Asymmetric synthesis of 3β-angeloyloxy-4β-hydroxyeudesman-8-one, purported sesquiterpene from *Pluchea quitoc*†

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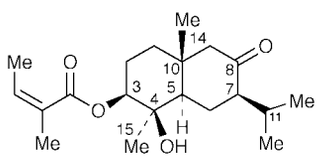
3β-Angeloyloxy-4β-hydroxyeudesman-8-one, purportedly isolated from the aerial parts of *Pluchea quitoc*, has been prepared by an unambiguous, stereocontrolled route and found to be different from the natural product.

Species of the genus *Pluchea*, which are often endowed with beneficial medicinal properties,[1–5] are an excellent source of eudesmanes.[6–10] Quite recently, Guilhon and Müller reported the isolation of a new eudesmane from the aerial parts of *Pluchea quitoc* DC (Compositae, tribe Inuleae), a plant that has been used in the northern and central-western areas of Brazil as an expectorant and for its digestive and anti-rheumatic properties,[5] to which they assigned on the basis of one and two dimensional NMR data the structure and relative stereochemistry depicted in **1**.[11] In this paper, an asymmetric synthesis is



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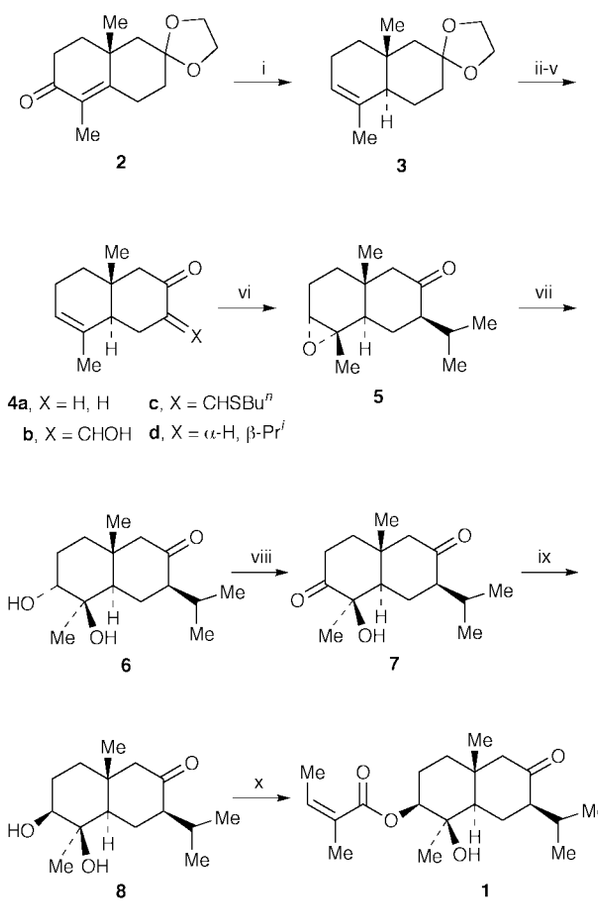
presented of this putative natural product, 3β-angeloyloxy-4β-hydroxyeudesman-8-one, which successfully addresses the stereochemically difficult problem of the introduction of the C-3,C-4 β-oxygen substituents.

The starting material for the synthesis was the known[12] octalone derivative **2** (Scheme 1), which was enantioselectively prepared by using d'Angelo and co-workers' effective deracemizing Michael addition procedure[13] with (*R*)-(+)-α-methylbenzylamine. The initial enantiomeric excess of 84% could be improved to 97% by simple recrystallization. That the proposed[12] absolute stereochemistry was, in fact, as depicted was demonstrated by transformation[14] of **2** into the dextrorotatory enone **9** of known[15] absolute stereochemistry (Scheme 2).

Reductive transposition of the enone function in **2** with the introduction of the *trans* ring fusion was next readily accomplished through application of Ireland's enol phosphate procedure.[16] The desired product, **3**, uncontaminated by the *cis* isomer,[17] was obtained in 61% yield.[18]

It appeared desirable, in order to avoid protection–deprotection sequences, to introduce the C-7 isopropyl group at this point in the synthesis, prior to oxidation of the double bond. Thus, the dioxolane **3** was hydrolyzed and the resulting ketone **4a** converted *via* its hydroxymethylene derivative **4b** into thioether **4c** (85% yield). On exposure to an excess of lithium dimethylcopper, the thioether underwent smooth double addition[19] to provide the desired isopropyl-substituted ketone **4d**,



Scheme 1 *Reagents and conditions*: i, Li, NH_3, THF–*t*-BuOH; CIPO-$(OEt)_2$; Li, $MeNH_2$ (61%); ii, AcOH–H_2O (95%); iii, NaH, HCO_2Et, Et_2O; iv, *n*-BuSH, *p*-TsOH, benzene (90%, 2 steps); v, $LiMe_2Cu$, Et_2O (99%); vi, *m*-$ClC_6H_4CO_3H$, Na_2CO_3, CH_2Cl_2 (93%); vii, H_2SO_4, Me_2CO–H_2O (40%); viii, $C_5H_5N{\cdot}SO_3$, Et_3N, DMSO (91%); ix, $Zn(BH_4)_2$, DME (70%); x, (*Z*)-MeC=C(Me)$CO_2COC_6H_2Cl_3$, DMAP, PhMe (74%).

exclusively β, in essentially quantitative yield. (Ketone **4d** was unchanged in the presence of DBU.)

