Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 9523–9536

TETRAHEDRON

Synthetic studies on the preparation of oxygenated spongiane diterpenes from carvone

Antonio Abad,[a,*] Consuelo Agulló,[a] Ana C. Cuñat,[a] Ana Belén García[a] and Carlos Giménez-Saiz[b,†]

[a]*Departamento de Química Orgánica, Universidad de Valencia, Dr. Moliner 50, 46100-Burjassot, Valencia, Spain*
[b]*Instituto de Ciencia Molecular, Universidad de Valencia, Dr. Moliner 50, 46100-Burjassot, Valencia, Spain*

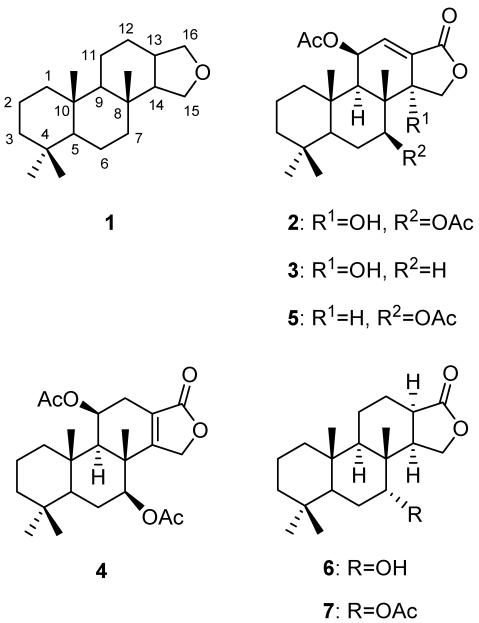
Received 20 May 2003; revised 2 October 2003; accepted 6 October 2003

Abstract—The paper describes a new diastereoselective approach to oxygenated spongiane diterpenes functionally related to natural dorisenones. The strategy followed for the preparation of the spongiane framework, a B→AB→ABC→ABCD approach, is based on the preparation of epoxydecalone **11** (AB rings) from *R*-(−)-carvone, followed by an intramolecular Diels–Alder reaction for the construction of the C ring (compound **26**). Further manipulation of the Diels–Alder adduct functionality allows the completion of the spongiane framework and the elaboration of several oxygenated spongiane-type compounds. The structures of two compounds **27** and **31**, has been established by single-crystal X-ray crystallography.

1. Introduction

A wide variety of diterpenes with the spongiane tetracyclic skeleton (**1**) has been isolated from various species of sponges and sponge-eating marine nudibranchs.[1] Many of these metabolites show a wide spectrum of biological properties,[2] that may be associated in some cases with the presence of an electrophilic γ-butenolide moiety at the D ring.[3] Such is the case of dorisenones A (**2**), B (**3**), C (**4**) and D (**5**), four spongiane diterpenoids recently isolated together with other related saturated compounds (e.g. **6** and **7**) from the Japanese marine mollusc *Chromodoris obsoleta* (Chromodorididae). These dorisenones showed strong cytotoxicity against several cell lines.[4] As has been previously suggested for related systems,[5] the enhanced biological activity of these and other highly oxygenated spongiane diterpenes may be due to the presence of polar groups (i.e. OH, acetate, epoxide, etc.) in the region of the Michael acceptor center.[6]

Although various strategies have been employed in the construction of the spongiane framework,[7,8] few of them are non-racemic synthesis and allow the incorporation of sufficient functionality for elaboration of the more oxygenated natural products. In fact, to the best of our knowledge, no synthetic approaches to oxygenated spongianes of the type of those showed above have been reported. Thus, and in connection with our previous work on the synthesis of spongianes[9] and the use of the readily available monoterpene carvone as the chiral building block for the synthesis of polycyclic terpenes,[10] we report here complete details of our efforts directed towards the preparation of spongiane-type diterpenoids structurally and functionally related to dorisenones.[11] Our interest was focused on the development

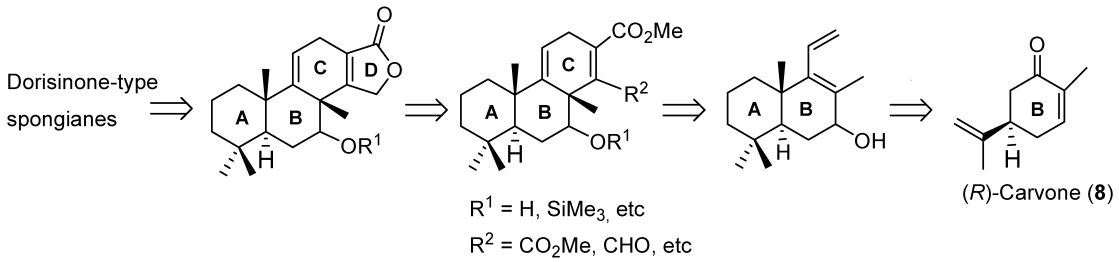


Keywords: terpene; spongiane; synthesis; carvone; Diels–Alder reaction; X-ray; epoxide rearrangement; cytotoxic activity.

* Corresponding author. Tel.: +34-96-3544509; fax: +34-96-3544328; e-mail: antonio.abad@uv.es; saiz@uv.es

† To whom correspondence should be addressed regarding the X-ray diffraction studies.

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.10.017



Scheme 1. The B→AB→ABC→ABCD approach to the spongiane tetracyclic framework from carvone.

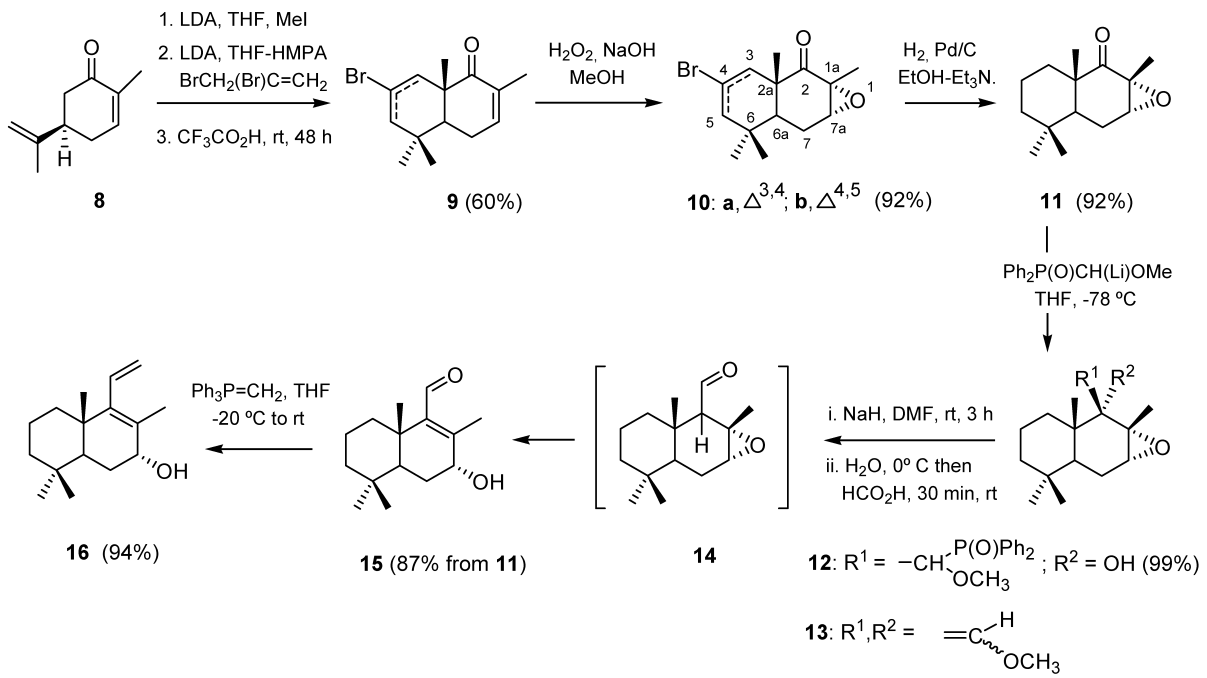
of a simple procedure for enantiomerically preparing the spongiane framework with a functionality that could permit us to prepare not only the natural compounds but also some non-natural analogues, which may be used to study the biological profile of these kinds of spongiane diterpenes.

2. Results and discussion

The approach followed for the construction of the spongiane framework was based (Scheme 1) on the initial conversion of (*R*)-(−)-carvone (**8**) into a *trans*-decalin, the AB ring system, having an oxygenated function at C-7 (spongiane numbering) and a diene moiety suitably to be used in a Diels–Alder reaction for the construction of the C-ring. In principle, the C-ring formed in this manner has an appropriate functionality for further elaboration of the γ-lactone D-ring and introduction of the oxygenated functionality at the C-11 position of the spongiane skeleton.

2.1. Preparation of the AB ring system from carvone

The first stage of the synthesis of the required bicyclic diene was the conversion of (*R*)-carvone (**8**) into the epoxy-decalone **11** (Scheme 2). This transformation was based on the methodology previously developed by Gesson for the stereoselective transformation of carvone into a decalone system.[12] Thus, the (*R*)-carvone was stereoselectively transformed into a chromatographically homogeneous 3:2 mixture of regioisomeric vinyl bromides **9** by double alkylation of its kinetic enolate, first with MeI and then with 2,3-dibromopropene, followed by trifluoroacetic acid catalyzed cationic cyclisation. The conjugate double bond of both vinyl bromides **9** was chemo- and stereoselectively epoxidated by treatment with alkaline hydrogen peroxide to provide a mixture of α,β-epoxy-enones **10a**,**b**, only partially separable by chromatography. Conversion of this mixture to the α-epoxy decalone **11** was finally completed by hydrogenation in EtOH, using 10% Pd–C as the catalyst and Et_3N to capture the HBr formed. The assigned stereochemistry of the epoxide **11** was supported by its NMR data. Particularly relevant was the signal due to C-6a[‡] (δ 39.0 ppm) in the ^{13}C NMR spectra which is shifted appreciably in this compound (ca. 8 ppm) with respect to the saturated decalone resulting from complete hydrogenation of **9**,[13] due to the shielding effect (γ-effect) exerted by the



Scheme 2.

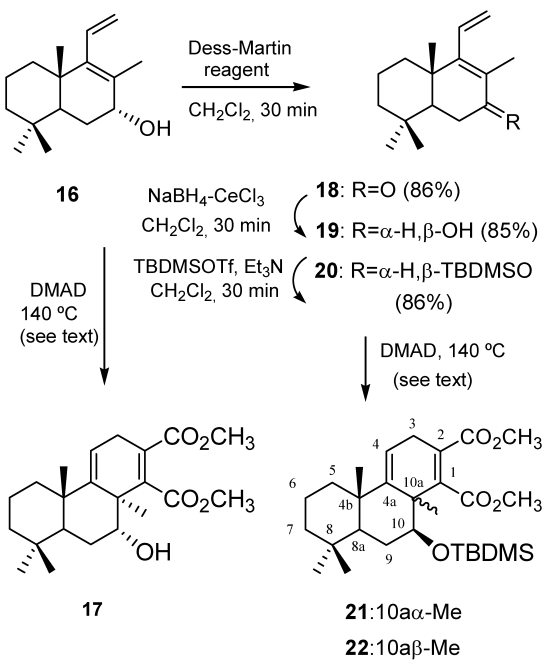
[‡] All compounds have been named throughout the paper as required by IUPAC nomenclature rules, with the exception of tetracyclic compounds that have been named as spongiane derivatives using the system numbering given in structure **1**.

α-oriented epoxide moiety. The global yield for the transformation of carvone into **11** via this five-step reaction sequence was around 50%.

Addition of the lithium derivative of α-methoxymethyldiphenylphosphine oxide to the carbonyl group of **11** took place stereoselectively in THF at low temperature to afford a mixture of two diastereoisomeric β-hydroxyphosphine oxides **12** in nearly quantitative yield after column chromatography. Subjection of the mixture of epimeric β-hydroxyphosphine oxides to *syn* elimination by treatment with sodium hydride in DMF at room temperature gave a mixture of isomeric vinyl ethers **13**, which were very labile, extensive hydrolysis occurring on attempted isolation and, particularly, with column chromatography. For this reason, they were not isolated but treated in situ with aqueous formic acid to effect hydrolysis of the vinyl ether moiety and subsequent opening of the initially formed β,γ-epoxy aldehyde **14**, providing the desired unsaturated hydroxy aldehyde **15** in 87% overall yield for the three-step reaction sequence from epoxy ketone **11**. Finally, the required diene moiety was completed in high yield via Wittig methylenation of the aldehyde group of **15** by reaction with methylidenetriphenylphosphorane ($Ph_3P{=}CH_2$) under standard conditions.

2.2. Construction of the C ring system

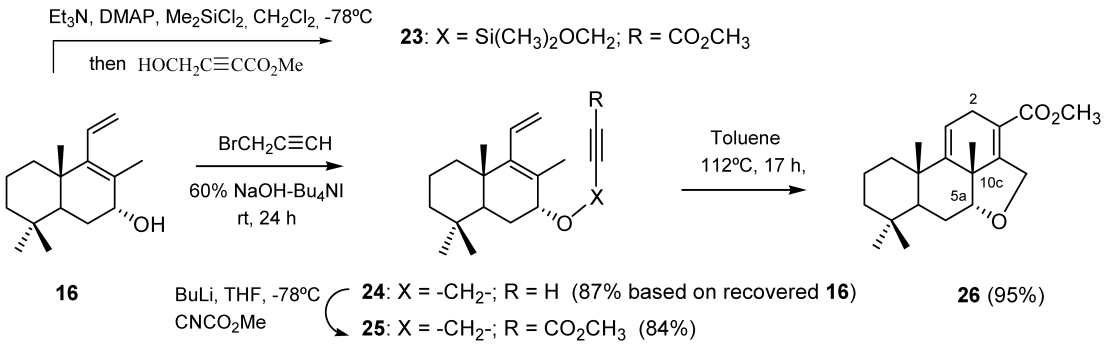
With compound **16** at hand, our next task focused on the elaboration of the C-ring through a Diels–Alder reaction. In a first approach we tried to construct the C-ring through an intermolecular Diels–Alder reaction of both the diene-alcohol **16** and its epimeric silylated alcohol **20**, readily obtained from **16** via an oxidation–reduction–trimethylsilylation procedure (Scheme 3), with dimethyl acetylenedicarboxylate (DMAD). However, in both cases the cycloaddition reaction was very slow and did not reach completion providing a very low yield of the corresponding



Scheme 3.

