Chem. Pharm. Bull. **41**(9) 1604—1607 (1993) Vol. 41, No. 9

Platelet Aggregation Inhibitors in a Bhutanese Medicinal Plant, Shug Chher

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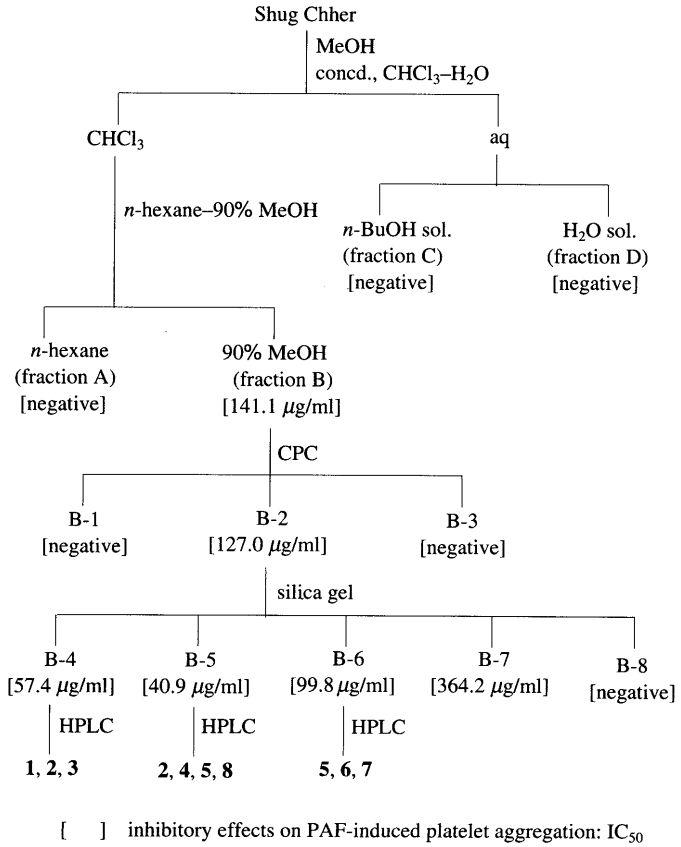
The 90% methanol-soluble fraction of a Bhutanese medicinal plant, Shug Chher, exhibited inhibition of platelet aggregation induced by platelet activating factor. Bioassay-directed fractionation led to the isolation of four new labdane diterpenoids, 3α, 15-dihydroxy-labda-8(17), 13*E*-diene (5), 3α-hydroxy-labda-8(17), 13*E*-dien-15-oic acid (6), 3α-hydroxy-labda-8(17), 12*E*, 14-trien-19-oic acid (7), and 3α-acetoxyisocupressic acid (8) and four known diterpenoids, manool (1), 3α-hydroxymanool (2), 3α-hydroxy-12, 13*E*-biformene (3), and isocupressic acid (4). The structures of the new compounds were determined spectroscopically. Compounds 2, 3, and 5 inhibited platelet aggregation.

Keywords platelet aggregation inhibitor; *Juniperus*; labdane; 3α-hydroxymanool; platelet activating factor

In our search for biologically active plant constituents, we isolated platelet aggregation inhibitors from Pyrolae Herba.[1] One fraction from a Bhutanese crude drug, Shug Chher, was found to inhibit platelet aggregation induced by platelet activating factor (PAF). We now report here the isolation of several labdane diterpenoids from the active fraction, the inhibition of PAF-induced platelet aggregation by the diterpendoids, and the structures of new compounds.

In Bhutan, indigenous medicine plays an important role in primary health care. Various medicinal plants, animal organs and tissues, and inorganic materials are used for the prevention of diseases and the treatment of various ailments. Shug Chher, tentatively assigned to *Juniperus communis* (Cupressaceae), is one of the traditional drugs used commonly in the Indigenous Hospital, Bhutan. The leaves of the plant are used for the treatment of rheumatoid arthritis, fever, and dysurea.



