Fern Constituents: Six New Triterpenoid Alcohols from *Adiantum capillus-veneris*

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Six new migrated hopane triterpenoid alcohols, *viz*. pteron-14-en-7α-ol (1), fern-9(11)-en-3α-ol (2), fern-7-en-3α-ol (3), adian-5(10)-en-3α-ol (4), adian-5-en-3α-ol (5) and fern-9(11)-en-28-ol (6) were isolated along with many other known triterpenoids from fresh fronds of *Adiantum capillus-veneris*. Their structures were elucidated by detailed two dimensional-NMR analyses and/or chemical correlations.

Key words triterpenoid alcohol; migrated hopane; fern; *Adiantum capillus-veneris*; Adiantaceae

Adiantum capillus-veneris L. (Adiantaceae) is a common fern widely distributed throughout the world. The dried whole plant is used as an antipyretic and diuretic, and also in the treatment of bronchitis in folklore medicine in China.[1] This fern is cultivated as an ornamental plant in Japan and Europe because of its beautiful evergreen frond.

During our chemotaxonomic investigation on *Adiantum* (*A*.) species, we reported many novel triterpenoids from *A. monochlamys*,[2] *A. pedatum*,[3] *A. edgeworthii*[4] and *A. cuneatum*.[5—7] In continuation of these studies, we undertook a detailed chemical investigation on the fresh fronds of *A. capillus-veneris* (collected at Yokohama city), and isolated six new migrated hopane triterpenoid alcohols characterized as pteron-14-en-7α-ol (**1**), fern-9(11)-en-3α-ol (**2**), fern-7-en-3α-ol (**3**), adian-5(10)-en-3α-ol (**4**), adian-5-en-3α-ol (**5**) and fern-9(11)-en-28-ol (**6**) (Chart 1). We report herein the structure elucidation of compounds **1**—**6**.

Results and Discussion

The triterpenoid constituents from the hexane extract of the fresh fronds were purified by various chromatographic techniques (see Experimental) to afford the pure triterpenoids **1**—**23**, whose physical data and yields are summarized in Table 1.

The electron impact high-resolution (EI-HR) MS of compound **1**, obtained as colorless needles, showed its molecular formula to be $C_{30}H_{50}O$ (M^+, *m*/*z* 426.3889, Calcd., 426.3861). Its IR spectrum exhibited the presence of hydroxyl group(s). The low resolution EI-MS of the compound exhibited fragment ion peaks at *m*/*z* 271 (**a**, 95), 257 (**b**, 13), 204 (**c**, 85) and 123 (**d**, 31), diagnostic[8] of the pteron-14-ene skeleton, while the fragment ions at *m*/*z* 302 (**e**) and 207 (**f**) indicated that the OH group must be located in either of the rings A and B of the molecule (Chart 2). The ^{1}H-NMR spectrum of **1** displayed signals due to six tertiary methyls, two secondary methyls, one trisubstituted vinylic methine proton and one equatorial carbinyl proton (Table 2). The ^{13}C chemical shifts (Table 3) of the compound were very close to those of pteron-14-ene,[9] except for those of C-5 to C-9 indicating that **1** must be a pteron-14-ene derivative with an axial hydroxyl group in ring B. The down-field shift of C-6, C-7 and C-8 signals by *ca*. 3.4, 30.0 and 6.2 ppm, and up-field shift of

