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Stereoselective Total Synthesis of (±)-Labdane-8α,15-diol and (±)-Eperuane-8β,15-diol[1)]

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(±)-Labdane-8α,15-diol and (±)-eperuane-8β,15-diol, diastereomeric diterpenes to each other, were prepared separately and stereoselectively, via a common 7-membered lactone from the known tricyclic keto alcohol.

A large number of diterpenoids possessing a labdane skeleton (**1**) occur in nature[2)] and labdanolic acid (**2**) and eperuic acid (**3**) are two of the representative labdane-type diterpenoids. These acids are antipodal except for the asymmetric center at C-13 position, which was assigned to be the same (*S*)-configuration. Stereochemical assignment at C-13 position has been difficult on most of labdane-type compounds,[3)] and therefore X-ray structure analysis of a derivative of labdanolic acid has been applied to establish the C-13 configuration.[4)]

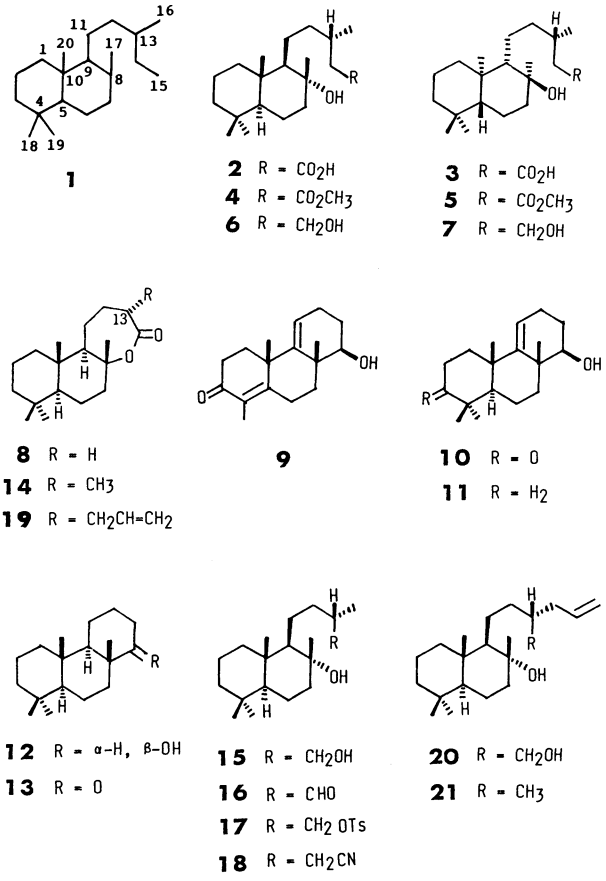
Concerning the synthetic works, Barltrop et al. have reported the total synthesis of methyl labdanolate (**4**) and its 13-epimer corresponding to an enantiomer of methyl eperuate (**5**), but their synthesis included non-stereoselective formation of the C-13 methyl group by hydrogenation at the final stage.[5)] In this paper, we wish to report the stereoselective total synthesis of (±)-labdane-8α,15-diol (**6**) and (±)-eperuane-8β,15-diol (**7**) from a common key intermediate ((±)-**8**).

Our fundamental synthetic strategies were based on the following considerations. i) Alkylation at the α-position of the lactone carbonyl group of **8** via an enolate ion would proceed stereoselectively from the sterically less-hindered α-side. ii) If a methyl group was introduced from the α-side at this position and then one carbon-unit was homologated at the lactone carbonyl carbon, (±)-labdane-8α,15-diol (**6**) would be afforded unambiguously. iii) On the other hand, if some C_2-unit equivalent was introduced from the α-side at this position and then the lactone carbonyl carbon was converted into a methyl group, (±)-eperuane-8β,15-diol (**7**) could be obtained stereoselectively.

Preparation of the Tricyclic Lactone ((±)-8). The racemic α,β-unsaturated ketone (**9**), which could be obtained easily via the known procedure,[6)] was treated with 3.5 equivalent moles of lithium in liquid ammonia, and the resulting alkoxy enolate was trapped with methyl iodide[7)] to afford a methylated keto alcohol (**10**) quantitatively. The carbonyl group of **10** was removed by Huang-Minlon reduction to give unsaturated alcohol (**11**) in 95% yield. Hydrogenation of **11** over platinum catalyst afforded a saturated alcohol (**12**) in 98% yield. Jones oxidation of the alcohol (**12**) gave the corresponding ketone (**13**) quantitatively. The ketone (**13**) was treated with perbenzoic acid[8)] to afford a single lactone (**8**), the Baeyer–Villiger oxidation product, in 61% yield.

