2$), 29.9 (*C*H$_2$), 32.4 (*C*H$_2$), 36.5 (*C*H$_2$), 110.2 (*C*H), 113.3 (*C*H), 114.3 (C), 118.2 (C), 119.2 (*C*H), 119.9 (*C*H), 123.8 (C), 124.6 (C), 125.4 (C), 125.8 (*C*H), 126.5 (C), 126.8 (*C*H), 126.9 (*C*H), 127.5 (C), 127.6 (*C*H), 127.9 (*C*H), 128.4 (*C*H), 128.5 (*C*H), 128.6 (C), 129.0 (C), 130.8 (C), 133.5 (*C*H), 134.8 (*C*H), 137.5 (C), 145.7 (*C*H), 148.7 (C), 152.4 (C), 153.4 (*C*H); MS (*m*/*z*, %): 248 (M^++2, 100), 246 (M^+, 11), 233 (M^++1, 73), 232 (M^+, 17).

4.5.6. 1,4-Dimethylphenanthrene (37). White crystalline solid (chloroform–hexane); R_f 0.81 (8:2 hexane–EtOAc); Yield 72%; mp 112–113 °C; IR (KBr): 2925, 1588, 1458, 1378; ^1H NMR (400 MHz, $CDCl_3$): δ 2.73 (s, 3H, C*H*$_3$), 3.11 (s, 3H, C*H*$_3$), 7.34 (d, *J*=7.3 Hz, 1H, Ar*H*), 7.38 (d, *J*=7.8 Hz, 1H, Ar*H*), 7.55–7.64 (m, 2H, Ar*H*), 7.75 (d, *J*=9 Hz, 1H, Ar*H*), 7.91 (d, *J*=7.3 Hz, 1H, Ar*H*), 7.95 (d, *J*=9 Hz, 1H, Ar*H*), 8.88 (d, *J*=9.2 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3 (*C*H$_3$), 29.6 (*C*H$_3$), 123.4 (*C*H), 125.3 (*C*H), 125.6 (*C*H), 126.8 (*C*H), 127.3 (*C*H), 127.6 (*C*H), 128.4 (*C*H), 130.2 (C), 130.6 (*C*H), 131.8 (C), 132.1 (C), 132.7 (C), 133.0 (C), 133.3 (C); MS (*m*/*z*, %): 206 (M^+, 88); Anal. calcd for $C_{16}H_{14}$ (206.29): C, 93.15; H, 6.84%. Found: C, 93.21; H, 6.75%.

4.6. Procedure for acid-induced hydrolysis-decarboxylation of 13b: synthesis of 17b

A suspension of **13b** (5 mmol) in water (5 mL), AcOH (5 mL), and concentrated H_2SO_4 (5 mL) was refluxed with stirring at 180 °C for 6 h (monitored by TLC). It was then cooled, poured into ice-cold water (25 mL), neutralized with saturated $NaHCO_3$ solution and extracted with $CHCl_3$ (3×50 mL). The combined organic layer was dried (Na_2SO_4), evaporated to give crude viscous residue that was purified by column chromatography over silica gel with hexanes–EtOAc (98:2) as eluent to give the pure product.

4.6.1. 7,8-Dihydro-3-hydroxy-6-methylthiobenzo[*c*]-phenanthrene (17b). Yellow low melting solid; R_f 0.41 (8:2 hexane–EtOAc); Yield 70%; IR (DCM): 2934, 1623, 1525, 1488 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H, C*H*$_3$), 2.74 (t, J=7.8 Hz, 2H, C*H*$_2$), 2.83 (t, J=7.8 Hz, 2H, C*H*$_2$), 4.94 (brs, 1H, O*H*), 6.95 (dd, J=9.2, 2.6 Hz, 1H, Ar*H*), 7.04 (d, J=2.7 Hz, 1H, Ar*H*), 7.21–7.29 (m, 3H, Ar*H*), 7.30 (s, 1H, Ar*H*), 7.73 (d, J=7.3 Hz, 1H, Ar*H*), 8.27 (d, J=9.2 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7 (S*C*H$_3$), 29.7 (*C*H$_2$), 30.2 (*C*H$_2$), 103.4 (*C*H), 105.5 (*C*H), 125.7 (C), 125.8 (*C*H), 125.9 (*C*H), 126.3 (*C*H), 127.5 (*C*H), 127.8 (*C*H), 128.4 (*C*H), 128.8 (C), 132.1 (C), 134.7 (C), 136.5 (C), 139.7 (C), 148.2 (C), 149.1 (C); MS (*m*/*z*, %): 292 (M^+, 60); Anal. calcd for $C_{19}H_{16}OS$ (292.39): C, 78.04; H, 5.51%. Found: C, 78.12; H, 5.43%.

Acknowledgements

S.N. and K.P. thank CSIR, New Delhi for senior research fellowship. Financial assistance under CSIR scheme is also acknowledged.

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Tetrahedron 60 (2004) 3675–3679
Tetrahedron

Bismuth compounds in organic synthesis. Bismuth nitrate catalyzed chemoselective synthesis of acylals from aromatic aldehydes

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Received 6 February 2004; revised 24 February 2004; accepted 24 February 2004

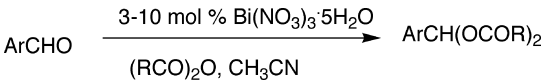
Abstract—Aromatic aldehydes are smoothly converted into the corresponding acylals in good yields in the presence of 3–10 mol% $Bi(NO_3)_3{\cdot}5H_2O$. Ketones are not affected under the reaction conditions. The relatively non-toxic nature of the catalyst, its ease of handling, easy availability and low cost make this procedure especially attractive for large-scale synthesis.

1. Introduction

Acylals (geminal diesters) are frequently used as protecting groups for aldehydes because they are stable to neutral and basic conditions.[1] In addition, the acylal functionality can be converted into other useful functional groups by reaction with appropriate nucleophiles.[2] For example, recently a novel synthesis of chiral allylic esters has been developed using palladium-catalyzed asymmetric allylic alkylation of *gem*-diesters.[3] The synthesis of homoallyl acetates by allylation of 1,1-diacetates has also been reported.[4] We have reported the use of bismuth triflate, $Bi(CF_3SO_3)_3{\cdot}4H_2O$ as a highly efficient and relatively non-toxic catalyst for the synthesis of acylals.[5] Although bismuth compounds are attractive due to their remarkably low toxicity,[6] low cost and ease of handling, one drawback of bismuth triflate is that it is not yet commercially available and must be synthesized in the laboratory. Our continued work with bismuth compounds has led to the discovery of bismuth nitrate pentahydrate, $Bi(NO_3)_3{\cdot}5H_2O$, an inexpensive, easy-to-handle, commercially available solid as a versatile catalyst for the chemoselective formation of acylals from aromatic aldehydes. The most commonly used reagent for acylal formation is acetic anhydride which results in the formation of 1,1-diacetates. Some examples of the reagents and catalysts that have been developed for this purpose include LiOTf,[7] ceric ammonium nitrate,[8] $InCl_3$,[9] H_2NSO_3H,[10] $LiBF_4$,[11] H_2SO_4,[12] PCl_3,[13] NBS,[14] I_2,[15] TMSCl-NaI,[16] anhydrous ferrous sulfate[17] and $FeCl_3$.[18] Several inorganic heterogeneous catalysts have also been developed as catalysts for synthesis of acylals.[19] Lewis acids such as $Cu(OTf)_2$ (2.5 mol%)[20] and $Sc(OTf)_3$ (2 mol%)[21] are also efficient for this conversion. Many of these reagents are highly corrosive and difficult to handle while some Lewis acid catalysts such as copper and scandium triflate are rather expensive and moisture sensitive. Some procedures require the use of a large excess (5–8 equiv.) of acetic anhydride to effect acylal formation.[7] Further, there are very few reports in the literature on formation of acylals using other anhydrides.[11] Given the synthetic utility of acylals, newer reagents that are inexpensive, non-toxic, chemoselective and effective for acylal formation with a variety of anhydrides would provide a valuable addition to the literature.

2. Results and discussion

We now report that bismuth nitrate, $Bi(NO_3)_3{\cdot}5H_2O$ is an efficient catalyst for the chemoselective conversion of aromatic aldehydes to a variety of acylals (Scheme 1 and Table 1).



Scheme 1.

The experimental procedure for the synthesis of the acylals is simple and involves stirring the aldehyde and the corresponding anhydride as a solution in acetonitrile. The product is isolated by extraction with a relatively non-toxic and industry-friendly solvent, ethyl acetate. A wide variety of aromatic aldehydes (Table 1, entries 1–6) underwent

Keywords: Bismuth nitrate; Acylals; Environment-friendly; Anhydrides.
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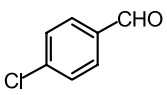
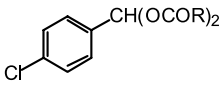
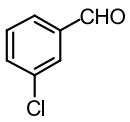
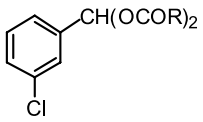
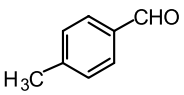
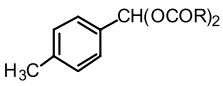
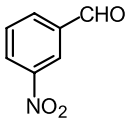
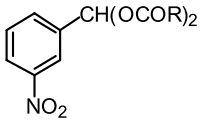
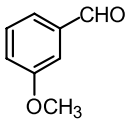
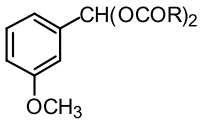
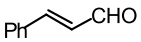
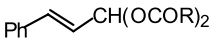
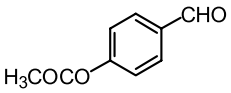
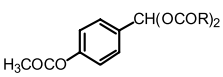
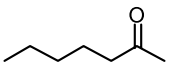
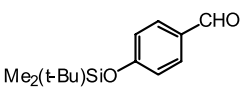
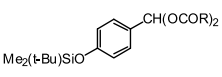
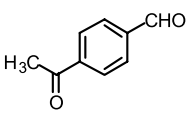
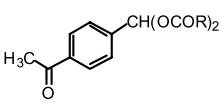
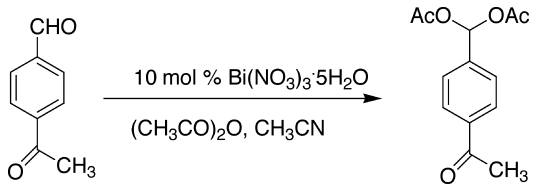
doi:10.1016/j.tet.2004.02.046

Table 1. Formation of acylals using $Bi(NO_3)_3{\cdot}5H_2O$ in CH_3CN

Entry[a]	Substrate	Anhydride $(RCO)_2O$	Time	Product	Yield[b]	^{13}C NMR data ($CDCl_3$)
1[18]	PhCHO	R=CH_3	1.5 h	$PhCH(OCOR)_2$	87	(R=CH_3) δ 20.5, 89.4, 126.4, 128,4, 129.5, 135.3, 168.5
		R=CH_3	6 h		80[c]	
		R=*n*-Pr	16 h		91	(R=*n*-Pr) δ 13.4, 18.1 35.8, 89.3, 126.5, 128.4, 129.5, 135.7, 171.3
		R=*i*Pr	4 h		68	(R=*i*-Pr) δ 18.4, 18.6, 39.7, 89.3, 126.3, 128.4, 129.3, 135.7, 174.6
2[26]		R=CH_3	3 h		76[c]	(R=CH_3) δ 20.5, 89.0, 128.1, 128.7, 133.9, 135.6, 168.6
		R=*n*-Pr	4 h		80	(R=*n*-Pr) δ 13.3, 18.1, 35.7, 88.7, 127.9, 128.7, 134.2, 135.4, 171.2
		R=*i*Pr	15 h		82	(R=*i*-Pr) δ 18.4, 18.6, 39.7, 85.7, 127.9, 128.6, 134.3, 135.3, 174.6
3[26]		R=CH_3	4 h		86	δ 20.7, 88.7, 124.9, 126.7, 129.8, 129.8, 134.4, 137.3, 168.5
4[26]		R=CH_3	2.5 h		79	δ 20.8, 21.2, 89.7, 126.5, 129.2, 132.5, 139.7, 168.7
		R=CH_3	14 h		77[d]	
5[26]		R=CH_3	2.5 h		85[e]	δ 20.6, 88.2, 121.7, 124.4, 129.7, 132.8, 137.4, 148.1, 168.5
6[7]		R=CH_3	15 h		57	δ 20.5, 54.9, 89.2, 111.9, 115.0, 118.6, 129.5, 136.7, 159.5, 168.5
7[18]		R=CH_3	6 h		82[c]	
		R=CH_3	18 h		94[d]	
8[26]		R=CH_3	16 h		91	δ 20.7, 20.9, 88.9, 121.7, 127.9, 132.9, 151.4, 168.5, 169.1
9		R=CH_3	[f]	NR		
10[7]		R=CH_3	14 h		59[c]	δ −4.5, 18.1, 20.8, 25.5, 89.6, 120.0, 128.0, 128.2, 156.8, 168.7
11[5]		R=CH_3	19 h		91	

[a] Superscript against the entry # refers to literature reference for the product.
[b] Refers to yield of isolated product. Yields are not optimized. Unless otherwise mentioned, the purity was estimated to be >98% by ^1H and ^{13}C NMR spectroscopy.
[c] Reaction was carried out with 5.0 mol% $Bi(NO_3)_3{\cdot}5H_2O$.
[d] Reaction was carried out with 3.0 mol% $Bi(NO_3)_3{\cdot}5H_2O$.
[e] Reaction carried out under solvent-free conditions at reflux temperatures. Based on ^1H NMR analysis, the crude product contained 4% aldehyde.
[f] No reaction occurred even under reflux conditions.

smooth reaction to give the corresponding acylal in good yield. Phenolic ester groups which are fairly unstable at low and high pH were stable to the reaction conditions (entry 8). In contrast to aromatic aldehydes, the results with saturated aliphatic aldehydes were less promising. Aliphatic aldehydes reacted sluggishly even under solvent-free conditions, and even after 12 h, 50% of unreacted starting material remained. Acylal formation employing acetic anhydride was attempted with several aldehydes including heptanal, hexanal and phenylpropionaldehyde. In all cases, the product mixture consisted of the expected acylal, unreacted starting material and several unidentifiable by-products. NMR analysis of the crude product in each case indicated that the side products were not consistent with the self-aldol condensation of these aldehydes. The spectra were also not consistent with the enol acetates that would form from the elimination of the expected acylal. Although *t*-butyldimethylsilyl (TBDMS) groups are relatively acid-sensitive, under the reaction conditions a moderate yield of the acylal from the TBDMS protected phenol (entry 10) was obtained. Deprotection of the TBDMS occurred to the extent of 15%. The pure acylal was obtained by column chromatography. In contrast, THP ethers proved unstable to the reaction conditions. When the THP ether of *p*-hydroxybenzaldehyde was subjected to the reaction conditions, acylal formation occurred but significant deprotection of the THP ether was also observed. Ketones proved completely resistant to acylal synthesis with acetic anhydride: no diacetate formed even under reflux conditions. The chemoselectivity of this method was demonstrated using acetylbenzaldehyde (entry 11). Smooth conversion of the aldehyde to the corresponding diacetate was observed while the ketone functionality remained unaffected (Scheme 2).

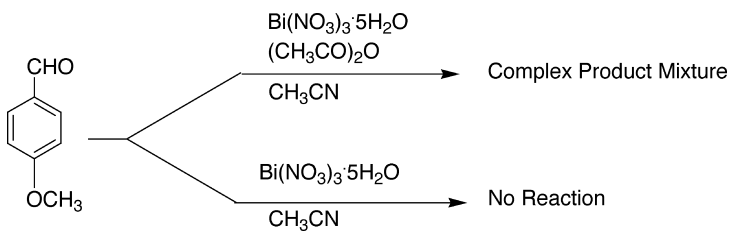


Scheme 2.

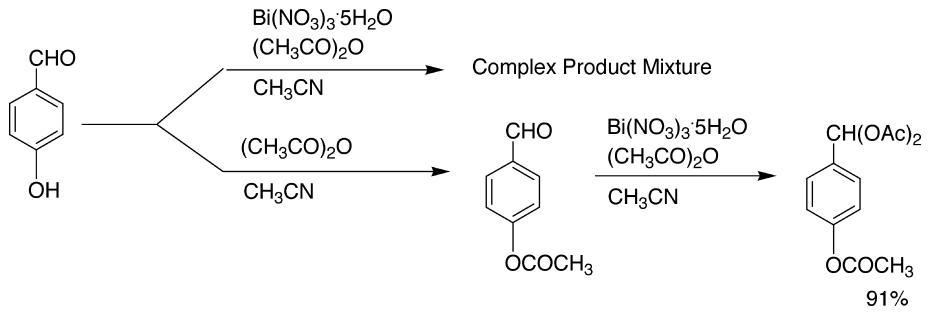
The formation of acylals from aromatic aldehydes bearing activating groups such as OCH_3 and OH proved troublesome. When *p*-anisaldehyde (*p*-methoxybenzaldehyde) was subjected to the reaction conditions with acetic anhydride, the resulting product mixture was found to be complex (Scheme 3). ^1H NMR analysis of the product mixture indicated that in addition to the expected acylal, at least three other compounds were present (^1H NMR indicated the presence of methoxy groups, δ 3–4). A control experiment in which a solution of *p*-anisaldehyde in CH_3CN was stirred with bismuth nitrate indicated that the starting aldehyde is stable to bismuth nitrate.

This observation suggested that the complex mixture results from reaction of the corresponding acylal product. It was not possible to get a pure sample of the acylal by column chromatography. In order to test whether the side-products arose as a result of activation of the acylal product by the electron-releasing *p*-methoxy group, the reaction was also attempted with *m*-methoxybenzaldehyde (at the *meta* position, the $-I$ effect of the OCH_3 group would be operative but not the $+R$ effect). In this case, it was possible to obtain the corresponding acylal in a 57% yield (unoptimized) after column chromatographic purification. When the pure acylal from *m*-methoxybenzaldehyde was subjected to the reaction conditions with acetic anhydride, nitration products were formed to the extent of 5–10%. It has also been reported in the literature that toluene can be nitrated by $Bi(NO_3)_3{\cdot}5H_2O$ impregnated on K10 montmorillonite in the presence of acetic anhydride.[22] However, the authors found that the nitration was quite solvent sensitive and no nitration occurred in acetonitrile. It is speculated that acetyl nitrate is an intermediate. We attempted the acylal formation reaction with *p*-tolualdehyde using both 3 and 10 mol% $Bi(NO_3)_3{\cdot}5H_2O$ as the catalyst. In both cases, in addition to the expected acylal, side products formed to the extent of 10–20%. NMR analysis of the crude product indicated that the use of 10 mol% $Bi(NO_3)_3{\cdot}5H_2O$ gave rise to more impurities than when 3 mol% $Bi(NO_3)_3{\cdot}5H_2O$ was used. While the side-products were not isolated, the spectral data of the crude material is consistent with formation of nitration products. The pure acylal was isolated by column chromatography. In contrast, it was not possible to obtain the acylal from *p*-hydroxybenzaldehyde in good yield. The product mixture was found to be very complex indicating that the OH group activates the ring toward substitution reactions. However, in the absence of bismuth nitrate, reaction of *p*-hydroxybenzaldehyde with acetic anhydride gave a good yield of *p*-acetoxybenzaldehyde (entry 8). When *p*-acetoxybenzaldehyde was subjected to the reaction conditions, smooth conversion to the acylal occurred. These results are consistent with the hypothesis that once the ring is no longer activated, ring substitution reactions do not occur and the acylal can be obtained in good yields (Scheme 4).

The reaction also worked with other acid anhydrides including butyric anhydride and isobutyric anhydride while most literature methods for acylal formation employ only acetic anhydride. It was difficult to separate the unreacted butyric and isobutyric anhydrides from the corresponding acylal product. The hydrolysis of higher



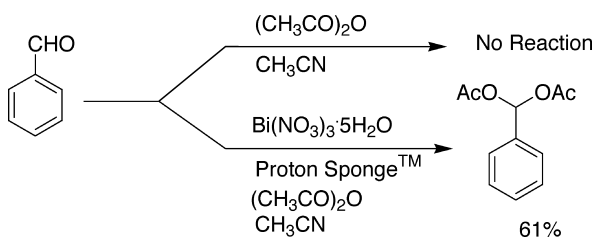
Scheme 3.



Scheme 4.

anhydrides with aqueous Na_2CO_3 is also considerably slower than the hydrolysis of acetic anhydride due to solubility problems. A practical solution to this problem was found by using methanol/aqueous Na_2CO_3 in the work-up. Pivalic anhydride and benzoic anhydride proved too unreactive at room temperature and significant reaction was not observed at higher temperatures. When bismuth nitrate is heated, it undergoes decomposition accompanied by the formation of a brown gas (NO_2). Therefore, all reactions were carried out at room temperature with the exception of entry 5.

While detailed mechanistic studies were not conducted, a few other points merit comment and are summarized in Scheme 5. No acylal formation was observed in the absence of bismuth nitrate. The possibility that the reaction is catalyzed by nitric acid released from bismuth nitrate pentahydrate in CH_3CN was considered. A suspension of bismuth nitrate in water as well as CH_3CN is acidic (pH=2). However, the reaction of benzaldehyde with acetic anhydride using 0.6 equiv. of HNO_3 did not afford the desired acylal in good yield. When the amount of HNO_3 was increased to 1.2 equiv. the starting aldehyde was recovered unchanged. The reaction of benzaldehyde with acetic anhydride catalyzed by bismuth nitrate in the presence of proton-sponge® (*N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine)[23] was also carried out. Although the reaction was slow, the desired product was formed in 61% yield after chromatographic purification. The lower yield resulted primarily from the small-scale of this experiment and the difficulty in separating the proton-sponge® from the acylal product. Although this result does suggest that the reaction is catalyzed by bismuth(III) acting as a Lewis acid, protic acid catalysis cannot be completely ruled out. In contrast, studies using bismuth bromide as a catalyst for deprotection of oximes as well as for synthesis of cyclic ethers using intramolecular etherification reactions of δ-trialkylsilyloxy aldehydes and ketones suggest that its main role is to generate HBr, which is the active catalyst.[24]



Scheme 5.

From our studies it is also evident that it is difficult to control the amount of nitric acid in the solution and hence bismuth nitrate is a more convenient reagent than nitric acid to catalyze this reaction. In the presence of water, bismuth nitrate is converted to bismuth subnitrate, $BiONO_3$. Bismuth subnitrate is commercially available and hence the reaction was also attempted with bismuth subnitrate. The reaction of benzaldehyde with acetic anhydride catalyzed by bismuth subnitrate was only 50% complete in 2 h.

3. Conclusions

In summary, a new catalytic method employing bismuth nitrate catalysis has been developed for the conversion of aromatic aldehydes to acylals with a variety of anhydrides. Advantages of this method include: (1) the use of an inexpensive, air-stable, commercially available and relatively non-toxic catalyst and (2) the observed chemoselectivity.

4. Experimental

4.1. General

NMR spectra were recorded on a JEOL Eclipse NMR spectrometer at 270 MHz (^1H) and 67.5 MHz (^{13}C) in $CDCl_3$ as the solvent. Flash chromatography was performed on Merck Silica gel (230–400 Mesh).[25] Reaction progress was monitored by TLC, GC analysis or by NMR spectroscopy. Thin layer chromatography was performed on aluminum backed silica gel plates. Spots were visualized under UV light or by spraying the plate with phosphomolybdic acid followed by heating. GC analysis was carried out on a Varian CP 3800 Gas Chromatograph. Although all the products have been previously reported in the literature, the ^{13}C spectral data for many of the acylals is not available. Hence, ^{13}C NMR data for selected acylals is reported in Table 1. Reagent grade acetonitrile was used for all reactions. The TBDMS ether from *p*-hydroxybenzaldehyde (entry 10, Table 1) was prepared by treatment of *p*-hydroxybenzaldehyde with *tert*-butyldimethylsilyl chloride in the presence of DMAP and triethylamine.

4.1.1. Representative procedure for formation of acylal using acetic anhydride. A solution of *p*-tolualdehyde (1.00 g, 8.32 mmol) in reagent grade CH_3CN (5 mL) was stirred as acetic anhydride (2.36 mL, 24.96 mmol, 3 equiv.) and $Bi(NO_3)_3{\cdot}5H_2O$ (0.404 g, 0.832 mmol, 10 mol%) were

added. The resulting mixture was stirred under N_2 at room temperature for 2.5 h and then aqueous saturated Na_2CO_3 solution (20 mL) was added. The resulting mixture was stirred for 20 min and then extracted with EtOAc (3×25 mL). The combined organic layers were washed with saturated NaCl solution (20 mL) and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 1.71 g of the crude product. A portion of the product (1.66 g) was purified by flash column chromatography on 70 g of silica gel (ethyl acetate/hexane, 1:9 as the eluent) to yield 1.43 g (overall yield 79%) of the acylal which was characterized by ^1H and ^{13}C NMR spectroscopy.

4.1.2. Representative procedure for formation of acylal using higher anhydrides. A solution of *p*-chlorobenzaldehyde (1.00 g, 7.11 mmol) in reagent grade CH_3CN (5 mL) was stirred as isobutyric anhydride (3.54 mL, 21.3 mmol, 3 equiv.) and $Bi(NO_3)_3{\cdot}5H_2O$ (0.345 g, 0.71 mmol, 10 mol%) were added. The resulting mixture was stirred under N_2 at room temperature for 15 h and then CH_3OH/aqueous Na_2CO_3/H_2O (1:1:1, v/v/v) was added. The mixture was then stirred for 30 min and then extracted with EtOAc (3×25 mL). The combined organic layers were washed with saturated NaCl solution (15 mL) and dried (Na_2SO_4). The solvents were removed on a rotary evaporator and the product was then placed under high vacuum at 40 °C (oil bath) to yield 1.74 g (82%) of the desired acylal which was characterized by ^1H and ^{13}C NMR spectroscopy.

Acknowledgements

The authors wish to acknowledge funding by the National Science Foundation (RUI grant 0078881). R. M. would also like to thank The Camille and Henry Dreyfus Foundation for a Henry Dreyfus Teacher Scholar Award.

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Transformations of the natural dimeric phthalide diligustilide

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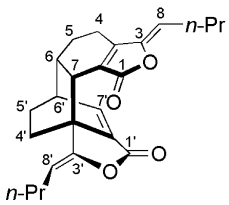
Received 4 February 2004; revised 24 February 2004; accepted 24 February 2004

Abstract—A series of intramolecular condensation products were obtained by base-catalyzed treatment of the natural bioactive dimeric phthalide diligustilide (**1**) using different reaction conditions and the yields remarkably depend on these. The reaction conditions to obtain selectively the intramolecular condensation derivatives or the hydrolysis products of diligustilide (**1**) are described.

1. Introduction

The natural bioactive dimeric phthalides diligustilide (**1**) and tokinolide B (**2**) were isolated as racemic mixtures, among other constituents, from the roots of *Ligusticum porteri* (Umbelliferae),[1,2] and together with *Myroxylon balsamum* (Leguminosae), both species comprise the 'chuchupate' complex which is used by the Tarahumara in the treatment of various ailments.[3–6] However, in spite of their pharmacological importance, little is known regarding their synthesis and chemical reactivity.



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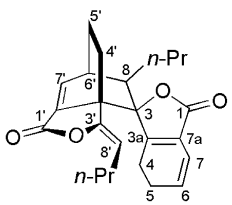

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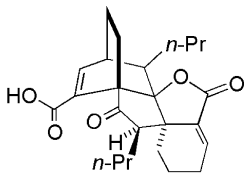

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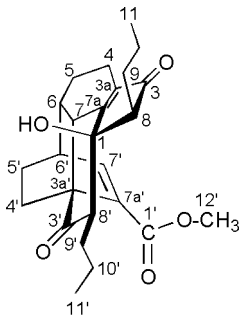
Recently, we reported the formation of a novel pentacyclic compound, cyclotokinolide B (**3**), obtained by treatment of the natural phthalide tokinolide B (**2**) under basic conditions,[2] and some years ago, the treatment of the dimeric phthalide diligustilide (**1**) with base afforded the crystalline mixture of **4**+**5** with novel intramolecular carbon–carbon and oxygen–carbon connectivities, which was analyzed by X-ray.[7] By the same time, we reported the hydrolysis of **1** in basic media, affording a mixture of demethylwallichilide (**6**) and the diketo diacid **7** in a 1.6:1 ratio, respectively.[8] In this context, we were interested in finding better conditions for obtaining the intramolecular condensation products **4** and **5** in a separated form, besides the hydrolysis products **6** and **7** in good yield. Therefore, we attempted different reaction conditions and herein we describe the results.



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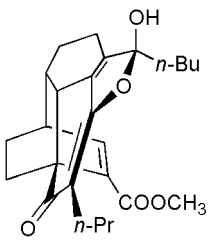

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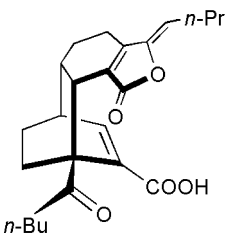

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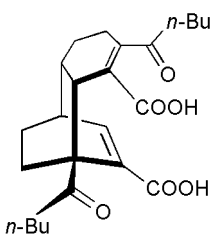

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Keywords: Diligustilide; Dimeric phthalides; Intramolecular condensations; Hydrolysis.
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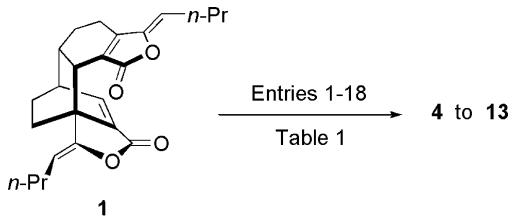
doi:10.1016/j.tet.2004.02.045

2. Results and discussion

Previously, we had already obtained the compound **4** from **1** (see Scheme 1),[7] however, we found that only 3.8 equiv. of methanol were enough and that an anhydrous medium was necessary (entry 1, Table 1). Under these conditions a white solid was obtained (94%). Recrystallization from ethyl acetate/*n*-hexane afforded colourless crystals, and the X-ray analysis confirmed the structure of the intramolecular condensation product **4** (depicted in Fig. 1).[9] Analysis of the NMR spectral data of **4** (not previously reported) allowed the unambiguous assignments of the signals (see Section 4).



Scheme 1.

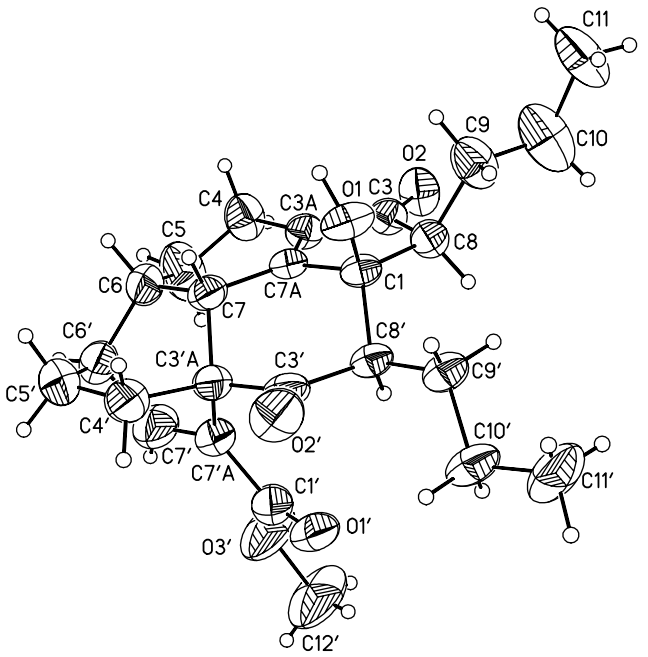
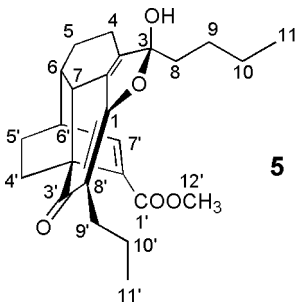


Figure 1. ORTEP-like view of compound **4**.

On the other hand, we tried to obtain compound **5** in a separated form, since it had been identified as a crystalline mixture with **4** (entry 2, Table 1). For that purpose, we attempted different experiments taking into account that the presence of water in the reaction mixture allows the formation of the intramolecular condensation product **5** (entries 1 and 2, Table 1). However, the use of a less polar solvent like tetrahydrofuran in the reaction mixture inhibits the formation of **5**, even in presence of water (entries 1 and 3, Table 1). Considering this last result, a series of experiments were performed using methanol and water as the reaction solvent mixture, and we found that increasing the amount of water the yield of the product **4** was reduced with an increase of **5**, although in all the cases its epimer **8** was obtained. Whereas compound **4** was separated from the epimeric mixture of **5** and **8** by column chromatography using methylene chloride/acetonitrile as the eluting system, the epimeric mixture was not (entries 4–7, Table 1). However, when the epimeric mixture was recrystallized from ethyl acetate/*n*-hexane, the X-ray analysis of the crystals obtained showed only the epimer with the hydroxy group at the β-position (**5**, Fig. 2).[10] At the same time, the ^{1}H NMR spectrum of a fresh prepared sample of the material recovered from the X-ray analysis showed the presence of only **5** and let us distinguish the signals of both epimers from the spectroscopic data of the mixture.



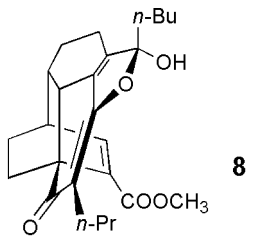


Table 1. Base-catalyzed treatment of diligustilide (**1**)

Entry	Conditions	**4**	**5**	**8**	**10**	**11**	**12**	**13**	**6**	**7**	**9**	**1** (rec.)
1	NaOH (2.3 equiv.) MeOH anh. (3.8 equiv.) THF anh. reflux, 2 h	94%	—	—	—	—	—	—	—	—	—	—
2	Na_2CO_3 (8.9 equiv.) Acetone/MeOH/H_2O (12:1:10) reflux, 3 h	65%		—	—	—	—	—	9%	10%	—	—
3	Na_2CO_3 (6 equiv.) THF/MeOH/H_2O (5:1:5) reflux, 30 min	69%	—	—	—	—	—	—	8%	7%	6%	—
4	Na_2CO_3 (12 equiv.) MeOH/H_2O (10:1) reflux, 1 h	13%	31%		—	—	—	—	—	—	31%	—
5	Na_2CO_3 (6 equiv.) MeOH/H_2O (1:1) reflux, 30 min	10%	55%		—	—	—	—	—	—	32%	—
6	Na_2CO_3 (12 equiv.) MeOH/H_2O (2:1) reflux, 3.5 h	14%	57%		—	—	—	—	—	—	—	—
7	Na_2CO_3 (12 equiv.) MeOH/H_2O (1:1) reflux, 3.5 h	3%	59%		4%	11%	11%	—	—	3%	—	—
8	Na_2CO_3 (3.7 equiv.) Acetone/H_2O (1:1) reflux, 3.5 h	—	—	—	—	—	—	—	45%	18%	—	—
9	Na_2CO_3 (1.5 equiv.) Acetone/H_2O (2.5:1) reflux, 3.5 h	—	—	—	—	—	—	—	40%	36%	—	14%
10	Na_2CO_3 (6 equiv.) Acetone/H_2O (1:1) reflux, 3.5 h	—	—	—	—	—	—	—	28%	66%	—	—
11	Na_2CO_3 (12 equiv.) Acetone/H_2O (1:1) reflux, 8 h	—	—	—	—	—	—	—	17%	68%	—	—
12	Na_2CO_3 (6 equiv.) THF/H_2O (1:1) reflux, 3.5 h	—	—	—	—	—	—	—	23%	12%	—	56%
13	NaOH (12 equiv.) Acetone/H_2O (1:1) reflux, 4 h	—	—	—	—	13%	20%	—	—	59%	—	—
14	NaOH (2.6 equiv.) Acetone/H_2O (1:1) reflux, 1 h	—	—	—	—	17%	22%	—	—	52%	—	—
15	NaOH (2.7 equiv.) Acetone/H_2O (1:1) rt, 2 h	—	—	—	—	—	—	32%	—	36%	—	—
16	NaOH (2.7 equiv.) Acetone/H_2O (1:1) rt, 10 h	—	—	—	—	—	—	19%	—	35%	—	—
17	NaOH (2.9 equiv.) THF/H_2O (1:1) rt, 2 h	—	—	—	—	—	—	21%	—	48%	—	—
18	NaOH (3.0 equiv.) THF/H_2O (1:1) reflux, 30 min	—	—	—	—	—	—	—	—	33%	—	—

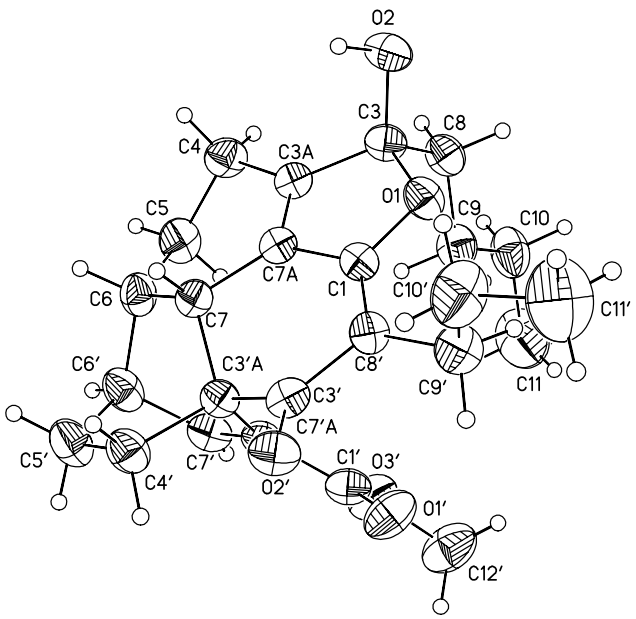
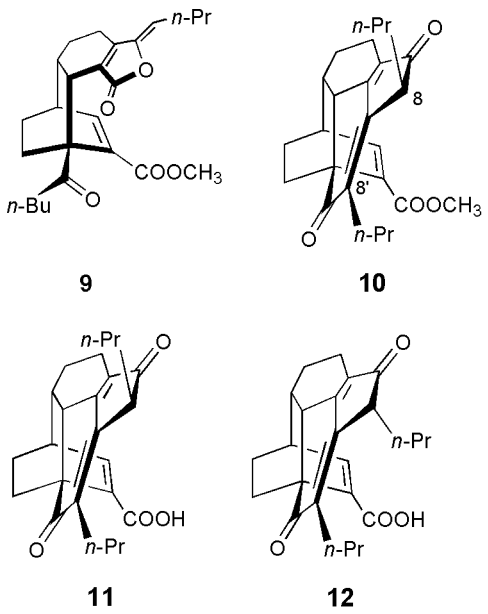


Figure 2. ORTEP-like view of compound **5**.

Furthermore, the assays gave evidence that a short reaction time (entries 4 and 5, Table 1) produces the methanolysis of the starting material (**1**), affording Wallichilide (**9**)[8] and low yields of the intramolecular condensation products, comparing with longer reaction times (entries 6 and 7, Table 1). Moreover, the spectroscopic data analysis of some minor products obtained in the experiment 7 (Table 1), allowed the isolation and characterization of additional products which corresponded to the intramolecular condensation compounds **10**, **11** and **12**.



