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Chemistry of (+)-aromadendrene. Part 6: Rearrangement reactions of ledene, isoledene and their epoxides

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Abstract—The chemistry of (+)-ledene and (−)-isoledene, both easily available from (+)-aromadendrene has been investigated. Reactions at the double bond of ledene take place preferably from the β-side. Under acidic conditions its C7–C8 β-epoxide and β-diol preferably react via carbocations, which are initially formed at C8. Rearrangement takes place to compounds with cubebane and cadinane skeletons. The reaction pattern of isoledene and its α-epoxide, under acidic conditions, is governed by the easy formation of an intermediate α-cyclopropylcarbinyl carbocation. Further reactions lead to products in which the C2–C3 bond of the cyclopropane ring is broken to give compounds with a guaiane skeleton. Guaiane-type dienes and unsaturated cyclic ethers are the final products of these rearrangements. Several derivatives of these compounds have been prepared.

1. Introduction

(+)-Aromadendrene (**1**) is the main constituent of the distillation tail[1] of the essential oil of *Eucalyptus globulus*. Pure (+)-aromadendrene cannot be isolated easily from this oil, but often the crude distillation tail can be used without further purification.[2] (+)-Ledene (**2**), a naturally occurring sesquiterpene that is also called viridiflorene, is present in small amounts in the essential oils of *Melaleuca alternifolia*,[3] *Melaleuca leucadendron*,[4] *Cassina uncata*,[5] *Valeriana officinalis* var. *sambucifolia*,[6] and a *Prostanthera* species.[7] Larger quantities of ledene can be obtained by isomerisation of (+)-aromadendrene (**1**) with K/Al_2O_3 at 100°C, which gives a 42% yield of **2** together with isoledene (**3**) and one other product.[8] Reactions of ledene and its epoxide usually proceed in an ambiguous way and lead to mixtures of products.[9–11]

(−)-Isoledene (**3**) is a sesquiterpene isolated in small amounts from the essential oil of *Citrus aurantifolia*[12] and *Cistus ladaniferus*.[13] Large amounts of isoledene can be synthesised in quantitative yield from (+)-aromadendrene in a reaction with K/Al_2O_3.[8]

We here report on the chemistry of (+)-ledene, (−)-isoledene and their epoxides, in particular, on the conversion of these compounds to products with a guaiane skeleton.

2. Results and discussion

Both (+)-ledene (**2**) and (−)-isoledene (**3**) can be obtained in one step from (+)-aromadendrene (**1**). Ledene can be obtained in a modest yield by isomerisation of (+)-aromadendrene (**1**) with K/Al_2O_3 at 100°C, but it was found that a good 80% yield of ledene can be obtained by isomerisation of (+)-aromadendrene with KO*t*Bu in DMSO (Scheme 1). When the crude distillation tail[1] of the essential oil of *Eucalyptus globulus* was subjected to this reaction a much lower yield of ledene was obtained due to purification problems. Epoxidation of ledene (**2**) with *m*CPBA[14] led to mixtures of products, however, the epoxidation of ledene with dimethyldioxirane selectively gave epoxide **4** as the sole product (Scheme 1). Its β configuration was confirmed by reaction with $LiNEt_2$, which afforded the unsaturated alcohol **5**, a sesquiterpene of known configuration present in *Laurencia subopposita*.[15] Ledene (**2**) could be converted to *cis*-diol **6** by reaction with $KMnO_4$, and also in this reaction only the β-product was obtained.[7] Attempts to form a *trans*-diol out of ledene or from epoxide **4** were unsuccessful and also the formation of a chloro- or bromohydrin from ledene did not work in our hands. Probably the steric hindrance at the α-side of ledene prevents many nucleophiles from attacking that side of the molecule.

Keywords: aromadendrene; ledene; ledene–epoxide; isoledene; isoledene–epoxide guaiazulene; guaianes; rearrangements.
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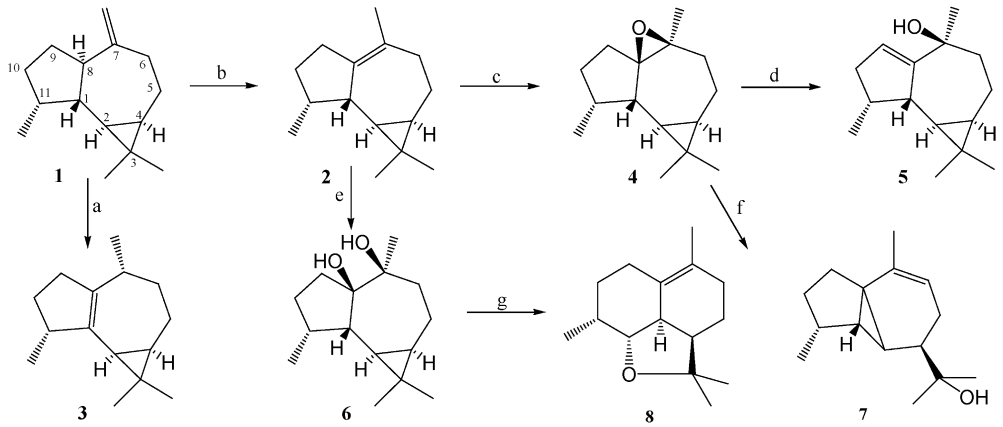


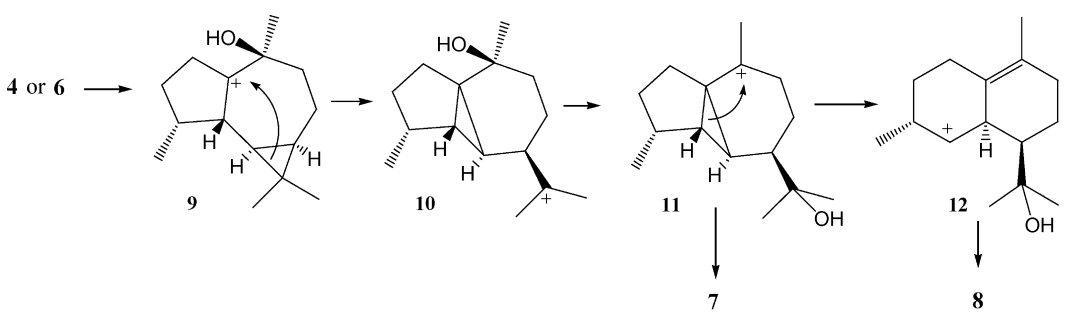
Scheme 1. (a) K/Al_2O_3, 100°C (96%); (b) KO*t*Bu, DMSO, 100°C (80%); (c) dimethyldioxirane (96%); (d) $LiNEt_2$, Et_2O (57%); (e) $KMnO_4$, EtOH (54%); (f) H^+, THF/H_2O; (g) HOAc, I_2 (35%).