[ ] inhibitory effects on PAF-induced platelet aggregation: IC_{50}

Fig. 1. Fractionation of Shug Chher Extract

Isolation of Platelet Aggregation Inhibitors The methanol (MeOH) extract of the plant was partitioned between chloroform ($CHCl_3$) and H_2O as shown in Fig. 1. The $CHCl_3$ fraction was further fractionated into an *n*-hexane fraction (fraction A) and a 90% MeOH fraction (fraction B). Fraction B inhibited PAF-induced platelet aggregation, but not arachidonic acid (AA)-induced aggregation. Fraction B was separated by centifugal partition chromatography (CPC), chromatography on silica gel, and reversed-phase high performance liquid chromatography (HPLC) with monitoring of the inhibitory activity. Eight compounds were isolated from the active fractions.

Structures of Isolated Compounds Manool (**1**),[2] 3α-hydroxymanool (**2**),[3] 3α-hydroxy-12,13*E*-biformene (**3**),[4] isocupressic acid (**4**)[5] are known compounds and were identified by direct comparison with authentic samples[6] or by comparison of their spectral data with previously reported data.[4] Because ^1H- and ^{13}C-NMR spectral data of **2** showed some deviation from those reported,[3] the relative configuration of **2** was confirmed by X-ray crystallographic analysis. The perspective view of the molecule is shown in Fig. 2. The absolute structure was established by the synthesis of **2** and its enantiomer.[7]

The structures of new compounds **5**, **6**, **7**, and **8** were determined as described below. The ^1H-NMR spectrum of **5** was similar to that of **2**. Nuclear Overhauser effects (NOE) were observed between signals at δ 3.43 (3β-H) and 0.96 (4α-CH_3), between signals at δ 3.43 and 0.83

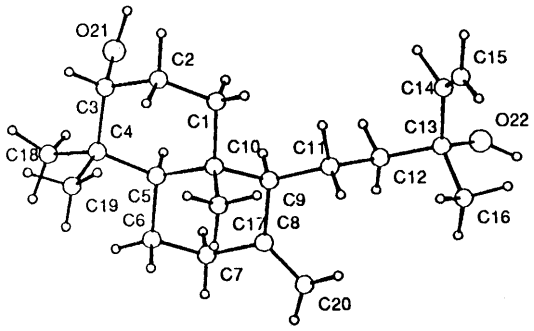


Fig. 2. Perspective View of the Molecule **2**

TABLE I. ^{1}H-NMR Spectra of Diterpenoids Isolated from Shug Chher

	1	2	5	6	7	8
3-H		3.43 (t, J=3)	3.43 (t, J=3)	3.44 (t, J=3)	4.10 (t-like)	5.30 (t-like)
12-H					5.41 (t, J=7)	
14-H	5.92 (dd, J=10, 17)	5.90 (dd, J=10, 17)	5.39 (t, J=7)	5.68 (br s)	6.33 (dd, J=10, 17)	5.39 (t, J=7)
15-H	5.06 (dd, J=1, 10)	5.06 (dd, J=1, 10)	4.15 (2H, d, J=7)		4.88 (d, J=10)	4.16 (2H, d, J=7)
	5.21 (dd, J=1, 17)	5.12 (dd, J=1, 17)			5.04 (d, J=17)	
13-Me	1.27 (s)	1.27 (s)	1.67 (s)	2.17 (s)	1.75 (s)	1.67 (s)
17-H	4.48 (br s)	4.49 (br s)	4.53 (br s)	4.51 (br s)	4.48 (br s)	4.54 (br s)
	4.81 (br s)	4.82 (br s)	4.84 (br s)	4.86 (br s)	4.85 (br s)	4.88 (br s)
4α-Me	0.87 (s)	0.96 (s)	0.96 (s)	0.96 (s)	1.35 (s)	1.22 (s)
4β-Me	0.80 (s)	0.83 (s)	0.83 (s)	0.84 (s)		
10-Me	0.67 (s)	0.69 (s)	0.69 (s)	0.70 (s)	0.66 (s)	0.61 (s)
3-OAc						2.11 (s)