Thus, (±)-**8** was obtained from the known ketone (**9**) via a five-step reaction sequence in 57% overall yield.

Synthesis of (±)-Labdane-8α,15-diol (6). The lactone (**8**) was treated with lithium diisopropylamide (LDA) followed by methyl iodide to afford a 13α-methylated lactone (**14**) in 72% yield. Since no peak due to the stereoisomeric compound could be detected in the ^{13}C NMR spectrum of the reaction product, it was concluded that the stereoselective methylation had



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occurred from the sterically less-hindered α-side of the enolate. Lithium aluminium hydride reduction of this lactone (**14**) gave the corresponding diol (**15**) quantitatively.

The C_1-unit homologation at the hydroxymethyl group of **15** was attempted by Wittig reaction. Pyridinium chlorochromate oxidation of the diol (**15**) gave an aldehyde (**16**) in 46% yield, which was treated with methylenetriphenylphosphorane and hydroboration was followed. A mixture of (±)-labdane-8α,15-diol (**6**) and (±)-eperuane-8β,15-diol (**7**) was obtained in a ratio of ca. 2:1 in 65% yield. This means that the isomerization at C-13 position would take place under the Wittig reaction conditions. Hence, the transformation of hydroxyl group into cyano group was next examined to synthesize **6** without isomerization at the C-13 position.

The diol (**15**) was treated with *p*-toluenesulfonyl chloride at 0 °C to afford a monotosylate (**17**) in 87% yield. On treatment with sodium cyanide,[9] **17** afforded a cyanide (**18**) in 93% yield, which was hydrolyzed with sodium hydroxide in the presence of aqueous hydrogen peroxide[10] to give (±)-labdanolic acid (**2**) stereoselec-

Table 1. ^{13}C NMR Spectra of Methyl Labdanolate (**4**), Methyl Eperuate (**5**), Labdane-8α,15-diol (**6**), and Eperuane-8β,15-diol (**7**) in $CDCl_3$

No. of carbon	Methyl labdanolate (**4**)		Methyl eperuate (**5**)	
	Synthetic	Authentic[a]	Synthetic	Authentic[a]
1	39.82	39.86	39.90	39.86
2	18.53	18.56	18.61	18.56
3	41.47	41.45	41.37	41.34
4	33.27	33.25	33.35	33.31
5	56.21	56.25	56.29	56.31
6	20.59	20.61	20.70	20.61
7	44.43	44.35	44.67	44.64
8	74.20	73.90	74.20	74.13
9	62.31	62.17	62.15	62.12
10	39.20	39.17	39.25	39.23
11	22.86	22.83	22.57	22.49
12	40.69	40.65	40.39	40.37
13	31.32	31.26	31.21	31.14
14	42.10	42.13	42.15	42.13
15	173.78	173.77	173.92	174.00
16	19.94	19.93	20.07	20.04
17	24.08	24.03	24.08	24.03
18	33.46	33.48	33.54	33.48
19	21.54	21.58	21.62	21.58
20	15.50	15.49	15.55	15.49
MeO	51.31	51.24	51.34	51.30

No. of carbon	Labdane-8α,15-diol (**6**)		Eperuane-8β,15-diol (**7**)	
	Synthetic	Literature[17]	Synthetic	Authentic[a]
1	39.77	39.8	39.82	39.91
2	18.50	18.5	18.50	18.56
3	42.04	42.1	42.02	42.13
4	33.27	33.3	33.27	33.31
5	56.16	56.2	56.16	56.25
6	20.56	20.6	20.56	20.61
7	41.15	40.9	40.45	40.42
8	74.44	74.4	74.47	74.47
9	62.47	62.5	61.79	61.89
10	39.17	39.2	39.23	39.29
11	24.03	24.0	24.08	24.14
12	44.43	44.3	44.51	44.58
13	30.61	30.6	30.07	30.12
14	39.77	39.8	39.23	39.29
15	60.98	60.3	61.25	61.21
16	19.83	20.1	20.07	20.10
17	23.00	23.2	22.16	22.15
18	33.43	33.5	33.43	33.48
19	21.51	21.5	21.51	21.58
20	15.50	15.5	15.47	15.49

a) Shift values were obtained from the ^{13}C NMR charts of authentic samples which were sent from Profs. E. L. Ghisalberti and P. R. Jefferies. Eperuane-8β,15-diol (**7**) was a natural compound and other samples (**4** and **5**) were derived from natural ones.

tively in 75% yield. This acid (**2**) was converted into (±)-methyl labdanolate (**4**) and then into (±)-labdane-8α,15-diol (**6**) via known procedures.[11]

The ^{13}C and ^{1}H NMR spectral data of synthetic **4** and **6** were completely identical with those of natural methyl labdanolate[5,12-15] and labdane-8α,15-diol[12,14,16,17] (see Table 1 for the comparison of ^{13}C NMR spectral data). Thus (±)-labdane-8α,15-diol (**6**) was synthesized stereoselectively from the lactone (**8**) by a seven-step reaction sequence in 43% overall yield.

