Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
Tetrahedron 62 (2006) 3266–3283
Tetrahedron

A unified synthetic approach to trachylobane-, beyerane-, atisane- and kaurane-type diterpenes

Antonio Abad,* Consuelo Agulló, Ana C. Cuñat, Ignacio de Alfonso Marzal, Ismael Navarro and Antonio Gris

Departamento de Química Orgánica, Universitat de Valencia, Dr. Moliner 50, 46100 Burjassot, Valencia, Spain

Received 1 December 2005; revised 17 January 2006; accepted 18 January 2006

Abstract—A general synthetic approach to the polycyclic carbon skeleton of biogenetically related trachylobane, beyerane, atisane, and kaurane diterpenes from carvone is described. The skeleton of these diterpenes is prepared from a common intermediate, that is, **25**, readily prepared from carvone using an IMDA reaction and an intramolecular diazo ketone cyclopropanation of an unsaturated ketone as key steps. The tetracyclic diterpene ring systems are obtained from this key trachylobane-type intermediate through the regioselective reductive cleavage of the cyclopropane ring, after adequate modification of the functionalization around the tricyclo[3.2.1.0^{2,7}]octane moiety.

1. Introduction

Trachylobanes, beyeranes, atisanes, and kaurane represent an important group of closely biosynthetically related polycyclic diterpenes,[1] many of which display a wide range of biological activities.[2–5] The usual mechanism proposed for the formation of the carbon skeleton of these diterpenes is based upon the original Wenkert biogenetic pathway to polycyclic diterpenes and implies the initial formation of the tetracyclic cation **2** from copalyl pyrophosphate, via the pymaranyl cation **1** (Scheme 1).[6,7] Closure of this intermediate takes place by either formation of a protonated cyclopropane or by loss of a proton forming the trachylobane skeleton **3**. The three different cleavage modes of the cyclopropane ring lead to the skeletons of kaurane **4** (path a), beyerane **5** (path b) or atisane **6** (path c).[†]

A large number of synthetic routes have been developed for the construction of the carbon framework of these diterpenes,[8] as well as for the elaboration of the tricyclo[3.2.1.0^{2,7}]-, bicyclo[3.2.1]-, and bicyclo[2.2.2]-octane moieties, characteristic of trachylobanes, beyeranes/kauranes, and atisanes, respectively.[9]

In connection with our continued interest for the synthesis of biologically active polycyclic terpenes from carvone,[10] we describe in this paper a unified approach for the construction of the carbocyclic skeleton of these diterpenes, which implies the initial preparation of a common key intermediate with a trachylobane-like skeleton that, in a way conceptually similar to that of the proposed biogenetic pathway, is regioselectively transformed into the atisane-, beyerane- or kaurane-framework. A preliminary communication of part of this work has appeared previously.[11‡]

2. Results and discussion

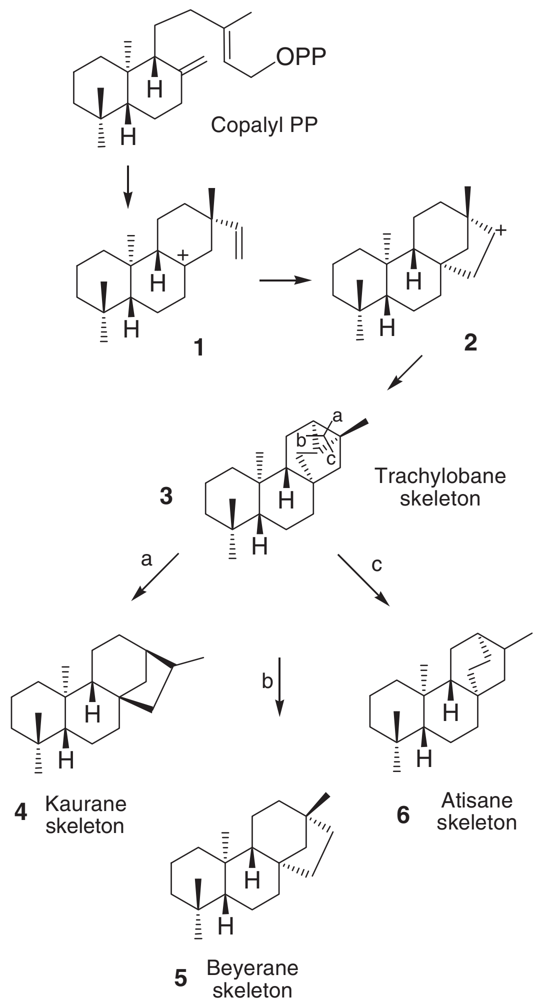
As illustrated in the retrosynthetic analysis in Scheme 2, we considered that a compound such as **7**, which contains all the carbon atoms of the diterpenoid framework and the tricyclo[3.2.1.0^{2,7}]octane moiety incorporated into the ring C, would be a versatile common key intermediate for the

Keywords: Terpenoids; Diels–Alder reaction; Diazo compounds; Ring opening; Cyclopropane.
* Corresponding author. Tel.: +34 6 3864509; fax: +34 6 3864328; e-mail: antonio.abad@uv.es

† All the diterpenes and related compounds described in this paper belong to the enantiomeric series having the 10α-methyl configuration (diterpene numbering), as shown in the structures of Scheme 1. However, the *ent* descriptor is omitted from the names of the diterpenes in the Section 2 for convenience (see heading in the Section 4 for complete systematic names, conforming to the IUPAC recommendations for systematic nomenclature of cyclic diterpenes). It should be noted that although most of the natural tetracyclic diterpenes isolated so far belong to the *ent*-series, some of them, for example, kauranes, are known in both antipodal forms. As will be seen, the approach described in this paper allows the preparation of compounds of both enantiomeric series.

‡ It must be noted that the synthesis described in this initial account starts with (*S*)-(+)-carvone, and therefore all the compounds described there belong to the opposite enantiomeric series of that of the compounds described herein.

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.062



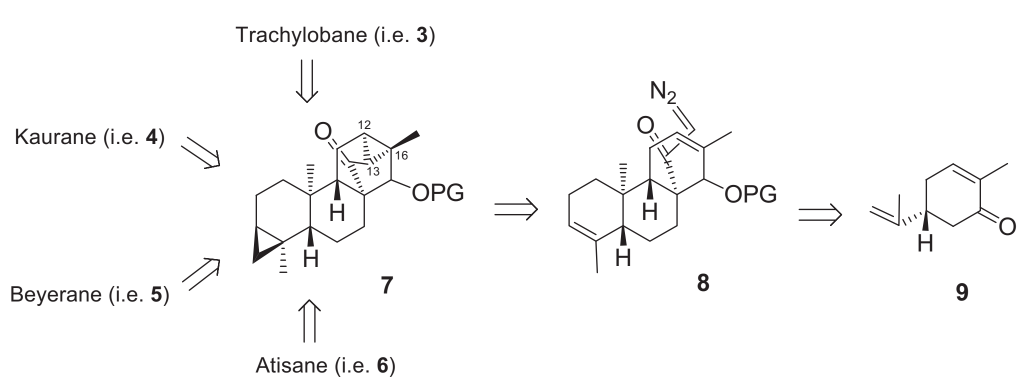
Scheme 1. Structural-biogenetic relationship of tetracyclic diterpenes.

construction of the carbocyclic skeleton of these diterpenes. The tricyclooctane moiety of **7** could be prepared by the intramolecular addition of an α-diazo carbonyl group to the double bond of a homochiral tricyclic system,[12] such as, for example, in **8**, which could conceivably be prepared from (*R*)-(−)-carvone (**9**) using a well-established methodology.[13] Transformation of the key intermediate **7** into the trachylobane skeleton should only require the completion of the gem-dimethyl group at C-4 (e.g., by hydrogenation of the cyclopropane moiety), while its transformation into the beyerane-, kaurane-, and atisane-frameworks should require additional regioselective fragmentation of the C12–C13, C12–C16 or C13–C16 cyclopropane bonds, respectively. This could be achieved, for example, via a reductive process after adequate modification of the functionalization around the cyclopropane ring.

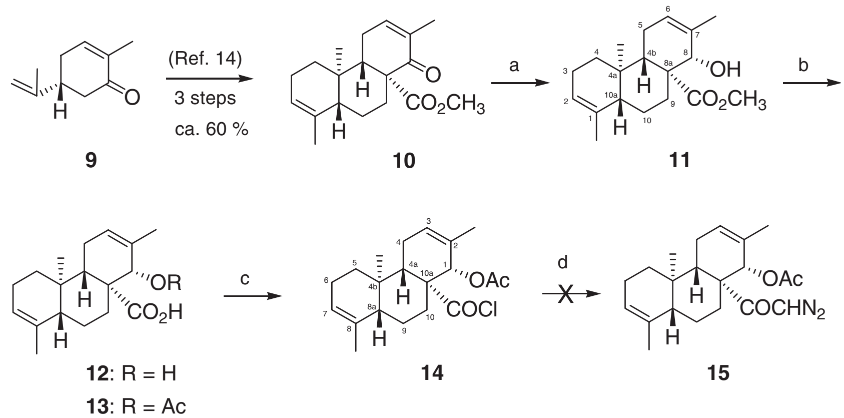
2.1. Preparation of the key intermediate. Construction of the tricyclo[3.2.1.0^{2,7}]octane moiety

A first approach to the required intermediate tricyclic α-diazoketone (Scheme 3), was based on the initial preparation of a carboxylic acid such as **13**, which, in principle, we expected could be easily converted into the required diazoketone by reaction of the corresponding acyl chloride with diazomethane. Accordingly, the (*R*)-(−)-carvone (**9**) was transformed into the known β-ketoester **10**, in three steps, with a 55–60% overall yield.[14] Luche reduction of the carbonyl function of **10** took place stereoselectively, affording the allylic alcohol **11** in 88% yield. The stereochemistry of the new stereogenic centre was determined by NOE measurement. Particularly relevant is the NOESY cross-peak observed between the axially oriented H-8 at δ 3.93 ppm and H-4b at δ 1.53 ppm that unequivocally determines the α-disposition of the hydroxyl function. It must be noted that the above ketone-to-alcohol reduction was necessary since the direct saponification of the methoxycarbonyl moiety of β-ketoester **10** gives rise the retro-Claisen fragmentation of the ring C. Thiolate nucleophile-catalysed hydrolysis of the hindered methyl ester functionality of **11** afforded the expected carboxylic acid **12**, which was transformed into the acetate **13** by acetylation of the alcohol function under standard conditions, in 75% overall yield for the two steps. Conversion of the carboxylic acid moiety of **13** to the corresponding acyl chloride **14** was readily accomplished in 85% yield by reaction of **13** with thionyl chloride and catalytic DMF in benzene.

Unfortunately, all attempts to transform the acyl chloride **14** into the α-diazoketone **15** met with disappointing results; treatment of **14** with diazomethane under a set of different reaction conditions always afforded starting material rather than the desired diazoketone. Although the acyl chloride **14** appeared to be relatively stable (e.g., it could be purified without substantial decomposition by rapid filtration through a short column of silica gel), its lack of reactivity with diazomethane was somewhat unexpected since it reacts smoothly with other weak nucleophiles, for example, MeOH, at rt.



Scheme 2. Retrosynthetic route to tetracyclic diterpenes.

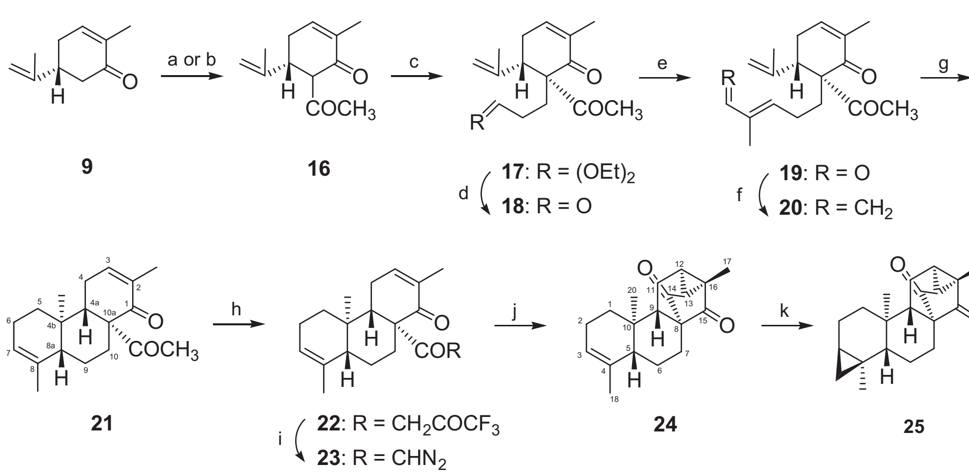


Scheme 3. Failed attempted approach to tricyclic α-diazoketone intermediate. Reagents and conditions: (a) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 1 h, 88%; (b) NaSPr, DMF, 85 °C, 2 h; (c) Ac_2O–DMAP-Py, rt, 2 h, 75% from **11**; $SOCl_2$, DMF–C_6H_6, rt, 3 h, 85%; (d) see text.

We also failed in all attempts to prepare the desired diazoketone using the conditions developed by Nicolaou for highly hindered carboxylic acids.[15] Thus, treatment of carboxylic acid **13** with mesyl chloride and Et_3N and then with diazomethane resulted, after aqueous work-up, in the recovery of the starting material. The same disappointing results were obtained using other protecting group of the hydroxyl function instead of the acetate, such as the methoxy methyl ether group, for example.

The resistance of the hindered carboxylic acid group of **13** to conversion into the corresponding α-diazoketone, prompted us to consider other possibilities. A very convenient alternative was found in the initial preparation of methyl-ketone **21** (Scheme 4), which was readily converted into the diazoketone **23** through a diazo-transfer reaction.[16] The synthesis of methyl-ketone **21** commences with the preparation of β-diketone **16** from (*R*)-(−)-carvone (**9**). This was done either by reaction of the kinetic enolate of carvone with acetaldehyde, followed by Swern oxidation of the resulting β-hydroxy-ketone or, more conveniently, in a single synthetic step, by reaction of the same enolate with acetyl cyanide (pyruvonitrile). In both cases, the β-diketone **16** was obtained in excellent yield as a mixture of epimers at C-6, as inferred through ^{1}H NMR analysis of the mixture. Alkylation of the β-diketone **16** with 6-bromo or 6-iodo-3-methyl-1,3-hexadiene, in order to directly obtain the compound **20** in a similar process to that used for the preparation of β-keto ester **10** (see Ref. 14), afforded a very low yield of the alkylation product, so a stepwise approach was followed for introduction of the 4-methyl-hexa-3,5-dienyl moiety. First, the tetrabutylammonium enolate of **16**, readily obtained by sequential treatment of **16** with 2 equiv of NaH and 1 equiv of $BuNHSO_4$ in THF–DMF,[17] was alkylated with 3-iodopropanaldehyde diethyl acetal in high yield and with very good diastereoselectivity. The diethyl acetal protecting groups of the alkylated product **17** was removed by acid hydrolysis with pyridinium *p*-toluenesulfonate (PPTS) in aq acetone, followed by chemoselective homologation of the aldehyde group by Wittig reaction with (α-formylethylidene)triphenyl phosphorane to give the α,β-unsaturated aldehyde **19** in 80% overall yield for the two steps.

The hexadienyl moiety was completed by Wittig methylenation of the unsaturated aldehyde **19**, which afforded the 1,3,9-decatriene **20** in 92% yield. Finally, the ABC-ring system was completed by intramolecular Diels–Alder reaction (IMDA) of **20**, which was conducted in toluene containing a small amount



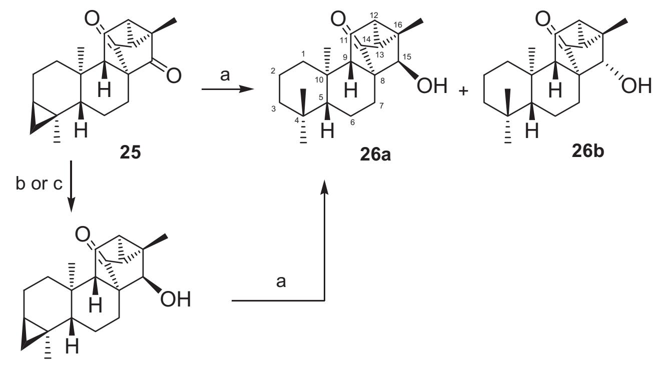
Scheme 4. Preparation of α-diazoketone intermediate and key polycyclic compound **25**. Reagents and conditions: (a) (i) LDA, THF, −78 °C then CH_3CHO, 92%; (ii): $(ClCO)_2$–DMSO, CH_2Cl_2, −30 °C then Et_3N, 90%; (b) LiHMDS, THF, −78 °C then $CNCOCH_3$, 93%; (c) NaH (2 equiv), THF, 0 °C then Bu_4NHSO_4–DMF and $ICH_2CH_2CH(EtO)_2$, 93%; (d) PPTS, H_2O–CH_3COCH_3, ref, 1 h, 93%; (e) $Ph_3P{=}C(Me)CHO$, C_6H_6, ref, 48 h, 86%; (f) Ph_3PCH_3Br–KHMDS, $PhCH_3$, −20 °C to rt, 1 h, 92%; (g) PhMe, propylene oxide, 190–200 °C; 6 days, 90%; (h) LiHMDS, THF, −78 °C then $CF_3CO_2CH_2CF_3$; (i) MsN_3, CH_3CN, H_2O–Et_3N, rt, 80% from **21**; (j) bis(*N*-*tert*-butylsalicylaldiminate)Cu(II), toluene, ref, 4 h, 95%; (k) CH_2I_2, $ZnEt_2$, toluene, 0 °C to rt, 3 h, 94%.

of propylene oxide as acid scavenger at 190–200 °C in a sealed ampoule for 6 days, affording stereoselectively the desired tricyclic methyl-ketone **21** in 90% yield. Although expected on the basis of previous IMDA reactions of related 1,3,9-decatrienes,[18] the stereochemistry of the Diels–Alder adduct **21** was confirmed through a detailed spectroscopic study, including HSQC and NOESY experiments, and comparison of the data with those of related systems (e.g., **10**).

