Structures and Spasmolytic Activities of Derivatives from Sesquiterpenes of *Alpinia speciosa* and *Alpinia japonica*

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Sesquiterpenes isolated from *Alpinia speciosa* and *Alpinia japonica*, and their derivatives were found to inhibit histamine- or barium chloride-induced contraction of excised guinea pig ileum when tested by the Magnus method. Major spasmolytic principles contained in those extracts were the sesquiterpenes, β-eudesmol, nerolidol, humulene epoxide II and 4α-hydroxydihydroagarofuran. Relationships between the chemical structures of the sesquiterpenes and their derivatives, and their spasmolytic activities were discussed.

Key words *Alpinia speciosa*; *Alpinia japonica*; sesquiterpene; spasmolytic activity

A number of crude drugs are used as a spasmolytic, stomachic, laxative, abortive, choletic or antihypertensive agent in Chinese and/or traditional folkloric medicine. Those drugs are considered to affect the smooth muscles. Methanolic extracts from rhizomes of *Alpinia speciosa*[1] and *A. japonica*[2] and ethanolic extracts from Zingiberaceous crude drugs were shown to significantly inhibit histamine- and barium chloride- (anti-HIST and anti-BA, respectively) induced contraction of excised guinea pig ileum when tested by the Magnus method. Thus the usage of those Zingiberaceus plants in traditional medicine as aromatic stomachic, choletic or spice is confirmed as appropriate reasonable.

Major spasmolytic compounds in *A. speciosa* and *A. japonica* were easily extracted with petroleum ether and chloroform, respectively, and were identified as the known sesquiterpenes, β-eudesmol (**1**), nerolidol (**2**), humulene epoxide II (**3**) and 4α-hydroxydihydroagarofuran (**4**). Sesquiterpenes, himacalol,[3] centdarol,[4] petasin[5] and cryptomeridiol,[6,7] monoterpenes[8] and flavonoids[9,10] are known to have varying degrees of spasmolytic activity on smooth muscles. However, the relationship between the chemical structures of these active compounds and their activity has not yet been fully discussed.

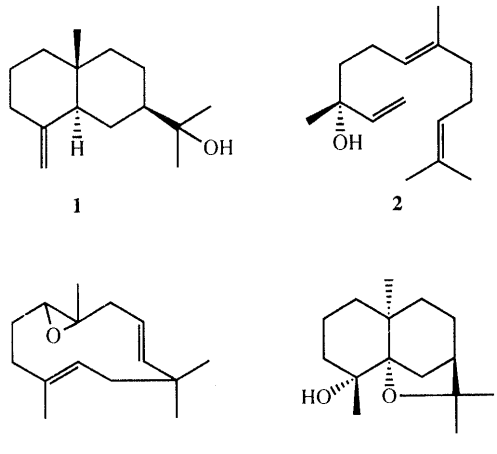
This paper deals with the structures and spasmolytic activity of sesquiterpenes isolated from *A. speciosa* and *A. japonica* and their chemically modified derivatives.

Results and Discussion

Extraction, Isolation and Chemical Modification The methanol extract of the rhizomes of *Alpinia speciosa* and *A. japonica* (Zingiberaceae) was successively partitioned between petroleum ether, chloroform, ethyl acetate and water. The spasmolytic activity was concentrated in each petroleum ether and chloroform soluble fraction. Repeated chromatographic purification of each fraction, conducted in conjunction with bio-assay of the inhibitory effect on histamine hydrochloride- or barium chloride-induced contraction of guinea pig ileum, led to the isolation of four sesquiterpenes, β-eudesmol (**1**) and nerolidol (**2**), racemic humulene epoxide II (**3**)[11] and 4α-hydroxydihydroagarofuran (**4**),[12] which were completely identical with authentic samples and spectroscopic data (Fig. 1).

In order to understand the mechanisms involved in the actions of sesquiterpenes and to study the structure–activity relationship, chemically modified β-eudesmol was prepared using β-eudesmol isolated from *Atractylodes lancea*. By combining of oxidation, reduction, acetylation, dehydroxylation and so on, twenty derivatives (**5**—**24**) were prepared from β-eudesmol as shown in Chart 1. The reaction condition is described in the Experimental section. The related sesquiterpenes, hinesol (**25**) isolated from *A. lancea* and its derivatives (**26**—**28**) were also prepared for comparison with the spasmolytic activity (Chart 2).