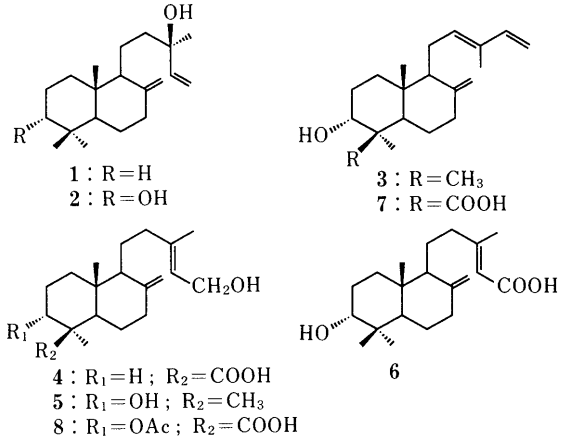


Chart 1

TABLE II. ^{13}C-NMR Spectral Data of Diterpenoids

Carbon	1[2)]	2	5	6	7	8
1	39.0	31.7	31.7	31.7	32.2	32.9
2	19.3	25.9	25.9	25.9	27.0	24.4
3	42.1	76.1	76.1	76.0	70.7	73.3
4	33.5	37.8	37.8	37.8	47.9	47.2
5	55.5	48.6	48.5	48.5	48.4	50.0
6	24.4	24.0	24.0	24.0	25.4	25.5
7	38.3	38.2	38.3	38.2	38.4	38.5
8	148.4	148.5	148.4	148.0	147.8	147.6
9	57.2	56.9	56.0	56.0	56.1	55.5
10	39.8	39.6	39.4	39.4	40.1	40.1
11	17.6	17.7	21.8	21.6	23.3	22.1
12	41.3	41.3	38.4	40.1	133.7	38.5
13	73.4	73.6	140.5	164.0	133.5	140.5
14	144.9	145.2	123.1	114.5	141.6	123.0
15	111.4	111.6	59.4	170.9	110.0	59.4
16	27.9	28.0	16.4	19.2	24.3	16.4
17	106.2	106.5	106.5	106.6	107.7	106.8
18	33.5	28.5	28.5	28.5	29.7	23.9
19	21.7	22.2	22.2	22.2	181.1	181.1
20	14.4	14.4	14.4	14.4	12.5	12.5
CH_3CO						21.3
						170.3

TABLE III. Inhibitory Effect on PAF-Induced Platelet Aggregation

Compound	IC_{50} (μg/ml)	(μM)
1	>200	
2	17.6	(49.6)
3	23.0	(79.7)
4	>200	
5	44.6	(145.8)
6	>200	
8	>200	
CV-3988	7.0	(11.4)

(4β-CH_3), and between signals at δ 0.83 and 0.69 (10-CH_3) similarly to **2**. The side-chain of **5** was suggested by the presence of a singlet at δ 1.67 (13-CH_3), a two-proton doublet at δ 4.15 (15-H) and a triplet at δ 5.39 (14-H) instead of a singlet at δ 1.27 and signals due to a vinyl group in **2**. The 13,14-*E* geometry was established from NOE observed between signals at δ 4.15 and 1.67. The structure of **5** was assumed to be 3α,15-dihydroxy-labda-8(17), 13*E*-diene. Compound **5** is new, although the 13,14-*Z* isomer of **5** has been reported.[3)]

The ^{1}H-NMR spectrum of **6** was similar to that of **5**. NOEs were observed between signals ascribed to 10-CH_3, 4β-CH_3, and 3β-H as seen in **5**. The IR and ^{13}C-NMR (δ_C 170.9) spectra and lack of a signal assignable to a CH_2OH group suggested the presence of a carboxyl group instead of the CH_2OH group of **5**. The 13,14-*E* geometry was indicated by the chemical shift of the signal due to 13-CH_3 and lack of NOE between signals assignable to 13-CH_3 and 14-H. From these observations the structure of **6** was established as 3α-hydroxy-labda-8(17), 13*E*-dien-15-oic acid.

