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Diastereoselective synthesis of antiquorin and related polyoxygenated atisene-type diterpenes

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Abstract—A diastereoselective approach to polyoxygenated atisene-type diterpenes starting from (*S*)-(+)-carvone is described. The key steps used in the preparation of the atisene framework are an intramolecular Diels–Alder reaction, an intramolecular diazoketone cyclopropanation, an endocyclic cyclopropane ring cleavage and the regioselective reduction of an allylic bromide by a low-valent chromium species. The synthesis of natural atisanes antiquorin (**1**), atis-16-ene-3,14-dione (**3**), atis-16-ene-2,3,14-trione (**8**) and 3β-hydroxy-atis-16-ene-2,14-dione (**9**) following this approach is presented. Also described is the synthesis of 18-hydroxy-atis-16-ene-3,14-dione (**5**), the structure erroneously assigned to an atisene isolated from the Fijian plant *Euphorbia fidjiana*. This work shows that the natural atisene isolated from this plant is, in fact, the epimer at C-4 of this compound.
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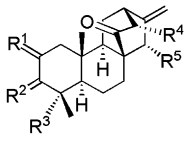
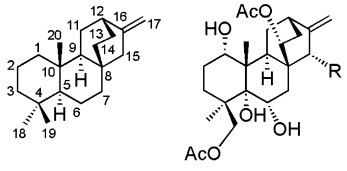
1. Introduction

Antiquorin (**1**) is a relevant member of a subclass of polyoxygenated tetracyclic atisane diterpenes, structurally based on the atisene skeleton (**2**) (Scheme 1), which is also common to the related atisine-diterpene alkaloids.[1] Initially isolated from *Euphorbia antiquorum*,[2,3] antiquorin has also been obtained from *Euphorbia fidjiana*,[4–6] *Euphorbia sieboldiana*,[7,8] *Euphorbia neriifolia*,[9] *Euphorbia quinquecostata*[10] and more recently *Euphorbia ebracteolata*.[11] The initial structure proposed for antiquorin[2] was later revised as **1** by X-ray diffraction analysis.[12,13] Other atisene diterpenes related to antiquorin, e.g., **3**,[4,5,14] **4**,[5,7,9,11] **5**–**7**,[5] and **8**,[14] have been obtained from other species of the *Euphorbia* genus, but others have been isolated from different sources. For example, compound **9** has been found in extracts from the Samoan tree *Homalanthus acuminatus*,[15] while **10** and **11** have been isolated from the New Zealand liverwort *Lepidolaena clavigera*.[16] In spite of the promising wide spectrum of biological activities exhibited by other atisane-type diterpenes,[17] only some of these compounds have been evaluated for their biological activity. Antiquorin (**1**)[5] and compounds **3**[5] and **10**[16] have shown cytotoxic activity, while compound **9** has shown AIDS antiviral activity.[15]



	R^1	R^2	R^3	R^4	R^5
1	H,H	O	CH_3	OH	H
3	H,H	O	CH_3	H	H
4	H,H	β-OH/α-H	CH_3	OH	H
5	H,H	O	CH_2OH	H	H
6	H,H	O	CH_2OH	OH	H
7	H,H	O	CH_3	OH	OH
8[a]	O	O	CH_3	H	H
9	O	β-OH/α-H	CH_3	H	H

(a) This compound exists in the enolic tautomeric form, at least in $CDCl_3$ solution



2 **10** R = H **11**: R = OH

Scheme 1. Some polyoxygenated atisenes.

The absolute stereochemistry for antiquorin and the rest of natural atisenes described here has not been rigorously established. It has been assumed that these atisenes belong to the *ent*-enantiomeric series on the basis of biogenetic considerations and their co-occurrence with other *ent*-atisanes

Keywords: Diterpene; Atisane; Carvone; Cyclopropane; Radical cleavage; Diels–Alder reaction.
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isolated from the same plants (see for example, Refs. 5 and 14). Some confusion also exists in the literature over the appropriate use of the *R*/*S* nomenclature to define the configuration at C-13 (see for example, Refs. 5 and 7). As confirmed by the data presented in this work, antiquorin belongs to the *ent*-enantiomeric series and has the following absolute configuration 5*S*,8*S*,9*S*,10*R*,12*S*,13*R* (i.e., *ent*-**1**).

A relatively important amount of effort has been dedicated to the synthetic preparation of atisane-type diterpenes. A large part of this work has been based on the transformation of the carbon skeleton of other polycyclic diterpenes into the atisane framework, generally via skeletal rearrangements, which are promoted either chemically or microbiologically.[18] On the other hand, and after the pioneering work of Ireland on the synthesis of atiserene (**2**),[19] most of the synthetic work aimed at the total synthesis of atisanes has been undertaken by Fukumoto et al., who have developed two conceptually and tactically different synthetic approaches for the elaboration of the bicyclo[2.2.0]octane moiety characteristic of the atisane framework based on an intramolecular double Michael reaction[20] and a homoallyl–homoallyl radical rearrangement reaction, respectively.[21] By using these strategies, they have completed the synthesis of several atisanes, e.g., atiserene,[22] methyl atis-16-ene-19-oate,[23] methyl gummiferolate,[24] and, more recently, serofendic acids A and B.[25]

We have recently described a general synthetic approach to the polycyclic carbon skeleton of biogenetically related beyerane, kaurane and atisane diterpenes from carvone.[26] This approach is based on the initial preparation of a pentacyclic hydrocarbonated system containing the tricyclo[3.2.1.$0^{2,7}$]-octane moiety, characteristic of the trachylobane-type diterpenes, which is regioselectively cleaved to obtain the bicyclo[3.2.1]- and bicyclo[2.2.2]octane moieties, characteristic of beyeranes/kauranes and atisanes, respectively. As a continuation of this work, we wish to report here the application of this strategy for the preparation of polyoxygenated atisane-type compounds such as antiquorin and the other related natural atisenes mentioned above. These following results show that this approach represents a complement to the existing strategies for the preparation of this type of terpenes, being particularly useful for the preparation of the highly functionalized atisane framework. A preliminary account of part of this work has previously been published.[27]

2. Results and discussion

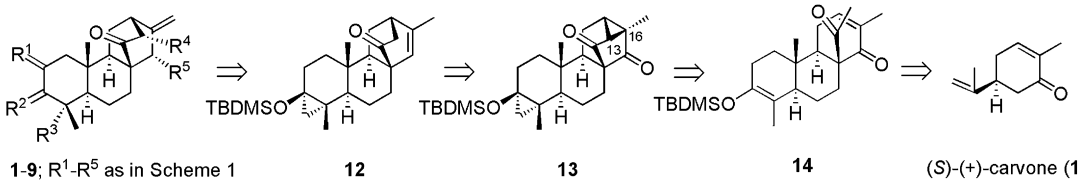
2.1. Retrosynthetic route to polyoxygenated atisanes from carvone

The retrosynthetic route to antiquorin and related atisenes is depicted in Scheme 2. The synthesis of these compounds is based on the preparation from carvone (**15**) of the pentacyclic intermediate **12**, which already contains the basic atisane skeleton. This compound has a functionalization at different positions of the atisane framework adequate for further elaboration of the required functionalization around the A, C and D rings of the target compounds. The bicyclo[2.2.2]octane moiety of the atisane skeleton is originated by regioselective cleavage of the C13–C16 cyclopropane bond of the key trachylobane-type intermediate **13**, which in turn is easily accessible from carvone, via the tricyclic intermediate **14**, using an IMDA reaction and an intramolecular diazoketone cyclopropanation of the unsaturated ketone moiety as key steps.

2.2. Preparation of key trachylobane-type intermediate 13

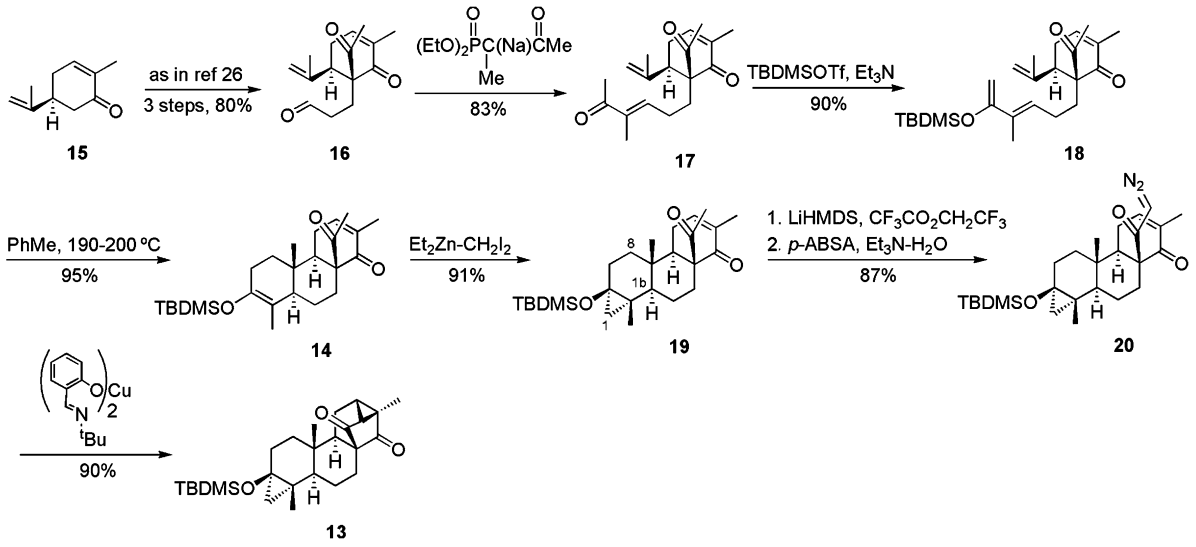
The synthesis of the key intermediate **13** is summarised in Scheme 3. The synthesis commences from the known aldehyde **16**, obtained stereoselectively from carvone by reaction of its kinetic enolate with pyruvonitrile, followed by C-alkylation of the resulting β-diketone with 3-iodopropanaldehyde diethyl acetal and then acid hydrolysis with PPTS, giving an overall yield of 80% for the three steps.[26] Elaboration of the oxygenated diene moiety required for the construction of the AB rings via an intramolecular Diels–Alder (IMDA) reaction was effected in two steps. First, Horner–Wadsworth–Emmons olefination reaction of the tricarbonyl compound **16** with the α-phosphonate carbanion derived from the reaction of 2-oxabutane-3-phosphonate and sodium hydride in THF at −40 °C.[28] Under these conditions, the reaction was completely chemo- and stereoselective, affording the (*E*)-enone **17** in 83% yield. The use of higher temperatures led to a significant lowering in the yield of **17**. In the second step, the enone **17** was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) and triethylamine (Et_3N) at low temperature. Under the kinetic conditions used, only the dienol silyl ether **18** was obtained in about 90% yield, without significant amounts of other possible enol ethers being observed.

The dienol silyl ether **18** underwent a stereoselective IMDA reaction when it was heated at 190–200 °C in a toluene solution containing a small amount of propylene oxide, for 7 days, to afford the adduct **14** in 95% yield after the chromatographic purification. The use of previously silylated ampoules and propylene oxide as acid scavenger in this reaction was essential to avoid partial hydrolysis of the dienol silyl ether moiety of **18**, which otherwise resulted in a marked lowering in the yield of the Diels–Alder adduct formed. Although expected from the results previously obtained in the IMDA reaction of 1,3,9-decatrienes,[26,29] the stereochemistry of compound **14** was firmly established by a detailed spectroscopic study that confirmed the *trans–anti–trans* ring configuration of the tricyclic framework.



1-**9**; R^1-R^5 as in Scheme 1 **12** **13** **14** (*S*)-(+)-carvone (**15**)

Scheme 2. Retrosynthetic route to atisene-type diterpenes from carvone.



Scheme 3. Preparation of the key trachylobane-type intermediate **13**.

Prior to the elaboration of the tricyclo[3.2.1.0^{2,7}]octane moiety of the trachylobane-type intermediate **13**, the tricyclic enol silyl ether **14** was submitted to Simmons–Smith cyclopropanation conditions to stereoselectively cyclopropanate the ring A double bond, necessary for the introduction of the geminal dimethyl group at C-4 in the natural compounds. This reaction takes place stereoselectively from the less hindered α-side of the double bond, affording the *tert*-butyldimethylsilyloxy cyclopropane **19** in 91% yield.

The synthesis of compound **13** was completed via the α-diazoketone **20**, which was prepared from methyl-ketone **19** in high yield using a diazo-transfer reaction.[30] First, the methyl-ketone **19** was transformed into the corresponding trifluoromethyl β-diketone by reaction of its lithium enolate with 2,2,2-trifluoroethyltrifluoroacetate, followed by diazo-transfer reaction and subsequent in situ retro-Claisen reaction on treatment with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and Et_3N in MeCN in the presence of a 1.5 equiv of water. Intramolecular addition of the α-diazoketone moiety to the enone double bond took place smoothly and efficiently when **20** was treated with a catalytic amount of bis(*N*-*tert*-butyl salicylaldiminate)copper(II) in refluxing toluene, affording the hexacyclic compound **13** in 90% yield.