Relationship between Chemical Structures and Activities The spasmolytic activity, *i.e.* inhibitory effect on histamine hydrochloride- or barium chloride-induced contraction of guinea pig ileum, was determined as described in the Experimental section and the data are shown in Table 1. Sesquiterpene hydrocarbons with no hydroxyl group (**5**, **6**) showed weak spasmolytic activity. The spasmolytic activity of a tigloyl derivative (**18**) was the strongest of all the sesquiterpenes tested in the present experiment. Mono hydroxyl derivative (**1**, **2**, **16**, **25**) and those derivatives with one hydroxyl group and acetyl groups (**8**, **12**, **14**, **19**) possessed stronger activities than those of sesquiterpene hydrocarbons. Those with two (**10**, **13**, **17**, **20**) or three hydroxyl groups (**22**, **23**) showed weaker activities than



1 2 3 4

Fig. 1. Structures of Four Sesquiterpenes (**1**—**4**) from *A. speciosa* and *A. japonica*

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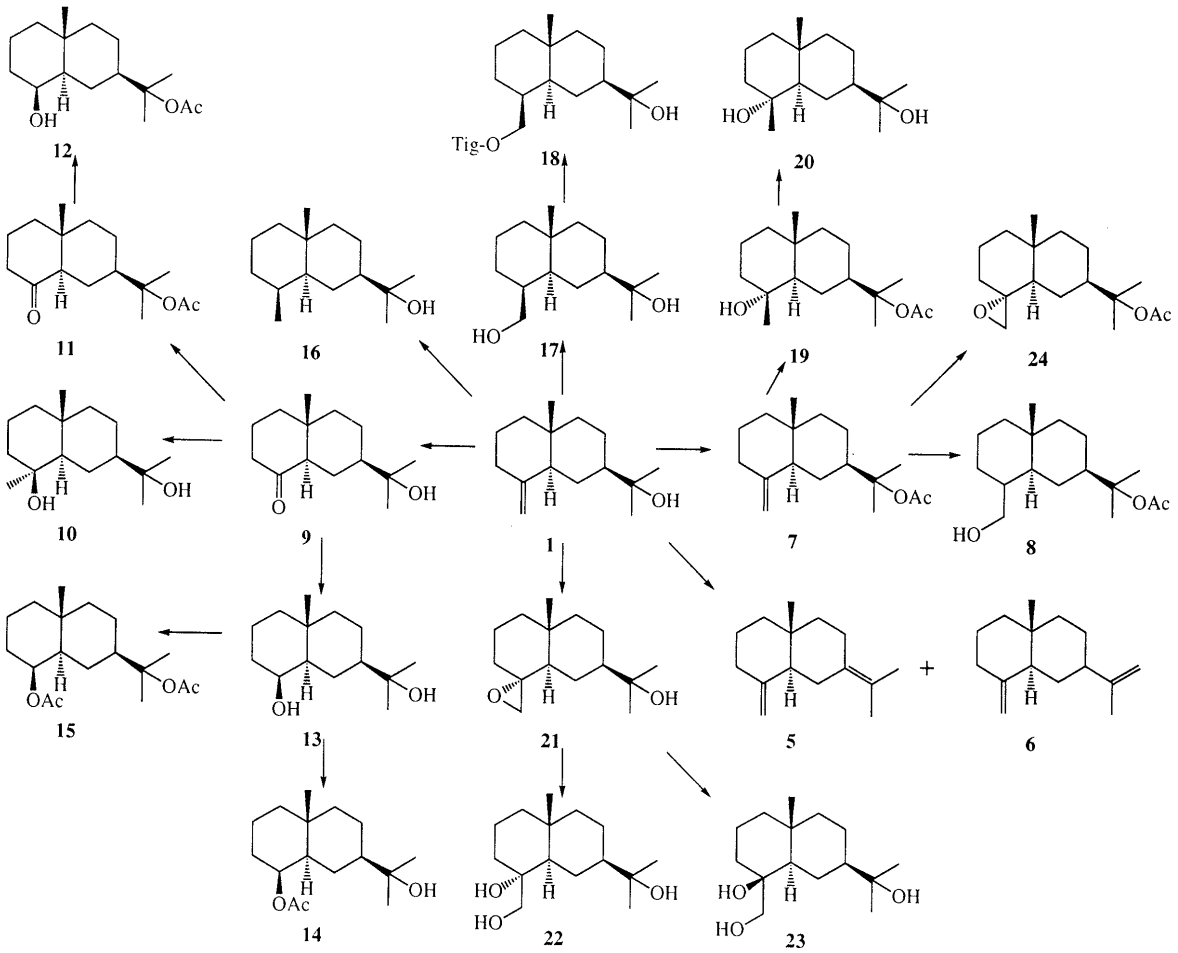

