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A revision of the positive sign of the optical rotation and its maximum value of α-eudesmol

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Abstract

The ether extract of the liverwort *Porella perrottetiana* afforded (−)-α-eudesmol, which showed an opposite sign of the optical rotation to that found in higher plants. Present work on the absolute configuration and an optical purity of (−)-α-eudesmol strongly suggested that the positive values (e.g. +28.5°) described in many previous papers should be revised. Since the absolute configuration of (−)-α-eudesmol was identical to that of (+)-β-eudesmol found in the higher plants, it was apparent that the expression of the positive sign might be revised to (−)-α-eudesmol. The optical purity, reconfirmation of the absolute configuration and synthesis of (−)-α-eudesmol will be discussed.

Keywords: (−)-α-Eudesmol; Sesquiterpene alcohol; Absolute configuration; Maximum optical rotation; Liverwort; *Porella perrottetiana*

1. Introduction

α-Eudesmol has been isolated from many species of plant kingdom, including liverworts. The first isolation of α-eudesmol has been reported from *Eucalyptus* species (McQuillin & Parrack, 1956). On the other hand, the first example of the isolation from the liverworts has been performed from *Porella stephaniana* as a major constituent (Asakawa, Yamamura, Waki & Takemoto, 1980). There are many publications, which reported the isolation or detection of α-eudesmol from essential oils of the plants. Recently, it was reported that α-eudesmol possesses the P-type Ca^{2+} channel antagonism (Kanemasa & Kagawa, 1999).

The absolute configuration of (+)-α-eudesmol (**1**) has been established by synthesis (Humber & Pinder, 1966; Humber, Pinder & Williams, 1967; Kutney & Singh, 1984; Chen, Xiong, Zhou, Yang & Li, 1997). A number of authors have indicated that the optical rotation of α-eudesmol is positive (Table 1). Furthermore, the maximum optical rotation is ambiguous. Recently our work resulted in the isolation of (−)-α-eudesmol from the liverwort *P. perrottetiana*. We report here the isolation and confirmation of the absolute configuration of (−)-α-eudesmol and revision of the value of optical rotation.

2. Results and discussion

The ether extract of the liverwort *P. perrottetiana* (Mont.) Trev. was subjected to silica gel column chromatography followed by preparative HPLC to give α-eudesmol (**1**). The ^{1}H NMR spectrum of **1** was completely identical to that of α-eudesmol (Kutney & Singh, 1984; Stoessl & Stothers, 1986; Schwartz & Willbrand, 1985), but different from the spectrum of known isomers of α-eudesmol, 7-epi-α-eudesmol (**2**), 5-epi-α-eudesmol (**3**), and 5-epi-7-epi-α-eudesmol (**4**) (Raharivelomanana et al., 1998; Schwarz & Willbrand, 1985). Furthermore, the ^{13}C NMR spectrum of **1** was

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Table 1
The values of specific optical rotation of α-eudesmol (**1**)

Source	$[\alpha]_D$[a]
Eucalyptus macarthuri (McQuillin & Parrack, 1956)	+31°
Machilus kusanoi (McQuillin & Parrack, 1956)	+31.4°
Melaleuca uncinata (McQuillin & Parrack, 1956)	+33.4°
Leptospermum flavescens (McQuillin & Parrack, 1956)	+38.9°
Balsamorrhiza sagittata (McQuillin & Parrack, 1956)	+37.2°
Synthetic (Humber & Pinder, 1966)	+28.5°
Synthetic (Kutney & Singh, 1984)	+28.6°
Porella stephaniana (Noma et al., 1996)	−6.4°
Porella perrottetiana[b]	−6.9°
Synthetic[b]	−8.0°

[a] All these data were measured in $CHCl_3$.
[b] Present work.

also identical to that of α-eudesmol (Stoessl & Stothers, 1986; Raharivelomanana, Bianchini, Cambon, Azzard & Faure, 1995) and did not accord with that of 7-epi-α-eudesmol (**2**) (Raharivelomanana et al., 1998). The GC–mass analysis using capillary column of **1** showed a single peak on the total ion chromatogram (TIC). The optical rotation of **1** exhibited a negative sign, which was opposite to that found in higher plants. This suggested that compound **1** was α-eudesmol. Liverworts often elaborate sesquiterpenes enantiomeric to those found in higher plants (Asakawa, 1995). However, further confirmations of the absolute configuration and the optical purity of (−)-α-eudesmol, $[\alpha]_D$ −6.9°($CHCl_3$) were necessary, since the optical rotation contrasted with the reported values. The chiral GC–mass analysis using capillary column β-DEX 120 showed a single peak on the TIC and indicated (−)-α-eudesmol was in an optically pure state.