The molecular formula of **10** ($C_{25}H_{30}O_4$, established by HRMS), indicated the loss of water with respect to the intramolecular condensation product **4** ($C_{25}H_{32}O_5$). The DEPT ^{13}C NMR data for **10** showed five methines and the main difference with the DEPT ^{13}C NMR data for **4** is the disappearance of the ^{13}C NMR signal assigned to the methine C(8′) in **4** (δ_c 54.1). Besides, the ^{13}C NMR data of

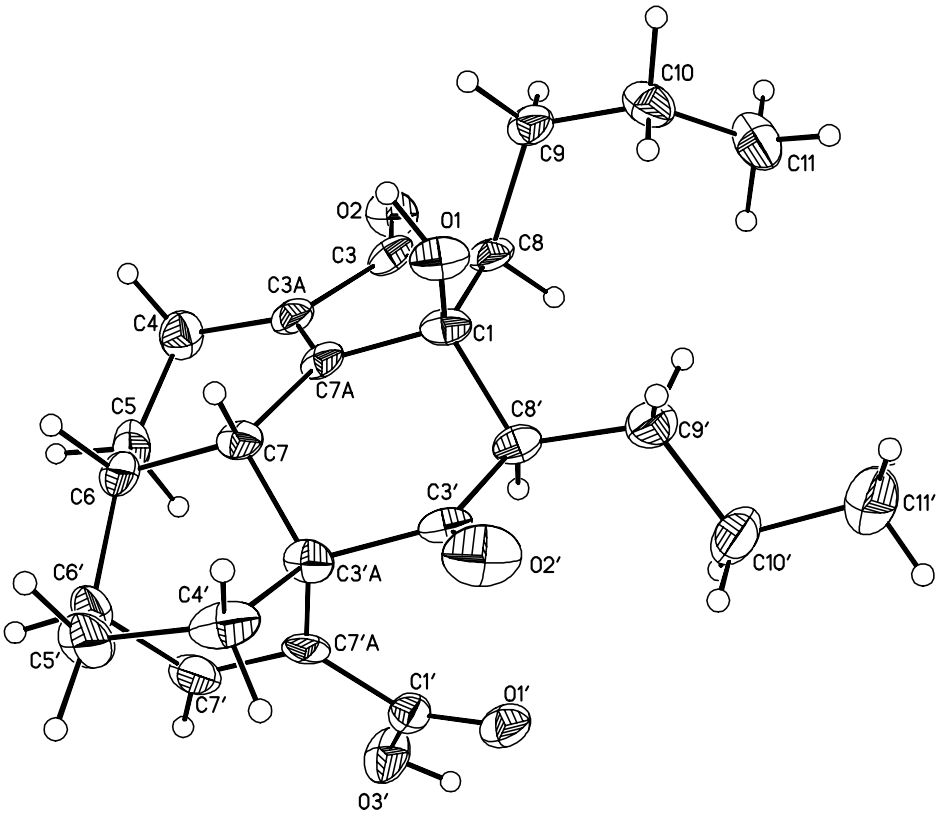
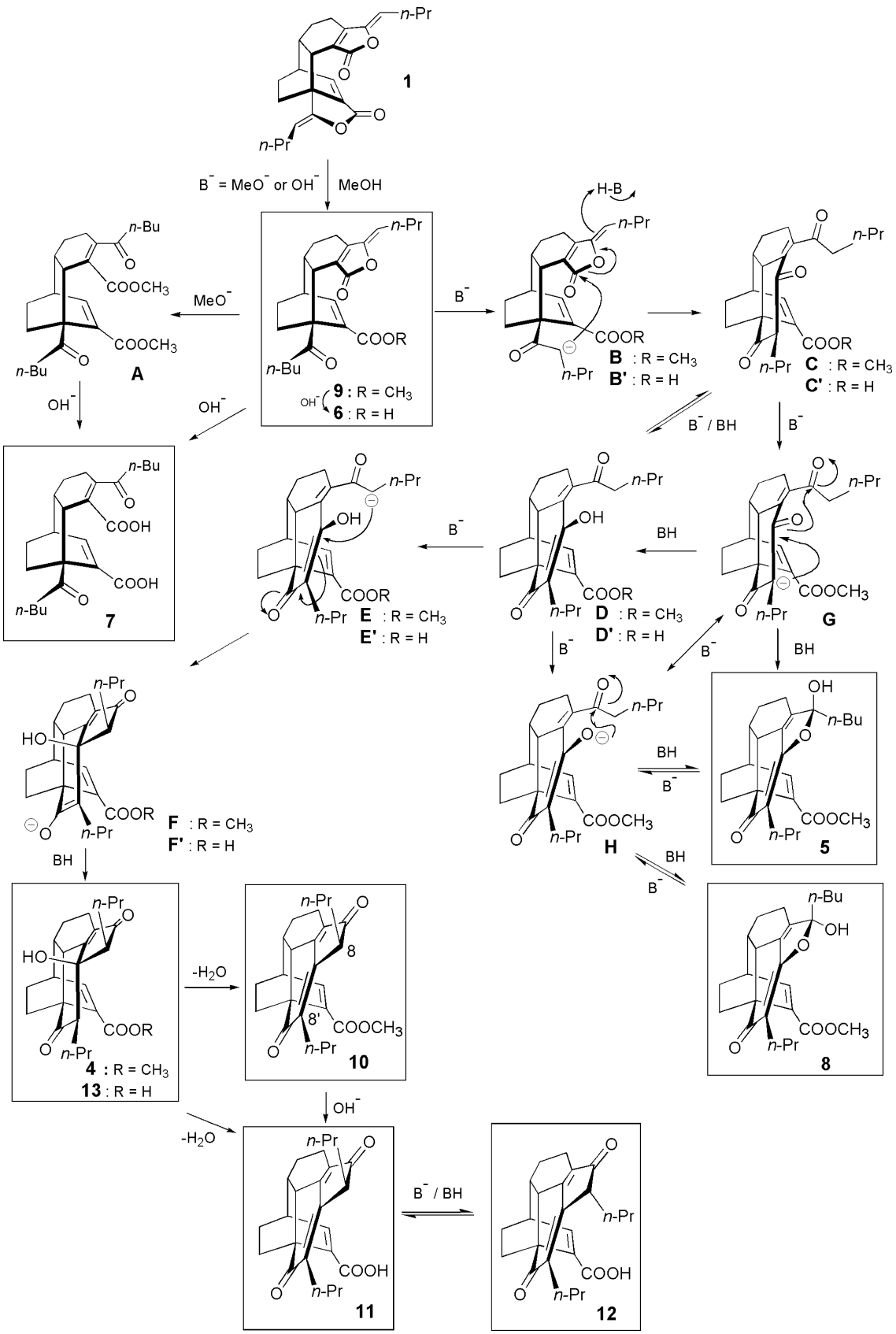


Figure 3. ORTEP-like view of compound **13**.

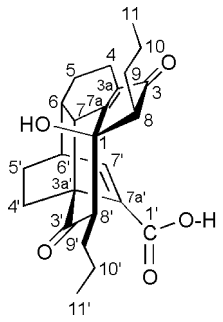

n-Pr
1
B⁻ = MeO⁻ or OH⁻
MeOH
n-Bu
COOCH3
A
MeO⁻
COOR
n-Bu
9 : R = CH3
6 : R = H
OH⁻
B⁻
H-B
B : R = CH3
B' : R = H
C : R = CH3
C' : R = H
B⁻ / BH
COOH
7
OH
E : R = CH3
E' : R = H
D : R = CH3
D' : R = H
BH
G
HO
F : R = CH3
F' : R = H
4 : R = CH3
13 : R = H
-H2O
8
8'
10
H
5
8
11
12

Scheme 2.

10 showed an additional quaternary carbon (δ_c 147.0) with respect to **4**, assigned to C(8′). Furthermore, the ^{1}H NMR spectra of both compounds **4** and **10** showed the chemical shift to low field of methine C(8) from δ_H 2.50 in **4** to δ_H 3.14 in **10**, as a result of the double bond produced by the dehydration of **4**. Concerning to compound **11**, its ^{1}H NMR did not show the signal assigned to the methoxy group (singlet at δ_H 3.59) in **10**, and the molecular formula for **11** ($C_{24}H_{28}O_4$, established by HRMS) agreed with the acid's structure. Finally, the spectroscopic data for the epimer of **11** (**12**) differed only by the chemical shift of the proton H(8) (δ_H 3.13 in **11** and δ_H 3.07 in **12**) since the negative shielding of the carboxyl group in **11** shifts the proton H(8) to low field, whereas in the epimer **12** the effect of the carboxyl group is not evident because the distance to the proton H(8) is longer.

In addition, treatment of diligustilide (**1**) under hydrolysis conditions led to a mixture of demethylwallichilide (**6**) and the diketo diacid **7**, favored in a mixture of acetone/water (entries 8–12, Table 1), presumably due to comparable rates of nucleophilic attack on both carbonyl groups, and the intramolecular condensation products were not detected. Presumptively, the absence of methanol in the reaction mixture does not favor the intramolecular condensation of diligustilide (**1**). However, during the experimentation to optimize the yield of **7**, the use of a stronger base than Na_2CO_3 (NaOH, entries 13 and 14, Table 1) afforded the epimers **11** and **12**, produced by the intramolecular condensation of **1**, besides the diketo diacid **7**. Less drastic reaction conditions (at room temperature) produced an additional intramolecular condensation product **13**, together with **7** (entries 15 and 16, Table 1). Product **13** was recrystallized from acetonitrile and the X-ray analysis of the crystals obtained confirmed the structure (Fig. 3).[11] In order to avoid the condensation of the solvent in a strong basic media, tetrahydrofuran was used instead of acetone. However the yield of the diketo diacid **7** was not notably improved, even under reflux, where compound **13** was transformed in a series of minor products not characterized (entries 17 and 18, Table 1). Moreover, treatment of **7** with NaOH in tetrahydrofuran/water for four hours at room temperature did not undergo any intramolecular condensation product and the starting material was recovered.

From the mechanistic point of view, wallichilide (**9**) is formed by methanolysis of diligustilide (**1**, Scheme 2) which could react either with another molecule of methoxy ion giving a diketo diester intermediate (**A**) and hydrolysis of both compounds would afford the acids demethylwallichilide (**6**) and the diketo diacid **7** respectively, or **9** undergoes intramolecular aldol reaction, by deprotonation of the acidic methylene at C(8′) (intermediate **B**) and opening of the lactone by addition to the carbonyl to produce tautomeric intermediates **C** and **D**, which in turn could react to give **4** via Michael-type addition of the carbanion at C(8) and equilibration (intermediates **E** and **F**, Scheme 2). Dehydration of **4** produces **10** and hydrolysis of the last one affords the epimers **11** and **12**. The formation of the enol ether **5** and its epimer **8** can be rationalized by the addition of the enolate to the ketone at C(3) (intermediates **G** or **H**, Scheme 2).



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When the reaction is performed in absence of methanol the hydrolysis of diligustilide (**1**, Scheme 2) is accomplished and demethylwallichilide (**6**) is formed. An excess of base could open the other lactone affording the diketo diacid **7**. Otherwise, the use of a strong base promotes the intramolecular condensation of **6** through intermediates **B′** to **F′** to produce **13** and the epimers **11** and **12** by dehydration of the former.

3. Conclusions

The reactivity of the natural dimeric phthalide diligustilide (**1**) in a basic media was studied, and the results showed that the isolated products were mainly solvent dependent. Under anhydrous conditions the formation of the intramolecular condensation product **4** was favoured, whereas in an aqueous and more polar system the epimeric mixture of **5** and **8** is obtained.

On the other hand, demethylwallichilide (**6**) and the diketo diacid **7**, products of the hydrolysis of diligustilide (**1**), were favored in a mixture of acetone/water, while the presence of methanol in the reaction mixture or the use of a strong base afford the intramolecular condensation of the starting material (**1**).

4. Experimental

Diligustilide (**1**) was isolated from the acetonic extract of the roots of *Ligusticum porteri* by successive column chromatographies, as described previously.[1] Melting points were determined on a Fisher Johns apparatus and are uncorrected. The NMR spectra were recorded on a Varian Unity-300 spectrometer at 300 MHz (^{1}H) and at 75 MHz (^{13}C), a Bruker DRX400 spectrometer (at 400/100 MHz) and a Bruker ARX500 spectrometer (at 500/125 MHz), and the chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane. Infrared spectra were recorded with a FTIR Bruker TENSOR 27 instrument. Ultraviolet spectra were determined on a SHIMADZU UV160U instrument. MS (FAB$^+$) and HRMS (FAB$^+$) spectra were recorded on a JEOL JMS-SX 102 A mass spectrometer, and the accurate mass was calculated using polyethylene glycol 400 as standard. Flash chromatography was performed on 60 Å 35–70 μm Matrex silica gel (Grace Amicon). The solvent system is specified in each experiment. Thin layer chromatography analyses (TLC) were made on Silica Gel 60 F_{254} (Merck) plates and visualization was accomplished

with either a UV lamp or a solution of sulfuric acid (10%) as spray reagent and heating. Crystallographic data were recorded on a Bruker SMART with CCD area detector, with graphite monochromated Mo K_α radiation, using omega scan for data collection with θ range scan 1.50–25.00°. Data were processed with SAINT program and corrected for Lorentz and polarization effects. Structures were solved by direct methods, and expanded using Fourier synthesis difference techniques. The non-hydrogen atoms were refined anisotropically. Positional parameters of hydrogen atoms were refined, and calculated geometrically and fixed with U_{iso}=1.2 times U_{eq} Å^2 of the preceding normal atom non-hydrogen. All calculations were performed using the SHELXS-97 and SHELXTL crystallographic package of Bruker AXS,[12] Inc.

All reactions were carried out under an atmosphere of nitrogen.

4.1.1. Preparation of 4. *Entry* 1. Under anhydrous conditions, to a mixture of diligustilide (**1**, 100 mg, 0.26 mmol) and NaOH (24 mg, 0.60 mmol) was added anh. THF (10 mL) and anh. MeOH (0.04 mL, 32 mg, 1 mmol). The heterogeneous mixture was refluxed and after 2 h the reaction mixture was coloured yellow. The reaction mixture was separated from the NaOH, and CH_2Cl_2 (40 mL) was added. The solution was washed with brine (2×10 mL), dried with Na_2SO_4 and concentrated in vacuum to afford **4**,[7,9] (102 mg, 94%) as a white solid.

Compound **4**: mp: 150–152 °C. IR ($CHCl_3$) ν_{max} (cm^{-1}): 3684, 3055, 2962, 2873, 1711, 1672, 1521, 1437, 1277, 1088, 928. ^{1}H NMR (400 MHz, $CDCl_3$; assignments by COSY and HMQC) δ: 7.36 (1H, d, J=6.9 Hz, H-7′), 3.64 (3H, s, OCH_3), 2.90 (1H, m, H-6′), 2.88 (1H, m, H-7), 2.50 (1H, dd, J_1=12.0 Hz, J_2=1.8 Hz, H-8′), 2.39 (1H, m, H-6), 2.25 (2H, m, H-8, H-4), 2.18 (1H, m, H-9′), 2.00 (1H, m, H-4′), 1.75 (3H, m, H-4, H-5, H-5′), 1.50 (4H, m, H-9, H-10), 1.45 (2H, m, H-4′, H-5′), 1.22 (4H, m, H-5, H-9′, H-10′), 0.93 (3H, t, J=6.7 Hz, H-11 or H-11′), 0.92 (3H, t, J=7.0 Hz, H-11 or H-11′). ^{13}C NMR (100 MHz, $CDCl_3$, assignments by DEPT, HMQC and HMBC) δ: 207.5 (C-3′), 206.2 (C-3), 169.0 (C-7′a), 164.1 (C-1′), 148.6 (C-7′), 138.5 (C-7a), 134.9 (C-3a), 81.8 (C-1), 59.1 (C-8′), 54.1 (C-8), 53.6 (C-3′a), 51.8 (C-12′), 40.5 (C-7), 38.4 (C-6), 37.6 (C-6′), 29.9 (C-9), 29.3 (C-4′), 26.4 (C-9′), 26.2 (C-5), 23.7 (C-5′), 21.4 (C-10), 20.6 (C-10′), 17.6 (C-4), 14.5 (C-11), 14.2 (C-11′). EIMS m/z (rel. int.): 412 [M$^+$] (69), 394 (11), 380 (10), 369 (30), 351 (6), 337 (13), 323 (17), 295 (4), 222 (100), 190 (58), 189 (14), 161 (28), 148 (20), 133 (5), 105 (11), 91 (8), 77 (8), 55 (12), 43 (6), 28 (28), 18 (15).

Entry 3. To a stirred solution of diligustilide (**1**, 100.8 mg, 0.26 mmol) in THF (5 mL) and MeOH (1 mL) was added a solution of Na_2CO_3 (165 mg, 1.56 mmol) in H_2O (5 mL). After refluxing for 30 min, the TLC of the reaction mixture did not show starting material and a more polar product was formed mainly. The mixture was cooled to room temperature and was neutralized with diluted HCl (10% to pH 3) and then extracted with EtOAc (4×10 mL). The organic layer was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography (*n*-heptane/EtOAc 7:3) to obtain **4**[7] (75 mg, 69%), demethylwallichilide (**6**,[8] 16 mg, 8%), the diketo diacid **7**[8] (8 mg, 7%) and wallichilide (**9**,[8] 7 mg, 6%) as white solids.

4.1.2. Preparation of the epimers, 5 and 8. *Entry* 7. To a stirred solution of diligustilide (**1**, 202 mg, 0.53 mmol) in MeOH (10 mL) was added a solution of Na_2CO_3 (678 mg, 6.39 mmol) in H_2O (10 mL). The yellow heterogeneous reaction mixture was refluxed for 3.5 h. The reaction mixture was cooled to room temperature, neutralized with HCl (10% to pH 3), and extracted with EtOAc (5×15 mL). The organic phases were joined and washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain a yellow oil. The crude product was purified by flash chromatography (CH_2Cl_2/CH_3CN gradient) and the following products were isolated: the epimeric mixture of **5** and **8** (1: 1, white solid, mp: 112–114, 118–123 °C, 129 mg, 59%), **4**[7] (6.8 mg, 3%), **7**[8] (7 mg, 3%), **10** (white semisolid, 8.6 mg, 4%), and the epimers **11** (pale yellow semisolid, 23 mg, 11%) **12** (pale yellow semisolid, 23 mg, 11%).

Compound **5**[10]: mp: 132–137 °C. ^{1}H NMR (500 MHz, $CDCl_3$; assignments by COSY and HMQC) δ: 7.28 (1H, d, J=6.9 Hz, H-7′), 3.57 (3H, s, OCH_3), 2.85 (1H, m, H-6′), 2.66 (1H, m, H-7), 2.39 (1H, m, H-6). ^{13}C NMR (125 MHz, $CDCl_3$, assignments by HMQC, HMBC, NOESY) δ: 200.5 (C-3′), 165.2 (C-1), 163.8 (C-1′), 146.5 (C-7′), 141.8 (C-3a), 136.7 (C-7′a), 133.7 (C-7a), 116.7 (C-3), 112.5 (C-8′), 51.5 (–OCH_3), 49.6 (C-3′a), 38.3 (C-6), 35.8 (C-8), 36.4 (C-6′), 36.3 (C-7), 29.4 (C-5), 27.9 (C-5′), 26.1 (C-9′), 25.2 (C-9), 24.0 (C-4′), 22.4 (C-10), 21.6 (C-10′), 20.1 (C-4), 14.4 (C-11′), 13.8 (C-11).

Compound **8**: ^{1}H NMR (500 MHz, $CDCl_3$; assignments by COSY and HMQC) δ: 7.10 (1H, d, J=6.8 Hz, H-7′), 3.55 (3H, s, OCH_3), 2.83 (1H, m, H-6′), 2.64 (1H, m, H-7), 2.38 (1H, m, H-6). ^{13}C NMR (125 MHz, $CDCl_3$, assignments by HMQC, HMBC, NOESY) δ: 200.4 (C-3′), 166.1 (C-1′), 165.7 (C-1), 146.3 (C-7′), 143.3 (C-3a), 137.0 (C-7′a), 132.4 (C-7a), 117.3 (C-3), 111.7 (C-8′), 51.8 (–OCH_3), 50.3 (C-3′a), 38.1 (C-6), 37.0 (C-8), 36.6 (C-7), 36.4 (C-6′), 29.6 (C-5), 27.3 (C-5′), 26.1 (C-9′), 25.5 (C-9), 24.4 (C-4′), 22.5 (C-10), 22.0 (C-10′), 20.4 (C-4), 14.2 (C-11′), 13.9 (C-11).

Compound **10**: UV (MeOH) λ_{max} nm (ε): 304 (15288), 218.5 (8666), 207 (8644). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3524, 2959, 3873, 1709, 1675, 1629, 1439, 1258, 1090, 910. ^{1}H NMR (400 MHz, $CDCl_3$; assignments by COSY and HMQC) δ: 7.36 (1H, d, J=6.9 Hz, H-7′), 3.59 (3H, s, –OCH_3), 3.14 (1H, m, H-8), 2.94 (1H, m, H-7), 2.91 (1H, m, H-6′), 2.50 (2H, m, H-6, H-9′), 2.43 (1H, m, H-4), 2.31 (1H, m, H-9′), 1.99 (2H, m, H-9, H-5), 1.91 (1H, m, H-4), 1.81 (4H, m, H-4′, H-5′, H-9), 1.63 (2H, m, H10′), 1.49 (1H, m, H-5′), 0.98 (3H, t, J=7.4 Hz, H-11′) 0.90 (1H, m, H-5), 0.85 (2H, m, H-10), 0.80 (3H, t, J=7.2 Hz, H-11). ^{13}C NMR (100 MHz, $CDCl_3$, assignments by DEPT, HMQC and HMBC) δ: 203.5 (C-3), 200.6 (C-3′), 164.7 (C-7′a), 163.6 (C-1′), 147.8 (C-7′), 147.0 (C-8′), 142.4 (C-3a), 136.2 (C-1), 136.0 (C-7a), 51.6 (*C*H_3OOC–), 49.5 (C-3′a), 48.0 (C-8), 41.0 (C-7), 39.5 (C-6), 37.0 (C-6′), 29.9 (C-9′), 29.7 (C-9), 29.4 (C-5), 27.4 (C-4′), 24.3 (C-5′), 22.1 (C-10′), 18.9 (C-4), 17.3 (C-10), 14.5 (C-11′), 14.2 (C-11). MS (FAB$^+$) m/z (rel.

int.): 395 [M^++1] (100), 394 (43), 363 (35), 352 (16), 333 (8), 307 (15), 289 (11), 279 (11), 263 (6), 215 (7), 178 (12), 154 (86), 136 (73), 107 (33), 91 (42), 57 (55), 55 (62), 44 (62), 31 (17). HRMS (FAB^+) *m/z*: Found 395.2219. Calcd for $C_{25}H_{30}O_4$+H^+ 395.2222 (MH^+).

Compound **11**: UV (MeOH) λ_{max} nm (ε): 304 (14288), 207 (9480). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3517, 2962, 2934, 2874, 1692, 1631, 1461, 1342, 1259, 1091, 909. ^{1}H NMR (400 MHz, $CDCl_3$; assignments by COSY and HMQC) δ: 7.53 (1H, d, J=6.9 Hz, H-7′), 3.13 (1H, m, H-8), 2.93 (1H, m, H-6′), 2.91 (1H, m, H-7), 2.51 (1H, m, H-6), 2.43 (2H, m, H-4, H-9′), 2.30 (1H, m, H-9′), 1.99 (2H, m, H-5, H-9), 1.88 (1H, m, H-4), 1.79 (4H, m, H-4′, H-5′, H-9), 1.61 (2H, m, H-10′), 1.49 (1H, m, H-5′), 0.97 (3H, t, J=7.3 Hz, H-11′) 0.89 (3H, m, H-5, H-10), 0.70 (3H, t, J=7.2 Hz, H-11). ^{13}C NMR (100 MHz, $CDCl_3$, assignments by DEPT, HMQC and HMBC) δ: 203.4 (C-3), 200.1 (C-3′), 167.5 (C-1′), 164.4 (C-7′a), 151.1 (C-7′), 147.3 (C-8′), 142.5 (C-3a), 136.1 (C-1), 135.2 (C-7a), 49.2 (C-3′a), 48.1 (C-8), 40.8 (C-7), 39.6 (C-6), 37.2 (C-6′), 29.9 (C-9′), 29.7 (C-9), 29.3 (C-5), 27.6 (C-4′), 24.0 (C-5′), 21.8 (C-10′), 18.9 (C-4), 17.4 (C-10), 14.6 (C-11′), 14.1 (C-11). MS (FAB^+) *m/z* (rel. int.): 381 [M^++1] (26), 380 (6), 363 (5), 338 (5), 307 (24), 289 (12), 191 (4), 165 (7), 154 (100), 136 (68), 120 (10), 107 (20), 89 (18), 77 (17), 55 (6), 51 (5), 39 (5).). HRMS (FAB^+) *m/z*: Found 381.2068. Calcd for $C_{24}H_{28}O_4$+H^+ 381.2066 (MH^+).

Compound **12**: UV (MeOH) λ_{max} nm (ε): 302.5 (13444), 207 (9916). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3521, 2962, 2933, 2873, 1692, 1630, 1422, 1343, 1258, 1169, 1087, 908. ^{1}H NMR (400 MHz, $CDCl_3$; assignments by COSY and HMQC) δ: 7.52 (1H, d, J=6.8 Hz, H-7′), 3.07 (1H, m, H-8), 2.96 (1H, m, H-7), 2.92 (1H, m, H-6′), 2.49 (1H, m, H-6), 2.43 (1H, m, H-4), 2.29 (2H, m, H-9′), 1.95 (2H, m, H-5, H-9), 1.87 (1H, m, H-4), 1.78 (3H, m, H-4′, H-5′), 1.71 (1H, m, H-9), 1.51 (1H, m, H-5′), 1.38 (2H, m, H-10′), 1.11 (1H, m, H-10), 0.99 (3H, t, J=7.3 Hz, H-11′), 0.88 (2H, m, H-5, H-10), 0.84 (3H, t, J=7.3 Hz, H-11). ^{13}C NMR (100 MHz, $CDCl_3$, assignments by DEPT, HMQC and HMBC) δ: 203.8 (C-3), 200.3 (C-3′), 167.6 (C-1′), 164.1 (C-7′a), 151.0 (C-7′) 147.9 (C-8′) 142.1 (C-3a), 135.6 (C-1), 135.0 (C-7a), 49.8 (C-3′a), 48.3 (C-8), 40.7 (C-7), 39.7 (C-6), 37.1 (C-6′), 31.9 (C-9), 30.7 (C-9′), 28.6 (C-5), 28.5 (C-4′), 23.6 (C-5′), 22.5 (C-10′), 18.8 (C-4), 18.0 (C-10), 14.8 (C-11′), 14.1 (C-11). MS (FAB^+) *m/z* (rel. int.): 381 [M^++1] (78), 380 (26) 363 (25), 338 (31), 336 (10), 307 (18), 289 (11), 178 (8), 155 (28), 154 (100), 136 (77), 109 (21), 95 (37), 81 (42), 69 (66), 55 (85), 44 (81), 42 (61), 31 (18). HRMS (FAB^+) *m/z*: Found 381.2068. Calcd for $C_{24}H_{28}O_4$+H^+ 381.2066 (MH^+).

4.1.3. Hydrolysis of diligustilide (1). Preparation of demethylwallichilide (6) and the diketo diacid 7. *Entry* 11. To a solution of diligustilide (**1**, 100 mg, 0.26 mmol) in acetone (5 mL) was added a solution of Na_2CO_3 (330 mg, 3.12 mmol) in water (5 mL), and the mixture was stirred and refluxed for 8 h. After cooling to room temperature the reaction mixture was acidified with a solution of HCl (10%, pH 3) and extracted with EtOAc (3×10 mL). The organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue (yellow solid) was purified by flash chromatography (CH_2Cl_2/MeOH, gradient) to obtain demethylwallichilide (**6**,[8] 18 mg, 17%) and the diketo diacid **7**,[8] (74 mg, 68%).

4.1.4. Preparation of 13. *Entry* 15. To a solution of diligustilide (**1**, 100 mg, 0.26 mmol) in acetone (5 mL) was added a solution of NaOH (28.5 mg, 0.71 mmol) in water (5 mL), and the heterogeneous yellow mixture was stirred at room temperature. After 2 h the reaction mixture became homogeneous, then was acidified with a solution of HCl (10%, pH 1) and extracted with EtOAc (3×10 mL). The organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue (yellow oil) was purified by preparative TLC (CH_2Cl_2/MeOH 95:5, three times) to afford the diketo diacid **7**,[8] (39 mg, 36%) and the intramolecular condensation product **13**,[11] as a white solid, mp: 188–190 °C. UV (MeOH) λ_{max} nm (ε): 305.5 (2020), 232.5 (2655). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3693, 3603, 3515, 2962, 2874, 1705, 1603, 1425, 1063, 926. ^{1}H NMR (300 MHz, CD_3OD; assignments by COSY and HETCOR) δ: 7.37 (1H, d, J=6.9 Hz, H-7′), 2.93 (1H, m, H-6′), 2.91 (1H, m, H-7), 2.55 (1H, dd, J_1=9.9 Hz, J_2=2.1 Hz, H-8′), 2.44 (1H, m, H-6), 2.24 (2H, m, H-8, H-9′), 2.15 (1H, m, H-4), 1.95 (1H, m, H-4′), 1.81 (3H, m, H-4, H-5, H-5′), 1.68 (1H, m, H-10), 1.54 (3H, m, H-9, H-10, H-10′), 1.44 (2H, m, H-4′, H-5′), 1.35 (2H, m, H-5, H-9), 1.24 (2H, m, H-9′, H-10′), 0.95 (3H, t, J=6.9 Hz, H-11), 0.90 (3H, t, J=6.9 Hz, H-11′). ^{13}C NMR (75 MHz, CD_3OD, assignments by DEPT, HETCOR and FLOCK) δ: 209.7 (C-3′), 209.1 (C-3), 172.4 (C-7′a), 167.1 (C-1′), 149.2 (C-7′), 138.8 (C-7a), 137.2 (C-3a), 82.4 (C-1), 60.6 (C-8′), 55.8 (C-8), 54.8 (C-3′a), 41.9 (C-7), 39.7 (C-6), 39.0 (C-6′), 30.9 (C-9), 30.2 (C-4′), 27.9 (C-9′), 27.4 (C-5), 25.0 (C-5′), 22.6 (C-10), 21.7 (C-10′), 18.6 (C-4), 14.9 (C-11), 14.6 (C-11′). MS (FAB^+) *m/z* (rel. int.): 399 [M^++1] (12), 381 (22), 363 (10), 329 (4), 307 (26), 289 (14), 191 (7), 176 (6), 154 (100), 136 (66), 120 (10), 107 (20), 89 (17), 77 (16), 55 (7), 41 (6), 39 (6). HRMS (FAB^+) *m/z*: Found 399.2175. Calcd for $C_{24}H_{30}O_5$+H^+ 399.2171 (MH^+).

Acknowledgements

Contribution 2463 from the Institute of Chemistry, UNAM. Taken in part from the PhD thesis of B. Q.-G. Financial support from Universidad Nacional Autónoma de México (DGAPA-PASPA, and PAEP 208322) and from STINT (Sweden) is gratefully acknowledged. We thank Rocío Patiño, Héctor Ríos, María Isabel Chávez, Angeles Peña, Elizabeth Huerta, Luis Velasco and Javier Pérez Flores for technical assistance.

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9. X-ray data for compound **4**: $C_{25}H_{32}O_5$, M=412.51, T=291 K, crystal system monoclinic, space group $P2_1/c$, (No. 14), a=9.8420(9) Å, b=9.6724(9) Å, c=23.419(2) Å, β=93.013(2)°, V=2226.3(4) Å^3, Z=4, D_c=1.231 g/cm^3, μ=0.084 mm^{-3}, F(000)=888.17743 reflections were collected and 3925 [R_{int}=0.0381] reflections were independent, S=1.017, R=0.07.14, Rw=0.2118. Largest diff. peak and hole were 0.693 and −0.284 e Å^{-3}. Crystallographic data have been deposited with Cambridge Crystallographic Centre as supplementary publication number CCDC 228132.
10. X-ray data for compound **5**: $C_{25}H_{32}O_5 \cdot 1/2C_6H_{14}$, M=455.59, T=291(2) K, crystal system monoclinic, space group $C2/c$ (No. 15), a=26.0298(16) Å, b=11.1079(7) Å, c=21.4951(13) Å, β=122.5960(10)°, V=5236.1(6) Å^3, Z=8, D_c=1.156 g/cm^3, μ=0.078 mm^{-1}, F(000)=1976. 20998 reflections were collected and 4618 [R_{int}=0.0614] reflections were independent, S=0.953, R=0.0577, Rw=0.1004, Largest diff. peak and hole were 0.157 and −0.140 e Å^{-3}. CCDC registration number 228133.
11. X-ray data for compound **13**: $C_{48}H_{60}O_{10}$, M=796.96, T=291 K, crystal system orthorhombic, space group, $Pna2_1$ (No. 33), a=15.6297(9) Å, b=13.5568(8) Å, c=19.3275(11) Å, V=4095.3(4) Å^3, Z=4, D_c=1.293 g/cm^3, μ=0.089 mm^{-1}, F(000)=1712, 32270 reflections were collected and 7210 [R_{int}=0.0872] reflection were independent s, S=0.890, R=0.0597, Rw=0.0743. Largest diff. peak and hole were 0.186 and −0.187 e Å^{-3}. CCDC registration number 228134. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax:+44-123-336033 or email: deposited@ccdc.cam.ac.uk).
12. *SHELXTL V 6.10* BRUKER AXS Inc, 5465 East Cheryl Parkway, Madison, WIS.

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Synthesis of (+)-zeylenone from shikimic acid

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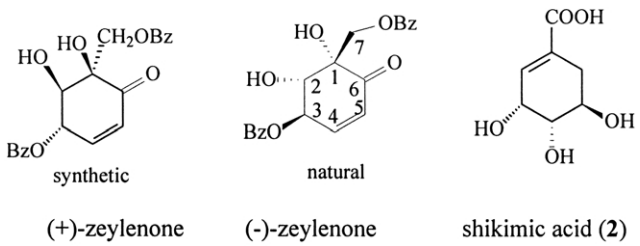
Received 19 November 2003; revised 16 February 2004; accepted 20 February 2004

Abstract—Starting from shikimic acid, the total synthesis of zeylenone was studied. The product was proved to be the (+)antipode of zeylenone through analysis and comparison of their respective spectra (including NMR, MS, IR and CD) and optical data. The absolute configuration of the natural product was thus determined to be (1*S*,2*S*,3*R*).

1. Introduction

A number of polyoxygenated cyclohexenes, which show anticancer, antiviral and antibiotic activities, have been isolated from the *Uvaria* genus.[1] As a part of our project of searching for the anticancer components from the plant source, zeylenone (Fig. 1) was isolated from *Uvaria grandiflora*, which showed remarkable inhibition of nucleoside transport in Ehrlich carcinoma cells and interesting cytotoxicity to cultured cancer cells.[2] The relative stereochemistry of zeylenone was assigned on the basis of the modern NMR techniques but the absolute configuration was not elucidated. Kunio Ogasawara and co-workers synthesized (−)tonkinenin A, which was isolated from *Uvaria tonkinensis*,[3] and corrected its structure to be the same as zeylenone.[4] As our continuous effort to confirm the structure and to study the structure–activity relationship of zeylenone, we report herein the enantioselective synthesis of the enantioisomer of zeylenone from shikimic acid (**2**).[5]



(+)-zeylenone (-)-zeylenone shikimic acid (**2**)

Figure 1. The structures of zeylenone and shikimic acid.

The retrosynthetic analysis for zeylenone is outlined in Scheme 1. Zeylenone could be obtained by oxidation of olefin **3** with SeO_2. The olefin **3** could be synthesized from the *trans* diol **4**, which could be derived from olefin **5** by oxidation with OsO_4. The olefin **5** could be obtained from shikimic acid (**2**) by reduction and selective protection.

2. Results and discussion

Our synthesis of **1** began with the methylation of shikimic acid (**2**), followed by regio-selective protection of *trans* vicinal diol **6** with 2,3-butanedione, (±)-camphorsulfonic acid (CSA, cat.) and trimethyl orthoformate in methanol at reflux to give compound **7** in 87% yield.[6] At the same time, we obtained the protected *cis* diol **8** in 10%. Fortunately, compound **8** could be converted into **7** with catalytic amount of (±)-CSA in refluxing methanol under Ar for 18 h in 92% yield, After introduction of *tert*-butyldimethylsilyl (TBDMS) group,[7] compound **9** was obtained in 97% yield from the protected diol **7**. After reduction of **9** with diisobutylaluminum hydride (DIBAL-H), alcohol **10** was obtained in 92% yield.[8] Benzoylation of **10** with benzoyl chloride afforded olefin **5** in 97% yield. The olefin **5** was dihydroxylated with OsO_4 and *N*-methylmorphorline-*N*-oxide (NMO) in THF/H_2O (1:1) under Ar to give stereoselectively the sole diol isomer **11** in 94% yield. The *cis* diol **11** was protected with 2,2-dimethylpropane to give acetonide **12** in 99% yield,[9] followed by selective deprotection with TFA/H_2O (1:1) to give the *trans* vicinal diol **4**(Scheme 2).[10]

Keywords: Zeylenone; Absolute configuration; Shikimic acid; Total synthesis; Enantiomer.
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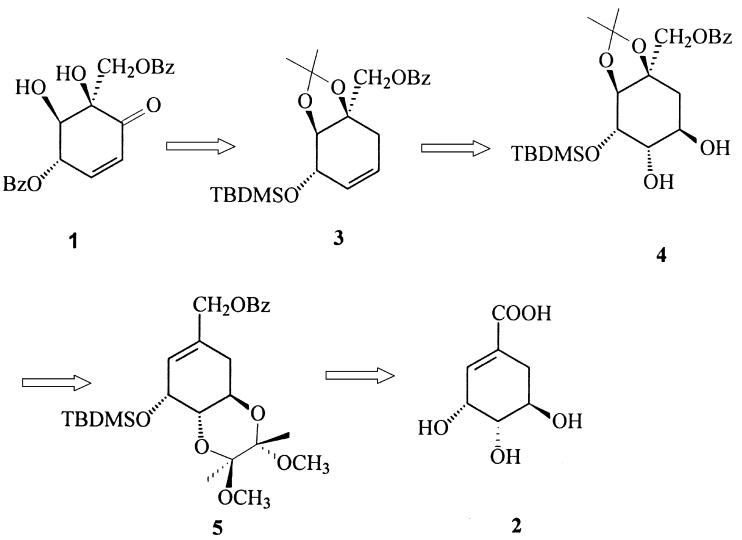
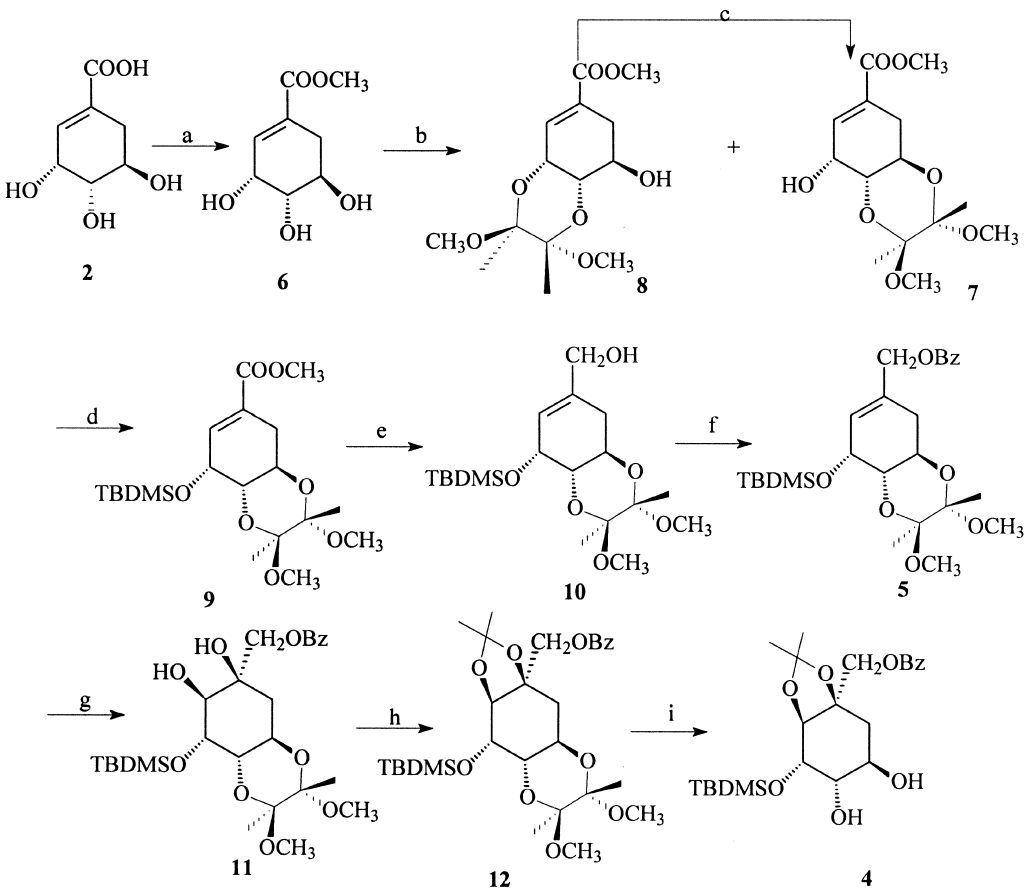
doi:10.1016/j.tet.2004.02.066



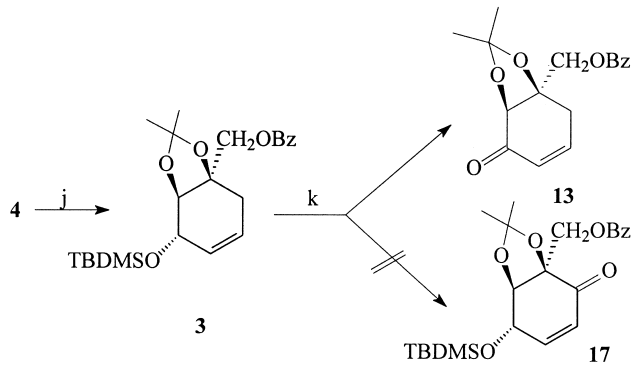
Scheme 1.

The treatment of *trans* vicinal diol **4** with Ph_3P, imidazole and iodine in toluene at reflux gave cyclohexene **3** in 87% yield.[10,11] We have tried to oxidize cyclohexene **3** by CrO_3/*t*-BuOOH, PCC, CuBr/*t*-BuOOH, or SeO_2 to synthesize enone. Unfortunately, we could not get the desired product **17**, only to obtain the TBDMS-deprotected enone **13** (Scheme 3).

So, the cyclohexene **3** was deprotected with *tetra*-butylammonium fluoride (TBAF) and benzoic acid in dry THF to



Scheme 2. (a) $SOCl_2$, MeOH, 10 °C, 93%; (b) $(CH_3CO)_2$, $CH(OMe)_3$, (±) CSA, MeOH, Ar, 48 h, 90 °C, 87%; (c) (±) CSA, MeOH, Ar, 18 h; (d) TBDMSCl, imidazole, DMAP, CH_2Cl_2, room temperature, 24 h, 97%; (e) DIBAL-H, toluene, −78 °C, 92%; (f) BzCl, DMAP, pyridine, room temperature 97%; (g) OsO_4, NMO, THF/H_2O (1:1), Ar, 94%; (h) $(CH_3)_2C(OCH_3)_2$, TsOH, CH_2Cl_2, Ar, room temperature, 99%; (i) TFA/H_2O (1:1), CH_2Cl_2, 79%.



