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Acid-catalyzed Rearrangement of Hinesol and Related Compounds to Eudesmane Derivatives

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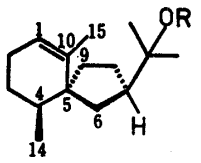
Acid-catalyzed rearrangement of hinesol α-epoxide (**5a**) gave 1α-hydroxyeudesmols (**9**, **10**, **11**) together with other spirane-type products (**6**, **8**, **14**). The same reaction of α- and β-epoxides of hinesol acetate also provided eudesmane derivatives. These results and mechanistic considerations led us to re-examine the formic acid dehydration reaction of hinesol and it was found that the main product does not have the structure **3** or **4** as assumed by Marshall *et al.*, but is identical with (+)-δ-selinene (**21**).

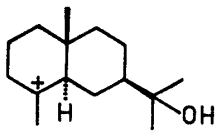
Keywords——hinesol; hinesol epoxide; eudesmane derivative; silica gel; acid-catalyzed rearrangement reaction; non-concerted rearrangement reaction

Hinesol (**1a**) is classified among the spirovetivane sesquiterpenes, and has the *cis*-configuration between the C-4-C-14 and C-5-C-6 bonds. Biogenetically, it is considered to be formed from a eudesmane-type intermediate (**2**) by a non-concerted skeletal rearrangement mechanism.[1]

In 1959, Yosioka *et al.*[2] reported that hinesol, on dehydration with formic acid, gave an oily diene product, whose structure was assumed by Marshall *et al.*[3] to be **3** or **4** on the basis of its ultraviolet (UV) spectral data.



1a: R=H
1b: R=$COCH_3$



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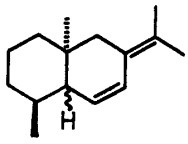

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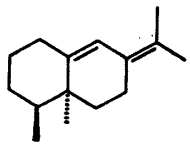

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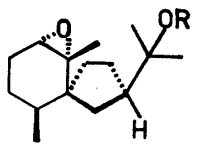
Chart 1

In connection with screening tests of sesquiterpenes having antispasmodic activity,[4] we prepared hinesol epoxide (**5a**) and found that the epoxide was readily decomposed on purification by silica gel column chromatography to give three eudesmane derivatives. In this paper we wish to describe the acid-catalyzed rearrangement reaction of hinesol epoxide and its acetate, as well as that of hinesol itself.



5a: R=H
5b: R=$COCH_3$

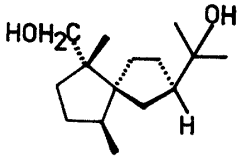


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Chart 2

Epoxidation of hinesol (**1a**) with *m*-chloroperbenzoic acid afforded a single product (**5a**), which was rapidly purified by high performance liquid chromatography (HPLC). Taking into account the structure of the rearrangement products described below, **5a** must possess an α-oriented epoxy ring.

This epoxide (**5a**) was treated with activated silica gel in a mixture of benzene and methylene chloride and the products were separated into four fractions by HPLC. The first fraction consisted of an oily product (**6**), which was shown to be an aldehyde by the infrared (IR) (1720

cm^{-1}) and ^1H-nuclear magnetic resonance (NMR) (δ 9.63 (1H, s)) spectra. Because of its instability, **6** was immediately reduced with lithium aluminum hydride and a pure sample of the alcohol (**7**) was obtained. The ^1H-NMR spectrum of **7** clearly revealed the presence of three tertiary methyl, a secondary methyl, and a hydroxymethyl groups. This indicates that the original aldehyde can be represented by the formula **6**. The aldehyde group must have α-orientation on the basis of mechanistic considerations (Chart 3).[5]

