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Total synthesis and stereochemistry of 13-hydroxy-α-eudesmol

Yonggang Chen, Zhaoming Xiong, Gang Zhou, Lijun Liu and Yulin Li *

National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

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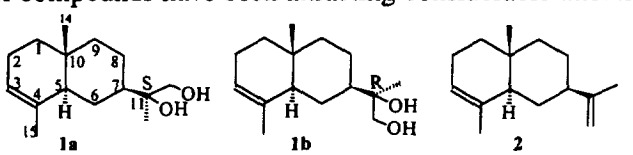
Abstract

The first total synthesis of both C-11 epimers of 13-hydroxy-α-eudesmol **1a** and **1b** by the use, as a key reaction, of the Sharpless asymmetric dihydroxylation of alkene **7** is presented. The absolute configuration of natural 13-hydroxy-α-eudesmol is established through comparison of the ^{1}H NMR spectrum of natural diol and synthetic diols. In our synthesis another natural product (+)-α-selinene **2** has also been accomplished. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Eudesmane type compounds are widely distributed in the plant kingdom. Due to their wide spectrum of biological properties, particularly antifeedant, cell growth inhibitory and plant growth regulating activities,[1,2] these kinds of compounds have been attracting considerable attention.



Recently, 13-hydroxy-α-eudesmol **1a** was first isolated from *C. uncata Cunn.* by King and Robinson et al.,[3] and its structure was determined by high field NMR techniques, however, the absolute configuration of C-11 remained unsolved. Herein, we report the first total synthesis and determination of the stereochemistry of 13-hydroxy-α-eudesmol. In our synthesis (+)-α-selinene has also been accomplished.

In recent years, the osmium-catalysed asymmetric dihydroxylation reaction of substituted alkenes with AD-mixes-α and -β has emerged as one of the most powerful and practical methods for controlling relative and absolute stereochemistry in secondary and tertiary alcohol derivatives[4] and the face-selection rule of Sharpless et al. has now become established as a reliable method for predicting absolute

* Corresponding author. Fax: (+86) 931 8911100; e-mail: liyl@lzu.edu.cn

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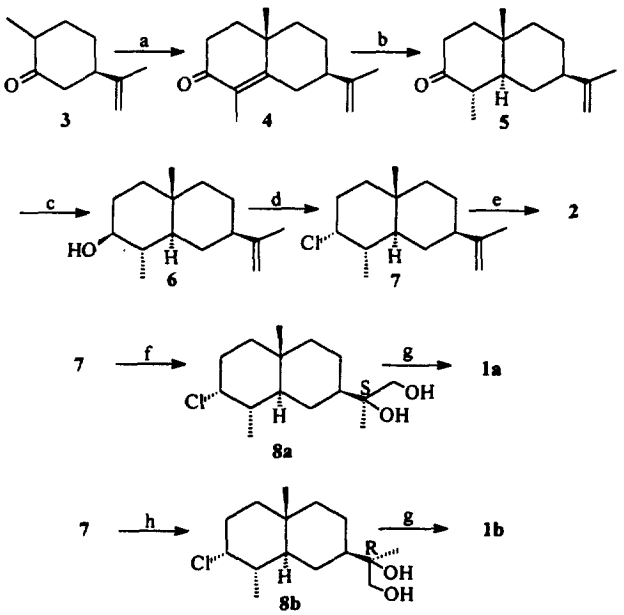
stereochemistry in the AD process.[4,5] Therefore we designed the following synthetic route to accomplish the first total synthesis of 13-hydroxy-α-eudesmol, by the use of the AD reaction as the key step (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) Ref.,[6] 50%; (b) Li, liq. NH_3, −78°C, 25 min, 86%; (c) $LiAl(OBu^t)_3H$, THF, 18 h, 92%; (d) PPh_3–NCS, THF, 3 h, 88%; (e) LiBr–Li_2CO_3, DMF, 138–140°C, 5 h, 86%; (f) AD-mix-α, *t*-BuOH–H_2O, 0°C, 88%; (g) LiBr–Li_2CO_3, DMF, 138–140°C, 5 h, 84%; (h) AD-mix-β, *t*-BuOH–H_2O, 0°C, 88%