Lewis acid-catalysed ring opening of epoxide **4** can in principle lead to carbocation formation at C7 or at C8 as a first step and calculations revealed that the heat of formation of these two carbocations is not much different (−39.53 kcal/mol for C8 and −39.34 kcal/mol for C7). When **4** was treated with $BF_3{\cdot}Et_2O$ or $MgBr_2$, complex mixtures of products were obtained, but when **4** was treated under mild acidic conditions a reasonable clean rearrangement took place to the known compounds **7** and **8** (Scheme 1).[14] The β-diol **6** rearranged to compound **7** upon treatment with wet HOAc.

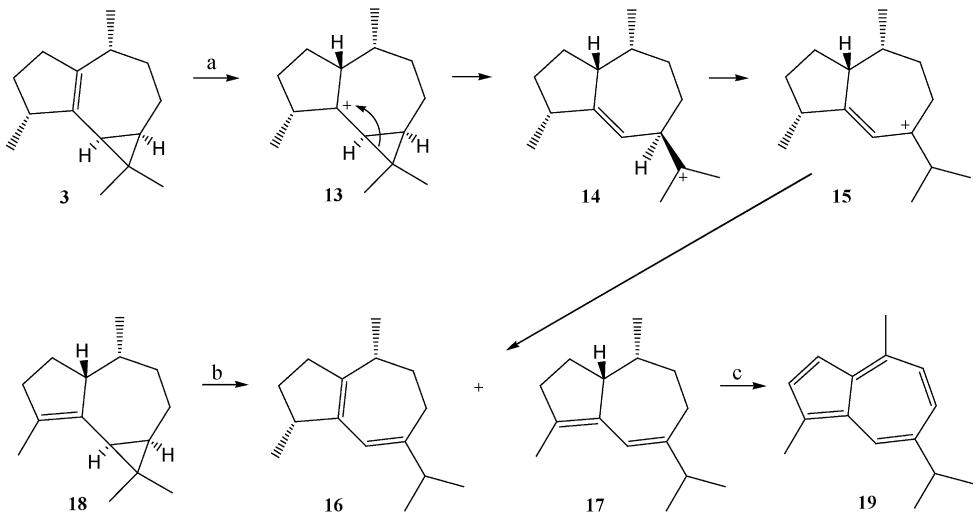
The products formed in these rearrangements can be explained by the formation of the C8 bridgehead carbocation **9** as the first step (Scheme 2). In this carbocation the cyclopropane ring is opened to intermediate **10**.[9,10] Carbocation **10** is converted to the more stable α-cyclopropylcarbinyl carbocation **11** by hydration–dehydration, or possibly via ring closure and re opening of an intramolecular ether. In carbocation **11** a proton can be eliminated to give the cubebane **7** or a further rearrangement to carbocation **12** can take place, resulting in the formation of the cadinane **8**. The product ratio in these reactions can be controlled by temperature and reaction time. For instance at higher temperature and longer reaction times more **8** is formed. When **7** was treated with acid it was converted to **8**, indicating that **7** and **8** were formed from the same intermediate carbocation **11**.

In our attempts to convert aromadendrene to industrially interesting compounds, suitable routes to guaiazulene (**19**) and to other guaiane-type natural products were explored. For this purpose, the conversion of aromadendrene to isoledene and its epoxide and their use as chiral starting materials for the synthesis of guaiane-type sesquiterpenes, have been investigated. Isoledene has better potentials for conversion to guaiane-type skeletons than ledene or aromadendrene because isoledene can be converted easily to the stabilised α-cyclopropylcarbinyl carbocation **13**, under acidic conditions. For instance, treatment of isoledene in superacidic media ($HSO_3F–SO_2FCl$) leads to the formation of a mixture of dienes **16** and **17** in high yield[11] (Scheme 3). The same dienes can be obtained when α-gurjunene (**18**) is treated with TsOH in HOAc.[16] When isoledene (**3**) is heated to 450°C, it is converted to γ-gurjunene in 80% yield.[8] Upon treatment of aromadendrene or ledene with acid also opening of the cyclopropane ring takes place, but in these reactions usually the C3–C4 bond is broken instead of the C2–C3 bond.[17]

Our first aim was the conversion of isoledene (**3**) to guaiazulene (**19**), a naturally occurring guaiane with a dark blue colour. Guaiazulene is present in the essential oil of *Cinnamomum cassia*,[18] *Chamomilla*,[19] *Camphor*[20,21] and several other plants. Guaiazulene is FDA-approved as colorant in externally applied cosmetics, so a cheap production of **19** may be interesting for industrial purposes. The conversion of several aromadendrane and guaiane sesquiterpenes to **19** is known,[16,22–27] but mostly this conversion has been used to prove the presence of the azulene skeleton in an unknown natural product, and in only a few cases the yield is given. The highest yield reported for the dehydrogenation of aromadendrene to guaiazulene with sulfur is 6.3%.[24]



Scheme 2.



Scheme 3. (a) HSO_3F-SO_2FCl; H^+ or $BF_3{\cdot}Et_2O$; (b) TsOH, AcOH; (c) sulphur, mesitylene, 160°C (22%).