In order to undertake the above mentioned diazo-transfer reaction, the methyl-ketone **21** was first transformed into the trifluoromethyl β-diketone **22** by reaction of its lithium enolate with 2,2,2-trifluoroethyltrifluoroacetate at low temperature. Further diazo-transfer reaction and subsequent in situ retro-Claisen reaction on treatment with mesyl azide or *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and Et_3N in CH_3CN in the presence of 1 equiv of water, afforded the α-diazoketone **23** in 80% overall yield for the two steps. It was gratifying to find, in contrast with the poor results obtained in the few examples of this reaction described so far,[19] that intramolecular addition of the α-diazoketone to the enone double bond took place very efficiently when **23** was slowly added to boiling toluene containing a catalytic amount of bis(*N-tert*-butyl salicylaldiminate)copper(II), thus completing the construction of the tricyclo[3.2.1.0^{2,7}]octane moiety. The carbon atom required for further elaboration of the characteristic diterpene C-4 gem-dimethyl group was introduced by cyclopropanation of the A-ring double bond of **24**, using standard Simmons–Smith cyclopropanation conditions. This reaction takes place stereoselectively from the less hindered β-side of the double bond, affording the key intermediate **25** in an excellent 94% yield.[§]

2.2. Completion of the trachylobane framework

The next objective after preparation of this key intermediate was its transformation into each of the target diterpenic systems. Transformation into a trachylobane-type compound was readily achieved by selective hydrogenolysis of the cyclopropane ring fused to the A ring. The hydrogenation of **25** was complete after 48 h at 35–40 °C under a hydrogen pressure of 65 psi using AcOH as the solvent and PtO_2 as the catalyst (Scheme 5). This treatment not only produces the hydrogenolysis of the cyclopropane bond, with formation of the C-4 geminal dimethyl group, but also regioselective reduction of the C-15 carbonyl group affording a ca. 2:1 mixture of C-15 epimeric trachylobanols **26a** and **26b** in 95% combined yield. The structure and stereochemistry of the major trachylobanol was established by detailed spectral analysis and comparisons with the data reported for related compounds.[20] In particular, the stereochemistry at the C-15 carbinolic centre was assigned on the basis of 2D NOESY experiments in which H-15 at δ 3.61 ppm clearly shows NOE with both H-7 at δ 1.78 and 1.20 ppm and Me-16 at δ 1.34 ppm, which, together with the remarkable shielding experienced by C-9 (7–8 ppm) in the ^{13}C NMR spectrum,



Scheme 5. Synthesis of trachylobane framework from **25**. Reagents and conditions: (a) H_2, PtO_2, AcOH, 4 atm, 35 °C, 48 h, 95% overall yield for **26a/26b** from **25** and 96% of **26a** from **27**; (b) $NaBH_4$, MeOH–CH_2Cl_2, 0 °C, 30 min, 96%; (c) H_2, 10% Pt/C, AcOEt, 4 atm, 24 h, 95%.

clearly establish a β disposition for the hydroxyl group at C-15. Alternatively, a highly chemo- and stereoselective reduction of the C-15 carbonyl group of **25** was effected by hydrogenation at ambient temperature in AcOEt with 10% Pt on carbon as the catalyst and also by sodium borohydride reduction in MeOH–CH_2Cl_2 at 0 °C. In both cases a very high yield of the alcohol **27** was obtained, which was converted to the trachylobanol **26a** in 95% yield by hydrogenolysis of the cyclopropane ring as described above for **25**.

2.3. Regioselective cleavage of the cyclopropane ring: completion of the beyerane, atisane, and kaurane frameworks

Having completed the elaboration of the trachylobane system, we focussed on our goal of regioselective cleavage of the cyclopropane bonds[21] in order to access to the atisane, beyerane, and kaurane carbocyclic systems. In spite of the previously reported results on electrophile-initiated selective ring cleavage of cyclopropyl-ketones, all attempts to open the cyclopropane ring of the cyclopropyl-diketone moiety of **25** under different electrophilic/acid reaction conditions were unsuccessful. Thus, reaction of this compound under relatively smooth acidic conditions, for example, cat. PTSA–LiBr–DMF,[22] $BF_3 \cdot Et_2O$–Ac_2O–CH_2Cl_2,[23] led to the recovery of the starting material, while more severe conditions, for example, hydrogen chloride–CH_2Cl_2,[24] aq HBr–AcOH,[25] TMSI–$CHCl_3$,[26] led only to the opening of the cyclopropane ring fused to the A ring. Only the treatment with 48% HBr in AcOH apparently led to the cyclopropane-ring opening, yielding a complex mixture of non-identified products. A brief exploration of the reactivity of hydroxy-cyclopropyl-ketone **27** towards some of this electrophilic reaction conditions was also undertaken. In general, complex reaction mixtures were obtained, probably due to the initial formation of a cyclopropyl carbocation.[¶]

However, when the 15-hydroxyl group was protected, for example, as acetate, the cyclopropyl-ketone moiety was not

[§] As described in the previous communication, the structure of this key intermediate, but of the antipodal series, has been firmly established by X-ray analysis. The crystallographic data has been deposited in the Cambridge Database (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 172270.

[¶] The easy formation of a carbocation of this type is illustrated by the result obtained in the solvolitic reaction of trachylobanol **26a** with HCOOH–0.5% Na_2CO_3 at 50 °C, which cleanly afforded an equimolecular mixture of C-15 epimeric formates.

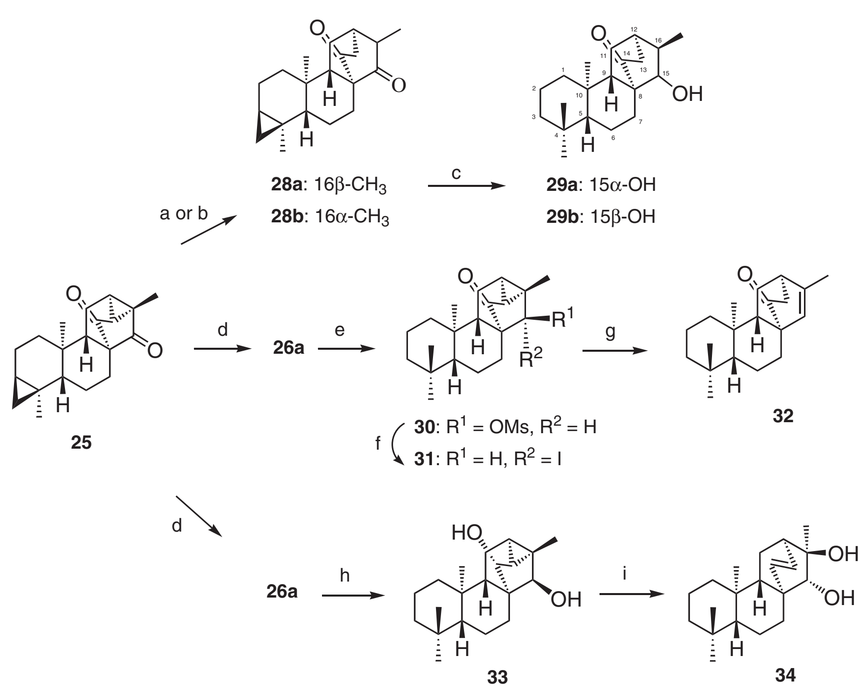
affected by these treatments. For example, the cyclopropyl-ketone moiety of the acetate derivative of **27** remained unaltered after treatment with hydrogen chloride in CH_2Cl_2 or aq HBr in acetic acid.

Highly satisfactory results were obtained via reductive cleavage of the cyclopropane ring. For example, a regioselective reductive cleavage of the C13–C16 cyclopropane bond took place when the cyclopropyl-diketone **25** was treated with lithium in liquid ammonia at low temperature or SmI_2 in THF–MeOH at rt, to give the cyclo-atisane-type diketone **28** as a ca. 2:1 mixture of epimers at C-16 in 83 and 89% yield, respectively (Scheme 6). Both isomers were readily separated by column chromatography and the stereochemistry at C-16 of each epimer was deduced from comparison of their carbon chemical shifts. The most salient feature is the shielding of C-11 in the major epimer **28a** and C-13 in the minor one **28b**, ca. 6 ppm, which is due to the γ-interaction with the, respectively, β- and α-oriented methyl group at C-16. The regioselectivity observed in the above reductive cyclopropane ring cleavage can be rationalized on the basis of the mechanism involved, which implies a two-electron reduction of the cyclopropyl-diketone to a dienolate. Obviously, the regioselective cleavage of the C13–C16 cyclopropane bond is controlled by the stabilization of the negative charge developed at C-13 by the adjacent carbonyl group.[27] Once the bicyclo[2.2.2]octane moiety that constitutes the CD-ring system had been elaborated, completion of the atisane framework was effected by cyclopropane ring hydrogenolysis. Hydrogenation of the major epimeric diketone obtained above, **28a**, under similar conditions to those used for **25** produces a 2:1 mixture of hydroxy-ketones **29a** and **29b**, as result of the hydrogenolysis of the cyclopropane ring and selective reduction of the C-15 carbonyl group. Both epimeric atisanols were also readily separated by chromatography and their stereochemistry was easily established by NMR. Thus, the stereochemistry (α-orientation) of the hydroxyl group at C-15 in the major epimer **29a** was established by the NOE observed between H-15 (δ 3.18) and H-7β (δ 0.86), H-9 (δ 1.34) and Me-16 (δ 1.16). In the same way, the correlation of H-16 (δ 1.65) with H-13 (δ 2.27) in the NOE spectrum confirmed the β-orientation of the methyl attached to C-16.

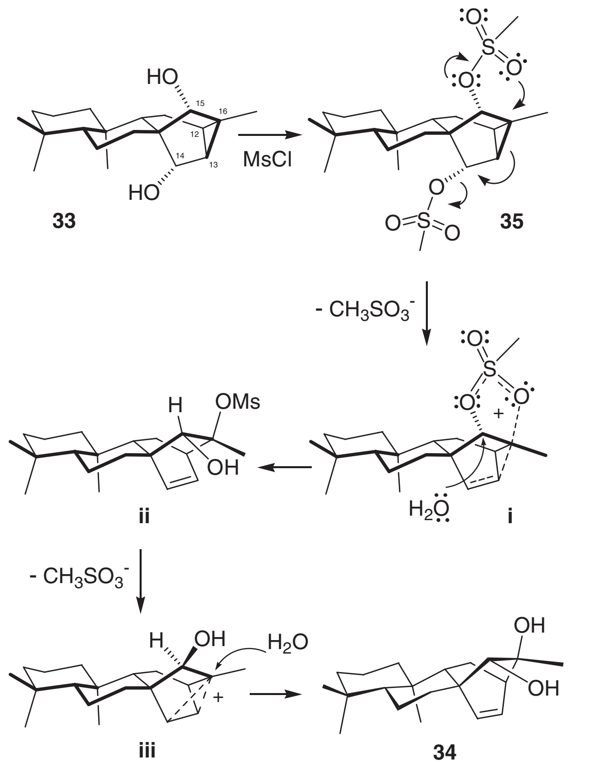
We also investigated alternative modes of regioselective fragmentation of the C13–C16 cyclopropane bond that could afford atisane-type compounds with a functionalization in the surroundings of the CD-rings complementary to that of the atisane system described above. Two additional procedures to complete the trachylobane-to-atisane transformation are described in the following paragraphs.

The first procedure is based on a radical-ring opening of the cyclopropane ring. First, the trachylobanol **26a** is transformed into the α-iodoketone **31** via the corresponding mesylate, in an overall yield for the two steps of 85% (Scheme 6). Treatment of **31** with samarium iodide in THF–MeOH produces the corresponding C15-centered cyclopropylcarbinyl radical, which then undergoes cleavage of the endocyclic cyclopropane bond to give the atisenone **32** in 85% yield.

In the second procedure, **25** is first converted to the trachylobanol **26a**, as described in Scheme 5, and this to the 1,3-diol **33** by stereoselective reduction of the C-14 ketone (Scheme 6). This transformation is effected in 88% yield by



Scheme 6. Synthesis of atisane framework from **25**. Reagents and conditions: (a) Li, NH_3(liq)–THF, −78 °C, 10 min, 57% of **28a** and 26% of **28b**; (b) SmI_2, THF–MeOH, rt, 1 h, 61% of **28a** and 28% of **28b**; (c) H_2, PtO_2, AcOH, 4 atm, 35 °C, 48 h, 45% of **29a** and 23% of **29b**; (d) as in Scheme 5; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (f) NaI, acetone, 40 °C, 2 h, 85% from **27**; (g) SmI_2, THF–MeOH, rt, 1 h, 85%; (h) $LiAlH_4\cdot 2THF$, Toluene–THF, 0 °C, 30 min, 88%; (i) MsCl, Et_3N, H_2O, CH_2Cl_2, 0 °C, 1 h, 66%.



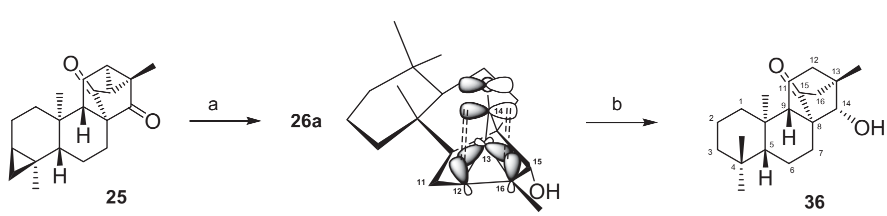
Scheme 7. Tentative mechanistic proposal for the formation of atisenediol **34**.

treatment of **26a** with $LiAlH_4$ in a 1:1 mixture of toluene and THF at 0 °C. The use of this solvent mixture is crucial for the success of the reduction reaction; no reaction is observed in toluene alone, probably due to precipitation of the initially formed aluminium alkoxide, and a complex mixture of products is obtained when THF is used as the only solvent. The stereochemistry at the new carbinolic centre was assigned on the basis of the strong NOESY cross-peak observed between both carbinolic protons at δ 3.75 ppm (H-14) and 3.32 ppm (H-15). Treatment of trachylobanediol **33** under the usual mesylation conditions but in the presence of water gives rise to a very rapid opening of the cyclopropane ring that leads to the atisenediol **34** in 66% yield, after chromatographic purification. The structure and stereochemistry of this compound were elucidated by means of detailed spectroscopic analysis involving comparison with data from literature of related atisane systems.[28] Particularly important for the assignment of the stereochemistry around the bicyclo[2.2.2]octane moiety was the NOESY correlation seen from H-15 (δ 3.15) to H-7β (δ 1.96) and H-9 (δ 1.34) which indicates an α-orientation of the hydroxyl group at C-15, as well as the cross-peak of Me-16 (δ 1.13) with H-13 (δ 6.18) that establishes the β-configuration of the other hydroxyl group at C-16.

At first sight, the transformation of trachylobanediol **33** into atisenediol **34** seems rather surprising, particularly because of the inversion of the configuration at the C15-carbinolic centre. Nevertheless, it can be mechanistically rationalized by considering the initial formation of a dimesylate intermediate. This assumption seems quite reasonable since control experiments showed that a very low yield of **34** is obtained when less than 2 equiv of mesyl chloride are used in this reaction. As shown in the proposed mechanism in Scheme 7, the initially formed dimesylate **35** may experience a rapid elimination of the methylsulfonyloxy group at C-14, probably propitiated by the steric acceleration[29] originated by the sterically congested nature of this position and the anchimeric assistance[30] provided by the neighbouring C-15 methylsulfonyloxy group. The cationic intermediate formed (**i**) should react with H_2O at C-15 with concomitant migration of the C-15 methylsulfonyloxy group to the neighbour C-16, affording the atisane-type intermediate **ii**. Nevertheless, since the assistance provide by the sulfonyloxy group is generally weak,[31] it seems quite reasonable to suppose that the formation of the latter intermediate could take place concertedly from dimesylate **35**. In any case, this intermediate should easily experience a unimolecular substitution of the C-16 methylsulfonyloxy group by H_2O, via the non-classical carbocation **iii**,[32] to give the isolated atisenediol **34**.