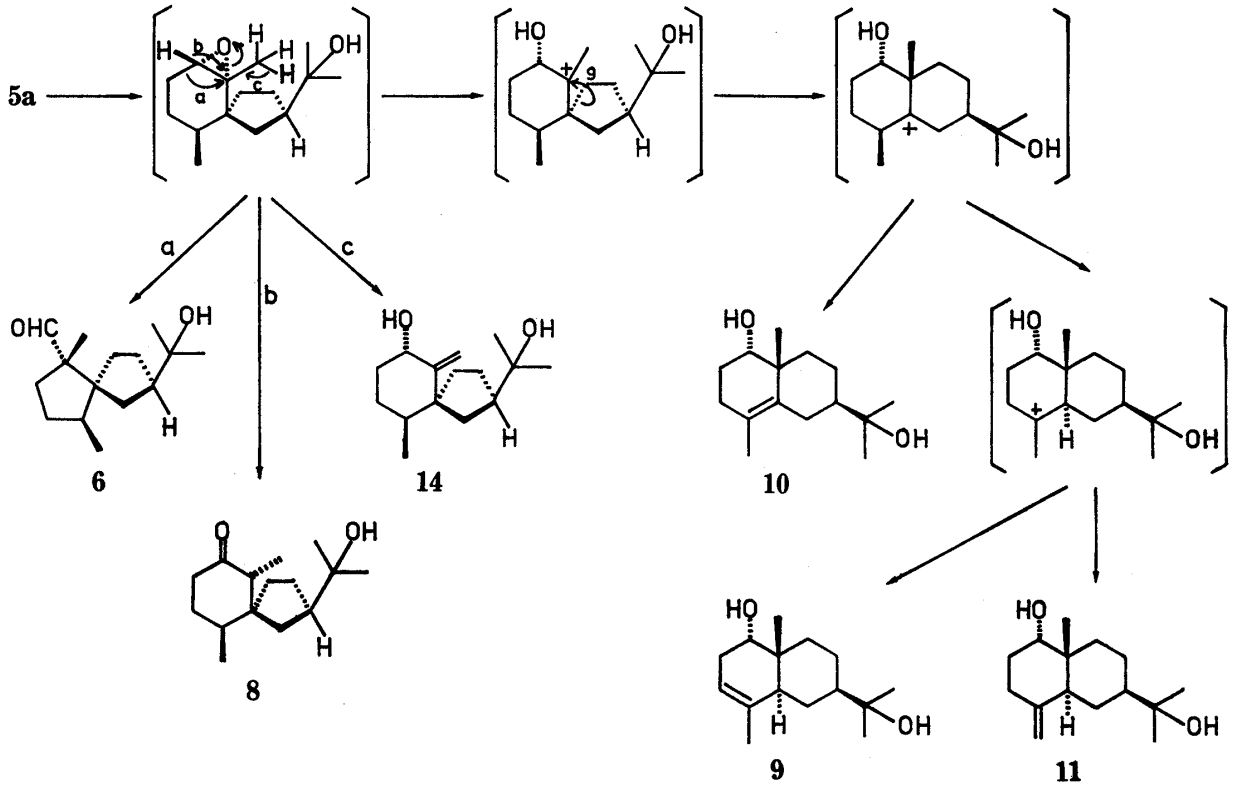
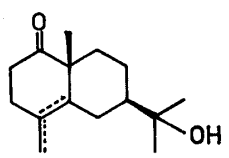


Chart 3

Further purification of the second fraction resulted in the isolation of the main product (**8**), which showed a carbonyl absorption band at 1700 cm^{-1} in the IR spectrum. The ^1H-NMR spectrum of **8** showed two doublet methyl signals at δ 1.05 (J=7 Hz) and δ 1.11 (J=7 Hz). The latter signal was demonstrated to be coupled with a quartet methine signal at δ 2.34 (J=7 Hz). Therefore, the structure of this product could be represented by the formula **8**. The configuration of the C-15 methyl group was proposed as α-equatorial from the ^1H-NMR solvent effect[6] ($\delta CDCl_3$–δbenzene-d_6: C-15 methyl, +0.06; C-14 methyl, +0.29; C-10 methine, +0.15) and the strong negative Cotton curve ($\Delta\varepsilon$ −11.7 (287 nm))in the circular dichroism (CD) spectrum.

The third fraction could be separated into three products (**9**, **10**, and **11**) by using an HPLC column packed with silver nitrate-impregnated silica gel.[7] Each of them showed a secondary hydroxyl signal in the ^1H-NMR spectrum. In addition, the chemical shift values of three methyl signals and the olefinic proton pattern of the products (**9**, **10**, and **11**) are quite similar to those of α-, γ-, and β-eudesmol, respectively.[8] Therefore, the products could be 1-hydroxy-eudesmols (**9**, **10**, and **11**). The carbon skeleton and the configuration of the 1-hydroxyl group were unambiquously proved by chemical and spectral evidence, as follows. Oxidation of **10** and **11** with pyridinium chlorochromate afforded ketone compounds (**12a** and **12b**), which were converted into known compounds, γ- and β-eudesmol, respectively, by Wolff–Kishner reduction. On the other hand, one (**12a**) of the above ketones was reduced with sodium borohydride

to give **10** and an epimeric alcohol (**13**) in the ratio of 1:4. On the basis of this formation ratio together with the coupling constants for the C-1 carbinyl proton of these alcohols (**10**,dd, J=5, 3 Hz; **13**, dd, J=8, 7 Hz) and the pyridine shift[9] ($\delta CDCl_3$–δpyridine-d_5: **10**, −0.18; **13**, −0.32) in the ^{1}H-NMR spectra, it was considered that **10** and **13** have a 1α-axial and a 1β-equatorial hydroxyl group, respectively.



