Fern Constituents: Triterpenoids Isolated from Rhizomes of *Pyrrosia lingua*. I

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Five new hopane derivatives, *viz.* 22,28-epoxyhopane (1), 22,28-epoxyhopan-30-ol (2), hopane-22,30-diol (3), hop-22(29)-en-30-ol (4) and hop-22(29)-en-28-ol (5), were isolated along with other known triterpenoids from the rhizomes of *Pyrrosia lingua*. Their structures were elucidated by detailed two dimensional-NMR analysis.

Key words fern; *Pyrrosia lingua*; Polypodiaceae; triterpenoid; hopane

In the course of chemotaxonomic study of Polypodiaceous ferns, we have reported many triterpenoids from various species belonging to the genera, *viz. Polypodium*,[1] *Polypodiodes*,[2] *Lemmaphyllum*,[3] *Colysis*[4] and *Microsorium*.[5] During the study, we found that although various classes of triterpenoid constituents are elaborated by fern species, some are peculiar to a particular genus and/or species.

The whole fern, *Pyrrosia lingua* L. (Polypodiaceae), has been used as a diuretic in folk medicine.[6] So far, only hop-22(29)-ene has been reported from this fern as a triterpenoid component.[7] We became interested in the triterpenoid constituents of this species because of the morphological differences from other species of Polypodiaceous ferns, and during our investigation, we isolated five new hopane derivatives, *viz.* 22,28-epoxyhopane (**1**), 22,28-epoxyhopan-30-ol (**2**), hopan-22,30-diol (**3**), hop-22(29)-en-30-ol (**4**), and hop-22(29)-en-28-ol (**5**), along with other known triterpenoids from the hexane extract of the fresh rhizomes of the fern. We report here the isolation and structure elucidation of **1**—**5**.

Results and Discussion

All five new triterpenoids (**1**—**5**) were isolated from the hexane extract of fresh rhizomes on repeated column chromatography over silica gel followed by preparative HPLC. Their molecular formulae, deduced from the high-resolution mass spectra, along with their physical constants and yields are summarized in Table 1. The low-resolution mass spectra of all five compounds showed an intense peak at *m/z* 191[9] (base peak in the spectra of all compounds except **2**). Moreover, the ^{1}H chemical shifts of H_3-23 to H_3-26 (Table 2) and the ^{13}C chemical shifts of C-1 to C-11 and C-23 to C-27 (Table 3) of **1**—**5** were found to be very close to those of hop-22(29)-ene (**6**).[8] These observations clearly suggested that all these triterpenoids possess the same A, B and C ring system and that no oxygen function is present in these rings.

The nature and location of the oxygen substitution in the D/E ring system of **1**—**5** were examined. The molecular formula of **1** showed the presence of one oxygen function. The IR spectrum showed no OH or C=O group in the molecule, and the ^{13}C-NMR spectrum showed no olefinic carbon signal. The ^{1}H-NMR spectrum (Table 2) displayed a pair of mutually coupled one-proton doublets at δ 3.160 and 3.993 with J=11.4 Hz. The marked difference in the chemical shifts of the two protons indicated the presence of a $-CH_2-O-$ grouping as a part of a cyclic ether. This was substantiated by the two down-field signals at δ 65.43 and 74.66 in the ^{13}C-NMR spectrum (Table 3) due to methylene and quaternary carbons, respectively, attached to oxygen. However, the skeleton of the compound could not be convincingly established from one dimensional (1D) NMR or mass spectral evidence. Detailed analysis of the heteronuclear multiple bond correlation (HMBC) spectrum of **1** (Table 4) showed the presence of two partial structures **A** and **B** (Fig. 1) in the molecule. While the partial structure **A** could form the A/B/C ring system of the molecule, **B** clearly constituted ring E of a hopane triterpenoid with an ether linkage between C-22 and C-28 (*cf.* **1a** in Fig. 2). Though no connectivity between C-13 and C-18 could be established from the HMBC spectrum, the other connectivities among the carbons shown by broken lines in Fig. 2 could be definitely established from the ^{1}H–^{1}H correlation spectroscopy (^{1}H–^{1}H COSY) spectrum. Based on the above observations, the 22,28-epoxyhopane structure was assigned for compound **1**. Finally, the relative stereochemistry at most of the chiral centers was ascertained from the nuclear Overhauser effect (NOE) interactions (Fig. 3) observed in the nuclear Overhauser enhancement spectroscopy (NOESY) spectrum of the compound.