The trachylobane-to-beyerane interconversion was also effected with great efficacy via reductive cleavage of the cyclopropane ring of trachylobanol **26a** (Scheme 8). Thus, regioselective fragmentation of the C12–C13 cyclopropane bond of **26a** by lithium–liquid ammonia reduction furnished the beyerane diterpene **36** in 85% yield. In this case, and in contrast with the previous result obtained with the cyclopropyl-diketone **25**, the use of the milder electron-transfer reagent samarium diiodide was unsatisfactory, and the cyclopropyl ketone unit remained intact after treatment of **26a** with this reductor system. The structure of the beyerane **36** was confirmed by detailed spectroscopic analysis and comparison with the data reported for this compound by Fetizon, who prepared it during the synthesis of (−)-hibaene.[33]

It must be noted that the bond cleaved in the above reductive cleavage of the hydroxy-cyclopropyl-ketone **26a** is the one that gives rise to the carbanion intermediate at the least substituted carbon atom, that is, C-12, a result that can be rationalized in terms of the previously reported mechanistic model. It is well established that the bond that breaks in a fused bicyclic cyclopropyl-ketone upon reduction by alkali



Scheme 8. Synthesis of beyerane framework from **25**. Reagents and conditions: (a) as in Scheme 5; (b) Li, NH_3(liq)–THF, −78 °C, 15 min, 85%.

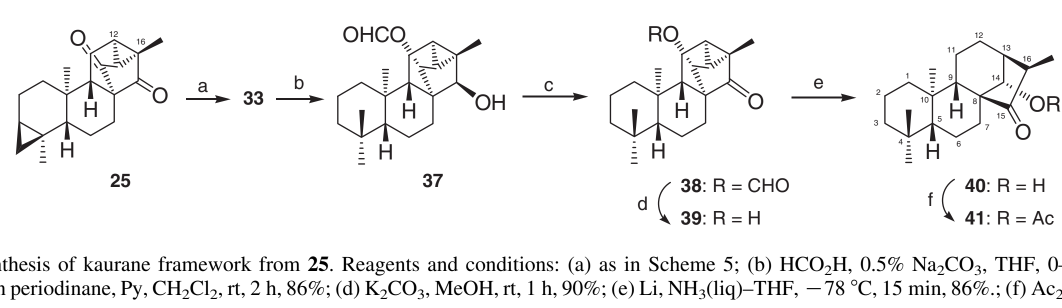
metals in liquid ammonia is governed by stereoelectronic effects, specifically the magnitude of overlap between the cyclopropane C–C bond and the π-orbital of the carbonyl group (geometrical control).[34] However, when equal π-orbital overlap to either cyclopropane bond exists, the principal factor that controls the cyclopropane ring opening is the relative thermodynamic stability of the carbanionic intermediates generated (electronic control). The optimized geometry of **26a** (see structure in Scheme 8) shows that the C-14 carbonyl group is situated in a bisected orientation with respect to the two contiguous cyclopropane bonds, such that a very similar π-orbital overlap to the C12–C13 and C13–C16 cyclopropane bonds exists, and thus the formation of the more stable secondary carbanion at C-12 versus the destabilized α-hydroxy tertiary carbanion at C-16 is the predominant factor controlling the course of the cyclopropane ring opening.

It was estimated, on the basis of the above mechanistic considerations, that an interchange of the carbonyl and hydroxyl functional groups at C-14 and C-15, respectively, of hydroxy-trachylobanone **26a** could lead to a preferred reductive cleavage of the C12–C16 cyclopropane bond, thus completing the desired trachylobane-to-kaurane skeletal interconversion. With this objective in mind, we investigated possible ways of effecting this functional group interconversion in a limited number of steps with good yield. After some experimentation, this transformation was achieved quite satisfactorily in four steps from **26a** via the previously prepared 1,3-diol **33**, through a sequence involving mono-protection of the C14–OH, oxidation of the C15–OH to the corresponding ketone and regeneration of the C14–hydroxyl group (Scheme 9). Initial attempts to selectively protect the C14–OH with various usual hydroxyl-protecting groups were unsuccessful, fundamentally due to the lack of selectivity in the reaction of both hydroxyl groups of diol **33** with the different reagents used. For example, attempted regioselective silylation of diol **33** using 1 equiv of the silylating reagent (e.g., TMSOTf, TBDMSTf or TMSCl) afforded a mixture of C14-and C15-mono-silyl ethers, di-silylated product and unreacted diol. Fortunately, it was found that the required mono-protection of the C14–OH of **33** as the corresponding formate ester could be accomplished indirectly under solvolytic conditions. Thus, treatment of this compound with buffered formic acid in THF at 0–5 °C overnight smoothly afforded the hydroxy-formate ester **37** in 80% yield. It must be mentioned that the control of the temperature was fundamental for the success of this formolysis reaction; an extremely slow reaction took place at lower temperatures, while a complex mixture of products was obtained at higher temperatures. The spectroscopic data of **37** are very similar to those of the diol precursor, with the exception of the expected changes due to the different substituent at C-14. As for the diol **33**, the stereochemistry at C-14 was confirmed by the strong NOESY cross-peak observed between H-14 at δ 4.92 ppm and H-15 at δ 3.44 ppm.

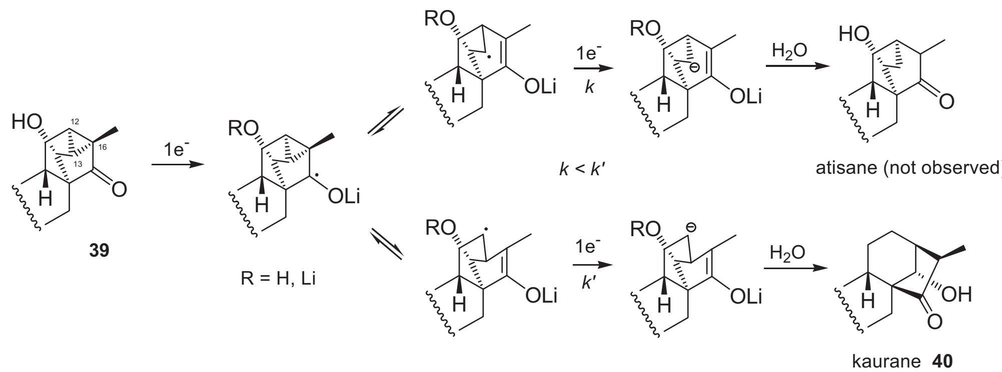
Some interesting observations can be made about the result obtained in the above formolysis of diol **33**, which leads to the formal protection of the C14–OH as the corresponding formate ester. Firstly, the preferential solvolysis at the more crowded C-14 position is remarkable, particularly considering that, as previously mentioned, formolysis at the C-15 position of the trachylobane system can also take place. Probably, as in the conversion of **33** to **34**, the higher reactivity of the C-14 position can be attributed to the higher relief of steric strain in the transition state relative to the ground state that takes place upon ionization at this position (steric acceleration). Secondly, the solvolytic reaction proceeds with retention of configuration at C-14. This stereochemical result is a consequence of the structural characteristics of the non-classical carbonium ion intermediate formed, which requires that the addition of formic acid take place from the same face as the OH group departs, and which, in this case, corresponds to the most hindered face of the cyclopropylcarbinyl cation.[32]

The synthesis of the desired hydroxy-ketone **39** was readily completed from the hydroxy-formate **37** by Dess–Martin oxidation of the hydroxyl group followed by smooth hydrolysis of the formate ester moiety with potassium carbonate in MeOH at rt. This transformation was accomplished, without the need of purification of the intermediate ketone-formate **38**, in 78% overall yield.

As initially estimated, reduction of the cyclopropyl-ketone **39** with lithium in liquid ammonia, under similar conditions to those previously used with **25**, led exclusively to the product resulting from reductive cleavage of the C12–C16 exocyclic cyclopropane bond, the kaurane-type compound **40**. The structure of this compound was initially assigned on the basis of its spectroscopic properties and by comparison of the spectral data with those of known closely related kaurane-type compounds.[35] Further unequivocal confirmation of the structure and stereochemistry of **40** was obtained from a detailed spectroscopic analysis of the corresponding acetate derivative, that is, **41**, which was based on a combination of HMQC, HMBC, and NOESY 2D experiments. Particularly important was the NOESY correlation seen from H-14 (δ 4.79) to H-16 (δ 2.37) which placed these two protons in a cis configuration



Scheme 9. Synthesis of kaurane framework from **25**. Reagents and conditions: (a) as in Scheme 5; (b) HCO_2H, 0.5% Na_2CO_3, THF, 0–5 °C 14 h, 80%. (c) Dess–Martin periodinane, Py, CH_2Cl_2, rt, 2 h, 86%; (d) K_2CO_3, MeOH, rt, 1 h, 90%; (e) Li, NH_3(liq)–THF, −78 °C, 15 min, 86%.; (f) Ac_2O–DMAP-Py, rt, 3 h, 93%.



Scheme 10.

relationship, thus establishing the stereochemistry at C-16 and C-14 positions. Additional cross-peaks between the signals for H-14 and the equatorially disposed (α-orientated) H-7 (δ 1.47) and for the angular methyl group at C-10 (δ 1.04) and the methyl acetyl group (δ 2.18) strongly support the stereochemistry assigned to **41** and therefore to the hydroxy-kauranone **40**.

The regioselectivity observed in the above reductive cleavage of cyclopropyl-ketone **39** contrasts with that obtained in the opening of a related, although structurally simpler, tricyclo[3.2.1.0^{2,7}]octane system that has a hydrogen atom in place of the C-14 hydroxyl group.[36] As shown in Scheme 10, the direction of the cyclopropane ring opening of **39** seems also to be controlled by the electronic factors. In this case, presumably, the destabilizing effect originated by the hydroxyl group at C-14 (or the lithium alkoxide generated from it) on the carbanionic intermediate that is originated upon cleavage of the C12–C16 cyclopropane bond seems to be the main factor favouring the regioselective fragmentation that leads to the kaurane framework.

3. Conclusion

In summary, we have developed a general unified protocol for the efficient preparation of four biogenetically related polycyclic diterpenes. The skeleton of these diterpenes can be obtained in both enantiomeric forms starting from (*R*)-(−) or (S)-(+)-carvone, via a common intermediate that possesses a tricyclo[3.2.1.0^{2,7}]octane moiety characteristic of the trachylobane framework, 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. The type of functionalization obtained around the CD-rings of these diterpenic skeletons and the possibility of easily introducing additional functionalization around the AB-rings and the C-20 angular position, by adequate modification of the synthetic route that gives access to the key trachylobane-like intermediate, enhances the versatility of this approach for the preparation of both non-natural and naturally occurring highly functionalised tetracyclic diterpenes.

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}. ^{1}H NMR spectra were recorded in $CDCl_3$ 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. A combination of COSY, HMQC, and NOE experiments was utilized when necessary for the assignment of ^{1}H and ^{13}C chemical shifts. IR spectra were measured as 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. Mass spectra were obtained by electron impact (EI) at 70 eV or chemical ionization (CI). Column chromatography refers to flash chromatography and was performed on Merck silica gel 60, 230–400 mesh. All operations requiring anhydrous conditions and/or involving air-sensitive reagents were performed under an inert atmosphere of dry argon using syringes, oven-dried glassware, and freshly distilled and dried solvents. Sodium hydride was thoroughly washed with pentane and dried under vacuum prior to use.

4.2. Synthesis of tricyclic acyl chloride 14

4.2.1. (4a*R*,4b*S*,8a*R*,10a*R*)-Methyl 1,4a,7-trimethyl-8-oxo-3,4,4a,4b,5,8,8a,9,10,10a-decahydrophenanthrene-8a-carboxylate (10). β-Keto ester **10** was prepared from (*R*)-(−)-carvone (**9**) in three steps and 60% overall yield as we described previously in Ref. 14.

4.2.2. (4a*R*,4b*S*,8*S*,8a*R*,10a*R*)-Methyl 8-hydroxy-1,4a,7-trimethyl-3,4,4a,4b,5,8,8a,9,10,10a-decahydrophenanthrene-8a-carboxylate (11). To a solution of tricyclic enone **10** (859 mg, 2.86 mmol) in MeOH (106 mL) was added $CeCl_3\cdot 7H_2O$ (1.6 g, 4.24 mmol). The mixture was stirred at rt until complete dissolution of the cerium salt and then cooled to 0 °C. $NaBH_4$ was then slowly added in small portions (318 mg, 5.72 mmol) while the reaction was monitored by TLC (hexane/AcOEt, 7:3). Upon the completion of the reduction (ca. 1 h), the reaction was quenched with water and extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and the residue was purified by column chromatography, using hexane/AcOEt 8:2 as eluent, affording hydroxy ester **11** (747 mg, 88%) as a solid. Mp 150–154 °C (from cold MeOH); $[\alpha]_D^{23}$ +19 (1.6, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3458s, 2939s, 2894s, 1720s, 1440s, 1380m, 1225s, 1155m, 1110m, 1075m, 1045m; ^1H NMR (300 MHz) δ 5.64 (1H, m, H-6), 5.28 (1H, br s, H-2), 3.93 (1H, br s, H-8), 3.65 (3H, s, OMe), 2.85 (1H, ddd, J=13.0, 6.0, 3.0 Hz, H-9α), 2.33 (1H, ddd, J=8.0, 5.0, 3.0 Hz, H-5α), 1.82 (1H, ddd, J=10.0, 7.0, 4.0 Hz, H-4), 1.71 (3H, s, Me-C_7), 1.61 (3H, s, Me-C_1), 1.53 (1H, dd, J=12.5, 5.0 Hz, H-4b), 1.22–1.09 (2H, m, H-9β and H′-4), 0.62 (3H, s, Me-C_{4a}); ^{13}C NMR (75 MHz), see Table 1; MS (EI) m/z (%) 286 (M^+-H_2O, 16), 241 (12), 225 (18), 197 (9), 127 (18), 111 (24), 105 (11), 85 (42); 69 (100); HRMS m/z calcd for $C_{19}H_{26}O_2$ [M^+-H_2O] 286.1933, found 286.1927. Anal. Calcd for $C_{19}H_{28}O_3$: C 74.96, H 9.27; found C 75.10, H 9.18.

4.2.3. (4a*R*,4b*S*,8*S*,8a*R*,10a*R*)-8-Acetoxy-1,4a,7-trimethyl-3,4,4a,4b,5,8,8a,9,10,10a-decahydro phenanthrene-8a-carboxylic acid (13). A solution of **11** (501 mg, 1.67 mmol) in DMF (11 mL) was added to a solution of *n*-PrSNa in DMF, prepared by treating a suspension of NaH (400 mg, 16.7 mmol) in DMF (25 mL) with *n*-PrSH (1.41 mL, 15.6 mmol) at rt for 30 min. The reaction mixture was heated at 85 °C for 2 h. After cooling to rt, the solvent was evaporated under vacuum and the residue was dissolved in CH_2Cl_2 and acidified to pH 4 with 1 N aq HCl solution. The organic phase was separated, washed with brine and dried over $MgSO_4$. After solvent removal, the crude hydroxy-acid **12** was used in the next step without further purification. A sample was purified by chromatography (CH_2Cl_2–MeOH 9.3:0.7) for analysis.

Data for **12**. A foam solid. $[\alpha]_D^{22}$ +22 (1.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3409s, 2941m, 2911w, 2850w, 1695s, 1436s, 1212m, 1049m, 1008m, 759m; ^1H NMR (300 MHz) δ 5.63 (1H, m, H-6), 5.28 (1H, br s, H-2), 3.96 (1H, s, H-8), 2.84 (1H, ddd, J=13.0, 6.0, 3.0 Hz, H-9α), 2.34 (1H, m, H-5α), 2.1–1.5 (8H, m), 1.72 (3H, s, Me-C_7), 1.61 (3H, s, Me-C_1), 1–25–0.9 (3H, m), 0.72 (3H, s, Me-C_{4a}); ^{13}C NMR (75 MHz), see Table 1; MS (EI) m/z (%) 290 (M^+, 4), 272 (6), 244 (24), 228 (19), 157 (23), 145 (47), 131 (38), 119 (54), 105 (100), 91 (96); HRMS m/z calcd for $C_{18}H_{26}O_3$ 290.1882, found 290.1885.

