Stereoselective synthesis of (−)-metasequoic acid B

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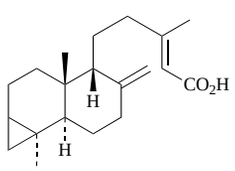
A stereoselective synthesis of the *ent*-labdane diterpene (−)-metasequoic acid B (*ent*-2) and its corresponding methyl ester (*ent*-3) starting from (*R*)-(−)-carvone 6 is described. The synthesis is based on the construction of a phenanthrenone system 5 which is converted into the *ent*-labdane skeleton after selective cleavage of the C(13)–C(14) bond.

Introduction

Metasequoic acids A **1** and B **2** are two new antifungal diterpenes recently isolated from *Metasequoia glyptostroboides* Hu et Cheng.[1] The methyl ester of metasequoic acid B **3** had previously been isolated from the resin *Pinus strobus*.[2] These compounds, which were found to inhibit the spore germination of *Pyricularia oryzae*, have a labdane skeleton with an unusual cyclopropane ring fused at C(3) and C(4).† Compounds with a cyclopropane moiety of this kind are rare among the diterpenoids,[3] and these two compounds represent one of the few labdanes known with a cyclopropane ring.[4] The structures of **1** and **2**, as well as that of the natural methyl ester **3**, were established by means of spectroscopic analysis, although the absolute configuration of these compounds has yet to be resolved.



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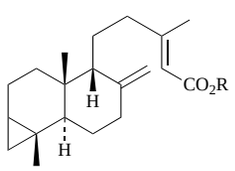
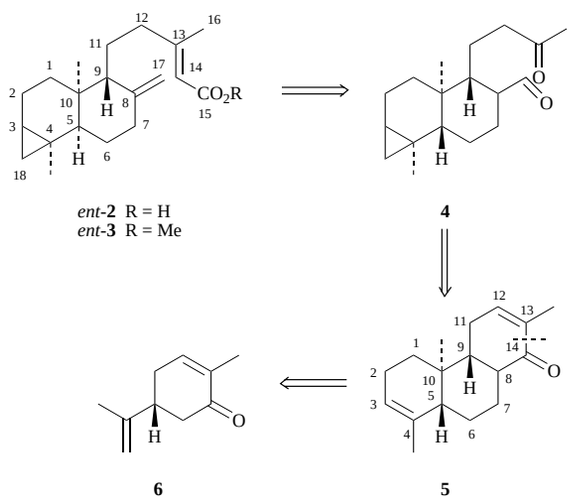


2 R = H
3 R = Me

As part of our research program related to the utilization of commercial carvone as the chiral starting material for the synthesis of polycyclic terpenes and steroids,[5] we wish to describe here the first and efficient stereoselective synthesis of (−)-metasequoic acid B *ent*-**2**‡ and its corresponding methyl ester *ent*-**3**. As shown in Scheme 1, the phenanthrenone **5**, easily prepared from carvone **6**, was considered to be a good chiral synthon for the elaboration of the labdane skeleton, since the stereogenic centres C(5), C(9) and C(10) of **5** can be elaborated into *ent*-**2** by selective and oxidative cleavage of the ring C as shown with a dotted line.

Results and discussion

As mentioned above, the synthesis of (−)-metasequoic acid B *ent*-**2** commences with the preparation of the tricyclic compound **5** (Scheme 2), which can also serve as a key intermediate in the synthesis of other polycyclic terpenes. Towards this end (*R*)-(−)-carvone **6** was transformed into the aldehyde **9** following the procedure previously described by us.[5] Thus, conversion of **6** into the β-keto ester **7** using Mander's methoxycarbonylation procedure,[6] followed by stereoselective alkylation of its sodium enolate with 3-iodopropionaldehyde diethyl acetal[7] in dimethylformamide (DMF) and removal of the aldehyde acetal function of **8** with pyridinium toluene-*p*-sulfonate (PPTS) in aqueous acetone, afforded the keto aldehyde **9** in 85% overall yield from **6**.



ent-**2** R = H
ent-**3** R = Me

4

6

5

Scheme 1

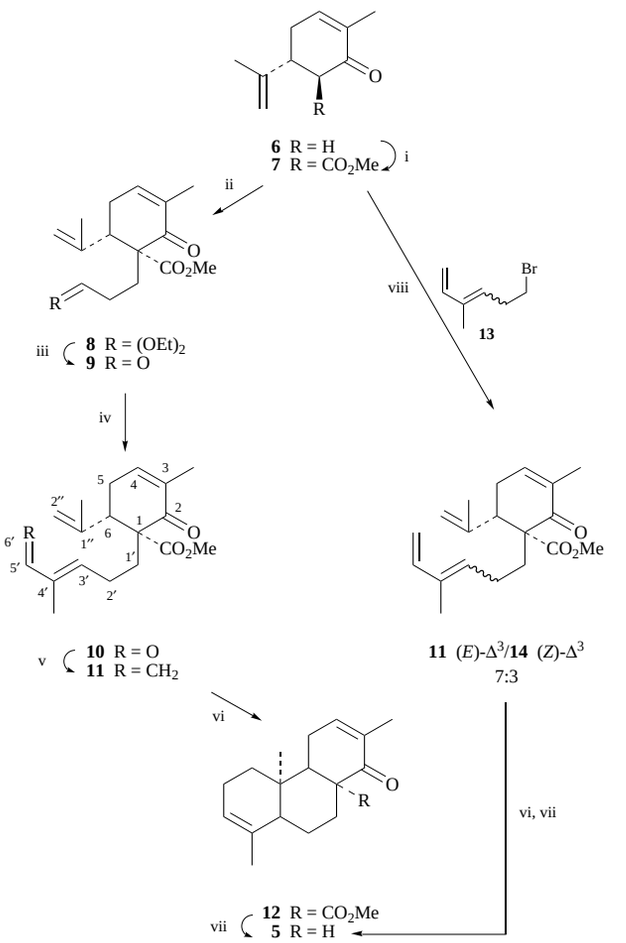
Wittig reaction of (α-formylethylidene)triphenylphosphorane[8] with the aldehyde **9** provided the chain-extended aldehyde **10** with little or no detectable trace of the corresponding *Z*-olefin. Subsequent standard Wittig methylenation of **10** gave the triene **11** in 78% overall yield for the two steps. The intramolecular Diels–Alder (IMDA) reaction of **11** was conducted at 185–190 °C in toluene solution to provide, after 5 days, the tricyclic product **12** in 92% yield. The use of a catalytic amount of propylene oxide was crucial for the success of the IMDA reaction since in its absence partial isomerization of the C(3)–C(4) double bond to the more stable C(4)–C(5) position occurred. The stereochemical assignment of **12**, the only diastereoisomer formed, was confirmed conclusively by nuclear Overhauser effect difference spectroscopy (NOEDS) measurements. In particular, irradiation of the C(10) methyl signal at δ 0.67 resulted in an enhancement of the signals corresponding to 3-H (δ 5.26), 2α-H (δ 2.0), 11α-H (δ 2.78) and the methyl group of the ester moiety at C(8) (δ 3.62). As noted earlier,[5] the diastereoselectivity observed in this IMDA reaction can be attributed to the severe non-bonding interactions developed in the transition state that would lead to the *cis-anti-trans* adduct, due to the presence of the methyl group at C(4) of the diene moiety.

† The usual diterpene nomenclature and numbering is used for all bicyclic and tricyclic compounds. Systematic IUPAC names are used for title compounds in the Experimental section.

‡ As it is deduced from the synthesis described in this paper, *vide infra*, the absolute configuration illustrated in structures **2** and **3** corresponds to that of the natural compounds. The compounds prepared by us belong to the enantiomeric *ent*-labdane series, *viz*. *ent*-**2** and *ent*-**3**.