Compound **2** contains two oxygens in the molecule. A comparison of its ^{13}C-NMR spectrum with that of **1** revealed that the spectra were different only with respect to the signals for C-21, C-22, C-29 and C-30. It is clear from the chemical shifts (Table 3) that one of the methyl groups on C-22 is transformed into a CH_2OH group (δ 69.95), which affected the chemical shifts of the α, β and γ carbons. Its NOESY spectrum showed correlations of the hydroxymethylene protons (H_2-30) with H_α-20, and the H_3-29 methyl protons with H_2-28 and H_α-16 (Fig. 3). On the basis of this evidence, **2** was concluded to be 22,28-epoxyhopan-30-ol (22*R*).

The molecular formula of compound **3** showed the presence of two oxygen functions in the molecule. Its IR spectrum indicated the presence of hydroxyl group(s). The electron impact (EI)-MS of the compound exhibited medium intensity peaks due to loss of CH_2OH and $C_3H_4O_2$ radicals from the molecular ion in the primary fragmentation process, demonstrating that both the oxygen functions are located in the side chain of the

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molecule. In agreement with the above observations, the ^{13}C-NMR spectrum also displayed signals due to a CH_2OH carbon at δ 69.28 and a hydroxylated quaternary carbon at δ 75.59, indicating that the two OH groups must be attached to C-22 and either C-29 or C-30. The close similarity of the ^{13}C chemical shifts of **3** with those of **6**, except for those of the side chain carbons, indicated that **3** also possesses a hopane (21βH) skeleton with a $-C(OH)(CH_2OH)-CH_3$ side chain. This contention was fully supported by the HMBC spectrum of the compound (Fig. 2). That the primary OH group is located at C-30 rather than C-29 was determined as follows: OsO_4 oxidation of hop-22(29)-ene (**6**) gave two isomeric diols, *viz.* hopane-22,30-diol (**7**) and hopane-22,29-diol (**8**), which were separated through their monoacetates (**9** and **10**). The ^{1}H-NMR spectra of **9** and **10** exhibited signals due to the terminal methyl protons at δ 1.227 and 1.159, respectively. On the basis of the reported down-field chemical shift of H_3-29 of hopan-30-yl acetate (dryocrassyl acetate)[8] at δ 1.013 compared to that of H_3-30 of hopan-29-yl acetate (neriiforliyl acetate)[8] (δ 0.897), it can be presumed that **9** and **10** have the primary hydroxy group at C-30 and C-29, respectively. Since the monoacetate of **3** was found to be identical with **9**, compound **3** can be represented as hopane-22,30-diol. It should be mentioned here that the NOESY spectra of **9** and **10** were inconclusive for determination of the location of the primary OH group, since both the spectra showed NOE interactions between the terminal methyl proton and H_3-28, indicating the predominance of a side chain conformer with the 22-OH group away from C-28 in both the compounds (Fig. 4).

The EI-MS of compound **4** exhibited a low-intensity peak due to loss of 31 mass units from the molecular ion, indicating the presence of a CH_2OH group in the molecule. Its ^{13}C-NMR spectrum showed the CH_2OH carbon signal at δ 67.37 and two olefinic carbon signals at δ 108.96 (CH_2) and 152.36 (quaternary carbon), indicating that a side chain such as $-C(CH_2OH)=CH_2$ might be present in the molecule. A comparison of the ^{13}C-NMR chemical shifts of **4** with those of hop-22(29)-ene (**6**) revealed that the spectra were different only with respect to the signals for C-21, C-22, C-29, and C-30 (Table 3). The shielding of C-21 and C-29 by *ca.* 4 and *ca.* 1 ppm and the down-field shift of C-22 and C-30 by *ca.* 4 and *ca.* 42 ppm, respectively, clearly indicated that **4** is a 30-hydroxy derivative of **6**. The HMBC data were also found to be in complete agreement with the proposed structure for **4** (Fig. 2). Based on the above evidence, the hop-22(29)-en-30-ol structure was assigned for **4**.