From earlier work with related molecules,[20] it seemed probable that vicinal dihydroxylation of **4d**, for steric reasons, would be α-face-selective; in the event, a very predominant diol issued from the reaction of **4d** with osmium tetroxide in modest yield (Scheme 3). The spectral data indicated that the expected α-face approach of the reagent had indeed occurred,[21] which was later

† The IUPAC name for angelic acid is (*Z*)-2-methylbut-2-enoic acid.

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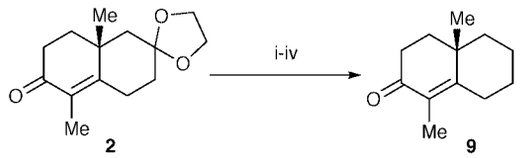
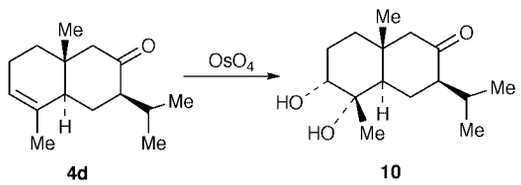


Scheme 2 *Reagents and conditions*: i, AcOH–H_2O, 80 °C, 20 min; ii, $NaBH_4$, EtOH, 0 °C, 0.5 h; iii, NaH, CS_2, CH_3I, THF, 20 °C, 5 h; iv, Bu_3SnH, AIBN, toluene, reflux, 3 h.



Scheme 3

confirmed indirectly by X-ray crystallography (see below). Since it seemed unlikely that an effective method for the direct introduction of the vicinal β-hydroxy functions would be found, an alternative, indirect procedure was developed to achieve this end.

Treatment of **4d** with *m*-chloroperbenzoic acid led in high yield to the formation of a unique epoxide, which was also assigned the α-configuration on the basis of its spectral data (a NOE was observed between the C-4 and C-10 methyls) and close precedent.[22] Both cyclic and acyclic trisubstituted epoxides tend to suffer acid-catalyzed ring opening at the more highly substituted terminus and with inversion of configuration.[23] Pleasingly, it was found that on exposure of epoxide **5** to dilute sulfuric acid in acetone, the major product formed was the desired C-3α,C-4β diol **6** (40%), with lesser amounts also generated of the C-3α,C-4α isomer (4%) and the $\Delta^{4(5)}$ and $\Delta^{4(15)}$ dehydration derivatives (22%). These products could have been, in principle, recycled in a few steps, but this was never attempted. The stereochemistry of the major diol was readily established on Parikh–von Doering oxidation[24] to give keto alcohol **7**, distinctly different from that secured by similar treatment of the C-3α,C-4α isomer **10**.

In the presence of zinc borohydride,[25] keto alcohol **7** underwent a highly regioselective carbonyl reduction[26] to afford an easily separable 55:45 mixture of the sought β,β-diol **8** and the original diol **6**, respectively. Diol **8** was suitable for X-ray diffraction analysis (Fig. 1) (see Experimental section), which confirmed the relative stereochemistry assigned to not only **8**, but also, indirectly, the other intermediates.

The final transformation required esterification of the secondary hydroxy to form the angelate ester. Yamaguchi's procedure[28] was successful for this purpose and furnished 3β-angeloyloxy-4β-hydroxyeudesman-8-one (**1**). Unfortunately, however, the optical rotation and the ^1H and ^{13}C NMR data for this eudesmane were in obvious disagreement with those reported for the native substance. With the forlorn hope that the natural product might simply be a C-3,C-4 diastereomer of what had been proposed, the 3 C-3,C-4 diastereomers of **1** were also prepared: the α,β and α,α diol derivatives by esterification of **6** and **10**, respectively, and the β,α by sequential oxidation, reduction, and esterification of **10**. Disappointingly, though, these too proved to be distinctly different from the natural product.

In conclusion, through the unequivocal preparation of 3β-angeloyloxy-4β-hydroxyeudesman-8-one (**1**) and its C-3,C-4 diastereomers, it has been shown that the natural product from *Pluchea quitoc* is neither the previously proposed **1**, nor a C-3,C-4 diastereomer, and, consequently, its published structure requires revision. The above synthesis, nevertheless, exemplifies a flexible approach that should be applicable to the preparation of a number of eudesmane natural products.

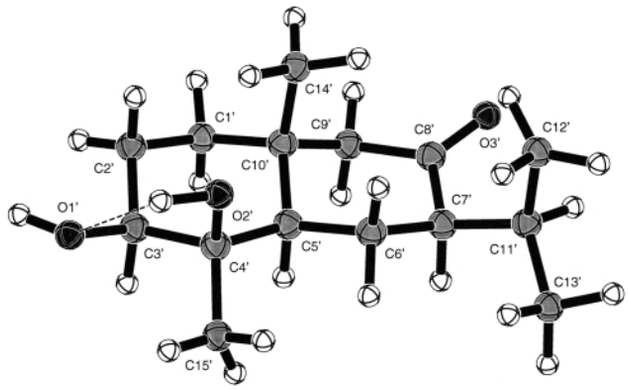


Fig. 1 Crystal structure of diol **8** (CHARON drawing,[27] representation of an independent molecule).