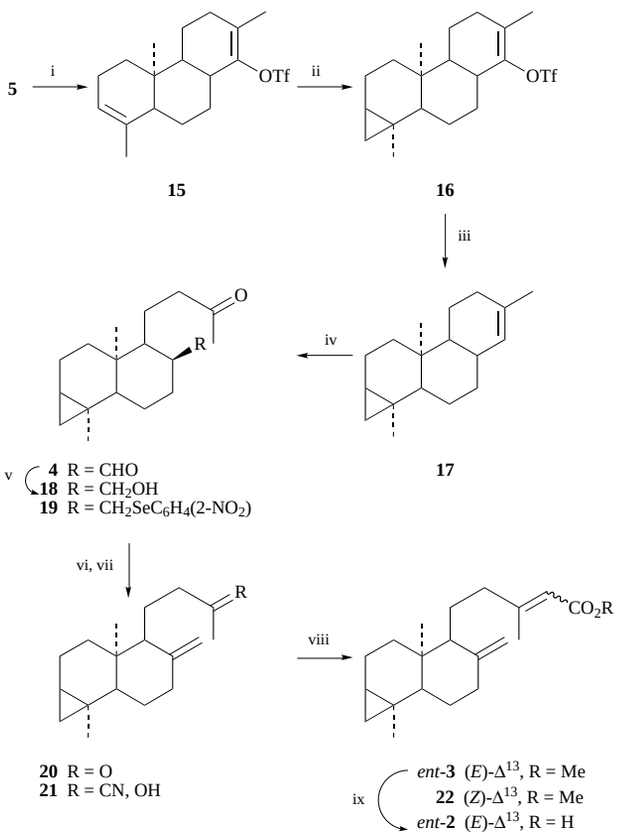
The synthesis of the key tricyclic intermediate **5** was completed by heating the β-keto ester **12** in water together with a catalytic amount of pyridine in a sealed tube at 230 °C for 24 h. The use of a catalytic amount of pyridine was necessary in this reaction to avoid, as occurred in the above IMDA reaction, isomerization of the C(3)–C(4) double bond. Smooth decarboxylation of **12** took place under these conditions to give **5** in 92% yield after column chromatography. The overall yield for the transformation of carvone into **5** (seven steps) was 56%.

As an alternative to the above described preparation of **11**, the Diels–Alder precursor was also synthesized from the β-keto ester **7** by direct incorporation of the 4-methylhexa-3,5-dienyl group through alkylation of its sodium enolate with 6-bromo-3-methylhexa-1,3-diene **13** in DMF at RT (Scheme 2). Since the alkylating reagent used, readily prepared in two steps from cyclopropyl methyl ketone,[9] is an inseparable 7:3 mixture of *E*/*Z* stereoisomers, the alkylation provided a similar mixture of *E*/*Z* olefin isomers, **11** and **14** respectively, in 70% yield. A small percent (10–15%) of unchanged **7** was always obtained, which could not be avoided by using longer reaction times or a larger excess of alkylating reagent. This fact suggests that competing elimination of the alkylating reagent also occurs during the alkylation.§[,10] Exposure of the diene mixture to the above reported IMDA reaction conditions, followed by aqueous thermolysis of the crude reaction mixture and chromatographic purification afforded the expected decarboxylated cycloadduct **5** in 59% overall yield for the two steps. The synthesis of **5** from **6** by this route (four steps) took place in 40% overall yield. This second option to prepare **5** from carvone, which avoids the use of expensive reagents and requires only two easy chromatographic purifications, seems the more appropriate for the preparation of **5** on a multigram scale.



Scheme 2 *Reagents and conditions*: (i) LDA, THF, −78 °C then HMPA, $NCCO_2Me$, 98%; (ii) NaH, DMF, 0 °C then $(EtO)_2CHCH_2CH_2I$, 94%; (iii) PPTS, acetone–H_2O, reflux, 92%; (iv) $Ph_3P{=}C(Me)CHO$, C_6H_6, reflux, 90%; (v) $Ph_3P{=}CH_2$, THF, −20 °C, 87%; (vi) toluene, 190 °C, 92%; (vii) H_2O/pyridine, 230 °C, 92% from **12** and 59% from **11**/**14** (see text); (viii), NaH, DMF then a 7:3 mixture of *E*/*Z*–**13**, 70%

The next objective after preparation of the tricyclic system **5** was the selective cleavage of the C(13)–C(14) bond necessary for completion of the labdane skeleton. The introduction of a double bond in this position followed by ozonolysis was considered to be the best for that purpose. Thus, conjugate reduction of the enone moiety of **5** (Scheme 3) with L-Selectride® and trapping of the intermediate enolate *in situ* with *N*-(5-chloro-2-pyridyl)triflimide[11] gave vinyl triflate **15** in 60% yield. Attempts to trap the enolate as the corresponding silyloxyalkene were unsuccessful and led exclusively to isolation of the saturated ketone. The different electron density of the two double bonds of **15** was utilized at this point to effect chemoselective cyclopropanation of the C(3)–C(4) double bond. Modified Simmons–Smith conditions (Et_2Zn, CH_2I_2) resulted in the formation of a single diastereoisomer, **16**, in 92% yield. The stereochemistry of the cyclopropanated compound was assigned on the basis of its spectral data and NOE experiments. In particular, irradiation of one of the cyclopropane methylene hydrogens (H-β) at δ −0.2 gave rise to enhancement of the signals corresponding to the other cyclopropane methylene hydrogen (H-α at δ 0.43) and the axially orientated hydrogens 1β-H at δ 0.58 and Hβ-5 at δ 1.01. On the other hand, irradi-



Scheme 3 *Reagents and conditions*: (i) L-Selectride, THF, −78 °C then *N*-(5-chloro-2-pyridyl)triflimide, −10 °C, 60%; (ii) Et_2Zn–I_2CH_2, toluene, RT, 92%; (iii) $Pd(OAc)_2(PPh_3)_2$, Bu_3N, HCO_2H, DMF, 60 °C, 86%; (iv) O_3, CH_2Cl_2–MeOH–pyridine, −78 °C then Me_2S, 88%; (v) $NaBH_4$, CH_2Cl_2–EtOH, −78 °C, 91%; (vi) *o*-$NO_2C_8H_4SeCN$, Bu_3P, THF, 0 °C then H_2O_2; (vii) KOH, MeOH, 70%; (viii) $(EtO)_2P(O)CHNaCO_2Me$, THF, 95%; (ix) KOH, EtOH–toluene, 78 °C, 85%

§ A similar alkylation reaction of **7** has been reported with 6-iodohexa-1,3-diene. Apparently no elimination occurs in this case; see reference 10.

ation of either of the cyclopropane methylene protons has no effect on the protons of the methyl group at C(10) (δ 0.79). These observations support the assignment of a β-stereochemistry to the cyclopropane ring in **16**. Since cleavage of the C(13)–C(14) double bond of **16** proved to be problematic, the triflate moiety was first reduced. Treatment of enol triflate **16** with the tributylammonium formate–palladium reducing system[12] afforded the olefin **17** in 86% yield. This underwent smooth cleavage of the double bond on treatment with ozone and reduction of the intermediate ozonide with dimethyl sulfide to generate the desired keto aldehyde **4** in 88% yield.

With the keto aldehyde **4** at hand, we were ready to introduce the exocyclic 8(17)-double bond of the target compound. This was realized through oxidation of a selenenyl compound. First, the keto aldehyde **4** was chemoselectively reduced to the keto alcohol **18**¶ in 91% yield by treatment with sodium borohydride in EtOH–CH_2Cl_2 at low temperature.[13] The alcohol **18** was then treated with 2-nitrophenyl selenocyanate[14] and tributyl phosphine in THF to give **19**, which was oxidized with aqueous hydrogen peroxide solution in THF in the presence of Na_2HPO_4 to give the ketone **20** contaminated with variable amounts of the cyanohydrin **21**. The isolation of **21** was not totally unexpected since formation of cyanohydrins by reaction of carbonyl compounds with aryl selenocyanates and tributylphosphine is a known reaction.[15] However, when the crude mixture obtained from **19** was treated with 1 M methanolic potassium hydroxide, prior to chromatographic purification, the ketone **20** was obtained as sole product in 70% yield for the whole process.