2. Results and discussion

By the published method, (+)-α-cyperone **4** was stereoselectively prepared from (+)-dihydrocarvone **3** in two steps with an overall yield of 50%.[6] Stereoselective lithium–liquid ammonia reduction of **4**, using ammonium chloride as the proton donor, gave the dihydro-α-cyperone **5**.[7] Utilizing the steric hindrances of 10β-methyl, stereoselective reduction of **5** by tri-*t*-butoxyaluminium hydride gave alcohol **6** in high yield. In a stereospecific manner, alcohol **6** was converted into its 3α-chloro derivative **7** by PPh_3–NCS in THF under milder conditions.[8] Oxidation of **7** with commercially available AD-mix-α in *t*-BuOH–H_2O provided **8a** (45% de) in 88% yield.[4] The diastereoselectivity for (−)-**8a** was determined by analysis of the ^1H NMR (400 MHz) data.[9] The absolute configuration of (−)-**8a**, predicted by the Sharpless model, was assigned to be 11*S*. The mixture of **8a** and **8b**, as well as the sequent mixture of **1a** and **1b**, cannot be separated by chromatography on silica gel. Elimination of the halide of (−)-**8a** (45% de) with LiBr–$LiCO_3$–DMF gave (−)-(11*S*)-13-hydroxy-α-eudesmol **1a** (39% de, determined by ^1H NMR spectrum) in 84% yield. Similarly, dihydroxylation of **7** with AD-mix-β instead of AD-mix-α followed by elimination of the halide to afford (−)-(11*R*)-13-hydroxy-α-eudesmol **1b** (33% de, determined by ^1H NMR spectrum) gave an overall yield of 74%. Oxidation of **7** with a catalytic amount of OsO_4, $K_3Fe(CN_6)_6$ as reoxidant, followed by elimination of the halide, gave a mixture of **1a** and **1b** in a ratio of 1:1.

In the earlier stage of our studies, by elimination of the halide from **7**, we obtained (+)-α-selinene **2** in 86% yield, which was known to occur in a number of essential oils[10] and also in the defense secretions of

Table 1
^{1}H NMR spectral data of natural diol, **1a** and **1b**, and the mixture of **1a** and **1b**

H	Natural diol	1a	1b	1a and 1b
14	0.80 s	0.77 s	0.77 s	0.77 s
12	1.18 s	1.16 s	1.14 s	1.14 s and 1.16 s
15	1.61 brs	1.60 brs	1.63 brs	1.60 brs and 1.63 brs
5	1.88 brd (J = 12 Hz)	1.88 brd (J = 12.0 Hz)	1.89 m	1.89 m
13	3.47 d	3.48 d	3.46 d	3.46 d and 3.48 d
	3.62 d (J = 10.5 Hz)	3.63 d (J = 10.9 Hz)	3.60 d (J = 11.0 Hz)	3.60 d and 3.63 d (J = 11.0 Hz)
3	5.32 brs	5.32 brs	5.32 brs	5.32 brs

termite soldiers in the genera Amitermes.[11] Although there have been some successful examples of the total synthesis of **2**,[12] the strategy described in this paper is more facile and is highly efficient. Our initial synthetic design was to employ **2** as a key intermediate, by a regioselective dihydroxylation, to obtain **1a** and **1b**. It failed due to the complex products obtained by dihydroxylation of **2** with AD-mix-α or -β.

With both C-11 epimers of 13-hydroxy-α-eudesmol **1a** (39% de), **1b** (33% de) and the mixture of **1a** and **1b** in hand, the C-11 configuration of the natural product could be established through comparison of the ^{1}H NMR spectrum (Table 1) of the natural diol and those of the synthetic diols. It is worthwhile to note that there is a remarkable difference between **1a** and **1b** in a chemical shift of 12-H and 15-H ($\delta_{15H}-\delta_{12H}$: **1a**: 0.44 ppm; **1b**: 0.49 ppm). It is the $\Delta\delta$ value of **1a** that coincides with that of natural diol ($\delta_{15H}-\delta_{12H}$=0.43 ppm). The mass spectra of synthetic (−)-**1a** is also identical to that of the natural diol.[3]

In conclusion, the present results have established the configuration of 13-hydroxy-α-eudesmol to be those represented by stereoformula as (−)-**1a**.

