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An efficient stereocontrolled synthesis of (−)-10-*epi*-5β,11-dihydroxyeudesmane and (−)-4,10-*epi*-5β,11-dihydroxyeudesmane

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Abstract

A concise and efficient synthesis of (−)-10-*epi*-5β,11-dihydroxyeudesmane **1** and (−)-4,10-*epi*-5β,11-dihydroxyeudesmane **2**, *via* (−)-10-*epi*-ɣ-eudesmol **5**, was accomplished starting from (+)-dihydrocarvone. The salient feature of our synthesis is the utilization of substrate-directable epoxidation and homogeneous hydrogenation to control the stereochemistry at the C-4 and C-5 positions of the title compounds.

1. Introduction

Eudesmane derivatives have been drawing considerable attention due to their wide spectrum of biological properties, particularly antifeedant, cell growth inhibitory and plant growth regulating activities.[1,2]

In 1987, Itokawa and coworkers reported[3] the isolation of a new eudesmane derivative (−)-4,10-*epi*-5β,11-dihydroxyeudesmane **2** and determination of its structure by spectroscopic methods and chemical conversion. (−)-10-*epi*-5β,11-Dihydroxyeudesmane **1**, 4-epimer of **2**, was isolated[4] in 1989 by Mathela et al. and its absolute configuration was determined by X-ray diffraction. Herein, we report a concise synthesis of two diastereomers **1** and **2** from (+)-dihydrocarvone in six and seven steps, respectively, using substrate-directable epoxidation and homogeneous hydrogenation as key reactions. Our synthetic strategy (outlined in Scheme 1) is to use epoxide **3** as a key intermediate.

(−)-10-*epi*-ɣ-Eudesmol **5** is also a natural product isolated from the rhizome of *Alpinia japonira*[5] and the essential oil of *Amyris balsamifera*.[6] Before its isolation two similar synthetic routes to **5** were reported in the literature.[7,8] We have developed a more facile procedure for the preparation of **5** by a modification of the procedure of Marshall and Pike.[7]

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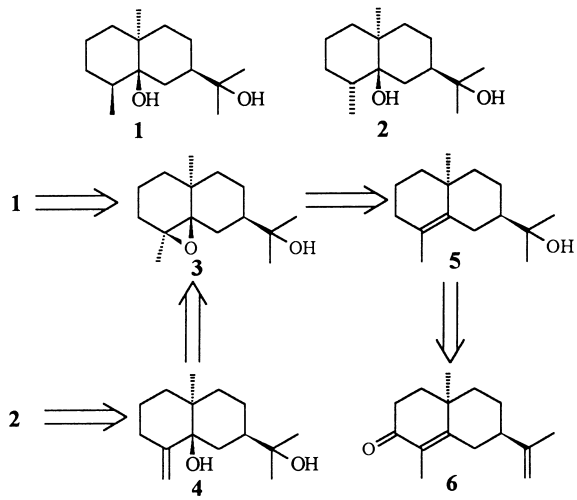


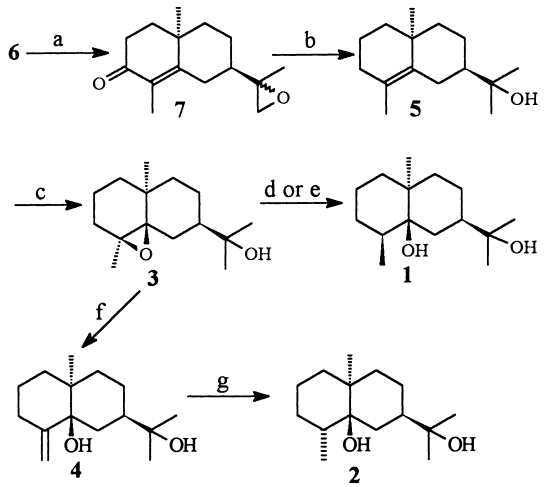
Scheme 1.