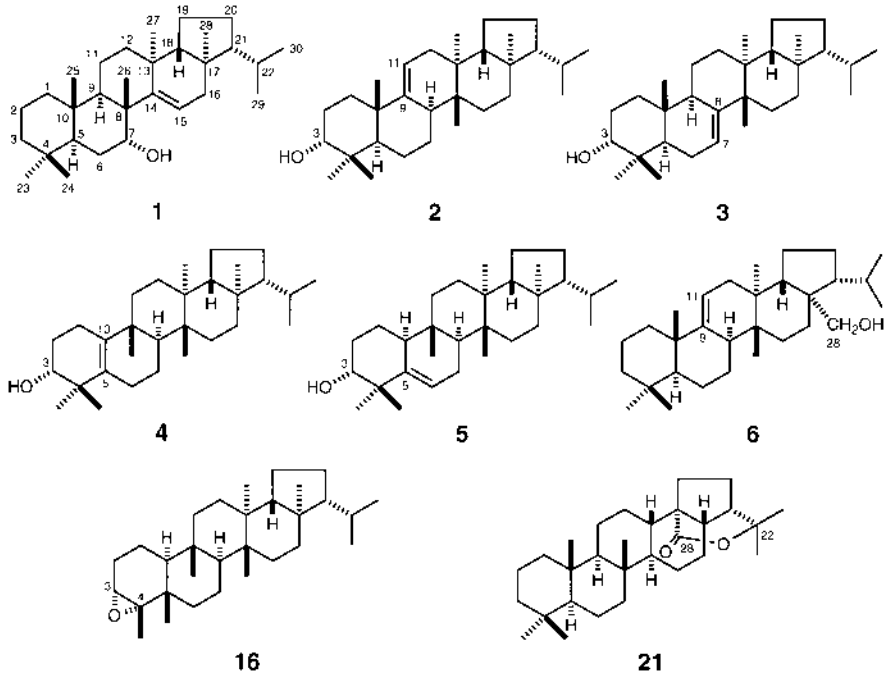

Chart 1

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C-5 and C-9 by *ca*. 9.6 and 6.5 ppm, respectively, suggested that the axial hydroxyl group of **1** must be located at C-7. The heteronuclear multiple bond correlation (HMBC) data also fully corroborated the above observation (Fig. 1). The relative stereochemistry at C-7, C-8, C-10, C-13 and C-17 were established by the nuclear Overhauser effect correlation spectroscopy (NOESY) of the compound. Thus, the spectrum showed nuclear Overhauser effect (NOE) interactions between H_3-25 and H_3-26, H_3-26 and H-7β, and between H_3-27 and H_3-28. Finally, the structure of **1** as pteron-14-en-7α-ol was confirmed by comparison of the NMR data with the synthetic compound.[10] This compound is the first example of a naturally occurring migrated hopane derivative with a Δ^{14} double bond.

Table 1. Triterpenoids Isolated from *Adiantum capillus-veneris*

Compound	mp (°C)	$[\alpha]_D^{23}$ (°)	Yield (%)[a]	Ref.
Pteron-14-en-7α-ol (**1**)	212—214	−16.5	0.0001	
Fern-9(11)-en-3α-ol (**2**)	219—220	−6.0	0.0020	
Fern-7-en-3α-ol (**3**)	239—240	−10.2	0.0004	
Adian-5(10)-en-3α-ol (**4**)	228—230	−35.5	0.0002	
Adian-5-en-3α-ol (**5**)	196—197	+57.3	0.0001	
Fern-9(11)-en-28-ol (**6**)	159.5—161.5	−9.3	0.0005	
Trisnorhopane (**7**)	161—163	+35.5	trace	5
Ferna-7,9(11)-diene (**8**)	202—203	−180.4	0.0049	5
Fern-9(11)-ene (**9**)	171—172	−18.3	0.0092	5
Fern-7-ene (**10**)	212.5—214	−29.0	0.0247	5
Filic-3-ene (**11**)	232—234	+58.0	0.0035	5
Adian-5-ene (**12**)	193.5—195	+51.9	0.0002	2
Neohop-12-ene (**13**)	210—212	+41.6	0.0046	5
Hop-22(29)-ene (**14**)	210—212	—	0.0062	2
17,29-Epoxyhopane (**15**)	263—265	+48.0	0.0002	15
Adiantoxide (**16**)	219—220	+41.6	0.5045	17
Fern-9(11)-en-12-one (**17**)	221—223	−30.3	0.0001	16
Adiantone (**18**)	227—230	+79.9	0.6124	5
Isoadiantone (**19**)	236—238	+3.6	0.0796	5
Isoglaucanone (**20**)	243—245	+140.1	0.0097	5
Hopan-28,22-olide (**21**)	267—277	+37.4	0.0013	14
Hydroxyhopane (**22**)	253—255	+40.5	0.0016	7
Hydroxyadiantone (**23**)	270—275	+50.0	0.0006	5

a) Yield was calculated as follows: yield={compound isolated (g)/[fresh material (g) −separated water (g)]}×100.

