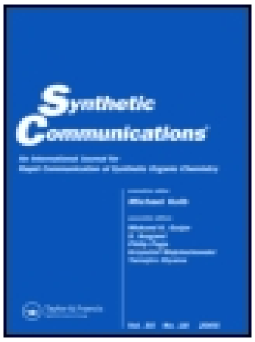

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A FACILE ROUTE TO (–)–3–OXOEUDESMA–1,4,11(13)–TRIEN –7αH –12–OIC ACID

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Abstract: *The first total synthesis of (–)– 3– oxoeudesma– 1, 4, 11(13)– trien– 7αH– 12– oic acid (**1**) has been described. The key step is one– pot reaction involving dehydrogenation and allylic oxidation with selenium dioxide.*

Eudesmane acids and eudesmane lactones 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] (–)–3–Oxoeudesma–1,4,11(13)–trien–7αH–12–oic acid (**1**) has recently been isolated from *Artemisia vulgaris* growing in Germany.[3] Now, we describe the first total synthesis of **1** from (+)–dihydrocarvone (**2**).[4] The salient feature of this synthetic program is the one–pot reaction of dehydrogenation at C–1 and C–2 and allylic oxidation at C–12 in (+)–α–cyperone (**3**) with selenium dioxide.

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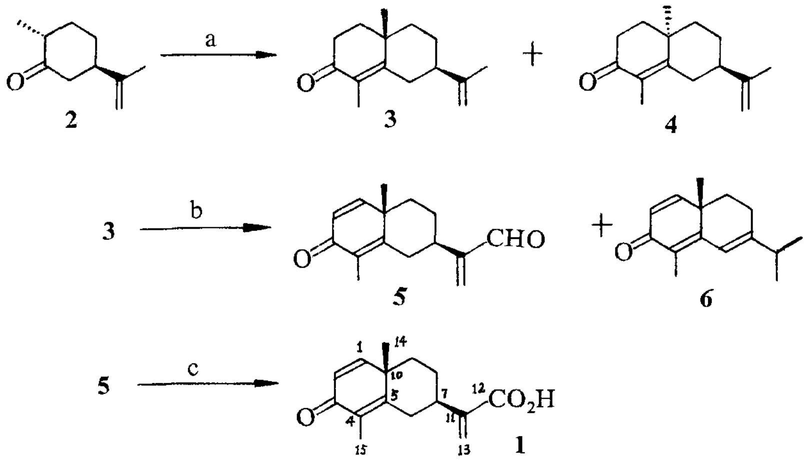

Reagents and conditions: a) EVK, conc. H_2SO_4, benzene, reflux, 14h; b) SeO_2, t–BuOH, AcOH, reflux, 10h; c) $AgNO_3$, KOH, EtOH, rt, 1h.

In the presence of catalytic amounts of concentrated sulfuric acid , one–step Robinson annulation[5] of **2** with ethyl vinyl ketone (EVK) afforded a mixture of **3** and its epimer **4** (in a combined yield of 61%) in a ratio of *ca* 3:2 (**Scheme**), which were separated *via* their oximes.[6] Howe *et al* have obtained very poor yield of **3** (less than 4% yield) by the condensation of **2** with 1–diethylaminopentan– 3– one methiodide under basic conditions.[6]

Oxidation of **3** with selenium dioxide furnished (–) – 3– oxoeudesma– 1, 4, 11(13)– trien– 7αH– 12– aldehyde (**5**) (43%) and minor amounts of 3–oxoeudesma–1, 4, 6–triene (**6**) (25%). The coupling of H–7 signal at δ 2.50, J= 12.4, 3.3 and 2.3Hz, indicated that the isopropenal group of compound **5** occupied an equatorial position subject to two equivalent axial–axial and two axial–equatorial couplings.[7] Oxidative dehydrogenation of cyclohexenone with selenium dioxide has been utilized in the synthesis of natural products,[8] but , to our knowledge, this is the first case in which dehydrogenation accompanied with allylic oxidation of isopropenyl substituent, because the methyl groups of isopropenyl substituents in cyclohexanes are not readily oxidized with either selenium dioxide or chromium (VI) reagents.[9,10]

Following the published procedure,[11] **5** was oxidized to the title compound **1** in 84% yield, whose spectral data agree well with those reported.[3]

The formation of the aldehyde **5** indicates that the selenium dioxide oxidation may provide a convenient synthetic procedure for other natural eudesmane acids.

The conversion of **1** to the corresponding lactone is in progress.

EXPERIMENTAL

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

(+)–α–Cyperone(3)

A stirred mixture of (+)–dihydrocarvone **2**[4] (0.76g, 5.0 mmol) in benzene (20 mL), EVK(0.5g, 6.0 mmol) and concentrated H_2SO_4(0.04 mL) was heated at reflux and with the continuous removal of water for 14h, during which time a brown solution resulted. After cooling, the solution was washed successively with 5% aqueous KOH (4× 15 mL) and brine (2× 15 mL), and dried over anhydrous $MgSO_4$. Removal of the solvent gave a brown oil, which was chromatographed on silica gel (elution with petroleum ether / ether, 5:1) to afford a mixture of **3** and its epimer **4** (0.66g, 61%) as yellow oils. Pure **3**(0.39g) was separated from the mixture *via* their oximes.[6]

(+)–α–Cyperone oxime: mp 148–149℃ ; $[\alpha]_D^{14}$ +125 ° (c = 2.0, $CHCl_3$)[Lit.[6]mp 150.5℃ ; $[\alpha]_{5461}$ +133.5 ° (c = 1.09, EtOH)]; υ_{max} 3260(OH), 2924, 1644(C = N), 1426, 955(N–O) cm^{-1}; δ_H (80 MHz) 1.12 (s, 3H, C_{10}–CH_3), 1.80(s, 3H, C_{11}–CH_3), 1.85(s, 3H, C_4–CH_3), 4.74(br s, 2H, C = CH_2).