Dehydration of (−)-α-eudesmol with *p*-toluenesulfonic acid gave a hydrocarbon **5**, whose spectral data were identical to those of δ-selinene derived from (+)-β-eudesmol (**6**). The optical rotation of δ-selinene, $[\alpha]_D$ +262°($CHCl_3$) derived from (−)-α-eudesmol found in the present species was satisfactorily close to that of authentic sample, $[\alpha]_D$ +250°($CHCl_3$) prepared from (+)-β-eudesmol (**6**). (+)-β-Eudesmol and its derivative, δ-selinene were recognized to be optically pure state by their chiral capillary GC–mass analyses. On the other hand, our present work resulted in the reconfirmation of the absolute configuration of (+)-β-eudesmol, (**6**) $[\alpha]_D$ +57.7°($CHCl_3$) {literature value; $[\alpha]_D$ +58.0°($CHCl_3$) (Varma & Bhattacharyya, 1964)} as shown in figure by X-ray crystallographic analysis for its crystalline derivative **7** (Toyota, Saito & Asakawa, 1999), although it has also been established by chemical means (Riniker et al., 1954). Judging from the evidence, it was suggested that the absolute configuration of (−)-α-eudesmol accorded with that of (+)-β-eudesmol (**6**).

The following experiments further confirmed the absolute configuration of (−)-α-eudesmol. Osmium catalyzed dihydroxylation of (−)-α-eudesmol gave a triol **8** and its isomer **9**. The ^1H NMR spectrum of triol **8** showed a proton signal at δ 3.29 (1H, *dd*, J = 5, 12 Hz) due to an axial carbinyl proton at C-3. Triol **8**, having the equatorial hydroxyl group at C-3 was converted to *R* (+)- and *S* (−)-α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) esters **10a** and **10b**, respectively. The δΔ values between **10a** and **10b** are displayed in Fig. 1. The values were applied to modified Mosher's method (Ohtani, Kusumi, Kashman & Kakisawa, 1991) and indicated the absolute configuration of (−)-α-eudesmol. Furthermore, α-eudesmol was obtained from (+)-β-eudesmol according to the procedure as shown in Scheme 1. The CD spectrum of **11** obtained in the first step showed Δε −1.4 (at 288 nm in methanol), which was identical to that of the reported value (Humber, Pinder & Wails, 1968). Finally, the optical rotation of the synthetic α-eudesmol, mp 87–89°C had $[\alpha]_D$ −8.0°($CHCl_3$, *c* 1.0).

Further evidence which confirmed the absolute configuration of **1** was provided. (−)-α-Eudesmol (**1**), $[\alpha]_D$ −6.4°($CHCl_3$, *c* 1.35) isolated from *P. stephaniana* was