Both compounds **2** and **3** were found to possess the same molecular formula from their HR-EIMS (M^+ at *m*/*z* 426.3850 and 426.3990, respectively). Their electron impact mass spectrum (EI-MS) exhibited very similar fragmentation pattern with slight differences in the intensities of the peaks. Their ^{1}H-NMR spectra (Table 2) displayed signals due to six tertiary methyl and two secondary methyl protons, one trisubstituted olefinic proton, and one equatorially oriented hydroxymethine proton. The splitting pattern[9] of the trisubstituted vinylic proton of **2** and **3** suggested that the compounds may have $\Delta^{9(11)}$ and Δ^7 double bond, respectively. This contention was further corroborated by the diagnostic[8] peaks at *m*/*z* 273 (**g**), 259 (**h**) and 247 (**i**) in the EI-MS of both compounds (Chart 2). A detailed comparison of the ^{13}C-NMR data (Table 3) of the two compounds with those of fern-9(11)-ene (**9**) and fern-7-ene (**10**)[9] revealed that **2** and **3** must be a C-3 hydroxylated derivative of **9** and **10** respectively. The carbon signals of C-1 and C-5 were shielded by *ca*. 7—8 ppm and those for C-2 and C-3 were deshielded by *ca*. 6.3 and *ca*. 33.8 ppm compared with those of the hydrocarbons (**9** and **10**), respectively. The assigned structure of **2** was fully supported by the correlations observed in the HMBC (Fig. 1) and NOESY (Fig. 2) spectra. On the basis of the above observations, **2** and **3** were considered to be fern-9(11)-en-3α-ol, and fern-7-en-3α-ol, respectively.

Compound **4** was obtained as colorless needles from acetone and its IR spectrum suggested the presence of hydroxyl group(s) in the molecule. Its molecular formula was deduced to be $C_{30}H_{50}O$ by EI-HRMS (M^+ at *m*/*z* 426.3889, Calcd., 426.3861). The ^{1}H-NMR spectrum of the compound (Table 2) exhibited signals for six tertiary and two secondary methyl groups and an equatorial hydroxymethine proton. Its ^{13}C-

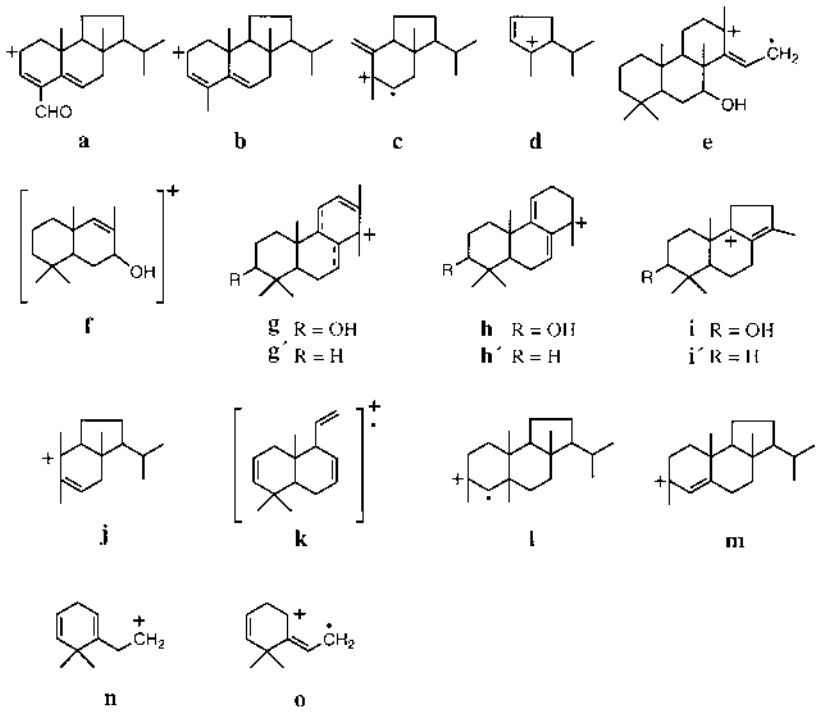

Chart 2

Table 2. ^{1}H-NMR Spectral Data (500 MHz, $CDCl_3$, δ) for Compounds **1**—**6**[a]