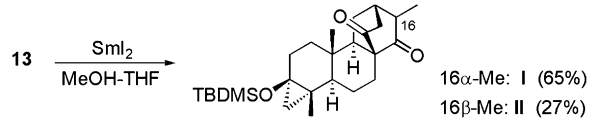
2.3. Trachylobane-to-atisane skeleton transformation. Synthesis of the pivotal atisane-type intermediate 12

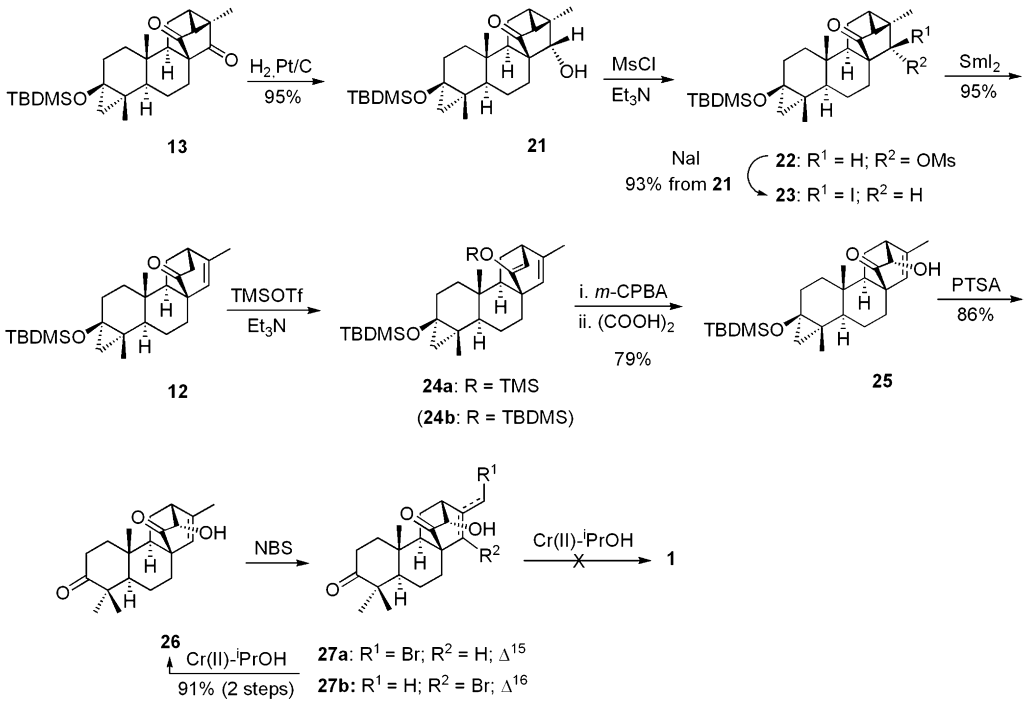
With the trachylobane-type compound **13** readily at hand, we then focused on the transformation of the tricyclo[3.2.1.0^{2,7}]octane moiety into the bicyclo[2.2.2]octane system characteristic of the atisane framework. This transformation was effected by regioselective reductive cleavage of the C13–C16 cyclopropane bond. First, the carbonyl group at C-15 of **13** was chemo- and stereoselectively reduced by hydrogenation at ambient temperature in AcOEt with 10% Pt on carbon as the catalyst to give the hydroxyketone **21** in 95% yield (Scheme 4). The same reduction was also effected in similar yield by $NaBH_4$ reduction in MeOH–CH_2Cl_2 at 0 °C. The α-disposition for the hydroxyl group at C-15 was supported, in addition to other spectroscopic data, by the strong shielding experienced by C-9 in **21** with respect to diketone **13** ($\Delta\delta$=12 ppm). Subjection of the hydroxyketone **21** to conventional mesylation conditions gave the mesylate **22**, which was then transformed into the iodide **23** by treatment with sodium iodide in acetone at 40 °C, in an overall yield for the two steps of 93%. The inversion of the configuration at C-15 in this substitution reaction was evident from the analysis of the NMR data of **23**, particularly through the strong deshielding experienced by C-9 in the ^{13}C NMR spectra with respect to the same carbon atom of the alcohol **21** ($\Delta\delta$=7.6 ppm), resulting from the disappearance of the γ-interaction that exists in the latter between this position and the hydroxylic oxygen atom. Finally, treatment of iodide **23** with samarium iodide in THF–MeOH produced the corresponding C15-centred cyclopropyl carbinyl radical, which then underwent cleavage of the endocyclic C13–C16 cyclopropane bond to give the atisene-type compound **12** in 95% yield. The transformation of iodide **23** into compound **12** was also effected, although in slightly lower yield, using the stronger lithium–liquid ammonia reductive system.[‡]

2.4. Functionalization of the atisane skeleton. Synthesis of antiquorin (1) and atis-16-ene-3,14-dione (3)

Our attention was now directed to the modification of the functionalization of the atisane-type compound **12** necessary for the preparation of the polyoxygenated target atisanes. Our first synthetic objective was antiquorin (**1**). The transformation of **12** into **1** requires (i) stereoselective introduction of the hydroxyl group at C-13, (ii) acid-catalysed opening of the siloxycyclopropane moiety that completes the

[‡] The regioselective reductive cleavage of the C13–C16 cyclopropane bond, thus completing the tricyclo[3.2.1.0^{2,7}]octane moiety to bicyclo[2.2.2]octane moiety transformation, was also effected directly from cyclopropyl diketone **13** by treatment with Li in liquid NH_3 or SmI_2 in THF–MeOH (see scheme below and Section 4). However, the functionalization around the bicyclo[2.2.2]octane moiety of the atisane-type compound obtained, i.e., **I**–**II**, in this transformation is less suitable for the preparation of the target atisanes.





Scheme 4. Trachylobane-to-atisane skeleton transformation. Failed attempted transformation of **12** into antiquorin (**1**).

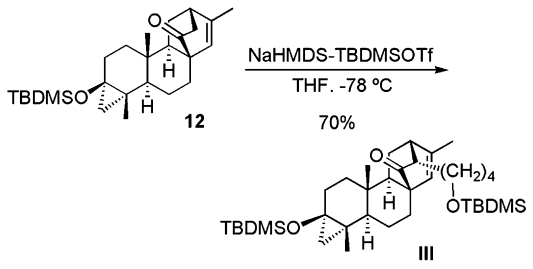
installation of the geminal dimethyl group at C-4 and the carbonyl group at C-3 and (iii) isomerisation of the endocyclic C15–C16 double bond to the exocyclic C16–C17 position.

Attempted direct introduction of the hydroxyl group at C-13 via reaction of the lithium enolate (generated at this position by treatment of **12** with LDA at low temperature) with the Vedejs reagent [oxidodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide), MoOPH][31] was unsuccessful. However, an alternative procedure, based on the epoxidation of a silyl enol ether, worked quite well (Scheme 4).[32] Thus, **12** was converted into the mildly acidic labile trimethylsilyl enol ether **24a** by treatment with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and Et_3N at rt. It must be noted that the formation of **24a** does not take place at a lower temperature, which suggests the existence of a relatively high steric hindrance around the oxygen atom of the C-14 carbonyl moiety of **12**. In fact, **12** did not react at all with the more sterically demanding TBDMSOTf to give the *tert*-butyldimethylsilyl enol ether **24b** under the same reaction conditions.[§] The silyl enol ether **24a** underwent stereoselective epoxidation from the less hindered face of the C13–C14 double bond on treatment with *m*-chloroperbenzoic acid (*m*-CPBA), providing the corresponding epoxide that was not purified, but directly hydrolysed to the α-hydroxyketone **25** by smooth acid treatment with oxalic acid in MeOH at rt, in an overall yield of 79% from **12**. The stereochemistry at the C-13 carbinolic centre of **25** was consistent with the absence of NOE enhancement at the methyl group at C-16 upon irradiation of H-13 and the small but significant deshielding observed in the ^{13}C NMR spectra for this methyl group relative to that of the precursor **12** ($\Delta\delta$=1.2 ppm), which is due to the *syn* orientation of the OH group with respect to this methyl group (δ-effect).[34]

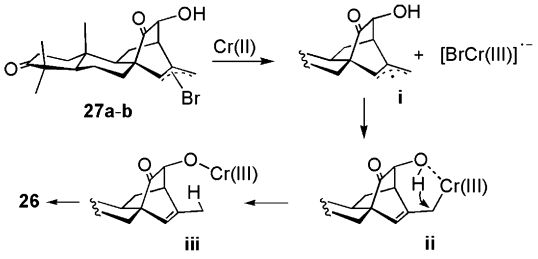
The functionalization of the A ring as in antiquorin (**1**) was readily achieved by treatment of **25** with 1 equiv of *p*-toluenesulfonic acid (PTSA) in refluxing chloroform, which promoted concomitant hydrolysis of the *tert*-butyldimethylsilyl protecting group and cyclopropane ring cleavage to give the hydroxy-atisenedione **26** in 86% yield. The use of alternative reaction conditions for the opening of the cyclopropane ring, such as TBAF in THF or 1 M HCl in MeOH, led to a much lower yield of **26**.

Finally, isomerisation of the C15–C16 double bond to the C16–C17 position, which is required to complete the synthesis of antiquorin (**1**), was attempted through a two-step procedure based on the reduction of an allylic bromide by a low-valent chromium species in the presence of a proton source.[35,36] In the first step, allylic bromination of **26** with *N*-bromosuccinimide (NBS) in a mixture of CH_2Cl_2 and MeOH afforded ca. 2:1 mixture of regioisomeric allylic bromides **27a** and **27b**, which could not be easily separated. Therefore the mixture of both was used directly in the next step. In principle, this should be irrelevant from the synthetic

[§] Even the reaction of the sodium enolate of **12**, generated by treatment of **12** with sodium hexamethyldisilazide, with TBDMSOTf in THF failed to produce the silyl enol ether **24b**, and instead the compound **III** (see below), originated by an unusual nucleophilic enolate opening of THF catalysed by TBDMSOTf, was obtained (see Ref. 33 for a related precedent for this reaction and Section 4 for details of the preparation of compound **III**).



point of view since both bromides should afford the same allylic radical intermediate in the subsequent reductive step. Contrary to expectation, however, reduction of the mixture of allylic bromides **27a** and **27b** with chromous chloride ($CrCl_2$), previously generated from the reaction of $CrCl_3$ with $LiAlH_4$ in THF, in the presence of isopropanol as proton source, did not afford the anticipated product antiquorin (**1**), but instead gave the starting atisene **26** in a 91% overall yield for the two steps. A tentative mechanism for the unexpected formation of the more substituted alkene in the above reductive process is given in Scheme 5.

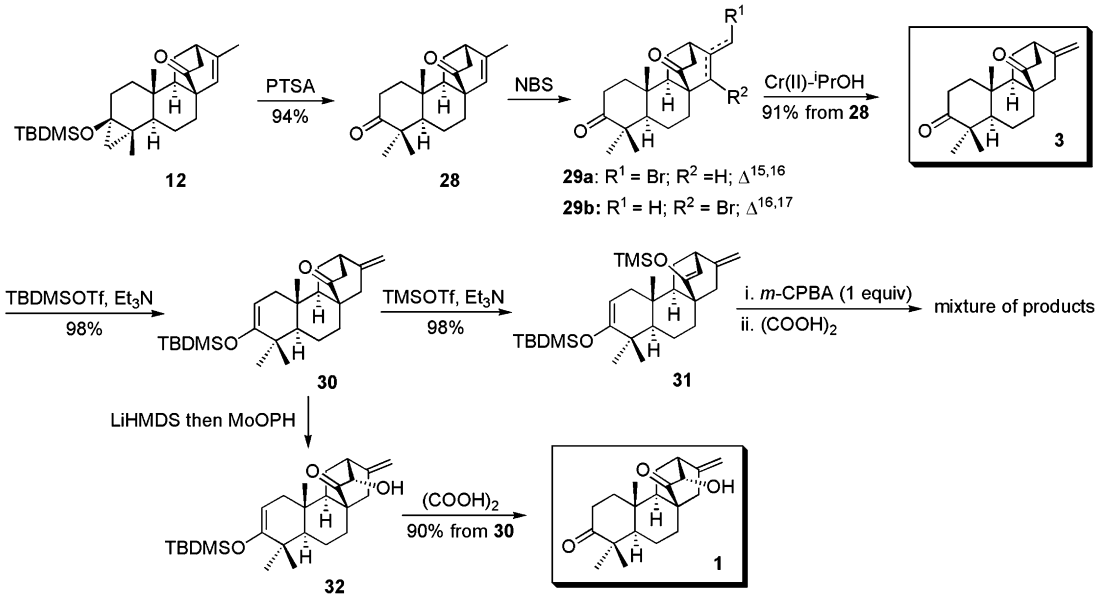


Scheme 5. Tentative mechanistic proposal for the formation of **26** from **27a–b**.

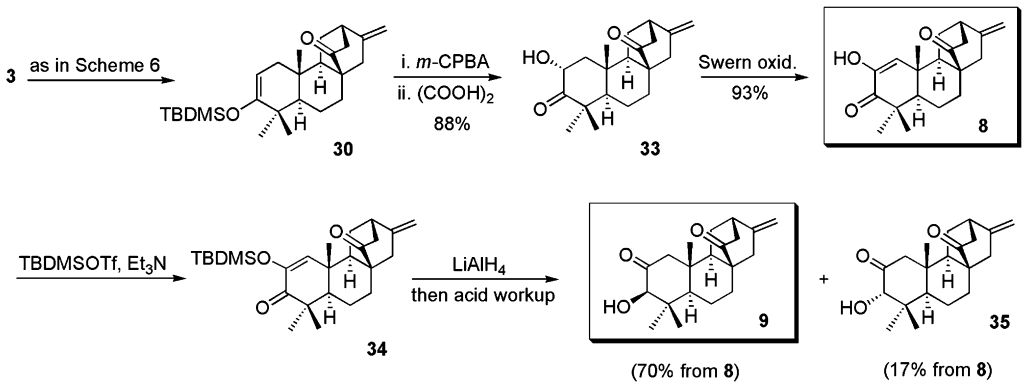
In accordance with this proposed mechanism, the reaction presumably involves the transference of the halogen atom from carbon to chromium to produce the allyl radical intermediate **i**, which is followed by formation of the allylchromium species **ii**. Probably, the formation of this regioisomeric σ-allyl metal intermediate is favoured by the stabilisation provided by the C-13 hydroxyl group, which also makes possible a rapid intramolecular transference of a proton to C-17, through a six-membered cyclic transition state, to afford the olefin **26**.

On the basis of the above mechanistic interpretation, it was hoped that the required less substituted double bond could be obtained by simply interchanging the order of the hydroxylation and double bond isomerisation steps. This modified approach to antiquorin (**1**) from **12** commences with the acid-catalysed cyclopropane ring opening that leads to atisenedione **28** (Scheme 6). The reaction was effected, as described above for **25**, by treatment of **12** with 1 equiv of PTSA in refluxing chloroform, affording the compound **28** in 94% yield. Allylic bromination of this compound in the conditions previously mentioned, and the subsequent treatment of the mixture of allyl bromides obtained, i.e., **29a/29b**, with the $CrCl_2$/*iso*-PrOH reductive system, led to atisene **3**, with a global yield for the two steps of 91%. As already mentioned in Section 1, this atisene has been isolated from the same *Euphorbia* species as antiquorin, which suggests that **3** is most probably the biogenetic precursor of antiquorin.

In order to introduce the required hydroxyl group adjacent to the C-14 carbonyl group that would complete the synthesis of antiquorin, it was previously necessary to block the more reactive C-2 methylenic moiety contiguous to the other carbonyl group of diketone **3**. This was effected by formation of the corresponding *tert*-butyldimethylsilyl enol ether by treatment of **3** with TBDMSOTf and Et_3N at low temperature. Under these conditions, only the enol silyl ether of the C-3 carbonyl group was formed, cleanly affording the *tert*-butyldimethylsilyl enol ether **30** in nearly quantitative yield. A first attempt to hydroxylate C-13 was carried out using the same procedure used previously to obtain **25** from **12** (see Scheme 4). Although the formation of the trimethylsilyl enol ether **31** could be performed in very high yield under similar reaction conditions as those described above for **24a**, the subsequent reaction with *m*-CPBA under a variety of reaction conditions was not selective, always affording, after the hydrolytic treatment with methanolic oxalic acid, mixtures of hydroxylated products at C-2 and/or C-13. However, reaction of the lithium or potassium enolate of **30**, formed by reaction with lithium or potassium hexamethyldisilazide, respectively, with the Vedejs reagent (MoOPH) in THF at low temperature afforded stereoselectively the α-hydroxy carbonyl compound **32**, which was directly



Scheme 6. Successful transformation of **12** into atisene **3** and antiquorin (**1**).