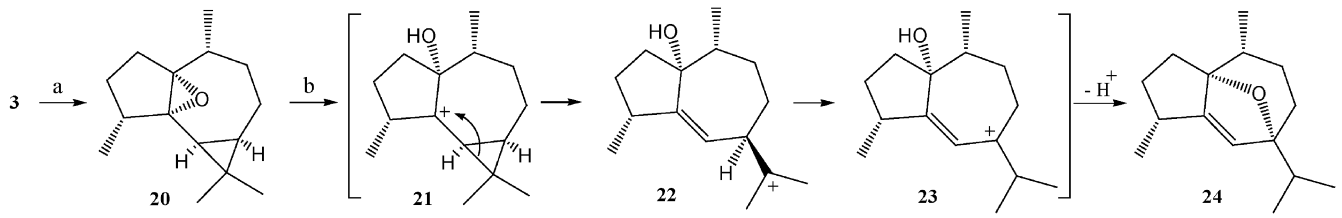
The conversion of a mixture of dienes **16** and **17**, which can be obtained from isoledene (**3**),[11] may be easier than a similar conversion of aromadendrene, ledene or isoledene, because a partly unsaturated azulene skeleton is already present in these dienes and just further dehydrogenation has to take place. Because the dienes are unstable compounds, the mixture was used without further purification in the dehydrogenation reactions. Indeed dehydrogenation of the mixture of **16** and **17** gave an improved 22% isolated yield of guaiazulene (**19**) (Scheme 3), when the dienes are dissolved in mesitylene and stirred overnight at 160°C in the presence of sulphur. Dehydrogenation of aromadendrene or isoledene under these conditions led to the formation of mixtures of products, including guaiazulene, but purification of these mixtures was difficult. According to Yamin et al.[28] aromadendrene can be dehydrogenated to guaiazulene with dithioglycolate esters under thermal or photochemical conditions in a yield up to 18%. When di-*tert*-butylperoxide is added to the reaction mixture, the yield even can be improved to 48%. However, when these reaction conditions were applied to the mixture of **16** and **17** or to the distillation tail of *Eucalyptus globulus*,[2] almost no guaiazulene was obtained in our hands.

Epoxidation of isoledene (**3**) gave the corresponding α-epoxide **20** as the sole product. The α configuration of **20** has not been proven in a direct manner, but has been deduced after its conversion to ether **24** followed by several reactions of the latter and n.O.e studies of the reaction products (Scheme 5). Epoxide **20** can be rearranged under the influence of Lewis acids. Reaction of **20** at room temperature with 1.3 equiv. of $BF_3{\cdot}Et_2O$ led to an 80% yield of **24** (Scheme 4).

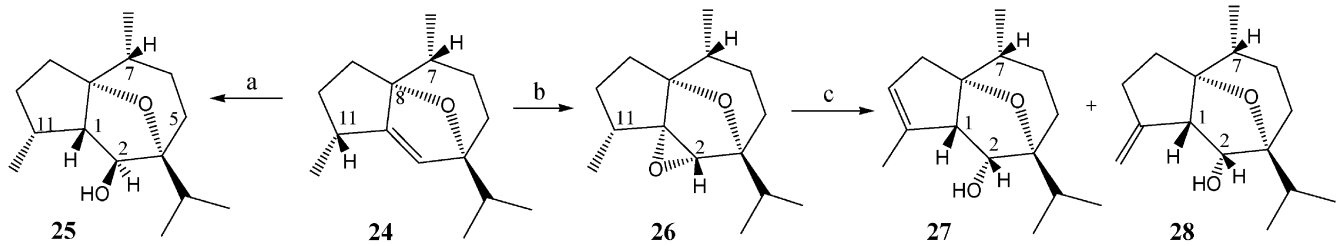
The formation of this product can be explained by opening of the epoxide to the α-cyclopropylcarbinyl carbocation **21**, which in turn undergoes opening of its cyclopropane ring to the homoallylic carbocation **22**. For stereochemical reasons no intramolecular ether formation can take place by reaction of this β orientated carbocation with the α-hydroxyl group at C8. So a hydride shift takes place in **22** (vide infra) to the more stable allylic carbocation **23**, which now can react intramolecularly with the hydroxyl group at C8 to form the α-ether bridge in **24**.

Hydroboration of **24** using $BH_3{\cdot}DMS$ resulted in a 71% yield of the β-alcohol **25** (Scheme 5). From n.O.e difference experiments on **25**, which revealed n.O.e.'s between H-2 and the Me group at C11 and between H-1 and H-7, it was concluded that BH_3 adds to the more sterically hindered β-face of the double bond in **24**. Addition to the more open α-face is in this specific case energetically less favourable because such a process will lead to a highly strained compound in which two 5-membered rings are *trans*-fused.

On the other hand, epoxidation of **24** with *m*CPBA gave the highly strained epoxide **26** as the sole product in 97% yield. Apparently, *m*CPBA is too large (much larger than BH_3) to overcome the steric hindrance caused by the C5–C6–C7 segment, leaving α-attack as the only possible reaction pathway. The stereochemistry of **26** could be established unambiguously using n.O.e difference experiments. Most relevant are the strong positive enhancements of H-11 and H-6β upon irradiation of H-2. Under the influence of $BF_3{\cdot}$etherate **26** showed a smooth reaction resulting in a 98% yield of a separable 3:1 mixture of **27** and **28**, respectively. Their 2D NOESY spectra in which strong



Scheme 4. (a) *m*CPBA, CH_2Cl_2 (97%); (b) $BF_3{\cdot}Et_2O$ (80%).



Scheme 5. (a) BH_3·DMS; H_2O_2 (71%); (b) *m*CPBA, CH_2Cl_2 (97%); (c) BF_3·Et_2O (72% of **27**, 26% of **28**).

n.O.e's between H-1 and H-2 and between H-1 and H-7 were observed for both **27** and **28**, are in agreement with the assigned stereochemistry. Their formation can easily be explained by opening of the epoxide ring followed by a C11→C1 1,2-H shift and proton loss. Relief of strain is most likely the driving force in this reaction since **27** and **28** are much less strained than **26**. These reactions on **24** and the NMR analyses of its reaction products indicate that the ether bridge is α-positioned and, consequently, the epoxide ring in **20** must have the same position.

A different rearrangement of **20** took place upon treatment with TsOH in acetone in the presence of some water (Scheme 6). Under these conditions ether **31** was obtained as the main product (41%), together with diene **32** (20%) and a small amount (10%) of **24**. The yield of **32** increased by using more acid or when a longer reaction time was applied.