12a: 4,5-unsaturated
12b: 4,14-unsaturated

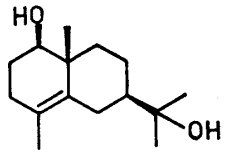


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Chart 4

The product finally eluted was shown to have a secondary hydroxyl and a terminal methylene group from the IR (3090, 905 cm^{-1}) and the ^{1}H-NMR (δ 4.19 (1H, br s), 4.93 (1H, br s), 5.08 (1H, br s)) signals. Therefore, the structure can be represented by the formula **14**.

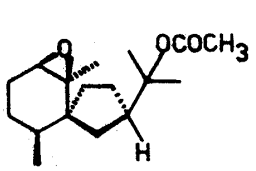
Hinesol epoxide (**5a**) was also treated with three other acids (Table I). In the case of boron trifluoride, the eudesmane derivative (**10**) was obtained in fairly good yield.

TABLE I. Acid-catalyzed Rearrangement Reaction of **5a**

Reaction conditions	Product (yield %)					
	6	8	9	10	11	14
Silica gel, benzene-CH_2Cl_2, r.t., 24 h	22.6	26.3		4.4		2.0
p-Toluenesulfonic acid, benzene, r.t., 1 h	4.8	—		8.8		2.4
80% Acetic acid, 0 °C, 4 h	Trace	—		4.2		—
BF_3·Et_2O, CH_2Cl_2, 0 °C, 30 min	Trace	—	4.1	17.4	Trace	—

We further examined the rearrangement reaction of the epoxide of hinesol acetate (**1b**), as follows. Hinesol acetate (**1b**) was treated with m-chloroperbenzoic acid in the above manner. The product was found to be a mixture of α-(**5b**) and β-epoxide (**15**) in the ratio of 6.2:1 as judged from the ^{1}H-NMR spectrum. Because of the marked instability of the β-epoxide to silica gel, the mixture, without purification, was immediately isomerized by boron trifluoride treatment. On HPLC separation, an oily product was obtained from the initial fraction. The presence of two signals in the formyl proton region of the ^{1}H-NMR spectrum (δ 9.68 (d, J=1 Hz) and δ 9.82 (s)) indicated that this product must be a mixture of epimeric aldehydes in the ratio of 3:1. The mixture was reduced with lithium aluminum hydride and the major product was found to be identical with the alcohol (**7**) obtained above. Thus, the major aldehyde could be represented by formula **16a** and the minor one by formula **16b**.

From the more polar fractions, another three products (**17**, **18a**, and **18b**) were isolated and their structures were assigned by comparing the spectral data with those of the corresponding 11-hydroxyl compounds (**8**, **10**, and **13**). The products **16b** and **18b** must be derived from the β-epoxide (**15**).



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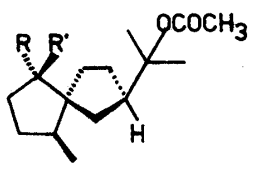
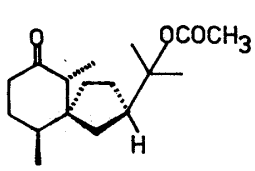


16a: R=CHO, R′=CH_3
16b: R=CH_3, R′=CHO



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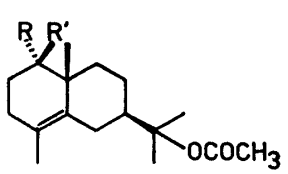
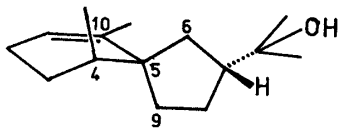


18a: R=OH, R′=H
18b: R=H, R′=OH

Chart 5

The formation process of the acid rearrangement products from **5a** could be as shown in Chart 3. The rearrangement reaction giving the spirane-type compounds must take place by the well-known concerted mechanism (pathways a, b, and c). The β-epoxide (**15**) is also efficiently converted to eudesmane derivatives through the ordinary pathways. However, formation of eudesmane-type compounds from α-epoxides (**5a** and **5b**) requires a *cis*-relationship between the departing ether bond and the migrating methylene group. Therefore, this rearrangement reaction could not proceed in a concerted fashion. This may be rationalized on steric grounds, as follows.



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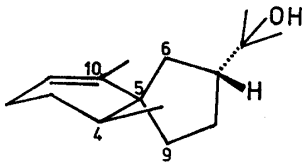

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Chart 6

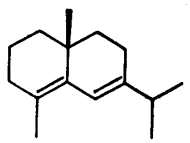

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Chart 7

The six-membered ring moiety of hinesane derivatives may exist in two alternative half-chair conformations. Fox example, conformers **19** and **20** can be drawn for hinesol. The former conformer (**19**) having a 4-axial methyl group is preferable, since the latter (**20**) would involve an interaction between the 4-equatorial methyl group and the five-membered ring moiety. Kimura[10] has previously shown that the stable conformer of hinesol, in solution, must be **19** from the result of conformational analysis of hinesol and 2-oxohinesol by ^{1}H-NMR and CD. In our experiment, hinesol (**1a**) and its acetate (**1b**) predominantly gave α-epoxides, whose ^{1}H-NMR signals due to the C-1 proton appeared as triplets (δ 2.92, J=2 Hz each). It seems likely that the series of hinesane-type compounds exists in a conformation similar to **19**. Consequently, in the carbonium ion intermediate formed by the epoxide ring cleavage, the axial C-9 methylene group probably migrates from C-5 to C-10.