Scheme 7. Transformation of **3** into atisenes **8** and **9**.

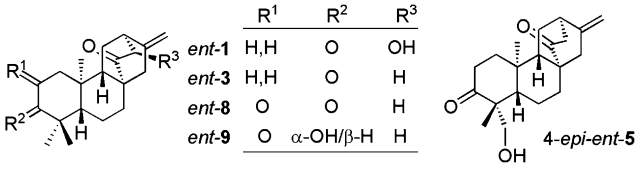
hydrolysed with methanolic oxalic acid to give antiquorin (**1**) in 90% overall yield for the last two steps.

Compound **3** was also a suitable intermediate for the preparation of other polyoxygenated natural atisenes, such as **8** and **9**. This transformation only required the adequation of the functionalization of the A ring of **3** to that of these natural compounds, which was done by taking advantage of the higher reactivity of the C-2 methylene group. Thus, as in the synthesis of **1**, the compound **3** was first transformed into the *tert*-butyldimethylsilyl enol ether **30** (Scheme 7), which after stereoselective epoxidation from the less α-hindered face by treatment with *m*-CPBA in the presence of $NaHCO_3$ in CH_2Cl_2 at 0 °C, followed by oxalic acid catalysed hydrolysis of the resulting *tert*-butyldimethylsilyloxy epoxide, furnished the α-hydroxy carbonyl compound **33** in 88% overall yield from **30**. The α-orientation, equatorial disposition, of the hydroxyl group in **33** was established by the analysis of the coupling constants of H-2, which appears in the ^{1}H NMR spectrum at 4.48 ppm as double double doublet with coupling constants of 13.6, 6.4 and 2.2 Hz, the two former being characteristic for axial–axial and axial–equatorial interaction with H-1α and H-1β, respectively.

All attempts to directly isomerise the acyloin moiety of **33** to obtain the regioisomeric atisene **9** were unsuccessful, and therefore we used an indirect procedure, based on one developed by Mori for a related acyloin isomerisation,[37] to achieve this objective. The first step involves the oxidation of the hydroxyl group of **33** to the corresponding carbonyl group. This was accomplished using standard Swern oxidation conditions and afforded the atisene-trione **8** in 93% yield. This compound is one of the most recent polyoxygenated atisenes to be isolated from natural sources,[14] and exists, at least in $CDCl_3$ solution, in the enolic tautomeric form depicted in Scheme 7.

The enolized α-hydroxyketone group of **8** was then protected as the corresponding *tert*-butyldimethylsilyl enol ether under conventional silylation conditions, and the C-3 carbonyl group was chemo- and stereoselectively reduced with $LiAlH_4$ in THF at low temperature to give, after acidic work-up of the reaction mixture, ca. 4:1 mixture of readily separable epimeric α-hydroxyketones **9** and **35**. These latter transformations were effected without purification of the intermediate enol silyl ether **34**, giving the atisene **9** in 70% yield after chromatographic purification.

The physical and spectroscopic properties of the synthetic atisenes prepared from (*S*)-(+)-carvone, i.e., **1**, **3**, **8** and **9**, were in good agreement with those reported in the literature for the corresponding natural products. The sole discrepancy in all cases was found in the sign of the optical rotation, which showed that we had synthesised the enantiomers of the natural atisenes. This evidence definitively confirms the absolute stereochemistry of the natural atisenes as that of the *ent*-atisane framework, i.e., *ent*-**1**, *ent*-**3**, *ent*-**8** and *ent*-**9** (Scheme 8).

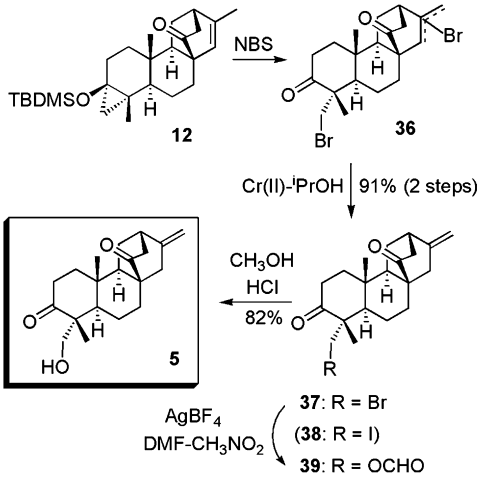


Scheme 8.

In the last part of this paper, we describe the synthesis of atisene **5**, which, as already mentioned, was isolated in 1990 from the heart-wood of *E. fidjiana*, an endemic plant from the Fidji Islands traditionally used in folk medicine. The differential functional characteristic of this atisene with respect to those previously synthesised is the hydroxylation of the C-18 position. As shown below, the synthesis of this atisene can also be completed from the intermediate **12**, which is therefore a common intermediate for all the polyoxygenated atisenes whose synthesis is described in this paper.

This transformation was initiated by the treatment of **12** with NBS under the allylic bromination conditions described above. This treatment not only produces the bromination of the allylic position to the double bond, but also the electrophilic opening of the cyclopropane ring to give **36** as a mixture of regioisomeric allyl bromides (Scheme 9).[38] Chemoselective reduction of the allyl bromide moieties of **36** to the less substituted exocyclic double bond by $CrCl_2$ in the presence of isopropanol in DMF at rt afforded the compound **37** in an overall yield of 91% for the two chemical steps from **12**. The structure and stereochemistry of this compound were confirmed by means of a detailed spectroscopic analysis and X-ray crystal structure determination. The X-ray structure of compound **37** (Fig. 1) shows ring C5–C6–C7–C8–C9–C10 in the expected chair conformation, with the methyl group at C-10 oriented axially, while

rings C1–C2–C3–C4–C5–C10 and C8–C9–C11–C12–C13–C14 are in half-chair (C10 is ca. 0.7 Å out of the plane) and boat conformations (atoms C8 and C12 at ca. 0.7 Å out of the main plane), respectively.



Scheme 9. Transformation of **12** into atisene **5**.

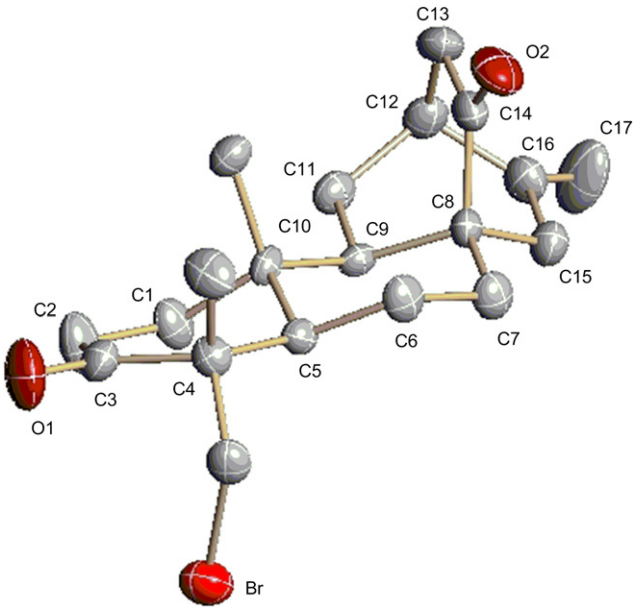


Figure 1. Thermal ellipsoids plot of **37** (50% probability levels) with the usual diterpene labelling scheme. Hydrogen atoms have been omitted for clarity.

The final substitution of bromine at C-18 by the hydroxyl group that completes the synthesis of atisene **5** was somewhat problematic due to the neopentylic nature of the C-18 position. Several well-established procedures available for this purpose failed to afford the desired alcohol **5**. For example, direct substitution of bromine by H_2O in HMPT at high temperature[39] afforded a complex mixture of products, while the indirect substitution, via the initial formation of the corresponding formate ester by treatment of bromide **37** with triethylammonium formate in acetonitrile or HMPT at temperatures of up to 100 °C,[40] or the tributyltin oxide intermediate by reaction with bis(tributyltin)oxide and silver tetrafluoroborate in DMF at 95 °C,[41] led essentially to the recovery of the starting bromide. However, we observed the formation of a small amount (ca. 2–3%) of the formate **39** in the last reaction (see Scheme 9), obviously originated by the nucleophilic substitution of bromine by DMF. This observation prompted us to explore whether this type of formyloxylation reaction with DMF could be used to accomplish the desired transformation in synthetically useful yield. After some investigation, it was found that the treatment of bromide **37** with silver tetrafluoroborate in a mixture of $MeNO_2$–DMF at 60 °C afforded the formate **39** in an excellent 88% yield. The same compound was also obtained in higher yield, under still milder reaction conditions, from iodide **38**, prepared from bromide **37** in 93% yield by using the Finkelstein reaction (NaI–acetone). In any case, hydrolysis of the formate ester with methanolic HCl at rt took place smoothly and efficiently to give the desired β-hydroxyketone **5** in 95% yield.[42] It must be noted that the overall yield of transformation of bromide **37** into **5** did not decrease when the two steps were performed successively without purification of the formate ester intermediate.

Our synthetic sample of atisene **5** showed somewhat different physical and spectroscopic properties from those reported in the literature for the natural compound isolated from *E. fidjiana*, suggesting a possible incorrect assignment of the original structure. In particular, comparison of the ^{13}C NMR data of the natural atisene with those of synthetic **5** reveals significant differences only in the chemical shift of the signals corresponding to the C-5 carbon atom ($\Delta\delta$=7.3 ppm) and, to a lesser extent, to the methyl group at C-4 ($\Delta\delta$=4.7 ppm), thus suggesting that both compounds are most probably epimers at C-4. The large shielding of C-5 in the synthetic atisene **5** is in good agreement with the equatorial disposition of the hydroxymethylene group at C-4 in this compound, which introduces the γ-interaction between the oxygen atom and C-5 responsible for this shielding effect. On the other hand, this γ-effect does not exist in the natural atisene, which is consistent with an axial orientation of the hydroxymethylene group at C-4. The epimeric relationship at C-4 in both compounds is also coherent with the different ^{13}C chemical shifts observed for the methyl group at C-4.[43] On the basis of this result, it is therefore necessary to modify the structure initially assigned to the atisene isolated from *E. fidjiana*, whose stereochemistry at C-4 should be reassigned as it appears in structure 4-*epi*-*ent*-**5** (see Scheme 8). The *ent*-stereochemistry is assumed for this compound in coherence with the absolute stereochemistry determined here for the other related natural atisenes.

3. Conclusions

In conclusion, we have developed a convenient diastereoselective approach for the construction of the complete carbon framework of atisene-type diterpenes. This approach involves the initial preparation of the pivotal atisane-type intermediate **12** from carvone, using an intramolecular Diels–Alder reaction, an intramolecular diazoketone cyclopropanation of an unsaturated ketone and a regioselective endocyclic cleavage of a cyclopropyl carbinyl radical as key synthetic steps. This approach has been successfully

applied to the efficient preparation of several naturally occurring highly polyoxygenated atisenes, e.g., antiquorin (**1**) and related atisenes **3**, **8** and **9**. In particular, the synthesis of antiquorin (**1**), the more representative member of this class of polyoxygenated atisenes, involves 16 synthetic transformations with an overall yield of approximately 25%. These syntheses have further served to unambiguously establish the hitherto unknown absolute configuration of the natural atisenes as *ent*-**1**, *ent*-**3**, *ent*-**8** and *ent*-**9**. Additionally, the synthesis of 18-hydroxy-16-atisene-3,14-dione (**5**), the structure originally proposed for the natural atisene isolated from the heart-wood of *E. fidjiana*, has also been completed and it has been shown that this initial structure assignment was erroneous and needs to be revised to 4-*epi*-*ent*-**5**. The strategy herein described is general and suitable for the synthesis of other natural and non-natural highly functionalised atisanes in both enantiomeric forms, since both antipodes of carvone are commercially available.

4. Experimental

4.1. General information

Reagents were obtained from commercial sources and were used without purification. Solvents were dried by distillation from the appropriate drying agents immediately prior to use. THF and Et_2O were distilled from sodium and benzophenone under an argon atmosphere. MeCN, CH_2Cl_2, Et_3N and diisopropylamine were distilled from calcium hydride under argon. Moisture- and air-sensitive reactions were carried out under an atmosphere of nitrogen or argon. The reactions were monitored with the aid of thin-layer chromatography (TLC) using 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and aq ceric ammonium molybdate solution or 50% (v/v) concd H_2SO_4 in water. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040–0.063 mm). 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}. ^{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. A combination of COSY, HSQC and NOE experiments was utilised when necessary for the assignment of ^{1}H and ^{13}C chemical shifts. IR spectra were measured using KBr pellets or liquid films; peak intensities are specified as strong (s), medium (m) or weak (w). 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 μ-Porasil column, 7.8×300 mm (semi-prep) column. Mass spectra were obtained by electron impact (EI) at 70 eV. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 626412. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.2. Preparation of the trachylobane-type intermediate 13

4.2.1. (5*R*,6*R*)-6-Acetyl-2-methyl-6-((*E*)-4-methyl-5-oxohex-3-enyl)-5-(prop-1-en-2-yl)cyclohex-2-enone (17). To a stirred slurry of pre-washed NaH (60% dispersion oil; 360 mg, 9.4 mmol) in THF (60 mL) at 0 °C was added, dropwise via syringe, diethyl 2-oxobutane-3-phosphonate (2.05 g, 2.22 mL, 9.84 mmol) over 45 min. After hydrogen evolution had ceased, the mixture was warmed to rt and stirred for 15–20 min. The resulting mixture was cooled down to −50 °C and a solution of the aldehyde **16**[26] (2.22 g, 8.95 mmol) in THF (40 mL) was added dropwise. After being stirred at the same temperature for 30 min, the mixture was treated with saturated aq NH_4Cl solution, then poured into water and worked up using hexane to extract it. Purification by chromatography (hexane–AcOEt 8:2) gave the enone **17** (2.21 g, 83%) as an oil. $[\alpha]_D^{24}$ +49.7 (*c* 1.9, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 2924s, 2819m, 1702s, 1664s, 1438m, 1364m, 1281w, 1186w; ^{1}H NMR (300 MHz) δ 6.75 (1H, br s, H-3), 6.52 (1H, ddd, *J*=7.16, 7.16, 1.51 Hz, H-3′), 4.88 (1H, t, *J*=1.5 Hz, H-2″), 4.75 (1H, br s, H-2″), 2.92 (1H, d, *J*=6.4, 6.4 Hz, H-5), 2.69 (1H, br d, *J*=19.4 Hz, H-2′), 2.52 (1H, br d, *J*=19.4 Hz, H′-2′), 2.37 (1H, ddd, *J*=12.8, 11.3, 5.0 Hz, H-4), 2.2–1.9 (2H, m, H_2-1′), 2.27 (3H, s, *Me*CO-C_1), 2.16 (3H, s, Me-$C_{6'}$), 1.82 (3H, s, Me-C_2), 1.81 (1H, m, H′-4), 1.71 (3H, br s, Me-$C_{4''}$), 1.68 (3H, br s, Me-$C_{1''}$); ^{13}C NMR (75 MHz) δ 207.86 (C_1), 200.02 ($C_{5'}$), 197.80 (*CO*Me), 144.45 (C_3), 144.40 ($C_{1''}$), 142.17 ($C_{3'}$), 138.06 ($C_{4'}$), 134.68 (C_2), 115.76 ($C_{2''}$), 65.37 (C_6), 48.92 (C_5), 32.10 ($C_{6'}$), 30.37 (*Me*CO), 28.99 (C_4), 25.45 ($C_{2'}$), 24.23 ($C_{1'}$), 22.27 (Me-$C_{1''}$), 16.38 (Me-C_2); MS (EI) *m*/*z* (%) 302 (M^+, 2.3), 274 (27), 192 (100), 177 (36), 163 (43), 151 (47), 121 (27), 82 (20); HRMS *m*/*z* calcd for $C_{19}H_{26}O_3$ 302.1881, found 302.1871.