Scheme 3. (j) Ph_3P, imidazole, I_2, reflux, 87%; (k) *t*-BuOOH, CrO_3, CH_2Cl_2, 36%.

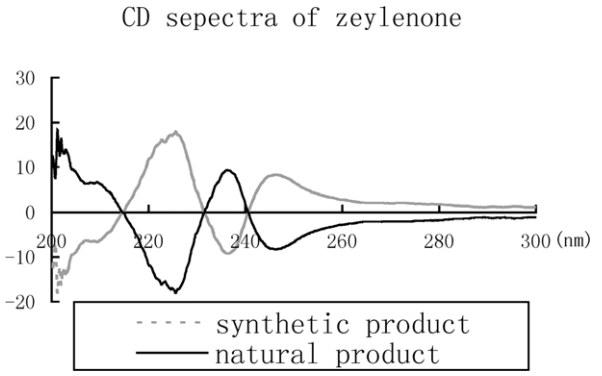


Figure 2. The CD spectra of zeylenone.

give alcohol **14**,[12] followed by the protection with benzoyl group to give olefin **15**. The enone **16** was obtained from **15** by oxidation with SeO_2 in dry THF at reflux for 24 h 40% yield.[13] Subsequent deprotection of **15** with TFA/H_2O (9:1) in CH_2Cl_2 at room temperature provided the target compound **1** in 85% yield (Scheme 4).

The spectral data (including NMR, MS and IR) of compound **1** were identical with those of natural zeyleone, which indicated that the relative stereochemistry of **1** was the same as that of the natural product. The positive Cotton effect[14] of the synthetic product **1** suggested the absolute stereochemistry of **1** to be of (1*R*,2*R*,3*S*). But the value and sign of the optical rotation of the compound **1** {$[\alpha]_D^{20}$=+118 (*c* 0.56, $CHCl_3$), $[\alpha]_D^{20}$=+26 (*c* 0.23, CH_3OH)} were opposite to those of the natural product {lit.[2] $[\alpha]_D^{20}$=−126.5 (*c* 0.747, $CHCl_3$); lit.[3] $[\alpha]_D^{20}$=−26.0 (*c* 0.89, MeOH); $[\alpha]_D^{20}$=−120 (*c* 0.60, $CHCl_3$), $[\alpha]_D^{20}$ −26 (*c* 0.26, CH_3OH)}. In addition, Cotton effects in CD spectra of the two compounds were opposite too (Fig. 2). All the data proved that compound **1** is the (+)-antipode of the natural product. So the absolute configuration of the natural product was determined to be (1*S*,2*S*,3*R*). This also proved that zeylenone and (−)-tonkinenin A were the same natural products.

3. Conclusion

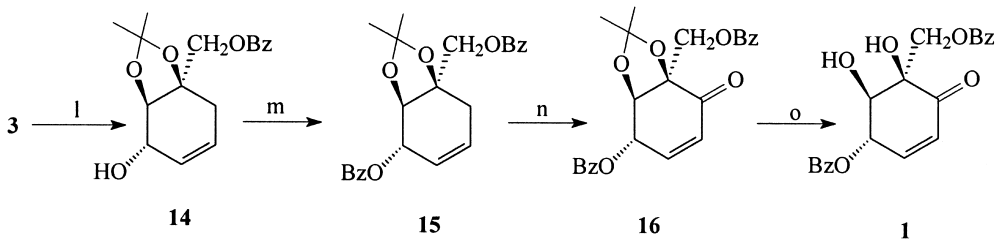
In summary, we have achieved the asymmetric total synthesis of (+)-antipode of zeylenone via a multi-step enantioselective route starting from shikimic acid. Our study shows the absolute configuration of the natural product zeylenone was proved to be (1*S*,2*S*,3*R*) and that zeylenone and (−)-tonkinenin A were the same natural products. Further work on the synthesis of the authentic natural product and its analogues is in progress.

4. Experimental

4.1. General

Melting points were obtained on a Yanaco apparatus and were uncorrected. Infrared spectra were measured on a Perkin–Elmer 683 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX-90Q spectrometer. Chemical shifts were reported in ppm with tetramethylsilane as the internal standard and *J* values in Hz. Mass spectra and high-resolution mass data were obtained on a VGZAB-2F spectrometer. Silica gel was used for flash column chromatography. All solvents were purified and dried by standard techniques or used as supplied from commercial sources as appropriate.

4.1.1. (3*R*,4*S*,5*R*)-3,4,5-Trihydroxy-1-cyclohexene-1-carboxylate methyl ester (6). To a solution of shikimic acid (**2**) (20 g, 0.11 mol) in MeOH, $SOCl_2$ (15 mL, 0.21 mol) was added dropwise during 1 h at 0 °C. Then the reaction mixture was warmed to room temperature and stirred overnight. Removal of the solvent and recrystallization from EtOAc afforded **6** as white solid (19.9 g, 93%). Mp 112–113 °C, $[\alpha]_D^{20}$=−125 (*c* 1.8, EtOH), IR (KBr): 3330, 2900, 1716, 1658, 1435, 1244, 1095, 1068, 930, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.71–6.73 (m, 1H, H-2), 4.83 (s, 3H, OCH_3), 4.31 (br s, 1H, H-3), 3.93 (dd, 1H, *J*=12.3, 5.1 Hz, H-5), 3.61–3.65 (m,1H, H-4), 3.25 (s, 1H, OH), 2.60–2.67 (m, 1H, H-6β), 2.17 (dd, 1H, *J*=18.0, 5.1 Hz, H-6α).



Scheme 4. (l) TBAF, benzoic acid, THF, room temperature, 94%; (m) BzCl, DMAP, pyridine, room temperature, 99%; (n) SeO_2, THF, reflux, 40%; (o) TFA/H_2O (9:1), CH_2Cl_2, 85%.

4.1.2. Methyl (3*R*,4*S*,5*R*)-3-hydroxy-4,5-(2,3-dimethoxybutan-2,3-dioxy)-cyclohex-1-ene-1-carboxylate (7) and methyl (3*R*,4*S*,5*R*)-5-hydroxy-3,4-(2,3-dimethoxybutan-2,3-dioxy)-cyclohex-1-ene-1-carboxylate (8). Trimethyl orthoformate (60 g, 0.57 mol) was added to a mixture of **6** (17.8 g, 0.095 mol), 2,3-butanedione (20 g, 0.23 mol) and catalytic amount of DMAP (0.12 g, 0.1 mmol) in MeOH (200 mL), and the whole mixture was refluxed under Ar for 48 h. After being cooled to room temperature, $NaHCO_3$ (20 g) was added to the mixture and stirred for 10 min. Removal of the solvent and purification of the residue by column chromatography (acetone/petroleum ether 1:5) afforded colorless oil **7** (24.9 g, 87%) and white solid **8** (3.7 g, 12%). Compound **7**: $[\alpha]_D^{20}=+23.1$ (*c* 0.89, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz) δ 6.90 (dd, 1H, *J*=5.1, 2.7 Hz, H-2), 4.39 (t, 1H, *J*=4.8 Hz, H-3), 4.06–4.15 (m, 1H, H-5), 3.76 (s, 3H, OCH_3), 3.62 (dd, 1H, *J*=10.8, 4.5 Hz, H-4), 3.28 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 2.84 (dd, 1H, *J*=17.7, 5.7 Hz, H-6a), 2.25 (ddd, 1H, *J*=17.7, 7.5, 2.7 Hz, H-6b), 1.34 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 135.0, 131.8, 100.0, 99.2, 70.5, 65.0, 62.4, 52.1, 48.0, 47.9, 30.0, 17.8, 17.7; EIMS *m*/*z*: 271, 213, 154, 139, 125, 101, 95, 75; FAB-HRMS: cacld for $C_{14}H_{22}O_7Na$ $[M+Na]^+$: 325.1263, found 325.1283. Compound **8**: mp 137–138 °C, $[\alpha]_D^{20}=-144.2$ (*c* 0.26, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (s, 1H, H-2), 4.39 (d, 1H, *J*=1.2 Hz, H-3), 4.17 (br s, 1H, H-5), 4.11 (br s, 1H, H-4), 3.73 (s, 3H, $COOCH_3$), 3.27 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 2.64 (ddd, 1H, *J*=18.3, 6, 3 Hz, H-6β), 2.40 (d, H, *J*=18.3 Hz, H-6α), 1.27 (s, 3H, CH_3), 1.24 (s, 3H, CH_3). EIMS *m*/*z*: 271, 154, 139, 122, 101, 95, 75. FAB-HRMS: cacld for $C_{14}H_{22}O_7Na$ $[M+Na]^+$: 325.1263, found 325.1283.

A solution of **8** (1.0 g, 3.3 mmol) and catalytic amount of (±)-CSA was stirred in MeOH (20 mL) at reflux under Ar for 18 h. After being cooled to room temperature, $NaHCO_3$ (0.5 g) was added to the mixture and stirred for 5 min. Removal of the solvent and purification of the residue by column chromatography (acetone/petroleum ether 1:5) afforded colorless oil **7** (0.92 g, 92%).

4.1.3. Methyl (3*R*,4*S*,5*R*)-3-*O*-*tert*-butyldimethylsilyl-4,5-(2,3-dimethoxybutan-2,3-dioxy)- cyclohex-1-ene-1-carboxylate (9). To a solution of **7** (10.0 g, 33.1 mmol), imidazole (3.8 g, 55.4 mmol) and catalytic amount of dimethylaminopyridine (DMAP, 0.05 g, 0.4 mmol) in dry CH_2Cl_2 (300 mL), *tert*-butyldimethyl-silyl chloride (5.0 g, 33.2 mmol) was added, and the mixture was stirred at room temperature for 24 h. After quenching the reaction with saturated aqueous NH_4Cl (150 mL), the reaction mixture was extracted with CH_2Cl_2 (3×150 mL), washed with brine (50 mL), and dried ($MgSO_4$). The solvent was removed and the product was purified by column chromatography (acetone/petroleum ether 1:10), which yielded **9** as white solid (13.3 g, 97%). Mp 71–72 °C, $[\alpha]_D^{20}=-15.6$ (*c* 0.18, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz) δ 6.75 (dd, 1H, *J*=5.7, 2.7 Hz, H-2), 4.29 (t, 1H, *J*=4.5 Hz, H-3), 4.10 (dt, 1H, *J*=10.5, 6 Hz, H-5), 3.73 (s, 3H, OCH_3), 3.46 (dd, 1H, *J*=10.2, 4.5 Hz, H-4), 3.23 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 2.88 (dd, 1H, *J*=17.4, 6 Hz, H-6α), 2.20 (ddd, 1H, *J*=17.4, 10.2, 2.7 Hz, H-6β), 1.27 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 0.87 (s, 9H, CH_3×3), 0.11 (s, 3H, CH_3), 0.08 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.1, 136.8, 129.7, 99.5, 98.7, 70.8, 66.0, 62.4, 52.0, 47.8, 47.6, 30.4, 25.8 (C×3), 18.3, 17.9, 17.7, −4.70 (C×2); HRFABMS: cacld for $C_{20}H_{36}O_7SiNa$ $[M+Na]^+$: 439.2122, found 439.2127.

4.1.4. (3*R*,4*S*,5*R*)-3-*O*-*tert*-Butyldimethylsilyl-4,5-(2,3-dimethoxybutan-2,3-dioxy)-cyclohex-1-ene-1-methanol (10). A solution of diisobutylaluminium hydride (1 M, 58 mL) in toluene was added dropwise to the solution of **9** (12.1 g, 29 mmol) in dry toluene under Ar at −78 °C. After being stirred for 20 min, water (100 mL) was added to the reaction mixture to quench the reaction. The mixture was extracted with diethyl ether (3×100 mL), washed with brine (50 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purified by column chromatography (acetone/petroleum ether 1:6) to yield alcohol **10** (11.3 g, 92%) as white solid. Mp 90–91 °C, $[\alpha]_D^{20}=+8.6$ (*c* 0.11, $CHCl_3$), IR ν_{max}^{KBr} cm^{-1}:: 3244, 2971, 1685, 1255, 1124, 839, 775, 673 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.69 (d, 1H, *J*=4.5 Hz, H-2), 4.22 (t, 1H, *J*=4.5 Hz, H-3), 4.14 (td, 1H, *J*=10.5, 6.0 Hz, H-5), 4.02 (s, 2H, H-7), 3.48 (dd, 1H, *J*=10.8, 3.9 Hz, H-4), 3.24 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 2.34 (dd, 1H, *J*=16.8, 6.0 Hz, H-6α), 2.09 (dd, 1H, *J*=16.8, 10.5 Hz, H-6β), 1.27 (s, 6H, CH_3×2), 0.90 (s, 9H, CH_3×3), 0.09 (6H, s, CH_3×2); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 138.2, 128.2, 99.4, 98.6, 71.3, 66.4, 65.9, 62.1, 48.2, 47.7, 31.5, 25.7 (C×3), 18.4, 17.9, 17.7, −4.6, −4.8.

4.1.5. (3*R*,4*S*,5*R*)-1-Benzoyloxymethyl-3-*O*-*tert*-butyldimethylsilyl-4,5-(2,3-dimethoxybutan-2,3-dioxy)-cyclohex-1-ene (5). Benzoyl chloride (5.3 mL, 43.5 mmol) was added dropwise to a solution of alcohol **10** (11.0 g, 28.4 mol) and catalytic amount of DMAP (0.05 g, 0.4 mmol) in dry pyridine (200 mL) at room temperature during a period 20 min. Stirring was continued for another 2 h and then saturated aqueous $NaHCO_3$ (100 mL) was added to the reaction mixture to quench the reaction. The mixture was extracted with CH_2Cl_2 (3×100 mL), washed with brine (30 mL) and dried ($MgSO_4$). The solvent was removed and the product purified by column chromatography (acetone/petroleum ether 1:10), which yielded protected alcohol **5** (13.8 g, 97%) as white solid. Mp 59–60 °C, $[\alpha]_D^{20}=+2.8$ (*c* 0.64, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}:: 2947, 2854, 1720, 1452, 1375, 1267, 1140, 1076, 1039, 987, 901, 860, 833, 781, 719 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.06 (d, 2H, *J*=7.5 Hz, H-2′ and 6′), 7.55 (d, 1H, *J*=7.5 Hz, H-4′), 7.45 (t, 2H, *J*=7.5 Hz, H-3′ and 5′), 5.80 (d, 1H, *J*=3.9 Hz, H-2), 4.75 (s, 2H, H-7), 4.22–4.27 (m, 1H, H-3), 4.19 (dd, 1H, *J*=10.5, 4.3 Hz, H-5), 3.53 (dd, 1H, *J*=10.8, 3.9 Hz, H-4), 3.25 (s, 6H, OCH_3×2), 2.44 (dd, 1H, *J*=17.5, 6.3 Hz, H-6α), 2.30 (ddd, 1H, *J*=17.5, 10.2, 1.8 Hz, H-6β), 1.28 (s, 6H, CH_3×2), 0.88 (s, 9H, CH_3×3), 0.10 (s, 3H, CH_3), 0.09 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.2, 133.8, 133.1, 130.0, 129.7 (C×2), 128.4 (C×2), 125.9, 99.4, 98.7, 71.0, 67.8, 66.3, 62.6, 47.8, 47.7, 32.1, 25.8 (C×3), 18.3, 17.9, 17.7, −4.6, −4.8.

4.1.6. (1*R*,2*R*,3*R*,4*S*,5*R*)-1-Benzoyloxymethyl-1,2-dihydroxy-3-*O*-*tert*-butyldimethylsilyl-4,5- (2,3-dimethoxybutan-2,3-dioxy)-cyclohexane (11). A suspension of olefin **5** (13 g, 26 mmol), *N*-methylmorpholine-*N*-oxide (NMO, 5.7 g, 42.0 mmol), and catalytic amount of OsO_4 (70.0 mg, 0.28 mmol) in THF/H_2O (250 mL, v/v 1:1) under

Ar was stirred violently at room temperature for 12 h. The solid $Na_2S_2O_3$ (25 g) and EtOAc (100 mL) were added to the reaction mixture and stirred for another 30 min. The mixture was loaded onto a flash chromatographic column and washed with EtOAc. Removal of the EtOAc and purification of the residue by column chromatography (acetone/petroleum ether 1:3) afforded white solid **11** (13.1 g, 94%). Mp 136–138 °C, $[\alpha]_D^{20}$=+73 (*c* 0.64, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ 4.85 (d, 1H, *J*=12 Hz, H-7a), 4.45 (d, 1H, *J*=12 Hz, H-7b), 4.16 (t, 1H, *J*=3.3 Hz, H-3), 3.90–3.96 (m, 1H, H-5), 3.83 (dd, 1H, *J*=10.5, 3.3 Hz, H-4), 3.81 (d, 1H, *J*=3.3 Hz, H-2), 2.42–2.50 (m, 1H, H-6a), 1.85–1.93 (m, 1H, H-6b), 3.25 (s, 3H, OCH3), 3.22 (s, 3H, OCH_3), 1.29 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 0.88 (s, 9H, CH_3×3), 0.15 (s, 3H, CH_3), 0.08 (s, 3H, CH_3), benzoyl groups: δ 8.04 (d, 2H, *J*=7.5 Hz), 7.59 (t, 1H, *J*=7.5 Hz), 7.46 (d, 2H, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, *J* in Hz) δ 167.2, 133.4, 129.7, 129.5 (2C), 128.5 (2C), 99.7, 99.0, 77.4, 77.0, 76.6, 74.2, 73.5, 71.9, 69.5, 62.4 (C×2), 47.8, 47.6, 34.1, 25.7 (C×3), 18.2, 17.8, 17.6, −4.9, −5.3; TOFMS *m*/*z*: 405, 315, 297, 237, 199, 197, 181, 169, 122, 105, 75; HRTOFMS: cacld for $C_{26}H_{42}O_9SiNa$ $[M+Na]^+$: 549.2490, found 549.2479.

4.1.7. (1*R*,2*R*,3*R*,4*S*,5*R*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-3-*O*-*tert*-butyldimethyl- silyl-4,5-(2,3-dimethoxybutan-2,3-dioxy)-cyclohexane (12). Dimethoxypropane (1.2 g, 11.4 mmol) was added to the solution of diol **11** (3.0 g, 5.7 mmol) and catalytic amount of *p*-toulenesulfonic acid (19 mg, 0.11 mmol) in dried CH_2Cl_2 (100 mL), and the mixture was stirred under Ar at room temperature for 3 h. After adding 10% aqueous $NaHCO_3$ (50 mL), the reaction mixture was stirred for 5 min and then extracted with CH_2Cl_2 (3×50 mL). The organic layers were combined, washed with brine, and dried ($MgSO_4$). The solvent was removed and the residue was purified by column chromatography (acetone/petroleum ether 1:10) to yield **12** as white solid (3.2 g, 99%). Mp 148–150 °C, $[\alpha]_D^{20}$=+19 (*c* 0.25, $CHCl_3$), ^{1}H NMR (300 MHz, CD_3Cl, *J* in Hz) δ 8.05 (d, 2H, *J*=7.8 Hz), 7.58 (t, 1H, *J*=7.8 Hz), 7.44 (t, 2H, *J*=7.8 Hz), 4.65–4.73 (m, 1H), 4.2–4.4 (m, 4H), 3.94–4.03 (m, 1H), 3.31 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 2.10–2.20 (m, 1H, H-6a), 1.85–1.94 (m, 1H, H-6b), 1.52 (s, 6H, CH_3), 1.36 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 0.84 (s, 9H, CH_3), 0.14 (s, 3H, CH_3), 0.17 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.1, 133.1, 130.0, 129.7 (C×2), 128.4 (C×2), 109.0, 99.9, 96.5, 80.6, 70.5, 69.8, 66.0, 62.6, 48.3, 48.4, 36.6, 28.1, 26.7, 25.6 (C×3), 23.6, 18.1, 18.0 (C×2), −4.5, −5.3.

4.1.8. (1*R*,2*R*,3*R*,4*S*,5*R*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-3-*O*-*tert*-butyldimethyl- silyl-4,5-dihydroxy-cyclohexane (4). To a violently stirred solution of **12** (3.1 g, 5.6 mmol) in CH_2Cl_2 (150 mL), 50% aqueous TFA (v/v, 1:1, 10.0 mL) was added. After 6 h, 100 mL 5% aqueous $NaHCO_3$ was added to the reaction mixture. Stirring for 5 min, the mixture was extracted with CH_2Cl_2 (3×100 mL), washed with brine (50 mL) and dried ($MgSO_4$). Removal of the solvent and purification of the residue by column chromatography (acetone/ petroleum ether 1:5) gave diol **4** (2.0 g, 80%) as white solid. Mp 46–48 °C, $[\alpha]_D^{20}$=−40 (*c* 0.20, $CHCl_3$), IR ν_{max}^{KBr} cm^{-1}: 3465, 2931, 1726, 1275, 1097, 1066, 839, 712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ 8.05 (2H, d, *J*=7.5 Hz), 7.57 (1H, t, *J*=7.5 Hz), 7.44 (2H, t, *J*=7.5 Hz), 4.66 (1H, d, *J*=12.3 Hz, H-7a), 4.38 (1H, t, *J*=3 Hz, H-3), 4.18–4.25 (1H, m, H-2), 4.20 (1H, d, *J*=12.3 Hz, H-7b), 3.74–3.80 (1H, m, H-5), 3.69 (1H, dd, *J*=9.3, 3 Hz, H-4), 2.25 (1H, dd, *J*=13.5, 4.2 Hz, H-6a), 2.03 (1H, t, *J*=13.5 Hz, H-6b), 1.50 (3H, s, CH_3), 1.35 (3H, s, CH_3), 0.86 (9H, s, CH_3×3), 0.14 (3H, s, CH_3), 0.10 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.1, 133.1, 129.9, 129.6 (C×2), 128.4 (C×2), 108.9, 80.4, 77.9, 73.9, 70.9, 67.2, 65.9, 38.1, 28.2, 26.7, 25.8 (C×3), 18.0, −4.8, −5.0; HRFABMS: cacld for $C_{23}H_{37}O_7Si$ $[M+H]^+$: 453.2303, found 453.2306.

4.1.9. (1*R*,2*R*,3*S*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-3-*O*-*tert*-butyldimethylsilyl- cyclohex-4-ene (3). To a solution of diol **4** (2.0 g, 4.4 mmol) in toluene (100 mL) were added triphenylphosphine (4.6 g, 18.0 mmol), imidazole (1.2 g, 18.0 mmol) and iodine (3.4 g, 13.0 mmol). The mixture was heated under reflux for 4 h. After cooling, the reaction mixture was diluted with EtOAc and washed successively with 10% aqueous sodium thiosulfate solution, saturated $NaHCO_3$ solution, brine and dried ($MgSO_4$). Removal of the solvent and purification of the residue by column chromatography (EtOAc/petroleum ether 1:10) gave olefin **3** (1.6 g, 87%) as colorless oil: $[\alpha]_D^{20}$=+48 (*c* 0.19, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ 8.08 (2H, d, *J*=7.5 Hz), 7.57 (1H, t, *J*=7.5 Hz), 7.44 (2H, t, *J*=7.5 Hz), 5.80–5.90 (2H, m, H-3 and 4), 4.46 (1H, d, *J*=11.4 Hz, H-7a), 4.35–4.43 (1H, m, H-6), 4.27 (1H, d, *J*=11.4 Hz, H-7b), 4.20 (1H, d, *J*=3.3 Hz, H-5), 2.44 (1H, dd, *J*=15.9, 3.3 Hz, H-6a), 2.30 (1H, t, *J*=15.9 Hz, H-6b), 1.42 (3H, s, CH_3), 1.40 (3H, s, CH_3), 0.86 (9H, s, CH_3×3), 0.09 (3H, s, CH_3), 0.08 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.2, 133.0, 130.0, 129.7 (C×2), 129.3, 128.3 (C×2), 126.5, 108.8, 80.8, 79.9, 68.1, 67.9, 32.3, 28.1, 27.1, 25.7 (C×3), 18.2, −4.7, −4.9; HRFABMS: cacld for $C_{23}H_{35}O_5Si$ $[M+H]^+$: 419.2248, found 419.2236.

4.1.10. (1*R*,2*S*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-cyclohex-4-en-3-one (13). A solution of **3** (72.0 mg 0.17 mmol) in dried CH_2Cl_2 was added to a solution of 70% *t*-BuOOH (0.25 mL, 1.8 mmol) and catalytic amount of CrO_3 (1.7 mg, 0.017 mmol) in CH_2Cl_2 (2 mL) under Ar. The reaction mixture was stirred at room temperature for 24 h, and then poured into column chromatography washing with EtOAc. The solvent was removed and the residue was purified by column chromatography (acetone/petroleum ether 1:15), to give enone **13** as a white solid (30 mg, 56%). Mp 43–45 °C, ^{1}H NMR ($CDCl_3$, 300 MHz, *J* in Hz) δ 8.00 (d, 2H, *J*=7.2 Hz), 7.58 (t, 1H, *J*=7.2 Hz), 7.44 (t, 2H, *J*=7.2 Hz), 6.90–7.01 (m, 1H, H-5), 6.24 (td, 1H, *J*=10.5, 2.1 Hz, H-4), 4.40 (d, 1H, *J*=11.4 Hz, H-7a), 4.39 (s, 1H, H-2), 4.34 (d, 1H, H-7b), 2.79–2.87 (m, 2H, H-6), 1.50 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); IR ν_{max}^{KBr} cm^{-1}: 3430, 1720, 1698, 1271, 1113, 714;

4.1.11. (1*R*,2*R*,3*S*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-3-hydroxy-cyclohex-4-ene (14). Tetrabutylammonium fluoride (1.0 M in THF, 14.4 mL, 14.4 mmol) and benzoic acid (2.0 g, 14.4 mmol) were added to the solution of **3** (1.5 g, 3.6 mmol) in dry THF (60 mL). The solution was stirred at room temperature for 24 h, and then

was evaporated under reduced pressure to leave a residue, which was partitioned between water and EtOAc. The organic layer was dried ($MgSO_4$). Removal of the solvent and purification of the residue by column chromatography (acetone/petroleum ether 1:5) gave alcohol **14** (1.0 g, 94%) as colorless oil: $[\alpha]_D^{20}=-4.7$ (*c* 0.32, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz) δ 8.06 (2H, d, *J*=7.5 Hz), 7.53 (1H, t, *J*=7.5 Hz), 7.40 (2H, t, *J*=7.5 Hz), 5.87 (2H, m, H-4 and 5), 4.37–4.43 (1H, m, H-2), 4.39 (1H, d, *J*=11.7 Hz, H-7a), 4.31 (1H, d, *J*=11.7 Hz, H-7b), 4.20 (1H, d, *J*=3.3 Hz, H-3), 2.52 (1H, dd, *J*=17.1, 5.4 Hz, H-6a), 2.29 (1H, d, *J*=17.1 Hz, H-6b), 1.45 (3H, s, CH_3), 1.42 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 147.7, 133.5, 129.7 (C×2), 129.0, 128.5 (C×2), 126.8, 109.2, 81.6, 79.7, 68.4, 67.9, 32.4, 28.3, 27.2; HRFABMS: cacld for $C_{17}H_{20}O_5Na$ $[M+Na]^+$: 327.1203, found 327.1221.

4.1.12. (1*R*,2*R*,3*S*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-3-benzoyloxy-cyclohex-4-ene (15). Benzoyl chloride (0.38 mL, 3.3 mmol) was added dropwise to a solution of alcohol **14** (0.66 g, 2.2 mol) and catalytic amount of DMAP (5 mg, 0.04 mmol) in dry pyridine (20 mL) at room temperature during a period 5 min. Stirring was continued for another 2 h and then saturated aqueous $NaHCO_3$ (10 mL) was added to the reaction mixture to quench the reaction. The mixture was extracted with CH_2Cl_2 (3×10 mL), washed with brine (5 mL) and dried ($MgSO_4$). The solvent was removed and the product was purified by flash chromatography (acetone/petroleum ether 1:5), to yield alcohol **15** (0.88 g, 99%) as colorless oil: $[\alpha]_D^{20}=+114$ (*c* 0.24, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03 (2H, d, *J*=7.5 Hz), 7.96 (2H, d, *J*=7.5 Hz), 7.50–7.57 (2H, m), 7.33–7.50 (4H, m), 6.00–6.07 (2H, m, H-4 and 5), 5.70 (1H, s, H-3), 4.55 (1H, d, *J*=11.7 Hz, H-7a), 4.48–4.52 (1H, m, H-2),4.38 (1H, d, *J*=11.7 Hz, H-7b), 2.43–2.58 (2H, m, H-6), 1.49 (3H, s, CH_3), 1.45 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.2, 165.6, 133.2, 133.1 (C×2), 129.7 (C×4), 129.4 (C×2), 128.5 (C×4), 124.7, 109.4, 79.3, 77.9, 69.4, 67.4, 32.2, 28.0, 27.3; HRFABMS: cacld for $C_{24}H_{25}O_6$ $[M+H]^+$: 409.1646, found 409.1650.

4.1.13. (1*R*,2*R*,3*S*)-1-Benzoyloxymethyl-1,2-*O*,*O*-isopropylidine-3-benzoyloxy-cyclohex-4-en-one (16). A suspension of olefin **15** (0.20 g, 0.49 mmol) and SeO_2 (0.22 g, 2.0 mmol) in dried THF were stirred under reflux for 24 h. After cooling, the reaction mixture was poured into a flash chromatography and washed with EtOAc. The solvent was removed and the product purified by flash chromatography (acetone/petroleum ether 1:10), which yielded enone **16** (83 mg, 40%) as colorless oil: $[\alpha]_D^{20}=+132$ (*c* 0.12, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 2989, 1726, 1691, 1452, 1273, 1093, 860, 710; ^1H NMR ($CDCl_3$, 300 MHz, *J* in Hz) δ 7.94 (2H, d, *J*=7.5 Hz), 7.84 (2H, d, *J*=7.5 Hz), 7.42–7.54 (2H, m), 7.36–7.42 (2H, m), 7.24–7.34 (2H, m), 7.04 (1H, ddd, *J*=1.5, 4.8 Hz, 10.2, H-4), 6.38 (1H, d, *J*=10.2 Hz, H-5), 5.97 (1H, d, *J*=4.05 Hz, H-3), 4.70 (1H, d, *J*=11.4 Hz, H-7a), 4.67–4.69 (1H, m, H-2), 4.62 (1H, d, *J*=11.4 Hz, H-7b), 1.48 (3H, s, CH_3), 1.41 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.5, 165.6, 165.2, 141.4, 133.6, 133.4 (C×2), 130.6 (C×2), 130.3 (C×4), 128.4 (C×4), 110.0, 80.0, 77.7, 66.0, 63.9, 27.4, 26.4; HRFABMS: cacld for $C_{24}H_{23}O_7$ $[M+H]^+$: 423.1438, found 423.1441.

4.1.14. (+)-Zeyleone (1). TFA/H_2O (9:1, v/v, 0.2 mL, 2.2 mmol) was added to the solution of **15** (70 mg, 0.18 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred violently for 6 h. Then, 5 mL 5% aqueous $NaHCO_3$ was added to the reaction mixture and stirred for 5 min. The mixture was extracted with CH_2Cl_2 (3×10 mL), washed with brine (3 mL) and dried ($MgSO_4$). Removal of the solvent and purification of the residue by column chromatography (acetone/petroleum ether 1:5) yielded **1** as white solid (54 mg, 85%). Mp 150–152 °C; $[\alpha]_D^{20}=+118$ (*c* 0.56, $CHCl_3$), $[\alpha]_D^{20}=+26$ (*c* 0.23, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.38 (dd, 1H, *J*=3.3, 1.5 Hz, H-2), 4.59 (d, 1H, *J*=11.4 Hz, H-7a), 4.86 (d, 1H, *J*=11.4 Hz, H-7b), 5.95 (td, 1H, *J*=4.2 Hz, 0.9, H-3), 6.35 (dd, 1H, *J*=10.2, 0.9 Hz, H-5), 6.96 (ddd, 1H, *J*=10.2, 4.2, 0.9 Hz, H-4), two benzoyl groups: δ 7.93–8.06 (m, 4H), 7.53–7.60 (m, 2H), 7.26–7.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 65.5 (C-7), 69.1 (C-3), 71.6 (C-2), 77.2 (C-1), 128.6 (C-5), 142.6 (C-4), 196.2 (C-6), two benzoyl groups: δ 128.4, 128.5, 128.7 (C×2), 129.7 (C×2), 129.8 (C×2), 133.4, 133.7, 165.3, 166.2; IR ν_{max}^{KBr} cm^{-1}: 3421, 1716, 1693, 1271, 1113, 714; EIMS *m/z*: 282, 260, 220, 136, 122, 105, 94; HRMS (TOF): cacld. for $C_{21}H_{19}O_7$ $[M+1]^+$ 383.1125, found 383.1126.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 39970084) and the Chinese Doctoral Grants of the Ministry of Science and Technology of China (No. 96-901-96-54) for financial support.

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Total synthesis of 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl, the proposed structure of a potent antioxidant found in beetroot (*Beta vulgaris*)

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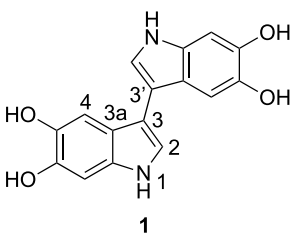
Received 15 December 2003; revised 27 January 2004; accepted 19 February 2004

Abstract—5,5′,6,6′-Tetrahydroxy-3,3′-biindolyl, the proposed structure of a phenolic antioxidant isolated from the red beetroot (*Beta vulgaris*), has been synthesised. The spectroscopic data of the synthetic material is not consistent with that reported for the natural product.

1. Introduction

Interest in phenolic antioxidants found in fruits and vegetables has recently increased[1] due to a possibility[2] that they may provide nutritional benefits.[3] A significant proportion of these compounds have been found to be more powerful antioxidants than vitamins C and E, and β-carotene using an in vitro model for heart disease.[4] The antioxidant activity of phenols is mainly due to their reductive properties, however, they also have the capacity for metal chelation.[5]

Ninety-two different phenol-containing plant extracts were recently screened and beetroot peel was shown to have the second-highest dry weight concentration of total phenols.[1a,6] Structural characterisation of these compounds is necessary in order to rationalise their mode of action. Kujala et al. recently isolated a highly unstable phenolic compound from the peel of the red beetroot (*Beta vulgaris*), and proposed its structure to be 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl **1**[7] (Fig. 1), a dimer of 5,6-dihydroxyindole.



1

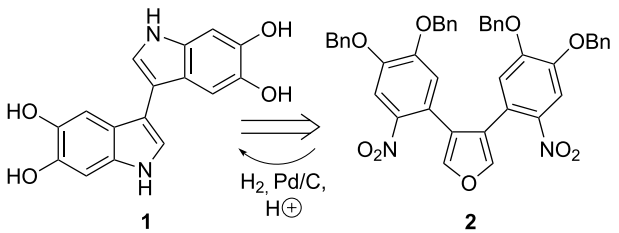
Figure 1. 5,5′,6,6′-Tetrahydroxy-3,3′-biindolyl (**1**).

5,6-Dihydroxyindole is an interesting compound, because it plays a central role in melanogenesis[8] (the process by which eumelanin, a black intractable biopigment, is formed from *L*-3,4-dihydroxyphenylalanine[9]). Extra interest in 5,6-dihydroxyindoles has arisen from the recent recognition of their exceptional radical scavenging and photoprotective abilities,[10] which makes them among the most effective endogenous antioxidants.[11] The corresponding 2,2′-linked isomer of **1** is known,[12,13] and forms under oxidative conditions from the monomer.[13] Unsubstituted 3,3′-bisindole is also known[14] and has been synthesised from unsymmetrical coupling partners, a route that does not take advantage of its symmetry.

2. Results and discussion

2.1. Retrosynthetic analysis

Towards our goal of synthesising 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl **1**, we proposed a short symmetrical synthesis that fully exploits its symmetry. This route features an acid-catalysed reductive cyclisation, dehydration and deprotection in the final step that should be compatible with the oxidative lability of the product (Scheme 1). The



1 **2**

Scheme 1. The proposed reductive cyclisation.

Keywords: Antioxidant; Beetroot; Biindolyl; 5,6-Dihydroxyindole.
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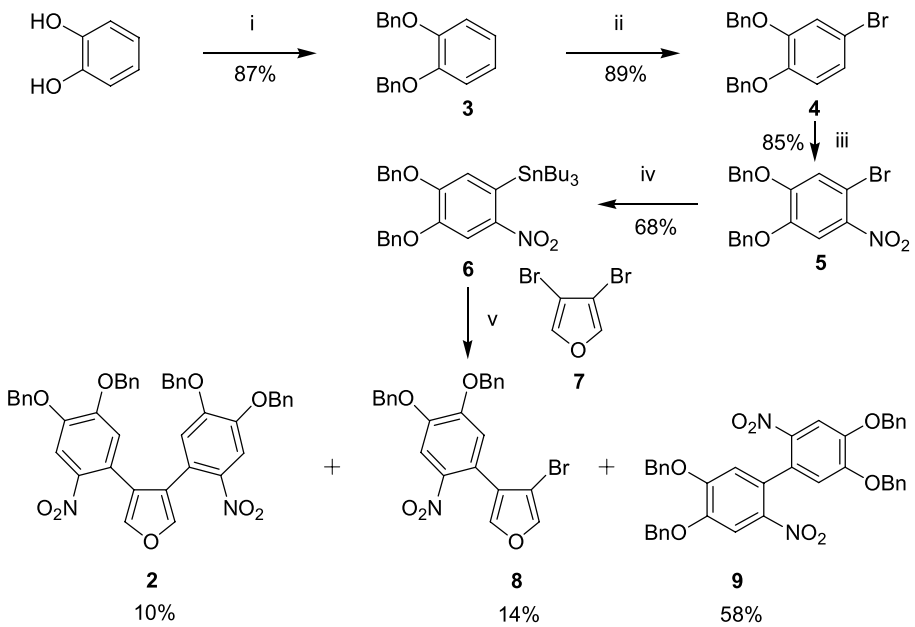
0040–4020/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tet.2004.02.043



Scheme 2. Synthesis of 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)furan (**2**) from catechol. Reagents and conditions: (i) BnCl, K_2CO_3, acetone, 65 °C, 4 days; (ii) NBS, CCl_4, 80 °C, 1 h; (iii) 70% HNO_3, AcOH, rt, 2 h; (iv) Bu_6Sn_2, $Pd(PPh_3)_4$, toluene, 120 °C, 48 h; (v) $Pd(PPh_3)_4$, CuBr, THF, 60 °C, 15 h, 10% of **2**.

3,4-disubstituted furan **2** was envisaged as an accessible, stable surrogate of the required dialdehyde.

2.2. Synthesis of 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)-furan 2

2.2.1. Double Stille coupling using 3,4-dibromofuran 7. Initially we envisaged that **2** could be obtained from a double Stille coupling of 3,4-dibromofuran **7** and 3,4-dibenzyloxy-2-tri-*n*-butylstannylnitrobenzene **6** (Scheme 2).

The preparation of **6** commenced with the reaction of catechol with benzyl chloride and potassium carbonate in acetone, providing 3,4-dibenzyloxybenzene **3** in 87% yield.[15] Bromination with *N*-bromosuccinamide in carbon tetrachloride gave 89% of compound **4**,[15] which was nitrated with 70% nitric acid in 85% yield to afford the *ortho*-substituted aryl bromide **5**.[16] Palladium catalysed tributylstannylation of *ortho*-substituted aryl halides is known to be relatively difficult.[17] However, by employing elevated temperatures and extended reaction times, the *ortho*-substituted tributylstannyl aryl **6** could be formed in 68% yield. The coupling partner, 3,4-dibromofuran **7**, was prepared from (*E*)-2,3-dibromo-2-butene-1,4-diol in 56% yield, using a slight modification of the procedure reported by Rewicki et al.[18]

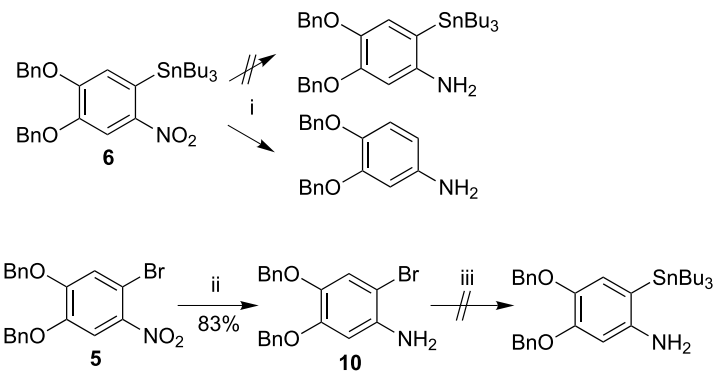
Stille couplings using electron-withdrawing *ortho*-substituted aryl stannanes are rare.[19] To the best of our knowledge there is only one previously published example in which the substituent is a nitro group.[19a] Initial attempts at the double Stille coupling using $Pd(PPh_3)_4$ in dioxane gave no product, with most of the starting materials being recovered. Copper(I) salts have been shown to accelerate Stille reactions,[20] and with the addition of CuBr and THF as the solvent, a small amount of disubstituted furan **2** was isolated in 10% yield together with the monosubstituted furan **8** in 14% yield. In addition 58% of the dimer **9**, which arose from homocoupling of the tin starting material **6**, was obtained from the reaction.