Diels–Alder adducts. In the former case most of the starting material was recovered and the only adduct isolated (less than 10% after 24 h of heating at 140°C) was identified as the adduct formed by β-approach of the dienophile, compound **17**, that has at the newly created stereogenic center the opposite configuration of the spongiane framework. In the second case, the reaction was less stereoselective, affording after heating **20** with DMAD for 60 h at 140°C, workup and chromatography, the starting material (80%), the 10aα-Me adduct **21** (6%) and the 10aβ-Me adduct **22** (6%). The stereochemistry at C-10a of the three adducts (C-8 of the spongiane skeleton) was readily deduced by comparison of the chemical shift of the Me-10a with that of related compounds.[14] This Me group resonates at higher fields when *anti* to the Me group at C-4b (1.25 and 1.32 ppm for **17** and **21**, respectively) than when *syn* to the same Me group (1.44 ppm for **22**). The reaction of **20** with the sterically less demanding dienophile $MeO_2CC{\equiv}CCHO$ was also non-stereoselective but much less clean, affording only trace amounts of the corresponding Diels–Alder adducts.

In view of the above results, we attempted to control the stereochemistry of the Diels–Alder adduct through an intramolecular process by linking an adequate acetylenic dienophile to the hydroxyl group of bicyclic dienol **16**. Several temporary bridging groups were explored with varying success.[15] Attempts to establish an ester linkage between the diene and the acetylenic dienophile moieties by reaction of the hydroxyl group of **16** with propiolic acid or propiolic acid derivatives were unsuccessful.[16] However, the silicon tethered diene-acetylenic ester **23** was easily prepared in one-pot reaction by successive treatment of **16** at −78°C with $(CH_3)_2SiCl_2$–Et_3N and then $HOCH_2C{\equiv}CCO_2CH_3$[17] and catalytic DMAP (Scheme 4) (see Section 4).[18] Heating of **23**, however, failed to give any cycloadduct even under forcing conditions (220°C in toluene), with only starting material being recovered. The inertia of **23** to undergo the IMDA reaction was somewhat unexpected, but may be explained by noting that in the TS leading to the cycloadduct, the diene methyl group and one of the methyl groups attached to silicon are in very close proximity. In the end, excellent results were obtained with the use of the ether tethering system previously used by Liu and co-workers in their synthetic approach towards forskolin.[19] Thus, propargylation of dienol **16** with propargyl bromide under phase-transfer conditions provided the propargyl ether derivative **24**. In contrast to the results obtained with related monocyclic dienols,[20] propargylation of **16** proceeded quite sluggishly giving only a 55–60% conversion after 28 h. Nevertheless, the unreacted starting material was efficiently recovered during purification by flash chromatography and conveniently recycled, thereby increasing the yield of propargyl ether **24** to 75–80%. Carboxylation of the acetylene group of **24** by sequential treatment with butyl lithium and methyl cyanoformate provided 84% of acetylenic ester **25**, which on heating at 112°C overnight in anhydrous toluene underwent a smooth and clean IMDA cycloaddition to afford the tetracyclic adduct **26** in 95% yield after column chromatography. The structure and stereochemistry of compound **26** was confirmed by 1D and 2D NMR spectroscopy, including NOE difference experiments. Particularly relevant was the



Scheme 4.

NOE enhancement of the signal due to the methyl group at C-10c at δ 1.10 ppm upon irradiation of either H-5aβ or H-2β at δ 3.87 and 2.64 ppm, respectively, that provides evidence not only of the β-orientation of the angular methyl group at C-10c but also of the boat conformation adopted by the C-ring as a consequence of the conformational constraint imposed by the ether bridge.[¶]

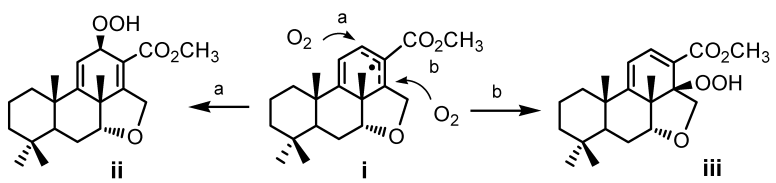
2.3. Construction and further functionalisation of the D ring system

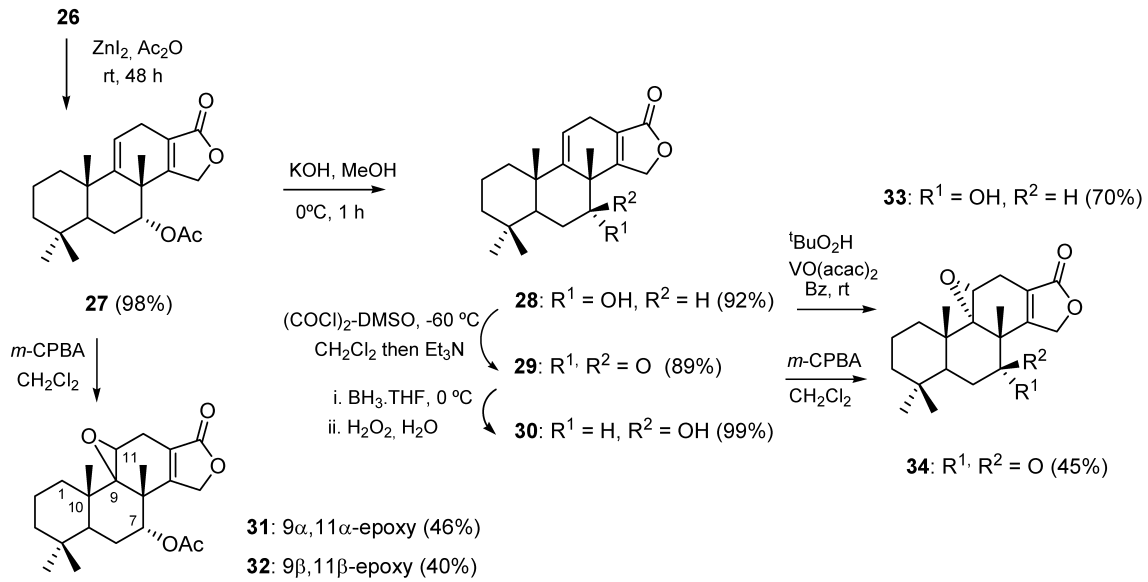
Once completed the C ring and the correct stereochemistry of the methyl group at C-8, we centered our attention on the elaboration of the γ-lactone D-ring, thus completing the natural spongiane framework, and the introduction of the oxygen functionality at C-11. The first task was readily accomplished in a single operation by treatment of the Diels–Alder adduct **26** with acetic anhydride and zinc iodide at room temperature.[21] Under these conditions, regioselective ring-opening of the dihydrofuran ring of **26** took place to give initially the corresponding 7-acetoxy-15-iodo-derivative, which rapidly underwent lactonization to cleanly afford the spongiane-type compound **27** in nearly quantitative yield for the whole process. The structure of the unsaturated γ-lactone **27** was initially assigned on the basis of a detailed spectroscopic study that included bidimensional correlations and NOE difference experiments. The final proof of the structure assignment was obtained by single-crystal X-ray diffraction analysis.

A variety of methods were investigated to introduce an oxygenated function at the C-11 position of the spongiane skeleton. Unfortunately, repeated attempts to hydrate the 9(11)-double bond of **27**, via the hydroboration–oxidation protocol, were unsuccessful. Thus, hydroboration of **27** under standard conditions (first treatment with BH_3·THF or BH_3·Me_2S in THF at 0°C or rt and then with aqueous H_2O_2–NaOH) resulted only in the formation of alcohol **28** (see Scheme 5). On the other hand, performing the hydroboration reaction at a higher temperature (50–60°C) resulted in the formation of complex reaction mixtures, from which the desired 9(11)-double bond hydroboration product could not be isolated. Similarly disappointing results were obtained with the alcohol **28**, obtained in high yield by controlled hydrolysis of the acetate moiety of **27** with methanolic KOH, and also with the ketone **29**, obtained by oxidation of alcohol **28** under Swern oxidation conditions. It should be mentioned that in the latter case, the low temperature hydroboration reaction afforded the equatorial alcohol **30** stereoselectively in nearly quantitative yield. The epimeric relationship at C-7 between alcohols **28** and **30** was evident by comparison of their ^{1}H NMR data and in particular of the coupling constant pattern observed for H-7. This proton appeared in **28** at δ 3.88 ppm as a broad singlet (two small coupling constants) and in **30** at δ 3.65 ppm with two coupling constants (double doublets, J=11.2, 4.9 Hz), the major one clearly indicating that H-7 was in this alcohol in an axial disposition. Thus, this two-step reaction sequence constitutes an efficient way to establish stereoselectively at C-7 the stereochemistry of the oxygenated function present in natural dorisenones.

We were also unable to conveniently functionalize the 9(11)-double bond of **27** via hydroxylation or bromohydrin formation. Thus, no reaction was observed under standard osmylation conditions, both catalytic and stoichiometric,[22] whereas complex reaction mixtures were obtained on treatment of **27** with *N*-bromosuccinimide in aqueous acetone.[23] However, epoxidation of diene **27** occurred smoothly on treatment with *m*-CPBA in dichloromethane at room temperature overnight, to provide regioselectively an approximately 1:1 mixture (determined by analysis of the

[¶] Although the Diels–Alder adduct **26** was relatively stable, it was partially but cleanly transformed into two more polar compounds when left at −20°C in the fridge for several months. These compounds were easily separated by column chromatography (hexane–ethyl acetate 8:2). The major and less polar compound was identified (HRMS, IR, ^{1}H and ^{13}C NMR, see Section 4) as the hydroperoxide **ii** (see below). The structure **iii** was tentatively assigned to the minor product (only traces of this more polar product were isolated), based on the analysis of its ^{1}H NMR spectrum (see Section 4). As shown below, the formation of these compounds could be explained by the initial formation of a stabilized diallyl radical from **26**, e.g. **i**, followed by its reaction with oxygen.





Scheme 5.

400 MHz ^{1}H NMR spectrum) of the α- and β-oriented epoxides, **31** and **32** respectively, in 86% combined yield. Both diastereomeric epoxides were separated by careful flash chromatography and their structures were initially assigned on the basis of detailed spectroscopic analysis. Particularly significant was the difference observed in the chemical shifts due to C-1 and C-11 in both epoxides, observed at δ 31.4/50.8 and 35.6/58.4 ppm for compounds **31** and **32**, respectively. The shielding of these carbon atoms observed in **31** reflexes a stronger γ-effect between them with respect to the same carbon atoms of **32**, which is clearly inferred from the analysis of the optimized geometry obtained for both compounds using MM2. Also in agreement with the α-orientation of the epoxide moiety in **31** were the NOE enhancements observed for the Me group at C-10 and H-1β at δ 1.26 and 1.14 ppm, respectively, upon irradiation of H-11 at δ 3.36 ppm. The geometry of this epoxide was confirmed when suitable crystals for X-ray analysis were obtained that unambiguously established that the epoxide moiety was on the α-face (Fig. 1).

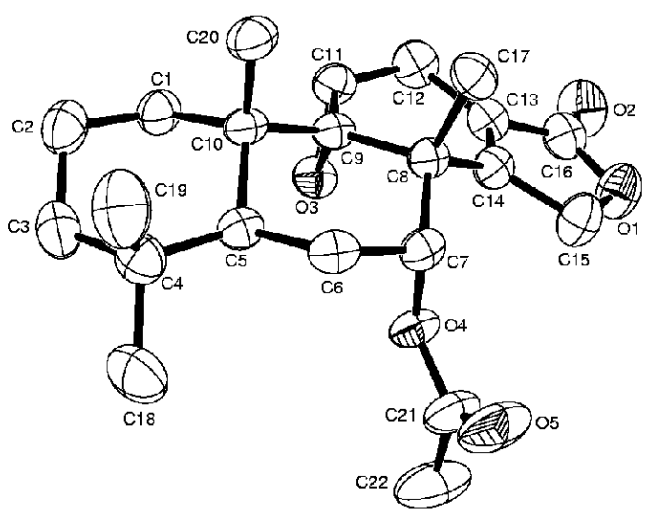
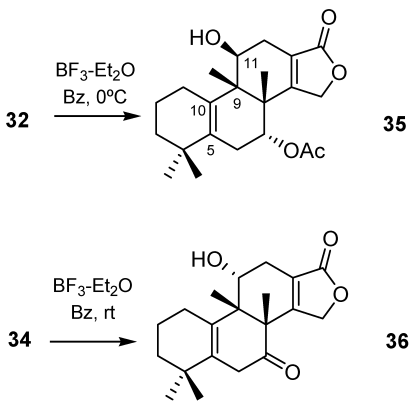


Figure 1. X-Ray structure of compound **31**.

It is interesting to note that the formation of **31** in the above reaction requires the approach of the peracid from the apparently more hindered concave face of **27** (see its X-ray structure), and it seems reasonable to assume that the epoxidation from this face occurs with the anchimeric assistance of the homoallylic acetate group. In this way, and in contrast to the stereochemical result obtained in the epoxidation of acetate **27**, epoxidation of alcohol **28** under catalytic non-asymmetric Sharpless epoxidation conditions afforded exclusively the α-epoxy alcohol **33** (Scheme 5), which has, with the exception of the expected modifications attributed to the acetate-hydroxyl group exchange produced at C-7, spectroscopic properties identical to that of **31**. Interestingly, the hydroxyl hydrogen is observed in the ^{1}H NMR spectrum of **33** as a doublet at δ 2.52 ppm, with a coupling constant with H-7β of 10 Hz. This coupling pattern suggests the existence of an intramolecular hydrogen bond between the 7α-OH and the 9α,11α-epoxide groups. Obviously in this case, the exclusive α-attack of the electrophilic epoxidation reagent is due to the directive effect of the 7α-hydroxyl group.