This different product formation can be also explained by initial opening of the epoxide in **20** to α-cyclopropylcarbinyl carbocation **21**. However, the homoallylic carbocation, which is formed after opening of the cyclopropane ring, is now attacked by water to give diol **29**. Protonation of the hydroxyl group at C8 in **29** and elimination of water then leads to the allylic carbocation **30**, which either can be captured intramolecularly by the hydroxyl group to afford the β-cyclic ether **31** (route a), or undergoes elimination of acetone to give the unstable diene **32** (route b).

Functionalisation of the double bond in cyclic ether **31** proved to be more difficult than in **24**. Epoxidation of **31** did take place, but the reaction time was much longer than with **24**. Hydrogenation of **31** did not work and also ether opening did not give good results in our hands. The different steric situations in the two ethers are probably responsible for this different behaviour.

3. Conclusions

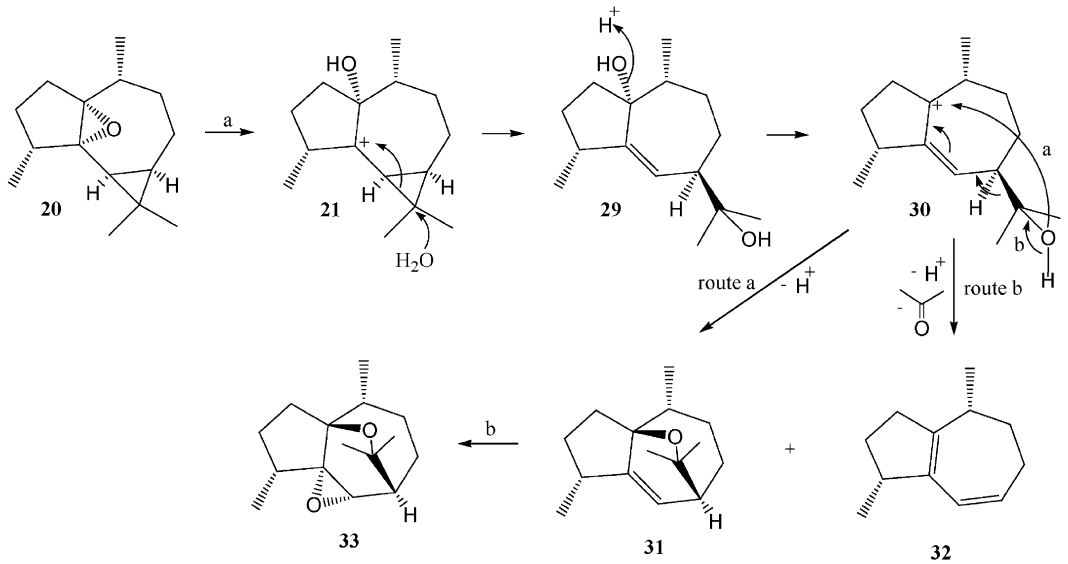
New chemistry of ledene has been developed, which leads to the conclusion that reactions take place preferably from the β-side. Rearrangement of the β-epoxide or β-diol derived from ledene preferably takes place via carbocations at C8, and lead to cubebane and cadinane skeletons.

Epoxidation of isoledene takes place from the α-side. The reaction pattern of isoledene and its epoxide is governed by the easy formation of a stable α-cyclopropylcarbinyl carbocation. In this carbocation the C2–C3 bond of the cyclopropane ring is broken, which leads to products with a guaiane skeleton. Guaiane-type dienes, guaiazulene, and unsaturated cyclic ethers are obtained, the latter can be functionalised further using standard chemistry.

4. Experimental

4.1. General

^{1}H NMR spectra (200 MHz) and ^{13}C NMR spectra



Scheme 6. (a) TsOH, acetone (42% of **31**); (b) *m*CPBA (86%).

(50 MHz) were recorded on a Bruker AC-E 200. The Varian Inova 400 and 600 were used to record ^{1}H NMR spectra at 400 and 600 MHz, respectively. $CDCl_3$ was used as solvent, unless stated otherwise, and chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). MS and HRMS data were obtained with a Finnigan Mat 95 spectrometer. MSD spectra were recorded on a HP5973 spectrometer. Analytical data were obtained using a Carlo Erba Analyzer 1106. GC analyses were performed using a Fisons GC 8000 gas chromatograph with a flame ionisation detector and a DB-17 fused silica capillary column (30 m×0.25 mm i.d., film thickness 0.25 μm). GC peak areas were integrated electronically with a Fisons integrator DP700 or the Lab Systems X-Chrom integrating system. For dry reactions flasks were dried at 125°C, flushed with nitrogen just before use and kept under nitrogen atmosphere during the reaction. Column and flash chromatography were performed with ICN silica gel 60 (230–400 mesh), using mixtures of petroleum ether bp 40–60°C (PE) and ethyl acetate (EA) as eluents, unless reported otherwise.

4.1.1. (1a*R*,7*R*,7a*S*,7b*R*)-1,1,4,7-Tetramethyl-1a,2,3,5,6,7,7a,7b-octahydro-1*H*-cyclopropa[*e*]azulene (ledene) (2). To a stirred solution of 15 g of the distillation tail of the oil of *Eucalyptus globulus*[1,2] in 500 mL of DMSO was added 18.1 g (0.16 mol) of KO*t*Bu. The reaction mixture was stirred at 100°C for 19 h, and an additional portion of 3.0 g (0.03 mol) of KO*t*Bu was added. The reaction mixture was stirred for another 4 h, and then allowed to come to room temperature. The reaction mixture was diluted with 750 mL of water and extracted with five 200-mL portions of PE. The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the remaining residue was column chromatographed twice (PE) to give 2.22 g (15%) of pure **2** and 5.67 g (38%) of a fraction with 74% of **2** (according to GC), both fractions as light yellow oils. ^{1}H NMR and ^{13}C NMR were in accordance with literature data.[3,29] HRMS calcd for $C_{15}H_{24}$ (M^+) 204.1878, found 204.1882.

A similar experiment on small scale with pure aromadendrene as starting material provided **2** in 80% yield.