The final elaboration of **20** to the *ent*-labdane skeleton only required introduction of the methoxycarbonylmethylene moiety at C(13). This was effected as previously in related systems[16] by a Wadsworth–Emmons reaction of **20** with the methyl diethylphosphonoacetate anion in THF. In this way, a *ca.* 5:1 mixture (^{1}H NMR analysis) of (*E*)- and (*Z*)-α,β-unsaturated methyl esters *ent*-**3** and **22** was obtained in 95% yield. The two isomers could be separated by either careful MPLC or preparative HPLC, and thus pure *ent*-**3** was obtained. The synthetic methyl ester *ent*-**3** thus obtained had spectral characteristics identical with those previously reported for the natural compound;[2] the only difference was in the sign of the optical rotation, which suggests that the natural compound has the absolute stereochemistry illustrated in formula **3**.

In an attempt to avoid the above described cyanohydrin formation, we exchanged the order of projected steps to transform the hydroxymethylene moiety into the exocyclic 8(17)-double bond. Accordingly, initially we introduced the methoxycarbonylmethylene group at C(13) by a Wadsworth–Emmons reaction of the keto alcohol **18**. Although the reaction of **18** with the methyl diethylphosphonoacetate anion occurred in good yield, surprisingly, and in sharp contrast with the stereochemical result previously obtained for the same reaction of **20** and analogous methyl ketones,[17] a 1:1 mixture of the corresponding (*E*)- and (*Z*)-α,β-unsaturated methyl esters was obtained in this case.

Finally, the synthesis of metasequoic acid B (*ent*-**2**) was completed by alkaline hydrolysis of the methyl ester moiety of *ent*-**3** using KOH in a 4:1 mixture of EtOH and toluene at reflux for 2 h. As reported earlier,[16] under these conditions isomerization of the 13(14)-double bond is reduced to a minimum allowing the isolation by column chromatography of pure *ent*-**2** in 85% yield; this proved also to be spectroscopically identical with natural metasequoic acid B except for the sign of the optical rotation.

The synthesis of (−)-metasequoic acid B (*ent*-**2**) reported above is adaptable to the synthesis of the natural form **2**, since the required chiral starting material, (*S*)-(+)-carvone, is commercially available. The facile preparation of both enantiomers of the tricyclic system **5** makes, in principle, this compound and its derivatives useful intermediates in the synthesis of other diterpenes and related compounds.

Experimental

General conditions have been described earlier.[18] Silica gel 60 (Macherey Nagel, 0.015–0.04 mm) was used for medium-pressure liquid chromatography (MPLC). HPLC was performed using a 7.8 × 300 mm long μPorasil column. Spectroscopic data and experimental details for the preparation of compounds **7**, **8** and **9**, which were given in part in ref. 5 are given here in full. NMR assignments for tricyclic, bicyclic and monocyclic compounds are given with respect to the numbering scheme shown in structures *ent*-**2**, **5** and **11**, respectively.

Methyl (−)-(1*S*,6*R*)-6-isopropenyl-3-methyl-2-oxocyclohex-3-enecarboxylate 7

To a solution of LDA in THF (0.7 M solution; 44.3 cm^3, 31.1 mmol) at −78 °C was dropwise added a solution of commercial (*R*)-(−)-carvone (3.98 g, 25.9 mmol) in THF (20 cm^3). After the reaction mixture had been allowed to warm to −10 °C and then stirred at this temperature for 1 h, it was cooled to −78 °C, and treated with HMPA (4.5 cm^3) followed by methyl cyanoformate (3.2 cm^3, 38.9 mmol). After 30 min the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ether. Work-up afforded an oily residue, which was purified by column chromatography, using hexane–ethyl acetate (9:1) as eluent, to give the *β-keto ester* **7** (5.4 g, 98%) as an oil, bp 103 °C (2 mmHg) [lit.,[6] 142 (15 mmHg)]; $[\alpha]_D^{18}$ −30 (*c* 2.8, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3040–2800, 1743, 1672, 1360, 1260 and 900; δ_H(300 MHz, $CDCl_3$), 6.72 (1 H, m, 4-H), 4.80 (2 H, m, 2′-H), 3.69 (3 H, s, OMe), 3.46 (1 H, d, *J* 13, 1-H), 3.1 (1 H, ddd, *J* 13, 10.5 and 5, 6-H), 2.5–2.2 (2 H, m, 5-H), 1.76 (3 H, m, 3-Me) and 1.72 (3 H, s, 1′-Me); δ_C(75.5 MHz, $CDCl_3$), 15.71 (3-Me), 19.66 (1′-Me), 30.36 (C-5), 45.65 (C-6), 51.97 (CO_2C), 58.23 (C-1), 112.80 (C-2′), 134.8 (C-3), 144.48 (C-4), 144.55 (C-1′), 170.32 (CO_2) and 194.74 (C-2); *m*/*z* (CI) 210 ($M^+ + 2$, 10), 209 ($M^+ + 1$, 100), 178 (10), 177 (90), 167 (75), 149 (46), 135 (15), 123 (15) and 51 (3).

Preparation of 3-iodopropionaldehyde diethyl acetal

To a vigorously stirred solution of anhydrous NaI (3.29 g, 21.9 mmol) and acrolein (1.32 cm^3, 17.8 mmol) in MeCN (45 cm^3) was rapidly added chlorotrimethylsilane (2.79 cm^3, 21.9 mmol).[7] After the resulting mixture had been stirred for 5 min it was treated with EtOH (2.6 cm^3), added rapidly, and stirred for a further 20 min; it was then poured into 5% aqueous $NaHCO_3$ and extracted with pentane. The combined organic layers were washed successively with 5% aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4) and evaporated. The residual oil was purified by MPLC, using hexane–ethyl acetate (9:1) as eluent, to give 3-iodopropionaldehyde diethyl acetal (4.08 g, 88%) as an oil: δ_H(200 MHz, $CDCl_3$), 4.56 (1 H, t, *J* 6, 1-H), 3.57 (4 H, m, 2 × OCH_2CH$_3$), 3.17 (2 H, t, *J* 6, 3-H), 2.11 (2 H, q, *J* 6, 2-H) and 1.19 (6 H, t, *J* 6, 2 × OCH$_2$CH_3).