Synthesis of (±)-Eperuane-8β,15-diol (7). As mentioned before, it is necessary to introduce a C_2-unit equivalent at the α-position of lactone carbonyl group of **8** to build up the side chain of **7**. Ethylene oxide being turned out to be ineffective,[18] the introduction of C_2-unit equivalent was achieved by allylation followed by ozonolysis. The lactone (**8**) was treated with LDA followed by allyl bromide to afford the 13α-allylated lactone (**19**) in 62% yield. No stereoisomer could be detected by ^{13}C NMR spectrum examination of the reaction product. This result indicates that allylation exclusively occurred from the sterically less-hindered α-side of the enolate. On reduction with lithium aluminium hydride, this lactone (**19**) gave the corresponding diol (**20**) in 97% yield, which was monotosylated with *p*-toluenesulfonyl chloride. The reaction product was then reduced with lithium aluminium hydride to afford an alcohol (**21**) in 80% yield, which was treated with ozone. A reductive treatment with sodium borohydride[19] was followed to give (±)-eperuane-8β,15-diol (**7**) in 82% yield. This diol (**7**) was transformed into (±)-eperuic acid (**3**) and methyl eperuate (**5**) by known procedures.[20]

The ^{13}C and ^{1}H NMR spectral data of synthetic **5** and **7** were completely identical with those of natural methyl eperuate[5,12,13,20] and eperuane-8β,15-diol,[12,20] respectively (see Table 1 for ^{13}C NMR spectral data).

Thus, (±)-eperuane-8β,15-diol (**7**) was synthesized stereoselectively by five step reactions in 39% overall yield from the same intermediate (**8**) as that used for a preparation of **6**.

Experimental

General Procedures. All melting points were measured on a Mel-temp capillary melting point apparatus (Laboratory Devices) and uncorrected. Infrared (IR) spectra were measured on a Hitachi 260-30 spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were taken using a Varian EM-390 and a JEOL FX-90Q (both 90 MHz) spectrometers at ambident temperature. ^{13}C NMR spectra were measured on a JEOL FX-90Q (22.5 MHz) spectrometer. Chloroform-*d* was used as the NMR solvent unless otherwise mentioned. Chemical shifts were expressed in δ (ppm) downfield from tetramethylsilane as an internal standard and coupling constants in Hz. Mass spectra (MS) were run on a JEOL JMS-D300 mass spectrometer operating at 70 eV. Thin-layer chromatography (TLC) was carried out on Kieselgel 60 GF_{254} coated in 0.25 mm thickness. Wakogel C-200 (Wako) was used for silica-gel column chromatography.

(±)-8β-Hydroxy-1,1,4aβ,8aβ-tetramethyl-3,4,4a,6,7,8,8a,9,10,10aα-decahydro-2(1*H*)-phenanthrenone (10). In a three-necked flask, lithium metal (570 mg) and liquid ammonia (150 ml) were placed at −78 °C and stirred for 10 min under a nitrogen atmosphere. A tetrahydrofuran (THF; 70 ml) solution of keto alcohol (**9**; 6.00 g) was added to the mixture and stirred at a refluxing temperature of ammonia for 1 h. At −78 °C methyl iodide (12 ml) was added to the mixture, and the whole was again stirred at a refluxing temperature of ammonia for 2 h. After removal of ammonia at room temperature, the reaction mixture was neutralized with about 2 M hydrochloric acid (1 M=1 mol dm^{-3}) and was extracted with chloroform four times. The combined chloroform extract was washed with saturated brine, and was dried over sodium sulfate. Removal of the solvent afforded keto alcohol (**10**; 6.37 g; quantitative yield) as white crystals (from acetone), mp 139.5—142.5 °C; IR (KBr) 3400 and 1710 cm^{-1}; ^{1}H NMR δ=1.08(6H, s), 1.17 (3H, s), 1.28 (3H, s), 3.41 (1H, dd, *J*=8.5 and 7 Hz), and 5.33 (1H, t, *J*=4 Hz); MS *m/z* (%) 276 (M^+, 37), 258 (100), and 232 (82); Found: *m/z* 276.2099. Calcd for $C_{18}H_{28}O_2$: M, 276.2090.