The ^{1}H-NMR spectrum of **7** suggested the presence of a side-chain similar to that of **3**. An NOE experiment established the 12,13-*E* geometry. Signals ascribable to 4α-CH_3 (δ 1.35) and 10-CH_3 (δ 0.66) were observed, but no signal due to 4β-CH_3 was seen. This fact, together with the IR and ^{13}C-NMR (δ_C 181.1) spectra, indicated the presence of a carboxyl group in place of the 4β-CH_3 of **3**. Irradiation of the signal at δ 1.35 showed NOE on the signal due to 3β-H, but not on the signal at δ 0.66. These observations suggested that the relative configuration of **7** was 3α-hydroxy-labda-8(17), 12*E*, 14-trien-19-oic acid.

The ^{1}H-NMR spectrum of **8** was similar to that of **4**, but the presence of an additional acetoxyl group was indicated. The 3α-configuration of the acetoxyl group was proposed from the coupling pattern of the signal at δ 5.30 (3β-H) and the NOEs observed between the signal at δ 5.30 and the signal at δ 1.22 (4α-CH_3), which showed no NOE on irradiation of 10-CH_3. An NOE experiment suggested the 13,14-*E* geometry. The structure of **8** was postulated to be 3α-acetoxy-15-hydroxy-labda-8(17), 13*E*-dien-19-oic acid