These considerations prompted us to re-examine the dehydration reaction of hinesol. According to the procedure reported by Yosioka *et al.*,[2] hinesol was treated with formic acid to afford an oily product, which gave almost the same physical properties as reported in the literature. However, combined gas chromatographic–mass spectrometric (GC–MS) analysis indicated that this product is a mixture of dienes having a molecular ion peak at m/z 204. The main component (about 70% yield) was found to be identical with authentic (+)-δ-selinene (**21**) by comparing the ^{1}H-NMR and GC–MS spectra.[11] We could not detect any product having the structure **3** or **4** proposed by Marshall *et al.*[3]

In conclusion, the skeletal rearrangement reaction of hinesol derivatives gives eudesmane-type compounds, and this is formally just the reverse process of hinesol biogenesis.[1]

Experimental

Melting points were determined on a micro hot stage and are uncorrected. Specific rotations were measured in $CHCl_3$ solutions on a JASCO DIP-4 digital polarimeter. UV spectra were recorded on a Hitachi 557 spectrometer, IR spectra on a JASCO IRA-1 or A-302 spectrometer, and CD spectra on a JASCO J-500C spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-PS-100 or Varian EM-390 spectrometer in $CDCl_3$ solutions, unless otherwise specified. Chemical shifts are expressed relative to tetramethylsilane as an internal standard. Symbols, s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; br s, broad singlet; m, multiplet. GC–MS measurements were run on a Hitachi M-80 mass spectrometer and a Hitachi K-53 gas chromatograph, using a column packed with OV-101 (1.5%): column temperature, 128°C. An HPLC system was constructed with a glass 22 mm I.D. × 30 cm CIG column system (Kusano Scientific Co., Tokyo) packed with Iatrobeads (60 μ spherically shaped silica gel, Iatron Co., Tokyo). The elution solvent used is given in parenthesis. Thin layer chromatography (TLC) was carried out on Kieselgel 60F_{254} precoated plates (Merck). For drying organic solutions, anhydrous magnesium sulfate was used.

Epoxidation of Hinesol (1a)——A solution of **1a** (3.07 g) and *m*-chloroperbenzoic acid (2.85 g) in CH_2Cl_2 (50 ml) was kept at 0°C for 1 h, then washed with 10% $Na_2S_2O_3$, saturated $NaHCO_3$ solution, and brine, dried, and evaporated. The residue was subjected to HPLC (benzene–AcOEt=7: 3) to give an oily epoxide **5a** (2.70 g), $[\alpha]_D$ −0.7° (c=0.29). High resolution MS, Calcd for $C_{15}H_{26}O_2$: 238.1933. Found: 238.1920. MS m/z (%): 238 (M^+, 5), 220 (22), 205 (30), 59 (100). ^{1}H-NMR δ: 0.82 (3H, d, J=6 Hz), 1.22 (6H, s), 1.31 (3H, s), 2.92 (1H, t, J=2 Hz).

Reaction of Epoxide 5a with Activated Silica Gel——Commercial silica gel (Kieselgel 60, 70—230 mesh, Merck) was slurried and washed with distilled water until the washing was neutral. The silica gel was further washed with EtOH, dried, and finally activated by heating at 130°C for 7 h. The activated silica gel (75 g) was added to a solution of **5a** (3.00 g) in benzene and CH_2Cl_2 (1: 1 mixture, 120 ml) and the suspension was stirred under a nitrogen atmosphere at room temperature for 24 h. After filtration, silica gel was washed with a mixture of Et_2O and MeOH (19: 1) and the washings and the filtrate were evaporated. The residue was subjected to HPLC (n-hexane–AcOEt=7: 3, 1: 1) to give **6** (678 mg), **8** (802 mg), a mixture of eudesmane derivatives (132 mg), and **14** (60 mg). The mixture was further separated by HPLC (benzene–AcOEt–acetonitrile=5: 5: 1) using a column packed with silver nitrate-impregnated silica gel[7] to afford **9**, **10**, and **11**.

6: Colorless oil. IR (neat): 3420, 2950, 2870, 2710, 1720 cm^{-1}. ^{1}H-NMR δ: 0.96 (3H, d, J=6 Hz), 1.05 (3H, s), 1.20 (6H, s), 9.63 (1H, br s).