(±)-4bβ,8,8,10aβ-Tetramethyl-1,2,3,4b,5,6,7,8,8aα,9,10,10a-dodecahydro-1β-phenanthrenol (11). To a suspension of keto alcohol (**10**; 3.70 g) in diethylene glycol (64 ml) were added 80% hydrazine hydrate (7 ml) and potassium hydroxide (9.1 g). After the mixture was heated for 2 h at 170 °C (bath temperature) about 10 ml of the solvent was distilled off and the mixture was heated for 1 h at 230 °C. Water (70 ml) and 6 M hydrochloric acid (70 ml) were added, and the mixture was extracted with benzene. The usual work-up yielded the reduction product (**11**; 3.34 g) in 95% yield as white crystals (from benzene), mp 153.5—155 °C; IR (KBr) 3300 cm^{-1}; ^{1}H NMR δ=0.87 (6H, s), 1.13 (6H, s), 3.41 (1H, dd, *J*=8.5 and 7 Hz), and 5.27 (1H, t, *J*=4 Hz); MS *m/z* (%) 262 (M^+, 21), 244 (61), 203 (75), and 106 (100); Found: C, 82.57; H, 11.61%; and *m/z* 262.2291. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52%; and M, 262.2298.

(±)-4bβ,8,8,10aβ-Tetramethyl-4aα*H*,8aα*H*-tetradecahydro-1β-phenanthrenol (12). A catalytic amount of platinum oxide was added to a solution of **11** (1.91 g) in acetic acid (60 ml) and the mixture was stirred under a hydrogen atmosphere at room temperature for 2.5 d. The reaction was monitored as follows; a small portion of the reaction mixture was treated with *m*-chloroperbenzoic acid. Only starting material (**11**), if present, was transformed into an epoxide, which could be differentiated from **12** by TLC examination. Filtration and evaporation afforded an alcohol (**12**; 1.89 g) in 98% yield as white crystals (from benzene), mp 179—182 °C; IR (KBr) 3300 cm^{-1}; ^{1}H NMR δ=0.81(3H, s), 0.86 (6H, s), 0.88 (3H, s), and 3.12 (1H, dd, *J*=10 and 5 Hz); MS *m/z* (%) 264 (M^+, 41), 249 (26), and 191 (100); Found: *m/z* 264.2452. Calcd for $C_{18}H_{32}O$: M, 264.2455.

(±)-4bβ,8,8,10aβ-Tetramethyl-3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-dodecahydro-1(2*H*)-phenanthrenone (13). Jones reagent (5 ml) was added to a solution of the saturated alcohol (**12**; 3.47 g) in acetone (450 ml) at 0 °C , and the mixture was stirred for 30 min at the same temperature. To the mixture, a saturated aqueous solution (ca. 100 ml) of sodium sulfite was added, and then acetone was removed under reduced pressure. The reaction product was extracted with benzene

three times and dried over sodium sulfate. The benzene solution was passed through a small amount of Florisil, and the solvent was evaporated to afford ketone (**13**; 3.44 g) quantitatively, as white crystals (from ether), mp 102.5—103 °C; IR (KBr) 1710 cm^{-1}. ^1H NMR δ=0.83 (3H, s), 0.87 (3H, s), 0.95 (3H, s), and 1.14 (3H, s); MS *m/z* (%) 262 (M^+, 78), 247 (43), and 191 (100); Found: C, 82.06; H, 11.82%; and *m/z* 262.2304. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52%; and M, 262.2298.

(±)-5aβ,8,8,11aβ-Tetramethyl-7aα*H*,11bα*H*-tetradecahydronaphth[2,1-*b*]oxepin-4-one (8). Perbenzoic acid (9.7 g) was added to a solution of the saturated ketone (**13**; 6.20 g) in chloroform (90 ml), and the mixture was stirred at room temperature for 2 d under dark. A saturated aqueous solution (20 ml) of sodium hydrogensulfite was added to the reaction mixture, and the chloroform layer was separated, washed three times with a saturated aqueous solution of sodium hydrogencarbonate, and dried over sodium sulfate. Purification by silica-gel column chromatography (0.6% acetone in benzene) afforded 7-membered lactone (**8**; 4.00 g) in 61% yield, as white crystals (from benzene), mp 100.5—102.5 °C; IR (KBr) 1705 cm^{-1}; ^1H NMR δ=0.83 (6H, s), 0.90 (3H, s), and 1.51 (3H, s); MS *m/z* (%) 278 (M^+, 42), 263 (72), and 137 (100); Found: C, 77.81; H, 11.18%; and *m/z* 278.2238. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86%; and M, 278.2247.