Methyl (+)-(6*S*,1*R*)-1-(3′,3′-diethoxypropyl)-6-isopropenyl-3-methyl-2-oxocyclohex-3-enecarboxylate 8

Compound **7** (2.55 g, 12.3 mmol) was added dropwise to a suspension of NaH (55%; 642 mg, 14.8 mmol, 1.2 equiv.) prewashed with pentane in DMF (25 cm^3) at 0 °C after which the mixture was warmed to RT and stirred for 1 h. It was then re-

¶ Although compound **18** was chromatographically homogeneous, its ^{1}H and ^{13}C NMR spectra showed the presence of a second minor component (10–15%), which could not be separated by any conventional purificiation procedure. We speculate on the possibility that an equilibrium between **18** and the corresponding intramolecular hemiketal is the origin of this observation. Several minor signals observed in the spectra of **18** seem to support this possibility, particularly the signal at 99.93 ppm observed in its ^{13}C NMR spectra, characteristic of a hemiketal carbon atom.

cooled to 0 °C and treated with 3-iodopropionaldehyde diethyl acetal (4.1 g, 15.9 mmol). After being stirred at RT for 2.5 h the reaction mixture was cooled in an ice-bath, quenched with water and extracted with ether. The combined extracts were washed with aqueous $Na_2S_2O_3$ and brine, dried, filtered and concentrated under reduced pressure. The residue was purified by chromatography, using hexane–ethyl acetate (9:1) as eluent, to afford *compound* **8** (3.89 g, 94%) as an oil [Found: M^+ (EI), 338.2089. $C_{19}H_{30}O_5$ requires *M*, 338.2093]; $[\alpha]_D^{20}$ +77 (*c* 2, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3070, 3015, 2990–2800, 1740, 1668, 1445, 1374, 1217, 1132, 1062, 913 and 734; δ_H(300 MHz, $CDCl_3$), 6.78 (1 H, m, 4-H), 4.89 (1 H, s, 2″-H), 4.80 (1 H, s, 2″-H′), 4.45 (1 H, dd, *J* 6 and 5, 3′-H), 3.62 (3 H, s, OMe), 3.61 (2 H, m, OCH_2CH_3), 3.47 (2 H, m, $OCH_2'CH_3$), 2.95 (1 H, dd, *J* 10 and 4.4, 6-H), 2.76 (1 H, m, 5α-H), 1.79 (3 H, m, 3-Me), 1.66 (3 H, s, 1″-Me) and 1.18 (6 H, t, *J* 6.5, 2 × OCH_2CH_3); δ_C(75.5 MHz, $CDCl_3$) 15.27 (2 × CH_3CH_2O), 16.41 (3-Me), 20.83 (1″-Me), 27.07 (C-1′), 28.42 (C-2′), 28.85 (C-5), 47.54 (C-6), 51.88 (CO_2C), 59.89 (C-1), 60.64 (OCH_2CH_3), 61.34 ($OC'H_2CH_3$), 103.02 (C-3′), 115.15 (C-2″), 134.75 (C-3), 144.11 (C-1″), 144.97 (C-4), 171.47 (CO_2) and 195.97 (C-2); *m*/*z* (CI) 339 (M^+ + 1, 4), 325 (4), 310 (3), 309 (15), 294 (20), 293 (100), 265 (10), 247 (8), 209 (5), 103 (6), 86 (4) and 85 (66).

Methyl (+)-(6*S*,1*R*)-6-isopropenyl-3-methyl-2-oxo-1-(3′-oxopropyl)cyclohex-3-enecarboxylate 9

PPTS (525 mg, 2.05 mmol) was added to a solution of the ketal **8** (1.16 g, 3.43 mmol) in 4% aqueous acetone (77 cm^3) and the resulting mixture was heated at reflux for 30 min and then poured into water. Extraction of the resulting mixture with ether and work-up of the extract afforded a residue, which was purified by MPLC, using hexane–ethyl acetate (8:2) as eluent, to afford *aldehyde* **9** (833 mg, 92%) as an oil [Found: M^+ (EI), 264.1360. $C_{15}H_{20}O_4$ requires *M*, 264.1361]; $[\alpha]_D^{20}$ +60 (*c* 5.6, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3070, 3040–2860, 2830, 2710, 1730, 1720, 1660, 1210 and 1050; δ_H(200 MHz, $CDCl_3$) 9.68 (1 H, s, 3′-H), 6.82 (1 H, m, 4-H), 4.85 (1 H, s, 2″-H), 4.75 (1 H, s, 2″-H′), 3.63 (3 H, s, OMe), 2.95 (1 H, dd, *J* 10 and 4.5, 6-H), 1.77 (3 H, m, 3-Me) and 1.63 (3 H, s, 1′-Me); δ_C(50 MHz, $CDCl_3$), 16.39 (C-3), 20.52 (1″-Me), 24.63 (C-1′), 28.87 (C-5), 39.27 (C-2′), 49.17 (C-6), 52.07 (OMe), 59.24 (C-1), 115.67 (C-2″), 134.72 (C-3), 143.95 (C-1″), 144.94 (C-4), 170.93 (CO_2), 195.68 (C-2) and 201.46 (C-3′); *m*/*z* (EI) 264 (M^+, 3), 236 (10), 209 (15), 208 (100), 207 (23), 189 (20), 175 (50), 161 (40) and 147 (23).

Methyl (+)-(6*S*,1*R*)-6-isopropenyl-3-methyl-1-[4′-methyl-5′-oxo-(*E*)-pent-3-enyl]-2-oxocyclohex-3-enecarboxylate 10

A solution of the aldehyde **9** (1.77 g, 6.42 mmol) and commercial (α-formylethylidene)triphenylphosphorane (2.65 g, 8.33 mmol) in benzene (44 cm^3) was warmed at 80 °C for 48 h after which it was allowed to cool to RT when it was treated with saturated aqueous NH_4Cl. The aqueous phase was separated and extracted with ethyl acetate. The combined extracts were washed with water and brine and then evaporated to give an oily residue. This was purified by flash chromatography, using hexane–ether (8:2) as eluent, to afford the *aldehyde* **10** (1.76 g, 90%) as an oil [Found: M^+ (EI), 304.1675. $C_{18}H_{24}O_4$ requires *M*, 304.1675]; $[\alpha]_D^{21}$ +41 (*c* 2.1, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3080, 2960–2820, 2705, 1735, 1680, 1660, 1435, 1370, 1225, 1190, 1025 and 900; δ_H(300 MHz, $CDCl_3$) 9.35 (1 H, s, 5′-H), 6.80 (1 H, m, 4-H), 6.40 (1 H, ddd, *J* 8, 8 and 3, 3′-H), 4.90 (1 H, m, 2″-H), 4.80 (1 H, s, 2″-H′), 3.62 (3 H, OMe), 2.96 (1 H, dd, *J* 13.5 and 7, 6-H), 2.79 (1 H, ddt, *J* 9, 5 and 2.5, 5α-H), 1.79 (3 H, dt, *J* 2.3 and 1.1, 3-Me), 1.68 (3 H, s, 4′-Me) and 1.64 (3 H, m, 1″-Me); δ_C(75.5 MHz, $CDCl_3$) 9.12 (4′-Me), 16.44 (3-Me), 20.43 (1″-Me), 23.99 (C-2′), 29.03 (C-5), 30.43 (C-1′), 48.19 (C-6), 52.08 (OMe), 59.71 (C-1), 115.51 (C-2″), 134.74 (C-3), 139.50 (C-4′), 143.96 (C-4), 145.27 (C-1″), 153.61 (C-3′), 171.04 (CO_2), 195.07 (C-5′) and 195.60 (C-2); *m*/*z* (EI) 304 (M^+, 5), 276 (10), 244 (5), 208 (100), 193 (10), 167 (75), 123 (10), 105 (7) and 82 (75).

Further elution afforded unchanged starting material **9** (131 mg, 7%).