Chart 1. Structures of β-Eudesmol (**1**) and Its Derivatives (**5**—**24**)

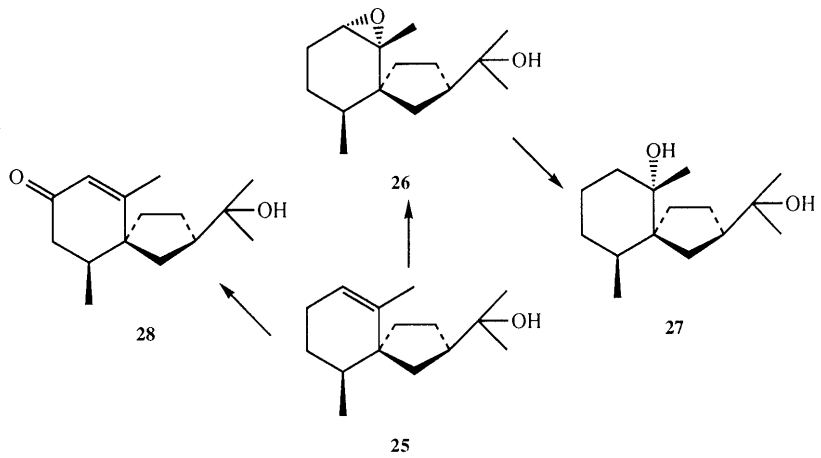

Chart 2. Structures of Hinesol (**25**) and Its Derivatives (**26**—**28**)

those of mono hydroxyl derivatives. However, the activity is not solely determined by the number of hydroxyl groups. For example, no hydroxyl group-containing compounds, such as (**15**) and humulene epoxide II (**3**) having one double bond and one epoxide, showed strong activity, and the compounds with one hydroxyl group-containing compound, such as 2-oxo-hinesol (**28**) with one α,β-unsaturated ketone group and compound **21** with one epoxy group possessed weak activities.

Carbon skeletons of the sesquiterpenes tested in this experiment, eudesman, spirovetivane, humulene, and agarofuran, appear to have no direct relation to the activity. Further analyses of the relationship between the chemical structures of these sesquiterpenes and their spasmolytic activity are currently being done in our laboratories.

Experimental

The melting point was obtained with a Yanagimoto MP-3 micro-melting point apparatus and is uncorrected. The optical rotation was measured on a JASCO DIP-4 polarimeter. The IR spectra were obtained on a JASCO A-302 spectrophotometer. Mass spectra were recorded on a Hitachi M-80 instrument. All NMR data were recorded on a JEOL

Table 1. Anti-HIST and Anti-BA Activities of Compounds **1**—**28**

Compound	Anti-HIST[a]	Anti-BA[b]
1	0.319	0.037
2	0.041	0.024
3	0.010	0.011
4	0.210	0.075
5	0.598	0.134
6	—	0.665
8	0.026	0.008
9	0.179	0.021
10	0.104	0.167
11	0.119	0.025
12	0.111	0.011
13	0.238	0.074
14	0.093	0.026
15	0.065	0.010
16	0.062	0.217
17	0.081	0.027
18	0.019	0.007
19	0.024	0.014
20	0.048	0.017
21	0.332	0.078
22	1.368	0.169
23	—	0.513
24	0.049	0.030
25	0.064	0.055
26	0.427	0.240
27	0.222	0.224
28	—	0.293

a) Anti-HIST: 50% inhibitory concentration (mmol/l) of contraction induced by histamine. *b*) Anti-BA: 50% inhibitory concentration (mmol/l) of contraction induced by barium chloride.