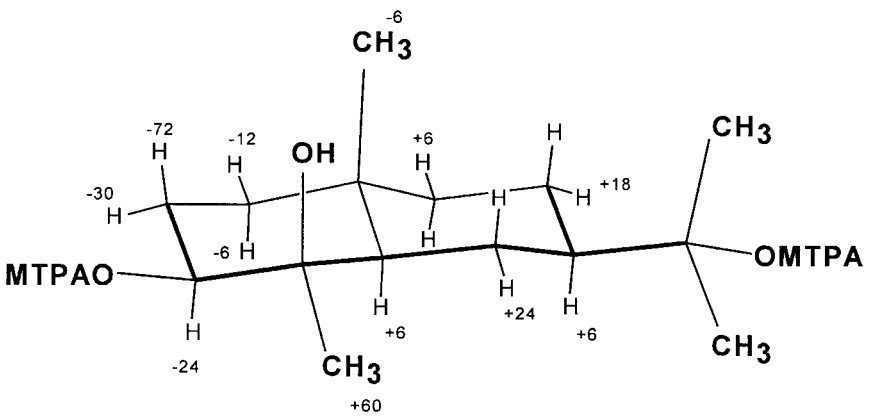
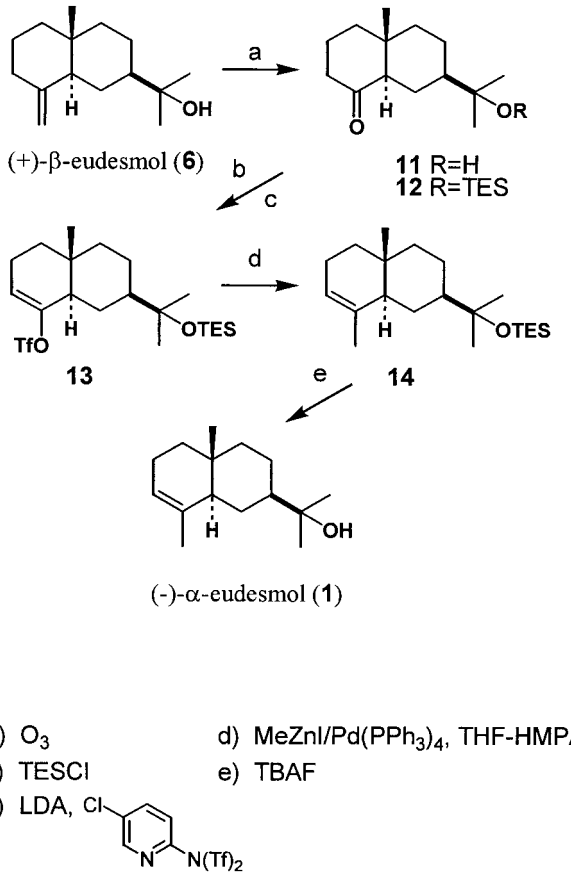


Fig. 1. The δΔ values between (**10a**) and (**10b**) are given in Hz.

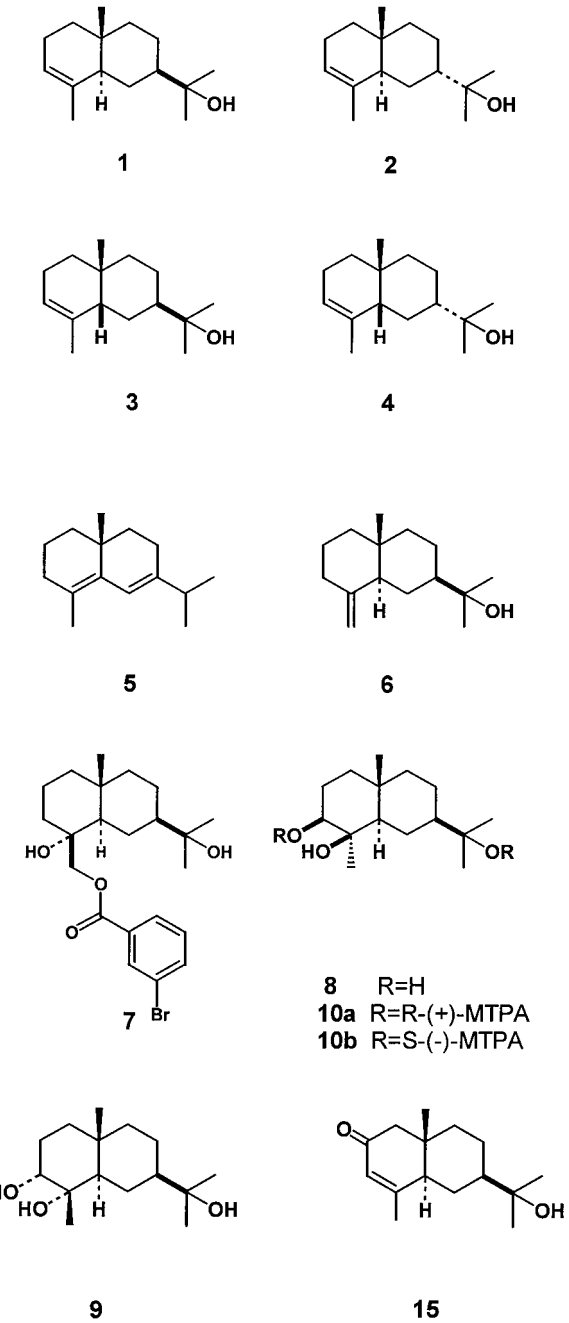


Scheme 1. Derivatization of (−)-α-eudesmol (**1**) from (+)-β-eudesmol (**6**).

biotransformed by the fungus *Aspergillus cellulosae* to the α,β-unsaturated ketone **15** in 23.3% yield (Noma, Hashimoto, Kikkawa & Asakawa, 1996). The ^{1}H, ^{13}C NMR, UV and IR spectral data for the metabolite **15** were in excellent agreement with those of isopterocarpolone (Kumar, Ravindrath & Seshadri, 1974; Kukla, Kumar, Sanduja & Seshadri, 1976) and both optical rotations {$[\alpha]_D$ +47.0°($CHCl_3$)} were satisfactorily identical.