Homocoupling has been observed in Stille reactions[21] and is an oxidative process.[22] Cu(I) alone is also capable of catalysing the reaction, especially when electron withdrawing substituents are present in conjugation with the tin.[23] Rigorous exclusion of oxygen accompanied by the addition of antioxidants, such as 2,6-di-*tert*-butyl-4-methyl phenol, led to no significant reduction of the unwanted product **9**.

Efforts to optimise[24] this reaction by using different catalysts ($Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(dppf)Cl_2$, $Pd(MeCN)_2Cl_2$, $Pd_2(dba)_3$), $Pd_2(dba)_3$ with ligands in different ratios (PPh_3, P(2-furyl)$_3$, $AsPh_3$, dppf, 1,3-bis(diphenylphosphino)-propane), different solvents (toluene, dioxane, THF, NMP, DMF, DMSO), different additives (CuI, CuBr, CuCl, LiCl) and slow addition of the tin starting material **6** led to no improvement. In all cases, especially with highly polar solvents, the major product was 4,4′,5,5′-tetrakisbenzyloxy-2,2′-dinitro-biphenyl **9**. It appears that this unwanted side-reaction is significantly faster than the Stille coupling.

2.3. Initial solutions to the unfavourable double Stille coupling

2.3.1. 3,4-Diiodofuran. In the effort to enhance the desired reaction, synthesis of 3,4-diiodofuran as an alternative starting material was investigated, as iodides tend to be more reactive than bromides in Stille reactions.[24] Three syntheses of 3,4-diiodofuran have previously been reported.[25] The most recent protocol, which involves oxidative cyclisation of (*E*)-2,3-diiodo-2-butene-1,4-diol with chromic acid, could not be reproduced in our hands as decomposition of the starting material occurred before oxidation.[26] The other two procedures were either laborious,[25c] or operationally unfavourable,[25b] so more

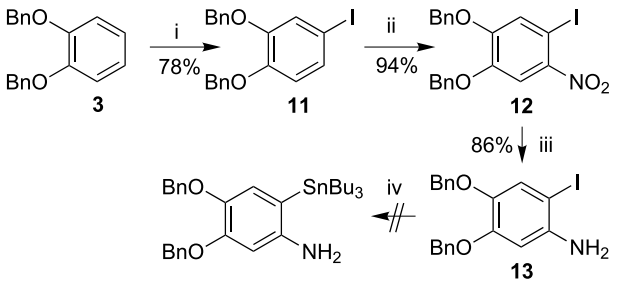


Scheme 3. Attempted synthesis of 4,5-dibenzyloxy-2-tri-*n*-butylstannylaminobenzene. Reagents and conditions: (i) $SnCl_2$, ethyl acetate, MeOH, 70 °C, 1.5 h; or $FeCl_3$, activated carbon, $N_2H_4{\cdot}H_2O$, MeOH, 70 °C, 15 h; (ii) iron powder, HCl (aq.), EtOH, 80 °C, 3 h; (iii) Bu_6Sn_2, $Pd(PPh_3)_4$, toluene, 120 °C, 48 h.

accessible solutions to the double Stille coupling were investigated in preference.

2.3.2. 4,5-Dibenzyloxy-2-tri-*n*-butylstannylaminobenzene. It was anticipated that reduction of the nitro group of 4,5-dibenzyloxy-2-tri-*n*-butylstannylnitrobenzene **6** to an amino group before the Stille coupling could provide two advantages. First, the presence of the mesomerically electron donating amino group might reduce or prevent homocoupling, and second it should make the tin compound more nucleophilic, causing an enhancement of the rate-limiting transmetallation step.[27] However, efforts to reduce the nitro group of arylstannane **6** under different conditions ($SnCl_2$, or $FeCl_3$, hydrazine and activated carbon) resulted in protodestannylation (Scheme 3). To avoid this unfavourable side reaction, we decided that the nitro group should be reduced prior to the introduction of the tributylstannyl group. Thus, the nitro group of arylbromide **5** was reduced with iron powder and hydrochloric acid in 83%.[28]

Unfortunately, 4,5-dibenzyloxy-2-aminobromobenzene **10** did not undergo the desired stannylation reaction, possibly because the mesomeric electron-donating amino group might slow down the oxidative addition step in the catalytic cycle. Next, iodide **13** was prepared in the hope that it would be sufficiently reactive to be stannylated (Scheme 4).



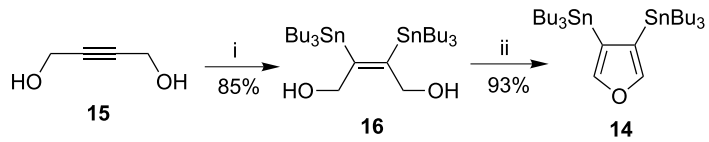
Scheme 4. 4,5-Dibenzyloxy-2-aminoiodobenzene (**13**) from 1,2-dibenzyloxybenzene (**3**). Reagents and conditions: (i) I_2, HgO, DCM, rt, 15 h; (ii) HNO_3 (aq.), AcOH, rt, 2 h; (iii) $FeCl_3$, activated carbon, $N_2H_4{\cdot}H_2O$, MeOH, 70 °C, 8 h; (iv) Bu_6Sn_2, $Pd(PPh_3)_4$, toluene, 120 °C, 48 h.

Iodination of 1,2-dibenzyloxybenzene **3** was most successful using iodine activated by mercury oxide,[29] yielding 78% of 3,4-dibenzyloxyiodobenzene **11**. Nitration of **11** furnished 94% of nitrobenzene **12**, which was reduced using catalytic iron(III) chloride with activated carbon and hydrazine,[30] giving 4,5-dibenzyloxy-2-aminoiodobenzene **13** in 86% yield. Disappointingly, attempts to exchange the iodine with tributyltin using $Pd(PPh_3)_4$ and hexabutylditin proved to be unsuccessful. Significant decomposition of **13** occurred under the reaction conditions.

It became apparent that the best option was to reverse the functional groups in the double Stille coupling. By switching the functional groups, both coupling partners would be electronically favoured—the halide conjugated with an electron withdrawing nitro group and the tin with an electron donating group. Both iodo **12** and bromo **5** versions of the required catechol moiety had already been synthesised, so only 3,4-bis(tri-*n*-butylstannyl)furan needed to be obtained.

2.3.3. 3,4-Bis(tri-*n*-butylstannyl)furan (14). Wong et al. have reported a synthesis of 3,4-bis(tri-*n*-butylstannyl)furan **14**,[31] but because it is operationally unfavourable and low yielding, the use of **14** in our synthesis did not appeal to us initially. Consequently, we developed an improved synthesis of 3,4-bis(tri-*n*-butylstannyl)furan **14** (Scheme 5).[32]

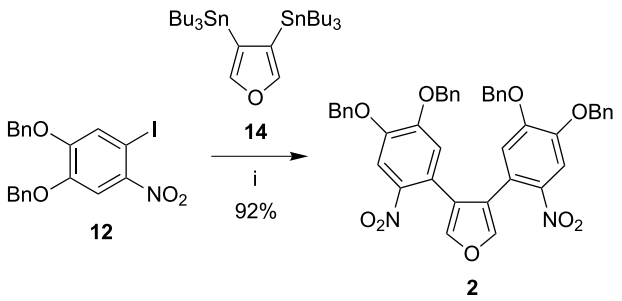
This route to **14** involved palladium catalysed addition of hexa-*n*-butylditin to 2-butyne-1,4-diol **15**, followed by oxidative cyclisation and dehydration of (*Z*)-2,3-bis(tri-*n*-butylstannyl)-2-butene-1,4-diol **16**. This gave the furan **14** in 79% overall yield. With the availability of both **12** and **14**, the coupling reaction was re-investigated.



Scheme 5. An efficient synthesis of 3,4-bis(tri-*n*-butylstannyl)furan. Reagents and conditions: (i) Bu_6Sn_2, $Pd(MeCN)_2Cl_2$, THF, rt, 48 h; (ii) IBX, DMSO, THF, rt, 2 h.

2.4. Double Stille coupling using 3,4-bis(tri-*n*-butylstannyl)furan 14

Reaction of 3,4-bis(tri-*n*-butylstannyl)furan **14** with 4,5-dibenzyloxy-2-nitroiodobenzene **12** using $Pd(PPh_3)_4$ and CuBr in THF (conditions equivalent to those used in earlier attempts), delivered 30% of the disubstituted furan **2** after 15 h. Re-optimising the Stille conditions[24]—$Pd_2(dba)_3$, $AsPh_3$ and CuI in DMF—55% of the product was isolated after 15 h, along with recovered starting material. Investigations into methods of generally accelerating this double coupling, led to the development of a new combination of reagents for the Stille coupling reaction. Initial studies have shown that the presence of cesium fluoride in conjunction with copper(I) iodide, as a co-catalyst to $Pd(PPh_3)_4$ in DMF, produces a large acceleration of the reaction rate. Fluoride sources have been used before in attempts to accelerate the Stille reaction, but not in conjunction with copper(I) salts.[33] Utilising these new conditions, the desired product **2** was isolated in 92% yield after only 2 h at 40 °C (Scheme 6). The scope of this new combination of reagents is reported elsewhere.[34]

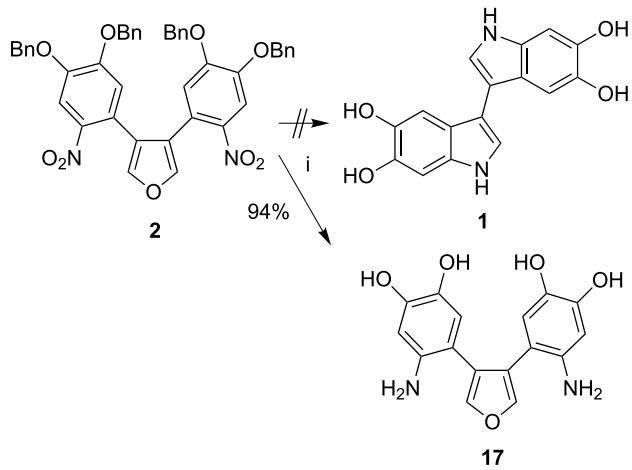


Scheme 6. Successful double Stille coupling. Reagents and conditions: (i) $Pd(PPh_3)_4$, CuI, CsF, DMF, 40 °C, 2 h.

2.5. The reductive cyclisation of 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)furan 2

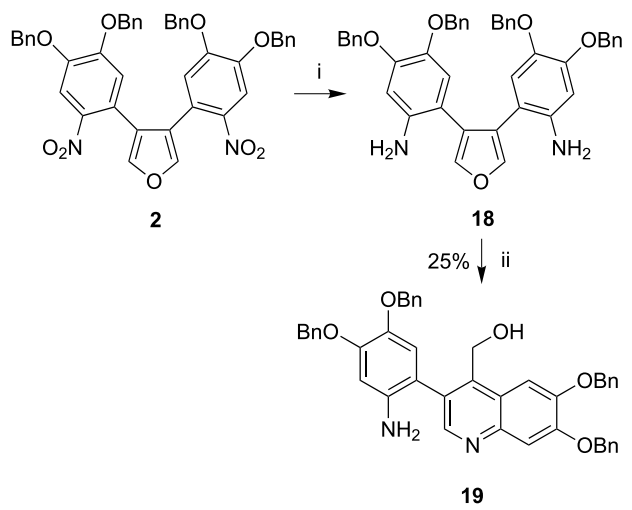
With an effective route to the 3,4-disubstitued furan **2**, the final step (reductive-cyclisation and deprotection) was investigated (Scheme 7).

Unfortunately hydrogenation with palladium on carbon in the presence of acetic acid gave only the deprotected reduced aminophenyl-furan **17** in 94% yield with no evidence of cyclisation. To investigate the conditions required for the desired cyclisation we decided to perform the final three transformations—reduction, cyclisation and deprotection—separately.



Scheme 7. Attempted cyclisation of 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)furan (**2**). Reagents and conditions: (i) H_2, Pd/C, AcOH, THF, rt, 15 h.

Thus, 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)furan **2** was reduced with tin(II) chloride under non-acidic conditions[35] to give 3,4-bis(3,4-dibenzyloxy-2-aminophenyl)furan **18** in 67% yield (Scheme 8). Reduction with iron powder and HCl later proved to give a higher yield of **18**. Cyclisation was then attempted by heating this compound to reflux in benzene with a catalytic amount of *para*-toluenesulfonic acid and powdered molecular sieves for 2 days. However, this afforded 25% of a solid compound that was clearly not the desired product, along with most of the remaining starting material. After detailed analysis of the spectroscopic data (specifically the NOSEY and HMBC spectra), it became apparent that the product was 3-(3,4-dibenzyloxy-2-aminophenyl)-4-(methyl-1-hydroxy)-6,7-dibenzyloxyquinoline **19**.



Scheme 8. Product of the cyclisation. Reagents and conditions: (i) $SnCl_2$, ethyl acetate, MeOH, 70 °C, 1.5 h, 67%; or iron powder, 38% HCl, EtOH, 80 °C, 3 h; (ii) *p*-TSA, benzene, mol. sieves, 85 °C, 2 days.

The structure of this product was not immediately obvious. The proton and HMQC spectra clearly indicated the structure contained a methylene group with two non-equivalent protons (J=12 Hz). So, initially we speculated the presence of stereocenters or ring systems that were not flat, however, none of these proposed structures fitted all the spectroscopic data. Eventually a deductive, stepwise approach, based on NOE interactions and long range proton–carbon correlations provided the correct structure. The absence of a stereocenter or a non-planar ring system led us to suggest that the observed magnetic non-equivalence of the methylene group is a result of restricted rotation around the aryl–aryl bond. If this were the case then one would expect the chiral environment to degenerate with heating, causing the methylene protons to become equivalent. Recording the proton spectra at increased temperatures demonstrates that the chiral environment is in fact temperature dependent, supporting this proposal (the

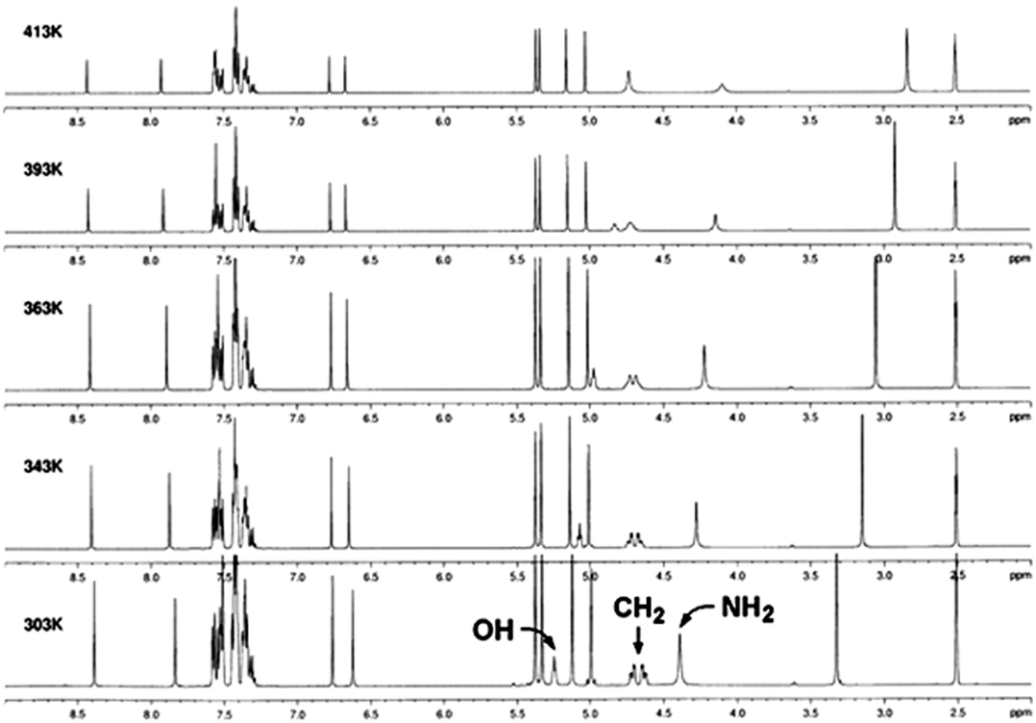
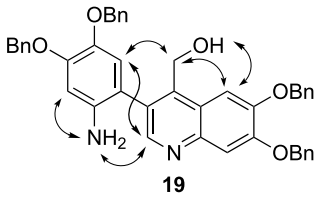


Figure 2. Variable temperature proton spectra of 3-(3,4-dibenzyloxy-2-aminophenyl)-4-(methyl-1-hydroxy)-6,7-dibenzyloxyquinoline (**19**) in DMSO-d_6, showing the methylene protons becoming equivalent.



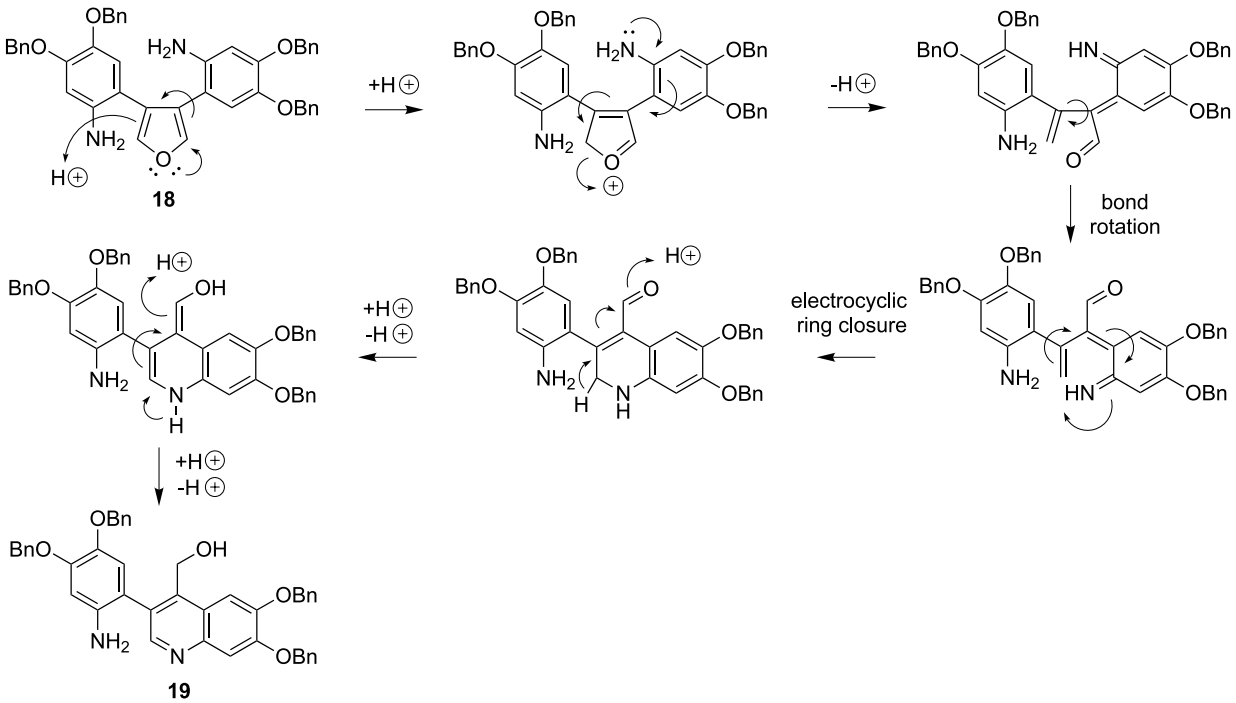
19

Figure 3. NOE interactions in 3-(3,4-dibenzyloxy-2-aminophenyl)-4-(methyl-1-hydroxy)-6,7-dibenzyloxyquinoline (**19**).

hydroxyl and amino peaks shift upfield with increased temperature as well) (Fig. 2).

The observed NOE interactions of **19** are indicated below (Fig. 3).

A possible mechanism that explains the formation of **19** from furan **18**, is for the furan to be protonated at C-3, followed by ring-opening of the furan, which could be



Scheme 9. Possible mechanism for the formation of **19**.

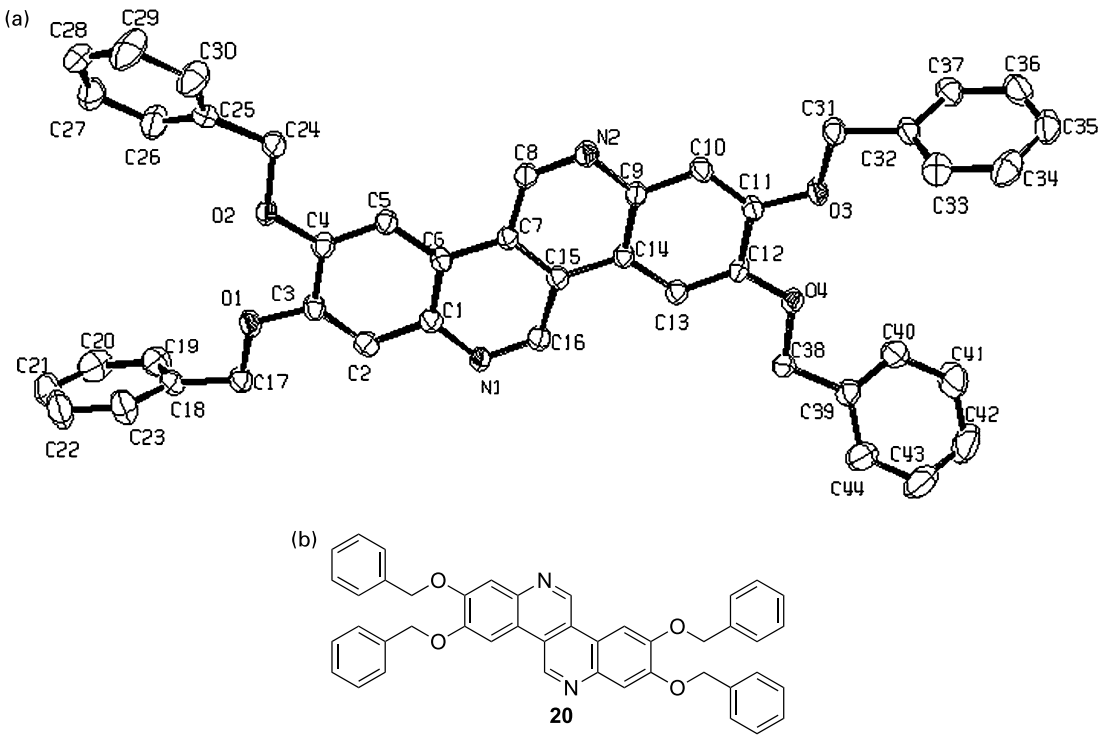


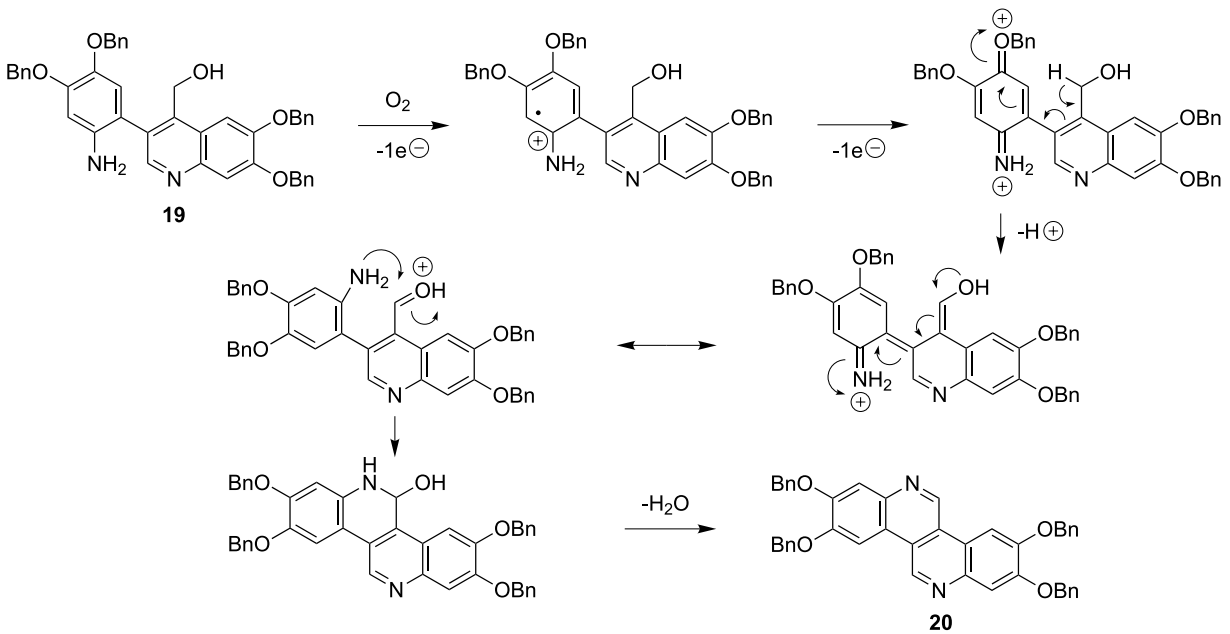
Figure 4. Crystal structure of 2′,2″,3′,3″-tetrakisbenzyloxy-dibenzo[*c*,*h*][2,6]naphthyridine (**20**).

facilitated by the nitrogen's lone pair of electrons. An electrocyclic reaction forms the dihydroquinoline, which aromatises to the quinoline through loss of a proton (Scheme 9).

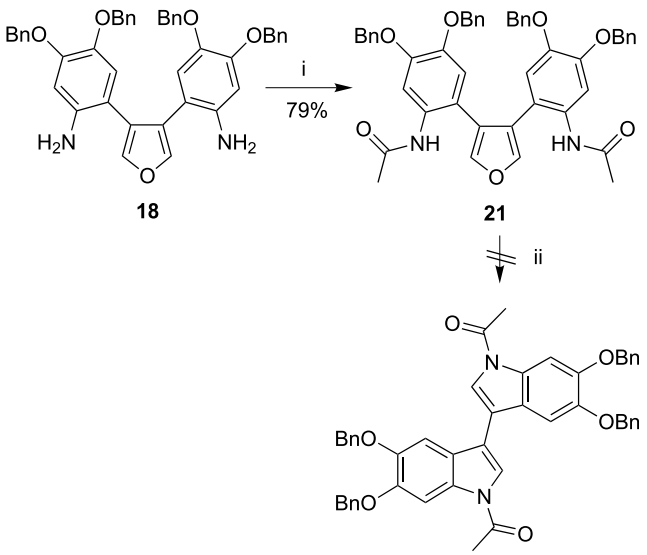
Recrystallisation of **19** did not yield a satisfactory crystal for X-ray diffraction studies, despite a number of attempts. However, we observed the formation of a crystalline material from an aged (3 months) NMR sample of **19** in DMSO-d_6. X-ray diffraction studies of these crystals revealed a symmetrical tetracyclic compound (Fig. 4).

The tetracycle **20** is highly crystalline and is only barely soluble in DMSO-d_6, nonetheless a ^{1}H NMR spectra was obtained and clearly showed that **20** is not the same as the product of the cyclisation reaction, 3-(3,4-dibenzyloxy-2-aminophenyl)-4-(methyl-1-hydroxy)-6,7-dibenzyloxy-quinoline **19**. However, it is reasonable to conclude that the tetracycle **20** was formed from **19** in the solution of DMSO, over a period of 3 months. This transformation would be the result of air oxidation of **19** followed by cyclisation and dehydration (Scheme 10).

The quinoline ring system of **19** is thermodynamically



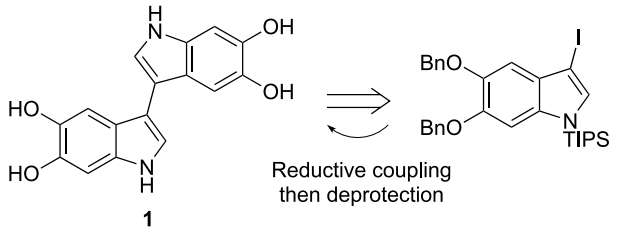
Scheme 10. Oxidation of **19** followed by cyclisation and dehydration would give **20**.



Scheme 11. Attempted cyclisation of the diacylated bisamine **21**. Reagents and conditions: (i) Ac_2O, DMAP, Et_3N, THF, 15 h; (ii) *p*-TSA, xylene, mol. sieves, 140 °C, 4 days.

stable under the reaction conditions and was not in equilibrium with furan **18**. This problem might be circumvented by making the quinoline formation reversible, which could be achieved by acylating the nitrogen, preventing aromatisation. Treatment of diamine **18** with acetic anhydride, *N*,*N*-dimethylaminopyridine (DMAP) and triethylamine in THF overnight, gave 3,4-bis(3,4-dibenzyloxy-2-*N*-acetamidophenyl)furan **21** in 79% yield (Scheme 11).

As before, a solution of **21** and *para*-toluenesulfonic acid in benzene was heated to reflux for 2 days, however, no reaction was observed. Presumably the *N*-acetyl groups were deactivating the nucleophilicity of the nitrogen. Switching to higher boiling xylene as the reaction medium did not lead to any product formation. The starting material **21** was recovered in almost quantitative yield. Other possible solutions to the problem of quinoline formation would detract from the efficiency of the original strategy, so a simple route to the target compound was developed using a reductive biaryl coupling of the monomer (Scheme 12).



Scheme 12. The biaryl coupling approach.

2.6. The reductive biaryl coupling approach

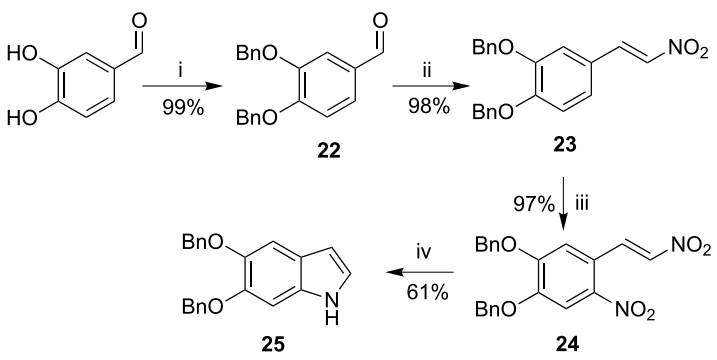
2.6.1. Synthesis of the monomer. The monomer **25** was synthesised using slight modifications of previous reactions (Scheme 13)

Protection of 3,4-dihydroxybenzaldehyde with benzyl chloride and potassium carbonate in DMF provided **22** in 99% yield.[36] The protected benzaldehyde **22** was subjected to a Henry reaction by heating to reflux in acetic acid with nitromethane, producing the nitrostyrene derivative **23** in 98% yield.[37] Nitration using standard conditions gave 97% of dinitrostyrene **24**, which was reductively cyclised to **25** in 61% yield with iron powder in acetic acid. The cyclisation protocol of Borchardt et al. was employed;[38] this includes a non-polar co-solvent like benzene with flash silica. The relatively non-polar starting material and product are maintained in the non-polar solvent, while the silica binds to the polar intermediates, thus minimising the intermolecular reactions involving these intermediates that lead to polymerisation. Although we noticed some improvement in yield over the standard conditions,[38] in our hands the increase was not as dramatic as has been reported elsewhere.[38]

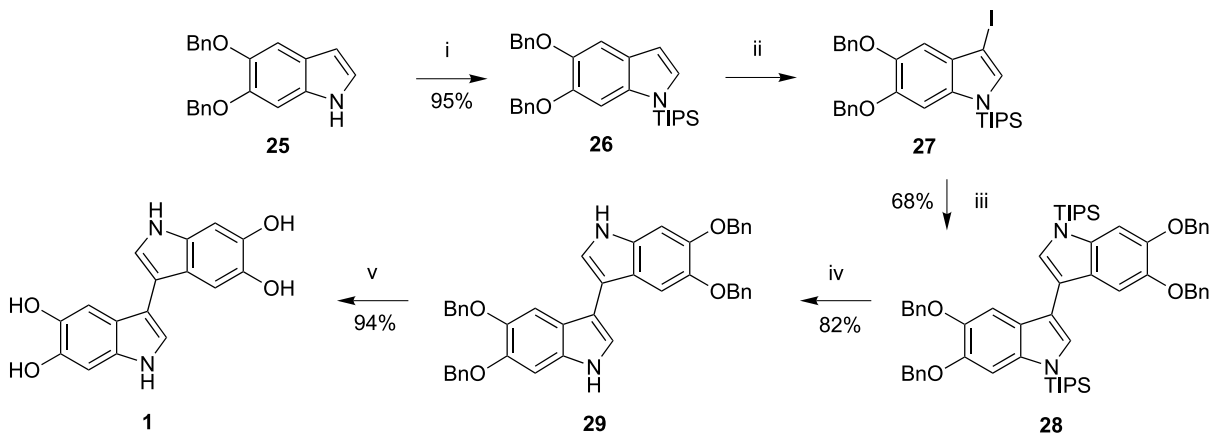
2.6.2. Coupling of the monomer. With the monomer realised, a triisopropylsilyl protecting group was incorporated to sterically direct iodination[39] and stabilise the required iodoindole for the biaryl coupling reaction (Scheme 14)

Deprotonation of indole **25** with *n*-butyllithium followed by addition of triisopropylsilyl chloride gave protected indole **26** in 95% yield. Iodination with mercury acetate and iodine quantitatively yielded the iodoindole **27**.[39] *N*-Iodosuccinimide in THF also afforded **27**, but in a slightly lower yield of 83%. The position of the iodine was confirmed by X-ray crystallography (Fig. 5).

Homocoupling of **27** was initially attempted by formation of the organozinc compound using butyllithium and zinc



Scheme 13. Synthesis of 5,6-dibenzyloxyindole (**25**). Reagents and conditions: (i) BnCl, K_2CO_3, DMF, 120 °C, 15 h; (ii) $MeNO_2$, NH_4OAc, AcOH, 120 °C, 40 min; (iii) 70% HNO_3, AcOH, rt, 2 h; (iv) iron powder, AcOH, benzene, cyclohexane, SiO_2, 120 °C, 30 min.



Scheme 14. Coupling and deprotection. Reagents and conditions: (i) *n*BuLi, THF, −78 °C, 15 min, then TIPSCl, −78 °C, 2 h; (ii) I_2, $Hg(OAc)_2$, DCM, 0 °C, 2 h, 100%; or NIS, THF, rt, 20 min, 83%; (iii) $Pd(PhCN)_2Cl_2$, TDAE, DMF, 50 °C, 1.5 h; (iv) TBAF, THF, rt, 10 min; (v) H_2, Pd Black, THF, 18 h.

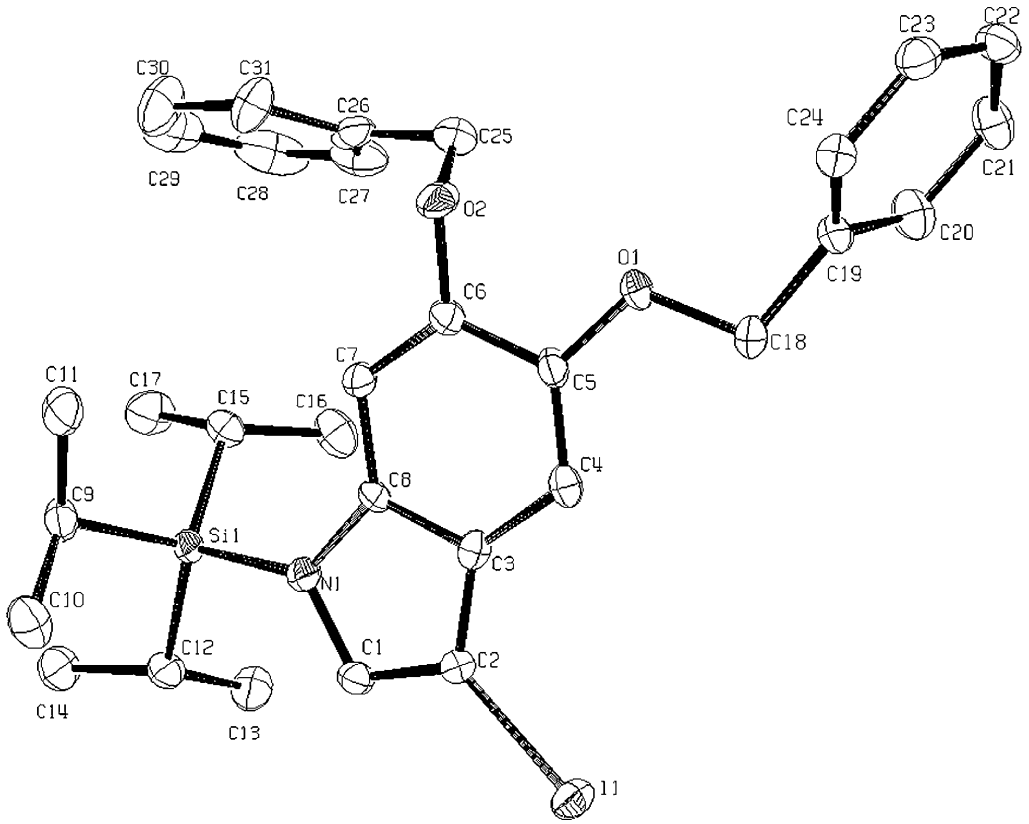


Figure 5. Crystal structure of 5,6-dibenzyloxy-3-iodo-*N*-triisopropylsilylindole (**27**).

chloride, followed by treatment with copper(I) salts.[40] However, reduction of the protected iodoindole **27** to the protected indole **26** was the main reaction. An alternative method for biaryl coupling was investigated using a Grignard reagent and catalytic palladium.[41] Formation of the Grignard reagent by treatment of **27** with ^{i}PrMgCl, was followed by the addition of a solution of **27** and $Pd(dppf)_2Cl_2$. This time the coupled product **28** was formed in 19% yield, but again the main product was indole **26**. Eventually, the coupling was achieved in 68% using catalytic $Pd(PhCN)_2Cl_2$ and the mild reductant tetrakis(dimethylamino)ethylene (TDAE).[42] Desilylation of **28** with tetrabutylammonium fluoride (TBAF) afforded 82% of the benzyl protected bisindole **29**. X-ray diffraction studies showed indeed the desired product **29** was obtained in the coupling reaction (Fig. 6).

Finally, hydrogenation with catalytic Palladium Black in THF revealed 5,5′,6,6′-tetrahydroxy-3,3′-bisindole **1** in 94% yield, the proposed structure of the natural product isolated from beetroot.

2.7. Spectroscopic analysis of 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl 1

The spectroscopic data we obtained from 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl **1** showed subtle differences to the data recorded from the natural product. A plausible

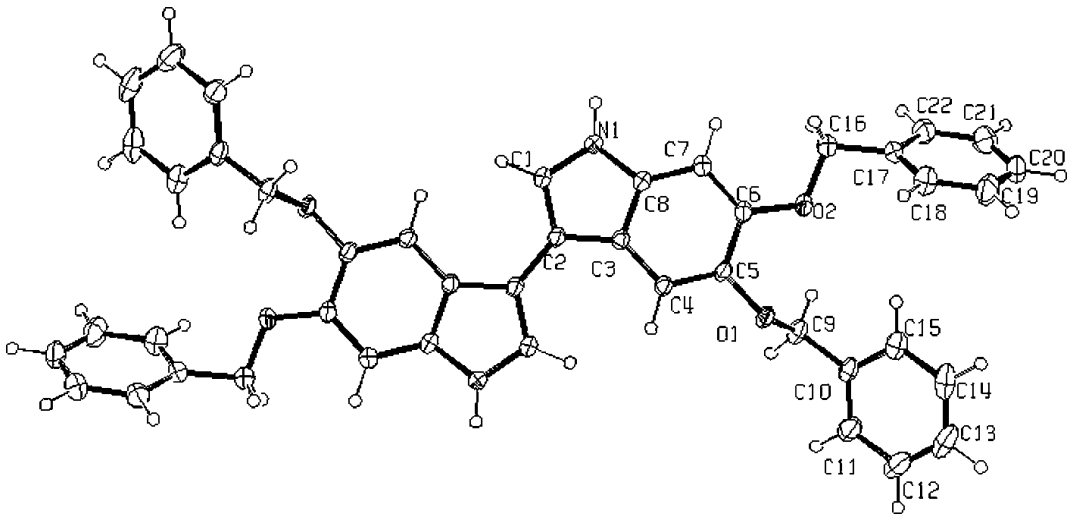


Figure 6. Crystal structure of 5,5′,6,6′-tetrabenzyloxy-3,3′-biindolyl (**29**).

alternative structure for the natural product is not immediately obvious, and so it remains inconclusive as to whether or not the natural product is 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl **1**.

2.7.1. Mass spectrometry. The high resolution mass spectrum of synthetic 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl **1** was obtained under electrospray (ES^-, CV −30) conditions and gave the parent ion as *m/z* 295.0717, $M-H^+$ requires *m/z* 295.0719. High resolution mass measurements on the natural product have only been obtained for fragments corresponding to the monomer.[7] The parent ion apparently was not forthcoming, although on occasion ESI^+ and ESI^- gave peaks at *m/z* 297 and 295, respectively.

2.7.2. UV spectroscopy. The ultraviolet spectrum of **1** in water showed one λ_{max} at 302 nm, while the spectrum recorded for the natural product showed two λ_{max} at 304 and 278 nm.