8: Colorless oil, $[\alpha]_D$ +26.0° (c=0.47). High resolution MS, Calcd for $C_{15}H_{26}O_2$: 238.1933. Found: 238.1943. MS m/z (%): 238 (M^+, 5), 220 (5), 205 (7), 180 (29). UV λ_{max}^{EtOH} nm (ε): 290 (42). CD (c=0.006, EtOH) $\Delta\varepsilon$ (nm): −11.7 (287). IR (neat): 3450, 2940, 1700 cm^{-1}. ^{1}H-NMR δ: 1.05 (3H, d, J=7 Hz), 1.10 (3H, d, J=7 Hz), 1.18 (6H, s), 2.51 (1H, q, J=7 Hz).

9: Colorless amorphous product, $[\alpha]_D$ +40.0° (c=0.05). High resolution MS. Calcd for $C_{15}H_{26}O_2$: 238.1933. Found: 238.1945. MS m/z (%): 238 (M^+, 1), 220 (14), 202 (26), 159 (100). IR (KBr): 3330, 2920, 1375, 1040, 905 cm^{-1}. ^{1}H-NMR δ: 0.72 (3H, s), 1.20 (6H, s), 1.66 (3H, t, J=1.5 Hz), 3.36 (1H, dd, J=8, 4 Hz), 5.21 (1H, br s).

10: Colorless plates (n-hexane), mp 86.0—87.5°C. $[\alpha]_D$ +77.3° (c=0.11). High resolution MS, Calcd for $C_{15}H_{26}O_2$: 238.1933. Found: 238.1916. MS m/z (%): 238 (M^+, 11), 220 (45), 202 (80), 159 (100). IR (KBr): 3340, 2920, 1455, 1370, 1140, 920 cm^{-1}. ^{1}H-NMR δ: 1.05 (3H, s), 1.19 (6H, s), 1.63 (3H, s), 2.59, 2.71 (1H, each, both m), 3.47 (1H, dd, J=5, 3 Hz).

11: Colorless amorphous product, $[\alpha]_D$ +87.5° (c=0.04). MS m/z (%): 220 ($[M-H_2O]^+$, 4), 202 (40), 187 (10), 159 (100). IR (KBr): 3320, 3070, 2930, 1640, 1375, 1135, 1050, 910, 880 cm^{-1}. ^{1}H-NMR δ: 0.72 (3H, s), 1.20 (6H, s), 3.44 (1H, t, J=2 Hz), 4.46, 4.74 (1H each, both br s).

14: Colorless oil, $[\alpha]_D$ +38.6° (c=0.07). MS m/z (%): 220 ($[M-H_2O]^+$, 18), 202 (22), 187 (20), 177 (27), 159 (47), 149 (57), 133 (91). IR (neat): 3380, 3090, 2950, 1640, 1460, 1380, 905 cm^{-1}. ^{1}H-NMR δ: 0.90 (3H, d, J=6 Hz), 1.17 (6H, s), 4.19 (1H, m), 4.93, 5.08 (1H each, both br s).

Lithium Aluminum Hydride Reduction of 6——The unstable aldehyde (**6**) (102 mg) was immediately treated with a large excess of lithium aluminum hydride in dry Et_2O under a nitrogen atmosphere at room temperature for 1.5 h. After work-up in the usual way, the product was subjected to HPLC (n-hexane–AcOEt=1: 1) to give **7** (40 mg), colorless needles (n-hexane), mp 99—100°C, $[\alpha]_D$ +19.6° (c=0.24). *Anal.* Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.20; H, 11.82. MS m/z (%): 223 (1), 149 (11), 59 (40), 43 (100). ^{1}H-NMR δ: 0.97 (3H, d, J=6 Hz), 1.00 (3H, s), 1.17 (6H, s), 3.46 (2H, br s).

Pyridinium Chlorochromate Oxidation of 10 and 11——A mixture (205 mg) of **10** and **11** was oxidized with pyridinium chlorochromate (283 mg) in CH_2Cl_2 (14 ml) under a nitrogen atmosphere at room temperature for 4 h. The products were extracted with Et_2O and the organic solvent layer was washed with brine, dried, and evaporated. The residue was purified by passing it through a silica gel HPLC column (n-hexane–AcOEt=3: 2) and the oily eluate was further separated by HPLC (benzene–AcOEt–acetonitrile=10: 2: 1) using a column packed with silver nitrate-impregnated silica gel[7] to give **12a** (120 mg) and **12b** (35 mg).

12a: Colorless needles (n-hexane), mp 78—80°C, $[\alpha]_D$ +4.0° (c=0.05). High resolution MS, Calcd for $C_{15}H_{24}O_2$: 236.1777. Found: 236.1774. MS m/z (%): 236 (M^+, 5), 218 (35), 59 (100). IR (KBr): 3440, 1705 cm^{-1}. ^{1}H-NMR δ: 1.22 (9H, s), 1.72 (3H, s).