With the aim of creating functionalisation at C-11 like that of the natural spongiane systems we examined the acid-catalyzed rearrangement of the 9,11-epoxide moiety of both **31** and **32** to the corresponding 11-carbonyl group. This ring opening reaction of epoxides is a synthetically useful reaction that has been successfully used many times in the terpene field.[24] However, all attempts to promote the rearrangement of **31** and **32** to the corresponding carbonyl compound failed. Both epoxides were stable under the relatively milder conditions used in this kind of transformation, e.g. $LiClO_4$ diethyl ether at rt[25] or $LiClO_4$ in benzene at reflux,[26] but eventually reacted when treated with the most commonly used reagent BF_3–etherate to give not the desired carbonyl compound, but products of skeletal rearrangement instead. Thus, treatment of the more reactive β-epoxide **32** with BF_3–etherate in benzene at 0°C gave a fast and clean reaction to afford nearly exclusively a single product, the alcohol **35**, formed by a [1,2]-suprafacial migration of the angular methyl group at C-10 (Scheme 6).



Scheme 6.

The structure and stereochemistry of **35** was established on the basis of a combination of spectroscopic data, including COSY, HSQC, and 2D NOESY experiments. Particularly relevant was the information deduced from the analysis of the coupling constants and NOESY spectrum that not only confirms the proposed structure for **35** but also sheds light on the preferred conformation adopted by this molecule. Thus, the coupling constants between H-7 and both H-6 in **35** are 10.8 and 5.4 Hz and the coupling constants between H-11 and both H-12 are 3.3 and 2.6 Hz, which fits well with the expected values calculated by MMX for the conformation represented in Figure 2. In the NOESY spectrum, the cross-peak patterns observed also strongly support the structure-conformation depicted in Figure 2.

In clear contrast to **32**, the α-epoxide **31** was fairly resistant to similar reaction conditions, being recovered practically unchanged after its treatment with BF_3–etherate at low temperature. Reaction of epoxide **31** required treatment with BF_3–etherate at rt over a long period of time. However, the reaction was not clean and a mixture of products was obtained, apparently resulting from skeletal rearrangements, and no definitive conclusions could be drawn from this reaction.

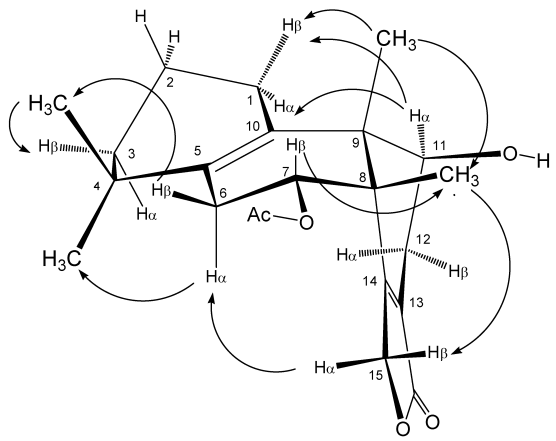


Figure 2. Cross-peaks observed in the 2D NOESY spectrum of **35**.

It was supposed that the 7α-acetoxy group was responsible for the different behaviour of the epoxide **31**, since it could interfere with the BF_3 in its approach towards the similarly α-oriented epoxide moiety. So it was decided to transform the epoxide **31** into the epoxy ketone **34** in a last attempt to promote the desired epoxide ring rearrangement. Successful epoxide–ketone rearrangements have been described in related tetracyclic systems.[27] Epoxy ketone **34** was readily prepared in a non-optimized 50% yield by oxidation of epoxy alcohol **33** under Swern oxidation conditions. As a alternative, **34** was also prepared by reaction of the previously obtained ketone **29** with *m*-CPBA in CH_2Cl_2, although in a rather low yield (ca. 45%). It is noticeable that only the α-epoxide (e.g. **34**) was isolated from this reaction, with no significant amounts of the diastereomeric β-epoxide being detected. This result is in contrast with the epoxidation of other structurally related β-keto-9(11)-olefins (see Ref. 27). Treatment of **34** with BF_3–etherate in benzene at rt resulted in a smooth reaction to give, after 8 h, a 7:3 mixture of two chromatographically homogeneous products in 88% yield. However, neither of these products was the desired 11-ketone. Analysis of the ^1H and ^{13}C NMR spectra of the mixture and comparison of these data with those of **35** allowed the identification of the major product of this mixture as the ketone **36**, formed as **35** by a [1,2]-shift of the methyl group at C-10 followed by elimination of a hydrogen atom (Scheme 6). No definitive structure could be assigned from these data to the minor component of the mixture, but the presence of an olefinic CH and the relatively large chemical shift changes experienced by some methyl groups suggested that it was also likely to be a product of skeletal rearrangement.

3. Conclusion

An efficient approach for preparing the spongiane framework in enantiomerically pure form has been developed. The synthetic sequence used follows a B→AB→ABC→ABCD approach and makes use of the monoterpene carvone as the starting chiral synthon. Since both (*R*)-(−)- and (*S*)-(+)-carvone are commercially available, this approach allows the synthesis of the spongiane skeleton in both enantiomeric forms. Although the adaptation of the functionalisation of the C-11 position to that present in natural dorisenones remains a problem, this study has allowed the efficient preparation of several oxygenated, non-natural, dorisinonone-type spongianes that can provide complementary and valuable information about structure-activity relationships for cytotoxicity in these kinds of spongiane diterpenes.[§]

[§] A selection of the prepared compounds has been tested for their cytotoxic activity against several human cancer cell lines in the NCI 3-cell line, one dose primary anticancer assay [NCI-H460 (Lung), MCF7 (Breast) and SF-268 (CNS) cell lines]. First preliminary results have shown a significant activity of some of them that have been passed on for evaluation in the full panel of 60 cell lines over a 5-log dose range. Paradoxically, the more active compounds of all tested so far do not have the natural spongiane framework. Thus, while compounds **27** and **31** have no significant activity at a 10^{-4} M concentration, the compound **26** reduces the growth of the above mentioned cell lines in comparison to the untreated control cells, to 3, 21 and 70%, respectively.

4. Experimental

4.1. General information

All melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined using a 5 cm path length cell. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were measured as KBr pellets or liquid films. Elemental analyses were performed by Servicio de semimicroanálisis of S.C.S.I.E. (Valencia); final purification of all products for microanalysis was done by preparative HPLC on a μPorasil column. Mass spectra were obtained by electron impact (EI) at 70 eV. ^{1}H NMR spectra were recorded in $CDCl_3$ or C_6D_6 at 300 or 400 MHz, and NMR ^{13}C spectra at 75 or 100 MHz. ^{1}H spectra were referenced to residual $CHCl_3$ (δ 7.26) and ^{13}C spectra to the central component of the $CDCl_3$ triplet at δ 77.0. Carbon substitution degrees were established by DEPT pulse sequences. Complete assignment of ^{1}H and ^{13}C chemical shifts of selected compound in the synthetic sequence, e.g. compounds **11**, **15**, **20**, **27**, **28**, **31** and **35**, was made on the basis of a combination of COSY, HMQC, and NOE experiments. Signals with the same superscript in the ^{1}H or ^{13}C NMR data may be interchanged. Column chromatography refers to flash chromatography and was performed on Merck silica gel 60, 230–400 mesh. All operations involving air-sensitive reagents were performed under an inert atmosphere of dry argon using syringe and cannula techniques, oven-dried glassware, and freshly distilled and dried solvents. The ampoules used for the Diels–Alder reactions were previously treated during at least 48 h with 5% solution of 1,1,1,3,3,3-hexamenthyldisilazane in ether, washed with dry acetone and THF, and dried at 120°C overnight. Unless stated otherwise, reactions mixtures were worked up by addition of water, and extraction with the appropriated solvent, the organic layer being washed with water and brine and dried using anhydrous sodium sulfate. Evaporation was performed under reduced pressure.

4.2. X-Ray structure determinations

Single crystals of compounds **27** and **31** were mounted on a Nonius Kappa CCD diffractometer and using a graphite monochromated Mo Kα radiation source (λ=0.71073 Å). Data collection was performed at room temperature. No absorption correction was performed and the structures were solved by direct methods (SIR97)[28] and refined against F^2 with a fullmatrix least-squares algorithm using SHELX-97[29] and the WinGX (1.64) software package.[30] The position of the hydrogen atoms were added in calculated positions and refined riding on the corresponding C atoms. The refined values of the Flack[31] parameters (0.4 (13) and −1.5 (12) for **27** and **31**, respectively) were inconclusive,[32] hence the Friedel pairs were merged before the final refinement. The absolute configurations were assigned to correspond with that of the known chiral centres in the precursor molecules, which remained unchanged during the synthesis of the compounds. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 199545 (compound **27**) and CCDC 203130 (compound **31**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3. Synthesis of the AB ring system from carvone

4.3.1. (4a*S*,8a*R*)-7-Bromo-2,5,5,8a-tetramethyl-4a,5,6,8a-tetrahydro-4*H*-naphthalen-1-one and (4a*S*,8a*S*)-7-bromo-2,5,5,8a-tetramethyl-4a,5,8,8a-tetrahydro-4*H*-naphthalen-1-one (9). A mixture of regioisomeric vinyl bromides **9** was prepared from (*R*)-(−)-carvone in three steps and 55–60% overall yield as described by Gesson and Seifert in Ref. 12.

4.3.2. (1a*R*,2a*R*,6a*S*,7a*R*)-4-Bromo-1a,2a,6,6-tetramethyl-2a,5,6,6a,7,7a-hexahydro-1aH-1-oxa-cyclopropa[*b*]naphthalen-2-one (10a) and (1a*R*,2a*S*,6a*S*,7a*R*)-4-bromo-1a,2a,6,6-tetramethyl-2a,3,6,6a,7,7a-hexahydro-1aH-1-oxa-cyclopropa[*b*]naphthalen-2-one (10b). 6 M NaOH (0.1 mL, 0.6 mmol) and 35% H_2O_2 (0.64 mL, 7.44 mmol) were added to a solution of the mixture of vinyl bromides **9** (615 mg, 2.17 mmol) in MeOH (5 mL) at 0°C. The mixture was stirred overnight at rt and then poured into a saturated aq. solution of NH_4Cl. The mixture was extracted with ether and worked up as usual. The yellowish oily residue obtained was purified by column chromatography, using hexane–ether (95:5) as eluent, to afford a 3:2 mixture (^{1}H NMR analysis) of regioisomeric vinyl bromides **10a** and **10b** (597.7 mg, 92%) as an oil. A small amount of each of the regioisomers could be partially separated during the chromatographic process and their spectroscopic data (^{1}H and ^{13}C NMR) were determined independently.

Compound **10a**. ^{1}H NMR (400 MHz) δ 6.39 (1H, d, *J*=2.7 Hz, H-3), 3.38 (1H, dd, *J*=1.9, 1.9 Hz, H-7a), 2.33 (1H, ddd, *J*=17.8, 13.1, 1.9 Hz, H-7β), 2.32 (1H, dd, *J*=14.0, 2.7 Hz, H-5), 2.19 (1H, dd, *J*=17.8, 1.9 Hz, H-7α), 1.90 (1H, dd, *J*=14.0, 1.5 Hz, H-5), 1.433 (3H, s, Me-C_{1a}), 1.81 (1H, dd, *J*=13.1, 2.8 Hz, H-6a), 1.151 (3H, s, Me-C_{2a}), 1.016 (3H, s, Meβ-C_6), 0.965 (3H, s, Meα-C_6); ^{13}C NMR (100 MHz) δ 203.6 (C_2), 129.9 (C_3), 121.9 (C_4), 59.7 (C_{7a}), 57.1 (C_{1a}), 51.1 (C_5), 50.7 (C_{2a}), 36.1 (C_{6a}), 35.3 (C_6), 30.3 (Meα-C_6), 23.6 (Meβ-C_6), 21.7 (C_7), 17.7[a] (Me-C_{2a}), 17.2[a] (Me-C_{1a}).

Compound **10b**. ^{1}H NMR (400 MHz) δ 5.73 (1H, dd, *J*=2.1, 1.0 Hz, H-5), 3.43 (1H, d, *J*=2.7 Hz, H-7a), 2.60 and 2.54 (2H, AB system, *J*=16.0, 2.0, 16.0, 1.0 Hz, H-3), 2.28 (1H, ddd, *J*=21.0, 11.0, 2.6 Hz, H-7β), 2.04-1.94 (2H, m, H-7α and H-6a), 1.427 (3H, s, Me-C_{1a}), 1.102 (3H, s, Me-C_{2a}), 1.016 (3H, s, Meβ-C_6), 1.040 (3H, s, Meα-C_6); ^{13}C NMR (100 MHz) δ 207.5 (C_2), 137.7 (C_5), 117.5 (C_4), 59.7 (C_{7a}), 56.8 (C_{1a}), 47.3 (C_{2a}), 42.9 (C_3), 38.1 (C_6), 36.3 (C_{6a}), 31.1 (Meα-C_6), 24.0 (Meβ-C_6), 21.9 (C_7), 18.3[a] (Me-C_{1a}), 16.2[a] (Me-C_{2a}).

4.3.3. (2*R*,3*R*,4a*S*,8a*S*)-1a,2a,6,6-Tetramethyl-octahydro-1-oxa-cyclopropa[*b*]naphthalen-2-one (11). 153 mg of palladium on charcoal (10% w/w) were added to a solution of the above mixture (576 mg, 1.93 mmol) in absolute EtOH (30 mL) and Et_3N (0.54 mL). The mixture was shaken under an atmosphere of hydrogen (using a balloon) for 24 h.