4.2.2. (5*R*,6*R*)-6-Acetyl-6-((*E*)-5-(*tert*-butyldimethylsilyloxy)-4-methylhexa-3,5-dienyl)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enone (18). Enone **17** (3.09 g, 10.2 mmol) in dry CH_2Cl_2 (98 mL) was cooled to −78 °C and treated sequentially with Et_3N (4.4 mL, 31 mmol) and TBDMSOTf (3.36 mL, 15 mmol). After 1 h at −78 °C, the reaction mixture was quenched with 5% aq $NaHCO_3$ solution, poured into water and extracted with hexane. Work-up as usual and purification by column chromatography (hexane–AcOEt 8:2, containing a 0.1% of Et_3N) as eluent, afforded dienol silyl ether **18** (3.8 g, 90%) as a colourless oil. $[\alpha]_D^{24}$ +43.3 (*c* 1.0, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2929s, 2858m, 1702s, 1595m, 1445m, 1354m, 1229m, 1016m, 834s, 780m; ^{1}H NMR (400 MHz, C_6D_6) δ 6.00 (1H, br s, H-3), 6.27 (1H, dd, *J*=7.53, 7.53 Hz, H-3′), 4.68 (1H, br s, H-2″), 4.67 (1H, br s, H-2″), 4.45 (1H, s, H-6′), 4.33 (1H, s, H-6′), 2.62 (1H, dd, *J*=6.6, 6.6 Hz, H-5), 2.44 (1H, ddd, *J*=13.5, 10.5, 6.0 Hz, H-4), 2.38 (1H, br d, *J*=19.2 Hz, H-2′), 2.16–2.03 (1H, m), 1.98 (3H, s, *Me*CO-C_1), 1.97–1.84 (1H, m), 1.76 (3H, br s, Me-$C_{4''}$), 1.71 (3H, s, Me-C_2), 1.52 (3H, br s, Me-$C_{1''}$), 0.99 (9H, s, Me_3CSi), 0.15 (6H, s, Me_2Si); ^{13}C NMR (75 MHz, C_6D_6) δ 206.88 (*C*OMe), 197.39 (C_1), 157.82 ($C_{5'}$), 145.32 (C_3), 143.67 ($C_{1''}$), 134.58 (C_2), 132.30 ($C_{4'}$), 128.29 ($C_{3'}$), 115.24 ($C_{2''}$), 91.41 ($C_{6'}$), 65.79 (C_6), 49.68 (C_5), 33.43 ($C_{2'}$), 29.91 (*Me*CO), 29.18 (C_4), 26.05 (Me_3CSi), 23.82 ($C_{1'}$),

22.45 (Me-$C_{1''}$), 18.3 (Me_3CSi), 16.60 (Me-C_2), 13.30 (Me-$C_{4'}$), −4.48 (Me_2Si); MS (EI) *m/z* (%) 416 (M^+, 3.3), 359 (3), 291 (4), 250 (9), 249 (44), 225 (47), 224 (44), 168 (100), 75 (40); HRMS *m/z* calcd for $C_{25}H_{40}O_3Si$ 416.2748, found 416.2730.

4.2.3. (4a*R*,4b*S*,8a*R*,10a*R*)-10a-Acetyl-7-(*tert*-butyldimethylsilyloxy)-2,4b,8-trimethyl-4,4a,5,6,8a,9,10,10a-octahydrophenanthren-1(4b*H*)-one (14). A solution of dienol silyl ether **18** (350 mg, 0.84 mmol) in toluene (5 mL) was transferred to a previously silylated ampoule and rigorously degassed by the freeze–thaw cycle. The ampoule was cooled down under argon, a drop of propylene oxide was added and it was then sealed under vacuum. After heating at 195–200 °C for 5 days, the solvent was eliminated under vacuum and the residue was chromatographed, using 8:2 hexane–AcOEt (containing 0.1% of Et_3N) as eluent, to give the Diels–Alder adduct **14** as a solid (332 mg, 95%). Mp 110 °C (with decomposition); $[\alpha]_D^{18}$ +60 (*c* 0.4, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2929s, 2857m, 1704s, 1663s, 1462m, 1355m, 1256m, 1178m, 837s, 778m; ^1H NMR (300 MHz) δ 6.87 (1H, br s, H-3), 3.06 (1H, ddd, *J*=19.2, 11.7, 2.5, 2.5 Hz, H-4), 2.85 (1H, ddd, *J*=14.7, 3.3, 3.3 Hz, H-10), 2.33 (1H, ddd, *J*=19.2, 4.5 Hz, H′-4), 2.18 (3H, s, *Me*CO-C_{10a}), 2.12–1.86 (3H, m, H-9, H_2-6), 1.86–1.71 (2H, m, H-4a, H-5), 1.72 (3H, s, Me-C_2), 1.55 (1H, m, H′-10), 1.54 (3H, s, Me-C_8), 1.48 (1H, dd, *J*=14.7, 3.8 Hz, H-8a), 1.39–1.15 (2H, m, H′-9, H′-5), 0.71 (3H, s, Me-C_{4b}), 0.93 (9H, s, Me_3CSi), 0.10 (3H, s, Me*S*i), 0.09 (3H, s, MeSi); ^{13}C NMR (75 MHz) δ 207.83 (C_1), 197.90 (*CO*Me), 148.52 (C_3), 142.13 (C_7), 131.17 (C_2), 111.91 (C_8), 63.81 (C_{10a}), 52.94 (C_{4a}), 48.14 (C_{8a}), 36.63 (C_{4b}), 33.92 (C_5), 32.38 (C_{10}), 28.50 (CO*Me*), 27.51 (C_6), 25.80 (C_4), 25.67 (Me_3CSi), 22.49 (C_9), 18.14 (Me_3CSi), 16.38 (Me-C_2), 14.02 (Me-C_8), 12.36 (Me-C_{4b}), −3.96 and −3.57 (Me_2Si); MS (EI) *m/z* (%) 417 (M^++1, 35), 416 (M^+, 100), 401 (33), 373 (53), 358 (25), 255 (80), 195 (12), 121 (13), 73 (30); HRMS *m/z* calcd for $C_{25}H_{40}O_3Si$ 416.2753, found 416.2747.

4.2.4. (1a*S*,1b*R*,3a*R*,7a*R*,7b*S*,9a*R*)-3a-Acetyl-9a-(*tert*-butyldimethylsilyloxy)-1a,5,7b-trimethyl-1b,2,3,3a,7,7a,7b,8,9,9a-decahydro-1*H*-cyclopropa[*a*]phenanthren-4-(1a*H*)-one (19). Diethyl zinc (1.0 M solution in hexane, 23.1 mL, 17.3 mmol) and diiodomethane (3.57 mL, 34.5 mmol) were added to a solution of **14** (1.20 g, 2.88 mmol) in anhydrous toluene (50 mL) at 0 °C. The reaction mixture was allowed to slowly warm to rt (ca. 1 h) and then stirred at this temperature for 2 h. The mixture was quenched by the addition of saturated aq NH_4Cl solution and extracted with hexane. The organic extracts were washed successively with 10% aq solution of $Na_2S_2O_3$, water and brine, then dried over $MgSO_4$ and concentrated to give a solid. Chromatography (hexane–AcOEt 9:1) yielded the diketone **19** (1.114 g, 91%) as a white solid. Mp 107–109 °C (from cold hexane); $[\alpha]_D^{18}$ +104 (*c* 4.4, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2953s, 2857m, 1700s, 1678s, 1435m, 1355m, 1256s, 1202m, 832s, 774m; ^1H NMR (300 MHz) δ 6.83 (1H, br s, H-6), 3.00 (1H, ddd, *J*=19.2, 11.5, 2.3, 2.3 Hz, H-7), 2.77 (1H, ddd, *J*=14.7, 3.5, 3.5 Hz, H-3), 2.24 (1H, ddd, *J*=19.2, 4.0, 4.0 Hz, H′-7), 2.14 (3H, s, *Me*CO-C_{3a}), 2.12–1.83 (4H, m), 1.70 (1H, m, H-8), 1.55 (1H, dd, *J*=11.5, 5.1 Hz, H-7a), 1.46–1.35 (2H, m), 1.69 (3H, s, Me-C_5), 0.99 (3H, s, Me-C_{1a}), 0.84 (9H, s, Me_3CSi), 0.80 (3H, s, Me-C_{7a}), 0.59 (1H, ddd, *J*=13.1, 13.1, 6.2 Hz, H′-8), 0.51 (1H, d, *J*=5.3 Hz, H-1), 0.21 (1H, d, *J*=5.3 Hz, H′-1), 0.09 (3H, s, MeSi), 0.03 (3H, s, MeSi); ^{13}C NMR (75 MHz) δ 207.49 (C_4), 198.03 (*CO*Me), 148.11 (C_6), 131.32 (C_5), 64.05 (C_{3a}), 58.11 (C_{9a}), 53.83 (C_{1b}), 52.09 (C_{7a}), 36.33 (C_{7b}), 34.01 (C_8), 32.43 (C_3), 28.90 (C_1), 28.81 (C_9), 28.06 (CO*Me*), 25.75 (Me_3CSi), 25.53 (C_7), 23.30 (C_2), 21.64 (C_{1a}), 17.88 (Me_3CSi), 16.56 (Me-C_5), 15.39 (Me-C_{1a}), 13.22 (Me-C_{7b}), −3.06 and −3.84 (Me_2Si); MS (EI) *m/z* (%) 431 (M^++1, 5), 430 (M^+, 18), 387 (79), 373 (100), 255 (11), 211 (30), 177 (27), 121 (22), 73 (65); HRMS *m/z* calcd for $C_{26}H_{42}O_3Si$ 430.2916, found 430.2903. Anal. Calcd for $C_{26}H_{42}O_3Si$: C, 72.51; H, 9.83. Found: C, 72.58; H, 9.90.

4.2.5. (1a*S*,1b*R*,3a*S*,7a*R*,7b*S*,9a*R*)-9a-(*tert*-Butyldimethylsilyloxy)-3a-(2-diazo acetyl)-1a,5,7b-trimethyl-1b,2,3,3a,7,7a,7b,8,9,9a-decahydro-1*H*-cyclopropa[*a*]-phenanthren-4(1a*H*)-one (20). A solution of methylketone **19** (330 mg, 0.76 mmol) in THF (2 mL) was added dropwise over a period of 30 min to a THF solution of lithium hexamethyldisilazide (LiHMDS) [prepared from 1.6 M BuLi in hexanes (0.51 mL, 0.82 mmol), hexamethyldisilazane (0.175 mL, 0.83 mmol) and THF (3 mL)] at −78 °C. The solution was stirred for an additional 30 min at −78 °C and then treated with 2,2,2-trifluoroethyltrifluoroacetate (0.13 mL, 0.95 mmol). The reaction mixture was stirred for 10 min, then poured into cool 5% aq HCl solution and extracted with ether. The organic layer was washed sequentially with 5% aq $NaHCO_3$ solution, water and brine, then dried over $MgSO_4$ and concentrated under vacuum to give the crude trifluoroketone derivative of diketone **19**.

A mixture of the residue obtained above, Et_3N (0.32 mL, 2.28 mmol), H_2O (20 μL, 1.14 mmol) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (730 g, 3.0 mmol) in MeCN (20 mL) was stirred at 35 °C for 7 h. The reaction mixture was diluted with ether and washed with 10% aq NaOH solution, then brine and dried over Na_2SO_4. The residue left after evaporation of the solvent was chromatographed (hexane–Et_2Ot 8:2) to afford α-diazoketone **20** (300 mg, 87% from **19**) as a white foam. $[\alpha]_D^{25}$ −60 (*c* 0.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2927s, 2851m, 2100s, 1665m, 1627m, 1335s, 1259m, 915m, 833s, 771m; ^1H NMR (300 MHz) δ 6.88 (1H, br s, H-6), 5.56 (1H, s, CHN_2), 3.05 (1H, ddd, *J*=19.2, 11.5, 2.3, 2.3 Hz, H-7), 2.45 (1H, ddd, *J*=14.0, 3.2, 3.2 Hz, H-3), 2.28 (1H, ddd, *J*=19.2, 3.8, 3.8 Hz, H′-7), 2.12 (1H, dd, *J*=13.9, 6.4 Hz, H-7a), 2.12–1.4 (5H, m, H_2-2, H-8, H_2-9), 1.74 (3H, s, Me-C_5), 1.02 (3H, s, Me-C_{1a}), 0.91 (3H, s, Me-C_{7a}), 0.84 (10H, s, Me_3CSi, H-1b), 0.62 (1H, ddd, *J*=13.2, 13.2, 5.9 Hz, H′-8), 0.52 (1H, d, *J*=5.3 Hz, H-1), 0.23 (1H, d, *J*=5.3 Hz, H′-1), 0.11 (3H, s, MeSi), 0.04 (3H, s, MeSi); ^{13}C NMR (75 MHz) δ 198.33 (C_4), 193.06 ($CO$$CHN_2$), 148.44 ($C_6$), 131.92 ($C_5$), 60.84 ($C_{3a}$), 58.11 ($C_{9a}$), 54.79 ($C_{7a}$), 54.00 ($CHN_2$), 52.48 ($C_{1b}$), 36.47 ($C_{7b}$), 34.14 ($C_8$), 32.42 ($C_3$), 28.91 ($C_1$), 28.84 ($C_9$), 25.52 ($Me_3CSi$), 25.51 ($C_7$), 22.93 ($C_2$), 21.70 ($C_{1a}$), 17.91 ($Me_3CSi$), 16.66 (Me-$C_5$), 15.84 (Me-$C_{1a}$), 13.03 (Me-$C_{7b}$), −3.03 and −3.82 ($Me_2Si$); MS (EI) *m/z* (%) 456 (M^+, 5), 428 (29), 399 (22), 371 (100), 211 (84), 75 (40), 73 (89); HRMS *m/z* calcd for $C_{26}H_{40}N_2O_3Si$ 456.2827, found 456.2808.