Experimental

General details

The reaction mixture was generally poured into water and the separated aqueous phase was then thoroughly extracted with the specified solvent. After being washed with 10% aqueous HCl and/or $NaHCO_3$ (if required), water, and saturated aqueous NaCl, the combined organic phases were dried over anhydrous Na_2SO_4 or $MgSO_4$ and then filtered and concentrated under reduced pressure on a Büchi Rotovapor to yield the crude reaction product. Tetrahydrofuran and ether were distilled from sodium–benzophenone, and methanol and ethanol from magnesium. Dichloromethane, DMSO, pyridine, toluene, and triethylamine were distilled from calcium hydride, and dimethoxyethane from lithium aluminium hydride.

(*R*)-5′,8′a-Dimethyl-1′,3′,4′,7′,8′,8′a-hexahydrospiro[[1,3]-dioxolane-2,2′-naphthalen]-6′-one 2[12,20,22]

A stirred solution of 2-methyl-4-ethylenedioxycyclohexanone[29] (5.40 g, 31.7 mmol), *R*-(+)-α-methylbenzylamine (15.80 cm^3, 14.85 g, 122.6 mmol), and toluene-*p*-sulfonic acid monohydrate (0.089 g, 0.47 mmol) in toluene (100 cm^3) was refluxed with removal of water for 3 h, whereupon the solvent and excess amine were removed by distillation under reduced pressure. The residue was dissolved in anhydrous THF (90 cm^3) and ethyl vinyl ketone (57.0 cm^3, 48.2 g, 57.3 mmol) was added. After being stirred for 4 days at 20 °C, the reaction mixture was treated with 20% aqueous AcOH–THF (1:1, 20 cm^3) and then stirred for an additional 3 h. The solvents were eliminated under reduced pressure and the crude reaction product was isolated with ethyl acetate in the usual way and purified on silica gel (pretreated with 2.5% triethylamine, v/v) with 30% ethyl acetate in pentane to afford first starting ketone (1.86 g) and then the desired Michael adduct (*R*)-7-methyl-7-(3-oxopentyl)-1,4-dioxaspiro[4,5]decan-8-one (3.08 g, 38% or 58% based on consumed starting material): $[a]_D^{25}$ −14.4 (*c* 1.0, $CHCl_3$), $[a]_D^{25}$ −14.2 (*c* 0.6, CH_2Cl_2) [lit.,[12] (enantiomer) $[a]_D^{25}$ +13.8 (*c* 0.6, CH_2Cl_2)]; ν_{max} (neat)/cm^{-1} 1716, 1461, 1367, 1310, 1276, 1180, 1111, 1089 and 1030; δ_H (300 MHz) 0.95 (3 H, t, *J* 7.3 Hz), 1.10 (3 H, s), 1.62–2.70 (12 H, m) and 3.80–4.00 (4 H, m); δ_C (75 MHz) 7.7, 23.5, 31.9, 34.3, 35.6, 35.7, 37.0, 45.2, 46.8, 64.1, 64.3, 107.2, 210.7 and 213.9; *m*/*z* (CI): 272 ($MH^+ + NH_3$, 20%), 255 (MH^+, 100%) and 237 (20%) [Found: C, 66.02; H, 8.67. $C_{14}H_{22}O_4$ requires C, 66.12; H, 8.72%].

To a solution of the above adduct (3.27 g, 12.9 mmol) in methanol (60 cm^3) was added sodium methoxide (1.31 g, 24.3 mmol). After being stirred at 20 °C for 3 h, the reaction mixture was concentrated under reduced pressure and the crude reaction product was isolated with ethyl acetate in the usual manner and purified on silica gel (pretreated with 2.5% triethylamine, v/v) with 35% ethyl acetate in hexane to give octalone **2** (2.53 g, 83%; 84% ee by HPLC). Recrystallization from ether–hexane

provided material of 97% ee (HPLC, see thioether **4c** below): mp 56 °C; $[\alpha]_D^{25}$ +165 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1651, 1613, 1451, 1419, 1367, 1330, 1316, 1270, 1206, 1122, 1095 and 1031; δ_H (200 MHz) 1.22 (3 H, s), 1.73 (3 H, s), 1.40–2.50 (9 H, m), 2.65 (1 H, ddd, *J* 16.5, 5.0, 3.2 Hz) and 3.70–4.00 (4 H, m); δ_C (75 MHz) 10.8, 23.4, 25.4, 33.2, 34.4, 36.7, 37.8, 48.3, 63.5, 64.4, 107.5, 128.5, 160.3 and 198.4; *m*/*z* (EI): 236 (M^+, 48%), 221 (12%), 99 (29%), 91 (61%), 86 (100%), 79 (40%), 55 (37%) and 43 (32%) [Found: C, 71.46; H, 8.52. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%].

(4′a*S*,8′a*R*)-5′,8′a-Dimethyl-3′,4′,4′a,7′,8′,8′a-hexahydro-1′*H*-spiro[[1,3]dioxolane-2,2′-naphthalene] 3[20,22]