The catalyst was removed by filtration through a short pad of celite. The filtrate was concentrated and the residue was purified by chromatography, using hexane–ether (95:5) as eluent, to provide the epoxy-ketone **11** (393.4 mg, 92%) as a white solid. Mp 72–74°C (from cold pentane). $[\alpha]_D^{23}$=+205.4° (0.7, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2920, 2860, 1695, 1430, 1370, 995. ^1H NMR (400 MHz) δ 3.34 (1H, dd, *J*=3.2, 1.7 Hz, H-7a), 2.25 (1H, ddd, *J*=15.1, 3.2, 3.0 Hz, H-7α), 1.92 (1H, ddd, *J*=15.1, 12.8, 1.7 Hz H-7β), 1.84 (1H, ddd, *J*=13.4, 4.9, 3.0 Hz, H-3β), 1.52 (1H, dd, *J*=12.8, 3.4 Hz, H-6a), 1.50 (2H, m, H-4), 1.42 (1H, m, H-5), 1.32-1.22 (1H, m, H-3α), 1.417 (3H, s, Me-C_{1a}), 1.14 (1H, ddd, *J*=13.0, 13.0, 5.0 Hz, H-5), 1.022 (3H, s, Meβ-C_6), 0.933 (3H, s, Me-C_{2a}), 0.902 (3H, s, Meα-C_6); ^{13}C NMR (100 MHz) δ 208.3 (C_2), 59.5 (C_{7a}), 56.3 (C_{1a}), 46.1 (C_{2a}), 41.4 (C_5), 39.0 (C_{6a}), 33.2 (C_6), 32.9 (C_3), 32.8 (Meα-C_6), 22.2 (Meβ-C_6), 22.0 (C_7), 17.8 (C_4), 16.9 (Me-C_{2a}), 16.7 (Me-C_{1a}); MS (EI) *m*/*z* 222 (M^+, 42), 207 (13), 166 (100), 123 (69), 153 (53), 123 (69), 109 (41); HRMS *m*/*z* calcd for $C_{14}H_{22}O_2$ 222.1619, found 222.1613. Anal. calcd for $C_{14}H_{22}O_2$: C 75.63, H 9.97; found: C 75.75, H 9.80.

4.3.4. (4a*S*,8a*S*)-3-Hydroxy-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydro-naphthalene-1-carbaldehyde (15). A solution of LDA in THF (12.5 mL, 0.5 M, 6.2 mmol) was added dropwise to a solution of $Ph_2POCH_2OCH_3$ (1.520 g, 6.2 mmol) in dry THF (15 mL) at 0°C. After stirring for 1 h at 0°C and then 30 min at room temperature, the mixture was cooled to −78°C and treated slowly with a solution of the epoxy-ketone **11** (687 mg, 3.1 mmol) in THF (11 mL). The reaction mixture was stirred for 4 h, during which time the temperature raised to −50°C, then treated with a saturated aq. solution of NH_4Cl and extracted with ether. Workup as usual afforded a solid residue, which was purified by silica gel chromatography, using hexane–ethyl acetate (8:2) as eluent, to afford a 3:2 mixture of two epimeric β-hydroxyphosphine oxides **12** as a white solid (1.43 g, 99% yield). ^1H NMR (300 MHz) for the major isomer: δ 5.29 (1H, s, OH), 4.60 (1H, d, *J*=4.7 Hz, CHP(O)), 3.15 (1H, br s, H-7a), 2.96 (3H, s, MeO), 1.140 (3H, s, Me-1a), 0.860 (3H, s, Me-2a), 0.831 (3H, s, Me-6α), 0.795 (3H, s, Me-6β); for the minor isomer: δ 5.88 (1H, s, OH), 4.41 (1H, d, *J*=8.2 Hz, CHP(O)), 3.02 (3H, s, MeO), 2.75 (1H, br s, H-7a), 1.244 (3H, s, Me-1a), 0.939 (3H, s, Me-2a), 0.883 (3H, s, Me-6α), 0.808 (3H, s, Me-6β).

To a suspension of NaH (305 mg of a 60% suspension in mineral oil, corresponding to 7.6 mmol), previously washed with anhydrous pentane, in anhydrous DMF (4.4 mL) maintained at 0°C, was added dropwise during 1 h a solution of the above mixture of β-hydroxyphosphine oxides **12** (1.43 g, 3.05 mmol) in the same DMF (15 mL). The resulting brownish suspension was stirred at the same temperature for 2.5 h, then cooled to −10°C and cautiously treated with water (4.9 mL) to decompose the excess NaH. The homogeneous reaction mixture obtained was stirred at the same temperature until the hydrogen evolution ceased and then treated with HCOOH (14.7 mL). After stirring at room temperature for 30 min the mixture was poured into water and the product was extracted with hexane and worked up. The crude product obtained was purified by column chromatography in silica gel, using an 8:2 mixture of hexane and ethyl acetate as eluent, to give the hydroxy-aldehyde **15** (627.4 mg, 87% from **11**) as a white solid. Mp 110°C (with decomp) (from cold AcOEt–hexane). $[\alpha]_D^{23}$=+61.0° (0.6, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3374, 2957, 2925, 2896, 2866, 1662, 1458, 1366, 1248, 1211, 1127, 1064. ^1H NMR (300 MHz) δ 10.10 (1H, s, CHO), 4.02 (1H, dd, *J*=4.5, 1.2 Hz, H-3), 2.36 (1H, dddd, *J*=13.2, 3.3, 3.2, 1.2 Hz, H-8β), 2.136 (3H, s, Me-C_2), 1.84 (1H, ddd, *J*=14.4, 2.1, 1.2 Hz, H-4α), 1.76 (1H, ddd, *J*=14.1, 12.9, 4.5 Hz, H-4β), 1.52 (1H, m, H-7), 1.46 (1H, m, H-6), 1.30 (1H, dd, *J*=12.9, 2.7 Hz, H-4a), 1.20 (1H, dd, *J*=13.9, 4.5 Hz, H-6), 1.165 (3H, s, Me-C_{8a}), 1.16 (1H, dd, *J*=9.0, 3.9 Hz, H-7′), 1.02 (1H, ddd, *J*=13.2, 13.2, 3.9 Hz, H-8α), 0.924 (3H, s, Meα-C_5), 0.871 (3H, s, Meβ-C_5); ^{13}C NMR (75 MHz) δ 194.2 (CHO), 145.1 (C_2), 109.5 (C_1), 70.2 (C_3), 45.8 (C_{4a}), 41.3 (C_6), 38.4 (C_{8a}), 35.8 (C_8), 33.1 (Meα-C_5), 32.8 (C_5), 28.1 (C_4), 21.6 (Meβ-C_5), 18.78 (Me-C_{8a}), 18.75 (C_7), 16.8 (Me-C_2); MS (EI) *m*/*z* 236 (M^+, 100), 221 (56), 207 (59), 119 (34); HRMS *m*/*z* calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1776. Anal. calcd for $C_{15}H_{24}O_2$: C 76.23, H 10.24; found: C 76.08, H 10.30.

4.3.5. (2*R*,4a*S*,8a*S*)-3,4a,8,8-Tetramethyl-4-vinyl-1,2,4a,5,6,7,8,8a-octahydro-naphthalen-2-ol (16). A suspension of methyltriphenylphosphonium bromide (2.15 g, 6.01 mmol) in THF (31 mL) at −20°C was treated with BuLi (3.78 mL of a 1.56 M solution in hexanes, 5.90 mmol). The mixture was stirred for 1 h while allowed to warm to room temperature. The resulting deep yellow solution was cooled to −20°C and a solution of the aldehyde **15** (590 mg, 2.50 mmol) in THF (4 mL) was added to give a pale yellow mixture that was stirred for 30 min and then allowed to warm to room temperature for 1 h. The reaction was quenched with aq. $NaHCO_3$, extracted with hexane and worked up. The residue was purified by column chromatography, using hexane–ethyl acetate (95:5) as eluent, to furnish the dienol **16** (549.3 mg, 94%) as a white solid. Mp 109–110°C (from cold pentane). $[\alpha]_D^{26}$=+83.1° (1.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3280, 2920, 1440, 1410, 1055, 1000, 910. ^1H NMR (300 MHz) δ 6.09 (1H, ddcd, *J*=17.5, 11.2, 1.0, 1.0 Hz, H-1′), 5.27 (1H, dd, *J*=11.2, 2.5 Hz, H-2′), 4.94 (1H, dd, *J*=17.5, 2.6 Hz, H-2′), 4.00 (1H, br s, H-2) 1.81 (1H, ddd, *J*=14.1, 4.2, 1.5 Hz, H-1), 1.795 (3H, d, *J*=0.75 Hz, Me-C_3), 1.72 (1H, ddd, *J*=14.1, 12.3, 4.5 Hz, H-1), 1.58 (1H, m, H-5), 1.50 (1H, m, H-6), 1.43 (1H, ddd, *J*=13.2, 3.4, 1.5 Hz, H-7), 1.34 (1H, dd, *J*=12.2, 3.2 Hz, H-8a), 1.21 (1H, dd, *J*=13.0, 4.0 Hz, H-7), 1.11 (1H, ddd, *J*=12.6, 12.3, 3.8 Hz, H-5), 0.968 (3H, s, Me-C_{4a}), 0.919 (3H, s, Meβ-C_8), 0.856 (3H, s, Meα-C_8); ^{13}C NMR (75 MHz) δ 146.3 (C_4), 134.4 ($C_{1'}$), 127.2 (C_3), 119.1 ($C_{2'}$), 70.2 (C_2), 45.7 (C_{8a}), 41.5 (C_7), 38.5 (C_{4a}), 37.6 (C_5), 33.0 (Meα-C_8), 32.9 (C_8), 28.6 (C_1), 21.6 (Meβ-C_8), 18.9 (C_6), 18.8 (Me-C_3)[a], 18.4 (Me-C_{4a})[a]; MS (EI) *m*/*z* 234 (M^+, 13), 219 (100), 110 (77); HRMS *m*/*z* calcd for $C_{16}H_{26}O$ 234.1983, found 234.1989. Anal. calcd for $C_{16}H_{26}O$: C 81.99, H 11.18; found: C 82.01, H 11.14.

4.4. Construction of the C ring system

4.4.1. Intermolecular Diels–Alder reactions of bicyclic dienes 16 and 20 with DMAD

4.4.1.1. Reaction of diene 16 with DMAD. A mixture of diene **16** (5.7 mg, 0.024 mmol), dimethylacetylene

dicarboxylate (DMAD) (15 mg, 0.10 mmol), and toluene (50 μL) contained in a sealed ampoule was heated at 140°C for 24 h. The toluene and the excess of DMAD were eliminated under reduced pressure. The resulting residue was purified by chromatography, using hexane–ethyl acetate from 8:2 to 1:1 as eluent, to give mainly the starting material **16** mixed with DMAD, and the adduct 10aα-Me **17** (less than 1 mg) as an amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) of **17**: δ 5.71 (1H, dd, *J*=6.6, 1.9 Hz, H-4), 4.41 (1H, t, *J*=8.2 Hz, H-10), 3.81 and 3.73 (3H each, each s, 2×CO_2Me), 3.11 (1H, dd, *J*=21.9, 6.6 Hz, H-3), 2.83 (1H, dd, *J*=21.9, 1.9 Hz, H′-3), 2.2–1.9 (2H, m, H-5), 1.267 (3H, s, Me-C_{10a}), 0.999 (3H, s, Me-C_{4b}), 0.923 (3H, s, Me-C_8), 0.857 (3H, s, Me′-C_8); MS (EI) *m*/*z* 377 (M^++1, 1.5), 13), 376 (M^+, 0.2), 344 (8.7), 327 (7.1), 326 (14.4), 311 (5.5), 284 (11.2), 283 (40.5), 273 (12.6), 272 (100); HRMS *m*/*z* calcd for $C_{22}H_{22}O_5$ 376.2249; found: 376.2207.

4.4.1.2. Preparation of diene 20 from 16. A solution of alcohol **16** (24 mg, 0.10 mmol) and pyridine (0.046 mmol, 37.8 μL) in anhydrous CH_2Cl_2 (0.5 mL) was added to a solution of Dess-Martin periodinane (54.8 mg, 0.13 mmol) in CH_2Cl_2 (0.8 mL). After stirring at 0°C for 30 min, the reaction mixture was stirred for a further 15 min period at rt. The reaction mixture was diluted with ethyl ether, cooled to 0°C and quenched with an aq. solution of $NaHCO_3$ and $Na_2S_2O_3$. After 10 min of vigorous stirring the organic phase was separated and worked up as usual. The residue obtained after evaporation of the solvent was filtered through a short pad of silica gel, using hexane–ether 9:1 as eluent, to give (4a*S*,8a*S*)-3,4a,8,8-tetramethyl-4-vinyl-4a,5,6,7,8,8a-hexahydro-1H-naphthalen-2-one ketone (**18**) (20.8 mg, 86%) as a semisolid. $[\alpha]_D^{28}$=+28.2° (0.6, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 3084, 2995, 2949, 2933, 2902, 1661, 1599, 1458, 1319, 1007, 916. ^{1}H NMR (300 MHz) δ 6.29 (1H, dcd, *J*=17.7, 11.8, 0.9 Hz, H-1′), 5.47 (1H, dd, *J*=11.8, 2.1 Hz, H-2′), 5.11 (1H, dd, *J*=17.7, 2.1 Hz, H′-2′), 2.53 (1H, dd, *J*=17.7, 4.0 Hz, H-1α), 2.39 (1H, dd, *J*=17.7, 13.9 Hz, H-1β), 1.785 (3H, d, *J*=0.9 Hz, Me-C_3), 1.130 (3H, s, Me-C_{4a}), 0.921 (3H, s, Meβ-C_8), 0.886 (3H, s, Meα-C_8); ^{13}C NMR (75 MHz) δ 200.9 (C_2), 165.4 (C_4), 133.2 ($C_{1'}$), 128.9 (C_3), 120.7 ($C_{2'}$), 49.9 (C_{8a}), 41.1 (C_7), 39.7 (C_{4a}), 35.3 (C_5), 37.2 (C_1), 33.1 (C_8), 32.4 (Meα-C_8), 21.2 (Meβ-C_8), 18.6 (C_6), 18.2 (Me-C_{4a}), 13.2 (Me-C_3); MS (EI) *m*/*z* 232 (M^+, 15), 217 (6), 189 (6), 149 (31), 109 (42), 69 (100); HRMS *m*/*z* calcd for $C_{16}H_{24}O$ 232.1827; found: 232.1831.