The above obtained crude hydroxy-acid **12** (495 mg) was dissolved in dry pyridine (30 mL) and treated with 4-(dimethylamino)pyridine (DMAP) (55 mg, 0.41 mmol) and Ac_2O (850 μL, 8.96 mmol). The mixture was stirred at rt for 2 h and then treated with MeOH (1.2 mL) and stirred for 30 min. The reaction mixture was concentrated under vacuum and the residue obtained was purified by chromatography, using hexane/AcOEt 7:3 as eluent, to give the carboxylic acid–acetate **13** (388 mg, 75% from **11**) as a very viscous oil that solidified in the freezer. $[\alpha]_D^{24}$ 12 (0.8, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3350m, 2929s, 2849s, 1740s, 1445m, 1370m, 1235s, 1025m; ^1H NMR (300 MHz) δ 5.70 (1H, br s, H-6), 5.45 (1H, br s, H-8), 5.25 (1H, br s, H-2), 2.49 (1H, ddd, J=13.5, 1.5, 1.5 Hz, H-9), 2.44 (1H, m, H-5), 2.14 (1H, m, H′-5), 2.077 (3H, s, OCOMe), 2.01 (1H,

Table 1. ^{13}C NMR chemical shifts (δ) in ppm for compounds **11–14**, **21** and **23**[a]

Compound	11	12	13	14	21	23
C-1	134.44	134.44	134.25	80.80	197.98	198.22
C-2	120.30	120.26	120.28	128.61	131.18	131.88
C-3	22.69	22.67	22.68	126.42	148.22	148.75
C-4	33.93	33.95	33.84	23.45	25.61	25.52
C-4a	35.72	36.48	35.95	51.39	53.17	53.42
C-4b	49.84†	49.79†	49.85	36.13	36.63	36.74
C-5	23.72	21.79	23.48	33.21	33.60	33.73
C-6	125.31	125.89	126.59	21.93	22.70	22.66
C-7	132.06	132.14	129.55	120.51	120.15	120.79
C-8	79.85	80.73	80.31	133.71	133.76	133.68
C-8a	49.74†	49.84†	48.08	48.32	48.32	48.49
C-9	36.57	35.89	36.00	22.70	21.93	21.47
C-10	21.97	23.63	22.51	37.76	32.42	32.10
C-10a	48.70	48.69	48.58	56.82	64.04	60.83
C-*CO*	174.71	179.45	178.36	170.77	207.73	193.23
Me-C_1	21.08	21.22	21.13	—	—	—
Me-C_2	—	—	—	18.44	16.62	16.97
Me-C_{4a}	11.60	11.19	11.34	—	—	—
Me-C_{4b}	—	—	—	12.69	13.84	13.65
Me-C_7	19.49	19.11	18.68	—	—	—
Me-C_8	—	—	—	21.03	21.05	21.34
Others	b	—	c	d	e	f

[a] The signals with the same superscript may be interchanged within the same column.
[b] CO_2*Me* at C_{8a} at 51.29 ppm.
[c] *O*COMe at 170.99 and OCO*Me* at 20.80 ppm.
[d] *O*COMe and OCO*Me* at C_1 at 174.40 and 20.75 ppm, respectively.
[e] CO*Me* at C_{10a} at 28.46 ppm.
[f] CO*C*HN$_2$ at C_{10a} at 54.94 ppm.

m, H-3), 1.92 (1H, m, H-10a), 1.75 (1H, ddd, $J=13.8$, 10.0, 3.6 Hz, H-10), 1.79 (1H, m, H′-10), 1.71 (1H, m, H-4), 1.67 (1H, m, H-4b), 1.59 (3H, s, Me-C_7), 1.55 (3H, s, Me-C_1), 1.18 (1H, m, H′-9), 1.14 (1H, m, H′-4), 0.72 (3H, s, Me-C_{4a}); ^{13}C NMR (75 MHz), see Table 1; FAB-HRMS *m/z* calcd for $C_{20}H_{29}O_4$ [M+H$^+$] 333.2065, found 333.2041. Anal. Calcd for $C_{20}H_{28}O_4$: C 72.26, H 8.49; found C 72.35, H 8.54.

4.2.4. (1*S*,4a*S*,4b*R*,8a*R*,10a*R*)-10a-(Chlorocarbonyl)-2,4b,8-trimethyl-1,4,4a,4b,5,6,8a,9,10,10a-decahydrophenanthren-1-yl acetate (14). DMF (280 μL, 3.6 mmol) and $SOCl_2$ 42 μL, 1.2 mmol) were successively added to a solution of the acid **13** (190 mg, 0.60 mmol) in benzene (6 mL) and the solution was stirred at rt for 3 h. Removal of excess $SOCl_2$ and solvents under reduced pressure gave the acid chloride **14** as a yellowish solid (200 mg), which was shown to be practically pure by NMR spectrum and could be used without further purification or filtered through a short pad of silica gel, which was washed with a mixture of hexane/AcOEt 1:1, to give pure acid chloride **14** as a foam solid (170 mg, 85%); ^1H NMR (300 MHz) δ 5.65 (1H, m, H-3), 5.57 (1H, s, H-1), 5.28 (1H, br s, H-7), 2.16 (3H, s, COMe), 2.82 (1H, m, H-10α), 2.33 (1H, m, H-4α), 2.15–1.62 (7H, m), 1.62 (3H, s, Me-C_2), 1.56 (3H, s, Me-C_8), 1.40 (1H, ddd, $J=13.2$, 13.2, 3.1 Hz), 1.18 (2H, m), 0.75 (3H, s, Me-C_{4b}); ^{13}C NMR (75 MHz), see Table 1; MS (EI) *m/z* (%) 352 (M+2, 2), 350 (M$^+$, 6), 308 (15), 286 (18), 273 (35), 245 (17), 228 (100), 189 (12), 171 (22), 157 (24), 145 (46), 105 (56); HRMS *m/z* calcd for $C_{20}H_{27}$ $^{35}ClO_3$ 350.1648, found 350.1645.

4.3. Synthesis of key intermediate 25 via α-diazoketone 23

4.3.1. (5*R*)-6-Acetyl-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enone (16). *Method A*. A solution of commercial (*R*)-(−)-carvone (0.70 mL, 670 mg, 4.47 mmol) in THF (5 mL) was added dropwise over 30 min to a solution of LHMDS in THF–hexane [prepared by addition of BuLi (4.2 mL of a 1.6 M solution in hexane, 6.7 mmol) to a solution of hexamethyldisylazane (1.45 mL, 6.70 mmol) in THF (2 mL)] at −78 °C and the reaction mixture was stirred at the same temperature for 45 min. Pyruvonitrile (0.45 mL, 6.35 mmol) was added at once to the mixture and the stirring was continued for 10–15 min, and then quenched by the addition of saturated aq NH_4Cl solution and extracted with a 1:1 mixture of hexane/ether. The combined organic layers were washed with 5% aq HCl and brine and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography, using hexane as eluent, to give β-diketone **16** (801 mg, 93%) as an oil, which was shown to be a mixture of mainly two epimers at C-6 on the basis of ^1H NMR spectroscopic data. Partial separation of the slightly more polar epimer, with the acyl group at C-6 equatorially oriented, was able to be achieved in some cases. This epimer has the following spectral data: $[\alpha]_D^{22}$ −63.5 (1.7, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2972m, 2922m, 2636w, 1716s, 1663s, 1439m, 1361m, 1225m, 899m; ^1H NMR (300 MHz,) δ 6.72 (1H, m, H-3), 4.78 (1H, s, H-2″), 4.74 (1H, s, H′-2″), 3.48 (1H, d, $J=12.2$ Hz, H-6), 3.09 (1H, ddd, $J=11.1$, 10.1, 5.1 Hz, H-5), 2.4 (2H, m, H_2-4), 2.13 (3H, s, CO*Me*), 1.72 (3H, s, Me-C_2), 1.68 (3H, s, Me-$C_{1''}$); ^{13}C NMR (75 MHz) δ 205.60 (C_1), 196.31 (*CO*Me), 144.83 ($C_{1''}$), 144.73 (C_3), 134.97 (C_2), 113.09 ($C_{2''}$), 64.64 (C_6), 45.06 (C_5), 30.70 (C_4), 29.87 (CO*Me*), 19.55 (Me-$C_{1''}$), 15.40 (Me-C_2); MS (EI) *m/z* (%) 193 (M$^+$1, 6), 192 (M$^+$, 46), 177 (17), 159 (15), 149 (100), 135 (30), 121 (22), 109 (40); HRMS *m/z* calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1149.

Method B. A solution of (*R*)-(−)-carvone (4.17 mL, 3.90 g, 26 mmol) in THF (28 mL) was added dropwise over a period of 2 h to a solution of LDA in THF [prepared from BuLi (21 mL of a 1.6 M solution in hexane, 33.8 mmol), diisopropylamine (4.72 mL, 33.8 mmol) and THF (42 mL)] at −15 °C. The reaction mixture was allowed to warm to 0 °C (ca. 2.5 h) and stirred at this temperature for 30 min, cooled to −78 °C, and treated with acetaldehyde (3 mL, 52 mmol). After 30 min the reaction mixture was quenched by the addition of saturated aq NH_4Cl solution, poured into 5% aq $NaHCO_3$ and extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography, using hexane–AcOEt (from 9/1 to 1/1) as eluent, to give a mixture of diastereoisomeric β-hydroxy-ketones (4.97 g, 92%) as an oil. ^1H NMR spectra of this product showed that it was a mixture of four diastereoisomers in the ratio 4:3:1:1.

A solution of DMSO (4.16 mL, 53 mmol) in CH_2Cl_2 (14 mL) was slowly added to a solution of oxalyl chloride (2.45 mL, 27.2 mL) in CH_2Cl_2 (70 mL) at −60 °C, and the resulting solution was stirred for 30 min. A solution of the above obtained mixture of β-hydroxy-ketones (4.60 g, 23.3 mmol) in CH_2C1_2 (34 mL) was added via cannula over 30 min, and the mixture was stirred for an additional 15 min; Et_3N (16.6 mL, 118.5 mmol) was added, and the resulting mixture was stirred for 15 min at −60 °C and then warmed slowly to rt (ca. 2 h). The reaction was quenched with water and extracted with CH_2C1_2. The combined organic extracts were washed successively with 5% aq HCl solution, 10% aq Na_2CO_3 solution and brine, filtered and dried over $MgSO_4$. Purification of the residue left after evaporation of the solvent by chromatography, using hexane/AcOEt 9:1 as eluent, gave diketone **16** (4.10 g, 90%) as an oil.

4.3.2. (5*S*,6*S*)-6-Acetyl-6-(3,3-diethoxypropyl)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enone (17). A solution of β-diketone **16** (1.30 g, 6.76 mmol) in THF (2 mL) was added dropwise to a stirring suspension of NaH (340 mg, 14.2 mmol, 2.1 equiv) in THF (8 mL) at 0 °C. When the evolution of hydrogen had ceased, a solution of Bu_4NHSO_4 (2.37 g, 6.76 mmol) in DMF (3 mL) was carefully added at the same temperature. After the evolution of hydrogen has ceased, the reaction mixture was warmed to rt and sonicated in a water bath for 15–20 min at 20 °C. The resulting white slurry was cooled to 0 °C and 3-iodopropanaldehyde diethylacetal[37] (2.61 g, 10.14 mmol) was added. The mixture was stirred at 5 °C for 12 h, then poured into water and extracted with hexane. The organic layer was washed with 5% aq sodium thiosulphate solution and brine, dried over Na_2SO_4 and then concentrated under vacuum. The crude oil was purified by chromatography, using hexane/AcOEt 9:1 as eluent, to yield compound **17**

(1.76 g, 93%) as a yellowish oil. $[\alpha]_D^{23}$ +48 (2.1, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2973s, 2926m, 2887m, 1700s, 1660s, 1443m, 1364m, 1189m, 1130m, 1130s, 1064s; ^{1}H NMR (300 MHz) δ 6.70 (1H, m, H-3), 4.83 (1H, s, H-2″), 4.71 (1H, s, H′-2″), 4.42 (1H, dd, J=5.6, 5.6 Hz, H-3′), 3.57 and 3.43 (4H, two m, 2×OCH_2), 2.91 (1H, dd, J=6.3, 6.2 Hz, H-5), 2.5 (2H, m, H_2-4), 2.16 (3H, s, CO*Me*) 1.78 (3H, m, Me-C_2), 1.68 (3H, s, Me-$C_{1''}$), 1.17 (6H, two t, J=7.0 Hz, 2×OCH_2*Me*); ^{13}C NMR (75 MHz) δ 208.37 (C_1), 198.04 (*CO*Me), 144.70 ($C_{1''}$), 143.92 (C_3), 134.64 (C_2), 115.21 ($C_{2''}$), 102.58 ($C_{3'}$), 61.02 and 60.62 (2×OCH_2), 65.13 (C_6), 48.31 (C_5), 28.34 (C_4), 30.34 (CO*Me*), 28.81 ($C_{2'}$), 28.36 ($C_{1'}$), 22.50 (Me-$C_{1''}$), 16.30 (Me-C_2), 15.21 (2× OCH_2*CH_3*); MS (EI) *m/z* (%) 323 (M^++1, 6), 322 (M^+, 1), 277 (90), 265 (19), 248 (11), 234 (20), 209 (15); HRMS *m/z* calcd for $C_{19}H_{30}O_4$ 322.2144, found 322.2136.

4.3.3. 3-((1*S*,6*S*)-1-Acetyl-3-methyl-2-oxo-6-(prop-1-en-2-yl)cyclohex-3-enyl)propanal (18). A solution of ketal **17** (794 mg, 2.46 mmol) and PPTS (306 mg, 1.5 mmol) in 4% aq acetone (50 mL) was heated at reflux for 1 h. The mixture was cooled down to rt, then poured into water and extracted with ether. The organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvent left a residue that was purified by column chromatography, using hexane/AcOEt 8:2 as eluent, to give aldehyde **18** (573 mg, 93%) as a colourless oil. $[\alpha]_D^{21}$ +63 (1.1, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2923m, 1723s, 1701s, 1657s, 1439m, 1355m, 1187m, 1044w, 904w; ^{1}H NMR (300 MHz) δ 9.68 (1H, s, H-3), 6.73 (1H, m, H-4′), 4.84 (1H, s, H-2″), 4.72 (1H, s, H′-2″), 2.83 (1H, dd, J=5.9, 5.9 Hz, H-6′), 2.5 (1H, ddd, J=13.4, 8.5, 6.4 Hz, H-5′), 2.14 (3H, s, CO*Me*), 1.78 (3H, m, Me-$C_{3'}$), 1.66 (3H, s, Me-$C_{1''}$); ^{13}C NMR (75 MHz) δ 207.86 ($C_{2'}$), 200.91 (C_1), 197.86 (*CO*Me), 144.45 ($C_{1''}$), 144.08 ($C_{4'}$), 134.78 ($C_{3'}$), 116.04 ($C_{2''}$), 64.71 ($C_{1'}$), 49.63 ($C_{6'}$), 39.23 (C_2), 30.45 (*CH_3*CO), 28.87 ($C_{5'}$), 25.64 (C_3), 22.32 (Me-$C_{1''}$), 16.25 (Me-$C_{3'}$); MS (EI) *m/z* (%) 249 (M^++1, 2), 248 (M^+, 5), 236 (33), 221 (15), 161 (54), 149 (13), 135 (24), 121 (100), 109 (17); HRMS *m/z* calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1408.