4.1.2. (1a*R*,4*R*,7*R*,7b*S*)-1,1,4,7-Tetramethyl-1a,2,3,4,5,6,7,7b-octahydro-1*H*-cyclopropa[*e*]azulene (isoledene) (3). To 100 g of mechanically stirred basic Al_2O_3 (dried at 250°C under reduced pressure) was carefully added 10 g (0.25 mol) of potassium in small portions at 200°C under an argon atmosphere. The resulting blue powder was allowed to come to room temperature, cooled to 0°C and mixed with 80 mL of dry hexane. To this stirred suspension a solution of 32.5 g of the distillation tail of the oil of *Eucalyptus globulus* in 50 mL of dry hexane was added. The ice bath was removed and the suspension was stirred overnight. The green suspension was filtered through a glass-filter and the filter cake was washed carefully with an ether/hexane mixture (1:1). The filtrate was evaporated under reduced pressure to yield 31.5 g (96%) of **3** as a colourless oil. ^{1}H NMR and ^{13}C NMR were in accordance with literature data.[30]

4.1.3. (1*R*,3a*R*,4a*S*,6a*R*,7a*R*,7b*S*)-1,4a,7,7-Tetramethyl-decahydrocyclopropa[7,8]azuleno-[3a,4-*b*]oxirene (4). To a stirred solution of 0.50 g (2.45 mmol) of **2** in 40 mL of CH_2Cl_2 were added 40 mL of acetone, 40 mL of water, 100 mg (0.38 mmol) of 18-crown-6 and 4.0 g (48 mmol) of $NaHCO_3$. The reaction mixture was cooled to 0°C and then a solution of 5.4 g of Oxone (min 4.5% of active oxygen) in 30 mL of water was added. After stirring for 2 h at 0°C, the reaction mixture was diluted with 200 mL of saturated aqueous $NaHCO_3$ and extracted with four 100-mL portions of CH_2Cl_2. The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure to yield 0.52 g (96%) of **4** as a colourless oil. ^{1}H NMR and ^{13}C NMR were in accordance with literature data.[14] HRMS calcd for $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1827.

4.1.4. (1a*R*,4*S*,7*R*,7a*S*,7b*R*)-1,1,4,7-Tetramethyl-1a,2,3,4,6,7,7a,7b-octahydro-1*H*-cyclopropa[*e*]azulen-4-ol (5). To a solution of 80 μL (1.25 mmol) of Et_2NH in 5 mL of dry Et_2O, cooled to 0°C, was added 0.78 mL 1.6 M *n*BuLi in hexane. After stirring for 15 min, a solution of 110 mg (0.50 mmol) of **4** in 2 mL of dry Et_2O was added. After 2 h, the reaction mixture was allowed to come to room temperature and stirring was continued for 1 day. The reaction mixture was diluted with 50 mL of water and extracted with four 25-mL portions of Et_2O. The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$ and evaporated. The residue was column chromatographed (PE/EA 10:1) to yield 70 mg (57%) of **5** as a colourless oil. ^{1}H NMR was in accordance with literature data.[15] ^{13}C NMR δ 15.6 (q), 16.2 (q), 19.4 (t), 20.1 (s), 25.1 (d), 28.0 (d), 28.9 (q), 30.0 (q), 37.8 (t), 38.4(d), 42.4 (t), 43.8 (d), 71.9 (s), 123.1 (d), 154.9 (s). MSD *m*/*z* (r.i.) 220 (M^+, 9), 159 (91), 125 (43), 123 (46), 117 (43), 105 (49), 95 (54), 91 (62), 77 (43), 43 (100).

4.1.5. 2-[(3*R*,3a*S*,3b*R*,4*R*)-3,7-Dimethyl-2,3,3a,3b,4,5-hexahydro-1*H* cyclopenta[2,3]cyclo-propa[1,2-*a*]benzen-4-yl]-2-propanol (7) and (2a*R*,8*R*,8a*R*,8b*R*)-2,2,5,8-tetramethyl-2a,3,4,6,7,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan (8). To a stirred solution of 110 mg (0.50 mmol) of **4** in 6 mL of THF/H_2O 1:1 were added 2 drops of concentrated H_2SO_4. After stirring for 2 h at 30°C, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with three 30-mL portions of CH_2Cl_2. The organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 10:1) to yield 50 mg (45%) of pure **8** and 20 mg of **7** (GC purity ca. 80%), both fractions as colourless oils. ^{1}H NMR and ^{13}C NMR of **7** and **8** were in accordance with literature data.[14,31,32]

4.1.6. (2a*R*,8*R*,8a*R*,8b*R*)-2,2,5,8-Tetramethyl-2a,3,4,6,7,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan (8) from epoxide 4. To a stirred solution of 128 mg (0.58 mmol) of **4** in 6 mL of THF/H_2O 1:1, cooled to 0°C, were added 2 drops of concentrated H_2SO_4. After stirring for 15 min at 0°C the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with three 30-mL portions of CH_2Cl_2. The organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to yield 150 mg of a 5.5:1 mixture of **7** and **8**, respectively.

To a stirred solution of this mixture in 5 mL of THF/H_2O 1:1 were added 2 drops of concentrated H_2SO_4. After stirring for 1 day, the reaction mixture was diluted with water and extracted with three 25-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to yield 100 mg of crude **8** (GC purity ca. 80%).

4.1.7. (1a*R*,4*S*,4a*R*,7*R*,7a*S*,7b*R*)-1,1,4,7-Tetramethyldecahydro-4a*H*-cyclopropa-[*e*]azulene-4,4a-diol (6). To a stirred solution of 1.65 g (8.1 mmol) of ledene (**2**) in 60 mL of 96% EtOH, cooled to 0°C, was added dropwise a solution of 1.54 g (9.7 mmol) of $KMnO_4$ in 38 mL of water over a period of 2 h. The reaction mixture was then diluted with 200 mL of water and extracted with four 100-mL portions of CH_2Cl_2. To remove the brown impurities, the organic layer was filtered through celite. The filtrate was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallised twice from PE to yield 1.03 g (54%) of pure **6**. IR (CCl_4) 3620, 3562, 2965, 2930, 2871, 1458, 1375 cm^{-1}. ^1H NMR and ^{13}C NMR were in accordance with literature data.[7] HRMS calcd for $C_{15}H_{26}O_2$ (M^+) 238.1933, found 238.1933.