Consideration of these chemical and spectral data led to the conclusion that the absolute configuration of (−)-α-eudesmol is as shown in **1**. The sign of the optical rotation for α-eudesmol possessing the absolute configuration of **1** is negative. It is strongly suggested that the expression of the positive sign of α-eudesmol should be revised to the negative value.

In certain cases, the natural product known as α-eudesmol has been recognized to be a mixture of two eudesmols, depending upon the source of the material. Particularly, the isolation of (−)-α-eudesmol, $[\alpha]_D$ −6.9°($CHCl_3$) from a crystalline mixture including (+)-β-eudesmol, $[\alpha]_D$ +57.7°($CHCl_3$) {$[\alpha]_D$ +58°($CHCl_3$) (Varma & Bhattacharyya, 1964)} and removal of the last trace of (+)-β-eudesmol by crystallization appeared to be difficult (McQuillin & Parrack, 1956; Stoessl & Stothers, 1986). Even when the purity of α-eudesmol obtained from the mixture is 90%, it still shows the positive sign, according to a calculation. Previously reported positive values are due to the mixture of (−)-α- and a very small amount of (+)-β-eudesmol.



Fortunately, since our material did not contain (+)-β-eudesmol, it was easy to isolate (−)-α-eudesmol from the liverwort *P. perrottetiana*. In many cases, α-eudesmol has been frequently encountered as a mixture of isomers in higher plants, although it was found in the liverwort *P. perrottetiana* as the major constituent (Fig. 2). Therefore, this is the first example of the iso-

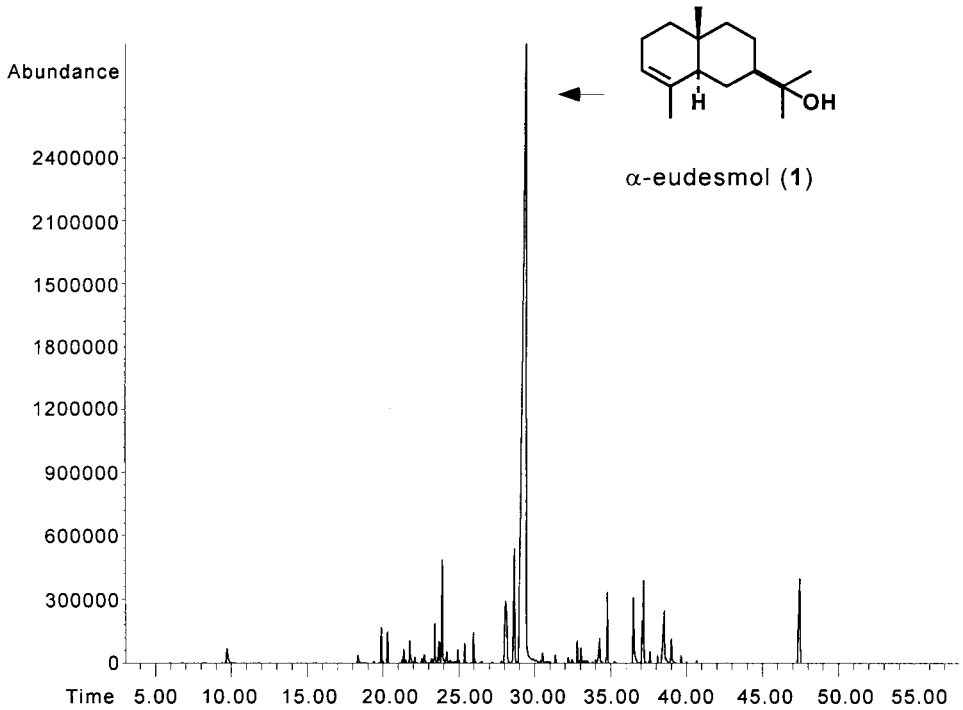


Fig. 2. Total ion chromatogram (TIC) of the ether extract of *P. perrottetiana*.

lation of (−)-α-eudesmol in a pure state from a natural source. Whereas the specific rotation of the natural product α-eudesmol have been recognized to be positive (e.g. +28.5°) for many years, it is now clear that the negative sign for its rotation is correct.