	H_3-23	H_3-24	H_3-25	H_3-26	H_3-27	H_3-28/H_2-28	H_3-29	H_3-30	H_β-3/H_β-7	Olefinic protons attached to C [ ]
1	0.881	0.820	0.876	1.045	1.126	0.782	0.903 (d, 6.4)[b]	0.843 (d, 6.4)	3.884 (dd, 3.0, 3.0)	5.462 [15] (dd, 3.7, 3.7)
2	0.938	0.918	1.082	0.735	0.823	0.756	0.890 (d, 6.4)	0.827 (d, 6.4)	3.423 br s	5.320 [11] (ddd, 4.9, 2.4, 2.4)
3	0.933	0.912	0.770	0.995	0.990	0.732	0.901 (d, 6.4)	0.829 (d, 6.4)	3.463 (dd, 3.2, 3.2)	5.365 [7] (ddd, 3.7, 3.1, 3.1)
4	0.989	1.034	0.984	0.913	0.936	0.791	0.890 (d, 6.4)	0.828 (d, 6.4)	3.467 br s	
5	0.957	1.139	0.823	0.995	0.923	0.780	0.888 (d, 6.4)	0.828 (d, 6.4)	3.236 (dd, 11.4, 7.3)	5.635 [6] (ddd, 5.8, 2.1, 2.1)
6	0.851	0.891	1.058	0.759	0.913	3.780 (d, 11.9) 3.907 (d, 11.9)	0.989 (d, 6.4)	0.877 (d, 6.4)	—	5.303 [11] (ddd, 5.2, 2.5, 2.5)

a) Assignments were made by ^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY, NOESY and HMBC spectra. *b*) Figures in parentheses denote the coupling constants in Hz.

Table 3. ^{13}C-NMR Spectral Data[a] (125 MHz, $CDCl_3$, δ) of **1**—**6** and **21**

	1	**2**	**3**	**4**	**5**	**6**	**21**
C-1	39.47	33.79	30.86	18.38	22.81	41.48	40.30
C-2	18.56	25.95	25.41	18.77	30.07	19.54	18.66
C-3	42.00	76.21	76.28	75.49	76.93	42.39	40.05
C-4	32.66	35.93	37.40	38.78	41.53	33.65	33.27
C-5	47.47	37.97	47.59	129.66	144.73	44.84	56.21
C-6	24.16	19.11	24.12	26.42	119.87	19.45	18.68
C-7	73.22	17.95	116.13	25.88	23.84	17.86	33.81
C-8	45.32	39.95	145.45	44.06	44.09	39.86	41.59
C-9	42.30	151.34	44.64	37.94	34.65	151.89	50.73
C-10	37.95	37.69	35.14	137.60	50.69	38.08	37.45
C-11	15.47	115.90	15.93	31.12	34.21	115.62	21.72
C-12	33.38	36.76	32.34	28.80	29.01	36.89	25.48
C-13	36.27	37.69	36.00	38.73	38.63	36.69	49.75
C-14	153.51	36.74	41.56	40.19	39.29	37.91	42.73
C-15	119.95	29.27	30.25	28.82	29.12	29.59	32.61
C-16	43.35	36.19	36.28	35.62	35.43	29.08	25.06
C-17	40.60	42.96	42.88	42.77	42.81	47.54	50.25
C-18	58.75	52.00	54.13	51.71	51.75	52.25	50.46
C-19	20.75	20.14	20.00	19.90	19.92	20.77	24.81
C-20	28.27	28.22	28.22	28.43	28.32	31.28	35.43
C-21	59.41	59.68	59.56	60.07	60.06	59.84	45.69
C-22	30.68	30.78	30.67	30.78	30.78	31.49	81.99
C-23	33.03	27.59	27.65	28.00	22.10	32.79	33.36
C-24	21.53	22.17	21.65	23.15	24.33	21.68	21.61
C-25	15.45	25.00	12.71	23.34	18.01	20.05	16.30
C-26	27.94	15.42	23.99	16.39	15.77	15.53	16.33
C-27	20.01	15.99	21.01	15.52	15.01	15.76	15.83
C-28	16.14	13.99	14.03	16.50	16.08	63.05	176.29
C-29	21.97	22.14	22.10	21.94	21.96	23.01	29.86
C-30	22.90	23.01	22.98	22.90	22.93	23.35	29.29

a) Assignments were made on the basis of DEPT, ^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY (or HSQC) and HMBC spectra.