4.2.6. 3(*R*)-3-(*tert*-Butyldimethylsilyloxy)-3α,18-*cyclo*-trachylobane-14,15-dione (13). A degassed solution of bis(*N*-*tert*-butylsalicylaldiminato)copper(II) (20 mg, 0.043 mmol) in anhydrous toluene (90 mL) was stirred and heated at reflux. Then, the α-diazoketone **20** (422 mg, 0.93 mmol) was added dropwise during 4 h using a syringe pump and the reaction mixture was stirred at the same temperature for 15 min. After this time, the reaction was allowed to cool down to rt. The solvent was evaporated under vacuum and the residue was purified by chromatography (hexane–AcOEt 8:2) to give compound **13** (357 mg, 90%) as a white solid. Mp 186–188 °C (from MeOH); $[\alpha]_D^{25}$ +40 (*c* 2.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2955s, 2842m, 1762s, 1705s, 1460m, 1260m, 1075m, 802s, 774s, 671m; ^1H NMR (300 MHz) δ 2.58 (1H, d, *J*=7.9 Hz, H-13), 2.46 (1H, ddd, *J*=7.7, 2.3, 2.3 Hz, H-12), 2.12 (1H, ddd, *J*=13.2, 10.0, 3.1 Hz, H-11), 2.01 (1H, ddd, *J*=13.6, 5.7, 2.5 Hz, H-7), 1.88 (1H, ddd, *J*=13.2, 7.9, 2.1 Hz, H′-11), 1.85–1.40 (6H, m), 1.38 (3H, s, Me-C_{16}), 1.33 (1H, ddd, *J*=13.6, 6.4, 6.4 Hz, H-1), 1.02 (3H, s, Me-C_4), 0.80 (1H, m, H-5), 0.75 (3H, s, Me-C_{10}), 0.84 (9H, s, Me_3CSi), 0.54 (1H, ddd, *J*=13.6, 13.6, 5.8 Hz, H′-1), 0.48 (1H, d, *J*=5.3 Hz, H-18), 0.21 (1H, d, *J*=5.3 Hz, H′-18), 0.07 (3H, s, MeSi), 0.02 (3H, s, MeSi); ^{13}C NMR (75 MHz) δ 207.26 (C_{14}), 206.62 (C_{15}), 58.56 (C_3), 57.27 (C_9), 55.29 (C_8), 52.01 (C_5), 49.54 (C_{16}), 47.11 (C_{13}), 43.09 (C_{12}), 36.95 (C_{10}), 34.53 (C_1), 28.24 (C_2), 28.24 (C_{18}), 25.73 (Me_3CSi), 21.87 (C_6), 21.53 (C_4), 21.43 (C_7), 19.71 (C_{11}), 17.89 (Me_3*C*Si), 15.60 (Me-C_4), 12.82 (Me-C_{16}), 11.02 (Me-C_{10}), −2.14 and −3.01 (Me_2Si); MS (EI) *m*/*z* (%) 429 (M^++1, 5), 428 (M^+, 25), 372 (29), 371 (100), 343 (11), 265 (11), 211 (51), 75 (16), 73 (39); HRMS *m*/*z* calcd for $C_{26}H_{40}O_3Si$ 428.2741, found 428.2747. Anal. Calcd for $C_{26}H_{40}O_3Si$: C, 72.85; H, 9.41. Found: C, 72.77; H, 9.48.

4.3. Trachylobane-to-atisane skeleton transformation. Preparation of the atisane-type intermediate 12

4.3.1. 3(*R*),16(*S*)-3-(*tert*-Butyldimethylsilyloxy)-3α,18-*cyclo*-atisane-14,15-dione (compounds I and II). A 0.1 M solution of SmI_2 in THF was added dropwise to a solution of cyclopropyl diketone **13** (20 mg, 0.046 mmol) in a 3:1 mixture of THF–MeOH (1.5 mL) until persistence of the blue colour. The reaction mixture was stirred at rt for 1 h, then treated with a saturated aq NH_4Cl solution and extracted with ether. The organic layer was washed with water, 5% aq $Na_2S_2O_4$ solution and brine, and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was chromatographed (hexane–AcOEt 95:5) to give atisane-dione **I** (13 mg, 65%) followed by the 16α-H epimer **II** (5.5 mg, 27%).

Data for the major epimer **I**: a white solid, mp 220–222 °C (from MeOH); $[\alpha]_D^{29}$ +13.3 (*c* 0.45, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2955s, 2842m, 1731s, 1700s, 1470m, 1225m, 1193m, 1091m, 917m, 840s, 773m; ^1H NMR (300 MHz) δ 2.56 (1H, dd, *J*=19.8, 3.6 Hz, H-13), 2.40–2.00 (5H, m, H-16, H′-13, H-12, H_2-11), 1.92–1.30 (8H, m), 0.89–0.70 (1H, m, H-5), 1.23 (3H, d, *J*=7.1 Hz, Me-C_{16}), 1.01 (3H, s, Me-C_4), 0.84 (9H, s, Me_3CSi), 0.71 (3H, s, Me-C_{10}), 0.56 (1H, dd, *J*=12.4, 12.4, 4.7 Hz, H-1), 0.49 (1H, d, *J*=5.0 Hz, H-18), 0.22 (1H, d, *J*=5.0 Hz, H′-18), 0.085 (3H, s, MeSi), 0.03 (3H, s, MeSi); ^{13}C NMR (75 MHz) δ 210.31 (C_{14}), 209.22 (C_{15}), 65.76 (C_8), 58.87 (C_3), 51.72 (C_5), 46.16 (C_9), 46.13 (C_{16}), 46.00 (C_{13}), 37.59 (C_{10}), 34.14 (C_1), 32.09 (C_{12}), 28.50 (C_2), 28.32 (C_{18}), 26.18 (Me_3CSi), 22.65 (C_{11}), 22.56 (C_7), 21.72 (C_4 and C_6), 21.56 (Me-C_{16}), 17.89 (Me_3*C*Si), 15.60 (Me-C_4), 11.25 (Me-C_{10}), −3.07 and −3.84 (Me_2Si); MS (EI) *m*/*z* (%) 431 (M^++1, 5), 430 (M^+, 19), 387 (65), 373 (100), 211 (50), 73 (72); HRMS *m*/*z* calcd for $C_{26}H_{42}O_3Si$ 430.2903, found 430.2902.

Data for the minor epimer **II**: an amorphous solid; IR ν_{max}/cm^{-1} (KBr) 2958s, 2845m, 1735s, 1703s, 1473m, 1197m, 1094m, 920m, 844s, 777m; ^1H NMR (300 MHz) δ 2.56 (1H, ddd, *J*=19.9, 3.0, 3.0 Hz, H-13), 2.42–2.21 (4H, m), 2.06 (1H, ddd, *J*=13.8, 5.6, 1.7 Hz, H-7), 1.96 (1H, m), 1.87 (1H, ddd, *J*=13.9, 6.4, 1.1 Hz), 1.83–1.70 (2H, m), 1.56–1.31 (3H, m), 1.09 (3H, d, *J*=7.1 Hz, Me-C_{16}), 1.00 (3H, s, Me-C_4), 0.95–0.75 (2H, m), 0.84 (9H, s, Me_3CSi), 0.71 (3H, s, Me-C_{10}), 0.59 (1H, ddd, *J*=13.6, 13.6, 5.6 Hz, H-1), 0.51 (1H, dd, *J*=5.0, 1.0 Hz, H-18), 0.22 (1H, d, *J*=5.0 Hz, H′-18), 0.09 (3H, s, MeSi), 0.04 (3H, s, MeSi); ^{13}C NMR (75 MHz) δ 210.79 (C_{14}), 208.95 (C_{15}), 65.85 (C_8), 58.95 (C_3), 52.75 (C_5), 45.26 (C_9), 31.69 (C_{12}), 45.20 (C_{16}), 40.15 (C_{13}), 37.50 (C_{10}), 34.02 (C_1), 29.69 (C_{11}), 28.49 (C_2), 28.33 (C_{18}), 26.18 (Me_3CSi), 23.06 (C_7), 21.75 (C_4), 21.62 (C_6), 17.89 (Me_3*C*Si), 15.65 (Me-C_4), 14.91 (Me-C_{16}), 11.32 (Me-C_{10}), −3.07 and −3.84 (Me_2Si); HRMS *m*/*z* calcd for $C_{26}H_{42}O_3Si$ 430.2903, found 430.2899.

4.3.2. 3(*R*),15(*S*)-3-(*tert*-Butyldimethylsilyloxy)-15-hydroxy-3α,18-*cyclo*-trachyloban-14-one (21). A solution of diketone **13** (226 mg, 0.53 mmol) in AcOEt (4 mL) was hydrogenated over 10% Pt/C (65 mg) at 66 psi (4.5 atm) for 24 h. The mixture was filtered through Celite and the filtrate concentrated under vacuum. Flash chromatography on silica gel, eluting with a 7:3 mixture of hexane–EtOAc, provided **21** (216 mg, 95%) as a white solid. Mp 175–176 °C (from MeOH); $[\alpha]_D^{25}$ +55 (*c* 0.65, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2955s, 2847m, 1686s, 1460m, 1260s, 1075m, 1004m, 973m, 835s, 758s, 666m; ^1H NMR (300 MHz) δ 3.58 (1H, s, H-15), 2.18–1.93 (2H, ddd, *J*=12.8, 10.0, 2.6 Hz, H-11), 1.93–1.6 (9H, m, H-13, H-12, H′-11, H-9, H-7, H_2-6, H_2-2), 1.45–1.1 (2H, m, H′-7, H-1), 1.33 (3H, s, Me-C_{16}), 0.99 (3H, s, Me-C_4), 0.89–0.75 (1H, m, H-5), 0.84 (9H, s, Me_3CSi), 0.69 (3H, s, Me-C_{10}), 0.57 (1H, ddd, *J*=13.8, 13.8, 5.9 Hz, H′-1), 0.46 (1H, d, *J*=5.0 Hz, H-18), 0.21 (1H, d, *J*=5.0 Hz, H′-18), 0.07 (3H, s, MeSi), 0.03 (3H, s, MeSi); ^{13}C NMR (75 MHz) δ 212.49 (C_{14}), 77.02 (C_{15}), 59.06 (C_3), 52.80 (C_5), 49.52 (C_8), 45.25 (C_9), 40.12 (C_{13}), 37.78 (C_{16}), 35.62 (C_{10}), 34.75 (C_{12}), 34.46 (C_1), 28.47 (C_2), 28.37 (C_{18}), 27.96 (C_7), 25.77 (Me_3CSi), 22.48 (C_6), 21.76 (C_4), 19.32 (C_{11}), 17.95 (Me-C_{16}), 17.91 (Me_3*C*Si), 15.58 (Me-C_4), 11.03 (Me-C_{10}), −3.84 and −3.02 (Me_2Si); MS (IE) *m*/*z* (%) 431 (M^++1, 15), 430 (M^+, 49), 415 (12), 374 (29), 373 (100), 281 (17), 212 (24), 211 (98), 75 (37), 73 (76); HRMS *m*/*z* calcd for $C_{26}H_{42}O_3Si$ 430.2903, found 430.2909.

4.3.3. 3(*R*),15(*R*)-3-(*tert*-Butyldimethylsilyloxy)-15-iodo-3α,18-*cyclo*-trachyloban-14-one (23). Et_3N (0.34 mL, 2.16 mmol) was added to a solution of alcohol **21**

(200 mg, 0.48 mmol) in CH_2Cl_2 (5 mL) at 0 °C, followed by MsCl (0.15 mL, 1.58 mmol) over a period of 5 min. The mixture was stirred at 0 °C for an additional 2 h and diluted with water. Work-up as usual afforded a yellowish residue of crude mesylate **22** (215 mg) that was used in the next step without further purification.

A mixture of the above-obtained mesylate in a 10% solution of NaI in dry acetone (4 mL) was stirred and heated at 40 °C for 2 h. The reaction mixture was cooled down to rt, diluted with water and worked up. Purification by chromatography (hexane–AcOEt 9:1) afforded iodo-ketone **23** (240 mg, 93% from alcohol **21**) as a white solid. Mp 189–191 °C (with decomposition) (from cold ethyl ether); $[\alpha]_D^{25}$ +61 (*c* 1.7, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2924s, 2842s, 1726s, 1460m, 1250m, 830s, 768m; ^1H NMR (400 MHz) δ 4.32 (1H, s, H-15), 2.12 (1H, m, H-11), 2.11 (1H, d, *J*=7.3 Hz, H-13), 2.02 (1H, m, H-2), 1.98–1.62 (6H, m, H-12, H′-11, H-9, H_2-6, H-2), 1.40 (1H, m, H-1), 1.32 (3H, s, Me-C_{16}), 1.23 (1H, m, H-7), 1.12 (1H, m, H′-7), 1.00 (3H, s, Me-C_4), 0.91 (1H, m, H-5), 0.84 (9H, s, *Me*$_3$CSi), 0.69 (3H, s, Me-C_{10}), 0.60 (1H, m, H′-1), 0.46 (1H, d, *J*=5.0 Hz, H-18), 0.27 (1H, d, *J*=5.0 Hz, H′-18), 0.09 (3H, s, MeSi), 0.035 (3H, s, MeSi); ^{13}C NMR (75 MHz) δ 207.14 (C_{14}), 58.90 (C_3), 52.90 (C_9), 52.79 (C_5), 52.42 (C_{15}), 49.49 (C_8), 43.23 (C_{12}), 38.53 (C_{10}), 38.05 (C_{12}), 36.26 (C_{16}), 34.52 (C_1), 28.53 (C_7), 28.47 (C_2 and C_{18}), 25.77 (*Me*$_3$CSi), 22.09 (C_6), 21.73 (C_4), 21.07 (Me-C_{16}), 17.91 (C_{11} and Me$_3$*C*Si), 15.49 (Me-C_4), 10.41 (Me-C_{10}), −3.03 and −3.82 (Me_2Si); MS (EI) *m*/*z* (%) 541 (M^++1, 15), 540 (M^+, 24), 483 (56), 413 (66), 391 (45), 281 (30), 211 (100), 75 (28), 73 (71); HRMS *m*/*z* calcd for $C_{26}H_{41}IO_2Si$ 540.1921, found 540.1916.