Octalone **2** (1.20 g, 5.08 mmol) dissolved in THF (6 cm^3) and *tert*-butyl alcohol (0.38 cm^3) was added slowly to liquid ammonia (25 cm^3, freshly distilled from sodium metal) at −78 °C, followed by lithium metal (until a blue color persisted, *ca*. 0.1 g). After being stirred at −78 °C for 1 h, the reaction mixture was treated with a few drops of isoprene, and the ammonia was allowed to evaporate. Anhydrous THF (5 cm^3) was then added and the reaction mixture was warmed briefly at 35 °C to ensure the complete removal of the ammonia. The resulting mixture at 0 °C was treated dropwise with diethyl chlorophosphate (3.60 cm^3, 4.30 g, 24.9 mmol) and after 1 h with methylamine (25 cm^3) and lithium metal (until a blue color persisted for 1 h, *ca*. 0.4 g). The mixture was stirred overnight at −10 to 0 °C and then the methylamine was allowed to evaporate and the excess lithium metal was removed. The crude product was isolated with ether in the usual way and chromatographed on silica gel (pretreated with 2.5% triethylamine, v/v) with 10% ethyl acetate in hexane to afford olefin **3** (0.690 g, 61%): $[\alpha]_D^{25}$ −2.3 (*c* 1.2, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3030, 1650, 1451, 1432, 1378, 1367, 1257, 1242, 1219, 1140, 1130, 1115, 1089, 1040 and 941; δ_H (300 MHz) 0.90 (3 H, s), 1.28–1.65 (9 H, m), 1.66–2.18 (5 H, m), 3.79–4.01 (4 H, m) and 5.25 (1 H, br s); δ_C (75 MHz) 15.9, 21.3, 21.9, 22.8, 33.6, 36.5, 38.3, 46.6, 48.0, 63.4, 64.5, 109.3, 121.1 and 134.3; *m*/*z* (EI): 222 (M^+, 8%), 160 (10%), 145 (18%), 126 (20%), 105 (24%), 99 (100%), 93 (20%), 86 (40%), 77 (59%) and 55 (24%) [Found: C, 75.44; H, 10.14. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97%].

(4a*S*,8a*R*)-5,8a-Dimethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one 4a[20]

A solution of olefin **3** (2.30 g, 10.4 mmol) in 85% aqueous acetic acid (10 cm^3) was heated at 100 °C for 1.5 h. After evaporation of the solvent, the residue was processed with ether in the usual manner and the crude product was purified by silica gel chromatography with 4% ethyl acetate in pentane to give keto olefin **4a** (1.75 g, 95%): $[\alpha]_D^{25}$ −103 (*c* 1.1, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3050, 1714, 1449, 1377, 1305, 1245 and 1203; δ_H (300 MHz) 0.70 (3 H, s), 1.25–1.55 (3 H, m), 1.60 (3 H, s), 1.85–2.45 (8 H, m) and 5.30 (1 H, br s); δ_C (75 MHz) 16.8, 21.0, 22.6, 24.5, 36.4, 37.2, 41.5, 45.4, 55.4, 121.8, 133.2 and 211.4.

(3*R*,4a*S*,8a*R*)-3-Isopropyl-5,8a-dimethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2(1*H*)-one 4d

To a suspension of sodium hydride (60% dispersion, 1.85 g, 46.2 mmol) in anhydrous ether (56 cm^3) and ethanol (0.185 cm^3) at 0 °C was added a solution of olefin **4a** (2.49 g, 14.0 mmol) in ethyl formate (1.55 cm^3, 1.42 g, 19.2 mmol). After being stirred for 4 h at 20 °C, the reaction mixture was treated carefully with water and then processed with ether in the normal manner to give crude hydroxy ketone **4b** (2.47 g): ν_{max} (neat)/cm^{-1} 3060, 3030, 1639, 1587, 1438, 1380, 1264 and 1173; δ_H (300 MHz) 0.81 (3 H, s), 1.30–1.50 (2 H, m), 1.65 (3 H, br s), 1.85–2.30 (6 H, m), 2.55 (1 H, d, *J* 10.4 Hz), 5.35 (1 H, br s), 8.75 (1 H, s) and 13.50 (1 H, s); δ_C (75 MHz) 16.9, 20.8, 22.2, 23.3, 30.9, 36.1, 42.8, 46.1, 108.2, 122.1, 133.0, 183.3 and 188.9; *m*/*z* (EI): 206 (M^+, 35%), 191 (21%), 163 (14%), 135 (22.5%), 121 (20.5%), 107 (80%), 91 (85%), 77 (100%), 65 (21%), 55 (31%), 41 (34%).

A solution of the above crude product (2.46 g) in benzene (100 cm^3) was refluxed for 30 min in the presence of $TsOH·H_2O$ (0.410 g, 2.16 mmol) and butanethiol (1.96 cm^3, 1.65 g, 18.3 mmol) with removal of water. After being allowed to cool to room temperature, the reaction mixture was processed with ether in the usual way and the crude product was purified by silica gel chromatography with 10% ethyl acetate in pentane to afford thioether **4c** [3.47 g, 90% from **4a**, 97% ee by HPLC: Whelk-01, 5 μm, hexane–isopropanol = 9 : 1, 1.0 cm^3 min^{-1}, t_r 5.66 min (*versus* 6.75 min)]; $[\alpha]_D^{25}$ −80.3 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3022, 1665, 1548, 1438, 1380, 1296, 1219 and 837; δ_H (200 MHz) 0.81 (3 H, s), 0.91 (3 H, t, *J* 7.2 Hz), 1.30–1.75 (9 H, m), 1.80–2.40 (6 H, m), 2.65 (1 H, ddd, *J* 16.3, 5.3, 1.4 Hz), 2.84 (2 H, t, *J* 7.3 Hz), 5.40 (1 H, br s) and 7.60 (1 H, m); δ_C (50 MHz) 13.3, 17.0, 20.6, 21.4, 22.1, 27.3, 32.4, 32.7, 34.1, 36.3, 42.5, 53.3, 122.0, 129.2, 133.1, 143.1 and 195.5; *m*/*z* (CI): 279 (MH^+, 100%), 221 (78%), 107 (7%) and 101 (12%) [Found: C, 73.54; H, 9.28. $C_{17}H_{26}OS$ requires C, 73.33; H, 9.41%].