NMR spectrum (Table 3) showed the presence of a tetrasubstituted double bond. However, its ^{1}H- and ^{13}C-NMR data were not conclusive in structure elucidation of the compound. Detailed analyses of 2D NMR spectra were therefore taken up. The two- and three-bond correlations of the methyl proton signals with those of the neighboring carbons observed in the HMBC spectrum of the compound (Table 4) clearly revealed (Fig. 1) the compound to be 3-hydroxyadian-5(10)-ene. The structure was also supported by mass spectral fragments, *viz*. the ion peaks at *m*/*z* 274 (**l**), 205 (**j**), and 135 (**n**) (Chart 2). Finally, the relative stereochemistry at most of the chiral centers of the compound was established by the NOE interactions observed in its NOESY spectrum (Fig. 2). The structure of **4** was, therefore, represented by adian-5(10)-en-3α-ol.

EI-MS of compound **5** exhibited the dehydrated ion peak

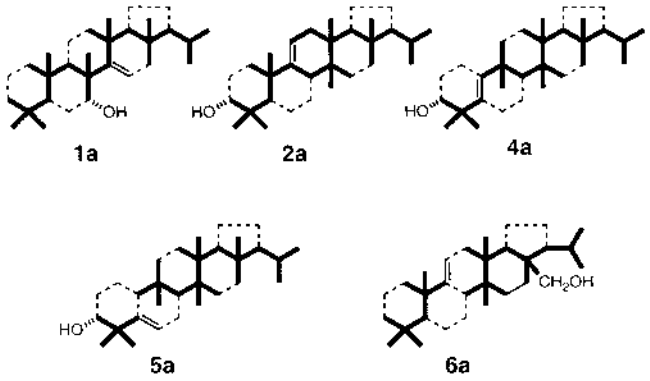

Fig. 1. Partial Structures of **1**, **2**, **4**—**6** Revealed by HMBC (Shown by Heavy Lines)

(*m*/*z* 408, $C_{30}H_{48}$) from the molecule, implying its molecular formula to be $C_{30}H_{50}O$. Its IR spectrum showed the presence of hydroxyl group(s). Its ^{1}H-NMR spectrum displayed signals for six tertiary and two secondary methyl groups, a trisubstituted vinylic proton and an axially oriented hydroxymethine proton (Table 2). The diagnostic[8] intense peaks at *m*/*z* 274 (**l**), 259 (**m**), and 134 (**o**) in its low resolution EIMS suggested that the compound belongs to adian-5-ene skeleton with the hydroxyl group located at A/B ring system. A comparison of its ^{13}C-NMR spectrum (Table 3) with that of adian-5-en-3β-ol (simiarenol, **24**)[11] revealed that the chemical shifts for most of the carbons of **5** were very close to those of **24** except for C-1, C-2, C-5, C-6 and C-23. The deshielding of C-1, C-2 and C-5 by 4.75, 2.29 and 2.76 ppm, respectively, and up-field shift of C-23 by *ca*. 7.0 ppm clearly demonstrated the location of the equatorial hydroxy group at C-3. The assignment of the structure of **5** as adian-5-en-3α-ol was finally corroborated by its HMBC (Fig. 1) and NOESY (Fig. 2) spectral analyses.

The molecular formula of compound **6** was found to be $C_{30}H_{50}O$ by HRMS (M^+ at *m*/*z* 426.3904, Calcd., 426.3861). Its ^{1}H-NMR spectrum exhibited signals for five tertiary and two secondary methyl groups, a trisubstituted vinylic proton and a pair of AB doublets for a CH_2OH grouping. The low resolution EI-MS exhibited diagnostic[8] fragmentation for triterpenoids with $\Delta^7/\Delta^{9(11)}$ double bond leading to the formation of ion peaks at 257 (**g**′), 243 (**h**′) and 231 (**i**′) suggesting that the CH_2OH group must be located in D/E ring system of the molecule. The ^{13}C chemical shifts of the compound were found to be very close to those of fern-9(11)-ene (**9**) except the signals for C-16, C-17 and C-28. The up-field shift of C-16 by *ca*. 7 ppm and down-field shift of C-17 and

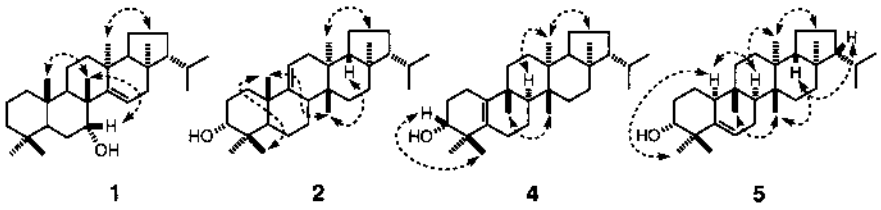

Fig. 2. NOEs Observed in the NOESY Spectra of **1**, **2**, **4** and **5**

C-28 by 4.57 and 40.05 ppm, respectively, clearly indicated that the hydroxy group must be located at C-28 of a fern-9(11)-ene skeleton. The HMBC data (Fig. 1) also fully substantiated the above conclusion. The structure of **6** was, therefore, represented by fern-9(11)-en-28-ol.