2. Results and discussion

Our synthesis started with (+)-dihydrocarvone (Scheme 2). By the published method,[9] (−)-10-*epi*-α-cyperone **6** was easily prepared from (+)-dihydrocarvone in 71% yield by a two-step procedure using (*S*)-(−)-α-phenylethylamine as a chiral auxiliary. Epoxidation of **6** gave epoxide **7** in excellent yield.[7] Compound **7** was reduced first with $LiAlH_4$ and then with $AlCl_2H$[10] in one pot to give (−)-10-*epi*-ɣ-eudesmol **5** in 70% yield. This result is remarkable, since cleavage of oxirane and deoxygenation[11] at C-3 in compound **7** are completed in one step. $AlCl_2H$ is usually used for deoxygenation of α,β-unsaturated carbonyl compounds and allylic alcohols.[10] It can also reduce epoxides in a complementary way to $LiAlH_4$ to give the less substituted alcohols.[12] So it is necessary to cleave oxirane in **7** first with $LiAlH_4$ (to give a tertiary alcohol) and then deoxygenate at the C-3 position by addition of $AlCl_2H$ to the reaction mixture. Our synthetic route to **5** is more efficient than those described in the literature.[7,8]

With (−)-10-*epi*-ɣ-eudesmol **5** in hand, the next task was the stereoselective functional group transformation at the C-4 and C-5 positions of compound **5**. In our synthesis, the stereochemistry of C-4 and C-5 in the title compounds **1** and **2** was stereospecifically controlled by using substrate-directable epoxidation and homogeneous hydrogenation as key reactions.[13] In the presence of a catalytic amount of $VO(acac)_2$, compound **5** was epoxidized with *t*-BuOOH to give **3** in quantitative yield and 100% diastereoselectivity.[14] The cleavage of the oxirane ring in **3** can not be achieved by reduction[15] with $LiAlH_4$ in ether at room temperature due to the steric effects with a tetra-substituted oxirane. Compound **1** was obtained by reduction of **3** with $LiAlH_4$–$AlCl_3$[16] in ether or with $LiAlH_4$ in refluxing THF. Epoxide **3** was treated with LDA in ether and afforded allylic alcohol **4** in 70% yield. In the presence of Wilkinson's catalyst, $RhCl(PPh_3)_3$, directed hydrogenation[17] of allylic alcohol **4** gave the alcohol **2** stereospecifically in 83% yield; its 4-epimer **1** was not detected in this reaction.[18] The spectral data of synthetic products match with those of natural products.[3,4] Thus the title compounds **1** and **2** were efficiently synthesized from (+)-dihydrocarvone in six and seven steps with overall yields of 33% and 27%, respectively.

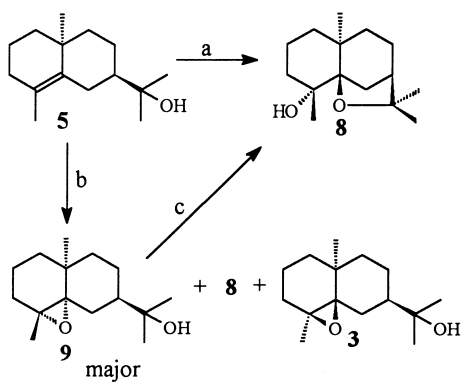
Marshall and Pike reported[7] that the epoxidation of **5** with *m*-chloroperoxybenzoic acid gave 4-hydroxydihydroagarofuran **8** instead of the normal epoxide (Scheme 3). They assumed that epoxide **9** is formed initially, but the geometry of **9** renders subsequent acid-catalyzed cyclization to **8** an exceedingly favourable process. In 1985, Itokawa et al. also reported[5] that the epoxidation of naturally-occurring (−)-10-*epi*-ɣ-eudesmol with *m*-chloroperoxybenzoic acid gave **8**. In our experiment, we found addition



Reagents and conditions: a. *m*CPBA, CH_2Cl_2, r.t., 7 h, 95%; b. $LiAlH_4$, dry ether, r.t., 7 h, then $AlCl_2H$, dry ether, 0 °C, 6 h, 70%; c. $VO(acac)_2$ (cat. amount), *t*-BuOOH (1.5 eq.), dry benzene, r.t., 3 h, 99%; d. $LiAlH_4$-$AlCl_3$ (2:1), dry ether, 1.5 h, 69%; e. $LiAlH_4$, dry THF, refluxing, 24 h, 64%; f. LDA, ether, r.t., 24 h, 70%; g. H_2, $(Ph_3P)_3RhCl$ (cat. amount), dry benzene, r.t., 40 h, 83%.