3. Experimental section

Melting points are uncorrected. MS were performed on a V.G.ZAB-HS spectrometer (EI, 70 eV). Elemental analyses were performed on a Carlo Erba-1106 instrument. IR spectra were recorded on a Nicolet 170 SXFT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC-80 and AM-400 instruments. Chemical shifts are referred to TMS on the 'δ' scale. Standard flash chromatography was employed to purify the crude reaction mixture using 200–300 mesh silica gel under a positive nitrogen pressure.

3.1. Dihydro-α-cyperone 5

Pure α-cyperone **4** (600 mg, 2.75 mmol) in dry ether (30 ml) was added slowly into a stirred solution of Li (340 mg, 24.3 mmol) in liq. NH_3 (60 ml) over 5 min. After the mixture was stirred for 25 min, excess NH_4Cl was added and the NH_3 was allowed to evaporate. The reaction mixture was diluted with water (35 ml) and extracted with ether. The extracts were washed with brine. After drying over anhydrous $MgSO_4$, the solution was evaporated to dryness in vacuo. The crude products were purified by flash chromatography. The compound **5** (520 mg, 86% yield) was isolated as a colorless liquid. $[\alpha]_D^{16}$ −27.3 (c, 1.05, $CHCl_3$); IR: 1711, 1642, 1458, 887 cm^{-1}; ^{1}H NMR (80 MHz): δ (ppm) 0.98 (d, 3H, J=5.6 Hz, 4-Me), 1.12 (s, 3H, 10-Me), 1.75 (s, 3H, 11-Me), 4.75 (brs, 2H, 13-H); EIMS m/z: 220 (M^+, 86), 205 (16), 191 (13), 177 (43), 149 (38), 109 (80), 67 (79), 55 (100).

3.2. *Dihydro-α-cyperol* **6**

Dry *t*-butanol (2.1 ml) was slowly added to a solution of LAH (398 mg, 10.5 mmol) in dry THF (42 ml) at 0°C. The solution of dihydro-α-cyperone **5** (450 mg, 2.05 mmol) in THF (21 ml) was added with stirring and the mixture allowed to stand at 0°C for 30 min and then at room temperature for 18 h. The reaction mixture was poured into ice-cold 1 N HCL (60 ml) and extracted with petroleum ether. The extracts were washed with sat. aq. $NaHCO_3$ and brine. After drying over anhydrous $MgSO_4$, the solution was evaporated to dryness in vacuo. The crude products were purified by flash chromatography. Compound **6** (420 mg, 92%) was obtained as white needles, m.p. 71–72°C. $[\alpha]_D^{20}$ −5.7 (c, 2.96, $CHCl_3$); IR: 3342, 1644, 1451, 1377, 1025, 887 cm^{-1}; ^1H NMR (80 MHz): δ (ppm) 0.88 (s, 3H, 11-Me), 0.98 (d, 3H, J=5.5 Hz, 4-Me), 1.63 (brs, 3H, 12-Me), 3.14 (ddd, 1H, J=5.5, 9.5 and 9.6 Hz, 3-H), 4.71 (brs, 2H, 13-H); EIMS m/z (%): 222 (M^+, 52), 204 (32), 189 (28), 175 (14), 161 (58), 122 (60), 41 (100).