A solution of the above thioether **4c** (0.780 g, 2.80 mmol) in anhydrous ether (13 cm^3) was added to a solution at −20 °C of lithium dimethylcopper (prepared by dropwise addition of methyllithium in ether (1.6 M, 10.2 cm^3, 16.3 mmol) to CuI (1.58 g, 8.30 mmol) in ether (18 cm^3) at −20 °C). The reaction mixture was stirred at 0 °C for 2 h and then quenched by the addition of aqueous ammonium chloride solution and filtered over Celite. The crude reaction product was isolated in the usual way and purified by silica gel chromatography with 5% ethyl acetate in pentane to afford ketone **4d** (0.610 g, 99%): $[\alpha]_D^{25}$ −45.9 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3030, 1710, 1458, 1381, 1296, 1199, 1148 and 1064; δ_H (200 MHz) 0.70 (3 H, s), 0.85 (3 H, d, *J* 6.8 Hz), 0.93 (3 H, d, *J* 6.8 Hz), 1.10–1.60 (3 H, m), 1.65 (3 H, s), 1.90–2.40 (8 H, m) and 5.30 (1 H, br s); δ_C (50 MHz) 16.7, 18.2, 20.7, 21.2, 22.6, 25.5, 25.7, 36.8, 37.0, 45.6, 55.8, 56.0, 121.8, 133.5 and 211.6; *m*/*z* (CI): 238 ($MH^+ + NH_3$, 100%) and 221 (MH^+, 40%) [Found: C, 81.73; H, 10.86. $C_{15}H_{24}O$ requires C, 81.76; H, 10.98%].

(1a*R*,3a*R*,6*R*,7a*R*,7b*S*)-6-Isopropyl-3a,7b-dimethyloctahydro-1-oxacyclopropa[*a*]naphthalen-5(1a*H*)-one 5

To a solution of ketone **4d** (1.82 g, 8.29 mmol) in dichloromethane (73 cm^3) was added aqueous sodium carbonate solution (0.5 M, 24 cm^3) and *m*-chloroperbenzoic acid (70–75%, 2.0 g, *ca*. 8.40 mmol). The reaction mixture was stirred at 20 °C for 1.5 h, whereupon the crude product was isolated with dichloromethane in the usual way and purified by florisil chromatography with 10% ethyl acetate in pentane to give epoxide **5** (1.82 g, 93%): mp 48–49 °C; $[\alpha]_D^{25}$ −12.9 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1710, 1451, 1380, 1245, 1206, 1173, 1070 and 883; δ_H (200 MHz) 0.62 (3 H, s), 0.78 (3 H, d, *J* 6.9 Hz), 0.84 (3 H, d, *J* 6.9 Hz), 1.20 (3 H, s), 0.90–1.40 (3 H, m), 1.75–2.40 (8 H, m) and 2.86 (1 H, br s); δ_C (50 MHz) 17.2, 18.2, 20.7, 21.0, 21.1, 25.6, 25.9, 33.4, 35.9, 46.4, 55.1, 55.8, 57.6, 60.4 and 210.5; *m*/*z* (EI): 236 (M^+, 23%), 221 (40%), 137 (35%), 79 (36%), 69 (60%), 55 (55%) and 43 (100%) [Found: C, 76.08; H, 9.99. $C_{15}H_{24}O_2$ requires C, 76.23; H, 10.23%].

(3*R*,4a*R*,5*R*,6*R*,8a*R*)-5,6-Dihydroxy-3-isopropyl-5,8a-dimethyloctahydronaphthalen-2(1*H*)-one 6

A solution of epoxide **5** (0.200 g, 0.846 mmol) in 1% aqueous H_2SO_4–acetone (7 : 3 mixture, 3 cm^3) was stirred at 0 °C for 1.5 h, whereupon a small amount of solid sodium bicarbonate was added. The solvent was evaporated under reduced pressure and the residue was processed with ethyl acetate in the usual manner to give the crude product, which was purified by silica gel chromatography with 20% acetone in hexane to give diol **6** (0.086 g, 40%): mp 110 °C; $[\alpha]_D^{25}$ −47.8 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3461, 1698, 1463, 1446, 1387, 1366 and 1068; δ_H (300 MHz)

0.82–0.95 (9 H, m), 1.11–1.40 (2 H, m), 1.30 (3 H, s), 1.45–2.30 (11 H, m) and 3.55 (1 H, br s); δ_C (75 MHz) 18.2, 19.1, 20.8, 22.5, 25.2, 25.9, 27.3, 33.9, 38.1, 44.6, 55.7, 58.5, 73.7, 75.3 and 211.3; *m/z* (EI): 254 (M^+, 51%), 236 (26%), 195 (80%), 161 (22%), 139 (21%), 130 (24%), 111 (61%), 95 (40%), 83 (100%), 69 (85%), 55 (66%) and 43 (70%) [Found: $(M + H)^+$, 255.1950. $C_{15}H_{27}O_3$ requires *M*, 255.1960].