The ^{13}C-NMR spectrum (Table 3) of compound **5** displayed the signals of a CH_2OH carbon (δ 62.07) and carbons of a $>C=CH_2$ group (δ 150.08 and 109.33). A comparison of the ^{13}C-NMR spectrum of **5** with that of

Table 1. Physical Data and Yields for **1**—**5**

	MF	HR-MS	mp (°C)	$[\alpha]_D^\circ$	Yield mg (%)
1	$C_{30}H_{50}O$	426.3869	214—216	+82.9	5.8 (0.0005)
2	$C_{30}H_{50}O_2$	442.3745	255—256	+70.9	4.7 (0.0004)
3	$C_{30}H_{52}O_2$	444.3976	284—287	+45.1	9.2 (0.0008)
4	$C_{30}H_{50}O$	426.3875	224—226	+59.2	6.4 (0.0006)
5	$C_{30}H_{50}O$	426.3842	170—172	+56.5	11.0 (0.0010)

Table 2. ^{1}H-NMR Spectral Data (500 MHz, $CDCl_3$, δ)

Protons	**1**	**2**	**3**	**4**	**5**	**6**
H_3-23	0.846	0.849	0.845	0.844	0.848	0.844
H_3-24	0.790	0.792	0.790	0.791	0.791	0.791
H_3-25	0.815	0.818	0.812	0.815	0.814	0.814
H_3-26	0.972	0.974	0.953	0.959	0.973	0.960
H_3-27	0.972	0.985	0.949	0.941	1.062	0.943
H_3-28			0.750	0.740	3.709	0.721
H_2-28	3.160 (d, 11.4)	3.196 (d, 11.3)				
	3.993 (d, 11.4)	4.024 (d, 11.3)				
H_3-29	1.294	1.330	1.225			
H_2-29				5.024	4.832	4.781
				5.144	4.873	4.781
H_3-30	1.114				1.774	1.751
H_2-30		3.290 (d, 11.0)	3.401 (d, 10.7)	4.015 (d, 14.0)		
		3.559 (d, 11.0)	3.526 (d, 10.7)	4.113 (d, 14.0)		

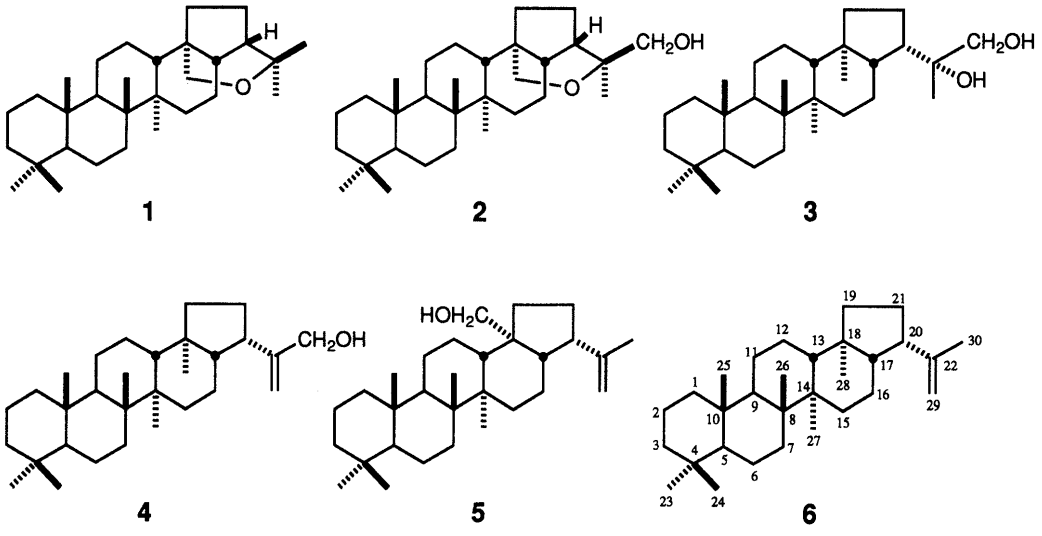
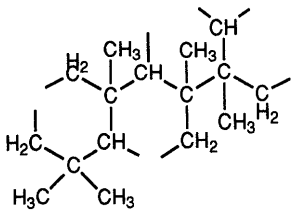