3.3. *3α-Chloro-4β-H-eudesma-11,12-ene* **7**

To a magnetically stirred solution of NCS (239 mg, 1.80 mmol) in THF (2.2 ml), a solution of PPh_3 (472 mg, 1.8 mmol) in THF (1 ml) was added dropwise. The solution was stirred at room temperature for 1 h. To this suspension, a solution of the alcohol **6** (350 mg, 1.58 mmol) in THF (3.5 ml) was added and stirring was continued until most of the solid was dissolved (ca. 3 h). The reaction mixture was stripped of solvent under reduced pressure and the residue was treated with water and ether. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated. The crude products were purified by flash chromatography. The compound **7** (334 mg, 88%) was obtained as a colourless oil. $[\alpha]_D^{26}$ −68.8 (c, 3.9, $CHCl_3$); IR: 1879, 1450, 886 cm^{-1}; ^1H NMR(400 MHz): δ (ppm) 0.85 (s, 3H, 10-Me), 0.94 (d, 3H, J=6.5 Hz, 4-Me), 1.73 (br s, 3H, 10-Me), 4.33 (br q, 1H, J=2.7 Hz, 3-H), 4.68 (br d, 1H, J=1.42 Hz, 13-H), 4.69 (br s, 1H, 13-H); EIMS m/z (%): 240 (M^+, 64), 225 (15), 197 (89), 161 (44), 81 (100). Found: C, 74.67%; H, 10.16%. Calcd for $C_{15}H_{25}Cl$: C, 74.81%; H, 10.46%.

3.4. *(+)-α-Selinene* **2**

A suspension of compound **7** (42 mg, 0.18 mmol), LiBr (46 mg, 0.53 mmol) and Li_2CO_3 (52 mg, 0.7 mmol) in dry DMF (1.5 ml) was heated at 138–140°C for 5 h. After the solution was cooled, it was diluted with ether and washed with water and brine. After drying over anhydrous $MgSO_4$, the solution was evaporated to dryness in vacuo. Purification by flash chromatography give pure **2** (31.6 mg, 86%). $[\alpha]_D^8$ +13.7 (c, 1.52, $CHCl_3$, lit[10] $[\alpha]_D$ +15.7); IR: 2967, 2929, 2844, 1642, 1447, 1375, 1216, 887 cm^{-1}; ^1H NMR (400 MHz): δ (ppm) 0.81 (s, 3H, 10-Me), 1.62 (brs, 3H, 11-Me) 1.77 (brs, 3H, 4-Me), 4.71 (s, 1H, 12-H), 4.74 (s, 1H, 12-H), 5.33 (brs, 1H, 3-H); EIMS m/z (%): 204 (M^+, 69), 189 (100), 175 (31), 161 (41), 147 (36), 133 (63), 119 (40), 105 (66), 91 (85), 79 (67), 41 (82).

3.5. *(−)-(11S)-3α-Chloro-13-hydroxy-α-eudesmol* **8a**

A 5 ml round-bottomed flask, equipped with a magnetic stirrer, was charged with 0.6 ml *tert*-butyl alcohol, 0.6 ml of water, and 870 mg AD-mix-α. The mixture was stirred at room temperature until both phases were clear, and then cooled at 0°C. Compound **7** (75 mg, 0.31 mmol) in 50% aqeous *t*-BuOH (1 ml) was added at once. The resulting mixture was stirred for 24 h at 0°C. Sodium sulfide (1.0 g) was added to the mixture which was then warmed to room temperature and stirred for 1 h. The reaction mixture was extracted several times with CH_2Cl_2. The extract was washed with 10% aqeous KOH, H_2O and brine,

dried over ($MgSO_4$). After evaporation, the crude product was purified by flash chromatography to afford **8a** (75 mg, 45% de) in 88% yield. $[\alpha]_D^{12}$ −95.2 (c, 0.47, $CHCl_3$); IR: 3364, 2937, 1450, 1380, 1040, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.83 (s, 3H, 10-Me), 0.94 (d, 3H, J=6.6 Hz, 4-Me), 1.14 (s, 3H, 11-Me), 1.90 (dd, 1H, J=3.13, 14.6 Hz, 5-H), 3.44 (d, 1H, J=10.8, 13-H), 3.59 (d, 1H, J=10.6, 13-H), 4.33 (m, 1H, 3-H). MS m/z (%): 259 (M^+−15, 1), 243 (100), 225 (58), 189 (24), 163 (7), 109 (11), 75 (20). Found: C, 65.38%; H, 9.76%. Calcd for $C_{15}H_{27}O_2Cl$: C, 65.56%; H, 9.90%.