FX-100 spectrometer. ^{1}H-NMR chemical shift is expressed in δ ppm from tetramethylsilane as internal standard and coupling constants (J) are given in Hz. Medium-pressure liquid chromatography (MPLC) was carried out on a CIG column (Kusano Scientific Co., Tokyo) packed with 60 μm silica gel as the stationary phase.

Plant Material The rhizomes of *A. speciosa* and *A. japonica* were collected on Miyake island, Tokyo, and Izu, Shizuoka, respectively, and the botanical identification was made by Dr. Kanai, National Science Museum in Japan. A voucher specimen has been deposited in the herbarium of Tokyo University of Pharmacy & Life Science.

Extraction and Isolation The fresh rhizome of *A. speciosa* (100 kg) was extracted with MeOH three times to give a MeOH extract which was partitioned between petroleum ether, chloroform, ethyl acetate and H_2O. The petroleum ether soluble fraction, which showed spasmolytic activity, was subjected to silica gel column chromatography using a *n*-hexane–ethyl acetate gradient system (1 : 0—1 : 1). The fraction eluted with 80% *n*-hexane was further subjected to silica gel MPLC using a benzene–ethyl acetate (50 : 1) to give nerolidol (**2**: 350 mg) and humulene epoxide II (**3**: 450 mg). The fraction eluted with 90% *n*-hexane was subjected to $AgNO_3$ silica gel MPLC with a *n*-hexane–ethyl acetate (4 : 1) to give β-eudesmol (**1**: 1.8 g). The fresh rhizome of *A. japonica* (16.7 kg) was extracted in the same manner, and β-eudesmol (**1**: 1.2 g), humulene epoxide II (**3**: 200 mg) and 4α-hydroxydihydroagarofuran (**4**: 470 mg) were also isolated.

β-Eudesmol (**1**): Colorless needles, mp 80.5—81.5 °C (sublim.), $[\alpha]_D$ +51.0° (c=0.10, EtOH). MS m/z: 222 (M^+, Calcd for $C_{15}H_{26}O$, 222.1983; Found 222.1957). IR ν_{max}^{KBr}: 3260 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, s), 1.20 (6H, s), 4.46 (1H, br s), 4.73 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 16.3 (q), 22.4 (t), 23.4 (t), 25.0 (t), 27.1 (q × 2), 35.9 (s), 36.9 (t), 41.1 (t), 41.9 (t), 49.5 (d), 49.8 (d), 72.9 (s), 105.3 (t), 151.1 (s).

Nerolidol (**2**): Colorless oil, $[\alpha]_D$ +14.5° (c=0.52, $CHCl_3$). MS m/z: 222 (M^+). IR ν_{max}^{neat}: 3360 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, s), 1.60 (6H, s), 1.68 (3H, s), 1.78 (1H, dissapeared on addition of D_2O, br s), 4.92—5.32 (4H, m), 5.92 (1H, dd, 10.5, 17.0 Hz).

Humulene Epoxide II (**3**): Colorless oil, $[\alpha]_D$ 0.0° (c=0.36, $CHCl_3$). MS m/z: 220 (M^+). IR ν_{max}^{neat}: 2970, 1445, 1385, 1070, 970, 820 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, s), 1.10 (3H, s), 1.29 (3H, s), 1.56 (3H, s), 5.00 (1H, br t), 5.18—5.30 (2H, m).

4α-Hydroxydihydroagarofuran (**4**): Colorless needles, mp 128.0—129.5 °C, $[\alpha]_D$ −71.6° (c=0.16, EtOH). MS m/z: 238 (M^+, Calcd for $C_{15}H_{26}O_2$, 238.1933; Found 238.1929). IR ν_{max}: 3430 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s), 1.21 (3H, s), 1.27 (3H, s), 1.36 (3H, s).