Methyl (+)-(6*S*,1*R*)-6-isopropenyl-3-methyl-1-[4′-methyl-(3′*E*)-hexa-3′,5′-dienyl]-2-oxocyclohex-3-enecarboxylate 11

A suspension of methyl(triphenyl)phosphonium bromide (1.16 g, 3.08 mmol) in THF (20 cm^3) was cooled to −20 °C after which a solution of BuLi in hexanes (1.6 M; 1.9 cm^3, 3.08 mmol) was added to it dropwise. After the mixture had been allowed to warm to RT it was stirred for 15 min and then cooled to −20 °C. Compound **10** (468 mg, 1.54 mmol) in THF (20 cm^3) was then added slowly to the mixture after which it was stirred at −20 °C for 30 min. After this time, the mixture was treated with saturated aqueous NH_4Cl (5 cm^3), poured into water and extracted with ethyl acetate. The combined extracts were washed sequentially with dilute hydrochloric acid, 5% aqueous $NaHCO_3$ and brine, dried and evaporated. Flash chromatography of the residue, using hexane–ether (9:1) as eluent, provided *compound* **11** (404 mg, 87%) as an oil [Found: M^+ (EI), 302.1883. $C_{19}H_{26}O_3$ requires *M*, 302.1882]; $[\alpha]_D^{21}$ +26 (*c* 0.5, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3095, 2963–2820, 1742, 1660, 1605, 1445, 1210, 985 and 900; δ_H(300 MHz, $CDCl_3$) 6.75 (1 H, m, 4-H), 6.31 (1 H, dd, *J* 18.5 and 10, 5′-H), 5.41 (1 H, dd, *J* 7 and 7, 3′-H), 5.04 (1 H, d, *J* 18, 6′-H), 4.88 (1 H, d, *J* 11.9, 6″-H′), 4.86 (1 H, s, 2″-H), 4.79 (1 H, s, 2″-H′), 3.61 (3 H, s, OMe), 2.98 (1 H, dd, *J* 10 and 5.0, 6-H), 2.75 (1 H, ddq, *J* 18.5, 10 and 2.5, 5α-H), 1.79 (3 H, dt, *J* 2.3 and 1.1, 3-Me), 1.68 (3 H, s, 4′-Me) and 1.65 (3 H, m, 1″-Me); δ_C(75.5 MHz, $CDCl_3$) 11.60 (4′-Me), 16.47 (3-Me), 20.74 (1″-Me), 23.13 (C-2′), 28.93 (C-5), 31.73 (C-1′), 47.81 (C-6), 51.89 (CO_2C), 60.00 (C-1), 110.72 (C-6′), 115.14 (C-2″), 132.12 (C-5′), 134.38 (C-4′), 134.83 (C-3), 141.40 (C-3′), 144.29 (C-1″), 144.67 (C-4), 171.40 (CO_2) and 195.88 (C-2); *m*/*z* (EI) 302 (M^+, 5), 271 (7), 208 (100), 193 (10), 167 (85), 148 (10) and 135 (12).

Methyl (+)-(2*S*,1*R*,7*R*,10*R*)-1,5,11-trimethyl-6-oxotricyclo-[8.4.0.0^{2,7}]tetradeca-4,11-diene-7-carboxylate 12

A toluene solution (23 cm^3) of **11** (576 mg, 1.9 mmol) and a catalytic amount of propylene oxide was sealed in a tube and heated at 185–190 °C for 5 days. After cooling, the tube was opened and the solvent removed *in vacuo* to give an oily residue. This was purified by flash chromatography, using hexane–ether (9:1) as eluent, to afford the *keto ester* **12** (532 mg, 92%) as a white solid, mp 110–112 °C (from hexane) [Found: M^+ (EI), 302.1882. $C_{19}H_{26}O_3$ requires *M*, 302.1882]; $[\alpha]_D^{23}$ +10 (*c* 1.9, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3020, 2970–2810, 1715, 1660, 1445, 1360, 1235, 1205, 1020 and 910; δ_H(300 MHz, $CDCl_3$) 6.88 (1 H, m, 12-H), 5.26 (1 H, br s, 3-H), 3.62 (3 H, s, OMe), 2.85 (1H, m, 7α-H), 2.78 (1 H, m, 11α-H), 2.33 (1 H, ddd, *J* 19.5, 6 and 6, 11β-H), 2.0 (2 H, m, 2-H), 1.75 (3 H, dt, *J* 2.6 and 1.4, 13-Me), 1.58 (3 H, s, 4-Me) and 0.67 (3 H, s, 10-Me); δ_C(75.5 MHz, $CDCl_3$) 11.67 (10-Me), 16.62 (13-Me), 20.38 (4-Me), 21.75 (C-6), 22.63 (C-2), 24.85 (C-11), 31.55 (C-7), 33.65 (C-1), 36.44 (C-10), 48.17 (C-9), 52.11 (C-5), 52.64 (OMe), 56.39 (C-8), 120.17 (C-3), 132.26 (C-13), 134.22 (C-4), 147.32 (C-12), 171.18 (CO_2) and 197.32 (C-14); *m*/*z* (EI) 302 (M^+, 56), 287 (2), 270 (2), 243 (48), 227 (13), 205 (5), 180 (14), 161 (18), 147 (24), 121 (57), 107 (28) and 82 (100).

(−)-(1*S*,7*S*,2*R*,10*R*)-1,5,11-Trimethyltricyclo[8.4.0.0^{2,7}]-tetradeca-4,11-dien-6-one 5

A suspension of the β-keto ester **12** (520 mg, 1.72 mmol) in a mixture of water–pyridine (99:1; 12 cm^3) was heated at 230 °C in a sealed tube for 22 h. After cooling, the mixture was diluted with water and extracted with ether. Work-up of the extract gave a solid residue which was purified by flash chromatography, using hexane–ether (9:1) as eluent, to afford the *enone* **5** (386 mg, 92%) as a white solid, mp 102–104 °C (from

hexane) [Found: M^+ (EI), 244.1827. $C_{17}H_{24}O$ requires *M*, 244.1827]; $[\alpha]_D^{25}$ −35 (*c* 3.8, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3015, 2985–2820, 1655, 1435, 1370 and 1070; δ_H(300 MHz, $CDCl_3$), 6.67 (1 H, m, 12-H), 5.31 (1 H, br s, 3-H), 2.15 (1 H, m, 7α-H), 1.98 (2 H, m, 2-H), 1.72 (3 H, m, 13-Me), 1.59 (3 H, s, 4-Me) and 0.79 (3 H, s, 10-Me); δ_C(75.5 MHz, $CDCl_3$) 12.65 (10-Me), 15.98 (13-Me), 21.44 (4-Me), 22.54 (C-6), 22.63 (C-2), 25.90 (C-11), 26.40 (C-7), 33.65 (C-1), 35.42 (C-10), 45.45 (C-8), 47.48 (C-9), 49.37 (C-5), 120.68 (C-3), 134.37 (C-13), 134.59 (C-4), 144.18 (C-12) and 202.60 (C-14); *m*/*z* (EI) 244 (M^+, 100), 229 (24), 215 (26), 201 (3), 189 (5), 173 (10), 161 (7), 147 (15), 136 (36), 123 (43), 109 (60), 91 (40) and 79 (31).

Alternative preparation of the tricyclic ketone 5 from 6 *via* the mixture of dienes 11 and 13

To a stirred slurry of pre-washed NaH (55% dispersion oil; 650 mg, 14.9 mmol) in DMF (15 cm^3) at 0 °C was added, dropwise *via* a syringe, a solution of the β-keto ester **7** (2.51 g, 12.1 mmol) in DMF (7.5 cm^3). After hydrogen evolution had ceased, the mixture was warmed to RT, stirred for 1 h and then re-cooled to 0 °C, when a 72:28 mixture of (*E*)- and (*Z*)-6-bromo-3-methylhexa-1,3-diene[9] **13** (5.28 g, 30.1 mmol) was added to it. After being stirred at RT for 4 days, the mixture was diluted with water and then poured into saturated aqueous NH_4Cl and extracted with ether. The combined extracts were washed with brine, dried and concentrated. Chromatography of the residue [hexane–ether (9:1) as eluent] afforded a 72:28 mixture (^{1}H NMR analysis) of the dienes **11** and **13**, respectively (2.53 g, 70%) as an oil followed by unchanged **7** (360 mg, 14%).

A toluene solution (60 cm^3) of the above mixture of dienes (2.31 g) and a catalytic amount of propylene oxide was sealed in a tube and heated at 185–190 °C for 5 days. After cooling, the tube was opened and the solvent removed *in vacuo* to leave an oily residue, which was filtered through a short pad of silica gel using hexane–ether (9:1) as eluent. The residue obtained after evaporation of the filtrate was introduced into a tube containing a mixture of water–pyridine (99:1; 60 cm^3), the tube sealed *in vacuo* and heated at 230 °C for 22 h. After this time the mixture was cooled to room temperature, poured into water and extracted with ether. Work-up afforded a brownish residue which was purified by chromatography, using hexane–ether (9:1) as eluent, to give the ketone **5** (1.11 g, 59%) identical in all respects with that previously obtained by the stepwise procedure.