TABLE IV. Atomic Coordinates for **2** with Their e.s.d.'s in Parentheses

Atom	x	y	z
Molecule A			
C1	0.8965 (2)	0.4862	0.2532 (4)
C2	0.8927 (2)	0.4929 (2)	0.1154 (4)
C3	0.8963 (2)	0.4321 (2)	0.0547 (4)
C4	0.8498 (2)	0.3885 (2)	0.0735 (4)
C5	0.8512 (2)	0.3842 (2)	0.2134 (4)
C6	0.8086 (2)	0.3396 (2)	0.2443 (5)
C7	0.8221 (2)	0.3278 (2)	0.3847 (5)
C8	0.8258 (2)	0.3850 (2)	0.4575 (5)
C9	0.8681 (2)	0.4301 (2)	0.4297 (4)
C10	0.8506 (2)	0.4452 (2)	0.2848 (4)
C11	0.8779 (2)	0.4857 (2)	0.5135 (4)
C12	0.9139 (2)	0.4721 (2)	0.6465 (4)
C13	0.9265 (2)	0.5279 (2)	0.7301 (4)
C14	0.9635 (3)	0.5726 (3)	0.6774 (6)
C15	0.9611 (4)	0.6275 (3)	0.6646 (7)
C16	0.8729 (3)	0.5552 (4)	0.7511 (6)
C17	0.7931 (2)	0.4777 (2)	0.2554 (4)
C18	0.7921 (2)	0.4089 (3)	−0.0114 (5)
C19	0.8622 (2)	0.3258 (2)	0.0257 (5)
C20	0.7925 (3)	0.3937 (3)	0.5352 (6)
O21	0.9528 (1)	0.4081 (2)	0.1089 (3)
O22	0.9604 (2)	0.5075 (2)	0.8481 (3)
Molecule B			
C1	0.9006 (2)	0.1612 (2)	0.2418 (4)
C2	0.8955 (2)	0.1647 (2)	0.1018 (4)
C3	0.9137 (2)	0.1071 (2)	0.0506 (4)
C4	0.8797 (2)	0.0525 (2)	0.0763 (4)
C5	0.8804 (2)	0.0505 (2)	0.2185 (4)
C6	0.8474 (2)	−0.0037 (2)	0.2533 (5)
C7	0.8612 (3)	−0.0119 (2)	0.3945 (5)
C8	0.8517 (2)	0.0456 (2)	0.4587 (4)
C9	0.8833 (2)	0.0994 (2)	0.4244 (4)
C10	0.8655 (2)	0.1090 (2)	0.2794 (4)
C11	0.8804 (2)	0.1569 (2)	0.5012 (4)
C12	0.9182 (2)	0.1535 (2)	0.6351 (4)
C13	0.9207 (2)	0.2117 (2)	0.7097 (4)
C14	0.9490 (5)	0.2598 (4)	0.6508 (6)
C15	0.9694 (6)	0.3025 (5)	0.6560 (9)
C16	0.8639 (3)	0.2296 (4)	0.7260 (6)
C17	0.8014 (2)	0.1266 (2)	0.2417 (4)
C18	0.8195 (2)	0.0565 (3)	−0.0113 (5)
C19	0.9089 (3)	−0.0045 (2)	0.0403 (5)
C20	0.8168 (3)	0.0485 (3)	0.5353 (6)
O21	0.9739 (1)	0.0988 (2)	0.1017 (3)
O22	0.9569 (1)	0.2006 (2)	0.8325 (3)
Molecule C			
C1	0.6023 (2)	0.3102 (2)	0.7272 (4)
C2	0.6084 (2)	0.3171 (2)	0.8671 (4)
C3	0.6055 (2)	0.2564 (2)	0.9294 (4)
C4	0.6512 (2)	0.2131 (2)	0.9075 (4)
C5	0.6479 (2)	0.2083 (2)	0.7655 (4)
C6	0.6913 (2)	0.1638 (2)	0.7348 (5)
C7	0.6761 (2)	0.1506 (2)	0.5944 (5)
C8	0.6707 (2)	0.2076 (2)	0.5185 (4)
C9	0.6295 (2)	0.2540 (2)	0.5505 (4)
C10	0.6477 (2)	0.2690 (2)	0.6938 (4)
C11	0.6197 (2)	0.3089 (2)	0.4646 (4)
C12	0.5814 (2)	0.2958 (2)	0.3334 (4)
C13	0.5722 (2)	0.3487 (2)	0.2442 (4)
C14	0.5387 (3)	0.3978 (3)	0.2867 (5)
C15	0.5512 (4)	0.4533 (3)	−0.6966 (7)
C16	0.6283 (2)	0.3693 (3)	0.2169 (5)
C17	0.7049 (2)	0.3026 (2)	0.7213 (4)
C18	0.6398 (2)	0.1501 (2)	0.9569 (5)
C19	0.7098 (2)	0.2337 (2)	0.9901 (4)
C20	0.7009 (2)	0.2152 (3)	0.4346 (5)
O21	0.5494 (1)	0.2317 (2)	0.8799 (3)
O22	0.5368 (1)	0.3253 (2)	0.1284 (3)
OW1	0.5000	0.8030 (2)	0.0000
OW2	0.5000	0.1321 (3)	0.0000

(3α-acetoxyisocupressic acid).

Structural differences between these compounds were also investigated by ^{13}C-NMR spectra. The tentative assingments of ^{13}C-NMR signals are shown in Table II.

Biological Activities Inhibition of platelet aggregation was tested using platelet rich plasma from rabbits. The inhibitory effects of the isolated compounds on PAF-induced platelet aggregation are shown compared with that of CV-3988[8] in Table III. Compounds **2**, **3**, and **5** exhibited activity. Compound **2** did not inhibit the platelet aggregation induced by AA, U-46619, collagen, or adenosine diphosphate (ADP). Oral administration of **2** did not inhibit platelet aggregation *in vivo* (10 mg/kg) and did not inhibit PAF-induced hypotension (30 mg/kg). Many PAF antagonists of plant origin, such as kadsurenone from *Piper futokadsura*[9] and ginkgolides from *Ginkgo biloba*,[10] have been reported. Compound **2** seems to have similar potential as a PAF antagonist.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Ultraviolet (UV) spectra were recorded on a Hitachi EPS-3T spectrophotometer and IR spectra were recorded on a JASCO A-702 infrared spectrometer. The 200 MHz ^{1}H- and 50.3 MHz ^{13}C-NMR spectra were recorded using a Varian XL-200 or Varian VXR-200 spectrometer. The 400 MHz ^{1}H-NMR spectra were determined on a Varian XL-400 spectrometer. Chemical shifts were expressed as δ (ppm downfield from the internal tetramethylsilane signal). MS were recorded using a Hitachi M-68 mass spectrometer. High resolution liquid secondary ion MS (HR-SIMS) were recorded using a Hitachi M-90 mass spectrometer. CPC was carried out using a model CPC-LLN chromatograph (Sanki Engineering Co.). High-performance liquid chromtography (HPLC) was performed using a Knauer type 64 HPLC pump equipped with a UV detector UVIDEC 100-V (Japan Spectroscopic Co.) and monitoring the UV absorption at 210 nm. Preparative HPLC was carried out on an ODS column (Capcell Pak C18 SG-120, 20 × 250 mm, Shiseido Co.) using 80% or 90% aq. MeOH as the mobile phase (3 ml/min).