(±)-3aα,5aβ,8,8,11aβ-Pentamethyl-7aα*H*,11bα*H*-tetradecahydronaphth[2,1-*b*]oxepin-4-one (14). Under an argon atmosphere, a hexane solution of butyllithium (1.6 M; 5.7 ml) and diisopropylamine (1.7 ml) were added successively to THF (80 ml) at −78 °C. The mixture was stirred for 20 min at room temperature and then kept to −78 °C, to which a THF (50 ml) solution of the lactone (**8**; 1.89 g) was added. After stirring for 30 min at −78 °C and addition of methyl iodide (0.90 ml), the whole mixture was stirred at room temperature for 2 h and then a mixture of 14% aqueous solution of ammonium chloride and a small amount of sodium sulfite was added. The reaction product was extracted with ether three times, worked up as the usual manner, and separated by silica-gel column chromatography (0.3% acetone in benzene) to afford methylated lactone (**14**; 1.42 g) in 72% yield as white crystals, mp 125.5—127 °C; IR (KBr) 1715 cm^{-1}; ^1H NMR δ=0.81 (6H, s), 0.90 (3H, s), 1.17 (3H, d, *J*=7 Hz), 1.15 (3H, s); ^{13}C NMR δ=15.1, 18.8, 18.8, 19.7, 21.8, 22.9, 24.4, 32.9, 33.4, 33.6, 38.8, 39.9, 40.3, 41.6, 43.7, 55.6, 57.9, 85.5, and 177.4; MS *m/z* (%) 292 (M^+, 34), 277 (56), and 137 (100); Found: *m/z* 292.2390. Calcd for $C_{19}H_{32}O_2$: M, 292.2404.

(±)-1β-[(3*S*)-4-Hydroxy-3-methylbutyl]-2β,5,5,8aβ-tetramethyl-4aα*H*-decahydro-2α-naphthalenol (15). Under an argon atmosphere, lithium aluminium hydride (140 ml) was added to a solution of the methylated lactone (**14**; 1.40 g) in ether (5 ml), and the mixture was stirred at 0 °C for 30 min. The reaction was stopped by addition of a small amount of water and the mixture was filtered. The filtrate, after addition of water (50 ml), was extracted with ether three times, and the ethereal layer was dried over magnesium sulfate and successively evaporated to give diol **15** (1.42 g) quantitatively as white crystals, mp 114—115 °C; IR (KBr) 3350 cm^{-1}; ^1H NMR δ=0.80 (6H, s), 0.88 (3H, s), 0.91 (3H, d, *J*=6 Hz), 1.15 (3H, s), and 3.46 (2H, br t, *J*=5 Hz); MS *m/z* (%) 296 (M^+, 8), 278 (21), 263 (25), and 69 (100); Found: *m/z* 296.2714. Calcd for $C_{19}H_{36}O_2$: M, 296.2717.

(±)-1β-[(3*S*)-3-Methyl-4-oxobutyl]-2β,5,5,8aβ-tetramethyl-4aα*H*-decahydro-2α-naphthalenol (16). A solution of diol **15** (300 mg) in dichloromethane (20 ml) was added to a solution of pyridinium chlorochromate (1.04 g) in dichloromethane (70 ml) and the mixture was stirred at room temperature for 40 min. A saturated aqueous solution (100 ml) of sodium hydrogencarbonate together with a small amount of sodium sulfite was added. After filtration with Celite under reduced pressure, the reaction mixture was extracted three times with chloroform, dried over magnesium sulfate, and separated by a silica-gel column chromatography (1% acetone in benzene). Pure hydroxy aldehyde **16** (140 mg) was obtained in 46% yield as a colorless oil; IR (neat) 3450 and 1720 cm^{-1}; ^1H NMR δ=0.78 (6H, s), 0.86 (3H, s), 1.08 (3H, d, *J*=9 Hz), 1.13 (3H, s), 2.33 (1H, br sextet, *J*=6 Hz), and 9.57 (1H, d, *J*=2 Hz); MS *m/z* (%) 294 (M^+, 7), 276 (28), and 109 (100); Found: *m/z* 294.2541. Calcd for $C_{19}H_{34}O_2$: M, 294.2560.