4.1.8. (2a*R*,8*R*,8a*R*,8b*R*)-2,2,5,8-Tetramethyl-2a,3,4,6,7,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan (8). To a stirred solution of 95 mg (0.40 mmol) of **6** in 4 mL of THF/H_2O 1:1, cooled to 0°C, were added 6 mL of HOAc and a few crystals of I_2. After stirring for 4 days at room temperature, the reaction mixture was diluted with 50 mL of 2% aqueous $Na_2S_2O_3$ and extracted with four 25-mL portions of CH_2Cl_2. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 10:1) to yield 40 mg of **8** (78% pure according to GC-analysis) as a colourless oil.

4.1.9. Guaiazulene (19). To a stirred solution of 0.80 g (3.9 mmol) of **3** in 80 mL of CH_2Cl_2 was added 0.2 mL of $BF_3{\cdot}Et_2O$. After stirring at room temperature for 3 h, the reaction mixture was diluted with 100 mL of saturated aqueous $NaHCO_3$ and extracted with three 100-mL portions of CH_2Cl_2. The combined organic layers were washed twice with saturated aqueous $NaHCO_3$ and once with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The remaining residue was chromatographed (PE) to give a ca. 4:3 mixture of the known dienes **16** and **17**,[11] respectively, in quantitative yield. A 200 mg-sample of this mixture was dissolved in 3 mL of mesitylene and 0.10 g of sulfur was added. The reaction mixture was heated at 160°C overnight, allowed to come to room temperature and chromatographed over basic Al_2O_3 (PE) to yield 42 mg (22%) of pure **19**. ^1H NMR and ^{13}C NMR were in accordance with literature data.[31,32,33]

4.1.10. (1*S*,3*R*,6*R*,7*R*,10*R*,11*S*)-2,2,6,10-Tetramethyl-12-oxatetracyclo[6.3.1.0^{1,3}.0^{7,11}]dodecane (20). To a stirred solution of 12.5 g (61.3 mmol) of **3** in 250 mL of CH_2Cl_2 was added dropwise a solution of 22.6 g (0.09–0.10 mol) of 70–75% *m*CPBA in 250 mL of CH_2Cl_2 at −10°C. The reaction mixture was then allowed to warm to 0°C. After stirring for 30 min, the mixture was diluted with 200 mL of saturated aqueous $Na_2S_2O_3$ and stirred for 30 min. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ and brine. The combined aqueous layers were extracted twice with 100 mL of PE and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine. The organic solution was dried and the solvent was evaporated under reduced pressure to yield 13.1 g (97%) of **20** as a colourless oil: IR (CCl_4) 2962, 2936, 2868, 1456, 1375 cm^{-1}; ^1H NMR δ 0.97 (s, 3H, *Me*), 1.03 (d, *J*=6.8 Hz, 3H, CH*Me*), 1.04 (d, *J*=6.4 Hz, 3H, CH*Me*), 1.07 (s, 3H, *Me*), 0.8–2.1 (m, 12H); ^{13}C NMR δ 14.1 (q), 18.0 (q), 18.3 (s), 19.4 (q), 23.6 (t), 25.5 (d), 27.0 (t), 28.3 (q), 28.8 (d), 30.4 (t), 31.1 (t), 38.6 (d), 39.2 (d), 74.2 (s), 75.1 (s). MS *m*/*z* (r.i.) 220 (M^+, 13), 205 (17), 202 (7), 177 (20), 159 (18), 123 (41), 112 (100), 83 (42). HRMS calcd for $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1821.

4.1.11. (1*R*,4*R*,7*R*,10*R*)-7-Isopropyl-4,10-dimethyl-11-oxatricyclo[5.3.2.0^{1,5}]undec-5-ene (24). To a stirred solution of 1.01 g (4.61 mmol) of **20** in 500 mL of dry Et_2O was added 0.65 mL (6.18 mmol) of $BF_3{\cdot}Et_2O$. After stirring for 10 min at room temperature, the reaction mixture was cooled to 0°C and diluted with 100 mL of saturated aqueous $NaHCO_3$. The organic layer was washed twice with saturated aqueous $NaHCO_3$ and once with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Flash chromatography on neutral alumina (PE) gave 812 mg (80%) of pure **24**. IR (CCl_4) 2959, 2931, 2872, 1673, 1460, 1376, 1042 cm^{-1}; ^1H NMR δ 0.91 (d, *J*=6.8 Hz, 3H, CH*Me*), 0.92 (d, *J*=6.8 Hz, 3H, CH*Me*), 1.05 (d, *J*=6.9 Hz, 3H, CH*Me*), 1.12 (d, *J*=6.6 Hz, 3H, CH*Me*), 1.15–1.79 (m, 8H), 1.91–2.11 (m, 2H), 2.41 (m, 1H, =CC*H*Me), 5.36 (d, *J*=2.5 Hz, 1H, CH=); ^{13}C NMR δ 13.7 (q), 17.2 (q), 17.6 (q), 17.7 (q), 23.5 (t), 26.0 (t), 30.6 (t), 30.9 (d), 31.3 (d), 34.6 (t), 35.6 (t), 95.9 (s), 97.5 (s), 118.0 (d), 159.7 (s). HRMS calcd for $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1828.

4.1.12. (1*R*,4*R*,5*R*,6*R*,7*R*,10*R*)-7-Isopropyl-4,10-dimethyl-11-oxatricyclo[5.3.2.0^{1,5}]undecan-6-ol (25). To a stirred solution of 532 mg (2.42 mmol) of **24** in 100 mL of dry THF was added dropwise 3.6 mL (7.26 mmol) of $BH_3{\cdot}DMS$ at room temperature. After stirring for 4 h, aqueous 4 M NaOH and 35% H_2O_2 were added in excess. After 30 min solid K_2CO_3 was added until saturation and the reaction mixture was extracted with three 100-mL portions of EA. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduce pressure. The residue was flash chromatographed (PE/EA 9:1) to yield 409 mg (71%) of **25** as white crystals: IR (CCl_4) 3635, 2959, 2933, 2875, 1466, 1375, 1085, 1057, 1037 cm^{-1}; ^1H NMR δ 0.92 (d, *J*=6.9 Hz, 3H, CH*Me*), 0.94 (d, *J*=6.9 Hz, 3H, CH*Me*), 1.01 (d, *J*=6.9 Hz, 3H, CH*Me*), 1.09 (d, *J*=6.5 Hz, 3H, CH*Me*), 1.15–2.27 (m, 13H), 4.01 (br s, 1H, C*H*OH); ^{13}C NMR δ 15.1 (q), 15.3 (q), 16.6 (q), 18.1 (q), 21.8 (t), 26.9 (t), 33.6 (t), 35.1 (d), 35.3 (t), 36.0 (d), 36.2 (d), 59.5 (d), 75.5 (d), 85.2 (s), 93.0 (s). MS *m*/*z* (r.i.) 238 (M^+, 56), 220 (32), 149 (62), 135 (29), 134 (79), 122 (31), 111 (100), 86 (32), 71 (31), 43 (33). HRMS calcd for $C_{15}H_{26}O_2$ (M^+) 238.1933, found 238.1938.