2.7.3. ^{1}H NMR. The ^{1}H NMR spectrum of **1** in D_2O showed three signals, but at different chemical shifts to those reported for the natural product in D_2O (Table 1).

Table 1. Comparison of ^{1}H NMR data from compound **1** and from the natural product

δ_H Compound **1**[a]	Assignment[b]	δ_H Natural product[c]	Assignment[c]
6.94 (d, *J*=0.3 Hz)	H7, 7′	7.03 (d, *J*=0.3 Hz)	H7, 7′
7.13 (d, *J*=0.3 Hz)	H4, 4′	7.12 (d, *J*=0.3 Hz)	H4, 4′
7.32 (s)	H2, 2′	7.22 (s)	H2, 2′

[a] Spectra recorded in D_2O at 500 MHz.
[b] Assigned with the help of HMBC and HMQC experiments.
[c] Taken from Ref. 7.

2.7.4. ^{13}C and HMBC NMR. 5,5′,6,6′-Tetrahydroxy-3,3′-biindolyl **1** does not dissolve in D_2O sufficiently to allow the preparation of an adequate sample for ^{13}C analysis (4000 scans at 500 MHz gave no signals). The natural product, however, is sufficiently soluble in D_2O to give clear ^{13}C signals. To prepare a sample of **1** in D_2O for ^{13}C analysis, it was necessary to add the D_2O before all the reaction solvent (THF) had been removed during work up (see Section 4). Differences are apparent between the ^{13}C spectra of **1** and the natural product (Table 2).

Table 2. Comparison of ^{13}C NMR data from compound **1** and from the natural product

δ_C Compound **1**[a]	Assignment[b]	δ_C Natural product[c]	Assignment[c]
98.48	C7, 7′	101.00	C7, 7′
105.19	C4, 4′	103.11	C3, 3′
109.10	C3, 3′	108.54	C4, 4′
119.50	C3a, 3a′	123.75	C3a, 3a′
121.20	C2, 2′	127.47	C2, 2′
131.57	C7a, 7a′	133.61	C7a, 7a′
139.76	C5, 5′	142.11	C5, 5′
142.21	C6, 6′	144.37	C6, 6′

[a] Spectra recorded in D_2O at 125.8 MHz.
[b] Assigned with the help of HMBC and HMQC experiments.
[c] Taken from Ref. 7.

In particular the peak assigned as C-3 (109.10 ppm) is clearly observed in the spectrum of **1**, but barely shows up in the natural product spectrum. It is evidently there in the natural product because it gives a correlation in the HMBC spectrum (Fig. 7).

Kujala et al. explain that the virtual absence of the C-3 peak in the ^{13}C spectrum is due to an extremely long relaxation time. Because the reported recycle time of the ^{13}C experiment was 3.8 s, we propose instead that the signal was not detected due to broadening under the conditions of the NMR experiment. The HMBC of **1** showed a very similar pattern to the natural product. However, the synthetic compound shows a strong correlation between H4 and C3, where the natural product does not. Furthermore, the correlations from H4 to C5, H7 to C6 and H7 to C7a do not disappear at higher thresholds, as they do in the spectrum of the natural product.[7] There is a difference between the optimised coupling constants in the two HMBC spectra (7.1 Hz for compound **1** vs 8.0 Hz for the natural product), but the difference would seem to be too small to explain the differences in the correlations outlined above. This is because a correlation is strong when its coupling constant is close to the optimised coupling constant used in

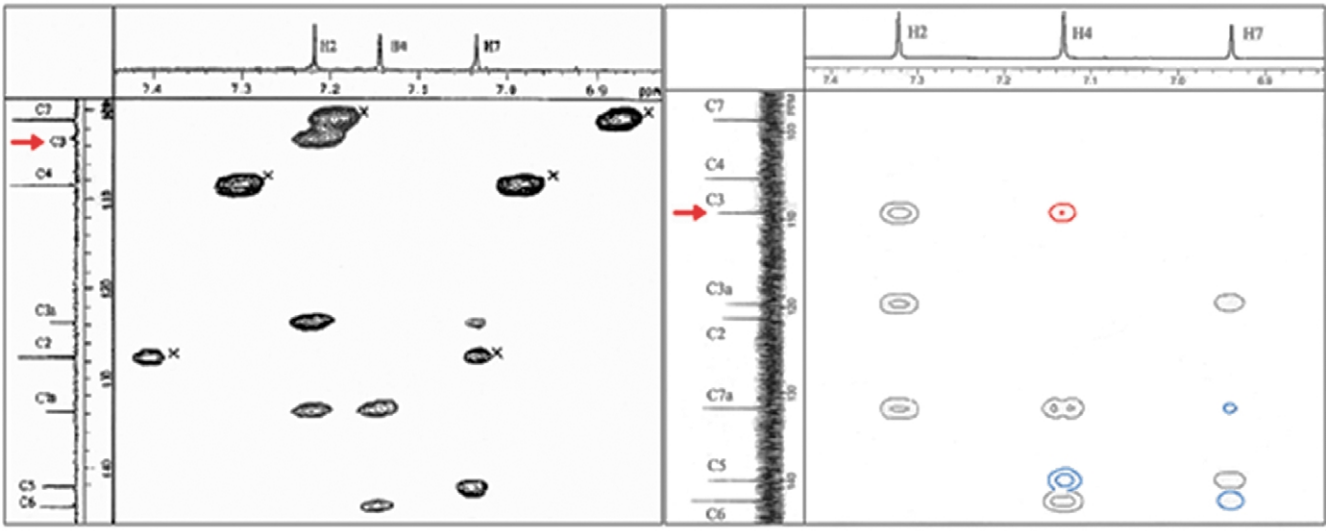


Figure 7. Comparision of HMBC spectra from the natural product (left) and from compound **1** (right). The correlations in the natural product spectrum marked with a cross are unsuppressed one-bond couplings.

the HMBC experiment, so the strong correlation seen in the HMBC of **1** between H4 and C3 will have a coupling constant near our optimised coupling constant of 8.0 Hz. Thus, it would be expected to be observed in an HMBC experiment with a similar optimised coupling constant of 7.1 Hz.

2.7.5. ^{1}H NMR and UV under different conditions. Because an alternative structure for the natural product is not immediately obvious, the possibility that the differences in the spectra are due to other reasons was explored. The ^{1}H NMR spectrum and the UV spectrum of **1** were recorded under a variety of different conditions.

2.7.6. ^{1}H NMR under different conditions. As a measure of the differences in the proton NMR spectrum, the three signals from the natural product have an overall spread of ca. 0.2 ppm, while the three signals from **1** have an overall spread of ca. 0.4 ppm. Under acidic or basic conditions (achieved by the addition of various amounts of formic acid—used in the isolation of the natural product—or sodium hydroxide, respectively), more concentrated conditions, doping with MeCN (also used in the isolation procedure), and recording spectra in deuterated methanol or deuterated DMSO, the overall spread of the three signals from **1** remained at ca. 0.4 ppm. Although, not surprisingly, the signals shifted along the spectrum slightly when the conditions were varied.

2.7.7. UV spectrum under different conditions. The natural product gives two λ_{max} at 304 and 278 nm. Under neutral conditions 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl **1** gives one λ_{max} at 302 nm. This λ_{max} shifted to 300 nm in 0.1% formic acid solution and to 324 nm in 0.1% sodium hydroxide solution. There was no appearance of the second reported λ_{max} at 278 nm even when the concentration of acid or base was increased.

2.7.8. Oxidation studies. As the differences between in the spectral data of **1** and the natural product persisted despite the variations in pH, concentration and solvent, we speculated that the natural compound might possibly be an oxidation product of 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl **1**. The ^{1}H NMR and UV spectrum of **1** was recorded every few hours over a period of 24 h. The three signals in the proton NMR spectrum decreased in intensity, but there was no appearance of signals corresponding to the natural product. The UV spectrum also decreased in intensity with no appearance of the reported λ_{max} at 278 nm. To preclude the possibility that the oxidation product that forms might decompose before accumulating to a detectable level, a sample of **1** was oxidised with H_2O_2. The signals slowly disappeared and a black precipitate was formed over a period of 1 h with no transient intermediate observed by either ^{1}H NMR or UV. Oxidation with 1 equiv. of dichlorodicyanoquinone (DDQ) in deuterated acetonitrile immediately gave a black precipitate.

3. Conclusion

There are clear spectroscopic differences between the natural product and 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl **1**. Varying the conditions of data collection for **1** did not resolve these differences. Oxidation of **1** gave a black precipitate and no transient intermediate corresponding to the natural product. These observations seem to suggest that the natural product is unlikely to be 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl **1**. However, there are no obvious alternative structures that are plausible. It is difficult to interpret the HMBC spectrum from the natural product without resorting to a 3,5,6-trisubstituted indole or benzofuran nucleus; however, a benzofuran structural isomer seems biogenetically less likely. The 5,5′- or 6,6′-linked bisindole isomers require a 3-hydroxy group, but these compounds would most likely exist in the keto-form ($K_{enol}(H_2O)$ for indoxyl is 0.086).[43] Thus without further investigation it remains unclear whether or not the natural product is 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl **1**.

4. Experimental

4.1. General experimental

Proton magnetic resonance spectra were recorded on a Brüker DPX200 (200 MHz), Brüker DPX400 (400 MHz), Brüker AMX500 (500 MHz) and Brüker DPX500 (500 MHz) spectrometers at ambient temperatures. Proton spectra assignments are supported by $^1H-^1H$ COSY where necessary. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced according to IUPAC recommendations, 2001.[44] Coupling constants (J) are recorded to the nearest 0.5 Hz.

Carbon magnetic resonance spectra were recorded on Brüker DPX200 (50.3 MHz), Brüker DPX400 (100.6 MHz), Brüker AMX500 (125.8 MHz) and Brüker DPX500 (125.8 MHz), spectrometers at ambient temperatures. Chemical shifts (δ_C) are reported in parts per million (ppm) and are referenced according to IUPAC recommendations, 2001.[44] Carbon spectra assignments are supported by DEPT analysis and $^{13}C-^1H$ correlations were necessary.

Low resolution mass spectra were recorded using a TRIO-1 GCMS spectrometer, a Micromass Platform (APCI) Spectrometer, Micromass Autospec spectrometer (CI^+) and a micromass ZAB spectrometer (CI^+, EI). Only molecular ions (M^+), fragments from molecular ions and other major peaks are reported. High-resolution mass spectra were recorded on a Micromass Autospec spectrometer and are accurate to ± 10 ppm.

Microanalyses were carried out by Elemental Microanalysis Limited, and are quoted to the nearest 0.1% for all elements except hydrogen, which is quoted to the nearest 0.05%.

Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer as a thin film between NaCl plates, or as KBr discs. Absorption maxima (ν_{max}) of the major peaks are reported in wavenumbers (cm^{-1}).

Ultraviolet spectra were recorded on a Perkin–Elmer Lambda 2 UV/VIS spectrometer in ethanol or water as indicated at ambient temperature. Absorption maxima (ν_{max}) are reported in nanometers (nm) and extinction coefficients (ε) are quoted to four significant figures.

Melting points were measured using a Cambridge Instruments Gallen™ III hot stage melting point apparatus and are uncorrected.

Thin layer chromatography (TLC) was performed using Merck aluminium foil backed plates pre-coated with silica gel 60 F_{254} (1.05554). Visualisation was affected by quenching of UV fluorescence (λ_{max}=254 nm), staining with phosphomolybdic acid in ethanol, followed by heating. Retention factors (R_f) are reported to two decimal places.

Column chromatography was performed using ICN silica 32–63, 60 Å.

Anhydrous tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl under nitrogen and anhydrous dichloromethane (DCM) was distilled from calcium hydride under nitrogen. PE refers to the fraction of light petroleum ether boiling between 40 and 60 °C, and was distilled before use. Triethylamine, dimethyl formamide (DMF), dimethyl sulfoxide and *N*-methylpyrrolidine (NMP) were distilled from calcium hydride under argon or reduced pressure and stored over 4 Å molecular sieves under argon until used. Toluene was dried over 4 Å molecular sieves under argon. All water used was distilled except where otherwise indicated. Solvents were evaporated on a Büchi R110 Rotavaporator.

4.2. Experimental procedure

4.2.1. 1,2-Dibenzyloxybenzene (3). A mixture of catechol (10.0 g, 90.8 mmol), anhydrous K_2CO_3 (38.0 g, 272.5 mmol) and benzyl chloride (31.0 mL, 269.4 mmol) was stirred rapidly in acetone (140 mL) and heated to reflux under argon for 4 days. The mixture was filtered and the solvent removed under reduced pressure. The residue was dissolved in DCM (200 mL) and refiltered, then the solvent was removed under reduced pressure. Recrystallisation from DCM/PE gave **3** (22.9 g, 87%). A small amount was further purified by column chromatography (PE/EtOAc, 9:1) to give a white solid. R_f 0.29 (PE/EtOAc, 9:1); mp 58–59 °C, lit.[15] 58–59 °C; δ_H (400 MHz, $CDCl_3$) 5.24 (4H, s, CH_2 of Bn), 6.95–7.00 (2H, m, H4, 5), 7.02–7.06 (2H, m, H3, 6), 7.36–7.57 (10H, m, C*H* of Bn).

4.2.2. 3,4-Dibenzyloxybromobenzene (4). To a solution of 1,2-dibenzyloxybenzene **3** (10.0 g, 34.4 mmol) in CCl_4 (35 mL) was added NBS (7.4 g, 41.6 mmol). After initiating of the reaction by heating, the heat was removed. The reaction boiled vigorously for 5–10 min without heating. After the reaction subsided, the solution was heated to reflux for 1 h, then diluted with DCM (50 mL), washed with water (100 mL), 1 M NaOH (50 mL) and again with water (100 mL). The organic layer was dried over Na_2SO_4 and $MgSO_4$, and the solvent removed. The residue was recrystallised from DCM/MeOH to give **4** (11.3 g, 89%). A small amount was further purified by column chromatography (PE/EtOAc, 9:1) to give a white solid. R_f 0.32 (PE/EtOAc, 9:1); mp 62–63 °C, lit.[15] 64–66 °C; m/z 386.0756, found 386.0753; microanalysis requires C 65.05, H 4.64, found C 65.08, H 4.59; δ_H (400 MHz, $CDCl_3$) 5.15, (2H, s, CH_2 of Bn), 5.16 (2H, s, CH_2 of Bn), 6.83 (1H, d, J=8.5 Hz, H5), 7.04 (1H, dd, J_1=8.5 Hz, J_2=2.5 Hz, H6), 7.12 (1H, d, J=2.5 Hz, H2), 7.33–7.50 (10H, m, C*H* of Bn).

4.2.3. 4,5-Dibenzyloxy-2-nitrobromobenzene (5). 3,4-Dibenzyloxybromobenzene **4** (9.0 g, 24.4 mmol) was dissolved in hot glacial acetic acid (120 mL). The solution was cooled to 35 °C and 70% HNO_3 (7.0 mL, 110.4 mmol) was added over 5 min. A yellow solid was precipitated and the mixture was stirred at room temperature for 2 h. Water (200 mL) was added and the yellow solid collected was dissolved in DCM then washed with K_2CO_3 solution until the aqueous layer remained basic. The organic layer was dried over $Na_2SO_4/MgSO_4$, and the solvent was removed under reduced pressure. The residue was recrystallised from DCM/MeOH to give **5** (8.6 g, 85%). A small amount was further purified by column chromatography (PE/EtOAc, 6:1) to give a pale yellow solid. R_f 0.26 (PE/EtOAc, 6:1);

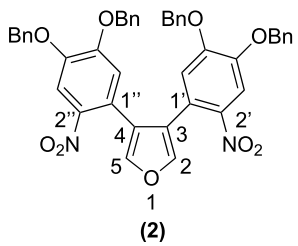
mp 104–105 °C, lit.[16] 105–107 °C; δ_H (400 MHz, $CDCl_3$) 5.18, (2H, s, CH_2 of Bn), 5.21 (2H, s, CH_2 of Bn), 7.20 (1H, s, H6), 7.33–7.47 (10H, m, C*H* of Bn), 7.65 (1H, s, H-3).

4.2.4. 4,5-Dibenzyloxy-2-tri-*n*-butylstannylnitrobenzene (6). A solution of 4,5-dibenzyloxy-2-nitrobromobenzene **5** (2.00 g, 4.83 mmol), Bu_6Sn_2 (3.60 mL, 7.15 mmol) and $Pd(PPh_3)_4$ (0.28 g, 0.24 mol) was heated to reflux in toluene (10 mL) under argon for 48 h. The cooled solution was stirred vigorously with saturated KF solution (10 mL) for 1 h, and then filtered through celite with DCM (100 mL) washings. The filtrate was washed with water (50 mL) and dried over $Na_2SO_4/MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (PE/EtOAc, 9:1) to give **6** (2.05 g, 68%) as a yellow oil. R_f 0.46 (PE/EtOAc, 9:1); ν_{max}/cm^{-1} (thin film) 2955 (s), 2921 (s), 2870 (s), 2852 (s), 1564 (m), 1515 (s, NO_2 str), 1454 (m), 1321 (m, NO_2 str), 1272 (s), 1205 (m), 1021 (s), 735 (m), 696 (m); *m/z* probe ES+ ($M(^{118}Sn)H^+-C_4H_{10}$) 565.8 (100%), 278.4 (65%), HRMS ($M(^{118}Sn)H^+-C_4H_{10}$) requires *m/z* 566.1504, found 566.1519; δ_H (400 MHz, $CDCl_3$) 0.91 (9H, t, J_1=7.5 Hz, CH_3), 1.00–1.20 (6H, m, SnCH_2), 1.27–1.39 (6H, sextet, J_1=7.5 Hz, CH_2CH$_3$), 1.39–1.60 (6H, m, CH_2CH$_2$CH$_3$), 5.25, (2H, s, CH_2 of Bn), 5.33 (2H, s, CH_2 of Bn), 7.08 (1H, s, H3), 7.33–7.54 (10H, m, C*H* of Bn), 8.02 (1H, s, H6); δ_C (100.6 MHz, $CDCl_3$) 11.06 (Sn*C*H$_2$), 13.71 (*C*H$_3$), 27.32, (*C*H$_2$CH$_3$), 29.06, (*C*H$_2$CH$_2$CH$_3$), 70.97 and 71.10 (*C*H$_2$ of Bn), 110.1 (C6), 120.3 (C3), 127.0, 127.4, 128.2, 128.2, 128.4, 128.7 and 128.7 (*C*H of Bn), 133.9 (quat. *C*), 136.2 and 136.2 (*ipso* of Bn), 146.6, 148.6 and 153.2 (quat. *C*).

4.2.5. 3,4-Dibromofuran (7).[15] (*E*)-2,3-Dibromo-2-butene-1,4-diol (20.0 g, 81.3 mmol) and 7% H_2SO_4 (50 mL) was added to a flask with distillation apparatus attached. The mixture was rapidly stirred at 110 °C to begin distillation. A solution of $K_2Cr_2O_7$ (25.1 g, 85.4 mmol) and H_2SO_4 (16.1 mL, 300.4 mmol) in water (160 mL) was then added over 1 h using a dropping funnel while distillation continued. After the chromic acid solution had been added, the mixture was further distilled for one more hour. The product was extracted from the distillate with PE (2×100 mL) and the organic layers were washed with sat. Na_2CO_3 solution, dried over $Na_2SO_4/MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (PE) gave **7** (10.3 g 56%) as a colourless liquid. R_f 0.46 (PE); ν_{max}/cm^{-1} (thin film) 3150 (m), 1795 (w), 1639 (w), 1543 (m), 1330 (m), 1215 (m), 1140 (m) 1037 (m), 972 (s), 865 (s), 783 (s), 589 (s); *m/z* probe CI+ ($M(^{79,79}Br)^{\cdot+}$) 223.9, HRMS ($M(^{79,79}Br)^{\cdot+}$) requires *m/z* 223.8472, found 223.8483; δ_H (200 MHz, $CDCl_3$) 7.46 (2H, s, H2, 5); δ_C (50.3 MHz, $CDCl_3$) 104.0 (C3, 4), 141.6 (C2, 5).

4.2.6. 3,4-Bis(3,4-dibenzyloxy-2-nitrophenyl)furan (2). *Method A*. A solution of 3,4-dibromofuran **7** (0.100 g, 0.443 mmol), 4,5-dibenzyloxy-2-tri-*n*-butylstannylnitrobenzene **6** (0.829 g, 1.328 mmol), CuBr (13 mg, 0.089 mmol) and $Pd(PPh_3)_4$ (0.102 g, 0.089 mmol) in THF 5 mL was stirred at 40 °C under argon for 15 h. The mixture was diluted with DCM (50 mL) and water (50 mL) then filtered through celite. The organic layer was dried over $Na_2SO_4/MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (DCM/PE, 7:3) to give **2** (33 mg, 10%) as a pale orange solid. Also isolated from the reaction was 3-bromo-4-(3,4-dibenzyloxy-2-nitrophenyl)furan (**8**) (0.030 g, 14%) as a pale orange solid and 4,4′,5,5′-tetrakisbenzyloxy-2,2′-dinitro-biphenyl (**9**) (0.258 g, 58%) as a yellow solid.

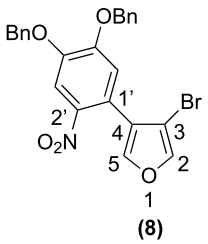
Method B. A solution of 3,4-bis(tri-*n*-butylstannyl)furan **14** (1.00 g, 1.55 mmol), 4,5-dibenzyloxy-2-nitroiodobenzene **12** (1.57 g, 3.40 mmol) and CsF (1.06 g, 7.00 mmol) in DMF (20 mL) was sonicated for a few minutes. CuI (0.29 g, 1.52 mmol) and $Pd(PPh_3)_4$ (0.36 g, 0.31 mmol) were added and the mixture was stirred at 40 °C under argon for 2 h. The mixture was diluted with DCM (50 mL) and water (50 mL) then filtered through celite. The organic layer was dried over $Na_2SO_4/MgSO_4$ and the solvent removed. The residue was purified by column chromatography (DCM/PE, 7:3) to give **2** (1.05 g, 92%) as a pale orange solid. R_f 0.44 (DCM/PE, 7:3); mp 55.5–56 °C; ν_{max}/cm^{-1} (KBr) 3089 (w), 3063 (w), 3031 (w), 2931 (w), 2867 (w), 1573 (m), 1519 (s, NO_2 str), 1454 (m), 1342 (s, NO_2 str), 1280 (s), 1203 (m), 1086 (m), 1023 (m), 868 (m), 738 (m), 696 (m); λ_{max} (EtOH) 245 (ε 10,390), 290 (ε 5200), 340 (ε 3780); *m/z* probe (MNH_4^+) 752.3 (100%), 702.2 (33%), HRMS (MNH_4^+) requires *m/z* 752.2608, found 752.2612; δ_H (400 MHz, $CDCl_3$) 5.15, (4H, s, CH_2 of Bn), 5.17 (4H, s, CH_2 of Bn), 6.87 (2H, s, H6′, 6″), 7.30–7.53 (24H, m, H2, H5, H3′, H3″, C*H* of Bn); δ_C (100.6 MHz, $CDCl_3$) 71.1 and 71.4 (*C*H$_2$ of Bn), 110.4 (C3′, 3″), 117.0 (C6′, 6″), 120.8 and 123.7 (quat. *C*), 127.2, 127.3, 127.4, 127.5, 128.2, 128.2, 128.3, 128.6 and 128.(*C*H of Bn), 135.7 and 135.9 (*ipso* of Bn), 140.0 (C2, 5), 141.6, 147.9 and 152.3 (quat. *C*) (Fig. 8).



(2)

Figure 8.

4.2.7. 3-Bromo-4-(3,4-dibenzyloxy-2-nitrophenyl)furan (8). R_f 0.30 (DCM/PE, 6:4); mp 108–109 °C; ν_{max}/cm^{-1} (KBr) 3147 (w), 3033 (w), 2921 (w), 1588 (m), 1514 (s, NO_2 str), 1452 (m), 1330 (s, NO_2 str), 1292 (s), 1270 (s), 1222 (s), 1063 (s), 1044 (s), 1007 (m), 872 (s), 812 (m), 734 (s), 695 (s), 591 (m); *m/z* probe CI+ (MH^+) 480.1 (50%), 452.1 (15%), 353.2 (20%), 336.1 (25%), 279.1 (100%), 263.1 (35%), 108.1 (53%), 91.0 (72%), HRMS (MH^+) requires *m/z* 480.0447, found 480.0454; δ_H (400 MHz, $CDCl_3$) 5.25, (2H, s, CH_2 of Bn), 5.26 (2H, s, CH_2 of Bn), 6.85 (1H, s, H6′), 7.33–7.52 (12H, m, H2, H5, C*H* of Bn), 7.77 (1H, s, H3′); δ_C (100.6 MHz, $CDCl_3$) 71.2 and 71.4 (*C*H$_2$ of Bn), 102.3 (*C*H), 110.7 (C6′), 116.9 (C3′), 119.7 and 124.3 (quat. *C*), 127.3, 127.4, 128.3 and 128.7 (*C*H of Bn), 135.7 and 135.8 (*ipso* of Bn), 140.3 and 141.5 (C2, 5), 141.6, 148.4 and 152.2 (quat. *C*) (Fig. 9).



(8)

Figure 9.

4.2.8. 4,4′,5,5′-Tetrakisbenzyloxy-2,2′-dinitro-biphenyl (9). R_f 0.30 (DCM/PE, 8:2); mp 189–190 °C; ν_{max}/cm^{-1} (KBr) 3063 (w), 3034 (w), 2915 (w), 1574 (m), 1518 (s, NO_2 str), 1454 (m), 1382 (m), 1333 (s, NO_2 str), 1270 (s), 1219 (s), 1066 (m), 1021 (m), 736 (m), 696 (m); *m/z* probe CI+ (MNH_4^+) 686.0 (33%), (MH^+) 669.0 (8%), 639.0 (16%), 623.0 (40%), 106.2 (100%), 91.2 (96%), HRMS (MNH_4^+) requires *m/z* 686.2502, found 686.2534; δ_H (400 MHz, $CDCl_3$) 5.14, (4H, d, *J*=12.0 Hz, CH_2 of Bn), 5.26 (4H, d, *J*=12.0 Hz, CH_2 of Bn), 6.66 (2H, s, H6, 6′), 7.33–7.53 (20H, m, C*H* of Bn), 7.89 (2H, s, H3, 3′); δ_C (100.6 MHz, $CDCl_3$) 71.22 and 71.41 (*C*H_2 of Bn), 110.6 (C3, 3′), 114.8 (C6, 6′), 127.3, 127.5, 128.3 and 128.7 (*C*H of Bn), 129.1 (quat. *C*), 135.6 and 135.9 (*ipso* of Bn), 139.8, 147.9 and 152.8 (quat. *C*).

4.2.9. 4,5-Dibenzyloxy-2-aminobromobenzene (10). To a solution of 4,5-dibenzyloxy-2-nitrobromobenzene **5** (3.0 g, 7.23 mmol) and 35% HCl (3.00 mL) in ethanol (25 mL), was added iron powder (1.21 g, 21.67 mmol). The mixture was heated to reflux under argon for 3 h. The cooled solution was diluted with DCM (100 mL) and water (100 mL), and then filtered through celite, washing with DCM (100 mL). The organic layer was separated and again water (100 mL) was added. K_2CO_3 was added until no more bubbling occurred and the aqueous layer was basic. The organic layer was separated, dried over $Na_2SO_4/MgSO_4$ and the solvent removed under reduced pressure. Purification by column chromatography (PE/EtOAc, 8:2) gave **10** (2.3 g, 83%) as a tan solid. R_f 0.19 (PE/EtOAc, 8:2); mp 98–99 °C; ν_{max}/cm^{-1} (KBr) 3448 and 3366 (w, N–H str), 3063 (w), 3033 (w), 2926 (w), 2868 (w), 1614 (m), 1596 (w), 1508 (s), 1452 (m), 1409 (m), 1381 (m), 1259 (m), 1225 (m), 1210 (m), 1178 (s), 1023 (m), 1007 (m), 982 (m), 917 (m), 873 (m), 846 (m), 763 (m), 750 (m), 734 (m), 700 (s); *m/z* probe ES+ ($M(^{79}Br)H^+$) 384.1 (85%), HRMS ($M(^{79}Br)H^+$) requires *m/z* 384.0599, found 384.0595; δ_H (400 MHz, $CDCl_3$) 3.64 (2H, br, NH_2), 5.04, (2H, s, CH_2 of Bn), 5.09 (2H, s, CH_2 of Bn), 6.43 (1H, s, H3), 7.06 (1H, s, H6), 7.30–7.45 (10H, m, C*H* of Bn); δ_C (100.6 MHz, $CDCl_3$) 71.31 and 73.07 (*C*H_2 of Bn), 99.49 (C1), 103.4 (C3), 121.0 (C6), 127.3, 127.7, 127.9, 127.9, 128.4 and 128.5 (*C*H of Bn), 136.9 and 137.2 (*ipso* of Bn), 139.1, 142.0 and 149.9 (quat. *C*).

4.2.10. 3,4-Dibenzyloxyiodobenzene (11). 1,2-Dibenzyloxybenzene **3** (50 g, 172 mmol), HgO (41 g, 189 mmol), and I_2 (48 g, 189 mmol), were stirred in DCM (700 mL) at room temperature for 24 h. The solution was filtered then washed with sat. $Na_2S_2O_3$ solution (200 mL). The organic layer was dried over $Na_2SO_4/MgSO_4$ and the solvent was removed under reduced pressure. Recrystallisation from DCM and MeOH gave **11** (56 g, 78%). A small amount was further purified by column chromatography (PE/EtOAc, 9:1) to give a white solid. R_f 0.33 (PE/EtOAc, 9:1); mp 63–65 °C, lit.[29] 65–67 °C; ν_{max}/cm^{-1} (KBr) 3062 (w), 3033 (w), 2935 (w), 2870 (w), 1575 (m), 1499 (s), 1454 (m), 1394 (m), 1382 (m), 1247 (s), 1206 (s), 1133 (s), 998 (s), 798 (s), 751 (s), 698 (s); *m/z* probe CI+ (MNH_4^+) 434.1 (100%), (MNH_4^+-I) 308.2 (55%), 290.2 (20%), 108.1 (12%), 91.1 (22%), HRMS (MNH_4^+) requires *m/z* 434.0617, found 434.0611; δ_H (400 MHz, $CDCl_3$) 5.13 (2H, s, CH_2 of Bn), 5.15 (2H, s, CH_2 of Bn), 6.70 (1H, d, *J*=8.5 Hz, H5), 7.22 (1H, dd, J_1=8.5 Hz, J_2=2.0 Hz, H6), 7.27 (1H, d, *J*=2.0 Hz, H2), 7.31–7.50 (10H, m, C*H* of Bn); δ_C (100.6 MHz, $CDCl_3$) 71.30 and 71.46 (*C*H_2 of Bn), 83.26 (C1), 117.0 (C5), 124.0 (C2), 127.3, 127.4, 127.9, 128.0, 128.6 and 128.6 (*C*H of Bn), 130.5 (C6), 136.7 and 136.9 (*ipso* of Bn), 149.1 and 149.9 (quat. *C*).

4.2.11. 4,5-Dibenzyloxy-2-nitroiodobenzene (12). 3,4-Dibenzyloxyiodobenzene **11** (50 g, 120 mol) was dissolved in hot glacial acetic (600 mL). The solution was cooled to 35 °C and 70% HNO_3 (35 mL, 552 mmol) was added over 30 min. A yellow solid precipitated and the mixture was stirred at room temperature for 2 h. Water (1 L) was added and the yellow solid collected was dissolved in DCM then washed with sat. K_2CO_3 solution until the aqueous layer was basic. The organic layer was dried over $Na_2SO_4/MgSO_4$ and the solvent was removed under reduced pressure. The residue was recrystallised from DCM/MeOH to give **12** (52 g, 94%). A small amount was further purified by column chromatography (PE/EtOAc, 6:1) to give a yellow solid. R_f 0.27 (PE/EtOAc, 6:1); mp 108.5–109 °C; ν_{max}/cm^{-1} (KBr) 3056 (w), 3027 (w), 2899 (w), 2858 (w), 1588 (w), 1575 (m), 1514 (s, NO_2 str), 1498 (s), 1450 (m), 1316 (s), 1266 (s), 1210 (m), 1196 (m), 1011 (m), 859 (m), 749 (m), 732 (m), 699 (m); *m/z* probe CI+ (MNH_4^+) 479.0 (20%), (MH^+) 462.0 (7%), 432.0 (100%), 340.0 (30%), 305.2 (67%), 91.1 (80%), HRMS (MNH_4^+) requires *m/z* 479.0468, found 479.0452; microanalysis requires C 52.08, H 3.50, N 3.04, found C 52.40, H 3.46, N 3.05; δ_H (400 MHz, $CDCl_3$) 5.19 (2H, s, CH_2 of Bn), 5.20 (2H, s, CH_2 of Bn), 7.33–7.47 (10H, m, C*H* of Bn), 7.49 (1H, s, C6), 7.68 (1H, s, C3); δ_C (100.6 MHz, $CDCl_3$) 71.31 and 71.41 (*C*H_2 of Bn), 77.60 (C1), 111.7 (C3), 125.5 (C6), 127.3, 127.4, 128.4, 128.5, 128.7 and 128.8 (*C*H of Bn), 135.3 and 135.6 (*ipso* of Bn), 145.1, 148.5 and 152.6 (quat. *C*).

4.2.12. 4,5-Dibenzyloxy-2-aminoiodobenzene (13). A mixture of 4,5-dibenzyloxy-2-nitroiodobenzene **12** (2.00 g, 4.33 mmol), activated carbon (0.21 g, 17.50 mmol), and $FeCl_3$ (70 mg, 0.43 mmol) in MeOH (15 mL) was heated to reflux under argon for 10 min. $N_2H_2{\cdot}H_2O$ (0.84 mL, 17.23 mmol) was added slowly and the mixture heated to reflux for 8 h. The cooled solution was diluted with DCM (50 mL) and water (50 mL), then filtered through celite, washing with DCM (100 mL). The organic layer was separated, dried over $Na_2SO_4/MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (PE/EtOAc, 8:2) to give **13** (1.60 g, 86%) as a pale yellow solid. R_f 0.19 (PE/EtOAc, 8:2); mp 92–94 °C; ν_{max}/cm^{-1} (KBr) 3437 and 3353 (m, NH str), 3061 (w), 3032 (w), 2926 (w), 2868 (w), 1609 (m), 1506 (s), 1404 (m), 1381 (m), 1255 (s), 1226 (m), 1210 (m), 1177 (s), 1018 (m), 1006 (m), 982 (m), 847 (m), 765 (m),

750 (m), 731 (m), 700 (s); *m/z* probe ES+ (MH^+) 432.1 (100%), (MH^+-NH_2) 415.0 (15%), 391.3 (17%), HRMS (MH^+) requires *m/z* 432.0461, found 432.0461; δ_H (400 MHz, $CDCl_3$) 3.82 (2H, br, NH_2), 5.04, (2H, s, CH_2 of Bn), 5.09 (2H, s, CH_2 of Bn), 6.43 (1H, s, H3), 7.27 (1H, s, H6), 7.32–7.50 (10H, m, C*H* of Bn); δ_C (100.6 MHz, $CDCl_3$) 71.12 (*C*H_2 of Bn), 72.28 (C1), 73.20 (*C*H_2 of Bn), 102.3 (C3), 126.8 (C6), 127.3, 127.8, 127.9, 128.0, 128.5 and 128.6 (*C*H of Bn), 136.9 and 137.3 (*ipso* of Bn), 142.3, 142.3 and 151.0 (quat. *C*).

4.2.13. 3,4-Bis(3,4-dihydroxy-2-aminophenyl)furan (17). 3,4-Bis(3,4-dibenzyloxy-2-nitrophenyl)furan **2** (51 mg, 0.07 mmol) and AcOH (4 μL, 0.07 mmol) were stirred in THF (1 mL) with 10% palladium on carbon (20 mg) under an atmosphere of H_2 for 15 h. The solution was filtered and the solvent removed to give **17** (21 mg, 94%) as a pale yellow solid. The lability of the compound prevented purification. Mp decomposed >190 °C; ν_{max}/cm^{-1} (KBr) 3374 (s, br, OH str), 1557 (m), 1514 (s), 1451 (m), 1308 (m), 1243 (m), 1052 (m), 876 (m), 804 (m); λ_{max} (EtOH) 313 (ε 45,850); δ_H (500 MHz, CD_3OD) 6.33 (2H, s, H3′, 3″), 6.49 (2H, s, H6′, 6″), 7.60 (2H, s, H2, 5); δ_C (125.8 MHz, CD_3OD), 105.0 (C3′, 3″), 110.2 (quat. *C*), 117.8 (C6′, 6″), 123.9 (C3, 4), 137.5 and 138.3 (quat. *C*), 141.4 (C2), 146.0 (quat. *C*) (Fig. 10).

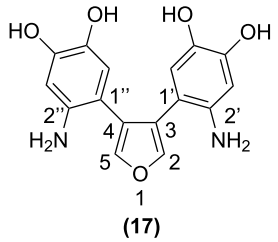


Figure 10.

4.2.14. 3,4-Bis(3,4-dibenzyloxy-2-aminophenyl)furan (18). *Method A*. A solution of 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)furan **2** (240 mg, 0.33 mmol) and $SnCl_2$ (743 mg, 3.92 mmol) in ethyl acetate (1.0 mL) and MeOH (0.5 mL) was heated to reflux for 1.5 h. The solution was poured into a slurry of ice and water (20 mL), and then DCM was added (20 mL). EDTA.2Na was added until the aqueous layer was basic. The mixture was shaken vigorously for a few minutes, and then filtered through celite, washing with DCM (100 mL). The organic layer was dried over $Na_2SO_4/MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (PE/EtOAc, 1:1) to give **18** (148 mg, 67%) as a pale brown solid.

Method B. Iron powder (0.46 g, 8.24 mmol) was added to a solution of 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)furan **2** (0.76 g, 1.03 mmol) and 35% HCl (1.20 mL) in EtOH (8 mL). The mixture was heated to reflux under argon for 3 h. The cooled solution was diluted with DCM (20 mL) and water (20 mL), and then filtered through celite, washing with DCM (100 mL). The organic layer was separated and again water (20 mL) was added. K_2CO_3 was added until no more bubbling occurred and the aqueous layer was basic. The organic layer was separated, dried over $Na_2SO_4/MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (PE/EtOAc, 1:1) gave **18** (0.61 g, 88%) as a pale brown solid. R_f 0.38 (PE/EtOAc, 1:1); mp 137–138.5 °C; ν_{max}/cm^{-1} (KBr) 3455, 3397, 3364 and 3324 (m, NH str), 3061 (w), 3032 (w), 2917 (w), 2867 (w), 1616 (m), 1552 (m), 1505 (s), 1454 (m), 1418 (m), 1370 (m), 1354 (m), 1262 (s), 1204 (s), 1171 (s), 1146 (s), 1054 (m), 1024 (m), 994 (m), 854 (m), 826 (m), 735 (s), 696 (s); λ_{max} (EtOH) 308 (ε 5560); *m/z* probe ES+ (MH^+) 674.0 HRMS (MH^+) requires *m/z* 675.2859, found 675.2864; δ_H (400 MHz, $CDCl_3$) 3.37 (4H, br, NH_2), 4.87, (4H, s, CH_2 of Bn), 5.08 (4H, s, CH_2 of Bn), 6.32 (2H, s, H3′, 3″), 6.56 (2H, s, H6′, 6″), 7.24–7.50 (20H, m, C*H* of Bn), 7.56 (2H, s, H2, 5); δ_C (100.6 MHz, $CDCl_3$) 71.05 and 72.70 (*C*H_2 of Bn), 103.3 (C3′, 3″), 109.6 (quat. *C*), 119.4 (C6′, 6″), 123.0 (quat. *C*), 127.2, 127.5, 127.6, 127.8, 128.3 and 128.5 (*C*H of Bn), 137.2 and 137.7 (*ipso* of Bn), 139.4 (quat. *C*), 141.2 (C2, 5), 141.4 and 149.9 (quat. *C*) (Fig. 11).

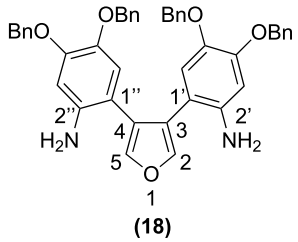
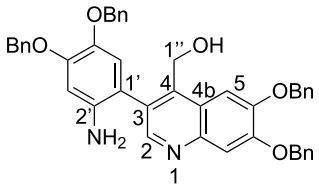


Figure 11.