(1*R*,4a*R*,7*R*,8a*R*)-1-Hydroxy-7-isopropyl-1,4a-dimethyloctahydronaphthalene-2,6-dione 7

A solution of Py·SO_3 (0.375 g, 2.36 mmol) in DMSO (2 cm^3) was added to a stirred solution of diol **6** (0.200 g, 0.79 mmol) in DMSO (2 cm^3) and triethylamine (1.10 cm^3, 0.799 g, 7.89 mmol) at 20 °C. The reaction mixture was stirred for 50 min, after which aqueous ammonium chloride solution was added. The crude product was isolated with ethyl acetate in the usual way and purified by silica gel chromatography with 40% ethyl acetate in pentane to give diketone **7** (0.180 g, 91%): mp 80 °C; $[a]_D^{25}$ +18.3 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3450, 1710, 1700, 1457, 1424, 1380, 1367, 1250, 1151, 1120, 1090 and 1053; δ_H (200 MHz) 0.80–1.05 (9 H, m), 1.35 (3 H, s), 1.62–1.85 (3 H, m), 1.95–2.52 (7 H, m), 2.62 (1 H, br s) and 2.70–2.92 (1 H, m); δ_C (50 MHz) 18.2, 18.7, 20.8, 23.4, 25.4, 25.8, 32.7, 37.8, 38.7, 52.0, 54.6, 57.0, 76.0, 210.2 and 213.7; *m/z* (CI): 270 ($MH^+ + NH_3$, 100%) and 253 (MH^+, 25%) [Found: $(M + H)^+$, 253.1799. $C_{15}H_{25}O_3$ requires *M*, 253.1804].

(3*R*,4a*R*,5*R*,6*S*,8a*R*)-5,6-Dihydroxy-3-isopropyl-5,8a-dimethyloctahydronaphthalen-2(1*H*)-one 8

To a stirred solution of diketone **7** (0.220 g, 0.87 mmol) in anhydrous DME (3 cm^3) at 0 °C was added dropwise a solution of $Zn(BH_4)_2$ in DME (0.18 M, 1.47 cm^3, 0.26 mmol). The resulting mixture was stirred at 0 °C for 1 h, after which time saturated aqueous ammonium chloride solution was added. The crude product was isolated with ethyl acetate in the normal way and purified by silica gel chromatography with 10% acetone in hexane to provide diol **8** (0.108 g, 49%) and diol **6** (0.088 g, 40%). The latter by oxidation–reduction gave additional diol **8** (0.047 g, 21%): mp 78 °C; $[a]_D^{25}$ −28.4 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3453, 1706, 1455, 1379, 1265, 1112, 1083, 1063 and 1022; δ_H (300 MHz) 0.86 (3 H, d, *J* 6.9 Hz), 0.93 (3 H, d, *J* 6.9 Hz), 0.95 (3 H, s), 1.20–2.16 (12 H, m), 1.33 (3 H, s), 2.25 (m, 1 H) and 3.37 (1 H, dd, *J* 10.6, 5.8 Hz); δ_C (75 MHz) 18.2, 19.0, 20.8, 22.7, 25.4, 25.9, 26.8, 37.8, 38.4, 49.5, 55.2, 58.1, 73.5, 75.6 and 211.1; *m/z* (EI): 254 (M^+, 30%), 236 (14%), 203 (10%), 195 (28%), 177 (10%), 161 (14%), 153 (25%), 137 (14%), 130 (14%), 125 (15%), 111 (32%), 95 (36%), 83 (40%), 69 (36%), 55 (34%) and 43 (100%) [Found: C, 70.89; H, 10.24. $C_{15}H_{26}O_3$ requires C, 70.83; H, 10.30%].

(*Z*)-2-Methylbut-2-enoic acid (1*R*,2*S*,4a*R*,7*R*,8a*R*)-1-hydroxy-7-isopropyl-1,4a-dimethyl-6-oxodecahydronaphthalen-2-yl ester (1) (angelate ester of C-3β,C-4β diol 8)

To a solution of angelic acid (7.8 mg, 0.08 mmol) in toluene (0.10 cm^3) was added 2,4,6-trichlorobenzoyl chloride (0.012 cm^3, 18.7 mg, 0.08 mmol) and triethylamine (0.011 cm^3, 8.0 mg, 0.08 mmol). After being stirred for 3 h at 20 °C, the mixture was treated with a solution of diol **8** (10.0 mg, 0.04 mmol) in toluene (0.10 cm^3) and DMAP (1.0 mg, 0.01 mmol) and then heated at 70 °C for 4 h, after which ether was added and the resulting precipitate filtered. The solvents were evaporated under reduced pressure and the crude product was purified by silica gel chromatography with 10% ethyl acetate in hexane to provide the angelate ester **1** (5.3 mg, 40%, or 74% based on non-recovered **8**), together with starting material (2.5 mg, 25%) and tiglate ester (2.8 mg, 21%). The tiglate ester could be hydrolyzed (MeOH, K_2CO_3, 20 °C, 12 h, 100%) to allow recovery of additional starting material. Angelate ester **1**: $[a]_D^{25}$ −10.9 (*c* 0.3, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3506, 1706, 1650, 1459, 1387, 1265, 1235, 1159, 1083 and 1045; δ_H (300 MHz) 0.89 (3 H, d, *J* 6.9 Hz), 0.94 (3 H, d, *J* 6.9 Hz), 1.00 (3 H, s), 1.24 (3 H, m), 1.38–2.18 (11 H, m), 1.90 (3 H, dq, *J* 1.4, 1.4 Hz), 1.98 (3 H, dq, *J* 7.2, 1.4 Hz), 2.28 (1 H, m), 4.74 (1 H, dd, *J* 11.5, 5.0 Hz) and 6.09 (1 H, qq, *J* 7.2, 1.4 Hz); δ_C (75 MHz) 15.9, 18.2, 19.2, 20.7, 20.8, 22.7, 23.3, 25.6, 26.0, 37.8, 38.4, 49.7, 55.1, 58.0, 73.2, 78.1, 127.8, 138.4, 167.1 and 210.8; *m/z* (EI): 336 (M^+, 29%), 318 (7%), 253 (6%), 236 (7%), 195 (28%), 153 (6%), 109 (14%), 99 (16%), 83 (95%), 71 (37%), 55 (100%) and 43 (81%) [Found: $(M + H)^+$, 337.2393. $C_{20}H_{33}O_4$ requires *M*, 337.2379]. This ester displayed the expected 98.5:1.5 enantiomeric ratio (HPLC: Chiracel OD-H, 5 μm, hexane–isopropanol = 9:1, 0.5 cm^3 min^{-1}, t_r 15.56 min (*versus* 14.05 min)).