X-Ray Structural Analysis of 2 Hydrate Crystal Data: $C_{20}H_{34}O_2 \cdot 1/3H_2O$; $M_r = 312.5$; monoclinic; $C2$; $a = 24.096(3)$, $b = 22.119(2)$, $c = 11.043(1)$ Å; $\beta = 104.12(1)°$; $V = 5708(1)$ Å^3; $Z = 12$; $D_C = 1.091$ g·cm^{-3}; $F(000) = 2080$.

TABLE V. Bond Distances (Å) of **2** with Their e.s.d.'s in Parentheses

Bond	Molecule A	Molecule B	Molecule C
C1–C2	1.509 (7)	1.523 (7)	1.523 (7)
C1–C10	1.535 (7)	1.547 (7)	1.536 (7)
C2–C3	1.515 (7)	1.502 (7)	1.518 (7)
C3–C4	1.530 (7)	1.524 (7)	1.523 (7)
C3–O21	1.448 (7)	1.434 (7)	1.437 (7)
C4–C5	1.540 (7)	1.567 (7)	1.554 (7)
C4–C18	1.543 (8)	1.537 (8)	1.545 (7)
C4–C19	1.539 (7)	1.542 (9)	1.551 (7)
C5–C6	1.521 (7)	1.538 (7)	1.533 (7)
C5–C10	1.565 (7)	1.541 (7)	1.558 (7)
C6–C7	1.527 (8)	1.524 (9)	1.532 (8)
C7–C8	1.490 (8)	1.501 (9)	1.502 (7)
C8–C9	1.510 (7)	1.510 (7)	1.528 (7)
C8–C20	1.324 (9)	1.332 (9)	1.321 (8)
C9–C10	1.588 (7)	1.568 (7)	1.571 (7)
C9–C11	1.522 (7)	1.540 (7)	1.523 (7)
C10–C17	1.524 (7)	1.548 (7)	1.530 (7)
C11–C12	1.542 (7)	1.538 (7)	1.544 (7)
C12–C13	1.527 (7)	1.522 (7)	1.511 (7)
C13–C14	1.538 (9)	1.495 (13)	1.495 (9)
C13–C16	1.494 (10)	1.477 (10)	1.525 (8)
C13–O22	1.432 (7)	1.443 (7)	1.449 (7)
C14–C15	1.222 (12)	1.060 (19)	1.267 (12)

Colorless plate crystals were grown from *n*-hexane–benzene. The diffraction intensities were collected from a single crystal with dimensions $0.2 \times 0.5 \times 0.02$ mm on a Rigaku AFC-5R four-circle diffractometer using graphite-monochromated CuK_α radiation. A total of 5465 unique reflections were measured within the θ range of 130°, of which 3500 with $F \geq 3\sigma$ (F_o) were considered as observed. The structure was solved by a direct method using MULTAN 84[11] and refined by the block-diagonal least-squares method. In the final refinement, anisotropic thermal parameters were used for non-hydrogen atoms. The final R value was 0.057. The final atomic coordinates and bond distances are given in Tables IV and V, respectively.