4.1.13. (1*S*,3*S*,4*R*,7*R*,8*R*,11*R*)-4-Isopropyl-7,11-dimethyl-2,12-dioxatetracyclo-[6.3.3.0^{1,3}.0^{1,8}]dodecane (26). To a stirred solution of 1.1 g (5.0 mmol) of **24** in 50 mL of

CH_2Cl_2 was added dropwise a solution of 1.5 g (6.0–6.5 mmol) of 70–75% *m*CPBA in 50 mL of CH_2Cl_2 at 0°C. After stirring for 1 h at 0°C, the reaction mixture was diluted with 50 mL of saturated aqueous $Na_2S_2O_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated under reduced pressure to yield 1.15 g (97%) of **26**: IR (CCl_4) 2966, 2943, 2906, 2872, 1463, 1081, 1053, 977, 903 cm^{-1}; ^1H NMR (600 MHz) δ 0.95 (d, *J*=6.9 Hz, 3H, CH*Me*), 0.97 (d, *J*=7.1 Hz, 3H, CH*Me*), 0.98 (d, *J*=7.1 Hz, 3H, CH*Me*), 1.04 (d, *J*=6.9 Hz, 3H, CH*Me*), 1.31 (dd, *J*=13.8, 5.4 Hz, 1H, CH_2CHCHMe), 1.32 (dd, *J*=13.8, 5.4 Hz, 1H, $CHCH_2$CHMe), 1.61–1.71 (m, 2H, CH_2CH_2CHMe), 1.65 (qd, *J*=6.9, 6.6 Hz, 1H, CHMe), 1.72 (ddd, *J*=13.8, 13.8, 5.4 Hz, 1H, $CHCH_2$CHMe), 1.82 (dddd, *J*=13.2, 13.2, 7.0, 3.6 Hz, 1H, CH_2CHCHMe), 1.87 (dddd, *J*=13.8, 13.8, 6.6, 5.4 Hz, 1H, CH_2CHCHMe), 1.98 (septet, *J*=7.1 Hz, 1H, $CHMe_2$), 2.27 (dddd, *J*=13.2, 9.8, 8.5, 8.5 Hz, 1H, CH_2CHCHMe), 2.51 (ddq, *J*=9.8, 7.0, 6.9 Hz, 1H, CHMe), 3.58 (s, 1H, CHOC); ^{13}C NMR δ 14.0 (q), 14.7 (q), 17.1 (q), 17.9 (q), 20.9 (t), 23.8 (t), 25.4 (d), 26.4 (t), 30.3 (d), 32.4 (d), 35.1 (t), 56.4 (d), 76.9 (s), 88.4 (s), 91.1 (s). MS *m*/*z* (r.i.) 236 (M^+, 11), 218 (4), 207 (8), 203 (10), 175 (10), 147 (100), 138 (54), 123 (45), 109 (64), 43 (35). HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1776.

4.1.14. (1*R*,5*S*,6*R*,7*R*,10*R*)-7-Isopropyl-4,10-dimethyl-11-oxatricyclo[5.3.2.0^{1,5}]undec-3-en-6-ol (27) and (1*R*,5*S*,6*R*,7*R*,10*R*)-7-isopropyl-10-methyl-4-methylene-11-oxatricyclo-[5.3.2.0^{1,5}]undecan-6-ol (28). To a stirred solution of 560 mg (2.37 mmol) of **26** in 100 mL of dry Et_2O was added 0.3 mL (2.85 mmol) of $BF_3{\cdot}Et_2O$ at 0°C. After stirring for 2 h at 0°C, the reaction mixture was diluted with 50 mL of saturated aqueous $NaHCO_3$. The organic layer was washed twice with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 19:1) to yield 403 mg (72%) of **27** and 145 mg (26%) of **28**.

Compound **27**: IR (CCl_4) 3578, 2961, 2877, 2840, 1709, 1466, 1400, 1377, 1075, 1047 cm^{-1}; ^1H NMR (400 MHz) δ 0.87 (d, *J*=6.8 Hz, 3H, CH*Me*), 0.99 (d, *J*=6.9 Hz, 3H, CH*Me*), 1.00 (d, *J*=6.9 Hz, 3H, CH*Me*), 1.15 (m, 1H), 1.43 (m, 1H), 1.44 (d, *J*=4.5 Hz, 1H), 1.52 (m, 1H), 1.71–1.79 (m, 2H), 1.83 (br s, 3H, =C*Me*), 2.05 (septet, *J*=6.9 Hz, 1H, $CHMe_2$), 2.14 (ddt, *J*=17.4, 4.7, 2.3 Hz, 1H), 2.35 (ddt, *J*=17.4, 4.0, 2.0 Hz, 1H), 3.17 (d, *J*=7.4 Hz, 1H, =CC*H*CHOH), 4.07 (dd, *J*=7.4, 4.5 Hz, 1H, C*H*OH), 5.39 (br s, 1H, CH_2CH=); ^{13}C NMR (100 MHz) δ 14.0 (q), 17.7 (q), 17.9 (q), 18.0 (q), 19.8 (t), 25.6 (t), 31.4 (d), 35.4 (d), 42.1 (t), 63.4 (d), 76.3 (d), 89.8 (s), 92.8 (s), 127.8 (d), 137.9 (s). MS *m*/*z* (r.i.) 236 (M^+, 87), 218 (7), 175 (11), 147 (62), 132 (49), 121 (23), 120 (22), 109 (100), 43 (21). HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1779.