3. Experimental

3.1. General

TLC was carried out on silica gel precoated glass plates with *n*-hexane–EtOAc (1:1 and 4:1). Detection was with Godin reagent (Godin, 1954). For normal phase column chromatography (CC), silica gel 60 (40–63 or 63–200 μm) was used. The mixture of CH_2Cl_2–MeOH (1:1) was used for CC on Sephadex LH-20 as solvent.

3.2. Spectral data

NMR spectra were recorded at 100, 75 or 50 MHz for ^{13}C and 400, 300 or 200 MHz for ^{1}H. The temperature programming of GC–mass analysis performed from 50° isothermal for 3 min, then 50–250° at 5° min^{-1}, and finally isothermal at 250° for 15 min. Injection temp was 250°. A fused silica column coated with DB-17 (30 m × 0.25 mm id, film thickness 0.25 μm) or β-DEX 120 (30 m × 0.25 mm id, film thickness 0.25 μm) were used.

3.3. Plant material, extraction and isolation

P. perrottetiana (Mont.) Trev. (dry wt 17.7 g) was collected in February 1995 at Katsuura-cho (altitude 460 m), Tokushima, Japan. The material was gently washed with water, impurities removed and ground mechanically, then extracted with Et_2O for 1 week. The crude Et_2O extract (545 mg) was chromatographed on silica gel to give (−)-α-eudesmol (**1**) (46.6 mg; 8.6% in yield of the total extract). (−)-α-Eudesmol (**1**): $[\alpha]_D$ −6.9°($CHCl_3$, *c* 2.33).

3.4. Dehydration of (−)-α-eudesmol(*1*) and (+)-β-eudesmol (*6*)

To a solution of (−)-α-eudesmol (10 mg) in benzene (1 ml), *p*-toluenesulfonic acid (1 mg) was added and the reaction mix was refluxed for 5 min. The mix was purified by prep-HPLC to give δ-selinene (**5**) {5.2 mg, $[\alpha]_D$ +262°($CHCl_3$, *c* 0.15)}. δ-Selinene (**5**) {19 mg, $[\alpha]_D$ +250°($CHCl_3$, *c* 1.9)} was obtained from (+)-β-eudesmol (**6**) (30 mg) in the same manner. (+)-β-Eudesmol (**6**), $[\alpha]_D$ +57.7°($CHCl_3$, *c* 1.32) was isolated from the purchased crude drug, *Atractylodes lancea* rhizome.

3.5. Osmium dihydroxylation of (−)-α-eudesmol (*1*)

To a solution of **1** (33 mg) in Et_2O (1 ml), osmium tetroxide (9 mg) and 30% H_2O_2 (0.3 ml) were added

and the reaction mixture was stirred for 24 h at room temp. The mixture was chromatographed on Sephadex LH-20 followed by prep.-HPLC to give triols **8** (4.0 mg) and **9** (3.0 mg), respectively.

3.6. Eudesm-3β,4β,11-triol (*8*)

Oil; $[\alpha]_D$ +1.7°($CHCl_3$; *c* 1.4), ^{1}H NMR (400 MHz; $CDCl_3$): δ1.01 and 1.25 (each 3H, *s*), 1.21 (6H, *s*), 3.29 (1H, *dd, J* = 5, 12 Hz). ^{13}C NMR (100 MHz; $CDCl_3$): δ 18.5 (CH_3), 21.4 (CH_2), 22.2 (CH_2), 25.0 (CH_3), 26.8 (CH_3), 27.2 (CH_2), 27.5 (CH_3), 33.3 (C), 39.1 (CH_2), 43.3 (CH_2), 49.8 (CH), 50.6 (CH), 73.1 (C), 74.1 (C), 75.9 (CH).

3.7. Eudesm-3α,4α,11-triol (*9*)

Oil; $[\alpha]_D$ −31.0°($CHCl_3$; *c* 1.0), ^{1}H NMR (400 MHz; $CDCl_3$): δ 0.88 and 1.12 (each 3H, *s*), 1.21 (*s*, 6H), 3.61 (1H, *t, J* = 3 Hz). ^{13}C NMR (100 MHz; $CDCl_3$): δ 18.2 (CH_3), 21.2 (CH_2), 21.7 (CH_3), 22.5 (CH_2), 25.6 (CH_2), 27.0 (CH_3), 27.4 (CH_3), 33.6 (CH_2), 34.0 (C), 44.2 (CH_2), 47.4 (CH), 49.9 (CH), 73.0 (C), 73.3 (C), 74.5 (CH).