12b Colorless needles (n-hexane), mp 93—94.5°C, $[\alpha]_D$ +110.0° (c=0.05). High resolution MS, Calcd for $C_{15}H_{24}O_2$: 236.1777. Found: 236.1795. MS m/z (%): 236 (M^+, 4), 221 (7), 203 (9), 178 (100). IR (KBr): 3325, 3080, 1695, 895 cm^{-1}. ^{1}H-NMR δ: 0.98 (3H, s), 1.22 (6H, s), 4.78, 4.99 (1H each, both br s).

Wolff-Kishner Reduction of 12a——A mixture of **12a** (120 mg), 80% hydrazine (0.9 ml), KOH (330 mg), and diethylene glycol (18 ml) was heated at 180°C for 3.5 h and then diluted with water. The product was extracted with Et_2O and the Et_2O layer was washed with brine, dried, and evaporated. The residue was purified by passing it through a silica gel HPLC column (n-hexane–AcOEt=3: 2), and the oily eluate was further separated by HPLC (benzene–AcOEt–acetonitrile=15: 2: 1) using a column of silver nitrate-impregnated silica gel[7] to give a colorless oil (41 mg), $[\alpha]_D$ +63.6° (c=0.33). High resolution MS, Calcd for $C_{15}H_{26}O$: 222.1983; Found: 222.1970. MS m/z (%): 222 (M^+, 12), 204 (90), 189 (100). ^{1}H-NMR δ: 1.01 (3H, s), 1.19 (6H, s), 1.60 (3H, s), 2.55, 2.67 (1H each, both m). This compound was identified as γ-eudesmol by comparison with an authentic specimen.

Wolff-Kishner Reduction of 12b——The ketone **12b** (35 mg) was also reduced in the same way as described

above to give colorless needles (16 mg), mp 81—82.5°C, $[\alpha]_D$ +58.2° (c=0.11). High resolution MS, Calcd for $C_{15}H_{26}O$: 222.1983. Found: 222.1988. MS m/z (%): 222 (M^+, 6), 204 (7), 59 (100). ^{1}H-NMR δ: 0.71 (3H, s), 1.19 (6H, s), 4.43, 4.70 (1H each, both br s). This compound was identified as β-eudesmol by comparison with an authentic specimen.

Sodium Borohydride Reduction of 12a——Ketone **12a** (73 mg) was treated with sodium borohydride (80 mg) in MeOH (30 ml). After work-up in the usual way, the products were separated by HPLC (n-hexane–AcOEt=1: 1) to give **10** (11 mg) and the epimeric alcohol **13** (44 mg), colorless plates (n-hexane), mp 136—137°C, $[\alpha]_D$ +102.4° (c=0.17). *Anal.* Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.34; H, 10.86. MS m/z (%): 238 (M^+, 6). ^{1}H-NMR δ: 1.00 (3H, s), 1.20 (6H, s), 1.60 (3H, s), 2.57, 2.70 (1H each, both m), 3.46 (1H, dd, J=8, 7 Hz).

Reaction of Epoxide 5a with *p*-Toluenesulfonic Acid——A solution of **5a** (448 mg) in benzene (7 ml) was added to a suspension of p-toluenesulfonic acid (1.41 g) in benzene (10 ml). The mixture was stirred under a nitrogen atmosphere at room temperature for 1 h and then filtered. The filtrate was washed with a saturated $NaHCO_3$ solution and brine, dried, and evaporated. The residue was subjected to HPLC (n-hexane–AcOEt= 7: 3, 1: 1) to give **6** (24 mg), a mixture of **9**, **10**, and **11** (43 mg), and **14** (12 mg).

Reaction of 5a with 80% Acetic Acid——A solution of **5a** (370 mg) in 80% AcOH (5 ml) was stirred at 0°C for 4 h and neutralized with a saturated $NaHCO_3$ solution. The reaction mixture was extracted with Et_2O and the Et_2O layer was washed with brine, dried, and evaporated. The residue was subjected to HPLC (n-hexane–AcOEt=1: 1, benzene–2-propanol=4: 1) to give a trace amount of **6** and a mixture of **9**, **10**, and **11** (22 mg).

Reaction of 5a with Boron Trifluoride——Boron trifluoride diethyl etherate (3 drops) was added dropwise to a solution of **5a** (350 mg) in CH_2Cl_2 (20 ml) under a nitrogen atmosphere at 0°C during 15 min. The mixture was further stirred at room temperature for 15 min, then the solvent was evaporated off. The residue was subjected to silica gel HPLC (n-hexane–AcOEt=7: 3, 1: 1) and silver nitrate-impregnated silica gel HPLC[7] (benzene–AcOEt–acetonitrile=5: 5: 1) to give **6** (9 mg), **9** (13 mg), **10** (56 mg), and **11** (5 mg).