The above obtained ketone (20.3 mg, 0.087 mmol) and $CeCl_3 \cdot 7H_2O$ (33.2 mg, 0.089 mmol) were dissolved in MeOH (0.21 mL). $NaBH_4$ (3.3 mg, 0.087 mmol) was added in one portion with stirring at room temperature. The stirring was maintained for 30 min, the reaction mixture was cooled to 0°C and the pH was adjusted to neutrality with diluted HCl. Work up as usual and chromatography, using hexane–ether 8:2, gave alcohol **19** (17.4 mg, 85%) as a solid. Mp 106–109°C (from cold hexane). $[\alpha]_D^{22}$=+133.8° (0.3, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3500–3100, 2922, 2846, 1456, 1374, 1022, 916. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.09 (1H, ddcd, *J*=17.6, 11.2, 1.2, 1.2 Hz, H-1′), 5.27 (1H, dd, *J*=11.2, 2.6 Hz, H-2′), 4.94 (1H, dd, *J*=17.6, 2.6 Hz, H′-2′), 4.10 (1H, br dd, *J*=8.5, 7.8 Hz, H-2), 2.09 (ddd, *J*=12.5, 7.4, 1.5 Hz, H-1α), 1.716 (3H, dd, *J*=1.2, 1.2 Hz, H, Me-C_3), 1.03 (3H, s, Me-C_{4a}), 0.87 (3H, s, Me-C_8), 0.84 (3H, s, Me′-C_8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7 (C_4), 134.5 ($C_{1'}$), 128.6 (C_3), 119.4 ($C_{2'}$), 73.3 (C_2), 49.6 (C_{8a}), 41.4 (C_7), 38.7 (C_{4a}), 37.6 (C_5), 32.99 (Meα-C_8), 32.95 (C_8), 29.6 (C_1), 21.5 (Meβ-C_8), 20.1 (Me-C_{4a}), 18.7 (C_6), 16.6 (Me-C_3); MS (EI) *m*/*z* 234 (M^+, 1), 201 (5), 131 (24), 110 (100), 69 (60), 57 (80); HRMS *m*/*z* calcd for $C_{16}H_{26}O$ 234.1984, found 234.1996. Anal. calcd for $C_{16}H_{26}O$: C 81.99, H 11.18; found: C 81.78, H 11.30.

A solution of the alcohol **19** (13.8 mg, 0.059 mmol) in CH_2C1_2 (0.8 mL) was treated at 78°C with Et_3N (25 μL, 0.18 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (22 μL, 0.094 mmol) and stirred for 1 h at the same temperature. The mixture was diluted with ether and worked up. Chromatography, using hexane–ether 9:1 as eluent, afforded *tert*-butyldimethyl silyl ether **20** (17.7 mg, 86%) as an oil. $[\alpha]_D^{19}$=+48.9° (0.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2928, 2856, 1473, 1256, 1027, 835, 772. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (1H, ddcd, *J*=17.6, 11.2, 1.9, 1 Hz, H-1′), 5.26 (1H, dd, *J*=11.2, 2.6 Hz, H-2′), 4.95 (1H, dd, *J*=17.6, 2.6 Hz, H′-2′), 4.12 (1H, br dd, *J*=8.1, 8.1 Hz, H-2), 1.92 (ddd, *J*=12.3, 6.8, 1.1 Hz, H-1), 1.664 (3H, br s, Me-C_3), 1.052 (3H, s, Me-C_{4a}), 0.921 (9H, s, Me_3CSi), 0.879 (3H, s, Meβ-C_8), 0.857 (3H, s, Meα-C_8), 0.102 (6H, s, 2×MeSi); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2 (C_4), 134.8 ($C_{1'}$), 129.9 (C_3), 119.0 ($C_{2'}$), 74.1 (C_2), 49.7 (C_{8a}), 41.4 (C_7), 38.6 (C_{4a}), 37.8 (C_5), 33.0 (Meα-C_8), 32.9 (C_8), 29.8 (C_1), 26.0 (*Me*$_3$CSi), 21.6 (Meβ-C_8), 20.1 (Me-C_{4a}), 18.8 (C_6), 18.2 (Me$_3$*C*Si), 17.1 (Me-C_3), −4.0 and −4.6 (Me_2Si); HRMS *m*/*z* calcd for $C_{22}H_{40}OSi$ 348.2848; found: 348.2855.

4.4.1.3. Reaction of diene 20 with DMAD. A mixture of diene **20** (17.1 mg, 0.049 mmol), DMAD (30 mg, 0.20 mmol), and toluene (0.25 mL) contained in a sealed ampoule was heated at 140°C for 60 h. The solvent and the excess of DMAD were eliminated at reduced pressure and the resulting residue was purified by chromatography, using hexane–ether from 9:1 to 7:3 as eluent, to give unreacted starting material **20** (13.6 mg, 80%), adduct 10aα-Me **21** (ca. 1 mg, 6%) and adduct 10aβ-Me **22** (ca. 1 mg, 6%).

^{1}H NMR (200 MHz, $CDCl_3$) of the more polar adduct 10aα-Me (**21**): δ 5.61 (1H, dd, *J*=5.6, 2.5 Hz, H-4), 4.19 (1H, dd, *J*=11.5, 5.1 Hz, H-10), 3.786 and 3.692 (3H each, each s, 2×CO_2Me), 3.06 (1H, dd, *J*=22.4, 5.6 Hz, H-3), 2.78 (1H, dd, *J*=22.4, 2.5 Hz, H′-3), 1.325 (3H, s, Me-C_{10a}), 1.147 (3H, s, Me-C_{4b}), 0.915 (9H, s, Me_3CSi), 0.850 (3H, s, Me-C_8), 0.823 (3H, s, Me′-C_8), 0.123 and 0.092 (3H each, each s, 2×MeSi); MS (EI) *m*/*z* 490 (M^+, 1.8), 475 (1.7), 444 (0.5), 435 (9.1), 434 (30.9), 433 (100), 418 (2.7), 417 (9.3), 366 (2.4), 328 (2.2), 327 (9.5), 326 (5.2), 331 (4.3); HRMS *m*/*z* calcd for $C_{28}H_{46}O_5Si$ 490.3114; found: 490.3151.

^{1}H NMR (200 MHz, $CDCl_3$) of the less polar adduct 10aβ-Me (**22**): δ 5.641 (1H, dd, *J*=5.1, 2.5 Hz, H-4), 4.43 (1H, d, *J*=7.9 Hz, H-10), 3.706 and 3.662 (3H each, each s, 2×CO_2Me), 3.07 (1H, dd, *J*=23.1, 5.1 Hz, H-3), 2.84 (1H, dd, *J*=23.1, 2.5 Hz, H′-3), 1.442 (3H, s, Me-C_{10a}), 1.253 (3H, s, Me-C_{4b}), 0.884 (3H, s, Me-C_8), 0.822 (3H, s, Me′-C_8), 0.789 (9H, s, Me_3CSi), 0.117 and −0.040 (3H each, each s, 2×MeSi); MS (EI) *m*/*z* 490 (M^+, 2.3), 475 (1.8), 474 (3.4), 444 (0.5), 443 (1.8), 435 (9.1), 434 (32), 433 (100), 431 (3.1), 418 (4.7), 418 (13.7), 417 (45.7), 366 (3.4),

343 (4), 328 (4.4), 327 (13), 326 (9.9), 312 (3.9), 311 (16.2); HRMS *m/z* calcd for $C_{28}H_{46}O_5Si$ 490.3114; found: 490.3035.

4.4.2. Construction of the C ring by intramolecular Diels–Alder reaction.

4.4.2.1. 4-[Dimethyl-(3,4a,8,8-tetramethyl-4-vinyl-1,2,4a,5,6,7,8,8a-octahydro-naphthalen-2-yloxy)-silanyl-oxy]-but-2-ynoic acid methyl ester (23). Et_3N (33 μL, 0.236 mmol), a solution of dienol **16** (18.4 mg, 0.078 mmol) in CH_2Cl_2 (0.3 mL) and a solution of DMAP (1.9 mg, 0.015 mmol) in CH_2Cl_2 (0.05 mL) were successively added to a solution of Me_2SiCl_2 (14.3 μL, 0.118 mmol) in anhydrous CH_2Cl_2 (0.1 mL) at 78°C. The mixture was stirred at the same temperature for 1 h and then was treated with a solution of $HOCH_2C{\equiv}CCO_2CH_3$ (17.9 mg, 0.156 mmol) in CH_2Cl_2 (0.1 mL). The mixture was stirred at 78°C for 1 h and then diluted with pentane. The white precipitated was filtered off and the filtrated concentrated in vacuum and rapidly chromatographed, using hexane–ethyl acetate 9:1 (with a few drops of Et_3N) as eluent, to afford the silylacetal **23** (21.6 mg, 68%) as a colorless oil. The compound was quite labile to the chromatographic process, being partially hydrolyzed to the starting alcohol during the purification. ^{1}H NMR (200 MHz) δ 6.12 (1H, dd, J=17.7, 11.4 Hz, H-1″), 5.27 (1H, dd, J=11.4, 2.7 Hz, H-2″), 4.95 (1H, dd, J=17.7, 2.7 Hz, H-2″), 4.50 (2H, s, H_2-4), 3.76 (3H, s, CO_2CH_3), 4.15 (1H, br s, H-2′), 1.704 (3H, br s, Me-$C_{3'}$), 0.935 (3H, s, Me-$C_{4'a}$), 0.882 (3H, s, Meβ-$C_{8'}$), 0.823 (3H, s, Meα-$C_{8'}$), 0.222 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, C_6D_6) δ 153.2 (C_1), 145.3 ($C_{4'}$), 134.8 ($C_{1''}$), 127.6 ($C_{3'}$), 118.7 ($C_{2''}$), 85.4 (C_3), 76.9 (C_2), 70.8 ($C_{2'}$), 51.6 (CH_3O), 50.1 (C_4), 44.9 ($C_{8'a}$), 41.4 ($C_{7'}$), 38.2 ($C_{4'a}$), 37.4 ($C_{5'}$), 32.8 ($C_{8'}$), 32.6 (Meα-$C_{8'}$), 29.0 ($C_{1'}$), 21.35 (Meβ-$C_{8'}$), 18.8 ($C_{6'}$), 18.76[a] (Me-$C_{3'}$), 18.2[a] (Me-$C_{4a'}$), −2.5 and −2.6 (both $SiCH_3$); MS (EI) *m/z* 404 (M^+, 22.8), 390 (19.4), 389 (65.9), 367 (3), 321 (5), 319 (7.5), 281 (6.8), 266 (9), 265 (43.9), 247 (12.6), 246 (21.6), 245 (100); HRMS *m/z* calcd for $C_{23}H_{36}O_4Si$ 404.2383; found: 404.2389.

4.4.2.2. (4a*S*,6*R*,8a*S*)-4,4,7,8a-Tetramethyl-6-prop-2-ynyloxy-8-vinyl-1,2,3,4,4a,5,6,8a-octahydro-naphthalene (24). The dienol **16** (200 mg, 0.84 mmol) was dissolved in the minimum amount of ethyl acetate in a cylindrical flask equipped with an efficient magnetic stirrer. The solvent was evaporated with the aid of a current of argon to leave an oily residue, to which tetrabutylammonium iodide (TBAI) (156 mg, 0.428 mmol) and propargyl bromide (1.6 mL, 14.5 mmol) were added successfully. The mixture was stirred while an aq. solution of 60% NaOH (1 mL) was added dropwise and the two phase reaction mixture was vigorously stirred in a bath thermostated at 25°C for 28 h. After this time, the brownish reaction mixture was poured into water, extracted with a mixture 1:1 of hexane–ether and worked up. The brown oily residue obtained was purified by column chromatography, using a 95:5 mixture of hexane–ethyl acetate as eluent, to afford in order of elution: propargyl ether **24** (130.2, 56%), as a colorless oil, and unreacted starting dienol **16** (72 mg, 36%). Data for **24**. $[\alpha]_D^{25}$=+30.6° (1.2, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 3308, 2924, 2862, 1459, 1440, 1370, 1070, 1059, 919. ^{1}H NMR (300 MHz) δ 6.11 (1H, ddcd, J=17.7, 11.4, 0.9, 0.9 Hz, H-1′), 5.28 (1H, dd, J=11.4, 2.6 Hz, H_{cis}-2′), 4.98 (1H, dd, J=17.7, 2.6 Hz, H_{trans}-2′), 4.26 (1H, dd, J=15.9, 2.4 Hz, H-1″α), 4.16 (1H, dd, J=15.9, 2.4 Hz, H-1″β), 3.83 (1H, br d, J=3.1 Hz, H-6), 2.40 (1H, t, J=2.4 Hz, H-3″), 1.91 (1H, dd, J=12.4, 1.1 Hz, H-5), 1.775 (3H, d, J=0.9 Hz, Me-C_7), 1.20 (1H, dd, J=13.6, 4.3 Hz, H-3), 1.11 (1H, ddd, J=12.1, 12.1, 3.8 Hz, H-1), 0.965 (3H, s, Meβ-C_4), 0.902 (3H, s, Meα-C_4), 0.856 (3H, s, Me-C_{8a}); ^{13}C NMR (75 MHz) δ 147.2 (C_8), 134.4 ($C_{1'}$), 125.7 (C_7), 119.1 ($C_{2'}$), 80.6 ($C_{2''}$), 76.8 (C_6), 73.8 ($C_{3''}$), 55.9 ($C_{1''}$), 45.5 (C_{4a}), 41.3 (C_3), 38.4 (C_{8a}), 37.3 (C_1), 32.9 (C_4), 32.8 (Meα-C_4), 23.1 (C_5), 21.6 (Meβ-C_4), 18.8 (C_2), 18.6[a] (Me-C_7), 18.4[a] (Me-C_{8a}); MS (EI) *m/z* 272 (M^+, 10), 257 (100), 123 (65), 105 (41), 91 (33); HRMS *m/z* calcd for $C_{19}H_{28}O$ 272.2140; found: 272.2133.