Compound **28**: IR (CCl_4) 3547, 2961, 2876, 1466 1376, 1176, 1115, 1079, 1055 cm^{-1}; ^1H NMR (400 MHz) δ 0.93 (d, *J*=6.8 Hz, 3H, CH*Me*), 1.00 (d, *J*=6.9 Hz, 3H, CH*Me*), 1.04 (d, *J*=6.9 Hz, 3H, CH*Me*), 1.25 (m, 1H), 1.37 (dt, *J*=13.1, 7.4 Hz, 1H), 1.49 (m, 2H), 1.74 (m, 2H), 1.93 (d, *J*=4.6 Hz, 1H), 1.96 (dd, *J*=13.0, 7.4 Hz, 1H), 2.12 (septet, *J*=6.9 Hz, H-3), 2.31 (dd, *J*=15.3, 7.3 Hz, 1H), 2.58 (m, 1H), 3.13 (d, *J*=8.1 Hz, 1H, =CC*H*CHOH), 4.10 (dd, *J*=8.1, 4.6 Hz, 1H, C*H*OH), 4.90 (br s, 1H, C*H*=), 5.29 (br s, 1H, C*H*=); ^{13}C NMR (100 MHz) δ 14.4 (q), 18.2 (q), 18.3 (q), 21.6 (t), 26.3 (t), 31.6 (d), 34.1 (t), 34.5 (t), 35.1 (d), 59.5 (d), 76.1 (d), 90.3 (s), 94.3 (s), 112.4 (t), 151.1 (s). MS *m*/*z* (r.i.) 236 (M^+, 64), 218 (5), 147 (54), 137 (31), 132 (14), 120 (21), 109 (100), 108 (16), 81 (18), 71 (31), 43 (30). HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1779.

4.1.15. (1*S*,4*R*,7*R*,10*R*)-4,10,12,12-Tetramethyl-11-oxatricyclo[5.3.2.0^{1,5}]dodec-5-ene (31) and (1*R*,4*R*)-1,4-dimethyl-1,2,3,4,5,6-hexahydroazulene (32). To a stirred solution of 200 mg (0.91 mmol) of **20** in 20 mL of acetone was added 16 mg (0.08 mmol) of $TsOH{\cdot}H_2O$ at room temperature. After stirring for 10 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with three 20-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was column chromatographed (PE–PE/EA 99:1) to yield 19 mg (10%) of **24**, 83 mg (42%) of **31** and 30 mg (20%) of **32** as an unstable oil.

Compound **31**: IR (neat) 1453, 1375, 1141, 1019 cm^{-1}; ^1H NMR δ 0.81 (d, *J*=7.1 Hz, 3H, CH*Me*), 1.00 (s, 3H, *Me*), 1.18 (d, *J*=6.8 Hz, 3H, CH*Me*), 1.28 (s, 3H, *Me*), 1.21–2.15 (m, 12H), 2.67 (m, 1H), 5.91 (dd, *J*=2.5, 7.7 Hz, 1H, C*H*=); ^{13}C NMR δ 18.5 (q), 19.1 (q), 22.0 (t), 30.1 (q), 30.5 (q), 32.7 (t), 32.2 (t), 35.5 (d), 38.7 (q), 40.4 (d), 42.4 (d), 75.4 (s), 86.8 (s), 121.5 (d), 149.1 (s); MS *m*/*z* (r.i.) 220 (M^+, 67), 205 (100), 177 (32), 162 (20), 149 (20), 138 (87), 123 (40), 109 (28), 105 (22), 91 (23). HRMS calcd for $C_{15}H_{24}O$ (M^+) 220.1827, found 220.1824.

Compound **32**: ^1H NMR (C_6D_6) δ 1.02 (d, *J*=7.0 Hz, 3H, CH*Me*), 1.11 (d, *J*=6.8 Hz, 3H, CH*Me*), 0.9–2.9 (m, 10H), 5.8–6.1 (m, 2H, C*H*=C*H*); ^{13}C NMR (C_6D_6) δ 19.8 (q), 20.2 (q), 26.9 (t), 31.3 (t), 31.7 (t), 35.8 (d), 36.0 (t), 44.5 (d), 124.4 (d), 132.1 (d), 142.4 (s), 144.1 (s). Due to the instability of diene **32**, no satisfactory HRMS data have been obtained.

4.1.16. (1*S*,4*R*,5*S*,7*R*,8*R*,11*R*)-4,11,13,13-Tetramethyl-6,12-dioxatetracyclo[6.3.2.0^{1,5}.0^{5,7}]tridecane (33). To a stirred solution of 450 mg (2.1 mmol) of **31** in 25 mL of CH_2Cl_2 was added dropwise a solution of 1.0 g (4.1–4.3 mmol) of 70–75% *m*CPBA in 25 mL of CH_2Cl_2 at room temperature. After stirring for 7 days, the reaction mixture was diluted with 50 mL of saturated aqueous $Na_2S_2O_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The combined aqueous layers were extracted with two 25-mL portions of ether. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was column chromatographed (PE/EA 49:1) to yield 415 mg (86%) of **33**: ^1H NMR δ 0.98 (d, *J*=6.9 Hz, 3H, CH*Me*), 1.07 (d, *J*=7.0 Hz, 3H, CH*Me*), 1.12 (s, 3H, *Me*), 1.45 (s, 3H, *Me*), 1.50–2.14 (m, 11H), 3.31 (d, *J*=6.2 Hz, 1H, CHOC); ^{13}C NMR δ 15.3 (q), 16.6 (q), 20.1 (t), 26.2 (t), 26.8 (q), 29.8 (q), 30.0 (t), 36.4 (d), 36.9 (t), 38.5 (d), 38.7 (d), 58.5 (d), 66.5 (s), 73.6 (s), 85.8 (s); MS *m*/*z* (r.i.) 236 (M^+, 6), 178 (62), 123 (100),

114 (57), 109 (45), 95 (43), 81 (70), 69 (42), 55 (47), 43 (62), 41 (63). HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1770.

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