3.8. Esterification of eudesm-3β,4β,11-triol (*8*) by R (+) and S (−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA)

To a solution of **8** (1.5 mg) in dry CH_2Cl_2 (0.7 ml), *R* (+)-MTPA (8.8 mg), DCC (5.5 mg) and DMAP (2.0 mg) were added and the reaction mixture was stirred for 48 h. To the mix, H_2O was added and the solution was washed with 1N HCl, saturated $NaHCO_3$ and NaCl. After evaporation, the CH_2Cl_2 layer was purified by prep.-TLC to give *R* (+)-MTPA ester **10a** (0.9 mg). *S* (−)-MTPA ester **10b** (1.2 mg) of **8** was obtained by *S* (−)-MTPA in the same manner.

3.9. R (+)-MTPA ester *10a*

^{1}H NMR (400 MHz; $CDCl_3$): δ 0.92, 0.99, 1.55 and 1.58 (each 3H, *s*), 3.54 and 3.57 (each 3H, *brs*), 4.75 (1H, *dd, J* = 5, 12 Hz), 7.38 (*m*, 3H), 7.42 (*m*, 3H), 7.53 (*m*, 4H).

3.10. S (−)-MTPA ester *10b*

^{1}H NMR(400 MHz; $CDCl_3$): δ 0.97, 1.02, 1.57 and 1.58 (each 3H, *s*), 3.51 and 3.52 (each 3H, *brs*), 4.72 (1H, *dd, J* = 5, 12 Hz), 7.39 (*m*, 3H), 7.43 (*m*, 3H), 7.52 (*m*, 3H).

3.11. Synthesis of (−)-α-eudesmol (*1*)

To a solution of crude (+)-β-eudesmol (**6**) (600 mg, 2.7 mmol) in EtOAc (20 ml), ozone gas was introduced at −78° until **6** was not detected on TLC. After removing excess ozone by bubbling in a N_2 stream, triethylamine (750 μl, 5.4 mmol) was added dropwise over 5 min. The cooling bath was then removed, and stirring was continued at room temp for 2 h. The mix was poured into ice water and extracted with EtOAc. The organic extract was washed with brine, dried, and concentrated. The residue was purified by chromatography on silica gel using *n*-hex-EtOAc gradient to give **11** (495 mg).

To a solution of **11** (394 mg, 1.76 mmol) in dry DMF (2 ml) were added chlorotriethylsilane (384 μl, 2.29 mmol) and imidazole (240 mg, 3.52 mmol) at 0°. The reaction mixture was stirred at 0° for 3.5 h and then poured into ice water. The mixture was extracted with EtOAc, and the organic extract was washed with brine, dried and concentrated. The residue was purified by silica gel chromatography using *n*-hex-EtOAc gradient to give **12** (574 mg).

To a solution of **12** (230 mg, 0.67 mmol) in dry THF (4 ml) was added lithium diisopropylamide (405 μl of 2 M heptane/tetrahydrofuran/ethylbenzene solution, 0.81 mmol) at −78°. After stirring for 20 min, 2-[*N, N-bis*(trifuruoromethylsulfonyl) amino]-5-chloropyridine (Comins & Dehghani, 1992) (318 mg, 0.81 mmol) in THF (1 ml) was added dropwise over 5 min. The mix was stirred at −40° for 30 min and then quenched with ice water and extracted twice with Et_2O. The organic extracts were washed with brine, combined, dried and concentrated. The residual oil was purified by silica gel chromatography using *n*-hexane to give triflate **13** (300 mg).

To a solution of **13** (303 mg, 0.64 mmol) in dry THF (2 ml) was added HMPA (508 mg, 2.8 mmol) and methyl zinc iodide (1.29 ml of 1.1 M THF sol, 1.41 mmol) at room temp. After stirring for 10 min, the reaction mix was heated to 60° and tetrakis(triphenylphosphine) palladium (0) (22 mg, 0.02 mmol) was added. After being heated at 60° for 10 min and then cooled, the mix was poured into ice water and extracted with Et_2O. The organic extract was washed with brine, dried and concentrated. Purification by silica gel chromatography using *n*-hexane gave olefin **14** (203 mg) (Tamura, Ochiai, Nakamura & Yoshida, 1986).