3 : $[\alpha]_D^{14}$ +111.7 ° (c=1.2, $CHCl_3$)[Lit.[6]$[\alpha]_{5461}$ +115.4 ° (c=1.3, $CHCl_3$)]; υ_{max}2928, 1666(C=O), 1452 cm^{-1}; δ_H(80 MHz)1.24(s, 3H, C_{10}–CH_3), 1.75(s, 3H, C_{11}–CH_3), 1.79(s, 3H, C_4–CH_3), 4.79(br s, 2H, C=CH_2); *m/z*(%) 218(M^+,100), 203(67).

4 $[\alpha]_D^{15}$ −207.6 ° (c=1.1, $CHCl_3$) [Lit.[6]$[\alpha]_{5461}$−225 ° (c=5.0, $CHCl_3$); Lit.[12]$[\alpha]_{5461}$ +210 ° (c=3.5, $CHCl_3$) for (+)–enantiomorph of **4**]; υ_{max} 2930, 1663(C=O), 1453 cm^{-1}; δ_H(80 MHz) 1.22(s, 3H, C_{10}–CH_3), 1.71(s, 3H, C_{11}–CH_3), 1.80(s, 3H, C_4–CH_3), 4.60, 4.78(2 br s, 2H, C=CH_2).

(−)–3–Oxoeudesma–1,4,11(13)–trien–7αH–12–aldehyde (5)

A stirred mixture of **3**(0.33g, 1.5 mmol) in *tert*–butyl alcohol (140 mL) and acetic acid(2.5 mL) and selenium dioxide(0.99g, 9 mmol) was refluxed for 10h (monitored by TLC). After filtering, the resulting solution was diluted with water (30 mL), and the organic phase was washed successively with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4. The crude products were separated by silica gel chromatography using ether / petroleum ether (1:1) as eluent to give **5** (0.15g, 43%) and **6** (0.08g, 25%) as viscous oils.

5: Rf (ether / petroleum ether, 1:1) 0.33; $[\alpha]_D^{11}$ −72.3 ° (c=1.5, $CHCl_3$); υ_{max}1690(CHO), 1659(C=O), 1626, 1606 cm^{-1}; δ_H(400 MHz) 1.28(s, 3H, C_{10}–CH_3), 1.93(s, 3H, C_4–CH_3), 2.25(dd, 1H, *J*=13.0, 12.4Hz, 6β–H), 2.50(qd, 1H, *J*=12.4, 3.3, 2.3Hz, 7–H), 2.92(dd, 1H, *J*=13.0, 2.3Hz, 6α–H), 6.10, 6.38(2 br s, 2H, 13–H), 6.25(d, 1H, *J*=9.9Hz, 2–H), 6.77(d, 1H, *J*=9.9Hz, 1–H), 9.58(s, 1H, CHO); *m/z*(%) 230(M^+, 100), 215(51), 202(24), 187(60).

6: Rf (ether / petroleum ether, 1:1) 0.61; $[\alpha]_D^{15}$ +93.4 ° (c=0.8, $CHCl_3$); υ_{max}1654(C=O), 1610, 1587 cm^{-1}; δ_H(80 MHz) 1.11(d, 6H, *J*=6.5Hz, C_{11}–CH_3), 1.24(s, 3H, C_{10}–CH_3), 1.93(s, 3H, C_4–CH_3), 6.20(d, 1H, *J*=10Hz, 2–H), 6.40(br s, 1H, 6–H), 6.70(d, 1H, *J*=10Hz, 1–H); *m/z*(%) 216(M^+,72), 201(100), 188(14), 173(94).

(−)–3–Oxoeudesma–1,4,11(13)–trien–7αH–12–oic Acid (1)

To a stirred solution of **5** (80 mg, 0.34 mmol) in ethanol(4 mL) was added a solution of silver nitrate(134 mg, 0.80 mmol) in distilled water (2.4 mL), and to this was added dropwise with stirring 1.6 mL of aqueous KOH(2.1g KOH dissolved in 35 mL of distilled water) over a period of 10 min, giving immediately a black suspension. The heterogeneous mixture was stirred at room temperature for 1h. The mixture was then filtered and black silver precipitate was washed with water (8 mL). After washing with ether (2 × 10 mL), the basic solution was made acidic(pH = 1) with conc. HCl (about 0.7 mL), extracted with $CHCl_3$ (4 × 10 mL), and dried over anhydrous Na_2SO_4. Silica gel chromatographic purification eluting with ether yielded **1** (72 mg, 84%) as a colorless oil: $[\alpha]_D^{14}$ $-76.2°$ (c = 0.12, $CHCl_3$)[Lit[3]. $[\alpha]_D^{24}$ $-80.0°$ (c = 0.36, $CHCl_3$)]; υ_{max}3330–2540 (CO_2H), 1695, 1657 (C=O) cm^{-1} ; δ_H(80 MHz) 1.26(s, 3H, C_{10}–CH_3), 1.93(s, 3H, C_4–CH_3), 5.79,6.42(2 br s, 2H, 13–H), 6.25(d, 1H, J = 9.8 Hz, 2–H), 6.78(d, 1H, J = 9.8 Hz, 1–H); m/z(%) 246(M^+,100), 231(54).

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