Extraction and Isolation of β-Eudesmol (1) and Hinesol (25) Column chromatography of 440 g of *n*-hexane extract from commercially obtained rhizome of *Atractylodes lancea* (3 kg) gave a crude mixture of β-eudesmol and hinesol (260 g). Ten percent silver nitrate impregnated silica gel chromatography of the mixture gave hinesol as colorless needles (102.5 g), mp 56.0—57.5 °C, when eluted with *n*-hexane–ethyl acetate (17 : 3), and β-eudesmol as colorless needles (72.8 g) mp 80.5—81.5 °C with *n*-hexane–ethyl acetate (7 : 3).

γ-Selinen (5) and β-Selinen (6) A solution of **1** (1.11 g) in thionyl chloride (3.3 ml) and pyridine (30 ml) was stirred under N_2 atmosphere at 0 °C for 1.5 h. The product was chromatographed on $AgNO_3$-impregnated silica gel to give colorless oil of **5** (152 mg, 20%) and **6** (370 mg, 38%). Compound **5**: Colorless oil, $[\alpha]_D$ +2.5° (c=0.12, $CHCl_3$). MS m/z: 204 $(M)^+$. IR ν_{max}^{neat}: 3060, 890 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, s), 1.69 (6H, s), 4.49, 4.74 (each 1H, s). Compound **6**: Colorless oil, $[\alpha]_D$ +46.7° (c=0.10, $CHCl_3$). MS m/z: 204 $(M)^+$. IR ν_{max}^{neat}: 3050, 885 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.76 (3H, s), 4.44 (1H, br s), 4.73 (3H, br s).

11-Acetoxyeudesm-4(14)-ene (7) Acetylation of **1** (4.40 g) with acetic anhydride (14 ml) and dry pyridine (20 ml) containing dimethylaminopyridine (DMAP, 500 mg) at 40 °C for 3 h, followed by MPLC gave colorless oil of **7** (3.88 g, 74%), $[\alpha]_D$ +98.8° (c=0.17, $CHCl_3$). MS m/z: 204 $(M-AcOH)^+$. IR ν_{max}^{neat}: 3080, 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.70 (3H, s), 1.43 (6H, s), 1.96 (3H, s), 4.42, 4.70 (each 1H, br s).

15-Hydroxyeudesm-11-yl Acetate (8) **7** (504 mg) in dry tetrahydrofuran (THF) (3 ml) was treated with a suspension of $NaBH_4$ (41 mg) in dry THF under N_2 with a dropwise addition of BF_3–Et_2O for over 1 h, followed by treatment with H_2O (1 ml), 3 M NaOH (0.5 ml), and 30% H_2O_2 (0.5 ml) and extracted with ether. The reaction mixture was purified by MPLC and gave colorless oil of **8** (345 mg, 64%), $[\alpha]_D$ +33.3° (c=0.27, $CHCl_3$). MS m/z: 222 $(M-AcOH)^+$. IR ν_{max}^{neat}: 3340, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, s), 1.41 (6H, s), 1.97 (3H, s), 3.57 (2H, d, J=4 Hz).

11-Hydroxy-15-noreudesm-4-one (9) Ozonolysis of **1** (440 mg) in MeOH (10 ml) at −78 °C for 10 min, followed by treatment with aq. AcOH (0.75 ml) and zinc powder (15 mg) at 30 °C for 1 h, extraction with CH_2Cl_2, and recrystallization from *n*-hexane gave colorless needles of **9** (395 mg, 89%), mp 122.0—123.0 °C, $[\alpha]_D$ +3.8° (c=0.13, $CHCl_3$). MS m/z: 224 $(M)^+$. IR ν_{max}^{KBr}: 3470, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, s), 1.20 (6H, s). *Anal.* Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.73; H, 10.77.