4.2.15. 3-(3,4-Dibenzyloxy-2-aminophenyl)-4-(hydroxymethyl)-6,7-dibenzyloxyquinoline (19). A mixture of 3,4-bis(3,4-dibenzyloxy-2-aminophenyl)furan **18** (500 mg, 0.74 mmol), *p*-toluenesulfonic acid (70 mg, 0.37 mmol) and powdered molecular sieves (100 mg, 4 Å) in benzene (10 mL) was heated to reflux for 2 days. DCM (20 mL) was added, the mixture filtered, then washed with sat. Na_2CO_3 solution (10 mL). The organic layer was dried over $Na_2SO_4/MgSO_4$ and the solvent was removed under reduced pressure to give a residue that was purified by column chromatography (PE/EtOAc, 3:7). **19** (125 mg, 25%) was obtained as a white solid, along with recovered starting material (332 mg, 64%). R_f 0.42 (PE/EtOAc, 3:7); mp 183.5–184 °C; ν_{max}/cm^{-1} (KBr) 3447 and 3355 (m, NH str), 3217 (w), 3028 (m), 2926 (w), 2870 (w), 1623 (s), 1546 (m), 1506 (s), 1454 (m), 1411 (m), 1385 (m), 1358 (m), 1260 (s), 1222 (s), 1208 (s), 1170 (m), 1150 (m), 1058 (m), 1014 (m), 866 (m), 735 (s), 696 (s); λ_{max} (EtOH) 242 (ε 56,550), 300 (ε 8840), 337 (ε 10,040); *m/z* probe APCI+ (MH^+) 675.7 (40%), HRMS (MH^+) requires *m/z* 675.2859, found 675.2861; δ_H (500 MHz, $CDCl_3$) 3.35 (2H, br, NH_2), 4.55 (1H, br, O*H*), 4.58 (1H, d, *J*=12.0 Hz, α-CH_2OH), 4.80 (1H, d, *J*=12.0 Hz, β-CH_2OH), 5.08 (1H, d, *J*=12.0 Hz, α-CH_2 of Bn), 5.10 (1H, d, *J*=12.0 Hz, β-CH_2 of Bn), 5.18 (1H, d, *J*=12.0 Hz, α-CH_2 of Bn), 5.20 (1H, d, *J*=12.0 Hz, β-CH_2 of Bn), 5.28–5.38 (4H, m, CH_2 of Bn), 6.50 (1H, s, H3), 6.72 (1H, s, H6), 7.28–7.56 (21H, m, H8, C*H* of Bn), 7.61 (1H, s, H5), 8.46 (1H, s, H2); δ_C (125.8 MHz, $CDCl_3$) 60.0 (*C*H_2OH), 70.3, 70.7, 71.2 and 72.5 (*C*H_2 of Bn), 104.4 (C5), 104.6 (C3), 110.2 (C8), 117.8 (quat. *C*), 119.3 (C6), 122.6 (quat. *C*), 127.0, 127.1, 127.3, 127.6, 127.7, 127.8, 127.8, 127.9, 128.3, 128.4, 128.5 and 128.5 (*C*H of Bn), 136.3, 136.4, 136.9, 137.2, 138.4, 142.1, 142.4 and 145.3

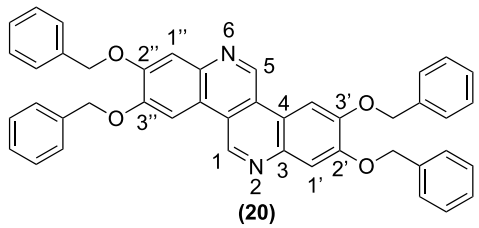
(quat. *C*), 149.3 (C2), 149.7, 150.1, 151.6 (quat. *C*); δ_H(400 MHz, DMSO) 4.41 (2H, s, NH_2), 4.62 (1H, dd, J_1=11.5 Hz, J_2=5.0 Hz, α-CH_2OH), 4.70 (1H, dd, J_1=11.5 Hz, J_2=5.0 Hz, β-CH_2OH), 4.98 (2H, s, CH_2 of Bn), 5.11 (2H, s, CH_2 of Bn), 5.28 (1H, t, J=5.0 Hz, O*H*), 5.32 (2H, s, CH_2 of Bn), 5.37 (2H, s, CH_2 of Bn), 6.61 (1H, s, H3), 6.75 (1H, s, H6), 7.28–7.62 (21H, m, H8, C*H* of Bn), 7.82 (1H, s, H5), 8.37 (1H, s, H2) (Fig. 12).



(19)

Figure 12.

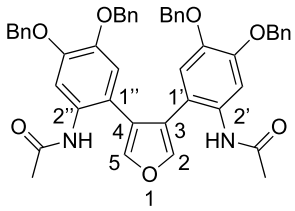
4.2.16. 2′,2″,3′,3″-Tetrakisbenzyloxy-dibenzo[*c*,*h*][2,6]-naphthyridine (20). 3-(3,4-Dibenzyloxy-2-aminophenyl)-4-(hydroxymethyl)-6,7-dibenzyloxyquinoline **19** (20 mg) was dissolved in DMSO-d_6 (0.8 mL), and left standing open to the air for 3 months to give pale yellow crystals of **20**. Due to the crystals being highly insoluble, only a ^{1}H NMR spectra was obtainable. Mp 264–265 °C; ν_{max}/cm^{-1} (KBr) 3428 (br,s), 1620 (w), 1516 (m), 1479 (w), 1448 (m), 1380 (w), 1287 (s), 1242 (m), 1184 (w), 1152 (w), 1026 (s), 824 (w), 727 (m), 693 (m); *m*/*z* probe ES+ (MH^+) 655.1 (30%), 413.0 (20%), 334.9 (68%), 256.8 (80%), 226.7 (94%), 175.6 (100%), HRMS (MH^+) requires 665.2597, *m*/*z* found 665.2602; δ_H (500 MHz, DMSO-d_6) 5.43 (4H, s, CH_2 of Bn), 5.53 (4H, s, CH_2 of Bn), 7.31–7.65 (20H, m, C*H* of Bn), 7.80 (2H, s, H4′, 4″), 8.59 (2H, s, H1′, 1″), 10.22 (2H, s, H1, H5) (Fig. 13).



(20)

Figure 13.

4.2.17. 3,4-Bis(3,4-dibenzyloxy-2-*N*-acylaminophenyl)-furan (21). A mixture of 3,4-bis(3,4-dibenzyloxy-2-aminophenyl)furan **18** (266 mg, 0.39 mmol), acetic anhydride (82 μL, 0.87 mmol), triethylamine (166 μL, 1.19 mmol) and a catalytic amount of DMAP in THF (6 mL) was stirred at room temperature for 15 h. The solvent was removed and the residue was purified by column chromatography (PE/EtOAc, 1:9) to give **21** (236 mg, 79%) as a pale yellow solid. R_f 0.33 (PE/EtOAc, 1:9); mp 64–65 °C; ν_{max}/cm^{-1} (KBr) 3271 (m, br), 3031 and 2930 (w), 1658 (s, C=O str), 1511 (s), 1454 (m), 1411 (m), 1369 (m), 1251 (s), 1205 (m), 1165 (m), 1146 (m), 1014 (m), 863 (m), 737 (m), 696 (s); *m*/*z* probe ES+ (MNa^+) 780.0 (38%), (MH^+) 759.0 (70%), HRMS (MH^+) requires *m*/*z* 759.3070, found 759.3078; microanalysis requires C 75.97, H 5.58, found C 75.70, H 5.54; δ_H (400 MHz, $CDCl_3$) 1.83 (6H, s, CH_3), 4.90 (4H, s, CH_2 of Bn), 5.13 (4H, s, CH_2 of Bn), 6.68 (2H, s, H3′, 3″), 7.25–7.48 (22H, m, H2, H5, C*H* of Bn), 7.52 (2H, s, N*H*), 7.59 (2H, s, H6′, 6″); δ_C (100.6 MHz, $CDCl_3$) 23.94 (*C*H_3), 71.01 and 71.87 (*C*H_2 of Bn), 110.5 (C6′), 116.6 (quat. *C*), 117.2 (C3′, 3″), 122.5 (quat. *C*), 127.2, 127.5, 127.8, 127.9, 128.4 and 128.5 (*C*H of Bn), 129.4 (quat. *C*), 136.8 and 137.1 (*ipso* of Bn), 141.1 (C2, 5), 145.9 and 148.8 (quat. *C*), 168.7 (*C*=O) (Fig. 14).



(21)

Figure 14.

4.2.18. 3,4-Dibenzyloxybenzaldehyde (22). A mixture of 3,4-dihydroxybenzaldehyde (5.00 g, 36.20 mmol), K_2CO_3 (25.02 g, 181.03 mmol) and benzyl chloride (10.00 mL, 86.89 mmol) in DMF (25 mL), was stirred rapidly at 120 °C under argon for 15 h. The solution was filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography (PE/EtOAc, 7:3) to give **22** (11.4 g, 99%) as a white solid. R_f 0.30 (PE/EtOAc, 7:3); mp 84–85 °C, lit.[36] 84–85 °C; δ_H (400 MHz, $CDCl_3$) 5.22 (2H, s, CH_2 of Bn), 5.26 (2H, s, CH_2 of Bn), 7.04 (1H, d, J=8.0 Hz, H2), 7.31–7.51 (11H, m, H6, C*H* of Bn), 7.52 (1H, d, J=2.0 Hz, H5), 9.83 (1H, s, *H*C=O).

4.2.19. (*E*)-3,4-Dibenzyloxy-β-nitrostyrene (23). A solution of 3,4-dibenzyloxybenzaldehyde **22** (10.0 g, 31.4 mmol), $MeNO_2$ (10.2 mL, 188.8 mmol), and NH_4OAc (9.7 g, 125.8 mmol) in AcOH (100 mL) was heated to reflux for 40 min. Most of the AcOH was removed under vacuum and the residue was dissolved in DCM (100 mL). The solution was washed with sat. K_2CO_3 solution until the aqueous layer was basic and then with water (100 mL). The organic layer was dried over Na_2SO_4/$MgSO_4$ and the solvent was removed under reduced pressure to give **23** (11.10 g, 98%) as a bright yellow solid. A small amount was purified by column chromatography (PE/DCM, 3:7) for spectroscopic analysis. R_f 0.38 (PE/DCM, 3:7); mp 115–116.5 °C, lit.[37] 117–118°; δ_H (400 MHz, $CDCl_3$) 5.20, (2H, s, CH_2 of Bn), 5.23 (2H, s, CH_2 of Bn), 6.97 (1H, d, J=8.0 Hz, H5), 7.10 (1H, d, J=2.0 Hz, H2), 7.12 (1H, dd, J_1=8.0 Hz, J_2=2.0 Hz, H6), 7.33–7.50 (11H, m, β H, C*H* of Bn), 7.90 (1H, d, J=13.5 Hz, α H).

4.2.20. (*E*)-4,5-Dibenzyloxy-2, β-dinitrostyrene (24). A mixture of (*E*)-3,4-dibenzyloxy-β-nitrostyrene **23** (10.9 g, 30.2 mmol), was dissolved in hot glacial acetic (150 mL). The solution was cooled to 35 °C and 70% HNO_3 (8.7 mL, 137.2 mmol) was added over 15 min. A yellow solid precipitated and the slurry was stirred at room temperature for 2 h. Water (300 mL) was added, and then the yellow solid collected was dissolved in DCM (200 mL) then washed with sat. K_2CO_3 solution until the aqueous layer was basic. The organic layer was dried over Na_2SO_4/$MgSO_4$ and the solvent was removed under reduced pressure. The residue was recrystallised from DCM/MeOH to give **24**

(11.9 g, 97%) as a yellow solid. A small amount was further purified by column chromatography (PE/DCM, 3:7) for spectroscopic analysis. R_f 0.32 (PE/DCM, 3:7); mp 161–162 °C, lit.[37] 162–163 °C; δ_H (400 MHz, $CDCl_3$) 5.27 (2H, s, CH_2 of Bn), 5.30 (2H, s, CH_2 of Bn), 6.97 (1H, s, H6), 7.25 (1H, d, J=13.5 Hz, β H), 7.34–7.50 (10H, m, C*H* of Bn), 7.82 (1H, s, H3), 8.55 (1H, d, J=13.5 Hz, α H).

4.2.21. 5,6-Dibenzyloxyindole (25). A mixture of (*E*)-4,5-dibenzyloxy-2, β-dinitrostyrene **24** (5.00 g, 12.30 mmol), iron powder (13.74 g, 246.02 mmol) and SiO_2 (18.50 g) in AcOH (75 mL), benzene (90 mL) and cyclohexane (30 mL) was heated to reflux for 30 min under argon. The mixture was filtered through celite with DCM/EtOAc (1:1) until the washings contained no product by TLC. The solution was washed with K_2CO_3 solution until the aqueous layer was basic then with water (100 mL). The organic layer was dried over $Na_2SO_4/MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (PE/EtOAc, 3:1) to give **25** (2.47 g, 61%) as a cream solid. R_f 0.30 (PE/EtOAc, 3:1); mp 111–113 °C, lit.[37] 113–114 °C; δ_H (400 MHz, $CDCl_3$) 5.14 (2H, s, CH_2 of Bn), 5.20 (2H, s, CH_2 of Bn), 6.43 (1H, m, H3), 6.92 (1H, d, J=0.5 Hz, H7), 7.02 (1H, dd, J_1=2.5 Hz, J_2=3.0 Hz, H2), 7.24 (1H, s, H4), 7.30–7.54 (10H, m, C*H* of Bn), 8.03 (1H, br, N*H*).

4.2.22. 5,6-Dibenzyloxy-*N*-triisopropylsilylindole (26). *n*-BuLi in hexanes (3.90 mL of a 1.62 M solution, 6.32 mmol) was added slowly to a solution of 5,6-dibenzyloxyindole **25** (1.74 g, 5.28 mmol) in THF (20 mL) at −78 °C under argon. After 15 min, TIPSCl (1.58 mL, 7.4 mmol) was added and the solution was stirred for 2 h at −78 °C then 30 min at room temperature. Most of the THF was removed under reduced pressure and replaced with DCM (50 mL). The solution was washed with water (50 mL) dried over $Na_2SO_4/MgSO_4$ and the solvent removed under reduced pressure to give a residue that was purified by column chromatography (PE/DCM, 6:4). **26** (2.43 g, 95%) was obtained as a white solid. R_f 0.18 (PE/DCM, 6:4); mp 84–85 °C; ν_{max}/cm^{-1} (KBr) 3090 (w), 3062 (w), 3031 (w), 2944 (s), 2865 (s), 1514 (m), 1497 (m), 1482 (s), 1452 (s), 1309 (m), 1263 (m), 1220 (s), 1188 (s), 1161 (s), 1016 (s), 884 (s), 868 (s), 736 (s), 722 (s), 690 (s), 652 (m); λ_{max} (EtOH) 206 (ε 54,080), 228 (ε 40,910), 268 (ε 6960), 300 (ε 7420); *m*/*z* probe ES+ (MH^+) 485.0 (57%), HRMS (MH^+) requires *m*/*z* 486.2828, found 486.2826; microanalysis requires C 76.65, H 8.09, found C 76.61, H 8.22; δ_H (400 MHz, $CDCl_3$) 1.08 (18H, d, J=7.5 Hz, CH_3 of TIPS), 1.52 (3H, heptet, J=7.5 Hz, C*H* of TIPS), 5.24 (4H, s, CH_2 of Bn), 6.50 (1H, dd, J_1=3.0 Hz, J_2=1.0 Hz, H3), 7.01 (1H, d, J=1.0 Hz, H7), 7.12 (1H, d, J=3.0 Hz, H2), 7.19 (1H, s, H4), 7.28–7.57 (10H, m, C*H* of Bn); δ_C (100.6 MHz, $CDCl_3$) 12.66 (*C*H of TIPS), 18.05 (*C*H_3 of TIPS), 71.96 and 72.50 (*C*H_2 of Bn), 102.5 (C7), 104.4 (C3), 105.6 (C4), 125.3 (quat. *C*), 127.1, 127.4, 127.5, 127.6 and 128.4 (*C*H of Bn), 130.3 (C2), 135.3, 138.0, 145.0 and 145.5 (quat. *C*).

4.2.23. 5,6-Dibenzyloxy-3-iodo-*N*-triisopropylsilylindole (27). *Method A*. A solution of I_2 (1.62 g, 6.38 mmol) in DCM (200 mL) was added slowly over 1 h to a mixture of 5,6-dibenzyloxy-*N*-triisopropylsilylindole **26** (2.82 g, 5.81 mmol) and $Hg(OAc)_2$ (2.04 g, 6.40 mmol) in DCM (100 mL) at 0 °C. The mixture was stirred for an additional hour at room temperature, then filtered through celite and washed with sat. $Na_2S_2O_5$ solution (50 mL). The organic layer was dried over $Na_2SO_4/MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (PE/DCM, 6:4) gave **27** (3.55 g, 100%) as a cream solid.

Method B. NIS (0.36 g, 1.60 mmol) was added to a solution of 5,6-dibenzyloxy-*N*-triisopropylsilylindole **26** (0.63 g, 1.30 mmol) in THF (10 mL) at 0 °C and stirred for 30 min. The solution was diluted with DCM (50 mL), washed with sat. $Na_2S_2O_5$ solution (20 mL), dried over $Na_2SO_4/MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography (PE/DCM, 6:4) gave **27** (0.66 g, 83%) as a cream solid. R_f 0.33 (PE/DCM, 6:4); mp 105–106 °C; ν_{max}/cm^{-1} (KBr) 2942 (m), 2864 (m), 1496 (m), 1474 (s), 1465 (s), 1454 (s), 1386 (m), 1308 (m), 1200 (s), 1168 (s), 1016 (s), 989 (m), 883 (m), 866 (s), 697 (s); λ_{max} (EtOH) 230 (ε 21,970), 297 (ε 6130); *m*/*z* probe ES+ (MH^+) 610.7 (40%), (MH^+-I) 484.4 (75%), HRMS (MH^+) requires *m*/*z* 612.1795, found 612.1791; δ_H (400 MHz, $CDCl_3$) 1.07 (18H, d, J=7.5 Hz, CH_3 of TIPS), 1.49 (3H, heptet, J=7.5 Hz, C*H* of TIPS), 5.25, (2H, s, CH_2 of Bn), 5.30 (2H, s, CH_2 of Bn), 6.98 (1H, s, H7), 7.03 (1H, s, H4), 7.16 (1H, s, H2), 7.29–7.48 (8H, m, C*H* of Bn), 7.59 (1H, s, C*H* of Bn), 7.61 (1H, s, C*H* of Bn); δ_C (100.6 MHz, $CDCl_3$) 12.62 (*C*H of TIPS), 17.97 (*C*H_3 of TIPS), 59.46 (C3), 71.49 and 72.44 (*C*H_2 of Bn), 102.4 (C7), 105.4 (C4), 127.0, (*C*H of Bn), 127.0 (quat. C), 127.6, 127.8, 128.5 and 128.5 (*C*H of Bn), 134.0, (C2), 134.5 (quat. *C*), 137.6 and 137.7 (*ipso* of Bn), 146.0 and 146.4 (quat. *C*).

4.2.24. 5,5′,6,6′-Tetrabenzyloxy-*N*,*N*′-triisopropylsilyl-3,3′-biindolyl (28). A mixture of 5,6-dibenzyloxy-3-iodo-*N*-triisopropylsilylindole **27** (0.50 g, 0.82 mmol), tetrakis-(dimethylamino)ethylene (0.38 mL, 1.63 mmol) and $Pd(PhCN)_2Cl_2$ (30 mg, 0.08 mmol) was stirred in DMF (4 mL) at 50 °C for 1.5 h under argon. The solution was diluted with DCM (20 mL), washed with water (20 mL), dried over $Na_2SO_4/MgSO_4$, and the was solvent removed under reduced pressure. Purification by column chromatography (PE/DCM, 3:7) gave **28** (269 mg, 68%) as a white gum. R_f 0.44 (PE/DCM, 3:7); ν_{max}/cm^{-1} (thin film) 2946 (s), 2866 (s), 1506 (m), 1470 (s), 1314 (m), 1192 (s), 1151 (s), 1016 (s), 883 (m), 733 (m), 695 (s), 652 (m); λ_{max} (EtOH) 304 (ε 14,000); *m*/*z* probe (MH^+) 968.5 (100%), 506.7 (13%), 485.3 (25%), HRMS (MH^+) requires *m*/*z* 969.5422, found 969.5508; microanalysis requires C 76.81, H 7.90, found C 76.76, H 8.03; δ_H (400 MHz, $CDCl_3$) 1.16 (36H, d, J=7.5 Hz, CH_3 of TIPS), 1.58 (6H, heptet, J C*H* of TIPS), 5.23, (2H, s, CH_2 of Bn), 5.30 (2H, s, CH_2 of Bn), 7.09 (2H, s, C*H* of Ar), 7.31–7.56 (24, m, Ar C*H*, Ar C*H* and C*H* of Bn); δ_C (100.6 MHz, $CDCl_3$) 12.77 (*C*H of TIPS), 18.17 (*C*H_3 of TIPS), 71.78 and 72.55 (*C*H_2 of Bn), 102.8 and 104.8 (Ar *C*H), 112.5 and 124.3 (quat. *C*), 127.1, 127.3, 127.5, 127.6, 127.6, 128.4 and 128.5 (Ar *C*H, *C*H of Bn), 135.8 (quat. *C*), 137.9 and 138.0 (*ipso* of Bn), 145.2 and 145.7 (quat. *C*).

4.2.25. 5,5′,6,6′-Tetrabenzyloxy-3,3′-biindolyl (29). TBAF in THF (0.24 mL of a 1.0 M solution, 0.24 mmol) was

added dropwise to a solution of 5,5′,6,6′-tetrabenzyloxy-*N*,*N*′-triisopropyl-3,3′-biindolyl **28** (105 mg, 0.11 mmol) in THF (1 mL) and stirred for 10 min. Cold MeOH (5 mL) was added and the white precipitate was collected, then washed with cold MeOH (10 mL) to give **29** (58 mg, 82%) as a white powder. Mp 225–225.5 °C; ν_{max}/cm^{-1} (KBr) 3399 (m, br), 3281 (s, NH str), 3063 (w), 3031 (w), 2935 (w), 2877 (w), 1629 (m), 1508 (m), 1475 (s), 1466 (s), 1454 (m), 1312 (s), 1244 (s), 1189 (s), 1137 (s), 1010 (m), 990 (m), 975 (m), 917 (m), 879 (m), 741 (s), 698 (s); λ_{max} (EtOH) 300 (ε 6480); *m*/*z* probe ES+ (MNa^+) 679.3 (57%), (MNH_4^+) 674.3 (56%), (MH^+) 657.3 (100%), HRMS (MH^+) requires *m*/*z* 657.2753, found 657.2765; δ_H (400 MHz, DMSO) 5.14, (4H, s, C*H*$_2$ of Bn), 5.19 (4H, s, C*H*$_2$ of Bn), 7.07 (2H, s, H7), 7.28–7.53 (24H, m, H2, H4, C*H* of Bn), 10.84 (2H, d, *J*=2.0 Hz, N*H*); δ_C (100.6 MHz, DMSO) 71.40 and 72.20 (*C*H$_2$ of Bn), 98.71 (C7), 106.4 (C4), 110.7 and 120.2 (quat. *C*), 121.2 (C2), 128.3, 128.4, 128.5, 128.5, 129.1 and 129.2 (*C*H of Bn), 132.0 (quat. *C*), 138.6 and 138.9 (*ipso* of Bn), 144.6 and 146.7 (quat. *C*).

4.2.26. 5,5′,6,6′-Tetrahydroxy-3,3′-biindolyl (1). 5,5′,6,6′-Tetrabenzyloxy-3,3′-biindolyl **29** (30 mg, 0.04 mmol) was stirred in THF (1 mL) with Palladium Black (3 mg) under an atmosphere of H_2 for 18 h. The solution was quickly filtered and the solvent removed at 30 °C under reduced pressure to give the target compound **1** (13 mg, 94%) as a greyish orange solid. The solid product did not dissolve in D_2O sufficiently to allow the preparation of a sample for ^{13}C NMR analysis (14,000 scans at 500 MHz gave no signals), although it was readily soluble in DMSO-d_6. To prepare a sample in D_2O, the reaction solution was quickly filtered and most of the THF was removed at 30 °C under reduced pressure. D_2O (0.8 mL) was added giving a pale orange solution. The remaining THF was removed under reduced pressure leaving an aqueous solution with a milky precipitate (the milky precipitate was soluble in DMSO-d_6 and gave clean spectra of the compound showing that the heteroatom protons had been deuterated). This was quickly filtered to give a pale orange aqueous solution. λ_{max} (H_2O) 302; *m*/*z* probe ES− ($M-H^+$) 295.07 (100%), HRMS ($M-H^+$) requires *m*/*z* 295.0719, found 295.0717; δ_H (500 MHz, D_2O) 6.94 (2H, s, H7, 7′), 7.13 (2H, s, H4, 4′), 7.32 (2H, s, H2, 2′); δ_C (125.8 MHz, D_2O) 98.47 (C7), 105.2 (C4), 109.1 (C3), 119.5 (C3a), 121.2 (C2), 131.6 (C7a), 139.8 (C5), 142.2 (C6); δ_H (500 MHz, DMSO-d_6) 6.78 (2H, s, H7, 7′), 7.03 (2H, s, H4, 4′), 7.16 (2H, d, *J*=2.0 Hz, H2, 2′), 8.23 (2H, s, O*H*-5), 8.50 (2H, s, O*H*-6), 10.40 (2H, d, *J*=2.0 Hz, N*H*); δ_C (125.8 MHz, DMSO-d_6) 98.10 (C7), 105.2 (C4), 110.6 (C3), 119.5 (C2), 119.8 (C3a), 131.5 (C7a), 141.2 (C5), 143.5 (C6).

Acknowledgements

This research was supported by the Overseas Research Student awards scheme and Professor Sir Jack Baldwin. We would like to thank Dr. Barbara Odell and Dr. Tim Claridge for their help with NMR processing, Dr. Peter Rutledge for his advice with the manuscript preparation and Professor Tytti Kujala for allowing us to reproduce his spectroscopic data.

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Tetrahedron 60 (2004) 3713–3716
Tetrahedron

Synthesis of pyrrolidine ring-fused metallofullerene derivatives

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Received 1 September 2003; revised 7 January 2004; accepted 18 February 2004

Abstract—The azomethine ylide generated from the reaction of sarconsine and formaldehyde adds to Gd@C_{82} to give the mono- through octo-adducts, while the direct interaction of sarcosine with Gd@C_{82} yields only the mono-adduct, which is characterized by HPLC, MALDI-TOF MS, UV–Vis–NIR and FT-IR. The reaction mechanism for this reaction is proposed to be a 1,3-dipolar addition.

1. Introduction

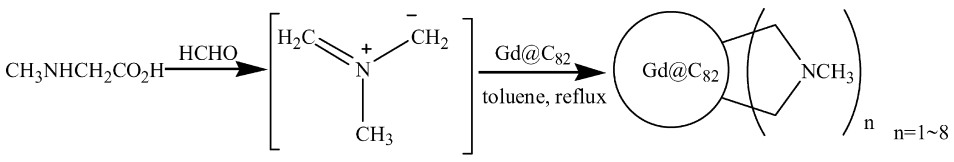
Because of their novel properties and potential applications, endohedral metallofullerenes (EMFs) have attracted wide attention. Early research focused mainly on the determination of their intrinsical properties, such as the electronic and geometrical structures, as well as their magnetic and optical properties.[1] Recently, exohedral modification of EMFs has produced some new materials such as therapeutic radiopharmaceuticals and MRI contrasting and X-ray imaging agents.[2–5] However, the organic functionalization of EMFs has developed slowly. Only a few reactions of EMFs with organic compounds have *hitherto* been investigated, such as the cycloaddition of disilirane onto La@C_{82},[6] reactions of diazocarbonyl compounds with La@C_{82} and Tb@C_{82},[7,8] Diels–Alder reaction of Sc_3N@C_{80} with *o*-quinomethane,[9] and the reaction of Gd@C_{60} with bromomalate.[4]

In contrast, the organic chemistry of empty fullerenes (mainly C_{60} and C_{70}) has been intensively studied and various derivatives of them have been synthesized. Among these derivatives, pyrrolidine ring-fused fullerenes have special interest because of their potential applications in such fields as biology and electronics.[10,11] Thus, pyrrolidine ring-fused metallofullerenes may also have important applications in these fields. Therefore, we designed the synthesis of pyrrolidine ring-fused metallofullerene derivatives.

Azomethine ylides are one of the most reactive 1,3-dipoles which can be easily generated by the 'decarboxylation route'.[12] Reactions between azomethine ylides and C_{60} have been well investigated.[11] However, the reactions of azomethine ylides with metallofullerenes have not been reported. Here, we report the reaction of azomethine ylides with Gd@C_{82} (Scheme 1).

2. Results and discussion

Figure 1 shows the matrix assisted (α-cyano-4-hydroxycinnamic acid, α-CCA as matrix) laser desorption/ionization time-of-flight (MALDI TOF) mass spectrum of the product **1**. It shows a series of molecular ion peaks at *m*/*z* 1142+(57)$_n$ (n=1–8) which are ascribable to the mono- through octo-adducts. It is well known that exohedral fullerene/metallofullerene derivatives tend to fragment under laser desorption, which always generates mass spectral peaks for derivatives having fewer adduct groups. As a result, sometimes the peak of the parent metallofullerene is the molecular ion peak.[6,7] However, in our



1

Scheme 1. Reaction of azomethine ylide with Gd@C_{82}.

Keywords: Azomethine ylides; Metallofullerene pyrrolidines; 1,3-Dipolar addition.
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doi:10.1016/j.tet.2004.02.061

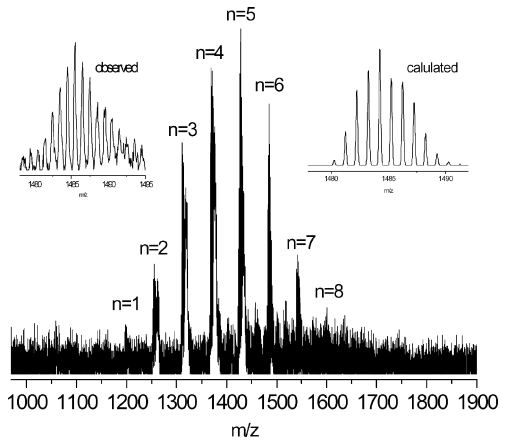
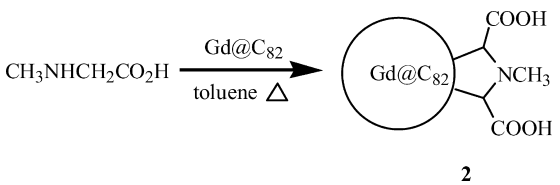


Figure 1. MALDI-TOF mass spectrum of **1**; the insets are the observed isotope distributions and the calculated results of $Gd@C_{82}[C_3H_7N]_6$.

experiment, the peak of $Gd@C_{82}$ (*m*/*z* 1142) is not found, which means that such pyrrolidine ring-fused metallofullerenes are very stable and obviously all $Gd@C_{82}$ was consumed during the reaction. Moreover, the observed isotope distribution of $Gd@C_{82}(C_3H_7N)_6$ agrees well with computer simulation results (insets in Fig. 1). These facts confirm that metallofullerene-pyrrolidines were successfully synthesized. However, because there are too many isomers in the reaction mixture and their solubility in toluene is very poor, they could not be separated from each other by HPLC. Moreover, our results show that $Gd@C_{82}$ is more reactive than C_{60} when reacting with azomethine ylides, because up to eight pyrrolidine rings can be added to the $Gd@C_{82}$ cage within 30 min while only monoadduct is formed for C_{60} after 2 h.[10]

When paraformaldehyde was replaced by other aldehydes containing more crowded substituents, such as *p*-hydroxylbenzaldehyde and 4-(4′-nitro-benzyloxy) benzaldyhyde, multiple pyrrolidine ring-fused metallofullerene derivatives could also be formed.[13] However, the mono-adduct was not obtained in these reactions because of the high reactivity of metallofullerenes towards azomethine ylides. During the experiments, we serendipitously found that the direct interaction of sarcosine with $Gd@C_{82}$ afforded monoadduct of the metallofullerene (Scheme 2).



2

Scheme 2. Reaction of sarcosine with $Gd@C_{82}$.

Figure 2 is the HPLC profile of the product mixture. The eluent between 10 and 25 min contains several isomers of the mono-adduct, as identified by MALDI TOF mass spectrometry. Because of the insufficiency of the sample and the difficulty in separating the isomers, all further characterizations are conducted on the product mixture. The sharp peak at 34.1 min is due to unreacted $Gd@C_{82}$. No peaks following $Gd@C_{82}$ are found in the chromatogram.

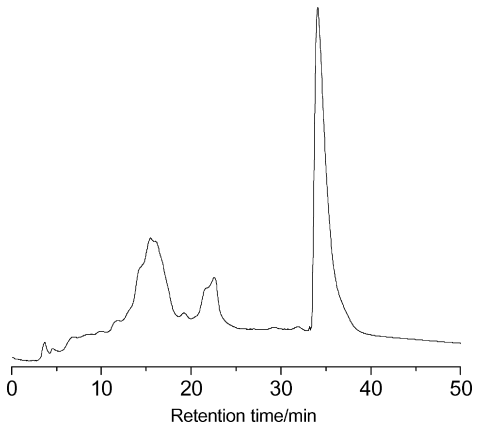


Figure 2. HPLC profile of the reaction mixture of $Gd@C_{82}$ with sarcosine at 70 °C.

The MALDI-TOF (α-CCA as matrix) mass spectrum of the product is shown in Figure 3. The peak at *m*/*z* 1142 is due to $Gd@C_{82}$ which was generated under laser desorption. The peak at *m*/*z* 1287 is ascribable to the mono-adduct **2** and the peak at *m*/*z* 1197 can be assigned to $Gd@C_{82}$ (C_4H_7N), which was derived from **2** by loss of two carboxyl groups. The observed isotope distributions of the peak at *m*/*z* 1287 agree well with the computer simulation results, which is strong proof for the structure of **2**. In addition, the presence of the peak at *m*/*z* 1197 gives supporting proof.

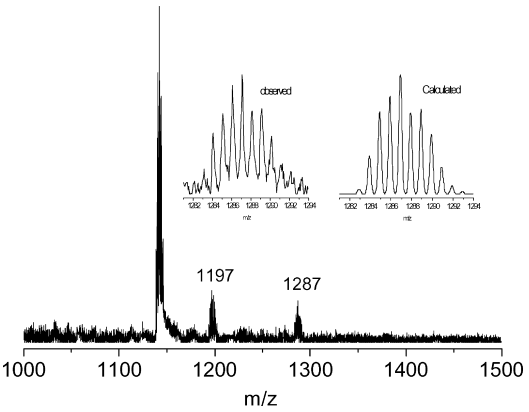


Figure 3. MALDI-TOF mass spectrum of **2**; the inset are the observed isotope distributions of the peak at *m*/*z* 1287 and the calculated results of **2**.

The UV–Vis–NIR spectrum of **2** (Fig. 4) shows fewer feature peaks as compared with that of $Gd@C_{82}$. The absorbance peaks at 636, 710 and 1405 nm disappear, while the peak at 980 nm remains. Akiyama et al. found that the absorbance peak at 980 nm always shows some dependence on the filling degree of the 4*f* orbital of the encapsulated lanthanoids for $M@C_{82}$-type metallofullerenes.[14] The presence of the 980 nm peak in our spectrum may indicate that the exohedral modification of $Gd@C_{82}$ has little effect on the electronic structure of the encaged metal Gd.

The macroscopic FT-IR spectrum of **2** is shown in Figure 5. The peaks centered at 1739 and 3400 cm^{-1} arise from the vibrations of the isolated carboxyl groups, and the C–H vibrations are found at approximately 2800 cm^{-1}. However, because of the insufficiency of the sample and its sensitivity

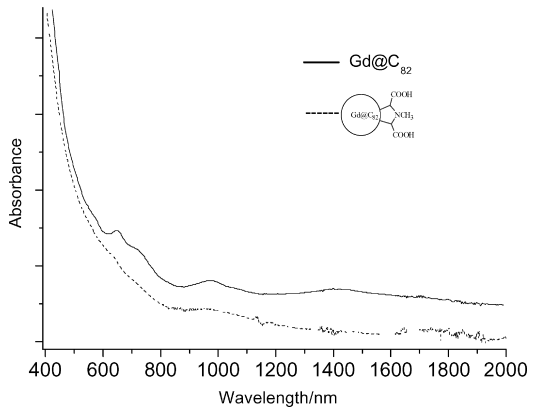


Figure 4. UV–Vis–NIR spectrum of **2** (dotted curve) and Gd@C_{82} (real curve).

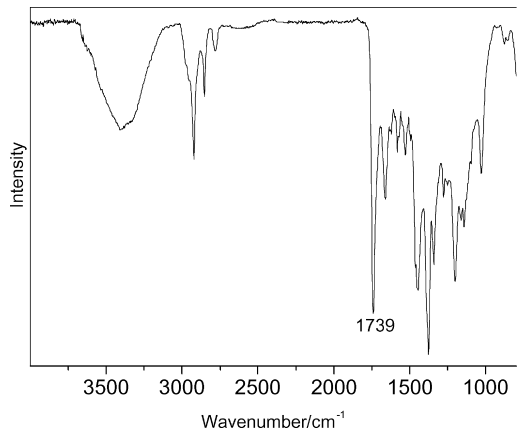
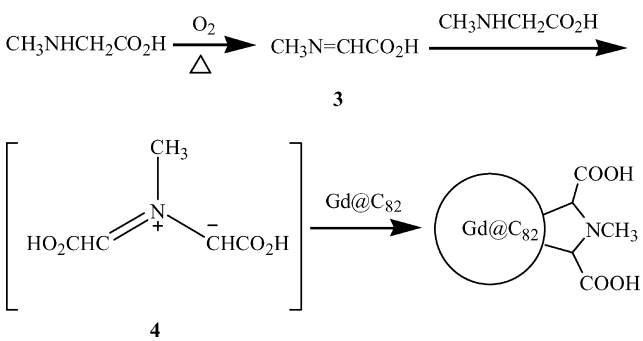


Figure 5. Macroscopic FT-IR spectrum of **2**.

to air and moisture, the IR spectrum provides limited reliable information.

We found that oxygen is essential for the reaction. When the solution containing both sarcosine and Gd@C_{82} was bubbled with argon, no product was found even after refluxing for 15 h. However, when the reaction flask was exposed to the lab environment (without the condensation tube) at 70 °C for 5 h, the bis-adduct was observed in the MALDI-TOF mass spectrum. Also, the methyl group in sarcosine was found to be very important for this reaction. When glycine was used, no pyrrolidine ring-fused metallofullerene derivatives were detected.



Scheme 3. Possible mechanism of the reaction between sarcosine and Gd@C_{82}.

From these experimental results, we speculate the reaction mechanism to be a 1,3-dipolar addition (Scheme 3). First, sarcosine is oxidized into an imine **3** which further reacts with sarcosine to form the 1,3-dipole **4**, which may have other structures. The intermediate **4** adds to Gd@C_{82} affording the novel pyrrolidine ring-fused metallofullerenes. Obviously, the methyl group in sarcosine can stabilize the imine **3**, which is less reactive than aldehydes, so that mono-adduct of pyrrolidine ring-fused metallofullerene derivatives could be obtained. However, when Gd@C_{82} was replaced by C_{60}, no fullerene pyrrolidines were found, which again indicates that Gd@C_{82} is more reactive than C_{60}.

In conclusion, we have successfully synthesized two kinds of pyrrolidine ring-fused metallofullerene derivatives via different 1,3-dipolar reactions. The introduction of the pyrrolidine rings to the carbon cage may help the development of novel applications of metallofullerenes in many fields.

3. Experimental

Gd@C_{82} was synthesized by an improved DC arc-discharge method and was purified by HPLC. The purity of Gd@C_{82} was confirmed to be more than 98% by both negative ion laser desorption time-of-flight mass spectrometry and analytical HPLC.

Procedure for the azomethine ylide reaction: 5 mg sarcosine and 7.5 mg paraformaldehyde were added to 50 mL toluene solution containing ~1 mg Gd@C_{82}. The mixture was refluxed for 30 min. The color of the solution did not change during the reaction. After cooling to room temperature, the solution was concentrated and filtered for further analysis.

Procedure for the reaction of sarcosine with Gd@C_{82}: 11.5 mg sarcosine was added to the toluene solution containing ~2 mg Gd@C_{82}. The solution was heated to 70 °C for 5 h under ambient atmosphere. After cooling, concentration and filtration, the crude mixture was separated by HPLC using a Buckyprep column (Nacalai Tesque Co.).

Acknowledgements

We gratefully acknowledge the financial support from the National Natural Science Foundation of China, No. 20151002.

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Unusual selectivity in the oxidative functionalization of *gem*-dibromocyclopropanes

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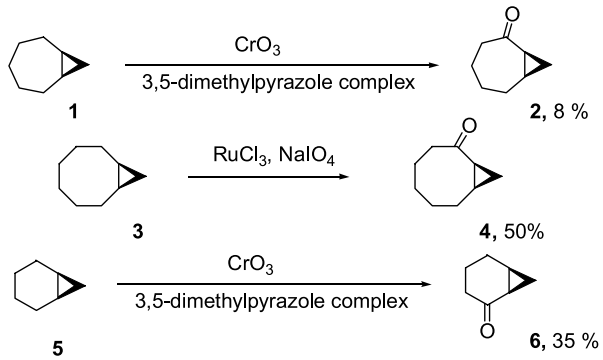
Received 17 October 2003; revised 19 January 2004; accepted 12 February 2004

Abstract—Oxidation of *gem*-dibromocyclopropanes with chromium trioxide in acetic acid or a number of other reagents is generally slower than that of the corresponding cyclopropane; in a number of cases moderate yields of products are obtained but these show unexpected oxidation patterns.