(*Z*)-2-Methylbut-2-enoic acid (1*R*,2*R*,4a*R*,7*R*,8a*R*)-1-hydroxy-7-isopropyl-1,4a-dimethyl-6-oxodecahydronaphthalen-2-yl ester (angelate ester of C-3α,C-4β diol 6)

The angelate ester of diol **6** was prepared as described above (but without DMAP): $[a]_D^{25}$ −58.6 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3514, 1706, 1645, 1463, 1390, 1235 and 1151; δ_H (300 MHz) 0.88 (3 H, d, *J* 6.9 Hz), 0.92 (3 H, d, *J* 6.9 Hz), 0.97 (3 H, s), 1.25 (3 H, m), 1.48–2.38 (18 H, m), 4.84 (1 H, br s) and 6.08 (1 H, qq, *J* 7.2, 1.4 Hz); δ_C (75 MHz) 15.9, 18.3, 19.1, 20.8, 22.5, 22.6, 26.0, 27.0 (2×), 35.0, 38.0, 46.5, 55.7, 58.7, 72.9, 76.4, 127.9, 138.4, 166.9 and 211.0; *m/z* (EI): 336 (M^+, 5%), 318 (1%), 293 (1%), 253 (2%), 236 (4%), 218 (12%), 195 (26%), 176 (6%), 153 (6%), 109 (10%), 95 (9%), 83 (100%), 71 (15%), 55 (39%) and 43 (21%) [Found: M^+, 336.2313. $C_{20}H_{32}O_4$ requires *M*, 336.2301].

(*Z*)-2-Methylbut-2-enoic acid (1*S*,2*R*,4a*R*,7*R*,8a*R*)-1-hydroxy-7-isopropyl-1,4a-dimethyl-6-oxodecahydronaphthalen-2-yl ester (angelate ester of C-3α,C-4α diol 10)

To a stirred solution of keto olefin **4d** (0.025 g, 0.11 mmol) in dry pyridine (0.63 cm^3) was added a 2.5 wt% solution of OsO_4 in *t*-BuOH (1.50 cm^3). After being stirred at 20 °C for 40 h, the reaction mixture was cooled to 0 °C and treated with pyridine (0.60 cm^3), 37% bisulfite solution (1.5 cm^3), and water (3.0 cm^3) and then stirred for 30 min. The crude product was isolated with ethyl acetate in the normal way and purified by silica gel chromatography with 30% ethyl acetate in hexane to give diol **10** (7 mg, 24%): $[a]_D^{25}$ −73.5 (*c* 1.6, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3438, 1698, 1463, 1387, 1366, 1083, 1060 and 1030; δ_H (300 MHz) 0.80 (3 H, s), 0.86 (3 H, d, *J* 6.8 Hz), 0.91 (3 H, d, *J* 6.8 Hz), 1.14 (3 H, s), 1.30–1.50 (1 H, m), 1.65–1.85 (5 H, m), 2.00–2.30 (5 H, m), 2.40 (1 H, br s), 2.69 (1 H, br s) and 3.63 (1 H, br s); δ_C (75 MHz) 18.4, 18.4, 21.0, 21.7, 23.2, 25.7, 25.9, 33.1, 38.8, 46.7, 56.3, 59.1, 73.1, 74.1 and 211.2; *m/z* (EI): 254 (M^+, 58%), 236 (11%), 221 (6%), 203 (5%), 195 (39%), 177 (8%), 153 (24%), 137 (11%), 130 (10%), 123 (9%), 111 (40%), 95 (29%), 83 (42%), 69 (30%), 55 (38%) and 43 (100%) [Found: M^+, 254.1882. $C_{15}H_{26}O_3$ requires *M*, 254.1882].