4.4.2.3. (2*R*,4a*S*,8a*S*)-4-(3,4a,8,8-Tetramethyl-4-vinyl-1,2,4a,5,6,7,8,8a-octahydro-naphthalen-2-yloxy)-but-2-ynoic acid methyl ester (25). A solution of propargyl ether **24** (200.1 mg, 0.735 mmol) in THF (5 mL) at −78°C was treated dropwise with a solution of BuLi in hexanes (563 μL, 1.6 M, 0.740 mmol). After a few minutes, the reaction mixture was treated with methyl cyanoformate (125 μL, 1.57 mmol) and stirred at the same temperature for 50 min. Saturated aq. NH_4Cl and hexane were added, and the aq. phase was extracted with hexane. Workup followed by column chromatography, using hexane–ethyl acetate (95:5) as eluent, afforded the acetylenic ester **25** (201.5 mg, 84.5%) as a colorless oil. $[\alpha]_D^{27}$=+34.0° (4.0, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2926, 2860, 2243, 1718, 1433, 1251, 1045. ^{1}H NMR (300 MHz) δ 6.11 (1H, ddcd, J=17.6, 11.2, 1.0, 1.0 Hz, H-1″), 5.29 (1H, dd, J=17.6, 2.4 Hz, H_{trans}-2″), 4.98 (1H, dd, J=11.4, 2.4 Hz, H_{cis}-2″), 4.38 and 4.30 (2H, AB system, J=17.0 Hz, H-4), 3.85 (1H, broad d, J=4.2 Hz, H-2′), 3.782 (3H, s, CH_3O), 1.779 (3H, s, Me-$C_{3'}$), 1.50 (1H, dd, J=13.7, 3.8 Hz, H-6′), 1.40 (1H, dd, J=12.9, 1.5 Hz, H-8a′), 1.20 (1H, dd, J=13.7, 4.6 Hz, H-7′), 1.13 (1H, ddd, J=12.9, 12.9, 4.2 Hz, H-5′), 0.964 (3H, s, Me-$C_{8'\beta}$), 0.900 (3H, s, Me-$C_{8'\alpha}$), 0.858 (3H, s, Me-$C_{4a'}$); ^{13}C NMR (75 MHz) δ 153.6 (C_1), 147.7 ($C_{4'}$), 134.3 ($C_{1''}$), 125.4 ($C_{3'}$), 119.2 ($C_{2''}$), 84.6 (C_3), 77.7 (C_2), 77.7 ($C_{2'}$), 55.8 (C_4), 52.7 (CH_3O), 45.6 ($C_{8a'}$), 41.3 ($C_{7'}$), 38.4 ($C_{4a'}$), 37.4 ($C_{5'}$), 32.9 ($C_{8'}$), 32.8 (Meα-$C_{8'}$), 23.2 ($C_{1'}$), 21.6 (Meβ-$C_{8'}$), 18.8 ($C_{6'}$), 18.6[a] (Me-$C_{3'}$), 18.4[a] (Me-$C_{4a'}$); MS (EI) *m/z* 330 (M^+, 2), 315 (25), 232 (35), 201 (29), 123 (100), 69 (89); HRMS *m/z* calcd for $C_{21}H_{30}O_3$ 330.2195; found: 330.2189.

4.4.2.4. (5a*R*,6a*S*,10a*S*,10c*R*)-7,7,10a,10c-Tetramethyl-2,5a,6,6a,7,8,9,10,10a,10c-decahydro-4*H*-5-oxa-acephenanthrylene-3-carboxylic acid methyl ester (26). A solution of diene **25** (224.0 mg, 0.678 mmol) in degassed anhydrous toluene (2 mL) was heated in a vacuum sealed ampoule at 112°C for 17 h. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel, using a 9:1 mixture of hexane–ethyl acetate as eluent, to afford the Diels–Alder adduct **26** (212.8 mg, 95%) as a white solid. Mp 95–96°C (from EtOH). $[\alpha]_D^{27}$=+52.9° (1.6, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2960, 2932, 2859, 2818, 1708, 1678, 1455, 1436, 1267, 1190, 1117. ^{1}H NMR (300 MHz) δ 5.64 (1H, dd, J=6.4, 1.5 Hz, H-1), 4.94 (1H, dd, J=14.1, 2.4 Hz, H-4α), 4.30 (1H, ddd, J=14.0, 3.9, 0.7 Hz, H-4β), 3.87 (1H, dd, J=3.7, 2.9 Hz, H-5a), 3.719 (3H, s, CH_3O), 3.32 (1H, dd, J=20.5, 6.4 Hz, H-2α), 2.64 (1H, dddd, J=20.6, 3.9, 2.4, 1.5 Hz, H-2β), 1.93 (2H, m, H-6), 1.82 (1H, ddd, J=12.6, 3.1, 1.6 Hz, H-10β), 1.59 (1H, ddd, J=12.6, 3.1, 3.0 Hz, H-9), 1.50 (1H, m, J=12.6, 7.0, 4.0 Hz, H-9), 1.40 (1H, m, H-8), 1.33 (1H, dd, J=12.6,

3.9 Hz, H-10α), 1.14 (1H, dd, *J*=12.6, 4.0 Hz, H-8), 1.125 (3H, s, Me-C_{10a}), 1.101 (3H, s, Me-C_{10c}), 1.15 (1H, dd partly overlapped with Me-C_{10a}, H-6a), 0.873 (3H, s, Me-C_7β), 0.870 (3H, s, Me-C_7α); ^{13}C NMR (75 MHz) δ 166.8 (CO_2), 164.0 (C_{3a}), 154.5 (C_{10b}), 121.3 (C_3), 117.4 (C_1), 82.8 (C_{5a}), 68.6 (C_4), 51.6 (CH_3O), 45.6 (C_{10c}), 43.8 (C_{6a}), 42.0 (C_8), 38.5 (C_{10}), 38.3 (C_{10a}), 33.2 (C_7), 32.8 (Meα-C_7), 27.0 (C_2), 24.8 (C_6), 24.6 (Me-C_{10c}), 21.7 (Meβ-C_7), 21.6 (Me-C_{10a}), 18.6 (C_9); MS (EI) *m/z* 330 (M^+, 100), 315 (38), 177 (30), 163 (55); HRMS *m/z* calcd for $C_{21}H_{30}O_3$ 330.2195, found 330.2198. Anal. calcd for $C_{21}H_{30}O_3$: C 76.33, H 9.15; found: C 76.5, H 9.01.

4.4.2.5. Spectroscopic data for compounds formed by oxidation of adduct 26 on storage. *2R,5aR,6aS,10aS,10cR)-2-Hydroperoxy-7,7,10a,10c-tetramethyl-2,5a,6,6a,7,8,9,10,10a,10c-decahydro-4H-5-oxa-acephenanthrylene-3-carboxylic acid methyl ester* (*Compound* **ii**). IR ν_{max}/cm^{-1} (film) 3400, 3000, 2940, 2360, 1710, 1690, 1623, 1440, 1280, 1065. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.2 (1H, br s, OOH), 5.76 (1H, d, *J*=5.8 Hz, H-1), 5.64 (1H, d, *J*=5.8 Hz, H-2), 4.88 (1H, d, *J*=14.6 Hz, H-4), 4.38 (1H, d, *J*=14.6 Hz, H′-4), 3.89 (1H, dd, *J*=4.3, 2.9 Hz, H-5a), 3.767 (3H, s, CO_2Me), 1.9 (1H, m, H-6), 1.82 (1H, m, H-10β), 1.573 (3H, s, Me-C_{10c}), 1.128 (3H, s, Hz, Me-C_{10a}), 0.870 (3H, s, Me-C_7), 0.847 (3H, s, Me′-C_7); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 172.9 (CO_2), 165.5 (C_{3a}), 120.5 (C_3), 115.3 (C_1), 82.6 (C_{5a}), 78.1 (C_2), 68.7 (C_4), 51.9 (OMe), 44.3 (C_{6a}), 47.5 (C_{10c}), 42.0 (C_8), 39.0 (C_{10a}), 38.02 (C_{10}), 34.4 (Me-C_{10c}), 33.4 (C_7), 32.7 (Meα-C_7), 24.9 (C_6), 21.7 (Meβ-C_7), 20.6 (Me-C_{10a}), 18.5 (C_9); MS (EI) *m/z* 362 (M^+, 20), 346 (15), 345 (25), 344 (99), 331 (13), 329 (31), 315 (28), 314 (76), 313 (47), 299 (49), 297 (44), 281 (24), 243 (54), 203 (100); HRMS *m/z* calcd for $C_{21}H_{30}O_5$ 362.20932; found: 362.20986.

(3aS,5aR,6aS,10aS,10cS)-3a-Hydroperoxy-7,7,10a,10c-tetramethyl-3a,5a,6,6a,7,8,9,10,10a,10c-decahydro-4H-5-oxa-acephenanthrylene-3-carboxylicacidmethylester (*Compound* **iii**). IR ν_{max}/cm^{-1} (film) 3350, 3000, 2930, 2855, 1680, 1580, 1445, 1460, 1310. ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 11.34 (1H, s, OOH), 7.10 (1H, d, *J*=6.2 Hz, H-2), 5.78 (1H, d, *J*=6.2 Hz, H-1), 4.65 (d, *J*=9.5 Hz, H-4), 3.63 (1H, d *J*=9.5 Hz, H′-4), 4.41 (1H, dd, *J*=2.7, 2.7 Hz, H-5a), 3.797 (3H, s, CO_2Me), 2.05 (1H, m, H-6), 1.76 (1H, m, H-10β), 1.132 (3H, s, Me-C_{10c}), 1.129 (3H, s, Me-C_{10a}), 0.901 (3H, s, Me-C_7β), 0.877 (3H, s, Me-C_7α).

4.5. Construction and further functionalisation of the D ring system

4.5.1. 7α-Acetyl-spongia-9(11),13-dien-16-one (27). A mixture of the Diels–Alder adduct **26** (100 mg, 0.303 mmol) and ZnI_2 (120 mg, 0, 376 mmol) in acetic anhydride (2 mL) was stirred at rt for 48 h. The reaction mixture was poured into water and extracted with ether. The organic extracts were washed with aq. $NaHCO_3$, brine and dried. Chromatography of the residue obtained after evaporation of the solvent, using hexane–acetate (8:2) as eluent, afforded the lactone **27** (107.5 mg, nearly quantitative) as a white solid. Mp 183–184°C (from hexane). $[\alpha]_D^{27}$=−47.7° (1.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2990, 2940, 2868, 1757, 1728, 1246, 1021. ^{1}H NMR (300 MHz) δ5.75 (1H, dd, *J*=4.5, 2.7 Hz, H-11), 4.95 (1H, dd, *J*=2.7, 2.7 Hz, H-7), 4.82 (1H, ddd, *J*=16.8, 3.3, 1.8 Hz, H-15), 4.47 (1H, ddd, *J*=16.8, 2.4, 2.4 Hz, H-15), 2.96 (1H, dddd, *J*=22.5, 4.5, 3.0, 1.8 Hz, H-12β), 2.81 (1H, dddd, *J*=22.5, 3.3, 2.7, 2.4 Hz, H-12α), 1.970 (3H, s, CH_3CO), 1.92 (1H, m, H-6), 1.81 (1H, m, H-6), 1.426 (3H, s, Me-C_8), 1.198 (3H, d, *J*=0.9 Hz, Me-C_{10}), 0.835 (3H, s, Meβ-C_4), 0.763 (3H, s, Meα-C_4); ^{13}C NMR (75 MHz) δ 173.4 (C_{16}), 170.4 ($COCH_3$), 164.6 (C_{14}), 147.7 (C_9), 123.4 (C_{13}), 116.7 (C_{11}), 75.5 (C_7), 68.6 (C_{15}), 45.6 (C_5), 41.7 (C_8), 41.6 (C_3), 40.1 (C_{10}), 39.0 (C_1), 33.2 (C_4), 32.8 (Meα-C_4), 27.6 (Me-C_8), 23.6 (Me-C_{10}), 23.0 (C_6), 22.3 (C_{12}), 21.3 (CH_3CO), 21.2 (Meβ-C_4), 18.8 (C_2); MS (EI) *m/z* 358 (M^+, 2), 316 (100), 298 (75), 175 (45); HRMS *m/z* calcd for $C_{22}H_{30}O_4$ 358.2144, found 358.2142. Anal. calcd for $C_{22}H_{30}O_4$: C 73.71, H 8.44; found: C 73.60, H 8.56.