4.3.4. 3(*R*)-(*tert*-Butyldimethylsilyloxy)-3α,18-*cyclo*-atis-15-en-14-one (12). A solution of iodo cyclopropyl-ketone **23** (240 mg, 0.44 mmol) in a 3:1 mixture of THF and MeOH (5.6 mL) was treated dropwise with a 0.1 M stock solution of SmI_2 in THF at rt until persistence of the blue colour. After being stirred at the same temperature for 1 h, saturated aq NH_4Cl solution was added and the mixture was poured into water and extracted with ether. The combined organic layers were washed with 10% aq $Na_2S_2O_3$ and then brine, dried over $MgSO_4$ and evaporated. Chromatography (hexane–AcOEt 9:1) gave the compound **12** (178 mg, 95%) as a white solid. Mp 213–215 °C (from MeOH); $[\alpha]_D^{20}$ −51 (*c* 1.3, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2924s, 2858m, 1705s, 1470m, 1250m, 1091m, 973m, 917m, 840s, 773s; ^1H NMR (400 MHz) δ 5.25 (1H, s, H-15), 2.58 (1H, m, H-12), 2.44 (1H, ddd, *J*=13.0, 3.4, 3.4 Hz, H-7), 2.14 (1H, ddd, *J*=18.0, 3.0, 3.0 Hz, H-13), 2.05 (1H, m, H-2), 1.99 (1H, dd, *J*=18.0, 3.0 Hz, H′-13), 1.88 (1H, ddd, *J*=13.6, 6.0, 1.1 Hz, H′-2), 1.83–1.35 (5H, m, H_2-11, H_2-6, H-1), 1.78 (3H, d, *J*=1.0 Hz, Me-C_{16}), 1.30 (1H, dd, *J*=11.2, 6.0 Hz, H-9), 1.15 (1H, m, H′-7), 1.01 (3H, s, Me-C_4), 0.92 (1H, dd, *J*=12.8, 3.8 Hz, H-5), 0.84 (9H, s, *Me*$_3$CSi), 0.66 (3H, s, Me-C_{10}), 0.64 (1H, ddd, *J*=13.4, 13.4, 6.0 Hz, H′-1), 0.49 (1H, dd, *J*=5.0, 1.1 Hz, H-18), 0.24 (1H, d, *J*=5.0 Hz, H′-18), 0.09 (3H, s, MeSi), 0.04 (3H, s, MeSi); ^{13}C NMR (75 MHz) δ 214.36 (C_{14}), 146.17 (C_{16}), 128.06 (C_{15}), 58.99 (C_3), 53.70 (C_9), 52.17 (C_8), 51.39 (C_5), 41.84 (C_{13}), 37.13 (C_{12}), 35.70 (C_{10}), 35.06 (C_1), 29.52 (C_7), 28.66 (C_{11}), 28.51 (C_{18}), 27.42 (C_2), 25.77 (*Me*$_3$CSi), 22.62 (C_6), 21.94 (C_4), 20.05 (Me-C_{16}), 17.92 (Me$_3$*C*Si), 15.61 (Me-C_4), 10.99 (Me-C_{10}), −3.03 and −3.82 (Me_2Si); MS (EI) *m*/*z* (%) 415 (M^++1, 15), 414 (M^+, 33), 358 (29), 357 (100), 211 (62), 105 (32), 75 (37), 73 (83); HRMS *m*/*z* calcd for $C_{26}H_{42}O_2Si$ 414.2954, found 414.2953.

4.3.5. 3(*R*)-(*tert*-Butyldimethylsilyloxy)-13(*S*)-(4-(*tert*-butyldimethylsilyloxy)butyl)-3α,18-*cyclo*-atis-15-en-14-one (compound III). A solution of ketone **12** (15 mg, 0.036 mmol) in THF (0.2 mL) was added dropwise to a 1 M solution of NaHMDS in THF (47 μL, 0.047 mmol) at −78 °C. After 30 min, TBDMSOTf (11 μL, 0.047 mmol) was added all at once and the mixture was stirred at the same temperature for 3 h, then poured into water and extracted with ether. The combined organic layers were washed with 5% aq HCl solution, 5% aq $NaHCO_3$ and brine and dried over $MgSO_4$. Chromatography (hexane–AcOEt 9:1) of the residue left after removal of the solvent afforded the compound **III** (15.5 mg, 70%) as a viscous oil. ^1H NMR (400 MHz) δ 5.25 (1H, s, H-15), 3.61 (2H, dd, *J*=6.0, 6.0 Hz, H-4′), 2.61 (1H, m, H-12), 2.41 (1H, ddd, *J*=13.0, 3.0, 3.0 Hz, H-7), 2.02 (1H, ddd, *J*=13.5, 5.8, 1.7 Hz, H-2), 1.88–1.60 (4H, m, H-13, H-11, H-6, H′-2), 1.77 (3H, d, *J*=1.0 Hz, Me-C_{16}), 1.60–1.05 (11H, m, H′-11, H-9, H′-7, H′-6, H-1, H_2-1′, H_2-2′, H_2-3′), 0.99 (3H, s, Me-C_4), 0.89 and 0.84 (9H each, each s, 2×*Me*$_3$CSi), 0.88 (1H, m, H-5), 0.63 (3H, s, Me-C_{10}), 0.64 (1H, m, H′-1), 0.49 (1H, dd, *J*=5.0, 1.0 Hz, H-18), 0.24 (1H, d, *J*=5.0 Hz, H′-18), 0.09, 0.07, 0.04 and 0.03 (3H each, each s, 2×Me_2Si); ^{13}C NMR (75 MHz) δ 215.77 (C_{14}), 145.23 (C_{16}), 127.35 (C_{15}), 62.94 ($C_{4'}$), 59.02 (C_3), 53.75 (C_5), 51.95 (C_8), 51.71 (C_{13}), 51.33 (C_9), 40.42 (C_{12}), 35.69 (C_{10}), 35.04 (C_1), 32.77 ($C_{3'}$), 30.58 ($C_{1'}$), 29.70 (C_2), 28.63 (C_{18}), 28.51 (C_7), 27.55 (C_{11}), 26.77 and 25.96 (2×*Me*$_3$CSi), 24.18 ($C_{2'}$), 22.66 (C_6), 21.41 (Me-C_{16}), 21.94 (C_4), 18.33, 17.92 (2×Me$_3$*C*Si), 15.60 (Me-C_4), 11.35 (Me-C_{10}), −3.03, −3.82, −5.26 and −5.26 (4×MeSi); MS (EI) *m*/*z* (%) 601 (M^++1, 5), 600 (M^+, 12), 543 (100), 487 (9), 211 (16), 75 (17), 73 (36); HRMS *m*/*z* calcd for $C_{36}H_{64}O_3Si_2$ 600.4394, found 600.4383.

4.4. Synthesis of atisene 3

4.4.1. 3(*R*),13(*S*)-3-(*tert*-Butyldimethylsilyloxy)-13-hydroxy-3α,18-*cyclo*-atis-15-en-14-one (25). Ketone **12** (35.7 mg, 0.086 mmol) and Et_3N (29.5 μL, 0.21 mmol) were dissolved in 0.7 mL of CH_2Cl_2 and cooled to 0 °C. TMSOTf (23 μL, 0.13 mmol) was added and the reaction mixture was allowed to warm slowly to rt and then stirred for 30 min. The reaction mixture was poured into a mixture of hexane and 5% aq $NaHCO_3$. The layers were separated and the organic phase was washed with water and then brine. The solution was dried over Na_2SO_4, filtered and then evaporated under vacuum to yield a yellowish oil (38.3 mg) as the crude product (compound **24a**). This trimethylsilyl enol ether was quite labile, being readily hydrolysed to the starting ketone when chromatographed on silica gel, so it was used in the next step without further purification.

The crude product obtained above was dissolved in CH_2Cl_2 (0.7 mL), $NaHCO_3$ was added (8.4 mg) and the resulting suspension was cooled to 0 °C. A solution of *m*-CPBA

(40 mg, 0.23 mmol) in CH_2Cl_2 (1 mL) was slowly added and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by the addition of saturated aq NH_4Cl solution and worked up using hexane to extract it. The residue left after evaporation of the solvent was dissolved in MeOH (1 mL) and treated with $(COOH)_2$ (8 mg). A white precipitate immediately appeared and the mixture was stirred at rt for 15 min. The reaction mixture was poured into a 1:1 mixture of hexane–ethyl ether, which was successively washed with 5% aq $NaHCO_3$, water and brine, then dried over $MgSO_4$ and concentrated to give a solid. Chromatography (hexane–AcOEt 8:2) gave the hydroxyketone **25** (28.3 mg, 79% from **12**) as a white solid. Mp 178–180 °C (from Et_2O); $[\alpha]_D^{22}$ −85 (*c* 1.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3534s, 2929s, 2852m, 1710s, 1455m, 1255m, 1193m, 1040m, 835s, 763s; ^1H NMR (400 MHz) δ 5.30 (1H, br s, H-15), 3.69 (1H, d, *J*=2.4 Hz, H-13), 2.78 (1H, br s, OH), 2.72 (1H, m, H-12), 2.49 (1H, ddd, *J*=13.3, 3.1, 3.1 Hz, H-7), 2.06 (1H, ddd, *J*=13.4, 5.8, 1.7 Hz, H-2), 1.92–1.66 (3H, m, H_2-6, H′-2), 1.59–1.38 (3H, m, H_2-11, H-1), 1.32 (1H, dd, *J*=12.3, 6.2 Hz, H-9), 1.80 (1H, ddd, *J*=13.3, 13.3, 4.3 Hz, H′-7), 1.83 (3H, d, *J*=1.0 Hz, Me-C_{16}), 0.90 (1H, dd, *J*=12.9, 3.3 Hz, H-5), 0.99 (3H, s, Me-C4), 0.84 (9H, s, *Me*$_3$CSi), 0.64 (1H, ddd, *J*=13.4, 13.4, 5.7 Hz, H′-1), 0.61 (3H, s, Me-C_{10}), 0.50 (1H, dd, *J*=5.0, 1.0 Hz, H-18), 0.25 (1H, d, *J*=5.0 Hz, H′-18), 0.09 and 0.04 (3H each, each s, Me_2Si); ^{13}C NMR (75 MHz) δ 216.12 (C_{14}), 145.82 (C_{16}), 126.13 (C_{15}), 73.55 (C_{13}), 58.94 (C_3), 53.56 (C_4), 51.61 (C_9), 49.98 (C_8), 43.21 (C_{12}), 35.65 (C_{10}), 34.65 (C_1), 28.78 (C_2), 28.66 (C_{18}), 28.46 (C_7), 26.18 (*Me*$_3$CSi), 24.89 (C_{11}), 21.85 (C_4), 21.56 (C_6), 21.27 (Me-C_{16}), 17.89 (Me$_3$*C*Si), 15.62 (Me-C_4), 12.12 (Me-C_{10}), −3.04 and −3.82 (Me_2Si); MS (EI) *m*/*z* (%) 430 (M^+, 29), 374 (30), 373 (100), 211 (79), 75 (32), 73 (81); HRMS *m*/*z* calcd for $C_{26}H_{42}O_3Si$ 430.2903, found 430.2893.

4.4.2. 13(*S*)-Hydroxy-atis-15-ene-3,14-dione (26). A solution of compound **25** (24 mg, 0.056 mmol) and PTSA (14 mg, 0.070 mmol) in $CHCl_3$ (4 mL) was heated at reflux for 1.5 h. The reaction mixture was treated with a 5% aq $NaHCO_3$ solution, poured into water, and then worked up using ether to extract it. After evaporation of the solvent, the crude product was purified by chromatography (hexane–AcOEt 8:2) to give the diketone **26** (14.8 mg, 86%) as a solid. Mp 145–147 °C (from MeOH); $[\alpha]_D^{25}$ −168 (*c* 0.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3528m, 2931s, 2850s, 1712s, 1694s, 1460m; ^1H NMR (300 MHz) δ 5.37 (1H, br s, H-15), 3.75 (1H, d, *J*=2.0 Hz, H-13), 2.77 (1H, m, H-12), 2.58 (1H, ddd, *J*=13.2, 3.3, 3.3 Hz, H-7), 2.56 (1H, ddd, *J*=15.6, 12.9, 6.3 Hz, H-2), 2.34 (1H, ddd, *J*=15.6, 5.4, 3.3 Hz, H′-2), 1.90–1.73 (2H, m, H-11, H-1), 1.86 (3H, d, *J*=2.1 Hz, Me-C_{16}), 1.62–1.49 (3H, m, H′-11, H_2-6), 1.48–1.18 (4H, m, H-9, H′-7, H-5, H′-1), 1.09 (3H, s, Meα-C_4), 1.01 (3H, s, Meβ-C_4), 0.84 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz) δ 216.12 (C_3), 213.50 (C_{14}), 146.24 (C_{16}), 125.74 (C_{15}), 73.34 (C_{13}), 55.23 (C_5), 52.44 (C_9), 51.81 (C_8), 47.54 (C_4), 37.70 (C_1), 43.06 (C_{12}), 37.02 (C_{10}), 34.21 (C_2), 28.71 (C_7), 24.25 (C_{11}), 26.13 (Meα-C_4), 21.29 (Me-C_{16}), 19.91 (C_6), 21.18 (Meβ-C_4), 13.73 (Me-C_{10}); MS (EI) *m*/*z* (%) 316 (M^+, 10), 290 (20), 288 (100), 118 (40), 105 (32), 91 (18); HRMS *m*/*z* calcd for $C_{20}H_{28}O_3$ 316.2039, found 316.2043. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.84; H, 8.90.