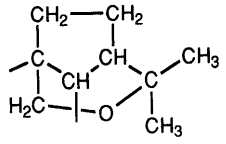
Chart 1

Table 3. ^{13}C-NMR Spectral Data (125.65 MHz, $CDCl_3$, δ)

C	1	2	3	4	5	6
1	40.32	40.32	40.31	40.32	40.29	40.31
2	18.73	18.71	18.69	18.70	18.67	18.70
3	42.08	42.07	42.10	42.11	42.08	42.10
4	33.26	33.26	33.25	33.26	33.26	33.25
5	56.16	56.16	56.10	56.12	56.08	56.10
6	18.67	18.67	18.69	18.70	18.70	18.70
7	33.49	33.46	33.23	33.26	33.46	33.25
8	41.93	41.94	41.90	41.91	42.08	41.90
9	50.55	50.52	50.33	50.37	50.55	50.37
10	37.43	37.43	37.39	37.40	37.39	37.39
11	21.05	21.03	20.89	20.89	21.44	20.91
12	23.53	23.51	24.16	23.98	25.73	23.99
13	47.80	47.85	49.76	49.38	50.42	49.42
14	41.88	41.89	41.80	42.03	42.08	41.07
15	32.67	32.64	34.28	33.51	33.82	33.61
16	23.37	23.30	22.18	21.57	21.65	21.67
17	49.56	49.39	53.58	54.67	54.75	54.88
18	42.95	43.51	44.09	44.91	49.24	44.80
19	35.91	35.95	41.23	41.98	36.36	41.90
20	26.36	25.38	25.32	27.95	27.59	27.39
21	47.70	44.57	47.03	41.91	46.43	46.47
22	74.66	76.05	75.59	152.36	150.08	148.78
23	33.39	33.38	33.41	33.41	33.40	33.41
24	21.57	21.57	21.59	21.60	21.60	21.60
25	15.96	15.96	15.83	15.85	15.91	15.84
26	16.56	16.55	16.70	16.70	16.83	16.70
27	17.10	17.04	16.99	16.75	16.68	16.75
28	65.43	65.64	15.83	16.06	62.07	16.07
29	26.00	21.10	24.12	108.96	109.33	110.06
30	30.07	69.95	69.28	67.37	25.29	25.02



A



B

Fig. 1

Table 4. C–H Long-Range Correlations of **1**—**5** by HMBC in $CDCl_3$

	^{1}H signals						
1	0.846 (H_3-23)	C-3	C-4	C-5	C-24		
	0.790 (H_3-24)	C-3	C-4	C-5	C-23		
	0.815 (H_3-25)	C-1	C-5	C-9	C-10		
	0.972 (H_3-26)	C-7	C-8	C-9	C-14		
	0.972 (H_3-27)	C-8	C-13	C-14	C-15		
	3.160 (H_a-28)	C-17	C-18	C-19	C-22		
	3.993 (H_b-28)	C-17	C-19				
	1.294 (H_3-29)	C-21	C-22	C-30			
	1.114 (H_3-30)	C-21	C-22	C-29			
2	0.849 (H_3-23)	C-3	C-4	C-5	C-24		
	0.792 (H_3-24)	C-3	C-4	C-5	C-23		
	0.818 (H_3-25)	C-1	C-5	C-9	C-10		
	0.974 (H_3-26)	C-7	C-8	C-9	C-14		
	0.985 (H_3-27)	C-8	C-13	C-14	C-15		
	3.196 (H_a-28)	C-17	C-18	C-19	C-22		
	4.024 (H_b-28)	C-17	C-19				
	1.330 (H_3-29)	C-21	C-22	C-30			
	3.559 (H_a-30)	C-22					
3	0.845 (H_3-23)	C-3	C-4	C-5	C-24		
	0.790 (H_3-24)	C-3	C-4	C-5	C-23		
	0.812 (H_3-25)	C-1	C-5	C-9	C-10		
	0.953 (H_3-26)	C-7	C-8	C-9	C-14		
	0.949 (H_3-27)	C-8	C-13	C-14	C-15		
	0.750 (H_3-28)	C-13	C-17	C-18	C-19		
	1.125 (H_3-29)	C-21	C-22	C-30			
	2.328 (H-21)	C-20	C-18	C-17	C-22	C-30	
4	0.844 (H_3-23)	C-3	C-4	C-5	C-24		
	0.791 (H_3-24)	C-3	C-4	C-5	C-23		
	0.815 (H_3-25)	C-1	C-5	C-9	C-10		
	0.959 (H_3-26)	C-7	C-8	C-9	C-14		
	0.941 (H_3-27)	C-8	C-13	C-14	C-15		
	0.740 (H_3-28)	C-13	C-17	C-18	C-19		
	5.144 (H_a-29)	C-21	C-30				
	4.113 (H_a-30)	C-21	C-22	C-29			
	2.734 (H-21)	C-17	C-18	C-20	C-22	C-29	C-30
5	0.848 (H_3-23)	C-3	C-4	C-5	C-24		
	0.791 (H_3-24)	C-3	C-4	C-5	C-23		
	0.814 (H_3-25)	C-1	C-5	C-9	C-10		
	0.973 (H_3-26)	C-7	C-8	C-9	C-14		
	1.062 (H_3-27)	C-8	C-13	C-14	C-15		
	3.709 (H_a-28)	C-13	C-18				
	3.709 (H_b-28)	C-13	C-18				
	4.832 (H_a-29)	C-21	C-22	C-30			
	1.774 (H_3-30)	C-21	C-22	C-29			
	2.139 (H-19)	C-17	C-18	C-21	C-28		
	2.736 (H-21)	C-17	C-18	C-22	C-29	C-30	