3.6. (−)-(11S)-13-Hydroxy-α-eudesmol *1a*

A suspension of compound **8a** (60 mg, 0.22 mmol), LiBr (57 mg, 0.66 mmol) and Li_2CO_3 (65 mg, 0.88 mmol) in dry DMF (2 ml) was heated to 138–140°C for 5 h. After the solution was cooled, it was diluted with ether and washed with water and brine. After drying over anhydrous $MgSO_4$, the solution was evaporated to dryness in vacuo. Purification by flash chromatography give pure **1a** (44 mg, 39% de) in 84% yield. $[\alpha]_D^{10}$ −6.8 (c, 0.735, $CHCl_3$); IR: 3403, 2910, 1452, 1376, 1046 cm^1; EIMS m/z (%): 238 (M^+, 18), 220 (19), 207 (75), 189 (100), 107 (28), 84 (81). Found: C, 75.46%; H, 10.82%. Calcd for $C_{15}H_{26}O_2$: C, 75.58%; H, 11.00%.

3.7. (−)-(11R)-3α-Chloro-13-hydroxy-α-eudesmol *8b*

By a procedure similar to the preparation of **8a**, the reaction of **7** (70 mg, 0.29 mmol), AD-mix-β (812 mg), *t*-BuOH (1.1 ml) and H_2O (1.1 ml), gave **8b** (70 mg, 46% de) in 88% yield; $[\alpha]_D^8$ −27.0 (c, 1.48, $CHCl_3$); IR: 3390, 2934, 1739, 1461, 1389, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.83 (s, 3H, 10-Me), 0.96 (d, 3H, J=6.6 Hz, 4-Me), 1.11 (s, 3H, 11-Me), 3.43 (d, 1H, J=10.9, 13-H), 3.58 (d, 1H, J=10.9, 13-H), 4.33 (m, 1H, 3-H). EIMS m/z (%): 259 (M^+−15, 1), 243 (100), 225 (39), 189 (16), 163 (6), 109 (9), 75 (17).

3.8. (−)-(11R)-13-Hydroxy-α-eudesmol *1b*

A suspension of compound **8b** (70 mg, 0.29 mmol), LiBr (67 mg, 0.77 mmol) and Li_2CO_3 (76 mg, 1.03 mmol) in dry DMF (2.5 ml) was heated at 138–140°C for 5 h. After the solution was cooled, it was diluted with ether and washed with water and brine. After drying over anhydrous $MgSO_4$, the solution was evaporated to dryness in vacuo. Purification by flash chromatography give pure **1b** (51 mg, 33% de) in 84% yield. $[\alpha]_D^{10}$ −3.0 (c, 0.78, $CHCl_3$); IR: 3378, 2910, 1451, 1377, 1046 cm^{-1}; EIMS m/z (%): 238 (M^+, 7), 220 (10), 207 (32), 189 (48), 101 (100), 75 (49), 43 (59).

Acknowledgements

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9. The stereoselectivities of the asymmetric dihydroxylation of 1,1-disubstituted olefins vary from 30% to 95% in the literature.[4] In our experiments, we found: oxidation of **7** with a catalytic amount of OsO_4, without chiral ligand, gave a mixture of **8a** and **8b** in satisfactory yield within 10 h. Hydroxylation of **7** with AD-mixes by standard procedure was not complete within 48 h. When two-times the amount of AD-mixes described in standard procedure was used, the hydroxylation of **7** was completed within 24 h and gave diol **8** in satisfactory yield. Based on the above experimental facts, we think that the deca-hydronaphthalene substitute in olefin **7** might be responsible for the low de values in dihydroxylation of **7** with AD-mix. Because the deca-hydronaphthalene substitute is rigid and big, the diastereoselectivities and reaction rates of dihydroxylation of **7** with AD-mix were lowered.
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