Scheme 2.

of $NaHCO_3$ to the reaction mixture can prevent the cyclization of **9** in the epoxidation of **5** with *m*-chloroperoxybenzoic acid, and epoxide **9** was obtained as a major product along with a mixture of compound **3** and **8** as minor products. Epoxide **9** is acid-sensitive and it can be cyclized to **8** on a chromatography column of silica gel. During purification of **9** by chromatography on silica gel, some drops of triethylamine must be added to the eluent to prevent its isomerization. These results verify the assumption of Marshall and Pike.



Reagents and conditions: a. *m*CPBA, CH_2Cl_2 or benzene, see ref. 5 and ref. 7; b. *m*CPBA, CH_2Cl_2, $NaHCO_3$, r.t., 0.5 h; c. acid or silica gel.

Scheme 3.

3. Experimental

Melting points are uncorrected. For column chromatography, 200–300 mesh silica gel and 60–90°C petroleum ether (PE) were used. Elemental analyses were performed on an Italian 1106 analyzer. IR

spectra were recorded on a Nicolet FT-170SX as liquid films. ^{1}H NMR spectra were measured on a Bruker AM-400 or a Varian FT-80A spectrometer (TMS, $CDCl_3$). Mass spectra were determined on a V.G.ZAB-HS spectrometer (EI, 70 eV).

3.1. *(−)-10*-epi-*γ-Eudesmol* **5**

To a suspension of $LiAlH_4$ (70 mg) in dry ether (5 mL) was added a solution of epoxide **7** (120 mg) in dry ether (4 mL) at 0°C under argon. The mixture was stirred at room temperature for 7 h. Then a solution of $AlCl_2H$[10] (1 M in ether, 18 mL) was added to the reaction miture *via* a syringe at 0°C. After stirring at this temperature for an additional 6 h, the reaction was poured into crushed ice. The organic layer was separated and the aqueous layer was extracted with ether (2×15 mL). The combined organic fractions were washed with water (2×10 mL), sat. aq. $NaHCO_3$ (2×10 mL), brine (2×10 mL), and dried ($MgSO_4$). After removal of the solvents, the oily residue was chromatographed on silica gel eluting with PE:ether (10:1) to give **5** (80 mg, 70% yield) as a colourless oil. $[\alpha]_D^{21}$ −55.6 (c 0.72, $CHCl_3$), [lit.[5] $[\alpha]_D$ −30.8 (c 0.16, EtOH)]; IR: 3403, 1459, 1375 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$): δ (ppm) 1.09 (s, 3H, 10-Me), 1.19 (s, 3H, 11-Me), 1.25 (s, 3H, 11-Me), 1.45 (m, 4H), 1.68 (s, 3H, 4-Me), 1.91 (m, 3H), 2.16 (m, 1H), 2.63, 2.82 (each br s, 1H); EIMS m/z (%): 222 (M^+, 10), 204 (49), 189 (72), 162 (18), 161 (55), 149 (49), 133 (39), 122 (20), 105 (38), 91 (48), 59 (73), 43 (100).