4.4.3. Atis-15-ene-3,14-dione (28). In the same manner as described above for **25**, a solution of **12** (209 mg, 0.50 mmol) and PTSA (125 mg, 0.63 mmol) in $CHCl_3$ (18 mL) was heated at reflux for 1.5 h. Work-up, followed by purification by chromatography (hexane–AcOEt 8:2), afforded the atisene diketone **28** (142 mg, 94%) as a solid. Mp 156–158 °C (from MeOH); $[\alpha]_D^{20}$ −98 (*c* 0.6, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2939s, 2873m, 1700s, 1459m, 1413m, 1372m, 1075m, 793w, 691w, 578w; ^1H NMR (300 MHz) δ 5.37 (1H, br s, H-15), 2.65 (1H, m, H-12), 2.56 (1H, ddd, *J*=15.6, 13.0, 6.6 Hz, H-2), 2.53 (1H, ddd, *J*=11.7, 2.8, 2.8 Hz, H-7), 2.31 (1H, ddd, *J*=15.6, 5.7, 3.1 Hz, H′-2), 2.18 (1H, ddd, *J*=18.1, 2.8, 2.8 Hz, H-13), 2.06 (1H, dd, *J*=18.1, 2.1 Hz, H′-13), 1.86–1.75 (1H, m, H-1), 1.80 (3H, d, *J*=1.7 Hz, Me-C_{16}), 1.68 (1H, ddd, *J*=12.9, 12.3, 3.4 Hz, H-11), 1.61–1.47 (3H, m, H′-11, H_2-6), 1.45–1.32 (3H, m, H-9, H-5, H′-1), 1.24 (1H, ddd, *J*=13.2, 12.9, 4.5 Hz, H′-7), 1.09 (3H, s, Meα-C_4), 1.01 (3H, s, Meβ-C_4), 0.89 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz) δ 216.58 (C_3), 213.94 (C_{14}), 146.28 (C_{16}), 128.21 (C_{15}), 55.38 (C_5), 53.93 (C_9), 52.34 (C_8), 47.64 (C_4), 41.63 (C_{13}), 38.11 (C_1), 37.04 (C_{10} and C_{12}), 34.26 (C_2), 29.40 (C_7), 26.68 (C_{11}), 25.94 (Meα-C_4), 21.72 (Me-C_{16}), 20.03 (C_6), 19.91 (Meβ-C_4), 12.69 (Me-C_{10}); MS (EI) *m*/*z* (%) 300 (M^+, 14), 259 (100), 258 (100), 240 (14), 139 (15), 135 (27), 105 (38); HRMS *m*/*z* calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2082. Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.86; H, 9.46.

4.4.4. Atis-16-ene-3,14-dione (3). MeOH (4.8 mL) was dropwise added to a light-protected, stirred solution of recrystallised NBS (96 mg, 0.54 mmol) and atisene **28** (110 mg, 0.36 mmol) in CH_2Cl_2 (14.5 mL) at 0 °C. After 45 min of stirring at this temperature, the reaction mixture was poured into hexane and worked up to afford a mixture of allyl bromides **29a** and **29b** (150 mg) in the proportion of about 3:1, as inferred from the analysis of the ^1H NMR of the crude mixture, which was used without further purification in the next step.

^1H NMR data for the major regioisomeric bromide was deduced from the spectrum of the mixture: δ 5.72 (1H, br s, H-15), 4.11 (2H, s, H_2-17), 2.98 (1H, m, H-12), 2.64–2.52 (2H, m, H-2 and H-7), 2.31 (1H, ddd, *J*=16.0, 5.6, 3.2 Hz, H′-2), 2.22 (1H, ddd, *J*=18.0, 2.8, 2.8 Hz, H-13), 2.15 (1H, dd, *J*=18.0, 2.8 Hz, H′-13), 1.69 (1H, ddd, *J*=13.2, 13.2, 4.0 Hz, H-11), 1.09 (3H, s, Meα-C_4), 1.01 (3H, s, Meβ-C_4), 0.92 (3H, s, Me-C_{10}).

A mixture of $CrCl_3$ (785 mg, 5 mmol) and $LiAlH_4$ (95 mg, 2.5 mmol) was dissolved in THF (5 mL) and stirred at rt until the hydrogen evolution ceased. Then, DMF (10 mL) and *iso*-PrOH (0.68 mL) were added, and the mixture was stirred at rt for 20 min. A solution of the above-obtained allyl bromides **29a–b** (150 mg) in DMF (5 mL) was added, and the resulting mixture was stirred at rt overnight. After this time, the reaction mixture was poured into a 1:1 mixture of hexane–Et_2O, the organic layer was washed sequentially with diluted hydrochloric acid, 5% aq $NaHCO_3$ and brine, and then dried over $MgSO_4$. Evaporation of the solvent and chromatography (hexane–AcOEt 8:2) provided compound **3** (100 mg, 91% for the two steps) as a white solid. Mp 153–155 °C (from MeOH); $[\alpha]_D^{22}$ −5.5 (*c* 0.7, $CHCl_3$)

{lit.[3,4] mp 160–164 °C; $[\alpha]_D^{25}$ +5.5}; IR ν_{max}/cm^{-1} (KBr) 2922s, 2855m, 1757s, 1710s, 1467m, 1265m, 1187w, 1156w, 1078w, 1011w, 835s, 767m; ^1H NMR (300 MHz) δ 4.89 (1H, br s, H-17), 4.68 (1H, br s, H′-17), 2.73 (1H, m, H-12), 2.56 (1H, ddd, J=19.8, 13.4, 6.4 Hz, H-2), 2.40–2.15 (6H, m, H_2-15, H_2-13, H-7, H′-2), 2.0–1.76 (2H, m, H-11, H-1), 1.75–1.44 (4H, m, H′-11, H-9, H_2-6), 1.35 (1H, ddd, J=13.2, 13.2, 5.3 Hz, H′-1), 1.27 (1H, dd, J=12.4, 2.5 Hz, H-5), 0.91 (1H, ddd, J=13.2, 13.2, 4.7 Hz, H′-7), 1.08 (3H, s, Meα-C_4), 1.01 (3H, s, Meβ-C_4), 0.87 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz) δ 216.42 (C_3), 216.14 (C_{14}), 147.07 (C_{16}), 42.61 (C_{15}), 55.33 (C_5), 51.84 (C_9), 47.59 (C_8), 47.68 (C_4), 44.56 (C_{13}), 37.18 (C_1), 38.30 (C_{12}), 37.18 (C_{10}), 34.09 (C_2), 31.17 (C_7), 27.86 (C_{11}), 25.95 (Meα-C_4), 107.15 (C_{17}), 20.02 (C_6), 21.83 (Meβ-C_4), 12.77 (Me-C_{10}); HRMS m/z calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2085.

4.5. Synthesis of antiquorin (1)

4.5.1. 3-(*tert*-Butyldimethylsilyloxy)-atis-2,16-diene-14-one (30). A solution of diketone **3** (25 mg, 0.083 mmol) in CH_2Cl_2 (0.5 mL) was cooled to −78 °C and treated sequentially with Et_3N (14 μL, 0.097 mmol) and TBDMSOTf (21 μL, 0.091 mmol). After 30 min at −78 °C, the reaction mixture was diluted with hexane and worked up as usual to give silyl enol ether **30** (34 mg, 98%) as an oil, which was proven to be nearly pure by ^1H NMR analysis and was used in the next step without further purification.

Spectroscopic data for **30**: ^1H NMR (300 MHz, C_6D_6) δ 4.75 (1H, dd, J=4.0, 2.4 Hz, H-17), 4.61 (1H, dd, J=6.6, 2.2 Hz, H-2), 4.53 (1H, dd, J=4.0, 2.2 Hz, H′-17), 2.27 (1H, quint, J=2.9 Hz, H-12), 2.37 (1H, ddd, J=13.2, 3.9, 2.9 Hz, H-7), 2.13–1.98 (2H, m, H-15, H-13), 1.91–1.72 (2H, m, H′-15, H′-13), 1.60 (1H, ddd, J=15.9, 6.6 Hz, H-1), 1.56–1.25 (5H, m, H-11, H-9, H_2-6, H′-1), 1.20 (1H, m, H′-11), 1.11 (3H, s, Me-$C_{4\beta}$), 1.04 (1H, dd, J=12.7, 2.7 Hz, H-5), 0.97 (3H, s, Me-$C_{4\alpha}$), 0.96 (9H, s, Me_3CSi), 0.69 (3H, s, Me-C_{10}), 0.6 (1H, ddd, J=13.2, 13.2, 4.6 Hz, H′-7), 0.15 and 0.12 (3H each, each s, Me_2Si); ^{13}C NMR (75 MHz, C_6D_6) δ 213.71 (C_{14}), 156.39 (C_3), 148.23 (C_2), 148.23 (C_{16}), 106.35 (C_{17}), 52.47 (C_5), 50.91 (C_9), 47.34 (C_8), 45.74 (C_4), 44.57 (C_{13}), 42.59 (C_{15}), 37.64 (C_1), 38.91 (C_{12}), 38.16 (C_{10}), 31.43 (C_7), 28.74 (Me-$C_{4\alpha}$), 27.25 (C_{11}), 25.98 (Me_3CSi), 20.40 (Me-$C_{4\beta}$), 20.04 (C_6), 18.37 (Me_3CSi), 12.96 (Me-C_{10}), −4.15 and −4.55 (Me_2Si).

4.5.2. 13(*S*)-13-Hydroxy-atis-16-ene-3,14-dione (antiquorin, 1). A solution of the above-obtained compound **30** (30 mg, 0.074 mmol) in THF (0.45 mL) was added dropwise over a period of 15 min to a 0.5 M solution of LiHMDS in THF (195 μL, 0.097 mmol) at −78 °C. The reaction mixture was allowed to warm to −30 °C, and then solid MoOPH[44] (48 mg, 0.112 mmol) was added all at once, while the headspace in the reaction flask was flushed with argon. After 30 min, the reaction mixture was poured into hexane and washed successively with 5% aq HCl solution, 5% aq $NaHCO_3$ and brine, then dried over $MgSO_4$. The residue obtained after evaporation of the solvent was dissolved in a solution of $(COOH)_2$ (3 mg) in MeOH (0.75 mL). The mixture was stirred at rt for 15 min, and then the resulting white suspension was diluted with a 1:1 mixture of hexane–Et_2O, and washed sequentially with 5% aq $NaHCO_3$ and brine, and then dried over $MgSO_4$. Chromatography (hexane–AcOEt 7:3) of the residue left after removal of the solvent, afforded antiquorin (**1**) (21.3 mg, 90% from **30**) as a white solid. Mp 174–176 °C (from MeOH); $[\alpha]_D^{27}$ −42 (c 0.4, $CHCl_3$) {lit.[3,4] mp 175–177 °C; $[\alpha]_D^{25}$ +44}, {lit.[6] mp 162–163 °C; $[\alpha]_D^{25}$ +42}; IR ν_{max}/cm^{-1} (KBr) 3534m, 2929s, 2852s, 1712s, 1694s, 1454m, 1190m, 1040m, 836s; ^1H NMR (400 MHz) δ 5.02 (1H, br s, H-17), 4.86 (1H, br s, H′-17), 3.96 (1H, s, OH), 3.88 (1H, d, J=3.2 Hz, H-13), 2.82 (1H, ddd, J=3.0, 3.0, 3.0 Hz, H-12), 2.55 (1H, ddd, J=15.8, 13.0, 6.3 Hz, H-2), 2.41 (1H, ddd, J=13.2, 3.8, 3.8 Hz, H-7), 2.34 (1H, ddd, J=15.8, 5.6, 3.2 Hz, H′-2), 2.32 (1H, m, H-15), 2.03 (1H, ddd, J=15.4, 11.6, 3.9 Hz, H-11), 1.86 (1H, ddd, J=13.3, 6.3, 3.3 Hz, H-1), 1.76 (1H, ddd, J=13.9, 6.3, 2.6 Hz, H′-11), 1.66 (1H, dd, J=11.6, 6.3 Hz, H-9), 1.56–1.47 (2H, m, H_2-6), 1.39 (1H, ddd, J=13.3, 13.0, 5.6 Hz, H′-1), 1.34–1.26 (2H, m, H-5, H′-1), 0.95 (1H, m, H′-7), 1.09 (3H, s, Me-$C_{4\alpha}$), 1.01 (3H, s, Me-$C_{4\beta}$), 0.84 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz) δ 217.96 (C_{14}), 216.06 (C_3), 142.3 (C_{16}), 111.13 (C_{17}), 75.16 (C_{13}), 55.21 (C_5), 51.16 (C_9), 43.77 (C_{15}), 47.50 (C_8), 47.35 (C_4), 44.86 (C_{12}), 37.58 (C_{10}), 36.73 (C_1), 34.04 (C_2), 30.42 (C_7), 26.21 (Me-$C_{4\alpha}$), 25.39 (C_{11}), 21.85 (Me-$C_{4\beta}$), 19.98 (C_6), 13.72 (Me-C_{10}); HRMS m/z calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2041.

4.6. Synthesis of atisenes 8 and 9

4.6.1. 2(*R*)-2-Hydroxy-atis-16-ene-3,14-dione (33). Solid $NaHCO_3$ (5 mg, 0.06 mmol) and a solution of *m*-CPBA (40 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) were successively added to a solution of enolsilyl ether **30** (36 mg, 0.087 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. After 15 min, the reaction mixture was quenched by the addition of 5% aq $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed sequentially with 5% aq $NaHSO_3$ solution, 5% aq $NaHCO_3$ solution and brine, then dried with Na_2SO_4, filtered and concentrated under vacuum to leave a solid. This crude material was dissolved in MeOH (2 mL), then solid $(COOH)_2$ (20 mg, 0.22 mmol) was added and the mixture was stirred at rt for 3 h. The mixture was diluted with a 1:1 mixture of hexane–Et_2O, washed sequentially with 5% aq $NaHCO_3$ solution, water and brine, and then dried over $MgSO_4$. Chromatography (hexane–AcOEt 8:2) of the residue left after removal of the solvent afforded the hydroxyketone **33** (22.7 mg, 88%) as a white solid. Mp 155–157 °C (from MeOH); $[\alpha]_D^{27}$ −8 (c 1.7, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3487m, 3421w, 2940m, 2899m, 1710s, 1449w, 1388m, 1260w, 1250m, 988w, 881m; ^1H NMR (400 MHz) δ 4.90 (1H, br s, H-17), 4.68 (1H, br s, H′-17), 4.48 (1H, ddd, J=13.6, 6.4, 2.2 Hz, H-2), 3.63 (1H, d, J=2.2 Hz, OH), 2.74 (1H, quint, J=2.7 Hz, H-12), 2.40–2.15 (6H, m, H_2-15, H_2-13, H-7, H-1), 1.95 (1H, dddd, J=10.9, 10.9, 5.8, 2.2 Hz, H-11), 1.74–1.55 (4H, m, H′-11, H-9, H-6, H′-1), 1.50 (1H, dddd, J=13.8, 4.9, 4.7. 2.8 Hz, H-6), 1.22 (1H, dd, J=12.4, 2.2 Hz, H-5), 0.91 (1H, ddd, J=13.2, 13.2, 4.9 Hz, H′-7), 1.16 (3H, s, Me-C_{10}), 1.09 (3H, s, Meα-C_4), 1.01 (3H, s, Meβ-C_4); ^{13}C NMR (75 MHz) δ 215.87 (C_3), 216.42 (C_{14}), 146.66 (C_{16}), 107.42 (C_{17}), 68.87 (C_2), 56.92 (C_5), 52.08 (C_9), 47.60 (C_8), 47.47 (C_4), 47.18 (C_1), 44.52 (C_{13}), 42.55 (C_{15}), 38.21 (C_{10}), 38.14 (C_{12}), 31.04 (C_7), 28.00 (C_{11}), 24.92

(Meα-C_4), 21.70 (Meβ-C_4), 19.75 (C_6), 13.96 (Me-C_{10}); MS (EI) *m/z* (%) 317 (M^++1, 3), 316 (M^+, 15), 260 (48), 124 (35), 109 (36), 85 (46), 71 (64), 69 (61), 57 (100), 55 (68); HRMS *m/z* calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2039.

