Facile Synthesis of 6β-Hydroxy-(7αH)-eudesm-4-en-3-one and β-Cyperone†

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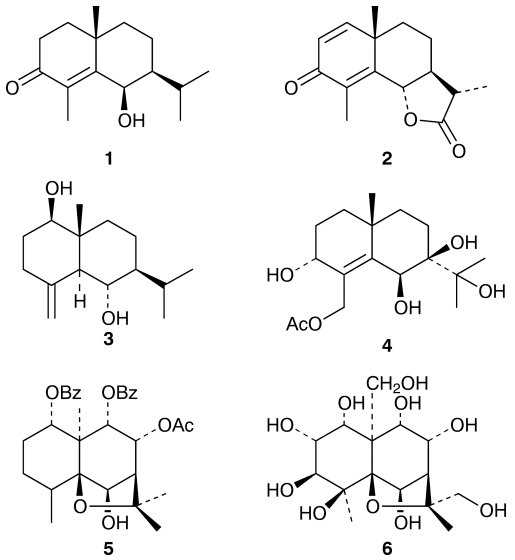
A stereoselective total synthesis of 6β-hydroxy-(7αH)-eudesm-4-en-3-one **1** and β-cyperone **12** starting from (+)-dihydrocarvone **7** is described.

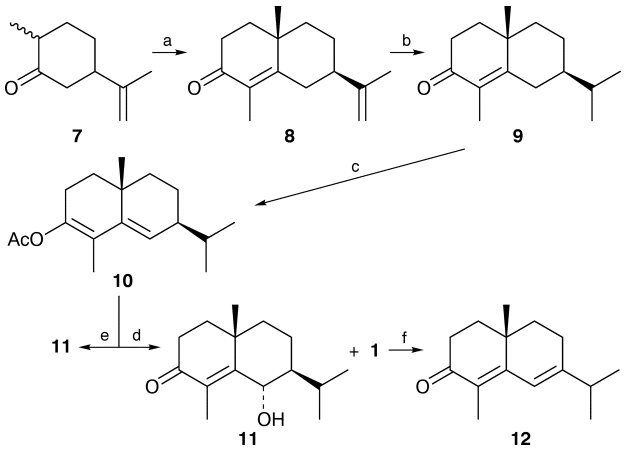
A number of C-6 oxyfunctionalized eudesmanes and β-dihydroagarofurans, such as compounds **3**–**6**,[1] have been isolated from natural sources. However reports on the synthesis of this particular kind of compound are few and generally start from α-santonin **2**.[2] Our interest of study on the synthesis of this kind of compound prompted us to investigate a new synthetic route from the cheap material (+)-dihydrocarvone **7**.

Recently, Syah and Ghisalberti[3] isolated the sesquiterpene 6β-Hydroxy-(7αH)-eudesm-4-en-3-one **1** from *Eremophila spectabilis subsp. brevis*, and determined its structure by spectroscopy and X-ray diffraction. Herein we report an efficient and practical synthesis of **1** from (+)-dihydrocarvone **7** in five steps.



Scheme 1

As shown in Scheme 2, α-cyperone **8** was diastereoselectively prepared from (+)-dihydrocarvone **7** by a two-step procedure.[4] Regiospecific hydrogenation of α-cyperone **8** with Wilkinson catalyst[5] for 48 h afforded **9** quantitatively. Treatment of **9** with acetic anhydride and acetyl chloride[6] gave the dienol acetate **10** in 98% yield, which was epoxidized with *m*-chloroperbenzoic acid (*m*CPBA)[7] at room temperature to give an epimeric mixture of **1** and **11** in a combined yield of 75% with a ratio 1:2 due to the hindrance of the β-methyl group at C-10 in **10**. It is worth noting that oxidation of **10** with Oxone[8] stereospecifically gave **11** in 50% yield. The spectral data of **1** are identical with those of the natural product.[3]



Scheme 2 *Reagents and conditions*: a, ref. 4; b, H_2, $[RhCl(PPh_3)_3]$, dry benzene; c, Ac_2O, AcCl; d, *m*CPBA, CH_2Cl_2; e, Oxone, H_2O–THF; f, $CuSO_4/SiO_2$, CCl_4

The mixture of **1** and **11** was dehydrated smoothly with $CuSO_4/SiO_2$[9] to afford β-cyperone **12** quantitatively. The overall yield of β-cyperone **12** from starting material is twice as much as that obtained previously.[10]

In summary, we have developed a synthetic methodology for introduction of a hydroxy group at C-6 in the eudesmane skeleton, which may be used in the synthesis of other 6-oxyfunctionalized natural eudesmanes and dihydroagarofurans, it is also an efficient synthetic route for synthesis of β-cyperone.

Experimental

For column chromatography, 200–300 mesh silica gel and 60–90 °C light petroleum were used. IR spectra were recorded on a Nicolet FT-170SX spectrometer as liquid films, ^1H NMR spectra on Bruker AM-400 spectrometers with $SiMe_4$ as internal standard and $CDCl_3$ as solvent and mass spectra on a V.G. ZAB-HS spectrometer (EI, 70 eV). Elemental analysis was performed on an Italian 1106 analyzer.

Hydrogenation of α-Cyperone **8**.—A solution of α-cyperone **8** (32 mg, 0.147 mmol) and $[RhCl(PPh_3)_3]$(catalyst) in dry benzene (5 ml) was stirred under a hydrogen atmosphere at r.t. for 48 h. After filtration, the solvent was removed and the crude product purified by silica gel chromatography to yield compound **9** (31 mg, 98%) as colourless oil, $[\alpha]_D^{12}$+146.1 ($c = 1.09$, $CHCl_3$); $\tilde{\nu}_{max}/cm^{-1}$ 2958, 2927, 2869, 1667; δ_H (80 MHz) 0.68 (3 H, br s, 11-Me), 0.96 (3 H, br s, 11-Me), 1.17 (3 H, s, 10-Me), 1.75 (3 H, s, 4-Me); *m*/*z* 220 (M^+, 84), 205 (24), 177 (85), 149 (47), 135 (100), 91 (64) (Found: C, 81.60; H, 10.61. Calc. for $C_{15}H_{24}O$: C, 81.82; H, 10.91%).