(+)-(1*S*,7*S*,2*R*,10*R*)-1,5,11-Trimethyltricyclo[8.4.0.0^{2,7}]-tetradeca-5,11-dien-6-yl trifluoromethanesulfonate 15

L-Selectride in THF (1 M solution; 0.95 cm^3, 0.95 mmol) was added to a solution of the enone **5** (201 mg, 0.82 mmol) in THF (4.2 cm^3) at −78 °C. After the mixture had been stirred for 3 h at −78 °C, a solution of *N*-(5-chloro-2-pyridyl)triflimide (357 mg, 0.91 mmol) in THF (2 cm^3) was added to it. The stirred mixture was then slowly allowed to warm to −10 °C during 4 h after which it was diluted with pentane. The layers were separated, and the aqueous phase was extracted with pentane. The combined organic layer and extracts were washed with 10% aqueous NaOH and brine, dried, and concentrated to give an oily residue that was purified by MPLC, using hexane–ethyl acetate (98:2) as eluent, to afford the vinyl triflate **15** (187 mg, 60%) as a clear oil [Found: M^+ (EI), 378.1477. $C_{18}H_{25}F_3O_3S$ requires *M*, 378.1477]; $[\alpha]_D^{23}$ +35 (*c* 5.1, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3030, 2960–2820, 1450, 1420, 1245, 1210, 1145, 1050 and 880; δ_H(300 MHz, $CDCl_3$) 5.30 (1 H, br s, 3-H), 2.5 (1 H, m, 8-H), 2.2–1.9 (4 H, m, 2-H + 12-H), 1.71 (3 H, m, 13-Me), 1.59 (3 H, s, 4-Me) and 0.73 (3 H, s, 10-Me); δ_C(75.5 MHz, $CDCl_3$) 11.54 (10-Me), 16.81 (13-Me), 21.21 (4-Me), 21.72 (C-6), 22.81 (C-7), 23.41 (C-2), 29.29 (C-11), 31.42 (C -12), 33.78 (C-1), 35.12 (C-10), 38.59 (C-8), 48.19 (C-5), 51.54 (C-9), 116.27 (CF_3), 120.57 (C-3), 126.33 (C-13), 134.30 (C-4) and 146.41 (C-14); *m*/*z* (EI) 378 (M^+, 98), 363 (100), 307 (8), 281 (18), 252 (23), 228 (61), 173 (15), 135 (20) and 107 (43).

(+)-(1*S*,7*S*,11*S*,2*R*,10*R*,13*R*)-1,5,11-Trimethyltetracyclo-[8.5.0.0.^{2,7}0^{11,13}]pentadec-5-en-6-yl trifluoromethanesulfonate 16

To a cooled (0 °C) solution of compound **15** (142 mg, 0.38 mmol) in toluene (6 cm^3) were added diethylzinc (1.0 M solution in hexane; 2.3 cm^3, 2.3 mmol) and diiodomethane (0.38 cm^3, 4.72 mmol). After being stirred at RT for 16 h, the mixture was quenched by the addition of saturated aqueous NH_4Cl and extracted with ether. The organic extracts were washed with water and brine, dried, and concentrated to give an oil. Flash chromatography of this, using hexane–ether (97:3) as eluent, yielded the *vinyl triflate* **16** (135 mg, 92%) as an oil [Found: M^+ (EI), 392.1632. $C_{19}H_{27}O_3F_3S$ requires *M*, 392.1633]; $[\alpha]_D^{23}$ +1 (*c* 2.3, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3040, 2990–2820, 1445, 1410, 1390, 1375, 1240, 1200, 1140 and 1045; δ_H(300 MHz, $CDCl_3$), 1.8–2.10 (3 H, m, 8-H and 12-H), 1.70 (3 H, m, 13-Me), 1.01 (1 H, dd, *J* 11 and 3.5, 5-H), 0.94 (3 H, s, 4-Me), 0.79 (3 H, s, 10-Me), 0.58 (2 H, m, 3-H and 1β-H), 0.43 (1 H, dd, *J* 9 and 4, 18α-H) and −0.2 (1 H, dd, *J* 6 and 4, 18β-H); δ_C(75.5 MHz, $CDCl_3$) 11.65 (10-Me), 16.09 (13-Me), 16.84 (C-4), 19.03 (C-3), 19.28 (C-2), 21.61 (C-18), 22.09 (4-Me), 23.63 (C-6), 25.17 (C-7), 29.48 (C-11), 31.42 (C-12), 32.81 (C-1), 35.17 (C-10), 38.76 (C-8), 51.05 (C-9), 51.25 (C-5), 116.32 (CF_3), 126.43 (C-13) and 146.54 (C-14); *m*/*z* (EI) 392 (M^+ 71), 378 (75), 350 (100), 309 (23), 281 (57), 252 (26), 217 (56), 187 (27), 159 (25), 135 (43) and 107 (94).

(−)-(1*S*,11*S*,2*R*,7*R*,10*R*,13*R*)-1,5,11-Trimethyltetracyclo-[8.5.0.0^{2,7}.0^{11,13}]pentadec-5-ene 17

To a mixture of the vinyl triflate **16** (118 mg, 0.30 mmol), tributylamine (0.22 cm^3, 0.92 mmol) and bis(triphenylphosphine)palladium acetate (12 mg, 0.02 mmol) in DMF (0.4 cm^3) was added 99% formic acid (0.04 cm^3, 0.60 mmol). The mixture was stirred at 60 °C for 2 h and then cooled to RT and diluted with ethyl acetate and water. The organic layer was separated, washed with water, dried and concentrated. The residue was purified by flash chromatography, using hexane–ether (95:5) as eluent, to give *olefin* **17** (64 mg, 86%) as an oil [Found: M^+ (EI), 244.2190. $C_{18}H_{28}$ requires *M*, 244.2191]; $[\alpha]_D^{22}$ −57 (*c* 3.2, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3060, 2990–2820, 1450, 1380, 1360, 1215 and 1020; δ_H(300 MHz, $CDCl_3$) 5.10 (1 H, br s, 14-H), 1.60 (3 H, s, 13-Me), 0.93 (3 H, s, 4-Me), 0.75 (3 H, s, 10-Me), 0.6 (2 H, m, 3-H and 1β-H), 0.40 (1 H, dd, *J* 9 and 4, 18α-H) and −0.01 (1 H, dd, *J* 6 and 4, 18β-H); δ_C(75.5 MHz, $CDCl_3$) 11.80 (10-Me), 16.29 (C-4), 19.13 (C-3), 19.43 (C-2), 21.92 (C-18), 22.80 (C-11), 23.20 (13-Me), 23.90 (4-Me), 25.90 (C-6), 31.69 (C-7), 32.73 (C-1), 34.34 (C-12), 34.88 (C-10), 35.91 (C-8), 49.67 (C-9), 51.43 (C-5), 127.50 (C-14) and 133.09 (C-13); *m*/*z* (EI) 244 (M^+, 86), 230 (73), 215 (60), 202 (78), 189 (35), 175 (24), 161 (49), 147 (35), 133 (90), 121 (60), 107 (100) and 93 (75).