4.3.4. (*E*)-5-((1*S*,6*S*)-1-Acetyl-3-methyl-2-oxo-6-(prop-1-en-2-yl)cyclohex-3-enyl)-2-methylpent-2-enal (19). A solution of aldehyde **18** (1.00 g, 4.05 mmol) and commercial (α-formylethylidene)triphenyl phosphorane (1.70 g, 5.33 mmol) in benzene (32 mL) was stirred at reflux for 48 h. The mixture was allowed to cool to rt and then treated with saturated aq NH_4Cl solution. The aqueous phase was separated and extracted with ethyl ether. The combined organic extracts were washed with water and brine and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was purified by chromatography, using hexane/AcOEt 9:1 as eluent, to afford the α,β-unsaturated aldehyde **19** (1.00 g, 86%) as a colourless oil: $[\alpha]_D^{23}$ +147 (1.9, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2921w, 1684s, 1654s, 1644s, 1438m, 1360m, 1179w, 904w; ^{1}H NMR (300 MHz) δ 9.34 (1H, s, H-1), 6.74 (1H, m, H-4′), 6.38 (1H, ddd, J=7.3, 7.3, 1.2 Hz, H-3), 4.84 (1H, s, H-2″), 4.74 (1H, s, H′-2″), 2.90 (1H, dd, J=7.0, 7.0 Hz, H-6′), 2.65 (1H, br d, J=19.8 Hz, H-4), 2.50 (1H, br d, J=19.8 Hz, H′-4), 2.4 (1H, ddd, J=13.0, 11.1, 5.3 Hz, H-5′), 2.14 (3H, s, CO*Me*), 1.83 (3H, m, Me-$C_{3'}$), 1.79 (3H, s, Me-C_2), 1.79 (3H, s, Me-$C_{1''}$); ^{13}C NMR (75 MHz) δ 207.68 ($C_{2'}$), 197.70 (*CO*Me), 195.06 (C_1), 153.05 (C_3), 144.38 ($C_{4'}$), 144.38 ($C_{1''}$), 139.72 (C_2), 134.72 ($C_{3'}$), 115.82 ($C_{2''}$), 65.36 ($C_{1'}$), 49.04 ($C_{6'}$), 30.32 (*Me*CO), 31.85 (C_4), 29.03 ($C_{5'}$), 24.12 (C_5), 22.24 (Me-$C_{1''}$), 16.33 (Me-$C_{3'}$), 9.11 (Me-C_2); MS (EI) *m/z* (%) 289 (M^++1, 1), 288 (M^+, 2), 260 (43), 245 (9), 220 (12), 205 (27), 192 (91), 177 (50), 163 (100), 149 (58), 135 (31), 121 (98), 105 (30), 91 (51); HRMS *m/z* calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1726.

4.3.5. (5*S*,6*S*)-6-Acetyl-2-methyl-6-((E)-4-methylhexa-3,5-dienyl)-5-(prop-1-en-2-yl)cyclohex-2-enone (20). Methyltriphenylphosphonium bromide (1.38 g, 3.9 mmol) was suspended in toluene (45 mL) and the mixture was cooled to −20 °C. A solution of KHMDS in toluene (1 M, 3.9 mL, 3.9 mmol) was added dropwise and the solution was allowed to warm to rt and then stirred for 15 min. After cooling to −20 °C, compound **19** (930 mg, 3.3 mmol) in toluene (45 mL) was added slowly and the mixture stirred while it was allowed to warm to rt. After 1 h, the mixture was treated with saturated aq NH_4Cl, poured into water and extracted with a 1:1 mixture of hexane/ethyl ether. The combined organic layers were washed sequentially with diluted hydrochloric acid, 5% aq $NaHCO_3$, and brine and dried over Na_2SO_4. Evaporation of the solvent and chromatography, using hexane/AcOEt 9:1 as eluent, provided compound **20** (849 mg, 92%) as an oil. $[\alpha]_D^{23}$ +81 (3.2, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2925m, 2353w, 1700m, 1660s, 1441w, 1361w, 1180w, 899w; ^{1}H NMR (300 MHz) δ 6.74 (1H, m, H-3), 6.30 (1H, dd, J=17.5, 10.7 Hz, H-5′), 5.40 (1H, dd, J=7.3, 7.3 Hz, H-3′) 5.07 (1H, d, J=17.4 Hz, H-6′), 4.92 (1H, d, J=10.7 Hz, H′-6), 4.85 (1H, s, H-2″), 4.72 (1H, s, H′-2″), 2.93 (1H, dd, J=6.4, 6.4 Hz, H-5), 2.60 (1H, br d, J=19.4 Hz, H-2′), 2.50 (1H, br d, J=19.4 Hz, H′-2′), 2.27 (1H, ddd, J=12.6, 11.4, 4.5 Hz, H-4), 2.15 (3H, s, CO*Me*), 1.81 (3H, br s, Me-C_2), 1.68 (3H, s, Me-$C_{4'}$), 1.68 (3H, s, Me-$C_{1''}$); ^{13}C NMR (75 MHz) δ 208.30 (C_1), 198.00 (*CO*Me), 144.80 ($C_{1''}$), 143.83 (C_3), 141.25 ($C_{3'}$), 134.83 (C_2), 134.83 ($C_{4'}$), 131.61 ($C_{5'}$), 115.26 ($C_{2''}$), 110.97 ($C_{6'}$), 65.44 (C_6), 48.58 (C_5), 33.26 ($C_{2'}$), 30.38 (*Me*CO), 28.96 (C_4), 22.48 ($C_{1'}$), 22.24 (Me-$C_{1''}$), 16.38 (Me-C_2), 11.56 (Me-$C_{4'}$); MS (CI) *m/z* 287 (M^++1, 50), 219 (23), 205 (12), 192 (100), 177 (27), 163 (5), 151 (21); HRMS *m/z* calcd for $C_{19}H_{27}O_2$ [M+H^+] 287.2011, found 287.2002.

4.3.6. (4a*S*,4b*R*,8a*R*,10a*S*)-10a-Acetyl-2,4b,8-trimethyl-4,4a,5,6,8a,9,10,10a-octahydrophenanthren-1(4*bH*)-one (21). A solution of triene **20** (510 mg, 1.8 mmol) in toluene (20 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 °C for 120 h, the solvent was eliminated on a rotary evaporator and the residue was chromatographed, using 9:1 hexane/AcOEt as eluent, to give the Diels–Alder adduct **21** as a solid (460 mg, 90%). Mp 83–84 °C (MeOH); $[\alpha]_D^{21}$ −104 (0.6, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2963s, 1703m, 1660s, 1437m, 1379m, 1147w; ^{1}H NMR (400 MHz) δ 6.90 (1H, m, H-3), 5.30 (1H, br s, H-7), 3.06 (1H, dddd, J=19.1, 11.5, 2.5, 2.5 Hz, H-4α), 2.85 (1H, ddd, J=14.5, 2.6, 2.7 Hz, H-10), 2.33 (1H, m, H-4β), 2.17 (3H, s, CO*Me*), 2.10 (1H, m, H-6), 1.97 (1H, m, H′-6), 1.86 (1H, m, H-9), 1.85 (1H, m, H-8a), 1.79 (1H, dd, J=13.0, 5.0 Hz, H-4a), 1.73 (1H, m, H-5), 1.70 (3H, m, Me-C_2), 1.60 (3H, s, Me-C_8), 1.49 (1H, ddd, $J=14.5$, 14.0, 3.0 Hz, H′-10), 1.32 (1H, ddd, $J=15.0$, 13.0, 3.0 Hz, H′-9), 1.15 (1H, m, H′-5), 0.70 (3H, s, Me-C_{4b}); ^{13}C NMR (100 MHz), see Table 1; MS (EI) *m/z* (%) 287 ($M^+ + 1$, 3), 286 (M^+, 10), 268 (9), 243 (100), 229 (8), 165 (20), 147 (26), 135 (24), 121 (94), 109 (41); HRMS *m/z* calcd for $C_{19}H_{26}O_2$ 286.1933, found 286.1934. Anal. Calcd for $C_{19}H_{26}O_2$: C 79.68, H 9.15; found: C 79.54, H 9.19.

4.3.7. (4a*S*,4b*R*,8a*R*,10a*R*)-10a-(2-Diazoacetyl)-2,4b,8-trimethyl-4,4a,5,6,8a,9,10,10a-octahydrophenanthren-1(4*bH*)-one (23). A solution of methyl-ketone **21** (1.50 g, 5.2 mmol) in THF (7 mL) was added dropwise over a period of 30 min to a THF solution of LHMDS [prepared from 1.6 M BuLi in hexanes (3.72 mL, 6 mmol), hexamethyldisilazane (1.30 mL, 6 mmol), and THF (4.5 mL)] at −78 °C. The solution was stirred for an additional 30 min at −78 °C and then treated with 2,2,2-trifluoroethyltrifluoroacetate (1.7 mL, 12 mmol). The reaction mixture was stirred for 10 min and then poured into 5% aq HCl solution, and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum to give crude β-diketone **22**, which was used in the next step without further purification.

Triethylamine (1.25 mL, 9 mmol), H_2O (122 μL, 6.7 mmol), and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (4.5 g, 18.6 mmol) were added to a solution of the above obtained β-diketone **22** in CH_3CN (14 mL) at rt. Although the reaction is usually complete in 3 h under these conditions, in this case, the mixture was allowed to stir overnight (12 h). Then, the reaction mixture was diluted with ether and washed with 10% aq NaOH solution and brine, and dried over Na_2SO_4. The solvent was removed under vacuum, leaving a brown oil that was chromatographed, using hexane/AcOEt 9:1, to afford α-diazoketone **23** (1.30 g, 80% from **21**) as a colourless oil. $[\alpha]_D^{25}$ −42 (2.1, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 2938m, 2104s, 1665s, 1620m, 1334s, 1148w; ^{1}H NMR (300 MHz) δ 6.92 (1H, m, H-3), 5.59 (1H, s, CHN_2), 5.27 (1H, br s, H-7), 3.09 (1H, dddd, $J=19.2$, 11.7, 2.5, 2.5 Hz, H-4α), 2.47 (1H, m, H-10), 2.33 (1H, ddd, $J=19.2$, 5.8, 5.8 Hz, H-4β), 2.09–1.96 (2H, m), 1.92 (2H, m), 1.85 (1H, dd, $J=11.0$, 4.0 Hz, H-8a), 1.75 (3H, m, Me-C_2), 1.73 (1H, m), 1.60 (3H, s, Me-C_8), 1.57–1.38 (2H, m), 1.12 (1H, $J=12.0$, 12.0, 8.0 Hz, H-1β), 0.81 (3H, s, Me-C_{4b}); ^{13}C NMR (100 MHz), see Table 1; MS (EI) *m/z* (%) 313 ($M^+ + 1$, 5), 312 (M^+, 15), 284 (28), 259 (10), 256 (14), 243 (21), 147 (36), 135 (20), 121 (100), 109 (35), 91 (54); HRMS *m/z* calcd for $C_{19}H_{24}N_2O_2$ 312.1838, found 312.1832.

4.3.8. 19-Nor-*ent*-trachylob-3-en-14,15-dione (24). A solution of α-diazoketone **23** (930 mg, 3 mmol) in toluene (90 mL) was added dropwise over a period of 4 h over a solution of bis(*N-tert*-butylsalicylaldiminate)Cu(II) (70 mg, 0.15 mmol) in refluxing toluene (90 mL). When the addition was complete, the solvent was evaporated under vacuum and the residue was purified by chromatography, using hexane/AcOEt 8:2 as eluent, to give compound **24** (803 mg, 95%) as a white solid. Mp 127–128.5 °C (from MeOH); $[\alpha]_D^{21}$ −26 (3.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2926m, 1757m, 1703s, 1454w, 1379w, 1297w, 1216w; ^{1}H NMR (400 MHz) δ 5.27 (1H, br s, H-3), 2.58 (1H, d, $J=7.8$ Hz, H-13), 2.49 (1H, ddd, $J=8.0$, 3.0, 1.8 Hz, H-12), 2.18 (1H, ddd, $J=13.0$, 9.0, 3.0 Hz, H-11), 2.02 (1H, dd, $J=17.0$, 5.0 Hz, H-9), 1.98 (1H, m, H′-11), 1.94 (1H, m, H-6), 1.92 (2H, m, H_2-2), 1.79 (1H, m, H′-6), 1.72 (2H, m, H_2-7), 1.58 (3H, s, Me-C_4), 1.49 (1H, m, H-5), 1.41 (1H, m, H-1), 1.39 (3H, s, Me-C_{16}), 1.07 (1H, $J=12.0$, 12.0, 8.0 Hz, H-1β), 0.71 (3H, s, Me-C_{10}); ^{13}C NMR (100 MHz), see Table 1; MS (EI) *m/z* (%) 285 ($M^+ + 1$, 18), 284 (M^+, 100), 269 (10), 255 (9), 241 (5), 122 (31), 107 (21), 91 (24), 77 (15); HRMS *m/z* calcd for $C_{19}H_{24}O_2$ 284.1776, found 284.1770. Anal. Calcd for $C_{19}H_{24}O_2$: C 80.24, H 8.51; found: C 80.06, H 8.46.

4.3.9. 3β,18-Cyclo-*ent*-trachylobane-14,15-dione (25). Diethyl zinc (1.0 M solution in hexane, 35.8 mL, 35.8 mmol) and diiodomethane (5.5 mL, 54 mmol) were added to a solution of **24** (807 mg, 4.5 mmol) in toluene (72 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 with water and brine, dried over $MgSO_4$, and concentrated to give a solid. Chromatography, using hexane/AcOEt 8:2 as eluent, yielded the diketone **25** (802 mg, 94%) as a white solid. Mp 142–143 °C (from MeOH); $[\alpha]_D^{27}$ −73 (2.7, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2926m, 2856m, 1754m, 1704s, 1444m, 1360m, 1297w, 1177w, 1016w, 918w; ^{1}H NMR (400 MHz) δ 2.55 (1H, d, $J=8.0$ Hz, H-13), 2.44 (1H, ddd, $J=8.0$, 5.0, 2.2 Hz, H-12), 2.12 (1H, ddd, $J=13.6$, 9.6, 3.1 Hz, H-11), 1.90 (1H, ddd, $J=7.3$, 7.3, 1.8 Hz, H′-11), 1.95–1.75 (2H, m, H-6 and H-7), 1.85 (1H, m, H-9), 1.72 (1H, m, H-2), 1.66 (1H, m, H′-7), 1.64 (1H, m, H-3), 1.60 (1H, m, H′-2), 1.39 (3H, s, Me-C_{16}), 1.20 (1H, ddd, $J=13.1$, 6.2, 6.2 Hz, H-1), 0.97 (1H, m, H-5), 0.94 (3H, s, Meα-C_4), 0.71 (3H, s, Me-C_{10}), 0.62–0.50 (2H, m, H′-6 and H′-1), 0.43 (1H, dd, $J=9.3$, 4.0 Hz, H-18α), −0.03 (1H, dd, $J=5.7$, 4.3 Hz, H-18β); ^{13}C NMR (100 MHz), see Table 2; MS (EI) *m/z* (%) 299 ($M^+ + 1$, 18), 298 (M^+, 58), 256 (100), 201 (21), 187 (21), 159 (15), 107 (22), 91 (43); HRMS *m/z* calcd for $C_{20}H_{26}O_2$ 298.1933, found 298.1932.

4.4. Completion of trachylobane, atisane, beyerane and kaurane frameworks from key intermediate 25

4.4.1. 15β-Hydroxy-*ent*-trachyloban-14-one (26a) and 15α-hydroxy-*ent*-trachyloban-14-one (26b). A solution of diketone **25** (72 mg, 0.24 mmol) and PtO_2 (15 mg) in AcOH (2 mL) was stirred under a hydrogen atmosphere (4 atm) at 35–40 °C for 48 h. The reaction mixture was then filtered through a Celite pad eluting with AcOEt and concentrated. The crude product was purified by chromatography, using hexane/AcOEt 7:3 as eluent, to afford hydroxy-ketone **26a** (46.5 mg, 64%) as a solid, followed by epimeric **26b** (26 mg, 31%) as a white solid.