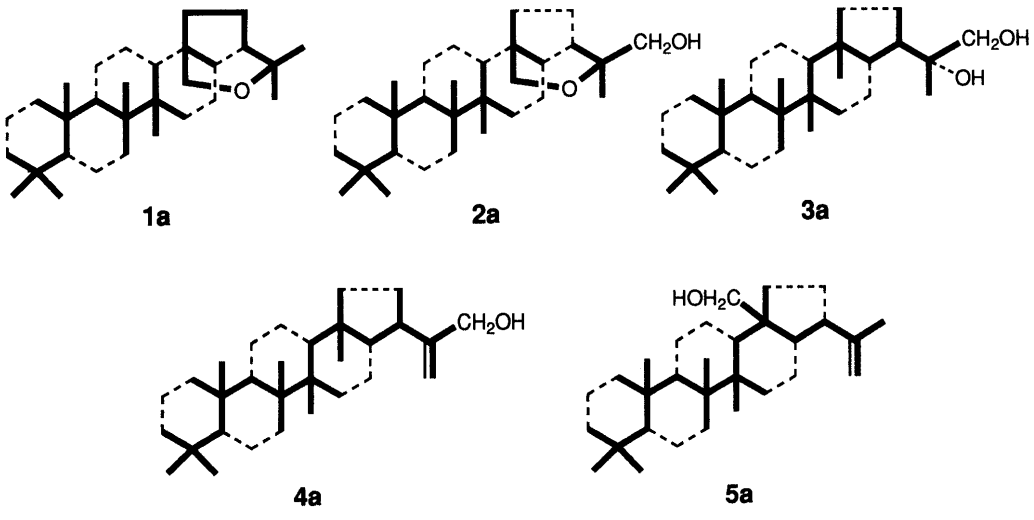
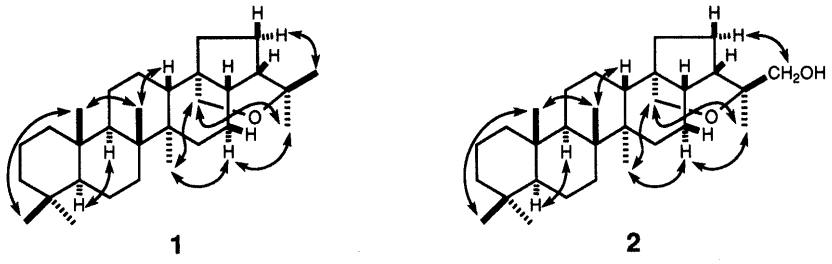
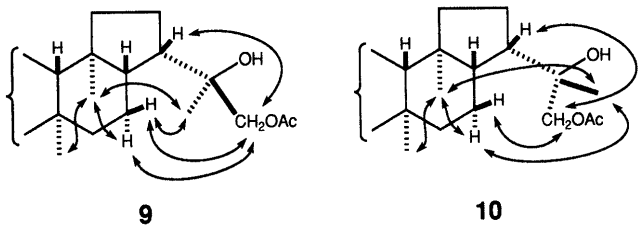