Acetylation of Hinesol (1a)——A solution of **1a** (4.40 g) in acetic anhydride (14 ml) and pyridine (20 ml) containing dimethylaminopyridine (500 mg) was kept at 40°C for 3 h. After work-up in the usual way, the product was subjected to HPLC (n-hexane–AcOEt=49: 1) to give the acetate (**1b**) (3.88 g), colorless oil, $[\alpha]_D$ −41.3° (c=0.16). High resolution MS, Calcd for $C_{17}H_{28}O_2$: 264.2091. Found: 264.2075. MS m/z (%): 264 (M^+, 8), 204 (72), 161 (100). ^{1}H-NMR δ: 0.92 (3H, d, J=6 Hz), 1.46 (6H, s), 1.70 (3H, s), 1.95 (3H, s), 5.30 (1H, br s).

Epoxidation of Hinesol Acetate (1b)——Hinesol acetate (**1b**) (3.26 g) was treated with m-chloroperbenzoic acid (3.00 g) in CH_2Cl_2 (60 ml) at 0°C for 1 h. After work-up in the same way as described above, the products were chromatographed on silica gel (n-hexane–AcOEt=9: 1) to give a mixture of epoxides **5b** and **15** (2.80 g), whose ratio was determined as 6.2: 1 from the intensities of the NMR signals of epoxide protons (**5b**: δ 2.92 (t, J=2 Hz); **15**: 3.00 (m)). Further chromatographic purification of the above mixture gave only the α-epoxide (**5b**), colorless amorphous material, in an almost pure state. MS m/z (%): 220 ($[M-AcOH]^+$, 22), 205 (8), 149 (44), 83 (100). ^{1}H-NMR δ: 0.80 (3H, d, J=7 Hz), 1.32 (3H, s), 1.48 (6H, s), 1.95 (3H, s), 2.92 (1H, t, J=2 Hz).

Reaction of the Mixture of Epoxides 5b and 15 with Boron Trifluoride——Boron trifluoride diethyl etherate (5 drops) was added dropwise to a solution of the mixture of **5b** and **15** (600 mg) in CH_2Cl_2 (25 ml) under a nitrogen atmosphere at 0°C during 15 min. The reaction mixture was further stirred at room temperature for 15 min and the solvent was evaporated off. The residue was subjected to HPLC (n-hexane–AcOEt=9: 1, 7: 3, 1: 1) to give an aldehyde mixture (43 mg), **17** (194 mg), and an alcohol mixture (160 mg). The alcohol mixture was separated by HPLC (benzene–AcOEt–acetonitrile=40: 2: 1) using a column packed with silver nitrate-impregnated silica gel[7] to afford **18b** (30 mg) and **18a** (110 mg).

Aldehyde Mixture (**16a** and **16b**): Unstable colorless oil. IR (neat): 2880, 2710, 1725 cm^{-1}. The ratio of **16a** and **16b** was determined as 3: 1 from the intensities of the NMR signals of the formyl proton (**16a**: δ 9.68 (d, J=1 Hz); **16b**: 9.82 (s)).

17: Colorless plates (n-hexane), mp 36.5—37.5°C, $[\alpha]_D$ +24.4° (c=0.55). *Anal.* Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.64; H, 10.24. MS m/z (%): 220 ($[M-AcOH]^+$, 52), 205 (15), 149 (100). CD (c=0.0055, EtOH) $\Delta\varepsilon$ (nm): −15.8 (287). IR (CCl_4): 1725, 1705 cm^{-1}. ^{1}H-NMR δ: 1.06 (3H, d, J=7 Hz), 1.09 (3H, d, J=7 Hz), 1.45 (6H, s), 1.98 (3H, s), 2.53 (1H, q, J=7 Hz).

18a: Colorless oil, $[\alpha]_D$ +68.1° (c=0.37). High resolution MS, Calcd for $C_{17}H_{28}O_3$: 280.2038. Found: 280.2028. MS m/z (%): 280 (M^+, 5), 220 (54), 202 (87), 43 (100). ^{1}H-NMR δ: 1.06 (3H, s), 1.46 (6H, s), 1.62 (3H, s), 1.98 (3H, s), 2.53, 3.63 (1H each, both m), 3.52 (1H, dd, J=5, 3 Hz).

18b: Colorless oil, $[\alpha]_D$ +58.0° (c=0.05). MS m/z (%): 220 ($[M-AcOH]^+$, 100), 202 (36). ^{1}H-NMR δ: 1.01 (3H, s), 1.46 (6H, s), 1.58 (3H, s), 1.98 (3H, s), 2.47, 2.58 (1H each, both m), 3.45 (1H, dd, J=8, 7 Hz).