To a solution of **14** (203 mg, 0.60 mmol) in dry THF (2 ml) was added tetrabutylammonium fluoride (0.90 ml of 1 M THF solution, 0.90 mmol) dropwise at room temp. After being stirred for 18 h, the mix was poured into ice water and extracted with EtOAc. The residue was purified by silica gel chromatography using *n*-hex-EtOAc gradient to give (−)-α-eudesmol (**1**) (133 mg). Recrystallization from pentane gave an analytically pure sample.

3.12. Compound **11**

Mp. 120–121°, $[\alpha]_D$ +5.5°($CHCl_3$; *c* 0.5), IRν_{max} cm^{-1}($CHCl_3$): 3609, 2944, 2848, 1703, 1466, 1384, 1249. $\Delta\epsilon_{288}$ −1.36 (MeOH). EIMS *m/z* (rel. int.): 224$[M]^+$, 111(100), *Anal.* Calcd. For $C_{14}H_{24}O_2$: C 74.95, H 10.78 found: C 74.67, H 10.70, ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.77 (3H, *s*), 1.20 and 1.21 (each 3H, *s*), 2.21 (1H, *m*), 2.33 (2H, *m*). ^{13}C NMR (75 MHz; $CDCl_3$): δ 17.0, 21.5, 21.9, 22.7, 26.7, 27.4, 39.4, 40.4, 40.8, 41.3, 48.4, 57.4, 72.7, 213.0

3.13. Compound **12**

IRν_{max} cm^{-1}: 2946, 2868, 1700, 1600, 1459, 1382, 1155, 1038, 1015. CD $\Delta\epsilon_{289.5}$ −1.40 (EtOH), LSI-MS *m/z*: 339$[M+H]^+$, 337$[M-H]^+$ *Anal.* Calcd. For $C_{20}H_{38}O_2Si$: C 70.94, H 11.31 found: C 70.64, H 11.32, ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.56(6H, *q*, *J* = 8 Hz), 0.75 (3H, *s*), 0.94 (9H, *t*, *J* = 7.5 Hz), 1.17 and 1.19 (each 3H, *s*), 1.94 (2H, *m*). ^{13}C NMR (75 MHz; $CDCl_3$): δ 6.8, 7.2, 16.9, 21.5, 21.8, 22.7, 27.1, 28.1, 39.4, 40.5, 41.0, 41.4, 49.6, 57.6, 75.1, 213.1.

3.14. Compound **13**

IRν_{max} cm^{-1}: 2954, 2875, 1675, 1455, 1413, 1382, 1244, 1141, 1038, 949, 878. ^{1}H NMR (300 HMz; $CDCl_3$): δ 0.58 (6H, *q*, *J* = 7.5 Hz), 0.83 (3H, *s*), 0.95 (9H, *t*, *J* = 7.5 Hz), 1.19 and 1.20 (each 3H, *s*), 2.23 (2H, *m*), 5.66 (1H, *s*) ^{13}C NMR (75 MHz; $CDCl_3$): δ 6.9, 7.2, 15.3, 21.6, 21.8, 22.3, 27.8, 28.0, 34.3, 36.2, 39.2, 46.1, 49.9, 74.9, 116.9, 151.1, 112.3, 116.5, 120.7, 125.0.

3.15. Compound **14**

IRν_{max} cm^{-1}: 2911, 2875, 1455, 1379, 1364, 1146, 1040, 1016, 937. ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.57 (6H, *q*, *J* = 7.8 Hz), 0.76 (3H, *s*), 0.95 (9H, *t*, *J* = 7.8 Hz), 1.17 and 1.20 (each 3H, *s*), 1.61 (3H, *br s*), 5.31 (1H, *br s*). ^{13}C NMR (75 MHz; $CDCl_3$): δ 6.9, 7.2, 15.6, 21.2, 22.5, 23.1, 24.3, 27.3, 28.3, 32.3, 38.0, 40.4, 46.7, 51.0, 75.5, 120.8, 135.6.

3.16. Synthetic (−)-α-eudesmol (**1**)

Mp. 87–89°, $[\alpha]_D$ −8.0° ($CHCl_3$; *c* 1.0).

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