Platelet Aggregation Platelet aggregation was examined by the method of Born[12] using a Type 61 Auto-ram aggregometer (Rika-Denki Co., Ltd. Tokyo).[13]

Extraction and Isolation Shug Chher (80 g) was extracted with MeOH and the extract concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ phase was further fractionated into *n*-hexane (fraction A, 2.15 g) and 90% MeOH (fraction B, 6.39 g) fractions. Fraction B (4.67 g) was separated by CPC (CH_2Cl_2–*n*-hexane–MeOH–H_2O, 40 : 10 : 34 : 16, descending mode) to give three fractions B-1 (587 mg), B-2 (2226 mg), and B-3 (1642 mg). Chromatography of fraction B-2 on silica gel (benzene–AcOEt, 4 : 1) gave five fractions (B-4 through B-8). Repeated chromatography on silica gel and reversed-phase HPLC of fractions B-5 and B-6 afforded compounds **2** (188 mg), **4** (211 mg), **5** (40 mg), **6** (6 mg), **7**(6 mg), and **8** (57 mg). Compounds **1** (7 mg) and **3** (9 mg) were similarly obtained from fractions B-3 and B-4.

3α-Hydroxymanool (2) Colorless needles, mp 73—74 °C. $[\alpha]_D$ +9.2° (c=0.40, $CHCl_3$). EIMS m/z: 306 (M^+), 288, 273, 255, 202, 175, 152, 135, 93. HR SIMS m/z: Calcd for $C_{20}H_{34}O_2$+Na: 329.2455. Found: 329.2485 $(M+Na)^+$. IR ν_{max}^{KBr} cm^{-1}: 3400 (br), 2935, 1640, 1410, 1382, 987, 923, 884.

3α,15-Dihydroxy-labda-8(17),13*E*-diene (5) Colorless oil. $[\alpha]_D$ +13.5° (c=0.53, $CHCl_3$). EIMS m/z: 306 (M^+), 288, 273, 255, 202, 175, 152, 135, 107. HR SIMS m/z: Calcd for $C_{20}H_{34}O_2$+Na: 329.2455. Found: 329.2457 $(M+Na)^+$. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3420 (br), 1640, 1445, 1390, 990, 895.

3α-Hydroxy-labda-8(17),13*E*-dien-15-oic Acid (6) Colorless oil. $[\alpha]_D$ +23.5° (c=0.52, $CHCl_3$). HR SIMS m/z: Calcd for $C_{20}H_{32}O_3$+Na: 343.2248. Found: 343.2253 $(M+Na)^+$. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—2500, 1685, 1636, 1438, 1383, 1062, 985, 890.

3α-Hydroxy-labda-8(17),12*E*,14-trien-19-oic Acid (7) Colorless needles, mp 163—167 °C. $[\alpha]_D$ +26.6° (c=0.33, $CHCl_3$). HR SIMS m/z: Calcd for $C_{20}H_{30}O_3$+Na: 341.2091. Found: 341.2101 $(M+Na)^+$.

3α-Acetoxyisocupressic Acid (8) Colorless oil or powder. $[\alpha]_D$ +3.6° (c=0.50, $CHCl_3$). EIMS m/z: 378 (M^+), 360, 345, 300, 285, 220, 187, 121, 81, 43. HR SIMS m/z: Calcd for $C_{22}H_{34}O_5$+Na: 401.2302. Found: 401.2310 $(M+Na)^+$. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—2400, 1725, 1450, 1380, 1035, 985, 895.

Acknowledgments We would like to thank Dr. Dhar, Regional Research Laboratory, India, and Prof. M. Shimizu, Toyama Medical and Pharmaceutical University for the identification of our compounds. We express our grateful acknowledgement to Drs. M. Narisada and S. Uyeo of these Laboratories for his valuable advice and encouragement during this work. We are also grateful to Drs. Y. Nakagawa, Y. Ikenishi, Y. Terui, and their collaborators for the determination of the MS and NMR spectra and for their valuable suggestions.

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