Lithium Aluminum Hydride Reduction of the Aldehyde Mixture (16a and 16b)——The aldehyde mixture (43 mg) was treated with a large excess of lithium aluminum hydride in tetrahydrofuran (10 ml) under a nitrogen atmosphere at room temperature for 2 h. After work-up in the usual way, the residue was separated by HPLC (benzene–2-propanol=9: 1) to give a product (18 mg), colorless needles (n-hexane), mp 97.5—98.5°C. This was identical with the alcohol (**7**) obtained above.

Dehydration of Hinesol (1a) with Formic Acid——A solution of **1a** (1.00 g) in formic acid (3 ml) was stirred at room temperature for 30 min and further heated at 120°C for 2.5 h. The reaction mixture was neutralized by addition of saturated $NaHCO_3$ solution, the product was extracted with Et_2O, and the extract was washed with brine, then dried, and evaporated. The residue was subjected to HPLC (*n*-hexane) to give a diene mixture (740 mg), yellow oil, $[\alpha]_D$ +92.5° (c=0.44). UV λ_{max}^{MeOH} nm (ε): 246 (10200), 240 (10400). IR (neat): 2960, 2920, 1615, 1455, 1370, 1225, 755 cm^{-1}. ^{1}H-NMR δ: 0.92 (s), 1.04 (d, J=7 Hz), 1.69 (s), 6.16 (br s). GC–MS: main peak, t_R=2.3 min, m/z (%): 204 (M^+, 100), 189 (100), 161 (99), 133 (56), 119 (35), 105 (51). The ^{1}H-NMR spectrum was almost identical with that of authentic (+)-δ-selinene (**21**), and GC–MS indicated that the product contains **21** at 70% purity.

Preparation of Authentic (+)-δ-Selinene (21)[11a]——A solution of β-eudesmol (1.32 g) in acetic acid (15 ml) and 60% perchloric acid (1 ml) was stirred at room temperature for 72 h. After addition of water, the product was extracted with Et_2O and the extract was washed with saturated $NaHCO_3$ solution and water, then dried, and evaporated. The residue was purified by HPLC (*n*-hexane) to give **21** (870 mg), colorless oil, $[\alpha]_D$ +286.5° (c=0.2). High resolution MS, Calcd for $C_{15}H_{24}$: 204.1879. Found: 204.1882. UV λ_{max}^{MeOH} nm (ε): 247 (17800), 241 (17100). IR (neat): 2970, 2920, 1620, 1460, 1370, 1295, 880 cm^{-1}. ^{1}H-NMR δ: 0.94 (3H, s), 1.05 (6H, d, J=7 Hz), 1.72 (3H, s), 6.18 (1H, br s). GC–MS: t_R=2.4 min, m/z (%): 204 (M^+, 89), 189 (100), 161 (93), 133 (32), 119 (25), 105 (42).

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References

1) G. Rücher, *Angew. Dhem. Int. Ed. Engl.*, **12**, 793 (1973); A. Stossel, J.B. Stothers, and E.W. Ward, *Phytochemistry*, **15**, 855 (1976).
2) I. Yoshioka, H. Hikino, and Y. Sasaki, *Chem. Pharm. Bull.*, **7**, 817 (1959).
3) J.A. Marshall, S.F. Brady, and N.H. Anderson, *Fortschr. Chem. Org. Naturst.*, **31**, 283 (1974).
4) M. Morita, H. Nakanishi, S. Mihashi, and H. Itokawa, Abstracts of Papers, 4th Symposium on the Development and Application of naturally Occurring Drug Materials, Osaka, 1982, pp. 25—27.
5) V.S. Joshi, N.P. Damodaran, and Sukh Dev, *Tetrahedron*, **27**, 475 (1971).
6) D.H. Williams and N.P. Bhacca *Tetrahedron*, **21**, 2021 (1965); D.H. Williams, *Tetrahedron Lett.*, **1965**, 2305.
7) M. Morita, S. Mihashi, H. Itokawa, and S. Hara, *Anal. Chem.*, **55**, 412 (1983).
8) F.J. McQuillin and J.D. Parrack, *J. Chem. Soc.*, **1956**, 2973; S. Hara, A. Ohsawa, J. Endo, Y. Sashida, and H. Itokawa, *Anal. Chem.*, **52**, 428 (1980).
9) P.V. Demarco, E. Farkas, D. Doddrell, B.L. Mylari, and E. Wenkert, *J. Am. Chem. Soc.*, **90**, 5480 (1968).
10) T. Kimura, Ph. D. Thesis, Osaka University, 1969.
11) *a*) M.L. Maheshwari, J.C. Jain, R.B. Bates, and S.C. Bhattacharyya, *Tetrahedron*, **19**, 1079 (1963); *b*) B.S. Tyagi, B.B. Ghatge, and S.C. Bhattacharyya, *ibid.*, **19**, 1189 (1963); G. Mehta and B.P. Singh, *J. Org. Chem.*, **42**, 632 (1977).