1. Introduction

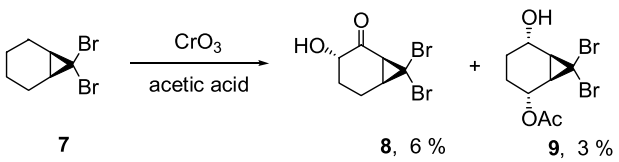
Functionalized dihalocyclopropanes are of considerable interest in view of their importance in the synthesis of a range of natural cyclopropane containing compounds or synthetic analogues.[1] Although there are many approaches to such compounds, one of the most effective starting points is the dihalocyclopropanation of an alkene using haloform and base, a reaction which generally, but not always proceeds through the formation and trapping of a dihalocarbene. Although simple alkenes are efficiently trapped in this way, more complex alkenes are either less readily available or undergo alternative reactions. In some cases this problem may be overcome by an appropriate use of protecting groups. However, an alternative approach would be to introduce carbonyl or hydroxy groups into a simple alkyldibromocyclopropane by oxidation of one or more C–H bonds. There is ample precedent for this reaction in the case of alkylcyclopropanes themselves. Such an oxidation has been used for many years in determining the structure of long chain cyclopropane containing fatty acids, oxidation with chromium trioxide occurring adjacent to the ring and allowing structure assignment by mass spectrometry.[2,3] Oxidation has also been applied to bicyclo[n.1.0]alkanes, as in the conversion of **1** into **2**,[4] **3** into **4**[5] and **5** into **6**[4] (Scheme 1).



Scheme 1.

The oxidation of such bicyclic systems with ozone is also reported. Compound **3** leads almost exclusively to the 2-one **4**, although a minor amount of the corresponding 4-one is also observed; none of the 3-one was isolated.[6] Highly selective oxidations of cyclopropanes leading to α-cyclopropyl ketones have been performed with the use of other oxidants, ruthenium tetroxide,[5,7] dimethyldioxirane,[8] and ozone in the presence of silica.[6,9] Oxidation of bicyclo[4.1.0]heptane with cytochrome P450[10] or with oxometalloporphinates and iodosylbenzene[11] leads predominantly to *endo*- and *exo*-bicyclo[4.1.0]heptan-2-ol.

In contrast, oxidation of dihalocyclopropanes is reported generally to be less effective. Thus chromium trioxide oxidation of 7,7-dibromobicyclo[4.1.0]heptane **7** leads to compounds **8** and **9** in low yields (Scheme 2).[12]



Scheme 2.

Keywords: Dibromocyclopropane; Oxidation.
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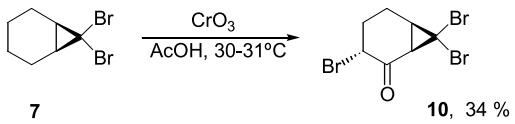
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.02.024

Other *gem*-dihalocyclopropanes have also been converted into the corresponding α-cyclopropylketones using chromium trioxide in glacial acetic acid[12,13] or dry ozonolysis,[14] but also in yields from low to modest. We now report the oxidation of a number of *gem*-dibromocyclopropanes, primarily using chromium trioxide in glacial acetic acid.

2. Results and discussion

We could not reproduce the results of oxidation of 7,7-dibromobicyclo[4.1.0]heptane **7** described above.[12] On reaction of **7** with chromium trioxide in glacial acetic acid, an unexpected tribromoketone **10** was obtained with a yield of 34% instead of **8** and **9** (Scheme 3).



Scheme 3.

The yield of **10** depended on the amounts of chromium trioxide and acetic acid (Table 1). It was necessary to use not less than 15 mol. equiv. of oxidant for complete conversion of starting material. Acid products were not obtained under these conditions. The reaction did not proceed when ether was used as a solvent instead of acetic acid.

Table 1. Oxidation of **7** with chromium trioxide in glacial acetic acid

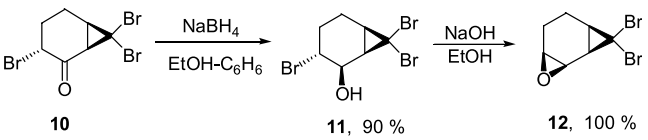
Amount of **7** (mmol)	CrO_3 (mol. equiv.)	AcOH (mL)	Unreacted **7**[a] (%)	Yield of **10**[b] (%)
3	5	8	78	—
3	10	15	32	—
3	15	15	0.5	—
3	20	60	0	36
10	15	100	8	—
10	15	50	0.5	34

[a] By GLC.
[b] Isolated yield.

Formation of **10** possibly occurs through replacement of hydrogen at C(3) in the proposed intermediate 7,7-dibromobicyclo[4.1.0]heptan-2-one by a bromine atom; the source of the bromine is not clear, but may be explained by the low yield of this product—presumably decomposition of the remainder leads to a species that is a brominating agent. Alternatively **8** may actually be an intermediate and again be brominated under the reaction conditions. The yield of **10** was not increased by addition to the reaction mixture of sodium bromide or dibromomethane, but when the reaction was carried out in the presence of carbon tetrabromide (10 mol. equiv.), product **10** was obtained in 38% yield.

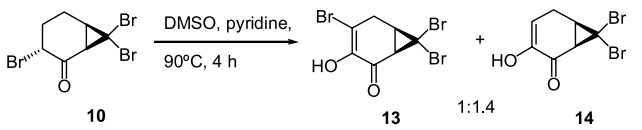
Attempts to dehydrobrominate the ketone **10** with potassium *tert*-butoxide in dichloromethane or ether, with sodium hydroxide under phase transfer conditions or with 1,5-diazabicyclonon-5-ene led to the consumption of starting material, but no products were isolated, while on reaction of **10** with phenylmagnesium bromide followed by water, 7,7-dibromobicyclo[4.1.0]heptan-2-one was formed.

For proof of structure, the tribromoketone **10** was reduced with sodium borohydride to the *trans*-alcohol **11** which on treatment with base gave the *syn*-3-oxatricyclo[5.1.0.0^{2,4}]-octane **12** (Scheme 4), suggesting that the tribromide **11** has the configuration shown. Epoxide **12**, which could be distinguished clearly from the *anti*-isomer by ^{1}H NMR,[15] represents the first example of such a *gem*-dihalogeno *syn*-ring system.



Scheme 4.

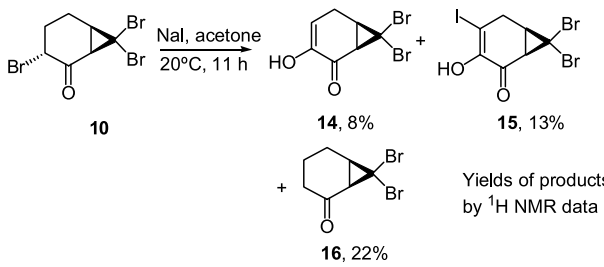
Attempts to ring-open the epoxide **12** using either phenyl magnesium bromide and copper (I) iodide in THF or benzylamine in the presence of $Yb(CF_3SO_3)_2$ were not successful. The alcohol **11** was readily converted into the corresponding acetate; attempts to dehydrobrominate this were largely unsuccessful, reaction with dimethylaminopyridine in DMSO for 3 h at 100 °C leading to the recovery of starting material; however, reaction with 1,5-diazabicyclo-undec-5-ene in DMSO for 3 h at 125 °C did lead to 2-acetoxy-7,7-dibrombicyclo[4.1.0]hept-3-ene, albeit only in 19% yield. Attempts to prepare an enamine by reaction of **10** with morpholine or a silyl enol ether by reaction with trimethylchlorosilane in the presence of triethylamine were not successful and starting material was recovered. Reaction with pyridine in DMSO, led unexpectedly to the formation of two enones **13** and **14** (Scheme 5).



Scheme 5.

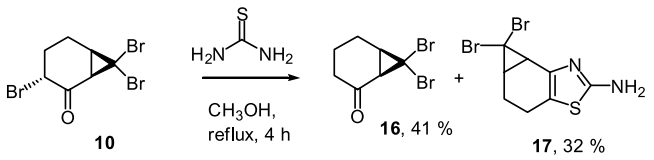
The mechanism of formation of enone **14** is probably similar to that involved in the oxidation of α-bromoketones with DMSO to α-dicarbonyl compounds,[16,17] and includes S_N2 attack of the sulfoxide oxygen at the brominated carbon (CHBr fragment) with subsequent elimination of dimethyl sulfide and then enolization. The mechanism of formation of **13** is not clear. When tribromoketone **10** was treated with potassium iodide and potassium carbonate in DMSO (reported conditions for a similar oxidation[17]), the product did not contain any **13** or **14**, but probably the α-iodoketone, 3-iodo-7,7-dibromobicyclo[4.1.0]heptan-2-one, related to **10** was formed. This was concluded based on the appearance of a new double doublet at lower field in the ^{1}H NMR spectrum compared to starting material (4.48 compared to 4.39 ppm for **10**) and a new carbonyl signal in the ^{13}C NMR (192.5 compared to 192.8 ppm for **10**). By TLC the product showed just one spot with the same R_f as starting material. An attempt to prepare this α-iodoketone by reaction of **10** with sodium iodide in acetone was not successful and the product of reduction—dibromoketone

16—was formed instead (Scheme 6), similar to reduction of α-bromoketones with NaI/Me_3SiCl[18] or HI.[19] As by-products enones **14** and **15** were formed. Unfortunately compounds **15** and **16** could not be separated and were analyzed as a mixture. The assignment of structure **15** was based on ^1H and ^{13}C NMR spectra, which had signals similar to those for **13** except one for the carbon next to the iodine, which was at higher field compared with **13** (93.1 ppm for **15** and 116.6 ppm for **13**). The mechanism of formation of **14** and **15** is again not understood.



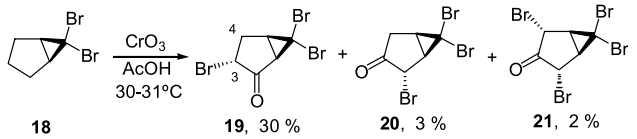
Scheme 6.

Treatment of **10** with thiourea in refluxing methanol, a standard procedure for thiazole formation from α-bromoketones,[20] led after 4 h to a mixture of **16** and thiazole **17** in modest yields (Scheme 7).



Scheme 7.

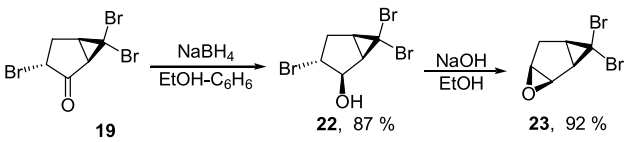
In a similar manner to 7,7-dibromobicyclo[4.1.0]heptane **7**, 6,6-dibromobicyclo[3.1.0]hexane **18** reacted with chromium trioxide in glacial acetic acid to give **19** as the major product albeit in poor yield, together with a mixture of tri- and tetrabromoketones **20**, **21** (Scheme 8).



Scheme 8.

The *exo*-ketone **19** was characterized on the basis of the larger coupling of H-3 to *endo*-H-4 than to *exo*-H-4. Isomer **20** showed an ABX pattern for the H-4, H-4′ and H-5, only the *endo*-H-4 coupling to H-5; in the same way H-1 was not split by H-2, suggesting an *exo*-configuration for the bromine at C-2. Compound **21** showed just two singlets in the ^1H NMR, (δ_H: 2.87 and 4.17) and four carbon signals; on the basis of the lack of coupling between H-1 and H-2 and the symmetry, it was assigned as the *exo*,*exo*-isomer. Once again, the tribromide **19** could be reduced to a single alcohol **22**, and this was dehydrobrominated to give the *syn*-epoxide **23** (Scheme 9).

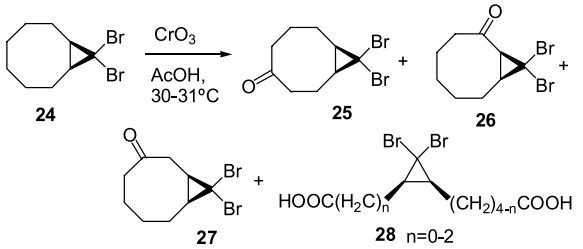
Chromium trioxide in acetic acid reacts with 9,9-dibromobicyclo[6.1.0]nonane **24** to give γ-cyclopropylketone **25** as



Scheme 9.

the major product (Table 2). The best yield of **25** was obtained when 8 mol. equiv. of oxidant were used (Table 2), but even in this case a small amount of the starting material (4%) remained unreacted. Among the other products isolated were the 2-one **26** (13%), the 3-one **27** (<0.5%),[21] and a mixture of (dibromomethano)suberic acids **28** (7%).

Table 2. Oxidation of **24** with chromium trioxide in glacial acetic acid[a]



CrO_3 (equiv.)	Product, isolated yield (%)				
	24	**25**	**26**	**27**	**28**[b]
5	20	39	14	1	—[c]
7	5	41	12	<0.5	7
8	4	48	13	<0.5	7
9	1	48	11	<0.5	9
15	—	33[d]	1	<0.5	—[c]

[a] All experiments were performed with 3 mmol of starting material in 20 mL of glacial acetic acid at 30–31 °C for 1 h.
[b] Isolated as dimethyl diester after treatment with diazomethane.
[c] Acid products were not worked-up.
[d] Also isolated as a 2,4-dinitrophenyl-hydrazone (21%).

It is interesting to note that oxidation of *exo*-9-bromobicyclo[6.1.0]nonane with dimethyldioxirane is reported to lead to the corresponding 4-one, although only in 4% yield and that the dibromide **24** does not react with this reagent.[8] A number of other dihalocyclopropanes are also reported to be inert to this reagent.[8]

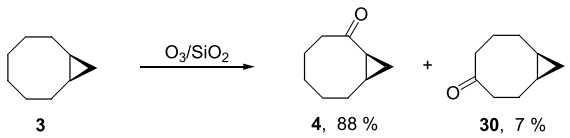
Similar results to those with chromium trioxide were obtained on oxidation of **24** with ruthenium tetroxide or ozone (Table 3) suggesting that the regioselectivity of the oxidation depends mostly on the electron withdrawing properties of the *gem*-dibromocyclopropane fragments.

Table 3. Yields of products in oxidation of **24** with different oxidants

Oxidant	Product (%)				
	24	**25**	**26**	**27**	**28**[a]
CrO_3 (8 mol. equiv.), AcOH	4	48	13	<0.5	7
H_5IO_6 (8 mol. equiv.), $RuCl_3$ (5 mol.%), 70–75 °C, 52 h	9	37	7	2	17
Ozone/SiO_2	31[b]	48[b]	6[b]	5[b]	—[c]

[a] Isolated as dimethyl diester after treatment with diazomethane.
[b] Yield by GLC data.
[c] Acid products were not worked-up.

It is necessary to note that oxidation of **24** with periodic acid required vigorous conditions, refluxing the reaction mixture for 52 h (at room temperature conversion of starting material was less 5%). By comparison oxidation of bicyclo[6.1.0]nonane **3** with 3 equiv. sodium metaperiodate in the presence of ruthenium trichloride proceeds at room temperature giving after 18 h bicyclo[6.1.0]nonan-2-one with an yield of 50%.[5] Dry ozonolysis of dibromocyclopropane **24** on silica also proceeds more slowly than the oxidation of the non-halogenated compound. Thus even when the ozonolysis was repeated three times, conversion of starting material was only 69%. Full conversion of the non-brominated analogue of **24**, bicyclo[6.1.0]nonane was observed even after one ozonolysis cycle,[6,22] and led primarily to a different regioselectivity, the α-cyclopropyl ketone **4** being obtained in a yield of 88% together with a small amount only of **30** (7%) (Scheme 10).[6]

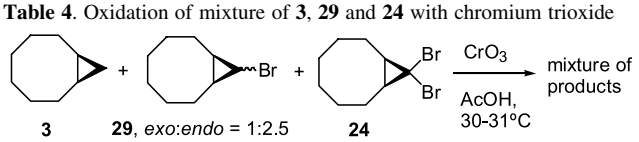


Scheme 10.

The bicycloalkane **3** is also oxidized with dimethyldioxirane, and in this case both the above ketones are isolated again in a ratio of 88:7.[8] 9,9-Dibromobicylo[6.1.0]nonane **24** does not react with dimethyldioxirane.[8] It is interesting to note that, unlike **24**, dibromide **7** was essentially unreactive to periodic acid (10 mol. equiv.) in the presence of ruthenium tetroxide (5 mol%) at 70 °C over 92 h. *gem*-Dibromocyclopropane **24** did not react with chromium trioxide in acetone or in dichloromethane in the presence of 3,5-dimethylpyrazole even when the reaction mixture was refluxed for 18 h. By comparison non-halogenated cyclopropanes react with chromium trioxide–3,5-dimethylpyrazole complex in dichloromethane even at −20 °C to give, after 3 h, α-ketones with modest yields.[4]

In order to examine the relative rates of oxidation of brominated and nonbrominated cyclopropanes, a mixture of **3**, **24** and 9-bromobicyclo[6.1.0]nonane (**29**, *exo*–*endo*=1:2.5) was treated with 8 equiv. of chromium trioxide in glacial acetic acid and the consumption of starting materials was followed by GLC (Table 4). At the start of the reaction the relative peaks areas for **3**, **29** and **24** were 37:32:31. The peak for **3** had disappeared after 10 min. Those for the two monobromides **29** had essentially disappeared after 45 min (it is interesting to note that ratio of remaining monobromides **29** did not significantly change during the experiment. This suggests that the position of bromine in the substrate does not influence the rate of oxidation). After 60 min, ca. 45% (by GC/MS data) of the dibromide **24** remained.

Table 4. Oxidation of mixture of **3**, **29** and **24** with chromium trioxide



Time of reaction	Contents of starting bicyclo[6.1.0]nonanes in the neutral fraction of the reaction mixture by GLC or GC/MS (%)		
	3	**29**	**24**
0	37[a]	32[a]	31[a]
5	4[a]	<19[a]	33[a]
10	—[a]	<7[a]	31[a]
15	—[b]	<3[b]	24[b]
60	—[b]	0[b]	14[b]

[a] By GLC.
[b] by GC/MS.

The selective oxidation of C–H bonds adjacent to cyclopropanes is usually considered to be due to activation by the ring of the neighboring methylene group. The two bromine atoms instead of hydrogen at C(9) of compound **3** seem to lead to a redistribution of the electron density in the bicyclo[6.1.0]nonane skeleton. Because of this, the propensity of an α-methylene group to be oxidized appears to be decreased. From an MO point of view, the oxidant removes an electron from the HOMO of the substrate. Optimization of geometries of both compounds **24** and **3** by ab initio methods using the STO-3G basis set followed by calculation of the HOMO location has shown, that in **24** this is located on the bromines and the quaternary carbon (energy −7.86 eV, Fig. 1), but in **3** it is located on positions 1, 2, 7 and 8 of the eight membered ring (energy −9.33 eV, Fig. 2). This suggests that oxidation of the dibromide begins

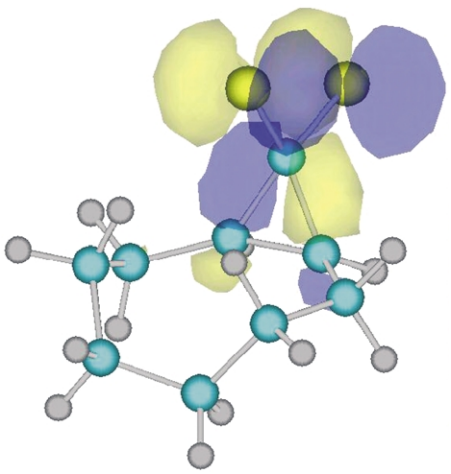


Figure 1. HOMO of 9,9dibromobicyclo-[6.1.0]-nonane **24**.

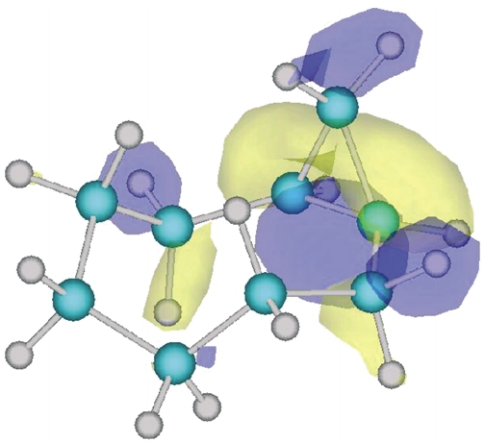
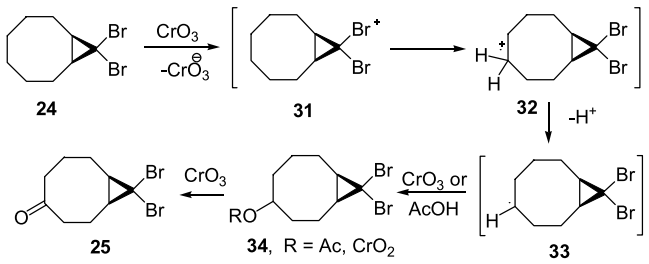


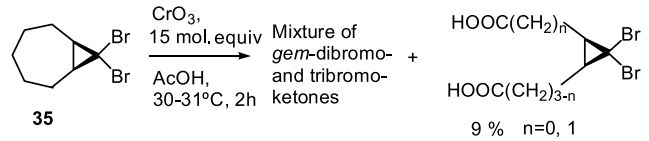
Figure 2. HOMO of bicyclo[6.1.0]nonane **3**.

by coordination of the oxidant to the bromine atoms followed by removal of an electron from the HOMO of substrate. Interaction of the derived cyclopropyl cation-radical **31** with a nearby γ-methylene group possibly produces the cation-radical **32** (Scheme 11). This loses a proton giving radical **33**. Reaction of this with solvent (AcOH) or chromium trioxide would give the ester **34**, this reacting with another molecule of oxidant forming γ-ketone **25**. The isolation of the corresponding alcohols from the ozonolysis of cyclopropane and *gem*-dichlorocyclopropane derivatives[9,14,23] can serve as evidence for participation in the reaction of intermediates of type **34**. The formation of 9,9-dibromobicyclo[6.1.0]nonan-2-one **26** can proceed by a similar process but the difference is in the redistribution of electrons in the intermediate **31** from the α-methylene groups (not from γ-links). A similar oxidation involving cation-radicals and radicals was suggested for reaction of 3,6-dehydrohomoadamantane with chromyl derivatives.[24]



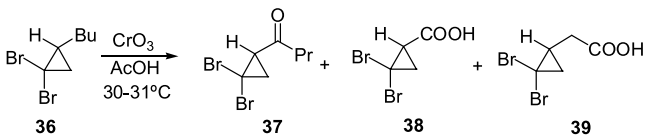
Scheme 11.

Oxidation of 8,8-dibromobicyclo[5.1.0]octane **35** with chromium trioxide in glacial acetic acid proceeds more slowly than for the other bicyclic *gem*-dibromocyclopropanes (full conversion of starting material with 15 of CrO_3 under the conditions of oxidation of 7,7-dibromobicyclo[4.1.0]heptane required 2 h at 30–31 °C instead of 1 h) and afforded a complex mixture of at least four dibromo- and tribromoketones which were not identified, together with a mixture provisionally characterized as (dibromomethano)pimelic acids (Scheme 12). The formation of tribromoketones was assumed based on the ^{1}H NMR spectrum which contained signals in the region 4.2–4.5 ppm, corresponding to the α-bromoketone CHBr fragment. The major *gem*-dibromo-ketone was not 8,8-dibromobicyclo[5.1.0]octan-4-one.[25] The reason for the lower rate of oxidation of this *gem*-dibromocyclopropane compared with reactions described above remains unclear.



Scheme 12.

Monocyclic *gem*-dibromocyclopropanes react with chromium trioxide less selectively than the bicyclic compounds above. The *gem*-dibromocyclopropylketones formed easily oxidize to carboxylic acids. Thus, e.g. 1,1-dibromo-2-butyl cyclopropane **36** reacted with chromium trioxide in acetic acid giving the ketone **37** together with acids **38** and **39** (Scheme 13). Changing the amount of oxidant from 10 to



Scheme 13.

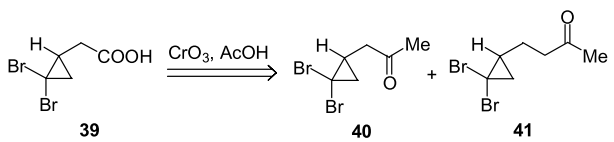
20 mol. equiv. did not change the yield of compound **37**, just the degree of conversion of starting material and the yield of acid products (Table 5). Increasing the amount of chromium trioxide to 30 mol. equiv. and the reaction time to a week led to the disappearance of neutral compounds in the reaction mixture. The acid **38** was isolated with a yield of about 36% as a single product under these conditions.

Table 5. Oxidation of **36** with chromium trioxide in glacial acetic acid

CrO_3 (mol. equiv.)	Time of stirring (h)	**36**	**37**	**38**+**39**[a]	Ratio **38**:**39**[b]
8	1	34	20	>12	1:2.6
10	1	23	24	>18	1:2.2
14	1	12	25	>24	1:2.1
20	1	0	26	>32	1:1.5
30	72	0	0	>36	100:0

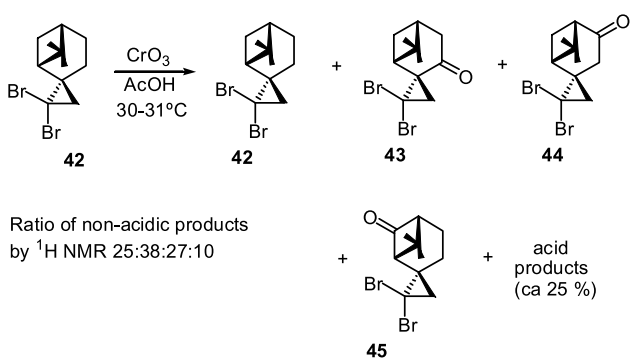
[a] Isolated as mixture of methyl esters after treatment with diazomethane.
[b] By GLC.

The formation of acid **39** is possible just from ketones **40** or **41** (Scheme 14), but not from **37**. The presence of **39** in the reaction mixture is an indirect proof of oxidation not only of an α-methylene group, but also of β- and (or) γ-groups in the chain. By comparison dry ozonolysis of butylcyclopropane led to oxidation of only the α-methylene group giving the butanoylcyclopropane with a yield of 87%.[6]



Scheme 14.

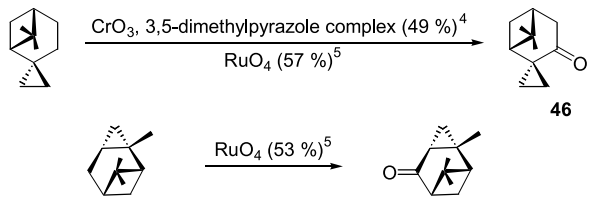
The oxidation of the tricycle **42** derived from (1*S*)-β-pinene can be used as an example of a reaction of a 1,1-dibromo-2,2-dialkylcyclopropane (Scheme 15).



Scheme 15.

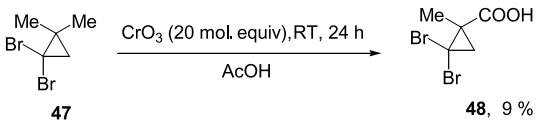
Just as in the case of 1,1-dibromo-2-butylcyclopropane **36**, oxidation occurs relatively equally at both the α- and

β-carbons to give a mixture of ketones **43**–**45**. Products of oxidation of the bridgehead carbons were not found. This can be contrasted to the non-halogenated system where oxidation occurs just at the CH_2-group next to the cyclopropane and a similar oxidation of the cyclopropane derived from β-pinene (Scheme 16).



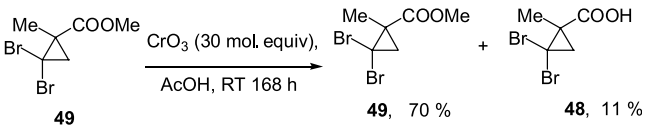
Scheme 16.

The oxidation of a methyl group is also possible under the conditions used in the present work. Thus, for example, reaction of 1,1-dibromo-2,2-dimethylcyclopropane **47** with 20 mol. equiv. chromium trioxide in glacial acetic acid led after 24 h to acid **48** in low yield (Scheme 17). The neutral fraction contained only starting material. Reaction of cyclopropane **47** with 30 mol. equiv. of oxidant for one week led to complete conversion of substrate but did not lead to an increased yield of acid **48**.



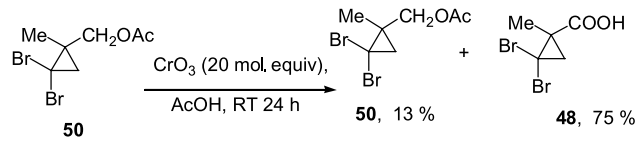
Scheme 17.

Introduction of a methoxycarbonyl group instead of one of methyl group leads to an increased stability to oxidation by chromium trioxide. Thus, in the reaction of ester **49** with 30 mol. equiv. of oxidant, 70% of the starting material was isolated from the reaction mixture even after one week (Scheme 18). The products of oxidation of the methyl group were not observed in this reaction.



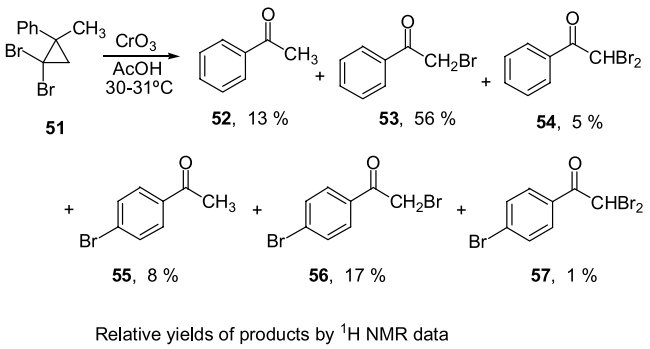
Scheme 18.

Oxidation of the methyl group was also not observed in the reaction of acetate **50**. Acid **48** was isolated in ca. 75% yield and almost 13% starting material was recovered (Scheme 19).



Scheme 19.

An unexpected result was found in the reaction of 1,1-dibromo-2-methyl-2-phenylcyclopropane **51** with chromium trioxide. Instead of oxidation of methyl or phenyl groups, opening of the cyclopropane ring was observed and a mixture of acetophenone and *p*-bromoacetophenone derivatives **52**–**57** was isolated (Scheme 20). It is necessary to note that oxidation of 1-bromo-2-methyl-2-phenylcyclopropane or of a homologue of **51**—1,1-dibromo-2-propyl-2-phenylcyclopropane—with ruthenium tetroxide led to the corresponding cyclopropanecarboxylic acids in good yields.[26,27]



Scheme 20.

3. Conclusion

Oxidation of *gem*-dibromocyclopropanes with chromium trioxide in acetic acid or a number of other reagents is found to be generally slower than that of the corresponding cyclopropane; in a number of cases moderate yields of products are obtained but these show unexpected oxidation patterns. Despite the yields, the products of these simple reactions may have synthetic potential.

This work was carried out as a part of a project supported by the INTAS programme.

4. Experimental

4.1. General

Commercial reagents were used without further purification unless stated. The dibromides (**7**),[28] (**18**),[29] (**24**),[28] (**35**),[30] (**36**),[31] the dibromocarbene adduct of (1*S*)-β-pinene (**42**),[32] and dibromides (**49**),[33] and (**51**)[34] were prepared from alkenes and bromoform in two phase reactions with cetrimide as a phase transfer catalyst using standard procedures. Bicyclo[6.1.0]nonane (**3**)[35] was prepared from (**24**) by reduction with lithium in a mixture of THF and *t*-butanol.[36] 9-Bromobicyclo[6.1.0]nonane (**29**)[37] was prepared from (**23**) by reduction with ethylmagnesium bromide in the presence of titanium isopropoxide.[26] 1,1-Dibromo-2,2-dimethylcyclopropane (**47**)[34] was prepared from isobutene and bromoform in pentane at −25 °C using potassium *tert*-butoxide as a base. The acetate of (2,2-dibromo-1-methylcyclopropyl)methanol (**50**) was prepared from **49** as described.[38] Diethyl ether and tetrahydrofuran were distilled over sodium wire. Petroleum was of boiling point 40–60 °C. Reactions requiring anhydrous conditions were performed using oven dried glassware (250 °C) that was cooled under either dry nitrogen or argon; experiments were conducted under a positive atmosphere

of argon. Unless stated, organic solutions were dried over anhydrous magnesium sulfate and evaporated at 14 mm Hg; yields quoted are for purified compounds and any ratios given are calculated by comparing integrals in the ^{1}H NMR spectrum or by GLC data.

New compounds were homogenous by GLC or TLC. GLC was conducted using a Carlo Erba HRGC 5300 F.I.D. on a capillary column (30 m×0.32 mm id Phase, DB5 split ratio of 50:1) with nitrogen carrier gas. TLC was performed using Aldrich silica plates coated with silica gel 60 (F254). Compounds were visualized by examination under an ultraviolet source, by exposure to iodine vapor or by contact with phosphomolybdic acid hydrate (2% in ethanol) followed by heating to 180 °C. Column chromatography was conducted with Matrex Silica 60 (Fisher Scientific Int.Co.) under medium pressure. Melting points are uncorrected. Unless stated, infrared spectra were obtained as solutions in $CHCl_3$ or as liquid films on a Perkin–Elmer 1600 FTIR spectrometer. Low-resolution mass spectra were measured using a Finnigan 8430 spectrometer using EI 70 eV unless stated. Accurate mass measurements refer to ^{79}Br isotopes unless stated and were carried out on a Micromass™ GCT spectrometer. Microanalyses were performed on a Carlo Erba Model 1106 CHN analyzer. NMR spectra were recorded in $CDCl_3$, using Bruker AC250 or A500 spectrometers at 250 or 500 MHz (^{1}H) and 62.9 or 125 MHz (^{13}C). ^{13}C spectra were broad-band decoupled and in most cases corresponding DEPT spectra were also recorded. The results of DEPT spectra are quoted in the form of signs + (corresponding to CH and CH_3 groups) and − (corresponding to CH_2 groups), signals which appear with no sign correspond to quaternary carbons. All previously described compounds were characterized by IR, ^{1}H and ^{13}C NMR and gave data identical to those in the literature.

All calculations were performed using Hyperchem Pro 6.0. Optimization of geometries was achieved by ab initio methods using an STO-3G basis set. The starting MO was the core Hamiltonian. Calculations were continued until the RMS (root-mean-square) gradient became less than 0.1 kcal/A mol. Conformations of all compounds were calculated in vacuo. At the beginning the conformations were calculated using the molecular-mechanics method MM+and then using ab initio methods. The displayed surfaces were generated for orbital contour value 0.06.

4.1.1. Oxidation of 7,7-dibromobicyclo[4.1.0]heptane (7). (a) *With chromium trioxide in acetic acid*. 7,7-Dibromobicyclo[4.1.0]heptane (**7**) (2.540 g, 10 mmol) was added to a suspension of chromium trioxide (15.00 g, 150 mmol) in glacial acetic acid (50 mL). The mixture was stirred at 30–31 °C for 1 h, then poured into a mixture of water (200 mL) and dichloromethane (100 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic layers were washed with water (2×50 mL), extracted with sat. aq. sodium bicarbonate (2×30 mL), water (30 mL), dried and concentrated in vacuo to give an oil (1.716 g). Chromatography on Silica (100 g) eluting with petrol–ether 10:1 gave *exo*-3,7,7-tribromobicyclo[4.1.0]heptan-2-one (**10**) (1.164 g, 34%, R_f 0.42) as a viscous oil which slowly solidified to give white crystals (mp 92–93 °C (hexane)) which showed δ_H: 2.13 (2H, m), 2.46 (3H, m), 2.77 (1H, d, J=9.3 Hz, H-1), 4.39 (1H, dd, J=6.5, 3.4 Hz, H-3); δ_C: 18.3−, 27.7, 30.2−, 32.5+, 36.9+, 49.5+, 192.8 (C=O); IR (cm^{-1}, film): 1711s (C=O), 1444m, 1312m, 1206m, 1181s, 1098m, 1020m, 993m, 944m, 808m, 785m, 736m, 695m, 677m; MS: 350 (0.1), 348 (0.6), 346 (0.6), 344 (0.1), 269 (10), 267 (19), 265 (10), 71 (100); calcd C 24.24, H 2.03%, found C 24.3, H 2.4%.

The combined sodium bicarbonate layers were washed with dichloromethane (2×10 mL), then acidified with hydrochloric acid to pH 1 and extracted with dichloromethane (3×15 mL). The combined organic layers were washed with water (10 mL), dried, filtered and concentrated in vacuo to give a yellow viscous oil (40 mg), which was not identified.

The product above could be also isolated by slow crystallization of the reaction mixture from hot hexane (7 mL per 1 g of mixture), compound (**10**) precipitating as slightly yellow sticks with mp 92–93 °C. If the melting point of product was below 90 °C purification could be achieved by slow crystallization from 10:1 hexane–ethanol (10 mL per 1 g of reaction mixture), giving shiny plates with mp 93–95 °C. The yield obtained by this method was 17–22%.

(b) *With chromium trioxide in ether*. Dibromide (**7**) (762 mg, 3 mmol) was added to a suspension of chromium trioxide (3.00 g, 30 mmol) in dry ether (20 mL) at 0 °C. A strong exothermic effect was observed. The mixture was stirred at 25–30 °C for 1 h, then poured into a mixture of water (100 mL) and ether (50 mL). The aqueous layer was extracted with ether (3×30 mL). The combined organic layers were extracted with sat. aq. sodium bicarbonate (3×10 mL), brine (3×10 mL), dried and concentrated in vacuo to give starting material (676 mg, 89%).

(c) *With periodic acid*. A mixture of dibromide (**7**) (762 mg, 3 mmol), carbon tetrachloride (10 mL), acetonitrile (10 mL), water (15 mL), periodic acid (6.84 g, 30 mmol) and ruthenium trichloride (42 mg, 0.15 mmol, 5 mol%) was stirred at 70–75 °C. After 92 h, the black mixture was cooled, poured in water (20 mL) and extracted with dichloromethane (3× L). The combined organic layers were washed with water (10 mL), sat. aq. sodium bicarbonate (2×10 mL) and water (10 mL), dried and concentrated in vacuo to give an oil (574 mg) which contained by GLC and ^{1}H NMR data starting material (76%), *exo*-3,7,7-tribromobicyclo[4.1.0]heptan-2-one (**10**) (7%) and two unidentified compounds.

The combined sodium bicarbonate layers were washed with dichloromethane (10 mL), then acidified with hydrochloric acid to pH 1 and extracted with dichloromethane (3×5 mL). The combined organic layers were washed with water (10 mL), dried, filtered and concentrated in vacuo to give a yellow viscous oil (1 g), which was not identified.

4.1.2. *exo*-3,7,7-Tribromobicyclo[4.1.0]heptan-*endo*-2-ol (11). Sodium borohydride (73 mg, 1.93 mmol) was added to *exo*-3,7,7-tribromobicyclo[4.1.0]heptan-2-one (**10**) (67 g, 1.93 mmol) in dry ethanol (6 mL) and benzene (3 mL), stirred at 15–20 °C for 1 h, then poured in water (30 mL)

and extracted with dichloromethane (4×10 mL). The combined organic layers were washed with water (15 mL), dried and concentrated in vacuo to give an oil (712 mg). Chromatography on Silica (20 g) eluting with 3:2 petrol–ether gave exo-3,7,7-tribromobicyclo[4.1.0]heptan-endo-2-ol (**11**) (608 mg, 90%, R_f 0.40) as white crystals (mp 76.5–79 °C) which showed δ_H: 1.63 (1H, dddd, J=14.7, 13.7, 5.5, 3.2 Hz, H-5^{endo}), 1.73–1.86 (1H, m), 2.09–2.15 (1H, m), 2.15 (1H, ddd, J=10.6, 10.2, 3.2 Hz, H-6), 2.24 (1H, dddd, J=14.7, 10.2, 5.0, 2.2 Hz, H-5^{exo}), 2.31 (1H, dd, J=10.6, 7.5 Hz, H-1), 2.59 (1H, d, J=4.9 Hz, O*H*), 4.19–4.34 (2H, m); δ_C: 23.0−, 31.5+, 33.5, 33.7−, 34.4+, 54.5+, 74.3+; IR (cm^{-1}, $CHCl_3$): 3441br.s (OH), 2949s, 2926s, 2864s, 1443s, 1387m, 1344s, 1289m, 1262s, 1225s, 1191m, 1174s, 1129m, 1112s, 1058s, 1023s, 973m, 959m, 911s, 858m, 820s, 804s, 754s, 718s; calcd C 24.10, H 2.60%, found C 24.4, H 2.4%.

4.1.3. *endo*-8,8-Dibromo-3-oxatricyclo[5.1.0.0^{2,4}]octane (12). Ethanolic sodium hydroxide (1.0 mL, C 0.44 M, 0.44 mmol) was added to *exo*-3,7,7-tribromobicyclo[4.1.0]-heptan-*endo*-2-ol (**11**) (106 mg, 0.3 mmol), stirred for 4 h at ambient temperature, then poured in water (5 mL), extracted with dichloromethane (4×2 mL), dried and concentrated in vacuo to give an oil (99 mg). This was purified on Silica (5 g) eluting with petrol–ether 10:1 to give endo-8,8-dibromo-3-oxatricyclo[5.1.0.0^{2,4}]octane (**12**) (81 mg, 100%, R_f 0.31) as white crystals (mp 75.5–76 °C) which showed δ_H: 1.25–1.41 (1H, m), 1.59–1.75 (2H, m), 1.90–2.05 (3H, m), 3.00 (1H, dd, J=3.7, 3.5 Hz), 3.46 (1H, ddd, J=4.0, 3.7, 0.8 Hz); δ_C: 16.3−, 21.2−, 24.4+, 26.6+, 31.2, 46.8+, 47.7+; IR (cm^{-1}, in $CHCl_3$): 3013m, 2940m, 1416m, 1349m, 1081s, 1053s, 984m, 893m, 834m, 818s, 622m; calcd C 31.38, H 3.01%, found C 31.6, H 2.7%.