Backbone rearrangement[12,13] of adiantoxide (**16**) with boron trifluoride etherate was applied to confirm structures **2**—**5**. That is, **16** was treated with 10% BF_3–etherate in ether to afford **2** (2%), **3** (20.5%), **4** (18.3%) and **5** (4.9%) with a recovery of the starting compound (30%). The physical data of all the synthetic compounds (**2**—**5**) were identical with those of natural compounds.

Hopan-28(22)-olide (**21**) was earlier reported from the Formosan fern, *Oleandra wallichii* and some of its ^{13}C chemical shifts were erroneously assigned.[14] The detailed analysis of ^{13}C chemical shift by 2D NMR led to the unambiguous assignment of all the carbons as listed in Table 3.

Experimental

Melting points were measured on a Yanagimoto micro melting point apparatus without correction. Optical rotations were observed in $CHCl_3$ solution (c=0.1—0.3) at 22—24 °C. ^1H- and ^{13}C-NMR spectra were taken at 500 and 125 MHz, respectively, in $CDCl_3$ solution with tetramethylsilane as an internal standard. MS was recorded (direct inlet) at 30 eV and the relative intensities of peaks were reported with reference to the most intense peak higher than *m/z* 100. Silica gel 60 (230—400 mesh, Merck) and silica gel (impregnated with 20% $AgNO_3$) were used for column chromatography (CC). HPLC was performed on a C_{18} reverse-phase column (5 μ, 8 i.d.× 250 mm, detector, RI) with CH_3CN–$CHCl_3$ (9 : 1) as a mobile phase.

Plant Material The fronds of *Adiantum capillus-veneris* were collected in November, 1994, at Kanazawa-ku, Yokohama city, Kanagawa Prefecture. A voucher specimen has been deposited in the Herbarium of Shôwa College of Pharmaceutical Sciences, Tokyo.

Extraction and Separation of Triterpenoids The fresh fronds (4.4 kg) were extracted with hexane three times by modified Soxhlet extraction method to give the extract (49 g) together with separated water (3775 g). The extract was refluxed with benzene for 1 h and kept for 1 d. The insoluble materials were filtered off (fraction A) and the filtrate was evaporated to dryness to afford a gummy residue which was chromatographed on silica gel to give eight fractions: fr. B (eluted with hexane), fr. C [hexane–benzene (8 : 2)], fr. D [hexane–benzene (6 : 4)], fr. E, F [hexane–benzene (3 : 7)], fr. G [benzene], fr. H [benzene–Et_2O (9 : 1)] and fr. I [Et_2O].

Trisnorhopane (7), Ferna-7,9(11)-diene (8), Fern-9(11)-ene (9), Fern-7-ene (10), Filic-3-ene (11), Adian-5-ene (12), Neohop-12-ene (13) and Hop-22(29)-ene (14) Chromatography of fr. B on 20% $AgNO_3$-impregnated silica gel followed by recrystallizations from acetone gave eight triterpenoid hydrocarbons in pure form, *viz*. **7** (2 mg), **8** (38 mg), **9** (70 mg), **10** (189 mg), **11** (27 mg), **12** (1 mg), **13** (35 mg), **14** (47 mg). These compounds were identified by direct comparison (GC, MS, ^1H-NMR, IR) with authentic samples.

17,29-Epoxyhopane (15), Adiantoxide (16) and Fern-9(11)-en-12-one (17) Repeated recrystallizations of fr. D from acetone gave **16** (3.86 g). The filtrate was evaporated and the residue was chromatographed on silica gel with hexane–benzene (7 : 3) and then subjected to preparative HPLC followed by crystallization from acetone to give **15** (2 mg) and **17** (1 mg). These compounds were identified by direct comparison (^1H-NMR, IR) with authentic samples.