4.5.2. 7α-Hydroxy-spongia-9(11),13-dien-16-one (28). A solution of the acetate-lactone **27** (86.1 mg, 0.241 mmol) in a 10% aq. solution of KOH in MeOH (3 mL) was stirred at 0°C for 1 h. The reaction mixture was poured into cold water and acidified with diluted HCl. Extraction with ether and workup as usual afforded a solid residue that was purified by chromatography, using hexane–ethyl acetate 7:3 as eluent, to afford the hydroxy-lactone **28** (69.6 mg, 92%) as a white solid. Mp 184–186°C (from EtOAc). $[\alpha]_D^{26}$=−32.8° (1.0, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 3500–3100, 2924, 2854, 1741, 1696, 1460, 1696, 1377, 1038, 750. ^{1}H NMR (400 MHz) δ 5.80 (1H, dd, *J*=4.5, 2.8 Hz, H-11), 5.04 (1H, ddd, *J*=16.2, 2.6, 2.4 Hz, H-15), 4.86 (1H, ddd, *J*=16.2, 3.2, 1.5 Hz, H-15), 3.88 (1H, br s, H-7), 2.95 (1H, dddd, *J*=22.3, 4.5, 2.6, 1.5 Hz, H-12β), 2.81 (1H, dddd, *J*=22.3, 3.2, 2.8, 2.4 Hz, H-12α), 1.99 (1H, ddd, *J*=14.4, 13.2, 2.4 Hz, H-6β), 1.80 (1H, m, H-1), 1.75 (1H, ddd, *J*=14.4, 3.3, 3.3 Hz, H-6α), 1.66 (1H, ddd, *J*=13.5, 3.3, 3.3 Hz, H-2), 1.55 (1H, dddd, *J*=13.5, 7.1, 3.6, 3.6 Hz, H-2), 1.42 (1H, m, H-3), 1.41 (1H, m partly overlapped with H-3, H-1), 1.35 (1H, dd, *J*=13.2, 2.5 Hz, H-5), 1.24 (1H, m, H-3), 1.395 (3H, s, Me-C_8), 1.193 (3H, d, *J*=0.9 Hz, Me-C_{10}), 0.873 (3H, s, Meβ-C_4), 0.852 (3H, s, Meα-C_4); ^{13}C NMR (75 MHz) δ 173.8 (C_{16}), 166.3 (C_{14}), 147.7 (C_9), 123.1 (C_{13}), 118.2 (C_{11}), 72.8 (C_7), 69.4 (C_{15}), 45.1 (C_5), 43.6 (C_8), 41.7 (C_3), 40.2 (C_{10}), 39.0 (C_1), 33.3 (Meα-C_4), 32.9 (C_4), 27.6 (Me-C_8), 26.2 (C_6), 23.4 (Me-C_{10}), 22.6 (C_{12}), 21.5 (Meβ-C_4), 18.8 (C_2); MS (EI) *m/z* 316 (M^+, 15), 301 (6), 298 (9), 283 (17), 164 (100); HRMS *m/z* calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2028. Anal. calcd for $C_{20}H_{28}O_3$: C 75.91, H 8.92; found: C 75.80, H 9.01.

4.5.3. 7-Oxo-spongia-9(11),13-dien-16-one (29). A solution of DMSO (51 μL, 0.70 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of oxalyl chloride (58 μL, 0.68 mmol) in CH_2Cl_2 (0.5 mL) at −60°C, the mixture was stirred for 5 min and then a solution of alcohol **28** (13.8 mg, 0.041 mmol) in CH_2Cl_2 (0.3 mL) was added. The mixture was stirred at −60°C for 30 min, Et_3N (30 μL, 0.21 mmol) was added and the stirring was maintained for 15 min. The mixture was warmed to 0°C and maintained at this temperature for 30 min, diluted with water, extracted with CH_2Cl_2 and worked up. Chromatography, using a mixture of hexane–ethyl acetate 8:2 as eluent yielded ketone **29** (11.9 mg, 89%). Mp 143–145°C (from cold methanol). $[\alpha]_D^{27}$=−8.8° (1.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2930, 2869, 1758, 1708, 1190, 1027, 1003, 748. ^{1}H NMR

(400 MHz) δ 5.82 (1H, dd, J=5.4, 2.1 Hz, H-11), 5.14 (2H, m, H-15), 2.99 (1H, dddd, J=22.3, 5.4, 2.1, 1.9 Hz, H-12β), 2.82 (1H, ddd, J=22.3, 3.0, 2.8, 2.1 Hz, H-12α), 2.69 (1H, dd, J 16.8, 14.4 Hz, H-6β), 2.53 (1H, dd, J 16.8, 3.5 Hz, H-6α), 1.96 (1H, m, H-1), 1.38 (1H, dd, J 14.4, 3.5 Hz, H-5), 1.516 (3H, s, Me-C_8), 1.333 (3H, s, Me-C_{10}), 1.19 (1H, ddd, J=13.5, 12.6, 4.2 Hz, H-3α), 0.907 (3H, s, Meβ-C_4)[a], 0.872 (3H, s, Meα-C_4)[a]; ^{13}C NMR (75 MHz) δ 210.6 (C_7), 173.7 (C_{16}), 162.9 (C_{14}), 149.9 (C_9), 125.0 (C_{13}), 117.6 (C_{11}), 71.5 (C_{15}), 48.8 (C_5), 52.4 (C_8), 41.4 (C_3), 39.5 (C_{10}), 39.3 (C_1), 36.4 (C_6), 33.7 (C_4), 32.4 (Meα-C_4), 22.30[a] (Me-C_8), 22.36[a] (Me-C_{10}), 30.5 (C_{12}), 21.1 (Meβ-C_4), 18.6 (C_2); MS (EI) m/z 314 (M^+, 15), 298 (7), 281 (10), 211 (17), 191 (100), 109 (68); HRMS m/z calcd for $C_{20}H_{26}O_3$ 314.1882; found: 314.1896.

4.5.4. 7β-Hydroxy-spongi-9(11),13-dien-16-one (30). Borane–THF complex (1.0 M borane solution en THF, 50 μL, 0.050 mmol) was added to a stirred solution of compound **29** (5.3 mg, 0.017 mmol) in dry THF (150 μL) at 0°C. After 30 min 10% aqueous NaOH (0.25 mL) was added cautiously followed by addition of 35% H_2O_2 (0.25 mL) within 15 min. After the addition, the bath was removed and the mixture stirred for an additional 30 min. The reaction mixture was worked up and subjected to flash chromatography (using hexane–ethyl acetate 7:3 as eluent) to give alcohol **30** (5.2 mg, 99%). ^{1}H NMR (250 MHz) δ 5.70 (1H, dd, J=4.6, 2.9 Hz), 4.98 (1H, ddd, J=16.2, 2.6, 2.4 Hz), 4.88 (1H, ddd, J=16.2, 3.2, 1.5 Hz,), 3.65 (1H, dd, J=11.2, 4.9 Hz), 2.92 (1H, dddd, J=22.3, 4.5, 2.6, 1.5 Hz), 2.79 (1H, dddd, J=22.3, 3.2, 2.8, 2.4 Hz), 1.306 (3H, s), 1.172 (3H, d, J=0.9 Hz), 0.864 (3H, s), 0.855 (3H, s); MS (EI) m/z 316 (M^+, 20), 301 (8), 298 (6), 283 (15), 164 (100); HRMS m/z calcd for $C_{20}H_{28}O_3$ 316.2038; found: 316.2034.

4.5.5. 7α-Acetyl-9α,11α-epoxy-spongi-13-en-16-one (31) and 7α-acetyl-9β,11β-epoxy-spongi-13-en-16-one (32). A solution of **27** (16.2 mg, 0.045 mmol) and *m*-CPBA, free of *m*-chlorobenzoic acid,[33] (23.3 mg, 0.136 mmol) in CH_2Cl_2 (0.85 mL) was stirred at room temperature for 17 h. The dichoromethane mixture was treated with sodium metabisulphate and extracted with CH_2Cl_2. The combined organic extracts were washed with water, aq. Na_2CO_3 and brine and dried (Na_2SO_4). The solid residue obtained after evaporation of the solvent was purified by flash chromatography (hexane–ethyl acetate, 8:2) to afford the following compounds.

More polar epoxide **31** (7.8 mg, 46%), a white solid. Mp 115–116°C (from EtOAc–hexane). $[\alpha]_D^{26}$=16.7° (1.6, $CHCl_3$). ^{1}H NMR (400 MHz) δ 4.99 (1H, dd, J=2.5, 2.3 Hz, H-7), 4.70 (1H, dd, J=17.0, 2.8 Hz, H-15β), 4.47 (1H, ddd, J=17.0, 2.8, 1.9 Hz, H-15α), 3.36 (1H, dd, J=2.3, 1.1 Hz, H-11), 2.95 (1H, ddd, J=18.6, 2.3, 1.9 Hz, H-12β), 2.47 (1H, dddd, J=18.6, 2.8, 2.8, 1.1 Hz, H-12α), 2.098 (3H, s, *Me*CO), 1.86 (1H, ddd, J=14.9, 12.8, 2.5 Hz, H-6β), 1.71 (1H, dd, J=12.8, 2.3 Hz, H-6α), 1.385 (3H, s, Me-C_8), 1.261 (3H, s, Me-C_{10}), 1.14 (1H, m, H-1β), 0.832 (3H, s, Meβ-C_4), 0.815 (3H, s, Meα-C_4); ^{13}C NMR (100 MHz) δ 173.5 (C_{16}), 170.6 (*CO*Me), 165.0 (C_{14}), 120.1 (C_{13}), 74.6 (C_7), 68.3 (C_9), 67.9 (C_{15}), 50.8 (C_{11}), 43.3 (C_5), 43.2 (C_8), 41.0 (C_3), 39.1 (C_{10}), 32.9 (C_4), 32.4 (Meα-C_4), 31.4 (C_1), 24.5 (Me-C_8), 23.0 (C_6), 22.0 (C_{12}), 21.37 (CO*Me*), 21.35 (Me-C_{10}), 21.20 (Meβ-C_4), 17.6 (C_2); MS (EI) m/z 374 (M^+, 15), 330 (23), 314 (83), 256 (100), 69 (98); HRMS m/z calcd for $C_{22}H_{30}O_5$ 374.2093; found: 374.2099.

Less polar epoxide **32** (6.8 mg; 40%), a white solid. Mp 114–116°C (from EtOAc–hexane). $[\alpha]_D^{26}$=21.0° (1.3, $CHCl_3$). ^{1}H NMR (400 MHz) δ 5.16 (1H, dd, J=3.0, 2.8 Hz, H-7), 4.71 (1H, ddd, J=16.8, 2.9, 2.4 Hz, H-15), 4.64 (1H, ddd, J=16.8, 3.1, 1.5 Hz, H-15), 3.89 (1H, dd, J= 2.1, 1.9 Hz, H-11), 2.84 (1H, dddd, J=19.3, 2.4, 1.9, 1.5 Hz, H-12), 2.54 (1H, dddd, J=19.3, 3.1, 2.9, 2.1 Hz, H-12), 1.924 (3H, s, *Me*CO), 1.427 (3H, s, Me-C_8), 1.198 (3H, s, Me-C_{10}), 0.872 (3H, s, Meβ-C_4), 0.842 (3H, s, Meα-C_4); ^{13}C NMR (75 MHz) δ 173.4 (C_{16}), 169.6 (*CO*Me), 161.7 (C_{14}), 122.0 (C_{13}), 74.7 (C_7), 69.5 (C_{15}), 68.1 (C_9), 58.1 (C_{11}), 45.5 (C_5), 44.0 (C_8), 41.8 (C_3), 39.5 (C_{10}), 35.6 (C_1), 33.4 (C_4), 32.8 (Meα-C_4), 23.1 (C_6), 22.1 (C_{12}), 21.8 (Meβ-C_4), 21.5 (CO*Me*), 20.9 (Me-C_8), 19.3 (Me-C_{10}), 18.3 (C_2); HRMS m/z calcd for $C_{22}H_{30}O_5$ 374.2093; found: 374.2098.

4.5.6. Rearrangement of epoxide 32. Boron trifluoride-diethyl ether (12.5 μL) was added to a stirred solution of the epoxide **32** (4 mg, 0.01 mmol) in dry benzene (265 μL) at 5°C. After stirring for 3 h at this temperature the mixture was allowed to warm to room temperature and stirred for an additional hour. The mixture was diluted with ether and washed with 5% aq. solution of $NaHCO_3$ and brine and dried. Purification of the residue left after evaporation of the solvent by chromatography, using hexane–ethyl acetate 7:3 as eluent, afforded the alcohol **35** (2.8 mg, 70%) as an amorphous solid. ^{1}H NMR (400 MHz) δ 5.09 (1H, dd, J=10.8, 5.4 Hz, H-7), 5.03 (1H, ddd, J=17.5, 3.5, 0.9 Hz, H-15), 4.87 (1H, ddd, J=17.5, 2.6, 2.6 Hz, H-15), 4.31 (1H, ddd, J=6.4, 3.3, 2.6 Hz, H-11), 2.42 (1H, dddd, J=17.7, 3.5, 3.3, 2.6 Hz, H-12α), 2.33 (1H, dddd, J=17.7, 2.6, 2.6, 0.9 Hz, H-12β), 2.126 (3H, s, *Me*CO), 2.28 (1H, ddd, J=14.8, 5.4, 2.1 Hz, H-6β), 2.15 (1H, m, H-1β), 1.76 (1H, dd, J=14.8, 10.8 Hz, H-6α), 1.75 (1H, m, H-1α), 1.64 (1H, m, H-2), 1.48 (2H, m, H-3βH-2′), 1.45 (1H, d, J=6.4 Hz, OH), 1.371 (3H, s, Me-C_8), 1.334 (3H, s, Me-C_9), 1.25 (1H, m, H-3α), 0.982 (3H, s, Meβ-C_4), 0.822 (3H, s, Meα-C_4); ^{13}C NMR (100 MHz) δ 176.2 (C_{16}), 170.1 (*CO*Me), 162.7 (C_{14}), 134.9 (C_{10})[a], 130.9 (C_5)[a], 124.5 (C_{13}), 73.5 (C_7), 71.5 (C_{11}), 71.3 (C_{15}), 47.7 (C_9), 43.4 (C_8), 39.2 (C_3), 34.5 (C_4), 28.7 (Meα-C_4), 27.3 (Meβ-C_4), 29.0 (C_6), 26.7 (C_1+C_{12}), 21.3 (CO*Me*), 19.8 (C_2), 19.5 (Me-C_8), 18.6 (Me-C_9); MS (EI) m/z 374 (M^+, 2), 332 (10), 314 (100), 299 (85); HRMS m/z calcd for $C_{22}H_{30}O_5$ 374.2093; found: 374.2076.