4.1.4. Reaction of *exo*-3,7,7-tribromobicyclo[4.1.0]heptan-2-one (10) with pyridine. A solution of pyridine (87 mg, 1.098 mmol, 3 mol. equiv.) and *exo*-3,7,7-tribromide (**10**) (127 mg, 0.366 mmol) in dry DMSO (3 mL) was stirred at 90–95 °C. After 4 h the mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and extracted with 1 M hydrochloric acid (15 mL). The water layer was extracted with dichloromethane (3×5 mL). The combined organic layers were washed with water (2×10 mL), dried and concentrated in vacuo to give a yellow solid (108 mg). Chromatography on Silica (25 g) eluting with 3:1 petrol–ether gave 4,7,7-tribromobicyclo-[4.1.0]hept-3-en-2-on-3-ol (**13**) (24.6 mg, R_f 0.31) as white crystals which showed δ_H: 2.49 (1H, dd, J=9.5, 8.5 Hz, H-6), 2.91 (1H, d, J=9.5 Hz, H-1), 3.19 (1H, d, J=20.2 Hz, H-5^{endo}), 3.36 (1H, dd, J=20.2, 8.5 Hz, H-5^{exo}), 6.37 (1H, br.s, O*H*); δ_C: 25.0, 31.7+, 32.4−, 36.7+, 116.6, 145.1, 182.2 (C=O); IR (cm^{-1}, in $CHCl_3$): 3382s, 3040m, 1667s, 1633s, 1375s, 1321s, 1284m, 1189s, 1077m, 944m; MS: 364 (1.3), 362 (4.5), 360 (4.5), 358 (1.3), 283 (29), 281 (100), 279 (36), 255 (1.3), 253 (3.2), 251 (1.3), 202 (7), 200 (7), 174 (11), 172 (11); found M^+ 359.7825; calcd for $C_7H_5O_2^{79}Br^{81}Br_2$ 359.7819; and 7,7-dibromobicyclo[4.1.0]-hept-3-en-2-on-3-ol (**14**)[39] (R_f 0.22) in a mixture with enone (**13**) (40.1 mg) as a white solid which showed δ_H: 2.47–2.52 (1H, m), 2.76–2.85 (2H, m), 2.92 (1H, ddd, J=21.1, 8.5, 4.1 Hz, H-5^{exo}), 5.85 (1H, ddd, J=4.7, 4.1, 0.9 Hz, H-4), 5.95 (1H, br.s, O*H*); δ_C: 22.6−, 25.9, 32.2+, 37.3+, 115.4+, 145.9, 185.5 (C=O). In the reaction mixture, the ratio (**13**): (**14**) was 1:1.4.

4.1.5. Reaction of *exo*-3,7,7-tribromobicyclo[4.1.0]heptan-2-one (10) with sodium iodide in acetone. A solution of *exo*-3,7,7-tribromide (**10**) (100 mg, 0.29 mmol) and sodium iodide (96 mg, 0.64 mmol, 2.2 mol. equiv.) in acetone (HPLC grade, 3 mL) was stirred at ambient temperature in the dark. After 11 h, the mixture was poured into water (15 mL), extracted with dichloromethane (4×5 mL), decolorized with aq. sodium thiosulfate, dried and concentrated in vacuo to give an oil (86 mg), which contained by ^{1}H NMR starting material (57%), (**14**) (8%), (**15**) (13%) and (**16**) (22%). Chromatography of this oil (60 mg) on Silica (20 g) eluting with petrol–ether 3:1 gave starting material (26 mg, R_f 0.68) as a colorless viscous oil with spectral data identical to those above, a mixture of 7,7-dibromobicyclo-[4.1.0]heptan-2-one (**16**) (for data see reaction of (**10**) with thiourea) and 4-iodo-7,7-dibromobicyclo[4.1.0]hept-3-en-2-on-3-ol (**15**) (16 mg, R_f 0.46, as a colorless oil with yellow crystals) which showed δ_H: 2.42–2.48 (1H, m), 2.91 (1H, d, J=9.5 Hz), 3.28 (1H, d, J=20.2 Hz), 3.44 (1H, dd, J=20.2, 8.5 Hz), 6.57 (1H, br.s); δ_C: 25.0, 34.1+, 36.1−, 37.1+, 93.1, 148.7, 179.8; MS (CI, 70 eV, methane): 410 (14), 409 (11), 408 (32), 407 (21), 406 (15), 405 (9), 329 (96), 327 (100), 301 (5), 299 (5); found $[M-H]^+$ 408.7596; calcd for $C_7H_4O_2^{81}Br_2I$ 408.7582; and 7,7-dibromobicyclo[4.1.0]hept-3-en-2-on-3-ol (**14**)[39] (3 mg, R_f 0.31) as a colorless viscous oil with spectral data identical to those above (this contained by ^{1}H NMR about 50% unidentified impurities).

4.1.6. Reaction of *exo*-3,7,7-tribromobicyclo[4.1.0]heptan-2-one (10) with thiourea. *exo*-3,7,7-Tribromobicyclo-[4.1.0]heptan-2-one (**10**) (173 mg, 0.5 mmol) and thiourea (114 mg, 1.5 mmol) were refluxed in methanol (1.5 mL) for 4 h. The mixture was cooled to room temperature, then poured into a mixture of dichloromethane (9 mL), water (4 mL) and sat. aq. sodium bicarbonate (1.5 mL). The water layer was extracted with dichloromethane (4×3 mL). The combined organic layers were washed with water (34 mL), dried, filtered and concentrated in vacuo to give mixture of a yellow oil with a yellow solid (149 mg). This was separated on Silica (20 g) eluting with 1:2 petrol–ether to give (**17**) (51 mg, 32%, R_f 0.36) as white solid with mp 138.5–139 °C (dec.) which showed δ_H: 2.13–2.27 (3H, m), 2.61 (1H, ddd, J=16.4, 8.7, 7.6 Hz), 2.70 (1H, dddd, J=16.4, 7.6, 5.4, 1.3 Hz), 2.77 (1H, d, J=10.4 Hz), 4.70–5.10 (2H, br.s); δ_C: 20.0−, 20.3−, 29.3+, 30.7+, 37.1, 120.0, 141.6, 164.7; IR (cm^{-1}, $CHCl_3$): 1621s, 1583m, 1540s, 1524s, 1431m, 1400m, 1364m, 1308s, 1113m, 1090m, 1070m; calcd C 29.65, H 2.49, N 8.65%, found C 30.0, H 2.7, N 8.8%. A mixture of other products (96 mg) was also isolated as white solid together with a colorless oil. This was again separated on Silica (15 g) eluting with 4:1 petrol–ether to give 7,7-dibromobicyclo-[4.1.0]heptan-2-one (**16**) (55 mg, 41%, R_f 0.38) as a colorless oil which showed δ_H: 1.72–1.82 (2H, m), 1.94–2.00 (1H, m), 2.20–2.28 (2H, m), 2.31–2.38 (1H, m), 2.40–2.47 (1H, m), 2.50 (1H, d, J=9.5 Hz); δ_C: 21.1−, 23.9−, 31.2, 35.0+, 38.1+, 38.4−, 202.2; IR (cm^{-1}, film): 2947m, 2867m, 1702s, 1445m, 1412m, 1354m, 1323s, 1306m, 1232m, 1179m, 1148s, 951m, 737s; calcd C 31.38, H 3.01%, found C 31.7, H 3.0%.

4.1.7. Oxidation of 6,6-dibromobicyclo[3.1.0]hexane (18) with chromium trioxide in acetic acid. 6,6-Dibromobicyclo[3.1.0]hexane (**18**) (2.399 g, 10 mmol) was added to a suspension of chromium trioxide (15.00 g, 150 mmol) in glacial acetic acid (50 mL). The mixture was stirred at 30–31 °C for 1 h, then poured into mixture of water (200 mL) and dichloromethane (100 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic layers were washed with water (2×50 mL), extracted with sat. aq. sodium bicarbonate (2×30 mL), water (30 mL), dried, filtered and concentrated in vacuo to give an oil (1.74 g). This was separated on Silica (100 g) eluting with 20:1 petrol–ether to give starting material (84 mg, 4%, R_f 0.91), *exo*-3,6,6-tribromobicyclo[3.1.0]hexan-2-one (**19**) (984 mg, 30%, R_f 0.30) as white crystals (mp 44.5–46.5 °C) which showed δ_H: 2.65 (1H, ddd, *J*=15.5, 6.7, 5.3 Hz, H-4^{exo}), 2.80 (1H, dd, *J*=6.7, 6.7 Hz, H-5), 2.88 (1H, dd, *J*=15.5, 8.2 Hz, H-4^{endo}), 2.90 (1H, d, *J*=6.7 Hz, H-1), 4.27 (1H, dd, *J*=8.2, 5.3 Hz, H-3); δ_C: 27.2, 25.5−, 37.9+, 42.7+, 44.8+, 200.42 (C=O); IR (cm^{-1}, $CHCl_3$): 1748s (C=O), 974m; MS: 255 (28), 253 (56), 251 (28), 55 (100); calcd C 21.65, H 1.51%, found C 21.8, H 1.7%; *exo*-2,6,6-tribromobicyclo-[3.1.0]hexan-3-one (**20**) (100 mg, 3%, R_f 0.39) as white crystals (mp 101–105 °C (dec.)) which showed δ_H: 2.48 (1H, d, *J*=19.5 Hz, H-4^{endo}), 2.54 (1H, dd, *J*=8.3, 6.4 Hz, H-5), 2.65 (1H, d, *J*=8.3 Hz, H-1), 2.87 (1H, dd, *J*=19.5, 6.4 Hz, H-4^{exo}), 4.08 (1H, s, H-2); δ_C: 31.2+, 33.9, 37.7−, 37.8+, 44.3+, 206.4 (C=O); IR (cm^{-1}, $CHCl_3$): 1753s (C=O), 1137m, 1034m; MS: 255 (31), 253 (62), 251 (31); calcd C 21.65, H 1.51%, found C 22.0, H 1.3%; exo,exo-2,4,6,6-tetrabromo-bicyclo[3.1.0]hexan-3-one (**21**) (64 mg, 2%, R_f 0.48) as white crystals (mp 110.0–115.0 °C (dec.)) which showed δ_H: 2.87 (2H, s, H-1, H-5), 4.17 (2H, s, H-2, H-4); δ_C: 30.2, 37.9+, 39.0+, 203.3 (C=O); IR (cm^{-1}, $CHCl_3$): 1761s (C=O); MS: 293 (4), 291 (12), 289 (12), 287 (4), 255 (36), 253 (72), 251 (36), 227 (25), 225 (50), 223 (25), 65 (100); calcd C 17.51, H 0.98%, found C 18.0, H 0.7%.

The combined sodium bicarbonate layers were washed with dichloromethane (2×10 mL), then acidified with hydrochloric acid to pH 1 and extracted with dichloromethane (3×15 mL). The combined organic layers were washed with water (10 mL), dried and concentrated in vacuo to give a yellow viscous oil (103 mg), which was not identified.

4.1.8. *exo*-3,6,6-Tribromobicyclo[3.1.0]hexan-*endo*-2-ol (22). Sodium borohydride (19.0 mg, 0.50 mmol) was added to a solution of (**19**) (167.5 mg, 0.50 mmol) in dry ethanol (4 mL) and benzene (0.8 mL) and stirred at ambient temperature. After 10 min, TLC showed no starting material. The mixture was poured in water (20 mL) and extracted with dichloromethane (4×5 mL). The combined organic layers were washed with water (10 mL), dried and concentrated in vacuo to give white solid (170 mg). This was purified on Silica (40 g) eluting with 3:1 petrol–ether to give *exo*-3,6,6-tribromobicyclo[4.1.0]heptan-endo-2-ol (**22**) (146 mg, 87%, R_f 0.33) as white crystals (mp 111.5–112 °C) which showed δ_H: 2.30 (1H, d, *J*=8.1 Hz, O*H*), 2.33 (1H, dd, *J*=7.9, 6.3 Hz, H-1), 2.49 (1H, dd, *J*=8.4, 6.3 Hz, H-5), 2.52 (1H, ddd, *J*=15.1, 8.4, 6.3 Hz, H-4^{exo}), 2.74 (1H, dd, *J*=15.1, 8.5 Hz, H-4^{endo}), 4.28 (1H, ddd, *J*=8.5, 6.9, 6.9 Hz, H-3), 4.86 (1H, ddd, *J*=8.1, 7.9, 6.9 Hz, H-2); δ_C: 31.0, 37.0+, 38.1−, 40.2+, 50.2+, 85.4+; IR (cm^{-1}, $CHCl_3$): 3300br.s (OH), 3050m, 1438m, 1329m, 1266m, 1083s, 1070s, 1028m, 932m, 904m, 856m, 806m, 790s, 720m; calcd C 21.52, H 2.11%, found C 21.4, H 2.2%.

4.1.9. *endo*-7,7-Dibromo-3-oxatricyclo[4.1.0.0^{2,4}]heptane (23). Ethanolic sodium hydroxide (1.78 mL, C 0.21 M, 0.366 mmol) was added to (**22**) (30.6 mg, 0.091 mmol) and stirred for 96 h at ambient temperature, then poured into water (25 mL), extracted with dichloromethane (4×5 mL), dried and concentrated in vacuo to give endo-7,7-dibromo-3-oxatricyclo[4.1.0.0^{2,4}]heptane (**23**) (21.4 mg, 92%) as a yellow oil which showed δ_H: 1.94 (1H, ddd, *J*=16.1, 7.6, 2.5 Hz), 2.04 (1H, dd, *J*=16.1, 2.5 Hz), 2.25 (1H, dd, *J*=8.3, 2.9 Hz), 2.73–2.76 (1H, m), 3.78–3.80 (2H, m); δ_C: 29.4−, 33.6+, 34.8, 47.4+, 58.2+, 68.3+; IR (cm^{-1}, film): 3031m, 2922m, 1424m, 1306m, 1232m, 1193m, 1053m, 1019s, 957m, 873m, 841s, 788m, 724m, 705m, 681m; MS (CI, 70 eV, methane): 257 (9), 255 (18), 253 (6), 176 (22), 175 (63), 174 (27), 173 (53), 147 (97), 145 (100); found $[M+H]^+$ 252.8858; calcd for $C_6H_7OBr_2$ 252.8864.

4.1.10. Oxidation of 9,9-dibromobicyclo[6.1.0]nonane (24) with chromium trioxide. (a) *In acetic acid*. 9,9-Dibromobicyclo[6.1.0]nonane (**24**) (846 mg, 3 mmol) was added to a suspension of chromium trioxide (2.40 g, 24 mmol) in glacial acetic acid (20 mL). The mixture was stirred at 30–31 °C for 1 h, then poured into a mixture of water (100 mL) and dichloromethane (50 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×30 mL). The combined organic layers were washed with water (2×30 mL), extracted with sat. aq. sodium bicarbonate (2×15 mL), brine (2×20 mL), dried, filtered and concentrated in vacuo to give an oil (680 mg). This was separated on Silica (70 g) eluting with petrol–ether 5:1 to give starting material (31 mg, 4%), 9,9-dibromobicyclo[6.1.0]nonan-4-one (**25**)[21] (424 mg, 48%, R_f 0.20) as white crystals (mp 55–56 °C), 9,9-dibromobicyclo[6.1.0]nonan-2-one (**26**) (116 mg, 13%, R_f 0.36) as white crystals (mp 66–69 °C from hexane) which showed δ_H: 1.05–1.27 (1H, m), 1.32–2.0 (6H, m), 2.05–2.43 (3H, m), 2.5–2.65 (1H, m), 2.58 (1H, d, *J*=11.7 Hz); δ_C: 24.4−, 27.0−, 27.3−, 28.1, 37.2+, 39.3+, 45.9−, 205.6; IR (cm^{-1}, in $CHCl_3$): 2930s, 2858m, 1708s, 1452m, 1355m; calcd C 36.52, H 4.09%, found C 36.9, H 4.0%; and 9,9-dibromobicyclo[6.1.0]nonan-3-one (**27**)[21] (7 mg, 1%, R_f 0.27) as a yellow viscous oil.

The combined sodium bicarbonate layers were washed with dichloromethane (10 mL), then acidified with hydrochloric acid to pH 1 and extracted with dichloromethane (3×5 mL). The combined organic layers were washed with water (10 mL), dried, filtered and concentrated in vacuo to give colorless oil (79 mg), which was dissolved in ether (1.5 mL), treated with diazomethane and evaporated in vacuo to give a mixture (77 mg, 7%) of dimethyl 2,3-(dibromomethano)suberate, dimethyl 3,4-(dibromomethano)-suberate and dimethyl 4,5-(dibromomethano)-suberate (analyzed as mixture of isomers) as a slightly yellow oil which showed δ_H: 1.15–2.15 (6H, m), 2.25–2.65

(4H, m), region 3.6–3.75 contained 5 singlets at 3.65, 3.66, 3.69, 3.71, 3.72 with ratio 9:7:4:7:9 respectively by ^{1}H NMR.

(b) *In dichloromethane in the presence of 3,5-dimethylpyrazole*. Chromium trioxide (6.00 g, 60 mmol) and dichloromethane were mixed and the resulting suspension was cooled to −20 °C when 3,5-dimethylpyrazole (5.768 g, 60 mmol) was added. The mixture was stirred at −15 to −20 °C for 15 min to give a dark solution, then (**24**) (846 mg, 3 mmol) was added. The mixture was stirred at −15 to −25 °C for 1 h, at 20 °C for 1 h, then refluxed for 18 h, cooled to room temperature and washed with 15% hydrochloric acid (3×20 mL), water (2×15 mL), dried and concentrated in vacuo to give starting material (810 mg, 96%).

(c) *In acetone*. Chromium trioxide (6.00 g, 60 mmol) was added in portions to acetone (20 mL) at 1 °C over 15 min at below 15 °C. Then (**24**) (846 mg, 3 mmol) was added in one batch. No exothermic effect was observed. The mixture was stirred at 19–20 °C for 1 h and analyzed by GLC. No products of oxidation were formed.

4.1.11. Oxidation of 9,9-dibromobicyclo[6.1.0]nonane (24) with periodic acid. A mixture of dibromide (**24**) (846 mg, 3 mmol), carbon tetrachloride (10 mL), acetonitrile (10 mL), water (15 mL), periodic acid (5.47 g, 24 mmol) and ruthenium trichloride (42 mg, 0.15 mmol, 5 mol%) was stirred at 70–75 °C. After 52 h the black mixture was cooled, poured into water (20 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were washed with water (10 mL), extracted with sat. aq. sodium bicarbonate (2×10 mL), washed with water (10 mL), dried, filtered and concentrated in vacuo to give an oil (574 mg). This was separated on Silica (70 g) eluting with 5:1 petrol–ether to give starting material (75 mg, 9%) as a colorless oil, **25**[21] (325 mg, 37%) as white crystals, **26** (61 mg, 7%) as white crystals and **27**[21] (18 mg, 2%) as a yellow oil with spectral and analytical data identical to those above.

The combined sodium bicarbonate layers were washed with dichloromethane (10 mL), then acidified with hydrochloric acid to pH 1. The mixture was extracted with dichloromethane (5×5 mL). The combined organic layers were washed with water (10 mL), dried and concentrated in vacuo to give a colorless oil (386 mg), which was dissolved in ether (1.5 mL), treated with diazomethane and evaporated in vacuo to give a mixture (192 mg, 17%) of dimethyl 2,3-(dibromomethano)suberate, dimethyl 3,4-(dibromomethano)suberate and dimethyl 4,5-(dibromomethano)-suberate as a slightly yellow oil with spectral data identical to those above.

4.1.12. Dry ozonolysis of 9,9-dibromobicyclo[6.1.0]-nonane (24). Silica gel (34 g) was added to a solution of (**24**) (846 mg, 3 mmol) in pentane (100 mL) and the solvent was evaporated in vacuo. The resulting powder was placed in a U-tube, cooled to −80 °C and a stream of ozone (2.5 g/h) was then passed through it for 20 min. It was then allowed to warm slowly, over 3 h, to room temperature and this cycle was repeated three times followed by elution of the organic material using ether. The resulting solution was concentrated in vacuo and analyzed by GLC (see Table 3).

4.1.13. Oxidation of bicyclo[6.1.0]nonane (3), 9-bromobicyclo[6.1.0]nonane (29) and 9,9-dibromobicyclo-[6.1.0]nonane (24) with chromium trioxide. A solution of a mixture of (**3**) (124 mg, 1 mmol), (**29**) (203 mg, 1 mmol, *exo*–*endo*=1:2.5) and (**24**) (282 mg, 1 mmol) in glacial acetic acid (2 mL) was added to a suspension of chromium trioxide (2.40 g, 24 mmol) in glacial acetic acid (18 mL). The mixture was stirred at 30–31 °C for 1 h. Aliquots (about 0.5 mL) were taken after each 5 min, quenched with sat. aq. sodium bicarbonate (20 mL) which was added until the formation of CO_2 was complete. This was extracted with ether (2 mL) and the organic layer was analyzed by GLC and GC/MS. The results of this are presented in Table 4.

4.1.14. Oxidation of 8,8-dibromobicyclo[5.1.0]octane (35) with chromium trioxide in acetic acid. 8,8-Dibromobicyclo[5.1.0]octane (**35**) (804 mg, 3 mmol) was added to a suspension of chromium trioxide (4.50 g, 45 mmol) in glacial acetic acid (15 mL). The mixture was stirred at 30–31 °C for 2 h and poured into a mixture of water (100 mL) and dichloromethane (50 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×30 mL). The combined organic layers were washed with water (2×30 mL), extracted with sat. aq. sodium bicarbonate (2×20 mL), brine (2×20 mL), dried and concentrated in vacuo to give an oil (409 mg), which contained at least four main products with retention time 7.55 (6%), 8.50 (30%), 10.65 (33%) and 11.65 min (25%). Starting material had retention time 4.55 min and it was fully converted after 2 h, but after 1 h the reaction mixture contained approximately 50% of dibromide (**35**). Chromatography on Silica (200 g) eluting with 5:1 petrol–ether gave 7 fractions (the reaction mixture showed on TLC at least 5 spots with R_f 0.46, 0.40, 0.35, 0.20, 0.15). One of the major products (with R_t 8.50 min) was isolated nearly pure; according to ^{1}H and ^{13}C NMR spectra, it was not 8,8-dibromobicyclo[5.1.0]octan-4-one[25] and showed δ_H: 1.03–1.26 (1H, m), 1.37–1.71 (3H, m), 1.82–2.06 (3H, m), 2.43–2.55 (3H, m); δ_C: 24.0−, 25.0−, 29.4−, 30.1, 32.0+, 41.2+, 44.4−, 202.2. The structure of this compound is unknown. According to ^{1}H NMR data some products contained the CHBr fragment (signals at 4.2–4.5 ppm), some of them not. According to ^{13}C NMR data all products contained a C=O fragment (δ_C: 200–202 ppm).

The combined sodium bicarbonate layers were washed with dichloromethane (10 mL), then acidified with hydrochloric acid to pH 1 and extracted with dichloromethane (5×10 mL). The combined organic layers were washed with water (10 mL), dried and concentrated in vacuo to give a yellow oil (109 mg), which was dissolved in ether (2 mL), treated with diazomethane, dried and evaporated in vacuo to give a mixture (95 mg, 9%) of, presumably, dimethyl 2,3-(dibromomethano)pimelate and dimethyl 3,4-(dibromomethano)pimelate in 54:36 ratio by GLC (attribution of peaks unknown) as a slightly yellow oil which showed δ_H: 1.62–2.12 (5H, m), 2.30–2.65 (3H, m), region 3.6–3.73 contained 4 singlets at 3.66, 3.68, 3.716, 3.723 with ratio 4:3:3:4 respectively by ^{1}H NMR; δ_C: 22.8−, 23.5−, 26.0−,

28.5, 29.2+, 32.0−, 32.2−, 32.3+, 33.4−, 33.8, 34.5+, 37.2+, 51.6+, 51.7+, 52.1+, 53.2+, 167.0, 171.5, 172.9, 173.5.

4.1.15. Oxidation of 1,1-dibromo-2-butylcyclopropane (36) with chromium trioxide in acetic acid. 1,1-Dibromo-2-butylcyclopropane (**36**) (768 mg, 3 mmol) was added to a suspension of chromium trioxide (3.00 g, 30 mmol) in glacial acetic acid (20 mL). The mixture was stirred at 30–31 °C for 1 h, then poured into water (100 mL) and dichloromethane (50 mL). The organic layer was separated and the aq. layer was extracted with dichloromethane (3×30 mL). The combined organic layers were washed with water (2×50 mL), extracted with sat. aq. sodium bicarbonate (3×20 mL), brine (2×20 mL), dried and concentrated in vacuo to give oil (606 mg). This was separated on Silica (70 g) eluting with petrol–ether 20:1 to give (**36**) (176 mg, 23%) and 1-(2,2-dibromocyclopropyl)-butan-1-one (**37**) (196 mg, 24%, R_f 0.35) as a colorless oil which showed δ_H: 1.00 (3H, t, J=7.4 Hz), 1.73 (2H, m), 1.93 (1H, dd, J=9.1, 7.4 Hz), 2.23 (1H, dd, J=7.8, 7.4 Hz), 2.68 (2H, m), 2.83 (1H, dd, J=9.1, 7.8 Hz); δ_C: 13.4+, 16.6−, 21.0, 27.0−, 38.5+, 46.4−, 201.5; IR (cm^{-1}, film): 2962m, 2874m, 1716s, 1370s, 1105m, 1069m; found M^+ 271.9047; calcd for $C_7H_{10}^{81}Br_2$ 271.9057.

The combined sodium bicarbonate layers were washed with dichloromethane (10 mL), acidified with hydrochloric acid to pH 1, then extracted with dichloromethane (4×10 mL). The combined organic layers were washed with water (20 mL), dried and concentrated in vacuo to give a colorless oil (151 mg) which was dissolved in ether (2 mL), treated with diazomethane and evaporated in vacuo to give a mixture (143 mg, ca. 18%) of methyl 2,2-dibromocyclopropanecarboxylate and methyl (2,2-dibromocyclo-propyl)-acetate[40] (ratio 1:2, respectively by ^1H NMR and GLC) as a colorless oil. Methyl (2,2-dibromocyclopropyl)acetate showed δ_H: 1.36 (1H, dd, J=7.1, 7.1 Hz), 1.85–2.02 (2H, m), 2.50 (1H, dd, J=17.0, 7.0 Hz), 2.73 (1H, dd, J=17.0, 6.8 Hz), 3.75 (3H, s); GC/MS: 274 (0.5), 272 (1), 270 (0.5), 243 (1), 241 (2), 239 (1), 53 (100); found M^+ 273.8846; calcd for $C_6H_8O_2^{81}Br_2$ 273.8850.

4.1.16. Oxidation of dibromocarbene adduct of (1*S*)-β-pinene (42) with chromium trioxide in acetic acid. *gem*-Dibromocyclopropane (**42**) (924 mg, 3 mmol) was added to a suspension of chromium trioxide (3.00 g, 30 mmol) in glacial acetic acid (20 mL). The mixture was stirred at 30–31 °C for 1 h, then poured into a mixture of water (100 mL) and dichloromethane (50 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×30 mL). The combined organic layers were washed with water (2×30 mL), extracted with sat. aq. sodium bicarbonate (2×15 mL), brine (2×20 mL), dried and concentrated in vacuo to give an oil (680 mg), which contained by ^1H NMR starting material (**42**) (25%), α-ketone (**43**) (38%), β-ketone (**44**) (27%) and cyclobutanone derivative (**45**) (10%). This oil was separated on Silica (70 g) eluting with 5:1 petrol–ether to give (**42**) (72 mg, 8%, R_f 0.95), α-ketone (**43**) (31 mg, R_f 0.56) as a colorless oil which showed δ_H: 0.92 (3H, s), 1.37 (3H, s), 1.63 (1H, d, J=7.3 Hz), 1.65 (1H, d, J=10.7 Hz), 2.17 (1H, dd, J=6.0, 6.0 Hz), 2.28 (1H, dddd, J=6.0, 5.0, 3.9, 2.5 Hz), 2.51 (1H, d, J=7.3 Hz), 2.61 (1H, dd, J=18.8, 2.5 Hz), 2.77–2.80 (2H, m) (for confirmation of structure of (**43**), a comparison of the ^1H NMR of this compound with spectra for the non-brominated ketone (**46**) and pinocarvone were made (supplementary information available)); δ_C: 21.5+, 25.4+, 30.6, 32.8−, 34.6−, 38.4+, 40.0, 44.5−, 44.8, 49.0+, 204.5; IR (cm^{-1}, film): 2950m, 1714s, 1463m, 1410m, 1388m, 1371m, 1336m, 1256m, 1123m, 1064m, 1020m, 911m, 705m; MS (CI, 70 eV, methane): 325 (55), 324 (26), 323 (100), 322 (14), 290 (7), 289 (10), 287 (10), 281 (7), 279 (18), 277 (9); found $[M+H]^+$ 324.9448; calcd for $C_{11}H_{15}O^{81}Br_2$ 324.9449; a mixture of α-ketone (**43**) with at least four unidentified compounds (170 mg, R_f 0.56, 0.49, 0.46, 0.39 and 0.34), one of them containing a COCHBr fragment based on the ^1H NMR data (dd at 4.85 ppm) and, as a colorless oil, a mixture of β-ketone (**44**) which showed in $CDCl_3$ δ_H: 1.07 (3H, s), 1.25 (3H, s), 1.66 (1H, d, J=7.4 Hz), 1.90–1.93 (1H, m), 2.02 (1H, d, J=7.4 Hz), 2.13–2.16 (2H, m), 2.36–2.39 (1H, m), 2.53 (2H, d, J=2.4 Hz); δ_C: 21.6+, 21.8+, 33.0, 35.7−, 37.8−, 39.3, 40.5−, 48.7, 54.0+, 61.0+, 215.6 and in C_6D_6 δ_H: 0.64 (3H, s), 0.66 (3H, s), 1.00 (1H, d, J=7.3 Hz), 1.31 (1H, dd, J=4.4, 1.6 Hz), 1.40 (1H, d, J=7.3 Hz), 1.50 (1H, dd, J=14.5, 4.7 Hz), 1.96 (1H, d, J=14.5 Hz), 2.03 (1H, dd, J=4.7, 1.6 Hz), 2.20 (1H, dd, J=18.3, 4.4 Hz), 2.48 (1H, d, J=18.3 Hz) (signals for this ketone were distinguished from crude NMR data by 2D spectra {COSY and HNQC} and selective decoupling experiments); GC/MS (R_t 15.75 min, EI, 70 eV): 324 (0.6), 322 (1.8), 320 (1), 243 (9), 242 (3), 241 (9), 240 (3), 214 (6), 212 (12), 210 (6); found M^+ 319.9411; calcd for $C_{11}H_{14}O^{79}Br_2$ 319.9425; with cyclobutanone derivative (**45**) which showed δ_H: two methyl groups at 0.97 and 1.40 ppm and two doublets for one proton each at 1.63 and 1.71 ppm with J=7.8 Hz; δ_C: for C=O bond 209.9 ppm (other signals were not distinguished from crude NMR); GC/MS (R_t 15.88 min, EI, 70 eV): 243 (5), 242 (2), 241 (5), 240 (2); found $[M-HBr]^+$ 240.0150; calcd for $C_{11}H_{13}O^{79}Br$ 240.0152. Assignment of structure for cyclobutanone derivative (**45**) is based on the MS spectrum, which was similar to that of β-ketone (**44**), and the IR spectrum for the mixture which showed signals for C=O bonds at 1750 cm^{-1}, attributed to (**45**) and 1717 cm^{-1}, attributed to (**44**). Treatment of this mixture (170 mg) in dry ethanol (2 mL) at 5 °C with 2,4-dinitrophenylhydrazine (123 mg, 0.62 mmol) in dry ethanol (2 mL) and sulfuric acid (0.26 mL) afforded after 5 min an orange precipitate, which was filtered after 2 h, washed with cold ethanol (2×5 mL), dried in vacuo over calcium chloride and recrystallized from 2:1 hexane–benzene (6 mL) to give the 2,4-dinitrophenylhydrazone of (**44**) (16 mg) as orange crystals (mp 168–169 °C (dec.)) which showed δ_H: 0.95 (3H, s), 1.43 (3H, s), 1.70 (1H, d, J=11.0 Hz), 1.73 (1H, d, J=7.9 Hz), 1.78 (1H, d, J=7.9 Hz), 2.17 (1H, dd, J=5.7, 5.4 Hz), 2.51 (1H, d, J=18.6 Hz), 2.73 (1H, ddd, J=11.0, 5.7, 5.4 Hz), 2.92 (1H, dd, J=5.4, 5.4 Hz), 3.37 (1H, d, J=18.6 Hz), 7.97 (1H, d, J=9.5 Hz), 8.31 (1H, dd, J=9.5, 2.5 Hz), 9.13 (1H, d, J=2.5 Hz), 11.04 (1H, s); δ_C: 23.3+, 25.5+, 27.4−, 30.7, 32.7−, 36.1, 36.5−, 42.3, 50.5+, 50.8+, 116.3+, 123.5+, 129.2, 130.0+, 137.9, 145.0, 160.7; IR (cm^{-1}, in $CHCl_3$): 3302m, 2964m, 1618s, 1584s, 1538m, 1517m, 1497s, 1426s, 1368m, 1338s, 1309s, 1273s, 1256s, 1129m, 1066m, 695m, 669m; calcd C 40.66, H 3.61, N 11.16%, found C 40.8, H 3.7, N 11.5%.

The combined sodium bicarbonate layers were washed with dichloromethane (2×10 mL), then acidified with hydrochloric acid to pH 1 and extracted with dichloromethane (3×10 mL). The combined organic layers were washed with water (10 mL), dried and concentrated in vacuo to give a colorless oil, which was dissolved in ether (3 mL), treated with diazomethane and evaporated in vacuo to give a mixture (191 mg) of unidentified methyl esters.

Oxidation of *gem*-dibromocyclopropane (**42**) (3.081 g, 10 mmol) as above with subsequent addition of 2,4-dinitrophenylhydrazine (1.183 g, 5.97 mmol) in dry ethanol (15 mL) and sulfuric acid (2.5 mL) to a solution of the neutral fraction of the reaction mixture (1.988 g) in dry ethanol (5 mL) and stirring over 24 h, afforded an orange precipitate. This was washed with cold water–methanol (1:1) and recrystallized from isopropanol (precipitation was very slow) to give 2,4-dinitrophenylhydrazone of α-ketone (**43**) (65 mg) as orange crystals (mp 180–183 °C (dec.)) which showed δ_H: 0.98 (3H, s), 1.23 (3H, s), 1.58 (1H, d, *J*=7.6 Hz), 1.87 (1H, m), 1.96 (1H, d, *J*=7.6 Hz), 2.09 (1H, d, *J*=13.9 Hz), 2.18 (1H, dd, *J*=13.9, 4.4 Hz), 2.68 (1H, dd, *J*=4.4, 1.6 Hz), 2.70 (2H, m), 7.88 (1H, d, *J*=9.6 Hz), 8.24 (1H, dd, *J*=9.6, 2.6 Hz), 9.08 (1H, d, *J*=2.6 Hz), 10.79 (1H, s); δ_C: 21.4+, 21.8+, 31.0−, 33.0, 38.0−, 38.4−, 39.2, 50.4, 54.5+, 55.2+, 116.4+, 123.6+, 129.1, 130.0+, 137.7, 145.1, 166.9; IR (cm^{-1}, in $CHCl_3$): 3308m, 3110m, 2991m, 2958m, 2940m, 1650m, 1613s, 1589s, 1638s, 1513s, 1470m, 1455m, 1420s, 1393m, 1364s, 1336s, 1312s, 1288s, 1268s, 1180m, 1137s, 1070s, 1042m, 1027m, 1015m, 922m, 842m, 833m, 691m; MS: 504 (39), 502 (91), 500 (37), 461 (8), 459 (16), 457 (8), 423 (20), 421 (20), 242 (16), 240 (20); found M^+ 499.9690; calcd for $C_{17}H_{18}N_4O_4Br_2$ 499.9695.

4.1.17. Oxidation of 1,1-dibromo-2,2-dimethylcyclopropane (47) with chromium trioxide. The dibromide (**47**) (684 mg, 3 mmol) was added to a suspension of chromium trioxide (6.00 g, 60 mmol) in glacial acetic acid (20 mL), stirred at room temperature for 24 h, then poured into water (100 mL) and dichloromethane (50 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×30 mL). The combined organic layers were washed with water (2×50 mL), extracted with sat. aq. sodium bicarbonate (2×20 mL), brine (2×20 mL), dried and concentrated at normal pressure to give starting material. The combined sodium bicarbonate layers were washed with dichloromethane (20 mL), acidified with hydrochloric acid to pH 1 and extracted with dichloromethane (5×10 mL). The combined organic layers were washed with water (20 mL), dried and concentrated in vacuo to give 2,2-dibromo-1-methylcyclopropanecarboxylic acid (**48**) (67 mg, 9%) as a white solid.[41]

4.1.18. Oxidation of methyl 2,2-dibromo-1-methylcyclopropanecarboxylate (49) with chromium trioxide. Methyl 2,2-dibromo-1-methylcyclopropanecarboxylate (**49**) (816 mg, 3 mmol) was added to a suspension of chromium trioxide (9.00 g, 90 mmol) in glacial acetic acid (20 mL), stirred at room temperature for 168 h, then poured into water (100 mL) and dichloromethane (50 mL). The organic layer was separated and the aq. layer was extracted with dichloromethane (3×30 mL). The combined organic layers were washed with water (2×20 mL), extracted with sat. aq. sodium bicarbonate (3×10 mL), brine (2×20 mL), dried and concentrated in vacuo to give starting material (**49**) (570 mg, 70%) as slightly yellow oil.

The combined sodium bicarbonate layers were washed with dichloromethane (20 mL), then acidified with hydrochloric acid to pH 1 and extracted with dichloromethane (4×10 mL). The combined organic layers were washed with water (20 mL), dried and concentrated in vacuo to give 2,2-dibromo-1-methylcyclopropanecarboxylic acid (**48**) (87 mg, 11%) as a white solid.[41]

4.1.19. Oxidation of acetate of (2,2-dibromo-1-methylcyclopropyl)methanol (50) with chromium trioxide. The acetate (**50**) (572 mg, 2 mmol) was added to a suspension of chromium trioxide (4.00 g, 40 mmol) in glacial acetic acid (12 mL). The mixture was stirred at ambient temperature for 24 h, then poured into water (100 mL) and dichloromethane (50 mL). The organic layer was separated and the aq. layer was extracted with dichloro-methane (3×30 mL). The combined organic layers were washed with water (2×50 mL), extracted with sat. aq. sodium bicarbonate (2×20 mL), water (30 mL), dried and concentrated in vacuo to give starting material (**50**) (74 mg, 13%) as slightly yellow oil.

The combined sodium bicarbonate layers were washed with dichloromethane (10 mL), acidified with hydrochloric acid to pH 1 and extracted with dichloromethane (4×10 mL). The combined organic layers were washed with water (10 mL), dried and concentrated in vacuo to give 2,2-dibromo-1-methylcyclopropancarboxylic acid (**48**) (385 mg, 75%) as a white solid.[41]

4.1.20. Oxidation of 1,1-dibromo-2-methyl-2-phenylcyclopropane (51) with chromium trioxide in glacial acetic acid. Dibromide (**51**) (870 mg, 3 mmol) was added to a suspension of chromium trioxide (6.00 g, 60 mmol) in glacial acetic acid (20 mL). The mixture was stirred at 30–31 °C for 1 h, then poured into water (100 mL) and dichloro-methane (50 mL). The organic layer was separated and the aq. layer was extracted with dichloromethane (3×30 mL). The combined organic layers were washed with water (2×50 mL), extracted with sat. aq. sodium bicarbonate (2×20 mL), water (30 mL), dried and concentrated in vacuo to give a mixture (672 mg) of acetophenone (**52**), α-bromoacetophenone (**53**),[42] α,α-dibromoacetophenone (**54**),[42] *p*-bromoacetophenone (**55**),[43] α,*p*-dibromoacetophenone (**56**)[42] and α,α,*p*-tribromoacetophenone (**57**),[44] in ratio 13:56:5:8:17:1 respectively by ^{1}H NMR. The identity of acetophenone derivatives was confirmed by direct comparison of ^{1}H NMR and GC/MS spectral data with those of authentic samples or by comparison with literature data.

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Corrigendum

Corrigendum to: "Michael reaction of indoles with 3-(2′-nitrovinyl)indole under solvent-free conditions and in solution. An efficient synthesis of 2,2-bis(indolyl)nitroethanes and studies on their reduction" [Tetrahedron 60 (2004) 1941–1949]☆

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On page 1944, of the above paper, in Scheme 6, structure 7 'c' should be 'f'.
On page 1944, of the above paper, in structure 13 'c' should be 'f'.
On page 1949, of the above paper, Ref. 23, should be, Chakrabarty, M.; Ghosh, N.; Basak, R.; Harigaya, Y. *Synth. Commun.* **2004**, *34*, 421.

☆ doi of original article 10.1016/j.tet.2003.12.021
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doi:10.1016/j.tet.2004.02.044