4-*epi*-Eudesma-4β,11-diol (10) Treatment of **9** (224 mg) in dry ether (6 ml) with dry ether solution of MeMgI from MeI (426 mg) and Mg (75 mg) in dry ether (7.5 ml), under N_2 in an ice bath, at 0 °C for 1 h, and subsequent MPLC of the product gave colorless needles of **10** (210 mg, 93%), mp 84.5—85.5 °C, $[\alpha]_D$ +11.1° (c=0.10, $CHCl_3$). MS m/z: 225 $(M-CH_3)^+$. IR ν_{max}^{KBr}: 3290 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, s), 1.17 (3H, s), 1.20 (6H, s). *Anal.* Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.23; H, 11.80.

11-Acetoxy-15-noreudesm-4-one (11) Acetylation of **9** (1.24 g) in Ac_2O (4.5 ml) and $(C_2H_5)_3N$ (6 ml) containing DMAP (140 mg) at 30 °C for 4 h, followed by MPLC yielded colorless oil of **11** (638 mg, 43%), $[\alpha]_D$ +12.3° (c=0.47, $CHCl_3$). MS m/z: 266 $(M)^+$, 206. IR ν_{max}^{neat}: 1720, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, s), 1.41 (6H, s), 1.94 (3H, s).

4β-Hydroxy-15-noreudesm-11-yl Acetate (12) Reduction of **11** (375 mg) with $NaBH_4$ (150 mg) in MeOH (25 ml) at room temperature for 15 min and subsequent purification by MPLC yielded colorless oil of **12** (297 mg, 79%), $[\alpha]_D$ +20.6° (c=0.16, $CHCl_3$). MS m/z: 268 $(M)^+$. IR ν_{max}^{neat}: 3430, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, s), 1.43 (6H, s), 1.96 (3H, s), 3.78 (1H, br s).

15-Noreudesma-4β,11-diol (13) Reduction of **9** (447 mg) with $NaBH_4$ (150 mg) at room temperature for 15 min, followed by ether extraction and recrystallization from *n*-hexane yielded colorless needles of **13** (400 mg, 89%), mp 130.5—131.5 °C, $[\alpha]_D$ +15.7° (c=0.14, $CHCl_3$). MS m/z: 226 $(M)^+$. IR ν_{max}^{KBr}: 3290 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, s), 1.20 (6H, s), 3.79 (1H, br s). *Anal.* Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.06; H, 11.74.

11-Hydroxy-15-noreudesm-4β-yl Acetate (14) Acetylation of **13** (357 mg) in Ac_2O (161 mg), pyridine (1 ml) and DMAP (40 mg) at 30 °C for 2 h, followed by recrystallization from acetone–H_2O gave colorless

needles of **14** (222 mg, 52%), mp 90.0—91.0 °C, $[\alpha]_D$ +22.5° (c=0.12, $CHCl_3$). MS m/z: 268 $(M)^+$. IR ν_{max}^{KBr}: 3250, 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, s), 1.18 (6H, s), 2.04 (3H, s), 4.90 (1H, br s). *Anal.* Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.83; H, 10.58.

15-Noreudesm-4β,11-yl Diacetate (15) Acetylation of **13** (400 mg) in Ac_2O (902 mg), pyridine (1.5 ml) and DMAP (44 mg) at 60 °C for 4 h and subsequent purification by MPLC gave colorless oil of **15** (298 mg, 54%), $[\alpha]_D$ +40.0° (c=0.20, $CHCl_3$). MS m/z: 250 $(M-AcOH)^+$. IR $\nu_{max}^{neat.}$: 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, s), 1.46 (6H, s), 1.96 (3H, s), 2.04 (3H, s), 4.88 (1H, brs).

Dihydroeudesmol (16) Hydrogenation of **1** (500 mg) in EtOH (10 ml) over PtO_2 (25 ml) in H_2 atmosphere for 6 h and subsequent recrystallization from H_2O–Me_2CO gave colorless needles of **16** (354 mg, 70%), mp 83.5—84.5 °C, $[\alpha]_D$ +15.0° (c=0.14, $CHCl_3$). The spectra data were identical with those of dihydroeudesmol.[13]

Eudesma-11,15-diol (17) Hydroboration of **1** (450 mg) was done in the same way as described for the synthesis of **8**, and purification by MPLC gave colorless rods of **17** (290 mg, 60%), mp 122.0—124.0 °C, $[\alpha]_D$ +37.5° (c=0.08, EtOH). MS m/z: 240 $(M)^+$. IR ν_{max}^{KBr}: 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 1.14 (6H, s), 3.57 (2H, d, J=4 Hz). *Anal.* Calcd for $C_{15}H_{28}O_2 \cdot H_2O$: C, 69.72; H, 11.70. Found: C, 69.94; H, 11.70.