Fig. 2. Partial Structures (of **1**—**5**) Shown by Heavy Lines in **1a**—**5a**, Derived from HMBC Data



1 2

Fig. 3



9 10

Fig. 4

6 showed that the C-18 signal was deshielded by *ca.* 5 ppm and that of C-19 was moved up-field by *ca.* 5 ppm, clearly indicating that C-28 of **6** is hydroxylated in **5**. This was confirmed by the HMBC spectrum of **5** (Fig. 2). Compound **5** is therefore hop-22(29)-en-28-ol.

It is interesting that all the new compounds, in contrast to the triterpenoids isolated from other Polypodiaceous ferns, are hopane triterpenoids in which C-22, C-28 and C-30 are oxygenated. Further investigations on the triterpenoids of this species are in progress.

Experimental

General Procedures Melting points were measured on a Yanagimoto micro apparatus without correction. Measurement of optical rotation was carried out on a JASCO DIP-140 in $CHCl_3$ solution ($c=0.1$—0.5) at 23 °C. ^1H (500 MHz)- and ^{13}C (125.65 MHz)-NMR spectra were recorded on a JEOL α-500 spectrometer using tetramethylsilane as an internal standard. The chemical shifts are expressed on the δ scale. The conditions used are given in reference 10. EI-MS and high resolution (HR)-MS were measured at 30 eV (direct inlet) with a JEOL JMS D300 or a JEOL JMS HX 110 and the relative intensities of peaks are reported with reference to the most intense peak higher than *m/z* 100. TLC was carried out on pre-coated Silica gel 60 (Merck 5721) with *n*-hexane–EtOAc as the developing phase. Detection was carried out by spraying with concentrated H_2SO_4 followed by heating. HPLC was performed on a JASCO PU-980 equipped with a JASCO RI-930 detector. The following column and solvents were used for elution: Senshu PAK, ODS-3251-D (25 cm × 8 mm i.d., 5 μm) with $CHCl_3$–MeOH or $CHCl_3$–CH_3CN.

Plant Materials The rhizomes of *Pyrrosia lingua* were collected in December, 1991 at Matsuzaki in Shizuoka prefecture. A voucher specimen (#911202) has been deposited in the Herbarium of Shôwa College of Pharmaceutical Sciences, Tokyo.

Extraction and Isolation The fresh rhizomes of *Pyrrosia lingua* (2.03 kg) were extracted with hexane to give the extract (22 g) and water (930 ml), which was separated by silica gel column chromatography (CC) into the following fractions: fr. 1—3 [eluted with *n*-hexane], fr. 4—9 [*n*-hexane–benzene (8 : 2)], fr. 10—17 [*n*-hexane–benzene (1 : 1)], fr. 18—26 [benzene], fr. 27—33 [benzene–ether (1 : 1)], fr. 34 [ether], fr. 35 [MeOH]. Each fraction was further purified by repeated chromatography (silica gel CC, alumina CC and HPLC) and recrystallization to furnish **1**—**5** in pure form.

22,28-Epoxyhopane (1) From fr. 17. IR ν_{max}^{KBr} cm^{-1}: 1060. EI-MS (rel. int.) *m/z*: 426 (M^+, 40), 411 (37), 394 (58), 191 (100), 189 (27), 147 (69).

22,28-Epoxyhopan-30-ol (2) From fr. 30. IR ν_{max}^{KBr} cm^{-1}: 3490, 3360, 1050. EI-MS (rel. int.) *m/z* : 442 (M^+, 2), 411 (100), 191 (20).

Hopane-22,30-diol (3) From fr. 32 and 33. IR ν_{max}^{KBr} cm^{-1}: 3400, 1042. EI-MS (rel. int.) *m/z* : 444 (M^+, 3), 426 (16), 413 (12), 369 (16), 223 (29), 205 (80), 191 (100), 189 (27), 147 (69).