Preparation of a Mixture of (±)-Labdane-8α,15-diol (6) and (±)-Eperuane-8β,15-diol (7) from the Hydroxy Aldehyde (16). Under a nitrogen atmosphere, a solution of methyltriphenylphosphonium iodide (426 mg) in THF (25 ml) was added to a hexane solution of butyllithium (1.6 M; 0.7 ml) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. A solution of the hydroxy aldehyde **16** (140 mg) in THF (10 ml) was added to the mixture, and was refluxed for 18 h. Addition of a saturated aqueous solution (30 ml) of ammonium chloride followed by evaporation of THF gave a residue, which was extracted with hexane three times and dried over magnesium sulfate. Separation by column chromatography on silica gel (0.5% acetone in benzene) afforded a diastereomeric mixture of the Wittig reaction product (60 mg) as an oil; IR (neat) 3450 and 1635 cm^{-1}; ^1H NMR δ=0.77 (6H, s), 0.85 (3H, s), 0.97 (3H, d, *J*=6 Hz), 1.11 (3H, s), 4.88 (1H, br d, *J*=11 Hz), 4.92 (1H, br d, *J*=17 Hz), and 5.63 (1H, ddd, *J*=17, 11, and 4 Hz); MS *m/z* (%) 292 (M^+, 19), 274 (10), and 69 (100); Found: *m/z* 292.2776. Calcd for $C_{20}H_{36}O$: M, 292.2768. To a solution of the diastereomeric mixture (60 mg) in THF (7 ml) was added a THF solution of diborane (0.4 M; 1 ml) at 0 °C under nitrogen atmosphere, and the mixture was stirred at room temperature for 1.5 h. Water (1 ml), 3 M aqueous solution of sodium hydroxide (1 ml), and 30% aqueous solution of hydrogen peroxide (1 ml) were successively added, and the mixture was stirred at 40 °C for 1.5 h, and then extracted with ether three times. The ethereal layer was dried over magnesium sulfate and purified by silica-gel column chromatography (5% acetone in benzene) to afford 27 mg of labdane-8α,15-diol (**6**; 42% yield) and 14.5 mg of eperuane-8β,15-diol (**7**; 23% yield), both as crystalline compounds. Physical and spectral data of these diols (**6** and **7**) were completely identical with those synthesized from separate routes mentioned below.

(±)-1β-[(3*S*)-3-Methyl-4-(*p*-tolylsulfonyl)butyl]-2β,5,5,8aβ-tetramethyl-4aα*H*-decahydro-2α-naphthalenol (17). The diol (**15**; 191 mg) and *p*-toluenesulfonyl chloride (300 mg) were dissolved into pyridine (6 ml), and the mixture was stirred at 0 °C for 12 h. After addition of water and 2 M hydrochloric acid, the reaction product was extracted. The ethereal extract was worked up as usual and subjected to separation by Florisil column chromatography to afford monotosylate (**17**; 254 mg; 87% yield) as white crystals (from ether), mp 97—98.5 °C; IR (KBr) 3600—3400, 1360, and 1180 cm^{-1}; ^1H NMR δ=0.75 (3H, s), 0.78 (3H, s), 0.86 (3H, s),

0.89 (3H, d, J=6 Hz), 1.06 (3H, s), 2.43 (3H, s), 3.80 (2H, d, J=6 Hz), 7.27 (2H, d, J=8 Hz), and 7.71 (2H, d, J=8 Hz); MS m/z (%) 450 (M^+, 6), 432 (59), 417 (42), and 191 (100); Found: m/z 450.2788. Calcd for $C_{26}H_{42}O_4S$: M, 450.2803.

(±)-1β-[(3*S*)-4-Cyano-3-methylbutyl]-2β,5,5,8aβ-tetramethyl-4aα*H*-decahydro-2α-naphthalenol (18). The monotosylate (**17**; 226 mg) and sodium cyanide (260 mg) were added to a mixture of tributylamine (0.2 ml) and water (1 ml), and the whole mixture was refluxed with vigorous stirring for 6 h. The reaction product was extracted with ether and worked up as usual. Column chromatography on Florisil afforded nitrile (**18**; 142 mg; 93% yield) as white crystals (from ether–hexane), mp 51—52 °C; IR (KBr) 3600—3400, 2250, and 940 cm^{-1}; ^1H NMR (CCl_4) δ=0.79 (6H, s), 0.85 (3H, s), 1.07 (3H, d, J=7 Hz), 1.09 (3H, s), and 2.26 (2H, m); MS m/z (%) 305 (M^+, 5), 290 (4), 287 (3), 272 (7), and 71 (100); Found: m/z 305.2689. Calcd for $C_{20}H_{35}NO$: M, 305.2717.