4.6.2. 2-Hydroxy-atis-1,16-diene-3,14-dione (8). A solution of DMSO (58 μL, 0.76 mmol) in CH_2Cl_2 (0.2 mL) was added dropwise to a solution of oxalyl chloride (37.5 μL, 0.40 mmol) in CH_2Cl_2 (0.3 mL) at −60 °C. After stirring for 5 min, a solution of the hydroxyketone **33** (22 mg, 0.070 mmol) in CH_2Cl_2 (0.25 mL) was added dropwise and the mixture was stirred at the same temperature for 15 min. Et_3N (277 μL, 1.96 mmol) was added, and the reaction was slowly warmed to 0 °C, at which it was stirred for 30 min. The reaction was quenched with water at 0 °C and worked up as usual. Concentration and filtration through a short plug of silica gel gave compound **8** (20.5 mg, 93%) as a white solid. Mp 159–162 °C (from hexane–Et_2O); $[\alpha]_D^{21}$ +17 (*c* 0.3, $CHCl_3$) {lit.[14] mp 161 °C; $[\alpha]_D^{25}$ −20}; IR ν_{max}/cm^{-1} (KBr) 3365m, 1714s, 1670s, 1654m, 1402m, 1385m, 1055m, 914s; ^1H NMR (300 MHz) δ 6.09 (1H, s, H-1), 6.02 (1H, br s, OH), 4.92 (1H, br s, H-17), 4.69 (1H, br s, H′-17), 2.78 (1H, quint, *J*=3.0 Hz, H-12), 2.4–2.21 (5H, m, H_2-15, H_2-13, H-7), 2.07 (1H, m, H-11), 1.90 (1H, dd, *J*=10.7, 6.4 Hz, H-9), 1.80 (1H, ddd, *J*=12.8, 7.4, 2.6 Hz, H′-11), 1.70–1.60 (2H, m, H-6, H-5), 1.55 (1H, m, H′-6), 1.21 (3H, s, Me-C_{10}), 1.08 (3H, s, Meα-C_4), 0.98 (3H, s, Meβ-C_4), 0.92 (1H, m, H′-7); ^{13}C NMR (75 MHz) δ 216.35 (C_{14}), 200.67 (C_3), 146.50 (C_{16}), 144.16 (C_2), 124.89 (C_1), 107.57 (C_{17}), 53.19 (C_5), 48.82 (C_9), 47.98 (C_8), 44.51 (C_{13}), 43.84 (C_4), 42.57 (C_{15}), 39.08 (C_{10}), 38.07 (C_{12}), 31.01 (C_7), 28.04 (C_{11}), 26.89 (Meα-C_4), 21.89 (Meβ-C_4), 19.13 (C_6), 17.17 (Me-C_{10}); HRMS *m/z* calcd for $C_{20}H_{26}O_3$ 314.1882, found 314.1893.

4.6.3. 3(*R*)-3-Hydroxy-atis-16-ene-2,14-dione (9). Et_3N (28 μL, 0.20 mmol) and TBDMSOTf (28 μL, 0.122 mmol) were added to a solution of compound **8** (21.6 mg, 0.069 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C. The reaction mixture was allowed to warm slowly to rt and stirred for 30 min. The mixture was diluted with hexane and washed sequentially with 5% aq $NaHCO_3$ solution and brine, then dried over K_2CO_3, filtered and concentrated under vacuum to give crude enolsilyl ether **34** (29 mg). A solution of this compound in THF (0.6 mL) was cooled to −78 °C and then $LiAlH_4$ (16 mg, 0.42 mmol) was added all at once while the headspace in the reaction flask was flushed with argon. The grey suspension was stirred at −78 °C for 1.5 h and then carefully treated with a few drops of water to destroy the excess of hydride and allowed to slowly warm to rt. A few drops of 1 M aq HCl solution were added and the stirring was continued for 15 min. The reaction mixture was poured into water and worked up using hexane to extract it. The residue left after evaporation of the solvent was purified by chromatography (hexane–EtOAc 8:2) to give pure atisene **9** (15.3 mg, 70% from **8**) as a white solid. Mp 164–165 °C (from MeOH); $[\alpha]_D^{26}$ +14 (*c* 1.0, $CHCl_3$) {lit.[15] mp 155 °C; $[\alpha]_D$ −15.7}; IR ν_{max}/cm^{-1} (KBr) 3489m, 2971m, 2890m, 1711s, 1448w, 1375m, 1252w, 1094m, 986w; ^1H NMR (400 MHz, C_6D_6) δ 4.76 (1H, dd, *J*=4.0, 2.4 Hz, H-17), 4.55 (1H, dd, *J*=4.0, 2.0 Hz, H′-17), 3.62 (1H, dd, *J*=5.2, 1.6 Hz, H-3), 3.60 (1H, d, *J*=5.2 Hz, OH), 2.32 (1H, ddd, *J*=13.2, 3.7, 2.4 Hz, H-7), 2.17 (1H, quint, *J*=2.9 Hz, H-12), 2.01 (1H, d, *J*=12.3 Hz, H-1), 2.02–1.8 (2H, m, H-13, H-15), 1.85 (1H, dd, *J*=18.8, 2.7 Hz, H′-13), 1.79 (1H, dt, *J*=18.1, 2.3 Hz, H′-15), 1.54 (1H, m, H-6), 1.39–1.31 (2H, m, H′-6, H′-1), 1.21 (1H, dddd, *J*=14.1, 11.2, 3.3, 3.3 Hz, H-11), 0.96–0.86 (2H, m, H′-11, H-5), 0.52 (1H, ddd, *J*=13.4, 13.4, 5.1 Hz, H′-7), 1.09 (1H, dd, *J*=10.8, 6.4 Hz, H-9), 1.08 (3H, s, Meα-C_4), 0.61 (3H, s, Meβ-C_4), 0.47 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz, C_6D_6) δ 213.25 (C_{14}), 209.43 (C_2), 147.65 (C_{16}), 106.74 (C_{17}), 82.62 (C_3), 53.42 (C_5), 51.69 (C_9), 50.62 (C_1), 47.61 (C_8), 45.36 (C_4), 44.29 (C_{13}), 43.88 (C_{10}), 42.44 (C_{15}), 38.55 (C_{12}), 31.28 (C_7), 27.27 (C_{11}), 29.31 (Meα-C_4), 19.19 (C_6), 16.51 (Meβ-C_4), 13.88 (Me-C_{10}); HRMS *m/z* calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2029.

Further elution with the same eluent afforded the C-3 epimeric alcohol **35** (3.7 mg, 17% from **8**) as an amorphous solid.

4.7. Synthesis of atisene 5

4.7.1. 18-Bromo-atis-16-ene-3,14-dione (37). A solution of NBS (48 mg, 0.27 mmol) in MeOH (2.4 mL) was added dropwise to a light-protected, stirred solution of compound **12** (55 mg, 0.18 mmol) in CH_2Cl_2 (7.2 mL) at 0 °C. After 50 min of stirring at this temperature, the reaction mixture was poured into hexane and worked up. Evaporation of the solvent afforded a mixture of the allyl bromides **36** that was dissolved in DMF (2.5 mL) and added to a solution of $CrCl_2$ [generated from $CrCl_3$ (392 mg, 2.5 mmol) and $LiAlH_4$ (47 mg, 1.25 mmol) in THF (2.5 mL)] in DMF (5 mL) and *iso*-PrOH (0.34 mL) at rt. The mixture was stirred at the same temperature overnight and then worked up in the same manner as described above for the preparation of **3**. Purification by column chromatography (hexane–AcOEt 8:2) afforded bromide **37** (50 mg, 91%) as a white solid. Mp 159–161 °C (from MeOH); IR ν_{max}/cm^{-1} (KBr) 2941s, 2930s, 2872m, 1710s, 1450m, 1074w, 652w; ^1H NMR (300 MHz) δ 4.90 (1H, br s, H-17), 4.69 (1H, br s, H′-17), 3.80 (1H, d, *J*=10.0 Hz, H-18), 3.17 (1H, d, *J*=10.0 Hz, H′-18), 2.76 (1H, quint, *J*=2.8 Hz, H-12), 2.54–2.26 (7H, m, H_2-15, H_2-13, H-7, H_2-2), 2.08 (1H, dd, *J*=12.7, 2.6 Hz, H-5), 1.95 (1H, m, H-11), 1.85–1.52 (3H, m, H′-11, H-6, H-1), 1.41 (1H, ddd, *J*=13.2, 13.2, 6.4 Hz, H′-1), 1.31 (1H, *J*=13.2, 4.9, 2.6, 2.6 Hz, H′-6), 1.04 (1H, ddd, *J*=13.4, 13.4, 4.9 Hz, H′-7), 1.65 (1H, dd, *J*=12.8, 3.4 Hz, H-9), 1.09 (3H, s, Meβ-C_4), 0.87 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz) δ 216.64 (C_{14}), 212.45 (C_3), 146.84 (C_{16}), 107.26 (C_{17}), 51.35 (C_4), 51.17 (C_9), 48.32 (C_5), 47.56 (C_8), 44.52 (C_{13}), 42.38 (C_{15}), 39.31 (C_1), 38.28 (C_{12}), 37.00 (C_{10}), 34.71 (Meα-C_4), 34.46 (C_2), 30.84 (C_7), 27.83 (C_{11}), 21.52 (Meβ-C_4), 19.83 (C_6), 12.38 (Me-C_{10}). MS (EI) *m/z* (%) 381 (M^++1 for ^{81}Br, 3), 380 (M^+ for ^{81}Br, 13), 379 (M^++1 for ^{79}Br, 4), 378 (M^+ for ^{79}Br, 11), 300 (20), 299 (100), 187 (19), 105 (20), 91 (22); HRMS *m/z* calcd for $C_{20}H_{27}{}^{81}BrO_2$ 380.1174, found 380.1180; calcd for $C_{20}H_{27}{}^{79}BrO_2$ 378.1194, found 378.1200.

*X-ray data for compound **37***: colourless prism grown by cooling a diethyl ether solution, 0.47×0.40×0.33 mm size, orthorhombic, $P2_12_12_1$, *a*=7.7732(16), *b*=9.0255(18), *c*=25.320(5) Å, *V*=1776.4(6) Å^3, *Z*=4, ρ_{calcd}=1.418 g cm^{-3}, θ_{max}=24.97, Mo Kα, λ=0.71073 Å, ω-scan, diffractometer Nonius CAD4, *T*=293(2) K, 3559 reflections

collected of which 3111 were independent (R_{int}=0.026), direct primary solution and refinement on F^2 (SHELXS-97 and SHELXL-97, G. M. Sheldrick, University of Göttingen, 1997), 210 refined parameters, methyl group hydrogen atoms refined as *rigid*, others *riding*, the absolute structure was established by anomalous dispersion effects (Flack parameter 0.010(15), Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876) and confirmed by reference to an unchanging chiral centre in the synthetic procedure, $R_1[I>2\sigma(I)]$=0.0503, wR_2(all data)=0.1009.

4.7.2. 18-Hydroxy-atis-16-ene-3,14-dione (5). A solution of bromide **37** (26.4 mg, 0.070 mmol) in DMF (0.3 mL, 3.5 mmol) was added to a light-protected, stirred solution of $AgBF_4$ (70 mg, 0.35 mmol) in $MeNO_2$ (3.2 mL). The reaction mixture was stirred at 60 °C for 15 h, and then filtered through a short pad of Celite, which was washed with ethyl ether. The filtrate was washed successively with water and brine, and then dried over $MgSO_4$. The solvent was removed and the resulting residue (which was shown to be nearly pure formate ester **39** by ^{1}H NMR analysis) was dissolved in MeOH (1 mL) containing a 1% of concd HCl. The mixture was stirred at rt for 5 h, then diluted with a 1:1 mixture of hexane–Et_2O and washed sequentially with 5% aq $NaHCO_3$ solution, water and brine, then dried over $MgSO_4$, and concentrated. Purification by chromatography (hexane–AcOEt 78:3) afforded atisene **5** (18.1 mg, 82%) as a white solid. Mp 150–152 °C (from hexane); $[\alpha]_D^{23}$ −10 (*c* 0.3, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3520m, 2950s, 1711m, 1706m, 1410m, 1039s, 804w; ^{1}H NMR (400 MHz) δ 4.90 (1H, br s, H-17), 4.69 (1H, br s, H′-17), 3.69 (1H, d, *J*=10.8 Hz, H-18), 3.35 (1H, d, *J*=10.8 Hz, H′-18′), 2.73 (1H, quint, *J*=2.8 Hz, H-12), 2.61 (1H, ddd, *J*=15.1, 13.0, 6.5 Hz, H-2), 2.40–2.15 (6H, m, H_2-15, H_2-13, H-7, H′-2), 1.98–1.55 (6H, m, H_2-11, H-9, H-6, H-5, H-1), 1.49–1.15 (2H, m, H′-1, H′-6), 0.98 (1H, ddd, *J*=12.4, 12.4, 5.6 Hz, H′-7), 0.96 (3H, s, Meβ-C_4), 0.94 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz) δ 217.91 (C_3), 216.49 (C_{14}), 146.99 (C_{16}), 107.26 (C_{17}), 66.52 (C_{18}), 51.68 (C_9), 51.63 (C_4), 48.51 (C_5), 47.75 (C_8), 44.62 (C_{13}), 42.61 (C_{15}), 38.36 (C_{12}), 37.39 (C_{10}), 36.98 (C_1), 34.97 (C_2), 30.89 (C_7), 28.03 (C_{11}), 19.63 (C_6), 17.06 (Meβ-C_4), 13.26 (Me-C_{10}). MS (EI) *m*/*z* (%) 316 (M^+, 7), 286 (100), 274 (25), 244 (29), 187 (17), 105 (40), 91 (36); HRMS *m*/*z* calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2048.

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