The angelate ester of diol **10** was prepared as described above (but without DMAP): $[a]_D^{25}$ −84.6 (*c* 0.1, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3515, 1715, 1646, 1454, 1387, 1259, 1150 and 1084; δ_H (300 MHz) 0.85 (3 H, s), 0.88 (3 H, d, *J* 6.8 Hz), 0.93 (3 H, d, *J* 6.8 Hz), 1.08–1.33 (3 H, m), 1.22 (3 H, s), 1.33–1.68 (5 H, m), 1.96 (3 H, dq, *J* 1.4, 1.4 Hz), 2.02 (3 H, dq, *J* 7.2, 1.4 Hz), 1.78–2.32 (4 H), 4.93 (1 H, deformed t, *J* 2.8 Hz) and 6.13 (1 H, qq, *J* 7.2, 1.4 Hz); δ_C (75 MHz) 16.0, 18.4, 18.5, 20.9, 21.0, 21.6, 23.0, 24.0, 25.9, 34.2, 38.6, 48.9, 56.2, 59.3, 72.3, 76.7, 127.7, 139.0, 167.4 and 210.6; *m/z* (CI): 337 (MH^+, 18%), 319 (100%), 312 (32%), 295 (6%) and 237 (12%) [Found: M^+, 336.2303. $C_{20}H_{32}O_4$ requires *M*, 336.2301].

(*Z*)-2-Methylbut-2-enoic acid (1*S*,2*S*,4a*R*,7*R*,8a*R*)-1-hydroxy-7-isopropyl-1,4a-dimethyl-6-oxodecahydronaphthalen-2-yl ester (angelate ester of the C-3β,C-4α diol)

Diol **10** was oxidized with the Py·SO_3 complex in DMSO as

described above to furnish the corresponding acyloin (76%), which was reduced with $NaBH_4$ in ethanol at 0 °C to give the C-3β,C-4α diol (75%): mp 114–116 °C; $[\alpha]_D^{25}$ −55.6 (*c* 0.7, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3438, 1706, 1462, 1394, 1166 and 1090; δ_H (300 MHz) 0.77 (3 H, s), 0.82 (3 H, d, *J* 6.8 Hz), 0.88 (3 H, d, *J* 6.8 Hz), 1.08 (3 H, s), 1.30–1.58 (3 H, m), 1.68–1.84 (1 H, m), 1.95–2.30 (7 H, m), 2.50–3.20 (2 H, br s) and 3.50 (1 H, dd, *J* 11.4, 4.3 Hz); δ_C (75 MHz) 16.6, 18.3, 18.9, 20.9, 22.9, 25.7, 27.5, 38.4, 39.1, 51.4, 55.4, 59.0, 75.7, 79.3 and 211.1; *m*/*z* (EI): 254 (M^+, 17%), 203 (5%), 195 (26%), 177 (6%), 153 (16%), 137 (8%), 123 (6%), 111 (20%), 95 (16%), 83 (24%), 69 (33%), 55 (32%), 49 (15%) and 43 (100%) [Found: M^+, 254.1884. $C_{15}H_{26}O_3$ requires *M*, 254.1882].

The angelate ester of this diol was prepared as described above (but without DMAP): $[\alpha]_D^{25}$ −50.3 (*c* 0.6, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3483, 1713, 1653, 1455, 1387, 1356, 1235, 1174, 1091 and 1045; δ_H (300 MHz) 0.84 (3 H, s), 0.87 (3 H, d, *J* 6.8 Hz), 0.92 (3 H, d, *J* 6.8 Hz), 1.17 (3 H, s), 1.36–1.72 (5 H, m), 1.91 (3 H, dq, *J* 1.5, 1.5 Hz), 2.00 (3 H, dq, *J* 7.2, 1.5 Hz), 1.85–2.20 (7 H, m), 4.80 (1 H, dd, *J* 11.5, 4.7 Hz) and 6.09 (1 H, qq, *J* 7.3, 1.4 Hz); δ_C (75 MHz) 15.9, 18.1, 18.4, 18.8, 20.6, 20.9, 23.0, 25.5, 25.9, 38.3, 38.8, 52.3, 55.5, 58.9, 74.3, 81.4, 127.8, 138.8, 168.4 and 210.7; *m*/*z* (EI): 336 (M^+, 13%), 321 (2%), 318 (4%), 293 (2%), 253 (5%), 236 (8%), 221 (8%), 218 (5%), 205 (3%), 195 (50%), 177 (6%), 153 (10%), 109 (8%), 95 (7%), 83 (100%), 71 (22%), 55 (63%) and 43 (35%) [Found: M^+, 336.2309. $C_{20}H_{32}O_4$ requires *M* 336.2301].

Crystal data for diol 8 (racemic)

X-Ray data collection of $C_{15}H_{26}O_3$ ($M = 254.37$) was carried out on an Enraf-Nonius CAD-4 diffractometer (λ Kα = 0.7107 Å) at 293 K.[30] The crystal was monoclinic ($P2_1/a$, no. 14), with unit cell $a = 10.453(4)$, $b = 23.017(9)$, $c = 12.223(3)$ Å, $\beta = 102.83(3)°$, $V = 2867(2)$ $Å^3$, $Z = 8$, $D_x = 1.178$ g cm^{-3}, $\mu = 0.800$ cm^{-1}. Crystal structure determination and refinements were performed with teXsan system.[31] The structure was solved by direct methods, SIR92.[32] Using 3055 reflections with $I > 2\sigma(I)$, final *R* and R_w values are 0.063 and 0.060 for 325 parameters. The weighting scheme is $w = 1/[\sigma^2(F_o) + 0.00010 F_o^2]$. The present racemic atomic arrangement is characterized by the existence of two crystallographically independent molecules. Examination of these two independent units shows very small geometrical differences between them except for the H bond scheme. CCDC reference number 207/392. See http://www.rsc.org/suppdata/p1/a9/a909112b/ for crystallographic files in .cif format.

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