Data for **26a**. Mp 155–156 °C (from pentane) $[\alpha]_D^{21}$ −48 (1.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3389s, 2921s, 2842m, 1692s, 1416m, 1442m, 1114m, 1080m; ^{1}H NMR (400 MHz) δ 3.61 (1H, s, H-15), 2.00 (1H, m, H-11), 1.95 (1H, dd, $J=8.0$, 5.0 Hz, H-9), 1.90 (1H, m, H-12), 1.78 (3H, m, H-13, H′-11 and H-7α), 1.71 (1H, m, H-6), 1.51 (3H, m,

Table 2. ^{13}C NMR chemical shifts (δ) in ppm for compounds **25–29**, **31–34** and **36–41**[a]

Compound	**24**	**25**	**26a**	**26b**	**27**	**28a**	**28b**	**29a**	**29b**	**31**	**32**	**33**	**34**	**36**	**37**	**38**	**39**	**40**	**41**
C-1	34.74	33.45	38.91	39.09	33.93	33.10	32.93	38.87	38.71	38.92	39.64	40.67	39.11	39.88	40.76	40.59	40.69	40.13	40.17
C-2	22.07	21.49	18.14	19.00	22.25	21.60	21.55	18.82	18.82	18.56	18.35†	18.79	18.03	18.51	17.41	18.56	18.63†	19.98†	18.80†
C-3	120.79	19.16	42.06	42.03	19.30	19.22	19.26	41.92	41.99	41.90	42.04	41.83	42.02	41.94	41.85	41.62	41.67	41.92	41.84
C-4	134.32	15.64	32.98	32.93	15.84	15.84	15.85	32.93	32.95	32.97	32.99	32.95	34.20	33.14	32.96	32.81	32.84	33.23	33.21
C-5	57.73	49.68	54.82	54.94	50.40	50.39	50.36	55.42	55.16	52.07	55.79	56.09	55.17	55.06	55.86	54.59	54.82	55.76	55.58
C-6	19.76	18.58	18.14	18.01	19.09	18.81	18.79	21.24	20.91	18.03	19.05†	19.90	19.11	19.41‡	19.59	18.56	19.03†	19.03†	18.62†
C-7	21.42	19.85	28.11	26.24	27.94	22.65	23.09	28.71	26.24	28.64	26.83	35.46	32.93	30.80§	34.88	28.73	29.22	33.42	32.85
C-8	55.92	55.62	50.26	51.58	49.81	66.06	66.78	52.73	53.00	50.22	66.55	43.48	44.62	55.16	42.73	48.74	49.70	54.72	53.80
C-9	47.24	57.36	49.66	57.08	45.83	46.24	45.26	49.23	41.89	54.82	55.07	43.11	50.47	46.93	43.00	56.56	56.47	52.66	52.68
C-10	37.26	37.22	37.18†	37.99†	35.85†	37.903	38.78	37.93	37.83	37.99	37.54	36.33	37.71	37.51†	36.65	37.70	37.32	38.49	38.75
C-11	19.73	21.23	18.76	19.22	19.43	22.68	28.61	18.23	18.28	17.08	29.98	18.79	22.38	19.31‡	18.75	17.59	17.79	16.61	16.55
C-12	43.09	43.15	34.94	35.34	34.85	32.17	31.71	32.88	33.53	38.37	37.14	20.53	44.26	30.60§	20.94	32.67	33.48	18.18	18.86
C-13	47.14	47.09	39.96	36.69	40.14	46.03	40.14	45.50	46.42	42.89	41.77	27.22	132.55	37.72†	24.30	33.97	35.68	39.87	36.76
C-14	207.41†	206.70†	212.11	214.10	212.42	210.35†	210.84†	215.78	217.93	206.95	214.57	79.50	133.20	81.07	79.99	77.30	76.55	79.32	79.43
C-15	206.40†	207.40†	77.22	82.01	77.12	209.42†	209.14†	85.68	71.10	56.94	128.91	79.32	87.76	220.03	78.66	209.89	211.85	221.95	218.8
C-16	49.20	49.01	37.54†	36.89†	38.63†	46.14	45.19	41.45	35.83	37.88	146.15	25.75	77.20	49.05	26.59	37.70	37.32	45.78	45.60
C-17	12.90	12.83	17.95	16.39	17.95	14.85	14.50	19.24	13.41	20.98	20.02	17.87	25.64	24.20	17.78	12.77	12.92	9.72	9.58
C-18	21.34	21.91	21.2	21.59	23.71	21.34	21.44	33.49	33.55	21.42	21.67	33.47	33.65	33.60	33.39	33.33	34.03	33.40	33.31
C-19		21.19	33.22	33.27	21.57	23.67	23.72	21.71	21.71	33.09	33.57	21.92	21.95	21.93	21.87	21.80	21.89	21.53	21.45
C-20	11.26	11.28	14.01	13.52	11.31	11.54	11.59	13.60	13.67	13.76	13.11	15.81	15.65	13.63	15.67	15.52	15.75	16.54	16.46
Others		—	—	—	—	—	—	—	—	—	—	—	—	—	[b]	[c]	—	—	[d]

[a] The signals with the same superscript may be interchanged within the same column.
[b] OCH at C-14 at 161.21 ppm.
[c] OCH at C-14 at 160.68 ppm.
[d] OCO*Me* and O*CO*Me at C-14 at 21.56 and 170.41 ppm, respectively.

H′-6, H-2 and H-1), 1.35 (1H, m, H-3), 1.34 (3H, s, Me-C_{16}), 1.34 (1H, m, H′-2), 1.20 (1H, ddd, J=12.9, 12.9, 4.2 Hz, H′-7β), 1.09 (1H, m, H′-3), 0.87 (3H, s, Meβ-C_4), 0.81 (3H, s, Meα-C_4), 0.80 (1H, m, H′-1), 0.74 (1H, m, H-5), 0.75 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz), see Table 2; MS (EI) m/z (%) 303 (M^+ + 1, 25), 302 (M^+, 100), 284 (65), 269 (50), 245 (54), 199 (14), 165 (62), 147 (36), 137 (43), 123 (66); HRMS m/z calcd for $C_{20}H_{30}O_2$ 302.2246, found 302.2244. Anal. Calcd for $C_{20}H_{30}O_2$: C 79.42, H 10.00; found: C 79.61, H 9.86.

Data for **26b**. Mp 180–183 °C (from cold pentane); $[\alpha]_D^{21}$ −44 (0.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3393s, 2914s, 2837m, 1690s, 1450m, 1388m, 1082m, 970w; ^{1}H NMR (400 MHz) δ 3.75 (1H, s, H-8), 2.10 (1H, ddd, J=12.8, 3.2, 3.2 Hz, H-7α), 1.99 (1H, m, H-11), 1.78 (1H, m, H′-11), 1.72 (1H, m, H-12), 1.68 (1H, m, H-13), 1.61 (1H, m, H-9), 1.56 (2H, m, H_2-2), 1.41 (1H, m, H-6), 1.40 (1H, m, H-1), 1.31 (1H, m, H-3), 1.29 (1H, m, H′-6), 1.14 (3H, s, Me-C_{16}), 1.05 (1H, m, H′-3), 0.98 (1H, m, H′-7), 0.84 (3H, s, Meβ-C_4), 0.78 (3H, s, Meα-C_4), 0.71 (1H, m, H′-1), 0.69 (3H, s, Me-C_{10}), 0.68 (1H, m, H-5); ^{13}C NMR (75 MHz), see Table 2; MS (EI) m/z (%) 303 (M^+ + 1, 14), 302 (M^+, 51), 287 (20), 242 (42), 227 (13), 178 (21), 165 (60), 137 (100), 119 (67), 91 (55); HRMS m/z calcd for $C_{20}H_{30}O_2$ 302.2246, found 302.2234.

4.4.2. 15β-Hydroxy-3β,18-cyclo-*ent*-trachyloban-14-one (27).

(A) *By catalytic hydrogenation of* **25**. A heterogeneous mixture of ketone **25** (75 mg, 0.25 mmol), 10% Pt/C (15 mg) and AcOEt (2 mL) was stirred under a hydrogen atmosphere (4 atm) at rt for 24 h. The reaction mixture was filtered and the filtrate was concentrated at reduced pressure. Purification of the residue by column chromatography, using hexane/AcOEt 7:3 as eluent, afforded **27** (72 mg, 95%) as a white solid.

(B) *By NaBH₄ reduction of* **25**. A solution of ketone **25** (433.2 mg, 1.44 mmol) in a 1:1 mixture of MeOH/CH_2Cl_2 (20 mL) was cooled to 0 °C and $NaBH_4$ (106 mg, 2.88 mmol) was added in small portions over a period of 45 min. Stirring was continued for 30 min at the same temperature, and then the reaction mixture was quenched with water and stirred for a few minutes until the evolution of hydrogen ceased. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent left a residue that was purified as above to give hydroxy-ketone **27** (420.2 mg, 96%) as a solid. Mp 174–175 °C (from MeOH); $[\alpha]_D^{27}$ +40 (0.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3393m, 2929s, 1694s, 1465m, 1377w, 1071m; ^{1}H NMR (400 MHz) δ 3.58 (1H, s, H-15), 2.05 (1H, ddd, J=12.8, 10.0, 2.6 Hz, H-11β), 1.92 (3H, m, H-9, H-12 and H-2), 1.86 (2H, m, H-13 and H-11α), 1.82 (1H, m, H-7), 1.75 (1H, m, H′-2), 1.66 (2H, m, H_2-6), 1.34 (3H, s, Me-C_{16}), 1.32 (1H, m, H-1), 1.23 (1H, m, H′-7), 0.96 (1H, m, H-5), 0.93 (3H, s, Meβ-C_4), 0.72 (3H, s, Me-C_{10}), 0.61 (1H, m, H′-1), 0.58 (1H, m, H′-3), 0.39 (1H, dd, J=9.2, 4.0 Hz, H-18α), −0.03 (1H, dd, J=5.8, 4.0 Hz, H-18β); ^{13}C NMR (75 MHz), see Table 2; MS (EI) m/z (%) 300 (M^+, 1), 282 (4); 258 (11), 240 (6), 227 (6), 185 (5), 145 (9), 119 (20), 105 (29), 83 (100); HRMS m/z calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2093.

4.4.3. 3β,18-Cyclo-16αH-*ent*-atisane-14,15-dione (28a) and 3β,18-cyclo-16βH-*ent*-atisane-14,15-dione (28b).

Cyclopropyl diketone **25** (31 mg, 0.10 mmol) was dissolved in a 3:1 mixture of THF/MeOH (2 mL) and a 0.1 M solution of SmI_2 in THF was added dropwise until persistence of the blue colour. The reaction mixture was stirred at rt for 1 h and 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, using 9.5:0.5 hexane/AcOEt as eluent, to give atisane–dione **28a** (19 mg, 61%) followed by the C-16 epimer **28b** (9 mg, 28%).

Data for **28a**. Mp 190–191 °C (MeOH); $[\alpha]_D^{29}$ −52 (1.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2935s, 2862m, 1728s, 1696s, 1444m, 1060m, 1032m, 705m, 649m; ^{1}H NMR (400 MHz) δ 2.55 (1H, dd, J=19.9, 3.8 Hz, H-13), 2.41 (1H, m, H′-13), 2.38 (1H, m, H-12), 2.30 (1H, m, H-11), 2.25 (1H, m, H-16), 2.08 (1H, m, H′-11), 1.82 (1H, m, H-7), 1.67 (2H, m, H_2-6), 1.61–1.49 (3H, m, H′-7 and H_2-2), 1.45 (1H, m, H-9), 1.38 (1H, m, H-1), 1.24 (3H, d, J=7.0 Hz, Me-C_{16}), 0.95 (1H, m, H-5), 0.94 (3H, s, Me-C_4), 0.73 (3H, s, Me-C_{10}), 0.55 (2H, m, H-3 and H′-1), 0.42 (1H, dd, J=9.2, 4.0 Hz, H-18α), −0.05 (1H, dd, J=5.8, 4.0 Hz, H-19β); ^{13}C NMR (75 MHz), see Table 2; MS (EI) m/z (%) 301 (M^+ + 1, 10), 300 (M^+, 25), 272 (39), 258 (100), 243 (35), 230 (31), 217 (20), 176 (30), 162 (34), 121 (29), 197 (27), 91 (26); HRMS m/z calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2099.

Data for **28b**. Mp 126–127 °C (cold MeOH); $[\alpha]_D^{29}$ −36 (0.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2979s, 2853m, 1731s, 1700s, 1419m, 1378m, 1040m, 968w; ^{1}H NMR (400 MHz) δ 2.54 (1H, dd, J=19.8, 3.9 Hz, H-13), 2.38 (1H, m, H′-13), 2.32 (1H, m, H-12), 2.40–2.20 (3H, m, H-16 and H_2-11), 2.10–1.20 (8H, m, H-9, H_2-7, H_2-6, H_2-2 and H-1), 1.10 (3H, d, J=7.0 Hz, Me-C_{16}), 0.95 (1H, m, H-5), 0.93 (3H, s, Me-C_4), 0.72 (3H, s, Me-C_{10}), 0.62 (2H, H-3, H′-1), 0.42 (1H, dd, J=9.0, 4.0 Hz, H-18α), −0.05 (1H, dd, J=5.8, 4.0 Hz, H-18β); ^{13}C NMR (100 MHz), see Table 2; MS (EI) m/z (%) 301 (M^+ + 1, 4), 300 (M^+, 21), 286 (14), 272 (40), 258 (100), 243 (40), 230 (44), 217 (35), 176 (38), 162 (44), 121 (72), 107 (75), 91 (94); HRMS m/z calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2088.

4.4.4. 15β-Hydroxy-16αH-*ent*-atisan-14-one (29a) and 15α-hydroxy-16αH-*ent*-atisan-14-one (29b).

Hydrogenation of diketone **28a** (35 mg, 0.12 mmol) as described above for **25** (4.4.1) gave a mixture of epimeric hydroxy-atisanones **29a** and **29b**, which were separated by chromatography using hexane/AcOEt 7:3, to afford, in order of elution, atisanone **29b** (8.2 mg, 23%) and C-15 epimeric **29a** (16 mg, 45%).

Data for **29a**. Mp 164–166 °C (cold pentane); $[\alpha]_D^{22}$ +16 (0.8, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3512m, 2939s, 2842m, 1716s, 1692s, 1459m, 1386m, 1367m, 1016m; ^{1}H NMR (400 MHz) δ 3.18 (1H, d, J=3.0 Hz, H-15), 2.54 (1H, ddd, J=12.8, 3.8, 2.8 Hz, H-7α), 2.27 (1H, dd, J=19.0, 3.2 Hz, H-13), 2.20 (1H, ddd, J=19.0, 5.3, 2.6 Hz, H′-13), 1.95 (1H, m, H-12), 1.84 (1H, m, H-6), 1.65 (1H, m, H-16), 1.58 (1H, m, H-1), 1.57 (2H, m, H_2-2), 1.39 (3H, m, H_2-11, H′-6 and H-3), 1.34 (1H, m, H-9), 1.16 (3H, d, J=7.1 Hz, Me-

C_{16}), 1.12 (1H, m, H′-3), 0.86 (2H, m, H-1 and H-7β), 0.85 (3H, s, Meβ-C_4), 0.78 (1H, m, H-5), 0.78 (3H, s, Meα-C_4), 0.69 (3H, s, Me-C_{10}); ^{13}C NMR (100 MHz), see Table 2; MS (EI) *m/z* (%) 305 (M^+ +1, 15), 304 (M^+, 75), 289 (22.4), 245 (100), 148 (66), 123 (36); HRMS *m/z* calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2399.

Data for **29b**. Mp 145–147 °C (cold MeOH); $[\alpha]_D^{29}$ +20 (0.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3493s, 2914s, 2863m, 1705s, 1465m, 1393m, 1055m, 1009m; ^{1}H NMR (400 MHz) δ 3.45 (1H, dd, *J*=9.6, 2.1 Hz, H-15), 2.29 (1H, dd, *J*=19.0, 2.8 Hz, H-13), 2.15 (1H, ddd, *J*=19.0, 4.5, 2.3 Hz, H′-13), 2.02 (1H, m, H-7), 2.01 (1H, m, H-16), 1.92 (3H, m, H-12, H-9 and H-6), 1.55 (1H, m, H-1), 1.52 (2H, m, H_2-2), 1.39 (3H, M, H_2-11, H′-7 and H-3), 1.36 (1H, m, H′-6), 1.12 (1H, m, H′-3), 1.09 (3H, d, *J*=7.3 Hz, Me-C_{16}), 0.86 (1H, m, H′-1), 0.85 (3H, s, Meβ-C_4), 0.79 (1H, m, H-5), 0.78 (3H, s, Meα-C_4), 0.69 (3H, s, Me-C_{10}); ^{13}C NMR (100 MHz), see Table 2; MS (EI) *m/z* (%) 305 (M^+ +1, 8), 304 (M^+; 39), 289 (10), 271 (14), 245 (57), 178 (40), 149 (92), 137 (50), 123 (85), 109 (60), 95 (52), 69 (72); 57 (100); HRMS *m/z* calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2396.

4.4.5. 15α-Iodo-*ent*-trachyloban-14-one (31). Et_3N (140 μL, 0.99 mmol) and mesyl chloride (65 μL, 0.73 mmol) were added to a solution of hydroxy-ketone **26a** (65 mg, 0.22 mmol) in CH_2Cl_2 (2.3 mL) at 0 °C. After stirring at rt for 2 h, the mixture was diluted with ether and washed successively with diluted hydrochloric acid, 5% aq $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure at rt afforded a yellowish residue of crude mesylate **30** (70 mg) that was used in the subsequent step without further purification.