(−)-(3a*S*,5*S*,7b*S*,1a*R*,4*R*,7a*R*)-3a,7b-Dimethyl-4-(3-oxobutyl)perhydrocyclopropa[*a*]naphthalene-5-carbaldehyde 4

A solution of compound **17** (104 mg, 0.44 mmol) in CH_2Cl_2–MeOH (1:1; 4 cm^3) containing pyridine (2 drops) was cooled to −78 °C. Ozone-enriched oxygen was then bubbled through the solution at this temperature until no starting material remained (TLC; *ca.* 7 min). Me_2S (0.5 cm^3) was added to the reaction mixture after which it was stirred at RT overnight. The solvent and the excess Me_2S were removed under reduced pressure from the reaction mixture and the residue was purified by flash chromatography, using hexane–ethyl acetate (8:2) as eluent, to afford the *keto aldehyde* **4** (104 mg, 88%) as an oil [Found: M^+ (EI), 276.2091. $C_{18}H_{28}O_2$ requires *M*, 276.2089]; $[\alpha]_D^{23}$ −40 (*c* 3.4, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3060, 3000–2900, 2870, 2720, 1725, 1715, 1450, 1380 and 1170; δ_H(300 MHz, $CDCl_3$) 9.51 (1 H, d, *J* 4, CHO), 2.06 (3 H, br s, *Me*CO), 0.93 (3 H, br s, 4-Me), 0.79 (3 H, br s, 10-Me), 0.6 (2 H, m, 3-H and 1β-H), 0.4 (1 H, dd, *J* 9 and 4, 18α-H) and 0.02 (1 H, dd, *J* 5 and 4, 18β-H); δ_C(75.5 MHz, $CDCl_3$) 11.86 (10-Me), 15.90 (C-4), 19.12 (C-3), 19.50 (C-2), 21.49 (C-18), 23.44 (4-Me), 23.58 (C-7), 23.90 (C-11),

26.70 (C-6), 29.85 (*Me*CO), 32.49 (C-1), 36.17 (C-10), 44.35 (C-12), 45.93 (C-8), 50.31 (C-5), 53.46 (C-9), 205.19 (CHO) and 208.34 (C-13); *m*/*z* (EI) 276 (M^+, 12), 258 (21), 246 (12), 234 (20), 218 (60), 203 (22), 187 (28), 175 (34), 161 (50), 147 (54), 133 (70), 121 (100), 107 (96) and 93 (87).

(−)-4-(3a*S*,5*S*,7b*S*,1a*R*,4*R*,7a*R*)-5-Hydroxymethyl-3a,7b-dimethylperhydrocyclopropa[*a*]naphthalen-4-ylbutan-2-one 18

A solution of the keto aldehyde **4** (50 mg, 0.18 mmol) in CH_2Cl_2–EtOH (7:3) (4 cm^3) was cooled at −78 °C and sodium borohydride (24 mg, 0.66 mmol) was added to it. After the mixture had been stirred for 3 h, during which time its temperature was allowed to rise to −60 °C, it was treated with acetaldehyde (1 cm^3) and then allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2, washed with 2% aqueous NaOH and brine, dried and concentrated to give an oily residue which was purified by flash chromatography, using hexane–ethyl acetate (75:25) as eluent, to afford the *keto alcohol* **18** (46 mg, 91%) as an oil [Found: M^+ (EI), 278.2248. $C_{18}H_{30}O_2$ requires *M*, 278.2246]; $[\alpha]_D^{22}$ −28 (*c* 2.5, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3500, 3040, 2990–2820, 1720, 1450, 1385, 1360, 1170 and 1020; δ_H(300 MHz, $CDCl_3$) 3.56 (2 H, br s, CH_2OH), 2.09 (3 H, br s, *Me*CO), 0.92 (3 H, br s, 4-Me), 0.77 (3 H, br s, 10-Me), 0.60 (2 H, m, 3-H and 1β-H), 0.39 (1 H, dd, *J* 10 and 5, 18α-H) and −0.01 (1 H, dd, *J* 5.5 and 5, 18β-H); δ_C(75.5 MHz, $CDCl_3$) 11.71 (10-Me), 16.17 (C-4), 19.44 (C-2), 19.62 (C-3), 21.48 (C-18), 22.68 (C-11), 24.01 (4-Me), 24.89 (C-6), 29.68 (*Me*CO), 30.46 (C-7), 33.05 (C-1), 36.74 (C-10), 41.18 (C-8), 45.50 (C-12), 47.34 (C-9), 50.78 (C-5), 65.98 (C-17) and 209.55 (C-13); *m*/*z* (EI) 278 (M^+, 3), 260 (100), 245 (14), 231 (5), 218 (9), 203 (17), 175 (20), 161 (25), 147 (31) and 121 (40).

(−)-4-(3a*S*,7b*S*,1a*R*,4*R*,7a*R*)-3a,7b-Dimethyl-5-methyleneperhydrocyclopropa[*a*]naphthalen-4-ylbutan-2-one 20

To a solution of the alcohol **18** (39 mg, 0.15 mmol) and *o*-nitrophenyl selenocyanate (39 mg, 0.18 mmol) in THF (1 cm^3) cooled in an ice-bath was added tributylphosphine (0.045 cm^3, 0.018 mmol) in THF (0.2 cm^3) over a 10-min period. The mixture was warmed to RT, stirred for 1.5 h, and then cooled in an ice-bath and treated with anhydrous Na_2HPO_4 (90 mg, 0.60 mmol). After the mixture had been stirred for a few minutes it was treated with 30% aqueous H_2O_2 (0.21 cm^3, 2 mmol), warmed to RT, stirred for 20 h and then diluted with CH_2Cl_2. After this the solution was washed with saturated aqueous $NaHCO_3$, and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried and concentrated. The residue, dissolved in MeOH (1 cm^3), was treated with 1 M aqueous KOH (1 cm^3) after which the mixture was stirred at RT for 30 min and then poured into water and extracted with ether. The combined extracts were washed with water and brine, dried and concentrated. The residue was purified by flash chromatography, using hexane–ethyl acetate (97:3) as eluent, to give the *ketone* **20** (24.3 mg, 70%) as an oil [Found: M^+ (EI), 260.2140. $C_{18}H_{28}O$ requires *M*, 260.2139]; $[\alpha]_D^{22}$ −54 (*c* 0.70, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3080, 3050, 2990–2820, 1712, 1640, 1440, 1380, 1350, 1160, 1015 and 885; δ_H(400 MHz, $CDCl_3$) 4.82 (1 H, s, =CH), 4.42 (1 H, s, =CH′), 2.08 (3 H, s, *Me*CO), 0.9 (3 H, br s, 4-Me), 0.64 (3 H, s, 10-Me), 0.40 (1H, dd, *J* 9 and 4.5, 18α-H) and 0.10 (1 H, dd, *J* 5 and 4.5, 18β-H); δ_C(75.5 MHz, $CDCl_3$) 11.47 (10-Me), 16.44 (C-4), 18.30 (C-11), 19.15 (C-3), 19.96 (C-2), 21.68 (C-18), 23.98 (4-Me), 28.32 (C-6), 30.00 (*Me*CO), 32.79 (C-1), 38.24 (C-7), 38.78 (C-10), 43.02 (C-12), 51.32 (C-5), 52.63 (C-9), 106.87 (8-CH_2), 148.32 (C-8) and 209.42 (C-13); *m*/*z* (EI) 260 (M^+, 48), 245 (26), 243 (14), 242 (73), 228 (13), 227 (58), 218 (15), 213 (14), 205 (21), 203 (17), 202 (100), 187 (64), 185 (23), 173 (42) and 159 (74).

Further elution with hexane–ethyl acetate (8:2) afforded the unchanged alcohol **18** (8 mg, 15%).