(±)-Labdanolic Acid (2). A mixture of the nitrile **18** (49 mg), sodium hydroxide (500 mg), ethanol (5 ml), and 30% aqueous hydrogen peroxide (5 ml) was stirred at ca. 70 °C for about 30 min until the evolution of oxygen ceased. Then the mixture was refluxed for 7.5 h. After addition of an aqueous solution of sodium sulfite, evaporation of ethanol, and then addition of 2 M hydrochloric acid, the reaction product was extracted with ether. The ethereal layer was washed with a saturated brine, dried over sodium sulfate and evaporated to give a crude reaction mixture, which was separated by silica-gel column chromatography. From the ether eluant, 39 mg (75% yield) of labdanolic acid (**2**) was obtained as white crystals (from hexane–ether), mp 150.5—152 °C; IR (KBr) 3400, 1705, and 1690 cm^{-1}; ^1H NMR δ=0.80 (6H, s), 0.87 (3H, s), 0.98 (3H, d, J=6.5 Hz), 1.15 (3H, s), and 2.27 (2H, m); MS m/z (%) 324 (M^+, 45), 306 (45), 291 (43), and 69 (100); Found: m/z 324.2671. Calcd for $C_{20}H_{36}O_3$: M, 324.2665.

(±)-Methyl Labdanolate (4). To an ethereal solution of labdanolic acid (**2**; 34 mg) was added an ethereal solution of diazomethane (about three equivalent moles), and the mixture was stood for 5 h at room temperature. Removal of ether afforded the corresponding methyl ester **4** quantitatively as an oil; IR (neat) 3500 and 1740 cm^{-1}; ^1H NMR δ=0.80 (6H, s), 0.86 (3H, s), 0.95 (3H, d, J=6.5 Hz), 1.15 (3H, s), 2.25 (2H, m), and 3.64 (3H, s); ^{13}C NMR (Table 1); MS m/z (%) 338 (M^+, 13), 320 (8), 305 (8), 144 (60), and 69 (100); Found: m/z 338.2802. Calcd for $C_{21}H_{38}O_3$: M, 338.2819.

(±)-Labdane-8α,15-diol (6). To a solution of methyl labdanolate (**4**; 31.5 mg) in THF (10 ml) was added lithium aluminium hydride (20 mg), and the mixture was stirred at room temperature for 1 h. After addition of 2 M hydrochloric acid, the reaction mixture was extracted with ether. The ethereal layer was worked up in the usual manner and separated by silica-gel column chromatography. Pure labdane-8α,15-diol (**6**; 28.5 mg) was obtained in 99% yield as white crystals (from chloroform–hexane), mp 111.5—112.5 °C; IR (KBr) 3350 cm^{-1}; ^1H NMR δ=0.79 (6H, s), 0.87 (3H, s), 0.90 (3H, d, J=6.5 Hz), 1.14 (3H, s), and 3.66 (2H, t, J=6 Hz); ^{13}C NMR (Table 1); MS m/z (%) 310 (M^+, 3), 292 (17), 277 (20), and 69 (100); Found: m/z 310.2856. Calcd for $C_{20}H_{38}O_2$: M, 310.2873.

(±)-5aβ,8,8,11aβ-Tetramethyl-3α-(2-propenyl)-7aα*H*, 11bα*H*-tetradecahydronaphth[2,1-*b*]oxepin-4-one (19). Under an argon atmosphere, a hexane solution of butyllithium (1.6 M; 6.3 ml) and diisopropylamine (1.75 ml) were added successively to THF (70 ml) at −78 °C. The mixture was stirred for 20 min at room temperature and then kept at −78 °C. A solution of the lactone (**8**; 2.10 g) in THF (60 ml) was added to the mixture and the stirring was continued for 30 min at −78 °C. Then a mixture of allyl bromide (1.7 g) and THF (5 ml) was added, and the whole mixture was stirred at room temperature for 2 h. The reaction mixture was subjected to the same work-up as that for **14** and separated on silica-gel column chromatography (0.3% acetone in benzene), and the allylated lactone **19** (1.49 g) was obtained in 62% yield as white crystals (from benzene), mp 78.5—79.5 °C; IR (KBr) 1720 and 1650 cm^{-1}; ^1H NMR δ=0.77 (6H, s), 0.85 (3H, s), 1.48 (3H, s), 5.00 (1H, br d, J=11 Hz), 5.03 (1H, br d, J=15 Hz), and 5.63 (1H, ddt, J=15, 11, and 5 Hz); ^{13}C NMR δ=15.0, 18.7, 19.6, 21.7, 22.9, 24.3, 29.6, 33.3, 33.5, 36.7, 38.7, 39.8, 41.5, 43.6, 45.1, 55.5, 57.9, 85.7, 116.8, 136.3, and 176.2; MS m/z (%) 318 (M^+, 18), 303 (39), and 191 (100); Found: m/z 318.2546. Calcd for $C_{21}H_{34}O_2$: M, 318.2560.