The above obtained mesylate was dissolved in a 10% solution of NaI in dry acetone (2 mL) and the mixture was heated at 40 °C for 2 h. The reaction mixture was cooled down to rt, poured into water and extracted with hexane. The combined organic phases were washed with dilute $Na_2S_2O_3$ and H_2O, dried over $MgSO_4$, filtered and the solvent evaporated under vacuum. Purification by column chromatography, using hexane/AcOEt 9:1 as eluent, afforded iodo-ketone **31** (73 mg, 85% for the two steps) as a white solid. Mp 151–153 °C (with decomposition) (from cold ethyl ether); $[\alpha]_D^{29}$ +8 (1.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2923s, 2866m, 1727s, 1462m, 1439m, 1389m, 1367m; ^{1}H NMR (400 MHz) δ 4.28 (1H, s, H-15), 2.14 (1H, ddd, *J*=10.5, 2.2, 2.2 Hz, H-11α), 2.06 (1H, d, *J*=7.2 Hz, H-13), 1.94 (1H, m, H-9), 1.89 (1H, m, H-12), 1.69 (2H, m, H-7 and H-2), 1.67 (1H, m, H′-11), 1.52 (2H, m, H-6 and H′-2), 1.43 (1H, m, H-1), 1.32 (3H, s, Me-C_{16}), 1.33 (1H, m, H′-6), 1.31 (1H, m, H-3), 1.28 (1H, m, H′-7), 1.05 (1H, m, H′-3), 0.85 (3H, s, Meβ-C_4), 0.77 (3H, s, Meα-C_4), 0.75 (1H, m, H′-1), 0.69 (1H, m, H-5), 0.71 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz), see Table 2; MS (EI) *m/z* (%) 413 (M^+ +1, 1), 412 (M^+, 0.1), 320 (9), 285 (100), 257 (25), 203 (6), 161 (10), 137 (44), 119 (32), 105 (37); HRMS *m/z* calcd for $C_{20}H_{30}IO$ [M+H^+] 413.1341, found 413.1338.

4.4.6. *ent*-Atis-15-en-14-one (32). Iodo-ketone **31** (35 mg, 0.085 mmol) in a mixture of THF (1.5 mL) and MeOH (0.5 mL) was treated dropwise with a 0.1 M solution of SmI_2 in THF at rt until persistence of the blue colour (ca. 1.5–2 mL). After being stirred for 1 h, saturated aq NH_4Cl solution was added and the mixture was poured into water and extracted with ether. The organic layer was washed with dilute $Na_2S_2O_3$ and brine, dried and evaporated under reduced pressure. Chromatography, using hexane/AcOEt 8:2 as eluent, yielded atisenone **32** (20 mg, 85%) as a solid. Mp 132–133 °C (from MeOH); $[\alpha]_D^{25}$ −142 (0.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2923s, 2858m, 1700s, 1427m, 1126m, 1071m; ^{1}H NMR (400 MHz) δ 5.32 (1H, s, H-15), 2.60 (1H, m, H-12), 2.46 (1H, ddd, *J*=13.2, 3.6, 3.6 Hz, H-11α), 2.13 (1H, ddd, *J*=18.0, 3.2, 3.2 Hz, H-13), 2.02 (1H, dd, *J*=18.0, 2.3 Hz, H′-13), 1.77 (3H, s, Me C_{16}), 1.65 (1H, m, H-7), 1.45 (2H, m, H_2-6), 1.42 (3H, m, H-9, H′-7, H-1), 1.29 (3H, m, H_2-2 and H-3), 1.15 (1H, m, H-11β), 1.10 (1H, m, H′-3), 0.86 (3H, s, Meβ-C_4), 0.85 (1H, m, H-5), 0.79 (3H, s, Meα-C_4), 0.78 (1H, m, H′-1), 0.71 (3H, s, Me-C_{10}); ^{13}C NMR (100 MHz), see Table 2; MS (EI) *m/z* (%) 286 (M^+, 6), 244 (100), 230 (31), 137 (31), 120 (33), 106 (54), 91 (22); HRMS *m/z* calcd for $C_{20}H_{30}O$ 286.2297, found 286.2287. Anal. Calcd for $C_{20}H_{30}O$: C 83.86, H 10.56; found: C 83.99, H 10.47.

4.4.7. *ent*-Trachylobane-14α,15β-diol (33). A 1 M solution of $LiAlH_4$·2THF in toluene (2.5 mL, 2.5 mmol) was added dropwise to a solution of hydroxy-ketone **26a** (154 mg, 0.50 mmol) in THF (3.8 mL) and toluene (2.2 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min, AcOEt (3 mL) was slowly added to destroy excess hydride, followed by the dropwise addition of H_2O until the appearance of a milky white solid (ca. 0.75 mL). Anhydrous Na_2SO_4 was then added until a fine white precipitate separated from the solution, which was removed by filtration and washed with AcOEt. The residue left after concentration of the clear filtrate under reduced pressure was purified by chromatography, using dichloromethane/AcOEt 4:1 as eluent, to give diol **33** (100.8 mg, 88%) as a white solid. Mp 192–193 °C (from $CHCl_3$); $[\alpha]_D^{29}$ −33 (1.7, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3301s, 2927m, 2863w, 1439m, 1316m, 1262m, 1075m, 1051s, 982m; ^{1}H NMR (400 MHz) δ 3.75 (1H, d, *J*=3.5 Hz, H-14), 3.32 (1H, s, H-15), 1.80 and 1.73 (1H each, two m, H_2-11), 1.54 (1H, m, H-2α), 1.48 (2H, m, H-1α), 1.37 (1H, m, H-3β), 1.35 (1H, m, H-2β), 1.29 (1H, m, H-9), 1.18 (3H, s, Me-C_{16}), 1.14 (1H, dd, *J*=3.5, 7.5 Hz, H-13), 1.11 (1H, m, H-3α), 1.00 (3H, s, Me-C_{10}), 1.00 (1H, m, H-6β), 0.91 (1H, m, H-12), 0.84 (3H, s, Meα-C_4), 0.83 (2H, m, H-1β), 0.81 (1H, m, H-6α), 0.80 (3H, s, Meβ-C_4), 0.76 (1H, m, H-5); ^{13}C NMR (100 MHz), see Table 2; MS (EI) *m/z* (%) 304 (M^+, 2.5), 286 (100), 271 (43), 230 (23), 213 (18), 137 (60), 123 (47), 109 (35), 105 (64), 95 (50); HRMS *m/z* calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2400. Anal. Calcd for $C_{20}H_{32}O_2$: C 78.90, H 10.59; found: C 79.05, H 10.49.

4.4.8. *ent*-Atis-13-en-15α,16β-diol (34). Et_3N (55 μL, 0.4 mmol, 6 equiv), H_2O (6 μL, 0.33 mmol, 5 equiv), and methanesulfonyl chloride (16 μL, 0.2 mmol, 3 equiv) were successively added to a solution of diol **33** (20 mg, 0.066 mmol) in CH_2C1_2 (1 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, quenched with saturated aq solution of $NaHCO_3$, and diluted with CH_2C1_2. The organic phase was washed with H_2O and brine, dried over $MgSO_4$. Purification of the residue left after evaporation of the solvent by column chromatography, using hexane/AcOEt from 4:1 to 2:3, afforded atisenediol **34** (13.2 mg, 66%) as an amorphous solid. $[\alpha]_D^{29}$ −20 (0.1, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3409s, 2915s, 2847m, 2353m, 2336m, 1636m, 1456m, 1112m, 1052m, 910w; ^{1}H NMR (400 MHz) δ 6.18 (1H, dd, J=7.0, 8.0 Hz, H-13) 5.77 (1H, dd, J=8.0, 1.0 Hz, H-14), 3.15 (1H, s, H-15), 2.37 (1H, ddd, J=3.0, 3.0, 7.0 Hz, H-12), 2.24 (1H, ddd, J=13.0, 3.0, 3.0 Hz, H-7α), 2.00 (1H, ddd, J=13.0, 9.0, 3.0 Hz, H-11β), 1.96 (1H, m, H-7β), 1.62 (1H, m, H-6), 1.47 (1H, m, H-2), 1.43 (1H, m, H-1) 1.39 (1H, m, H-3), 1.35 (1H, m, H′-2), 1.34 (1H, m, H-9), 1.32 (1H, m, H′-6), 1.26 (1H, m, H-7α), 1.14 (1H, m, H′-3), 1.13 (3H, s, Me-C_{16}), 0.95 (1H, ddd, J=13.0, 7.0, 3.0 Hz, H-11α), 0.90 (1H, m, H′-1), 0.88 (3H, s, Meβ-C_4), 0.84 (1H, m, H-5), 0.80 (3H, s, Meα-C_4), 0.61 (3H, d, J=0.8 Hz, Me-C_{10}); ^{13}C NMR (75 MHz), see Table 2; MS (EI) *m/z* (%) 304 (M^+, 1), 286 (M^+ −H_2O, 7), 230 (44), 145 (28), 131 (100), 119 (67), 106 (23), 100 (20), 91 (32); HRMS *m/z* calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2405.

4.4.9. 14α-Hydroxy-*ent*-beyeran-15-one (36). A solution of cyclopropyl-ketone **26a** (29.0 mg, 0.095 mmol) in THF (1 mL) was added dropwise to a solution of lithium (5 mg, 0.83 mmol) in liquid ammonia (1 mL) and THF (0.5 mL) at −78 °C. After stirring for 10–15 min, isoprene was added dropwise until disappearance of the blue colour. The ammonia was allowed to evaporate, saturated aq NH_4Cl solution was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent and chromatography of the residue, using hexane/AcOEt 8:2 as eluent, afforded hydroxy-beyeranone **36** (24.9 mg, 85%) as a solid. Mp 165–166 °C (from pentane); $[\alpha]_D^{29}$ +42 (1.6, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3440m, 2949s, 2864m, 1713s, 1460m, 1150m, 1108m, 1038m; ^{1}H NMR (400 MHz) δ 3.17 (1H, s, H-14), 2.25 (1H, d, J=19.0 Hz, H-16), 1.85 (1H, d, J=19.0 Hz, H′-16), 1.55 (1H, br s, OH), 1.07 (3H, s, Me-C_{13}), 0.86 (3H, s, Meβ-C_4), 0.83 (3H, s, Meα-C_4), 0.80 (3H, s, Me-C_{10}); ^{13}C NMR (75 MHz), see Table 2; MS (EI) *m/z* (%) 305 (M^++1, 25), 304 (M^+, 100), 289 (46), 286 (62), 245 (40), 244 (56), 229 (47), 138 (39), 123 (91), 95 (34); HRMS *m/z* calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2397. Anal. Calcd for $C_{20}H_{32}O_2$: C 78.90, H 10.59; found: C 78.79, H 10.66.

4.4.10. 14α-Formyloxy-*ent*-trachyloban-15β-ol (37). A solution of diol **33** (48.1 mg, 0.15 mmol) in buffered formic acid (4.5 mL of a solution of 50 mg of anhydrous Na_2CO_3 in 10 mL of formic acid) and THF (1.5 mL) was stirred at 5 °C for 14 h. The mixture was diluted with cold ether and washed with saturated aq $NaHCO_3$ solution until basic, then with water until neutral and then with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield an oily residue, which was purified by chromatography, using hexane/Et_2O 1:1 as eluent, to afford formate **37** (41.3 mg, 80%) as a colourless oil. $[\alpha]_D^{29}$ −12 (0.5, $CHCl_3$); IR ν_{max}/cm^{-1} (film) 3414m, 2923s, 2859m, 1716s, 1463m, 1439m, 1166s, 1092m, 983w, 745m; ^{1}H NMR (400 MHz) δ 8.17 (1H, d, J=0.8 Hz, OC*H*O), 4.92 (1H, d, J=3.5 Hz, H-14), 3.44 (1H, s, H-15), 1.76–1.95 (2H, m, H_2-11), 1.72 (1H, m, H-9), 1.56 (1H, m, H-2α), 1.53 (1H, m, H-1α), 1.44 (1H, m, H-6β), 1.38 (1H, m, H-2β), 1.37 (1H, m, H-3β), 1.30 (1H, dd, J=3.5, 7.5 Hz, H-13), 1.20 (3H, s, Me-C_{16}), 1.20 (1H, m, H-6α), 1.14 (1H, m, H-3α), 1.00 (3H, s, Me-C_{10}), 0.99 (1H, m, H-12), 0.86 (1H, m, H-1β), 0.83 (3H, s, Meβ-C_4), 0.785 (3H, s, Meα-C_4), 0.71 (1H, m, H-5); ^{13}C NMR (75 MHz), see Table 2; MS (EI) *m/z* (%) 332 (M^+, 0.2), 314 (M^+ −H_2O, 9), 286 (48), 257 (34), 230 (44), 137 (57), 131 (35), 131 (35), 105 (68), 100 (20), 91 (81); HRMS *m/z* calcd for $C_{21}H_{32}O_3$ 332.2351, found 332.2451.

4.4.11. 14α-Formyloxy-*ent*-trachyloban-15-one (38). Pyridine (30 μL, 0.37 mmol) was added to a solution of alcohol **37** (39.2 mg, 0.12 mmol) in CH_2Cl_2 (3 mL), followed by Dess–Martin periodinate reagent (78 mg, 0.18 mmol) in one portion. The resulting reaction mixture was stirred at rt for 2 h before being quenched with saturated aq $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by chromatography, using hexane/AcOEt 8:2 as eluent, to afford ketone **38** (33.6 mg, 86% yield) as an oil. $[\alpha]_D^{29}$ −4 (1.5, $CHCl_3$); IR ν_{max}/cm^{-1} (NaCl) 2923m, 2858s, 1716s, 1465m, 1388m, 1164s, 984w; ^{1}H NMR (400 MHz) δ 8.19 (1H, d, J=0.8 Hz, OC*H*O), 5.19 (1H, d, J=3.5 Hz, H-14), 2.17 (1H, m, H-7), 2.15 (1H, m, H-12), 1.94 (2H, m, H_2-11), 1.91 (1H, m, H-13), 1.54 (1H, m, H-2), 1.37 (1H, m, H′-2), 1.49 (1H, m, H-9), 1.47 (1H, m, H-1), 1.39 (1H, m, H-7), 1.35 (1H, m, H-3), 1.26 (3H, s, Me-C_{13}), 1.23 (1H, m, H-6), 1.12 (1H, m, H′-6), 1.10 (1H, m, H′-3), 0.98 (3H, s, Me-C_{10}), 0.84 (3H, s, Meβ-C_4), 0.79 (3H, s, Meα-C_4) 0.79 (1H, m, H′-1), 0.72 (1H, dd, J=12.2, 2.1 Hz, H-5); ^{13}C NMR (75 MHz), see Table 2; MS (EI) *m/z* (%) 330 (M^+, 2.4), 315 (2), 284 (15), 269 (7), 178 (12), 161 (7), 137 (11), 123 (13), 86 (62), 84 (100); HRMS *m/z* calcd for $C_{21}H_{30}O_3$ 330.2194, found 330.2191.

4.4.12. 14α-Hydroxy-*ent*-trachyloban-15-one (39). A solution of formate ester **38** (35 mg, 0.11 mmol) and Na_2CO_3 (50 mg, 0.46 mmol) in MeOH (1 mL) was stirred at rt for 1 h. After addition of H_2O, the solution was extracted with AcOEt. The organic layers were washed with H_2O, then brine and dried. Evaporation of the solvent and purification by chromatography, using hexane/AcOEt 7:3 as eluent, gave alcohol **39** (29 mg, 90%) as a white foam solid. $[\alpha]_D^{29}$ −19 (1.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3420m, 2912s, 2874m, 1694s, 1448m, 1388m, 1099s; ^{1}H NMR (400 MHz) δ 4.09 (1H, m, H-14), 2.15 (1H, ddd, J=14.3, 14.3, 5.9 Hz, H-7β), 2.02 (1H, dd, J=7.2, 3.8 Hz, H-13), 1.93 (3H, m, H-12 and H_2-11), 1.51 (2H, m, H-6 and H-2), 1.42 (2H, m, H-1 and H-9), 1.32 (3H, m, H′-7, H′-6 and H′-2), 1.30 (1H, m, H-3), 1.24 (3H, s, Me-C_{16}), 1.12 (1H, m, H′-3), 1.04 (3H, s, Me-C_{10}), 0.84 (3H, s, Meβ-C_4), 0.80 (1H, m, H′-1), 0.69 (1H, dd, J=12.1, 1.3 Hz, H-5), 0.80 (3H, s, Meα-C_4); ^{13}C NMR (75 MHz), see Table 2; MS (EI) *m/z* (%) 302 (M^+, 65), 287 (25), 269 (16), 165 (50), 137 (10), 123 (68), 105 (40), 84 (100), 69 (82); HRMS *m/z* calcd for $C_{20}H_{30}O_2$ 302.2246, found 302.2232.