4.5.7. 7-Oxo-9α,11α-epoxy-spongi-13-en-16-one (34). A solution of *tert*-butyl hydroperoxide in benzene (450 μL, 0.051 mmol; prepared from 50 μL of a 5.5 M solution of a *tert*-BuOOH in nonane and 2.5 mL of benzene) was added to a mixture of vanadyl acetoacetonate (2 mg, 2.5 mol%, 0.0008 mmol) and homoallylic alcohol **28** (15 mg, 0.048 mmol) at 0°C. After 10 min, the solution was allowed to warm to room temperature and stirred for a further 24 h. The reaction mixture was filtered through a short pad of silica gel, washing with a mixture of hexane–ethyl acetate 9:1, to give the hydroxy epoxide **33** (11.1 mg, 70%), as a solid. Mp 263–267°C (from benzene–hexane). ^{1}H NMR (300 MHz) δ 5.13 (1H, ddd, J=16.9, 2.7, 2.5 Hz, H-15), 4.78 (1H, dd, J=16.9, 3.6 Hz, H-15), 3.87 (1H, ddd, J=10.0,

2.8, 1 Hz, H-7), 3.42 (1H, dd, *J*=2.5, 1 Hz, H-11), 2.92 (1H, ddd, *J*=19.0, 2.7, 2.5 Hz, H-12), 2.52 (1H, d, *J*=10.0 Hz, OH), 2.49 (1H, dddd partly overlapped with OH, *J*=19.0, 3.6, 2.5, 1 Hz, H-12), 1.358 (3H, s, Me-C_8), 1.252 (3H, s, Me-C_{10}), 0.906 (3H, s, Meβ-C_4), 0.874 (3H, s, Meα-C_4); MS (EI) *m/z* 332 (M^+, 10.1), 317 (5.8), 314 (13.3), 299 (24.3), 281 (36.4), 271 (19.4), 125 (17.5), 205 (13.8), 189 (40.8),123 (100); HRMS *m/z* calcd for $C_{20}H_{28}O_4$ 332.1987; found: 332.1985.

A solution of DMSO (26 μL, 0.36 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of oxalyl chloride (30 μL, 0.35 mmol) in CH_2Cl_2 (0.5 mL) at −60°C. The mixture was stirred for 5 min, a solution of the above alcohol (10.7 mg, 0.031 mmol) in CH_2Cl_2 (0.2 mL) was added and the mixture was stirred at the same temperature for 30 min. Et_3N (15 μL, 0.108 mmol) was added to the solution, which was stirred at −60°C for 15 min, then warmed and maintained at 0°C for 30 min. The reaction mixture was diluted with water, extracted with CH_2Cl_2 and worked up. Chromatography, using a mixture of hexane–ethyl acetate 8:2 as eluent yielded epoxyketone **34** (5.4 mg, 50%). ^{1}H NMR (300 MHz) δ 5.26 (1H, ddd, *J*=18.5, 3.2, 2.3 Hz, H-15), 5.02 (1H, ddd, *J*=18.5, 3.4, <1 Hz, H′-15), 3.53 (1H, dd, *J*=2.8, 1.1 Hz, H-11), 2.98 (1H, dddd, *J*=18.7, 2.8, 2.3, <1 Hz, H-12), 2.70 (1H, dd, *J*=15.8, 14.3 Hz, H-6β), 2.55 (1H, dd, *J*=15.8, 3.4 Hz, H-6α), 2.51 (1H, dddd, *J*=18.7, 3.4, 3.2, 1.1 Hz, H-12), 1.76 (1H, dd, *J*=14.3, 3.4 Hz, H-5), 1.555[a] (3H, s, Me-C_8), 1.423[a] (3H, s, Me-C_{10}), 0.902 (3H, s, Meβ-C_4), 0.896 (3H, s, Meα-C_4); MS (EI) *m/z* 330 (M^+, 28), 315 (16), 123 (74), 109 (100), 69 (53); HRMS *m/z* calcd for $C_{20}H_{26}O_4$ 330.1831; found: 330.1823.

4.5.8. Rearrangement of epoxide 34. A solution of the epoxide **34** (4.4 mg, 0.13 mmol) in dry benzene (250 μL) was treated with boron trifluoride-diethyl ether (12 μL, 0.094 mmol) at room temperature for 8 h. Work-up as for **35** afforded a residue which was purified by chromatography, using hexane–ethyl acetate 8:2 as eluent, to give 3.8 mg of a 7:3 mixture of two compounds. The major compound was identified as the alcohol **36** by analysis of its spectroscopic data deduced from the spectra of the mixture. Data for **36**. ^{1}H NMR (400 MHz) δ 4.87 (1H, ddd, *J*=17.6, 2.8, 2.8 Hz, H-15), 4.72 (1H, ddd, *J*=17.6, 3.4, 1.8 Hz, H′-15), 4.11 (1H, dd, *J*=3, 1.7 Hz, H-11), 2.25 (1H, dt, *J*=17, 1.9 Hz, H-6), 2.45 (1H, dt, *J*=17, 1.6 Hz, H′-6), 1.050 (3H, s, Me-C_8)[a], 1.046 (3H, s, Me-C_9)[a], 1.002 (3H, s, Meβ-C_4), 0.949 (3H, s, Meα-C_4); ^{13}C NMR (75 MHz) δ (only some signals assigned), 82.3 (C_{11}), 71.6 (C_{15}), 162.2 (C_{14}), 136.1, 128.3 and 130.5 (C_{10}, C_{13} and C_5), 38.7 (C_3), 36.9 (C_6), 28.0 (C_1), 26.8 (C_{12}), 28.6 and 27.4 (2×Me-C_4), 19.7 (C_2), 12.5 (Me-C_9), 9.6 (Me-C_8).

Acknowledgements

Financial support from the Dirección General de Enseñanza Superior e Investigación Científica (Grants PB98-1421-C02-01and BQU2002-00272) is gratefully acknowledged. We are also grateful to the Ministerio Español de Ciencia y Tecnología for providing a research fellowship to A. B. G.

References

1. (a) Connolly, J. D.; Hill, R. A.; 1st ed. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991; Vol. 2, p 895. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1–48, and previous reviews of this series.
2. (a) Walker, R. P.; Thompson, J. E.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 4976. (b) Capelle, N.; Braeckman, J. C.; Daloze, D.; Tursch, B. *Bull. Soc. Chim. Belg.* **1980**, *89*, 399. (c) Gonzalez, A. G.; Estrada, D. M.; Martín, J. D.; Martín, V. S.; Pérez, C.; Pérez, R. *Tetrahedron* **1984**, *40*, 4109. (d) Kohmoto, S.; McConnell, O. J.; Wrigth, A.; Cross, S. *Chem. Lett.* **1987**, 1687. (e) Cimino, G.; Crispino, A.; Gavagnin, M.; Sodano, G. *J. Nat. Prod.* **1990**, *53*, 102. (f) Gunasekera, S. P.; Schmitz, F. J. *J. Org. Chem.* **1991**, *56*, 1250. (g) Potts, B. C. M.; Faulkner, D. J.; Jacobs, R. S. *J. Nat. Prod.* **1992**, *55*, 1701. (h) Betancur-Galvis, L.; Zuluaga, C.; Arnó, M.; González, M. A.; Zaragoza, R. J. *J. Nat. Prod.* **2002**, *65*, 189.
3. (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94. (b) Spring, O.; Kupka, J.; Maier, B.; Hager, A. *Z. Naturforsch.* **1982**, *C37*, 1087.
4. Miyamoto, T.; Sakamoto, K.; Arao, K.; Komori, T.; Higuchi, R.; Sasaki, T. *Tetrahedron* **1996**, *52*, 8187.
5. La Clair, J. J.; Lansbury, P. T.; Zhi, B.; Hoogsteen, K. *J. Org. Chem.* **1995**, *60*, 4822, and references cited therein.
6. (a) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147. (b) Sasaki, S.; Maruka, K.; Naito, H.; Maemura, R.; Kawahara, E.; Maeda, M. *Chem. Pharm. Bull.* **1998**, *46*, 154.
7. For partial synthesis of spongianes, see: (a) Immanura, P. M.; Gonzalez-Sierra, M.; Rúveda, E. A. *J. Chem. Soc., Chem. Commun.* **1981**, 734. (b) De Miranda, D. S.; Brendola, G.; Inmamura, P. M.; González-Sierra, M.; Marsaioli, A. J.; Rúveda, E. A. *J. Org. Chem.* **1981**, *46*, 4851. (c) González-Sierra, M.; Mischne, M. P.; Rúveda, E. A. *Synth. Commun.* **1985**, *15*, 727. (d) Nakano, T.; Hérnandez, M. I. *Tetrahedron Lett.* **1982**, *23*, 1423. (e) Nakano, T.; Hérnandez, M. I. *J. Chem. Soc., Perkin Trans. 1* **1983**, 135. (f) Nakano, T.; Hérnandez, M. I.; Gómez, M.; Medina, J. D. *J. Chem. Res. Synop.* **1989**, 54. (g) Arnó, M.; González, M. A.; Zaragoza, R. J. *Tetrahedron* **1999**, *55*, 12419. (h) Arnó, M.; González, M. A.; Marín, M. L.; Zaragoza, R. J. *Tetrahedron Lett.* **2001**, *42*, 1669. (i) Arnó, M.; González, M. A.; Zaragoza, R. J. *J. Org. Chem.* **2003**, *68*, 1242.
8. For total synthesis of spongianes and spongiane-type compounds, see: (a) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *Chem. Lett.* **1983**, 1459. (b) Zoretic, P. A.; Shen, Z.; Wang, M.; Ribeiro, A. A. *Tetrahedron Lett.* **1995**, *36*, 2925. (c) Sakamoto, T.; Kanematsu, K. *Tetrahedron* **1995**, *51*, 5771. (d) Pattenden, G.; Roberts, L. *Tetrahedron Lett.* **1996**, *37*, 4191. (e) Zoretic, P. A.; Wang, M.; Zhang, Y.; Shen, Z.; Ribeiro, A. A. *J. Org. Chem.* **1996**, *61*, 1806. (f) Zoretic, P. A.; Wang, M.; Zhang, Y.; Fang, H.; Ribeiro, A. A.; Dubay, G. *J. Org. Chem.* **1998**, *63*, 1162. (g) Pattenden, G.; Roberts, L.; Blake, A. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 863. (h) Goeller, F.; Heinemann, C.; Demuth, M. *Synthesis* **2001**, 1114.
9. (a) Abad, A.; Arnó, M.; Marín, M. L.; Zaragozá, R. J. *J. Org. Chem.* **1992**, *57*, 6861. (b) Abad, A.; Arnó, M.; Marín, M. L.; Zaragozá, R. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1861. (c) Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Marín, M. L.; Zaragozá, R. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2193.

10. (a) Abad, A.; Agulló, C.; Cuñat, A. C.; Navarro, I.; Ramírez de Arellano, M. C. *Synlett* **2001**, 349. (b) Abad, A.; Agulló, C.; Cuñat, A. C.; Navarro, I. *Tetrahedron Lett.* **2001**, *42*, 8965, and references cited therein.
11. A preliminary communication of this work has been published: Abad, A.; Agulló, C.; Cuñat, A. C.; García, A. B. *Tetrahedron Lett.* **2002**, *43*, 7933.
12. (a) Gesson, J. P.; Jacquesy, J. C.; Renoux, B. *Tetrahedron* **1989**, *45*, 5853. (b) Hersel, U.; Steck, M.; Seifert, K. *Eur. J. Org. Chem.* **2000**, 1609.
13. Abbassi, K. Diastereoselective Synthesis of Biologically Active Polycyclic Terpenes. Ph.D. Thesis, University of Valencia, Valencia, Spain, 2003.
14. Abad, A.; Agulló, C.; Castelblanque, L.; Cuñat, A. C.; Navarro, I.; Ramírez de Arellano, M. C. *J. Org. Chem.* **2000**, *65*, 4189.
15. For a recent review of disposable tethers in synthetic organic chemistry, see: Gauthier D. R., Jr.; Zandi, K.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289.
16. (a) Balas, L.; Jousseaume, B.; Langwost, B. *Tetrahedron Lett.* **1989**, *30*, 4525. (b) Nicolau, K. C.; Li, W. S. *J. Chem. Soc., Chem. Commun.* **1985**, 421. (c) Saigo, K.; Usui, M.; Kikuchi, K.; Shimada, E.; Mukaiyama, T. *Bull. Chem. Soc. Jpn* **1977**, *50*, 1863.
17. Earl, R. A.; Townsend, L. B. *Org. Synth.* **1981**, *60*, 81.
18. Walkup, R. D. *Tetrahedron Lett.* **1987**, *28*, 511.
19. Liu, Z. Y.; Zhou, X. R.; Wu, Z. M. *J. Chem. Soc., Chem. Commun.* **1987**, 1868.
20. Nagashima, S.; Kanematsu, K. *Tetrahedron: Asymmetry* **1990**, *1*, 743.
21. Benedetti, V. M. O.; Monteagudo, E.; Burton, S. G. *J. Chem. Res. (S)* **1990**, 248.
22. (a) Baran, J. S. *J. Org. Chem.* **1960**, *25*, 257. (b) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.
23. White, J. D.; Bolton, G. L.; Dantanarayana, A. P.; Foc, M. J.; Hiner, R. N.; Jackson, R. W.; Sakuma, K.; Warrier, U. S. *J. Am. Chem. Soc.* **1995**, *117*, 1908.
24. Rickborn, B. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 3, pp 733–775.
25. Sudha, R.; Narasimhan, M.; Saraswathy, V. G.; Sankararaman, S. *J. Org. Chem.* **1996**, *61*, 1877.
26. Bull, J. R.; Koning, P. D. *Eur. J. Org. Chem.* **2001**, 1189.
27. See, for example: Paryzek, Z. *J. Chem. Soc., Perkin Trans. 1* **1978**, 329, and references cited therein.
28. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115.
29. Sheldrick, G. M. *SHELX-97*: An Integrated System for Solving and Refining Crystal Structures from Diffraction Data; University of Götingen, Germany, 1997.
30. Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.
31. Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876.
32. Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143.
33. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed. Pergamon: Oxford, 1988; p 123.