15-Hydroxyeudesm-11-yl-tiglate (18) Dropwise addition of tigloyl chloride (0.1 ml) to **17** (309 mg) in dry pyridine (3 ml) and dry ether (5 ml) with stirring, followed by heating at reflux for 2.5 h gave colorless oil, **18** (157 mg, 38%) after purification by MPLC. Compound **18**: MS m/z: 305 $(M-17)^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, s), 1.13 (6H, s), 1.77 (6H, br s), 4.10 (2H, br d, J=6 Hz), 6.77 (1H, m).

11-Acetoxyeudesm-4α-ol (19) Dropwise addition of **7** (528 mg) in THF (2 ml) a stirred solution of $Hg(OAc)_2$ (640 mg) in H_2O (2 ml) and THF (2 ml), followed by the addition of a solution containing 3 M NaOH and 0.5 M $NaBH_4$ after stirring at room temperature for 1 h, and subsequent extraction and evaporation on MPLC gave colorless oil of **19** (234 mg, 41%), $[\alpha]_D$ −15.8° (c=0.53, $CHCl_3$). MS m/z: 222 $(M-AcOH)^+$. IR $\nu_{max}^{neat.}$: 3370, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, s), 1.10 (3H, s), 1.42 (3H, s), 1.46 (3H, s), 1.98 (3H, s).

Cryptomeridiol (20) Treatment of **19** (340 mg) with a large excess of $LiAlH_4$ in dry Et_2O (4 ml) under N_2 at room temperature for 1.5 h and subsequent to MPLC gave colorless needles of **20** (234 mg, 81%), mp 134.0—136.0 °C, $[\alpha]_D$ −17.9° (c=0.14, $CHCl_3$). The spectral data were identical with those of cryptomeridiol[14]: MS m/z: 240 $(M)^+$. IR ν_{max}^{KBr}: 3330 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, s), 1.05 (3H, s), 1.14 (6H, s). *Anal.* Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.77; H, 11.77.

4α,15-Epoxyeudesm-11-ol (21) *m*-Chloroperbenzoic acid (*m*-CPBA, 0.99 g) in dry CH_2Cl_2 (12 ml) was added dropwise to a stirred solution of **1** (1.01 g) in dry CH_2Cl_2 (15 ml) under N_2 in an ice bath, followed by stirring at 0 °C for 1.5 h. The reaction mixture was washed with 10% aq. $Na_2S_2O_3$, sat. $NaHCO_3$ and brine, and then purified by MPLC to give colorless plates of **21** (840 mg, 78%), mp 53.0—55.0 °C, $[\alpha]_D$ −14.0° (c=0.20, $CHCl_3$). MS m/z: 220 $(M-H_2O)^+$. IR ν_{max}^{KBr}: 3410 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, s), 1.13 (6H, s), 2.50, 2.70 (each 1H, d, J=4 Hz). *Anal.* Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.37; H, 11.25.

Eudesma-4α,11,15-triol (22) and 4-*epi*-Eudesma-4β,11,15-triol (23) Hydrolysis of **21** (660 mg) in H_2O (10 ml) and dimethyl sulfoxide (DMSO, 130 ml) with a solution of 1 N H_2SO_4 (10 ml) in DMSO (10 ml) at room temperature for 24 h and subsequent MPLC gave colorless needles of **22** (30 mg, 5%), mp 80.5—82.0 °C, $[\alpha]_D$ −23.8° (c=0.08, EtOH) and colorless plates of **23** (29 mg, 4%), mp 174.0—176.0 °C, $[\alpha]_D$ +20.0° (c=0.03, EtOH). The physical data of **22** were MS m/z: 238 $(M-H_2O)^+$. IR ν_{max}^{KBr}: 3300 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, s), 1.18 (6H, s), 3.47, 3.64 (1H, each d, J=10 Hz). *Anal.* Calcd for $C_{15}H_{28}O_3 \cdot 1/2H_2O$): C, 67.89, H, 11.01. Found: C, 68.19; H, 11.01. The physical data for **23** were MS m/z: 225 $(M-CH_2OH)^+$, 207. IR ν_{max}^{KBr}: 3310 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.05 (3H, s), 1.16 (6H, s), 3.13, 3.48 (each 1H, d, J=10 Hz). *Anal.* Calcd for $C_{15}H_{28}O_3$: C, 70.28; H, 11.01. Found: C, 69.98; H, 11.06.