If the above described KOH–MeOH treatment was suppressed less of compound **20** was obtained and, instead, a new compound, the cyanohydrin **21**, was obtained in yields in the range 30–60%; δ_H(200 MHz, $CDCl_3$) 4.88 (1 H, s, =CH), 4.55 (1 H, s, =CH′), 1.58 (3 H, s, 13-Me), 0.91 (3 H, s, 4-Me), 0.66 (3 H, s, 10-Me), 0.41 (1 H, dd, *J* 9 and 4, 18α-H) and 0.01 (1 H, dd, *J* 5 and 4, 18β-H); *m*/*z* (FAB) 287 (M^+, 5), 260 (23), 242 (25), 228 (40), 202 (50), 187 (40), 175 (40), 159 (40), 147 (50), 133 (65), 119 (85) and 107 (100).

Methyl (−)-(*E*)-5-(3a*S*,7b*S*,1a*R*,4*R*,7a*R*)-3a, 7b-dimethyl-5-methyleneperhydrocyclopropa[*a*]naphthalen-4-yl-3-methylpent-2-enoate *ent*-3

Methyl diethylphosphonoacetate (69.8 mg, 0.37 mmol) was dropwise added to a suspension of oil-free NaH (8.6 mg, 0.36 mmol) in THF (0.72 cm^3) and allowed to react until no further hydrogen evolution was observed (*ca.* 1 h). A solution of the ketone **20** (24 mg, 0.09 mmol) in THF (0.37 cm^3) was then added to the mixture after which it was stirred at RT for 20 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl to the mixture which was then extracted with ether. The combined organic extracts were washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$ and brine and dried. The residue obtained after evaporation of the solvent was purified by chromatography, using hexane–ethyl acetate (85:15) as eluent, to give a 85:15 mixture (^{1}H NMR analysis) of the (*E*)- and (*Z*)-α,β-unsaturated methyl esters *ent*-**3** and **22** (27.7 mg, 95%). Both isomers were easily separated by HPLC, using hexane–ethyl acetate (9:1) as eluent. The first eluted compound was the (*Z*)-α,β-unsaturated ester **22** (3.5 mg) followed by the (*E*)-α,β-unsaturated ester *ent*-**3** (23 mg).

The (*E*)-α,β-unsaturated methyl ester *ent*-**3** was an oil [Found: M^+ (EI), 316.2395. $C_{21}H_{32}O_2$ requires *M*, 316.2402]; $[\alpha]_D^{21}$ −78 (*c* 1.64, $CHCl_3$) [lit.,[2] +87.5]; ν_{max}(NaCl)/cm^{-1} 3070, 3040, 3000–2820, 1705, 1630, 1420, 1370, 1340, 1210 and 1130; δ_H(300 MHz, $CDCl_3$), 5.62 (1 H, s, 14-H), 4.86 (1 H, s, =CH), 4.5 (1H, s, =CH′), 3.66 (3 H, s, OMe), 2.12 (3 H, d, *J* 1, 13-Me), 0.9 (3 H, s, 4-Me), 0.71 (1 H, ddd, *J* 13, 13 and 6, 1β-H), 0.63 (3 H, s, 10-Me), 0.54 (1 H, m, 3-H), 0.4 (1 H, dd, *J* 9 and 4, 18α-H) and 0.02 (1 H, dd, *J* 6 and 4, 18β-H); δ_C($CDCl_3$, 75.5 MHz) 11.59 (10-Me), 16.48 (C-4), 18.90 (13-Me), 19.14 (C-3), 20.00 (C-2), 21.68 (C-18), 22.34 (C-11), 23.98 (4-Me), 28.32 (C-6), 32.89 (C-1), 38.24 (C-7), 38.70 (C-10), 39.89 (C-12), 50.76 (OMe), 51.34 (C-5), 52.49 (C-9), 106.87 (=CH_2), 114.82 (C-14), 148.27 (C-8), 161.07 (C-13) and 167.29 (C-15); *m*/*z* (EI) 316 (M^+, 30), 315 (14), 302 (27), 301 (98), 288 (16), 287 (27), 275 (17), 274 (22), 261 (63), 242 (85), 227 (30), 203 (65), 189 (26), 175 (46), 161 (56), 147 (71), 135 (98), 121 (72) and 107 (100).

The (*Z*)-α,β-unsaturated methyl ester **22** was an oil; δ_H(300 MHz, $CDCl_3$) 5.60 (1 H, d, *J* 1, 14-H), 4.87 (1 H, d, *J* 1, =CH), 4.65 (1 H, br s, =CH′), 3.64 (3 H, s, OMe), 1.86 (3 H, d, *J* 1, 13-Me), 0.90 (3 H, s, 4-Me), 0.74 (1 H, ddd, *J* 13, 13 and 6, 1β-H), 0.62 (3 H, s, 10-Me), 0.57 (1 H, m, 3-H), 0.42 (1 H, dd, *J* 8 and 4, 18α-H) and 0.02 (1 H, dd, *J* 6 and 4, 18β-H); δ_C($CDCl_3$, 75.5 MHz) 11.58 (10-Me), 16.52 (C-4), 19.03 (C-3), 20.07 (C-2), 21.69 (C-18), 23.19 (C-11), 24.01 (4-Me), 25.35 (13-Me), 28.36 (C-6), 32.76 (C-12), 32.87 (C-1), 38.31 (C-7), 38.80 (C-10), 50.80 (OMe), 51.39 (C-5), 53.42 (C-9), 106.93 (=CH_2), 115.58 (C-14), 148.42 (C-8), 160.98 (C-13) and 166.68 (CO_2).

(−)-(*E*)-5-(3a*S*,7b*S*,1a*R*,4*R*,7a*R*)-3a,7b-Dimethyl-5-methyleneperhydrocyclopropa[*a*]naphthalen-4-yl-3-methylpent-2-enoic acid *ent*-2

A mixture of 15% ethanolic KOH (1.4 cm^3), toluene (0.36 cm^3) and the methyl ester **22** (25 mg, 0.08 mmol) was heated at 78 °C for 2 h after which it was poured into dilute hydrochloric acid and extracted with chloroform. The combined organic extracts were washed with water and brine, dried and evaporated to give a solid residue. This was purified by column chromatography, using ethyl acetate–hexane (9:1) as eluent, to give pure (−)-*metasequoic acid B ent*-**3** (20 mg, 85%) as a white solid; mp 137–138 °C (from hexane) (lit.,[1] 124–125) [Found: M^+ (EI),

302.2242. $C_{20}H_{30}O_2$ requires *M*, 302.2246]; $[\alpha]_D^{21}$ −94 (*c* 1.0, $CHCl_3$) (lit.,[1] +94); ν_{max}(NaCl)/cm^{-1} 3080, 3040, 2990–2800, 1680, 1630, 1250, 1170 and 1010; δ_H(300 MHz, $CDCl_3$) 5.65 (1 H, s, 14-H), 4.87 (1 H, s, =CH), 4.51 (1 H, s, =CH′), 2.14 (3 H, s, 13-Me), 0.9 (3 H, s, 4-Me), 0.71 (1 H, ddd, *J* 13, 13 and 6, 1β-H), 0.63 (3 H, s, 10-Me), 0.57 (1 H, m, 3-H), 0.4 (1 H, dd, *J* 9 and 4, 18α-H) and 0.03 (1 H, dd, *J* 6 and 4, 18β-H); δ_C($CDCl_3$, 100 MHz) 11.58 (10-Me), 16.48 (C-4), 19.13 (13-Me), 19.21 (C-3), 20.00 (C-2), 21.69 (C-18), 22.32 (C-11), 23.98 (4-Me), 28.32 (C-6), 32.90 (C-1), 38.24 (C-7), 38.72 (C-10), 40.17 (C-12), 51.34 (C-5), 52.48 (C-9), 106.92 (=CH_2), 114.47 (C-14), 148.22 (C-8), 163.97 (C-13) and 171.1 (C-15); *m*/*z* 302 (M^+, 15), 287 (73), 273 (13), 246 (30), 203 (50), 189 (15), 175 (30), 161 (40), 135 (80), 107 (91) and 84 (100).

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