Adiantone (18), Isoadiantone (19), Isoglaucanone (20) and Hopan-28,22-olide (21) Repeated recrystallizations of fr. E from MeOH–$CHCl_3$ gave **18** (4.68 g). The filtrate was evaporated and the residue was chromatographed over silica gel with hexane–benzene (1 : 1), followed by preparative HPLC to give **19** (598 mg), **20** (76 mg), and **21** (10 mg). These compounds were identified by direct comparison (^1H-NMR, IR) with authentic samples.

Pteron-14-en-7α-ol (1), Fern-9(11)-en-3α-ol (2), Fern-7-en-3α-ol (3), Adian-5(10)-en-3α-ol (4), Adian-5-en-3α-ol (5), Fern-9(11)-en-28-ol (6) and Hydroxyhopane (22) Fraction F was chromatographed over silica gel with hexane–benzene (4 : 6) and then each of the fractions was subjected to preparative HPLC followed by crystallization to give **1**—**6** and **22**. **1**: (1.1 mg). IR ν_{max}^{KBr} cm^{-1}: 3540, 1073, 1049, 1021, MS *m/z*: 426 (M^+, 100), 411 (M^+-CH_3, 49), 408 (M^+-H_2O, 27), 393 ($M^+-CH_3-H_2O$, 55), 383 ($M^+-C_3H_7$, 7), 302 (5), 287 (8), 271 (95), 257 (13), 207 (21), 204 (85), 189 (36), 161 (23), 123 (31). **2**: (13 mg). IR ν_{max}^{KBr} cm^{-1}: 3410, 1068, 1042. MS *m/z*: 426 (M^+, 49), 411 (M^+-CH_3, 100), 408 (M^+-H_2O, 9), 393 ($M^+-CH_3-H_2O$, 40), 273 (10), 259 (73), 255 (12), 241 (29), 229 (7), 202 (13), 189 (13). **3**: (3 mg). IR ν_{max}^{KBr} cm^{-1}: 3450, 1068, 1050, 1016. MS *m/z*: 426 (M^+, 46), 411 (M^+-CH_3, 100), 408 (M^+-H_2O, 4), 393 ($M^+-CH_3-H_2O$, 41), 273 (10), 259 (62), 241 (35) 205 (12), 189 (15). **4**: (2 mg). IR ν_{max}^{KBr} cm^{-1}: 3425, 1048, MS *m/z*: 426 (M^+, 34), 411 (M^+-CH_3, 100), 408 (M^+-H_2O, 59), 393 ($M^+-CH_3-H_2O$, 70), 365 ($M^+-H_2O-C_3H_7$, 24), 340 (43), 274 (28), 259 (20), 205 (90), 135 (72). **5**: (1 mg). IR ν_{max}^{KBr} cm^{-1}: 3440, 1095, 1030, MS *m/z*: 408 (M^+-H_2O, 56), 393 ($M^+-CH_3-H_2O$, 47), 365 ($M^+-H_2O-C_3H_7$, 23), 274 (89), 259 (100), 134 (55). **6**: (4 mg). IR ν_{max}^{KBr} cm^{-1}: 3484, 1096, 1034, MS *m/z* 426 (M^+, 49), 411 (M^+-CH_3, 100), 393 ($M^+-CH_3-H_2O$, 49), 257 (12), 243 (83), 231 (26). Compound **22** (12 mg) was identified by direct comparison (^1H-NMR) with an authentic sample.

Hydroxyadiantone (23) Fraction A was repeatedly recrystallized from MeOH–$CHCl_3$ to give **23** (5 mg) which was identified by direct comparison (IR) with an authentic sample.

Synthesis of Compounds 2—5 Compound **16** (100 mg) was dissolved in ether (180 ml) and BF_3–etherate (20 ml) was added into the solution, which was then kept at room temperature for 3 h. Ice-water was carefully added into the reaction solution and the mixture was extracted with ether to afford a white crystalline material. The product was separated by silica gel CC followed by preparative HPLC [CH_3CN–$CHCl_3$ (9 : 1), flow rate 4 ml/min.] to give pure compounds: **2** (HPLC t_R 26.2 min, 4.9 mg), **3** (t_R 32.0 min, 20.4 mg), **4** (t_R 28.3 min, 18.3 mg), **5** (t_R 34.1 min, 4.9 mg) and starting material (t_R 43.0 min, 30.1 mg). These compounds were identified by comparisons (mp, MS, ^1H-NMR, IR) with natural compounds (**2**—**5**).

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