3.2. *(−)-4β,5β-Oxido-10*-epi-*γ-eudesmol* **3**

To a solution of 10-*epi*-γ-eudesmol **5** (80 mg) in dry benzene (10 mL) was added a catalytic amount of $VO(acac)_2$. Then a solution of *t*-BuOOH (3.1 M in toluene, 0.17 mL) was added to the mixture. After stirring at ambient temperature for 3 h, the reaction mixture was diluted with ether (30 mL), washed with water (3×10 mL) and brine (2×10 mL), and dried ($MgSO_4$). The crude product was chromatographed on silica gel (eluent PE:ether, 8:1) to yield **3** (85 mg, 99% yield) as a colourless oil. $[\alpha]_D^{21}$ −56.3 (c 0.71, $CHCl_3$); IR: 3609, 1457, 1381 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.12 (s, 3H, 10-Me), 1.22, 1.28 (each s, 3H, 11-Me), 1.31 (s, 3H, 4-Me), 1.54 (m, 2H), 1.74–1.83 (m, 4H), 1.89–2.06 (m, 3H); EIMS m/z (%): 238 (M^+, 1), 223 (3), 221 (1), 220 (3), 205 (4), 187 (4), 165 (11), 162 (37), 147 (24), 122 (36), 107 (37), 105 (37), 77 (30), 59 (50), 43 (100).

3.3. *(−)-10*-epi-*5β,11-Dihydroxyeudesmane* **1**

Method A: To a solution of epoxide **3** (20 mg) in dry ether (2 mL) was added 2 mL of an ether suspension of $LiAlH_4$–$AlCl_3$ (3 mmol of $LiAlH_4$ and 1.5 mmol of $AlCl_3$ in 30 mL of dry ether) under argon at room temperature. After stirring at ambient temperature for 1.5 h, the reaction mixture was poured into crushed ice, and extracted with ether (3×10 mL). The extracts were washed with water (2×5 mL), sat. aq. $NaHCO_3$ (2×5 mL), brine (2×5 mL), and dried ($MgSO_4$). Silica gel chromatographic purification eluting with PE:ether (6:1) afforded **1** (14 mg, 69%) as colourless crystals. $[\alpha]_D^8$ −12 (c 0.60, $CHCl_3$), mp 108–109°C, [lit.[4] $[\alpha]_D^{25}$ −9.0 (c 0.80, $CHCl_3$), mp 120–121°C]; IR: 3438, 3315, 1464, 1458, 1418, 1378 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$): δ (ppm) 0.85 (d, 3H, *J*=6 Hz, 4-Me), 1.06 (s, 3H, 10-Me), 1.26 (s, 6H, 11-Me), 1.34–1.65 (m, 6H), 1.83 (m, 2H); EIMS m/z (%): 240 (M^+, 19), 222 (11), 207 (27), 189 (13), 164 (34), 149 (61), 126 (84), 109 (59), 95 (39), 59 (77), 43 (100); anal. calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.82; H, 11.69%.

Method B: To a suspension of $LiAlH_4$ (40 mg) in dry THF (6 mL) was added a solution of epoxide **3** (20 mg) in dry THF (4 mL) under argon. Then the mixture was heated at reflux for 24 h. After cooling,

0.1 mL of water was added to the reaction mixture followed by 0.1 mL of 10% aq. NaOH, and 0.1 mL of water, and stirring was continued for an additional 0.5 h. The reaction mixture was filtered and the white residue was washed with hot THF (10 mL), the combined filtrates were dried over $MgSO_4$. Purification by chromatography on silica gel afforded **1** (13 mg, 64% yield) as colourless crystals, which is identical to the product prepared by procedure A.

*3.4. (−)-10-*epi-*5β-Hydroxy-β-eudesmol **4***

To a freshly prepared solution of LDA (0.5 M in ether, 5 mL) was added a solution of epoxide **3** (40 mg) in dry ether (4 mL) under argon at room temperature. The reaction mixture was stirred at ambient temperature for 24 h and then some water was added to quench the reaction. After the usual work-up, **4** (28 mg, 70%) was obtained as colourless crystals: mp 110–112°C, $[\alpha]_D^8$ −81.1 (c 0.74, $CHCl_3$); IR: 3295, 3076, 1382, 896 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ (ppm) 0.92 (s, 3H, 10-Me), 1.32 (s, 6H, 11-Me), 1.73 (m, 2H), 1.87 (m, 3H), 1.99 (m, 3H), 2.19 (br t, *J*=3.6 Hz, 1H), 4.15 (br s, 2H, OH), 4.72 (br t, *J*=1.3 Hz, 1H), 4.83 (br t, 1H, *J*=1.5 Hz); EIMS m/z (%): 238 (M^+, 6), 220 (20), 205 (42), 192 (25), 187 (17), 177 (18), 163 (29), 162 (72), 147 (100), 109 (47), 95 (94); anal. calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.76; H, 10.87%.