(±)-1β-[(3*R*)-3-Hydroxymethyl-5-hexenyl]-2β,5,5,8aβ-tetramethyl-4aα*H*-decahydro-2α-naphthalenol (20). Under an argon atmosphere, lithium aluminium hydride (160 mg) was added to a solution of the allylated lactone (**19**; 1.40 g) in ether (7 ml), and the mixture was stirred at 0 °C for 30 min. The same work-up as that for **15** was followed to afford diol **20** (1.38 g) in 97% yield as white crystals, mp 109—110 °C; IR (KBr) 3350 and 1640 cm^{-1}; ^1H NMR δ=0.79 (6H, s), 0.86 (3H, s), 1.14 (3H, s),2.09 (2H, br t, J=7 Hz), 3.47 (1H, dd, J=11 and 3 Hz), 3.65 (1H, dd, J=11 and 3 Hz), 4.96 (1H, br d, J=11 Hz), 5.02 (1H, br d, J=16 Hz), and 5.80 (1H, ddt, J=16, 11, and 7 Hz); MS m/z (%) 332 (M^+, 4), 304 (9), 289 (16), and 95 (100); Found: C, 78.10; H, 11.95%; m/z 322.2867. Calcd for $C_{21}H_{38}O_2$: C, 78.20; H, 11.87%; M, 322.2873.

(±)-1β-[(3*R*)-3-Methyl-5-hexenyl]-2β,5,5,8aβ-tetramethyl-4aα*H*-decahydro-2α-naphthalenol (21). Under an argon atmosphere, *p*-toluenesulfonyl chloride (1.60 g) was added to a solution of the diol **20** (1.30 g) in pyridine (50 ml) at 0 °C, and the mixture was stirred at room temperature for 10 h. The reaction mixture was subjected to the same work-up as that for **17**, and separated by silica-gel column chromatography (0.7% acetone in benzene) to afford monotosylate (1.80 g) as an oil. To a solution of this crude monotosylate, without further purification, in ether (60 ml) was added lithium aluminium hydride (1.20 g), and the mixture was refluxed for 7 h under an argon atmosphere. The reaction was completely stopped by addition of water, and the mixture was filtered under reduced pressure. The filtrate was extracted with ether three times, and the ethereal extract was worked up as usual to yield olefinic alcohol **21** (1.00 g) in 80% yield as white crystals, mp 47—47.5 °C; IR (KBr) 3350 and 1640 cm^{-1}; ^1H NMR δ=0.78 (6H, s), 0.86 (3H, s), 0.89 (3H, d, J=6.5 Hz), 1.15 (3H, s), 4.97 (1H, br d, J=10 Hz), 4.99 (1H, br d, J=17 Hz), and 5.78 (1H, ddt, J=17, 10, and 7 Hz); MS m/z (%) 306 (M^+, 15), 288 (12), 273 (16), and 69 (100); Found: C, 82.25; H, 12.78%; m/z 306.2927. Calcd for $C_{21}H_{38}O$: C, 82.29; H, 12.49%; M, 306.2924.

(±)-Eperuane-8β,15-diol (7). To a solution of the olefin alcohol **21** (935 mg) in chloroform (45 ml) was introduced ozone (8%; 0.015 mol h^{-1}) at −20 °C for 1.5 h with stirring. Sodium borohydride (935 mg) in a 50% ethanol aqueous solution (80 ml) was added at 0 °C, and the whole mixture was stirred at 50 °C for 1 h, and then at room temperature for 5 h. After neutralization with 10% sulfuric acid, the reaction product was extracted with chloroform three times and the

organic layer was worked up as usual. Evaporation followed by silica-gel column chromatography (5% acetone in benzene) afforded eperuane-8β,15-diol (**7**; 773 mg) in 82% yield as white crystals (from benzene), mp 126—128 °C; IR (KBr) 3300 cm^{-1}; ^1H NMR δ=0.79 (6H, s), 0.87 (3H, s), 0.91 (3H, d, J=7.5 Hz), 1.15 (3H, s), 3.68 (2H, td, J=6 and 1.5 Hz); ^{13}C NMR (Table 1); MS m/z (%) 310 (M^+, 11), 292 (8), 277 (9), and 69 (100); Found: C, 75.16; H, 12.44%. Calcd for $C_{20}H_{38}O_2 \cdot 1/2\ H_2O$: C, 75.18; H, 12.30%; Found: m/z 310.2893. Calcd for $C_{20}H_{38}O_2$: M, 310.2873.

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