11-Acetoxy-4α,15-epoxyeudesmane (24) Epoxidation of **7** (554 mg) was made with *m*-CPBA (460 mg) in CH_2Cl_2 at 0 °C for 3.5 h and subsequent MPLC gave colorless oil of **24** (301 mg, 52%), $[\alpha]_D$ −7.1° (c=0.28, $CHCl_3$). MS m/z: 280 $(M)^+$, 220 $(M-AcOH)^+$. IR $\nu_{max}^{neat.}$: 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, s), 1.39 (6H, s), 1.94 (3H, s), 2.49, 2.67 (each, 1H, d, J=4 Hz). *Anal.* Calcd for $C_{17}H_{28}O_3$; C, 72.82; H, 10.06. Found: C, 72.58; H, 10.07.

1α,10α-Epoxyhines-11-ol (26) Epoxidation of **25** (3.07 g) was made with *m*-CPBA (2.85 g) in CH_2Cl_2 (50 ml) at 0 °C for 1 h and subsequent MPLC gave colorless oil of **26** (2.74 g, 83%). MS m/z: 238 $(M)^+$. IR $\nu_{max}^{neat.}$: 3410 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, d, J=6 Hz), 1.22 (6H, s), 1.31 (3H, s), 2.92 (1H, t, J=2 Hz).

Hinesa-10α,11-diol (27) Reduction of **26** (213 mg) was carried out with a large excess of $LiAlH_4$ in dry Et_2O (4 ml) at room temperature for 4 h, followed by MPLC and gave colorless needles of **27** (92 mg, 43%), mp 95.0—98.0 °C, $[\alpha]_D$ +46.7° (c=0.06, $CHCl_3$). MS m/z: 222 $(M-H_2O)^+$. IR ν_{max}^{KBr}: 3370 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, d, J=7 Hz), 1.16 (3H, s), 1.19 (6H, s).

2-Oxo-hinesol (28) Treatment of a solution of **25** (691 mg) in pyridine (10 ml) with a suspension of CrO_3 (1.0 g) in pyridine (10 ml) at room temperature for 1 month and subsequent MPLC gave yellowish needles of **28** (200 mg, 27%), mp 67.0—69.0 °C, $[\alpha]_D$ −90.4° (c=0.28, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{24}O_2$; C, 76.22; H, 10.24. Found: C, 76.12; H, 10.22. MS m/z: 221 $(M-CH_3)^+$. UV λ_{max}^{EtOH} (ε): 241 (15500). IR ν_{max}^{KBr}: 3520, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, J=6 Hz), 1.26 (6H, s), 1.98 (3H, br s), 5.74 (1H, br s).

Spasmolytic Activity A piece of ileum of guinea pig (3—4 cm long) was suspended in 10 ml of an aerated (5% CO_2 in O_2) modified Lock Ringer solution at 30—31 °C. The tissue was brought into contact with histamine hydrochloride (1×10^{-7} g/ml) or barium chloride (2×10^{-4} g/ml) for 20—25 s. Contraction produced by spasmogen alone or in the presence of the antagonistic terpenoids of various concentrations added 3 min before the addition of the spasmogen was recorded automatically on a chart. Between the measurements of contractions, the ileum was washed three times by changing the solution each 3 min. The concentration producing 50% reduction of contraction was calculated by plotting the log molar concentration and percent inhibition curve. Papaverin, well known as a spasmolytic agent, showed 45% inhibitory at 1×10^{-6} mol/l against the contraction induced by histamine hydrochloride (1×10^{-7} g/ml).

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