Acetylation of compound **9**.—A mixture of compound **9** (30 mg, 0.135 mmol), acetic anhydride (1 ml) and acetic chloride (1.5 ml) was heated at reflux under an argon atmosphere for 1.5 h. After cooling, the resulting light yellow solution was concentrated to dryness *in vacuo*. The residue was dissolved in Et_2O (30 ml) and washed with sat. $NaHCO_3$ (3 × 5 ml), water (10 ml) and brine (2 × 5 ml), and dried over anhydrous $MgSO_4$. After removal of the solvent, the oily residue was chromatographed on silica gel to give the dienol acetate **10** (35 mg, 98%) as a light yellow oil, $[\alpha]_D^{12}$+24.8 ($c = 2.22$,

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$CHCl_3$); $\tilde{\nu}/cm^{-1}$ 3397, 2951, 2928, 2875, 1755, 1660; δ_H (80 MHz) 0.88 (3 H, d, *J* 6.6, 11-Me), 0.92 (3 H, d, *J* 6.6, 11-Me), 1.02 (3 H, s, 10-Me), 1.65 (3 H, br s, 4-Me), 2.17 (3 H, s, Ac-H), 5.49 (1 H, d, *J* 2.4 Hz, 6-H); *m*/*z* 262 (M^+, 6), 220 (14), 203 (12), 177 (100), 133 (14), 105 (4). (Found: C, 75.89; H, 9.81. Calc. for $C_{17}H_{26}O_2$: C, 77.09; H, 9.92%).

Epoxidation of Dienol Acetate **10**.—To a solution of compound **10** (25 mg, 0.095 mmol) in CH_2Cl_2 (5 ml) was added *m*CPBA (70%, 24 mg) with stirring at r.t. The mixture was stirred at r.t for 24 h. After the usual work-up, the crude products were purified by flash chromatography to give **1** (6 mg, 27%) and **11** (11 mg, 48%) as white needle crystals. Compound **1**: mp 97–98 °C; $[\alpha]_D^{15}$+63.8 ($c = 0.61$, $CHCl_3$); $\tilde{\nu}/cm^{-1}$ 3455, 2937, 1656, 1598; δ_H (400 MHz) 1.00 (3 H, d, *J* 6.8, 11-Me), 1.03 (3 H, d, *J* 6.8, 11-Me), 1.38 (3 H, s, 10-Me), 1.86 (3 H, s, 4-Me), 4.98 (1 H, br d, *J* 2.6 Hz, 6-H); *m*/*z* 236 (M^+, 47), 221 (9), 193 (100), 175 (9), 149 (5), 137 (46), 123 (55), 111 (13), 91 (29) (Found: C, 76.01; H, 10.10. Calc. for $C_{15}H_{24}O_2$: C, 76.27; H, 10.17%). Compound **11**: mp 102–103 °C; $[\alpha]_D^{15}$+86.6 ($c = 1.22$, $CHCl_3$); δ_H (400 MHz) 0.88 (3 H, d, *J* 6.8, 13-H), 0.97 (3 H, d, *J* 6.8, 12-H), 1.20 (3 H, s, 14-H), 2.04 (3 H, s, 15-H), 4.44 (1 H, br d, *J* 10.8 Hz, 6-H); *m*/*z* 236 (M^+, 25), 208 (6), 193 (18), 147 (8), 123 (100), 109 (19); $\tilde{\nu}/cm^{-1}$ 3422, 2955, 2931, 1594 (Found: C, 76.05; H, 10.10. Calc. for $C_{15}H_{24}O_2$: C, 76.27; H, 10.17%).

Oxidation of Dienol Acetate **10** *to* **11**.—To a solution of compound **10** (10 mg, 0.048 mmol) in aqueous THF (3 ml) was added $NaHCO_3$ (3 mg) and Oxone (20 mg) at 0 °C. The resulting cloudy slurry was stirred for 8 h at r.t. After dilution with H_2O, the mixture was extracted with diethyl ether (30 ml). The organic phase was washed with water (2 × 5 ml) and brine (2 × 5 ml), dried over anhydrous $MgSO_4$, then concentrated to dryness *in vacuo*. Purification by flash chromatography gave pure **11** (5 mg, 56%).

Dehydration of Compounds **1** *and* **11**.—To a solution of the mixture of compound **1** and **11** (1:2, 10 mg, 0.042 mmol) in dry $CHCl_3$ (5 ml) was added $CuSO_4/SiO_2$ (1:3, 25 mg). The mixture was heated at reflux for 2 h. After usual work-up, the crude products were purified by flash chromatography, leading to the product **12** (9 mg, 98%) as a colorless oil. $\tilde{\nu}/cm^{-1}$ 2963, 2922, 2869, 1655, 1617. δ_H (80 MHz) 0.88 (3 H, d, *J* 6.6, 11-Me), 0.92 (3 H, d, *J* 6.6, 11-Me), 1.02 (3 H, s, 10-Me), 2.17 (3 H, s, 4-Me); *m*/*z* 218 (M^+, 25), 203 (21), 175 (47), 147 (55), 119 (69), 91 (100) (Found: C, 82.43; H, 10.00. Calc. for $C_{15}H_{22}O$: C, 82.57; H, 10.09%).

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