4.4.13. 14α-Hydroxy-*ent*-kauran-15-one (40). A solution of cyclopropyl-ketone **39** (22.8 mg, 0.075 mmol) in THF (0.5 mL) was added dropwise to a solution of lithium (5 mg, 0.71 mmol) in liquid ammonia (1 mL) and THF (0.5 mL) at −78 °C. After stirring for 15–20 min, the reaction mixture was worked-up as described above for the preparation of **36**. The crude product was purified by chromatography, using hexane/AcOEt 9:1 as eluent, to obtain kauranone **40** (19.6 mg, 86%) as a white solid. Mp 186–187 °C (from pentane); $[\alpha]_D^{29}$ −20 (0.2, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 3416s, 2919s, 2852m, 1716s, 1460m, 1449m, 1378m, 1209m, 1137w; ^{1}H NMR (400 MHz) δ 3.82 (1H, dd, J=4.7 Hz, H-14), 2.35 (2H, m, H-13 and H-16), 1.90 (1H, m, H-12), 1.87 (1H, m, H-7), 1.68 (1H, ddd, J=11.8, 11.8, 3.0 Hz, H-1β), 1.58 (2H, m, H-6 and H-2), 1.57 (1H, m, H-11), 1.52 (1H, m, H′-12), 1.44 (2H, m, H′-6 and H′-2), 1.43 (1H, m, H′-7), 1.36 (1H, m, H′-11), 1.35 (1H, m, H-3), 1.17 (1H, m, H-9), 1.16 (3H, d, J=7.0 Hz, Me-C_{16}), 1.12 (1H, m, H′-3), 1.06 (3H, s, Me-C_{10}), 0.91 (1H, dd, J=13.5, 3.5 Hz, H-5), 0.86 (3H, s, Meβ-C_4), 0.72 (1H, ddd, J=12.6, 12.6, 3.2 Hz, H-1), 0.80 (3H, s, Meα-C_4); ^{13}C NMR (75 MHz), see Table 2; MS (EI) m/z (%) 304 (M^+,16), 289 (14), 246 (17), 167 (35), 137 (41), 123 (100), 109 (34), 83 (76); HRMS m/z calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2388.

4.4.14. 14α-Acetoxy-*ent*-kauran-15-one (41). A solution of alcohol **40** (11.3 mg, 0.037 mmol), Ac_2O (70 μL, 0.74 mmol), pyridine (30 μl, 0.36 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (2 mL) was stirred at rt for 3 h. The reaction was quenched by the addition of H_2O and extracted with AcOEt, the organic phase was washed successively with 5% aq HCl solution, 10% aq Na_2CO_3 solution and brine, and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography, using hexane/AcOEt 9:1 as eluent, to give acetate **41** (11.6 mg, 93%) as a solid. Mp 125–127 °C (from cold MeOH); $[\alpha]_D^{29}$ −8 (0.5, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr) 2923s, 2863s, 2852m, 1732s, 1454m, 1361m, 1241s, 1115w, 1055w; ^{1}H NMR (400 MHz) δ 4.79 (1H, d, J=4.8 Hz, H-14), 2.50 (1H, m, H-13), 2.37 (1H, quin, J=6.5 Hz, H-16), 2.18 (3H, s, *Me*COO), 1.94 (1H, ddd, J=13.6, 13.6, 4.3 Hz, H-7β), 1.75 (1H, m, H-12), 1.71 (1H, m, H-1α), 1.60 (1H, m, H-11), 1.56 (1H, m, H′-12), 1.47 (1H, m, H-7α), 1.45 (1H, m, H-6), 1.40 (1H, m, H-3), 1.32 (1H, m, H′-11), 1.23 (1H, m, H′-6), 1.22 (1H, m, H-9), 1.18 (1H, m, H′-3), 1.16 (3H, d, J=7.0 Hz, Me-C_{16}), 1.04 (3H, s, Me-C_{10}), 0.90 (1H, dd, J=12.3, 2.2 Hz, H-5), 0.85 (3H, s, Meβ-C_4), 0.80 (3H, s, Meβ-C_4), 0.77 (1H, ddd, J=12.8, 12.8, 3.5 Hz, H-1β); ^{13}C NMR (100 MHz), see Table 2; MS (EI) m/z (%) 346 (M^+, 1), 303 (10), 286 (19), 258 (96), 230 (41), 137 (100), 121 (51), 81 (68); HRMS m/z calcd for $C_{22}H_{34}O_3$ 346.2508, found 346.2482. Anal. Calcd for $C_{22}H_{34}O_3$: C 76.26, H 9.89; found: C 76.39, H 9.78.

Acknowledgements

Financial support from the Dirección General de Enseñanza Superior e Investigación Científica (Grant BQU2002-00272) is gratefully acknowledged. We are grateful to the Conselleria d′Educació i Ciència de la Generalitat Valenciana and the Ministerio de Educación y Ciencia for providing research fellowships to I. Navarro and I. de Alfonso Marzal, respectively.

References and notes

1. (a) Connolly, J. D.; Hill, R. A., 1st ed. In *Dictionary of Terpenoids*, *Vol. 2*; Chapman and Hall: London, 1991; pp 906–970. (b) Hanson, J. R. *Nat. Prod. Rep.* **2004**, *21*, 785–793 and previous reviews of these series.
2. For recent examples of biologically active trachylobanes, see: (a) Block, S.; Gerkens, P.; Peulen, O.; Jolois, O.; Mingeot-Leclercq, M.-P.; de Pauw-Gillet, M.-Cl.; Quetin-Leclercq, J. *Anticancer Res.* **2005**, *25*, 363–368. (b) Block, S.; Baccelli, C.; Tinant, B.; Van Meervelt, L.; Rozenberg, R.; Habib Jiwan, J. L.; Llabres, G.; De Pauw-Gillet, M. C.; Quetin-Leclercq, J. *Phytochemistry* **2004**, *65*, 1165–1171. (c) Hernandez-Terrones, M. G.; Aguilar, M. I.; King-Diaz, B.; Lotina-Hennsen, B. *Arch. Biochem. Biophys.* **2003**, *418*, 93–97.
3. For recent examples of biologically active beyeranes, see: (a) Akihisa, T.; Mizushina, Y.; Ukiya, M., Jpn. Kokai Tokkyo Koho JP 2005162634, 2005. (b) Lin, L.-H.; Lee, L.-W.; Sheu, S.-Y.; Lin, P.-Y. *Chem. Pharm. Bull.* **2004**, *52*, 1117–1122. (c) Han, L.; Huang, X.; Sattler, I.; Dahse, H.-M.; Fu, H.; Lin, W.; Grabley, S. *J. Nat. Prod.* **2004**, *67*, 1620–1623.
4. For recent examples of biologically active atisanes, see: (a) Kume, T.; Kawai, Y.; Yoshida, K.; Nakamizo, T.; Kanki, R.; Sawada, H.; Katsuki, H.; Shimohama, S.; Sugimoto, H.; Akaike, A. *Neurosci. Lett.* **2005**, *383*, 199–202. (b) Osakada, F.; Kawato, Y.; Kume, T.; Katsuki, H.; Sugimoto, H.; Akaike, A. *J. Pharmacol. Exp. Ther.* **2004**, *311*, 51–59. (c) Akaike, A.; Sugimoto, H.; Nishizawa, Y.; Yonaga, M.; Asakawa, N.; Asai, N.; Mano, N.; Terauchi, T.; Doko, T. U.S. Patent US2004180930, 2004.
5. For recent examples of biologically active kauranes, see. (a) Morris, B. D.; Foster, S. P.; Grugel, S.; Charlet, L. D. *J. Chem. Ecol.* **2005**, *31*, 89–102. (b) Giang, P. M.; Son, P. T.; Hamada, Y.; Otsuka, H. *Chem. Pharm. Bull.* **2005**, *53*, 296–300. (c) Nagashima, F.; Kondoh, M.; Fujii, M.; Takaoka, S.; Watanabe, Y.; Asakawa, Y. *Tetrahedron* **2005**, *61*, 4531–4544. (d) Vieira, H. S.; Takahashi, J. A.; Pimenta, L. P. S.; Boaventura, M. A. D. *Z. Naturforsch., C: Biosci* **2005**, *60*, 72–78.
6. Wenkert, E. *Chem. Ind. (London)* **1955**, 282–284.
7. Coates, R.; Bertram, E. *J. Org. Chem.* **1971**, *36*, 3722–3729.
8. (a) Goldsmith, D. In *The Total Synthesis of Tri- and Tetracyclic Diterpenes*; ApSimon, J., Ed.; The Total Synthesis of Natural Products; Wiley: New York, 1992; Vol. 8, pp 101–131. For examples of recent synthesis, see: (b) Marcos, I. S.; Cubillo, M. A.; Moro, R. F.; Caballares, S.; Diez, D.; Basabe, P.; Llamazares, C. F.; Beneitez, A.; Sanz, F.; Broughton, H. B.; Urones, J. G. *Tetrahedron* **2005**, *61*, 977–1003. (c) Marcos, I. S.; Moro, R. F.; Caballares, M. S.; Urones, J. G. *Synlett* **2002**, 458–462. (d) Terauchi, T.; Asai, N.; Yonaga, M.; Kume, T.; Akaike, A.; Sugimoto, H. *Tetrahedron Lett.* **2002**, *43*, 3625–3628. (e) Toyota, M.; Yokota, M.; Ihara, M. *J. Am. Chem. Soc.* **2001**, *123*, 1856. (f) Toyota, M.; Wada, T.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 4565–4570. (g) Toyota, M.; Yokota, M.; Ihara, M. *Org. Lett.* **1999**, *1*, 1627–1629. (h) Toyota, M.; Wada, T.; Fukumoyo, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916–4925. (i) Snider, B. B.; Kiselgof, J. Y.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 7945–7952. (j) Hofner, D.; Haslinger, E. *Monatsh. Chem.* **1998**, *129*, 393–407. (k) Berettoni, M.; De Chiara, G.; Iacoangeli, T.; Lo Surdo, P.; Bettolo, R. M.; di Mirabello, L. M.; Nicolini, L.; Scarpelli, R. *Helv. Chim. Acta* **1996**, *79*, 2035–2041. (l) Abad, A.; Agulló, C.; Arnó, M.; Marín, M. L.; Zaragozá, R. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2987–2991.
9. For some recent examples, see: (a) Fukushima, M.; Endou, S.; Hoshi, T.; Suzuki, T.; Hagiwara, H. *Tetrahedron Lett.* **2005**, *46*, 3287–3290. (b) Abad, A.; Agullo, C.; Cunat, A. C.; de Alfonso, I.; Navarro, I.; Vera, N. *Molecules* **2004**, *9*, 287–299. (c)

Kitagawa, O.; Yamada, Y.; Sugawara, A.; Taguchi, T. *Org. Lett.* **2002**, *4*, 1011–1013. (d) Patil, G. S.; Nagendrappa, G. *Indian J. Chem., Sect. B* **2002**, *41*, 1019–1024. (e) O'Connor, S. J.; Overman, L. E.; Rucker, P. V. *Synlett* **2001**, 1009–1012. (f) Hong, B.-C.; Chin, S.-F. *Synth. Commun.* **1999**, *29*, 3097–3106. (g) Filippini, M. H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27–76 and literature cited therein.

10. Abad, A.; Agulló, C.; Cuñat, A. C.; García, A. B. *Tetrahedron* **2005**, *61*, 1961–1970.
11. Abad, A.; Agulló, C.; Cuñat, A. C.; Navarro, I.; Ramirez de Arellano, M. C. *Synlett* **2001**, 349–352.
12. Davies, H. M. L. In *Addition of Ketocarbenes to Alkenes, Alkynes and Aromatic Systems*; Trost, B. M., Fleming, I., Eds.; Comprehensive Organic Synthesis; Pergamon: Oxford, 1991; Vol. 4, (Semmelhach, M.F. Ed.) Chapter 4.8, pp 1031–1067.
13. (a) Shing, T. K. M.; Jiang, Q. *J. Org. Chem.* **2000**, *65*, 7059–7069. (b) Abad, A.; Agulló, C.; Castelblanque, L.; Cuñat, A. C.; Navarro, I.; Ramírez de Arellano, M. C. *J. Org. Chem.* **2000**, *65*, 4189–4192 and references cited therein.
14. Abad, A.; Agulló, C.; Arnó, M.; Cantín, A.; Cuñat, A. C.; Meseguer, B.; Zaragozá, R. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1837–1843.
15. Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Fong, K. C.; He, Y.; Yoon, W. H. *Org. Lett.* **1999**, *1*, 883–886.
16. (a) Regitz, M. *Synthesis* **1972**, 351. (b) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–1964.
17. To our knowledge, this simple procedure for the generation of tetrabutylammonium enolates of β-diketones has not been previously used. For alternative procedures, see: Shono, T.; Kashimura, S.; Sawamura, M.; Soejima, T. *J. Org. Chem.* **1988**, *53*, 907–910.
18. Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Meseguer, B.; Zaragozá, R. J. *Synlett* **1994**, 733–735.
19. (a) Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361–475. (b) Podder, R. K.; Sarkar, T. K.; Sarkar, R. K.; Ray, S. *Indian J. Chem., Sect. B* **1988**, *27*, 217–224.
20. (a) Harrigan, G. G.; Bolzani, V. da. S.; Gunatilaka, A. A. L.; Kingston, D. G. I. *Phytochemistry* **1994**, *36*, 109–113. (b) Arnone, A.; Mondelli, R.; St Pyrek, J. *Org. Magn. Reson.* **1979**, *12*, 429–431. (c) Kelly, R. B.; Eber, J.; Hung, H.-K. *J. Chem. Soc., Chem. Commun.* **1973**, 689–690.
21. Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198.
22. Zoller, T.; Uguen, D. *Tetrahedron Lett.* **1999**, *40*, 6249–6252.
23. Rugby, J. H.; Senanayake, C. *J. Org. Chem.* **1988**, *53*, 440–443.
24. Iio, H.; Isobe, M.; Hawai, T.; Goto, T. *Tetrahedron* **1979**, *35*, 941–948.
25. (a) House, H. O.; Boots, S. G.; Jones, V. K. *J. Org. Chem.* **1965**, *30*, 2519–2527. (b) Grieco, P.; Masaki, Y. *J. Org. Chem.* **1975**, *40*, 150–151.
26. Demuth, M.; Mikhail, G. *Tetrahedron* **1983**, *39*, 991–997.
27. (a) Buttler, T.; Fleming, I. *Chem. Commun.* **2004**, *21*, 2404–2405. (b) Iwata, C.; Yamashita, M.; Aoki, S.; Suzuki, K.; Takahashi, I.; Arakawa, H.; Imanishi, T.; Tanaka, T. *Chem. Pharm. Bull.* **1985**, *33*, 436–439.
28. de Heluani, C. S.; Catalán, C. A. N.; Hernández, L. R.; Burgueño-Tapia, E.; Joseph-Nathan, P. *Magn. Reson. Chem.* **1998**, *36*, 947–950.
29. (a) Carey, F. A.; Sandberg, R. J. In *Advanced Organic Chemistry. Part A: Structure and Mechanisms*, *Vol. A*; Kluwer Academic/Plenum: , 2000; Chapter 5, pp 298–300. (b) Tobe, Y.; Hayauchi, Y.; Sakai, Y.; Odaira, Y. *J. Org. Chem.* **1980**, *45*, 637–641. (c) Jefford, C. W.; Gunsher, J.; Waegell, B. *Tetrahedron Lett.* **1965**, 3405–3411.
30. Carey, F. A.; Sandberg, R. J.; Advanced Organic Chemistry. Part A: Structure and Mechanisms; Kluwer Academic/Plenum, 2000; Vol. A, Chapter 5, pp 309–316.
31. Lambert, J. B.; Mark, H. W.; Holcomb, A. G.; Magyar, E. S. *Acc. Chem. Res.* **1979**, *12*, 317–324.
32. Carey, F. A.; Sandberg, R. J.; Advanced Organic Chemistry. Part A: Structure and Mechanisms; Kluwer Academic/Plenum: New York, 2000; Vol. A, Chapter 5, pp 327–334.
33. Duc, D. K.; Fetizon, M.; Lazare, S. *Tetrahedron* **1978**, *34*, 1207–1212.
34. (a) Dauben, W. G.; Deviny, E. J. *J. Org. Chem.* **1966**, *31*, 3794–3798. (b) Dauben, W. G.; Wolf, R. E. *J. Org. Chem.* **1970**, *35*, 374–379. (c) Srikrishna, A.; Krishnan, K.; Yelamaggad, V. *Tetrahedron* **1992**, *48*, 9725–9734. (d) Srikrishna, A.; Krishnan, K. *J. Org. Chem.* **1993**, *58*, 7751–7755 and references given therein.
35. (a) Nagashima, F.; Kondoh, M.; Fujii, M.; Takaoka, S.; Watanabe, Y.; Asakawa, Y. *Tetrahedron* **2005**, *61*, 4531–4544. (b) Tazaki, H.; Iwasaki, T.; Nakasuga, I.; Kobayashi, K.; Koshino, H.; Tanaka, M.; Nabeta, K. *Phytochemistry* **1999**, *52*, 1427–1430. (c) Garcia-Granados, A.; Martinez, A.; Onorato, M. E. *J. Org. Chem.* **1987**, *52*, 606–615. (d) Grande, M.; Segura, M.; Mancheno, B. *J. Nat. Prod.* **1986**, *49*, 259–264.
36. Cory, R. M.; Bailey, M. D.; Tse, D. W. C. *Tetrahedron Lett.* **1990**, *31*, 6839–6842.
37. Larson, G. L.; Klesse, R. *J. Org. Chem.* **1985**, *50*, 3627.