*3.5. (−)-4,10-*epi-*5β,11-Dihydroxyeudesmane **2***

Method A: A solution of allylic alcohol **4** (18 mg) and a catalytic amount of $RhCl(PPh_3)_3$ in dry benzene (5 ml) was stirred under an atmospheric pressure of hydrogen at room temperature for 40 h. The reaction mixture was then evaporated and the residue was chromatographed on silica gel (eluent PE:ether, 6:1) to afford **2** (15 mg, 83%) as colourless crystals: mp 130–132°C, $[\alpha]_D^{10}$ −46.2 (c 0.68, $CHCl_3$), [lit.[3] mp 130.0–132.0C, $[\alpha]_D$ −21.8 (c 0.12, $CHCl_3$)]; IR: 3235, 1458, 1157, 1016, 946 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.06 (d, *J*=7.6 Hz, 3H, 4-Me), 1.12 (s, 3H, 10-Me), 1.28 (s, 6H, 11-Me), 1.55–1.91 (m, 9H), 1.97 (dt, *J*=14.0, 5.0 Hz, 1H), 2.05 (dd, *J*=15.0, 7.5 Hz, 1H); EIMS m/z (%): 240 (M^+, 6), 222 (10), 207 (34), 189 (17), 164 (29), 149 (83), 126 (89), 109 (57), 59 (94), 43 (100); anal. calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.88; H, 11.79%.

Method B: A mixture of allylic alcohol **4** (25 mg), 10% Pd–C (10 mg) and triethylamine (0.1 mL) in absolute ethanol (5 mL) was stirred under an atmospheric pressure of hydrogen at room temperature for 45 h. The reaction mixture was then filtered and the filtrate was evaporated. The residue was chromatographed on silica gel eluting with PE:ether (8:1) to give **1** (5 mg) and **2** (15 mg).

*3.6. (−)-4α,5α-Oxido-10-*epi-*γ-eudesmol **9***

To a mixture of (−)-10-*epi*-γ-eudesmol **5** (30 mg) and $NaHCO_3$ (60 mg) in CH_2Cl_2 (6 mL) was added *m*CPBA (70%, 35 mg). After stirring at ambient temperature for 0.5 h, the reaction mixture was diluted with ether (20 mL), washed with 5% aq. NaOH (2×5 mL), water (2×5 mL), brine (2×5 mL), and dried ($MgSO_4$). After removal of the solvents, the residue was chromatographed on silica gel eluting with PE:ether:Et_3N (8:1:0.005) to give a mixture of **8**[5] and **3** (6 mg, **8**:**3**=1:1.2, determined by their ^1H NMR spectra), and **9** (20 mg, 62%) as a colourless oil. $[\alpha]_D^8$ −43.1 (c 0.60, $CHCl_3$); IR: 3443, 1463, 1377 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ (ppm) 1.07 (s, 3H, 10-Me), 1.18 (s, 3H, 11-Me), 1.21 (s, 3H, 11-Me), 1.30 (s, 3H, 4-Me), 1.42–1.54 (m, 3H), 1.65 (m, 2H), 1.79 (m, 1H), 1.95 (m, 2H); EIMS m/z (%): 238 (M^+, 10), 223 (17), 220 (9), 205 (13), 187 (7), 177 (23), 162 (55), 159 (25), 149 (37), 135 (26), 119 (41), 107 (46), 93 (32), 84 (33), 59 (69), 43 (100).

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18. Hydrogenation of **4** can also be catalyzed by 10% palladium on charcoal in the presence of triethylamine in ethanol, which gave an epimeric mixture of **2** and **1** with a ratio of 3:1 in a combined yield of 79%. This reaction must be performed in the presence of triethylamine, otherwise the products are more complex and the yields of **1** and **2** are very low.