Hop-22(29)-en-30-ol (4) From fr. 21. IR ν_{max}^{KBr} cm^{-1}: 3440, 1640, 1030, 900. EI-MS (rel. int.) *m/z* : 426 (M^+, 16), 411 (11), 408 (5), 395 ($M^+ - CH_2OH$, 5) 299 (11), 205 (54), 191 (100), 187 (42).

Hop-22(29)-en-28-ol (5) From fr. 16 and 17. EI-MS (rel. int.) *m/z*: 426 (M^+, 23), 411 (15), 408 (7), 395 (88), 353 (12), 203 (92), 191 (100), 189 (65).

Hop-22(29)-ene (6) Fr. 3 was recrystallized repeatedly from acetone to give **6** (2.28 g), mp 214—217 °C. IR ν_{max}^{KBr} cm^{-1}: 3070, 1642, 886. Identical (IR, MS and ^1H-NMR) with an authentic sample.

OsO_4-Oxidation of 6 A solution of **6** (230 mg) in anhydrous ether (30 ml) and pyridine (1 ml) was treated with OsO_4 at room temperature for 30 h. The reaction product was poured into Na_2SO_3–EtOH solution and the solution was refluxed for 4 h. This reaction gave a mixture (1 : 1) of two isomeric diols (150 mg). The product was separated by HPLC with MeOH to give **7** and **8**.

Acetylation of 7 and 8 Compounds **7** and **8** were treated with pyridine and Ac_2O in the usual manner to give the monoacetates **9** and **10**.

Hopane-22,30-diol Monoacetate (9) ^1H-NMR δ: 0.844 (H_3-23), 0.790 (H_3-24), 0.812 (H_3-25), 0.953 (H_3-26), 0.953 (H_3-27), 0.763 (H_3-28), 1.227 (H_3-29), 3.998 (s, H_2-30), 2.105 ($COOCH_3$). ^{13}C-NMR δ: 40.31 (C-1), 18.70 (C-2), 42.11 (C-3), 33.23 (C-4), 56.10 (C-5), 18.70 (C-6), 33.26 (C-7), 41.91 (C-8), 50.33 (C-9), 37.40 (C-10), 20.90 (C-11), 24.16 (C-12), 49.79 (C-13), 41.81 (C-14), 34.31 (C-15), 22.10 (C-16), 53.66 (C-17), 44.09 (C-18), 41.21 (C-19), 25.46 (C-20), 47.21 (C-21), 74.24 (C-22), 33.41 (C-23), 21.60 (C-24), 15.83 (C-25), 16.71 (C-26), 16.91 (C-27), 15.79 (C-28), 24.87 (C-29), 70.81 (C-30), 171.23 (–$\underline{C}OCH_3$), 20.99 (–CO$\underline{C}H_3$).

Hopane-22,29-diol Monoacetate (10) ^1H-NMR δ: 0.844 (H_3-23), 0.790 (H_3-24), 0.811 (H_3-25), 0.953 (H_3-26), 0.957 (H_3-27), 0.769 (H_3-28), 3.885 (d, $J=11.0$, H_a-29), 4.403 (d, $J=11.0$, H_b-29), 1.159 (H_3-30), 2.101 ($COOCH_3$). ^{13}C-NMR δ: 40.31 (C-1), 18.69 (C-2), 42.10 (C-3), 33.25 (C-4), 56.09 (C-5), 18.69 (C-6), 33.22 (C-7), 41.91 (C-8), 50.32 (C-9), 37.59 (C-10), 20.89 (C-11), 24.18 (C-12), 49.84 (C-13), 41.91 (C-14), 34.38 (C-15), 21.83 (C-16), 53.75 (C-17), 44.08 (C-18), 41.24 (C-19), 25.99 (C-20), 46.34 (C-21), 74.66 (C-22), 33.41 (C-23), 21.59 (C-24), 15.82 (C-25), 16.71 (C-26), 17.06 (C-27), 16.08 (C-28), 71.43 (C-29), 22.90 (C-30), 171.19 (–O$\underline{C}OCH_3$), 20.98 (–OCO$\underline{C}H_3$).

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