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New Lanostane-Type Triterpenoids from *Ganoderma applanatum*

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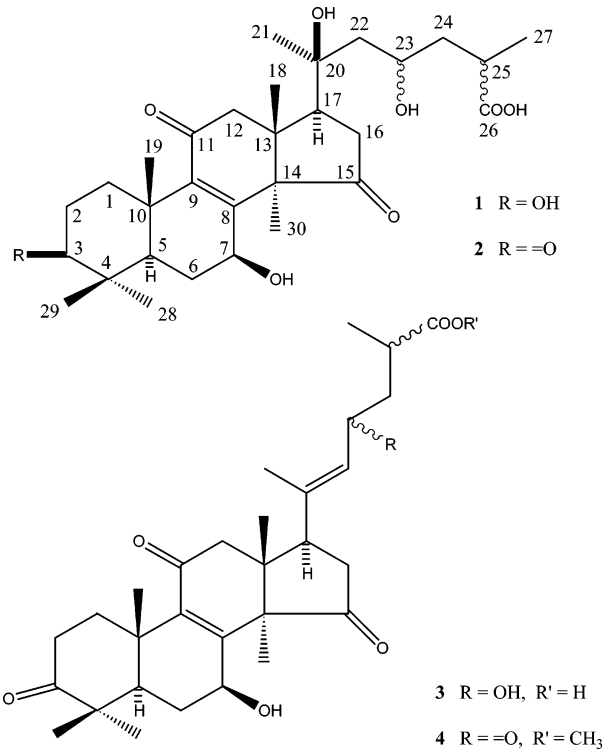
Four new lanostane-type triterpenes were isolated from the MeOH extract of the fruiting bodies of *Ganoderma applanatum*. Their structures were established as 3*β*,7*β*,20,23ξ-tetrahydroxy-11,15-dioxolanosta-8-en-26-oic acid (**1**), 7*β*,20,23ξ-trihydroxy-3,11,15-trioxolanosta-8-en-26-oic acid (**2**), 7*β*,23ξ-dihydroxy-3,11,15-trioxolanosta-8,20*E*(22)-dien-26-oic acid (**3**), and 7*β*-hydroxy-3,11,15,23-tetraoxolanosta-8,20*E*(22)-dien-26-oic acid methyl ester (**4**), respectively, by extensive spectroscopic analyses.

The fruiting bodies of *Ganoderma lucidum* (Leyss. ex Fr.) Karst. (Polyporaceae) are a well-known crude Chinese drug that has been used clinically in China, Japan, and Korea for a long time. More than 130 highly oxygenated lanostane-type triterpenoids have been isolated from the fruiting bodies, mycelia, and spores of *G. lucidum*, including common fungal steroids derived from ergosterol, some of them exhibiting a bitter taste and useful biological activities.[1] Other *Ganoderma* spp. have also been used in traditional Chinese, Japanese, and Korean medicines for the treatment of cancer, hypertension, chronic bronchitis, diabetes, and arteriosclerosis and as a tonic or sedative.[2−4] In the case of *G. applanatum* (Fr.) Pat. [=*Elfvingia applanata* (Pers.) Pat.], lanostane-type triterpenes, such as elfvingic acids,[3] ganoderenic acids,[2,5,6] ganoderic acids,[6] and applanoxidic acids,[6−8] have been isolated in addition to some aromatic compounds,[2] ergostane-type steroids,[2,5] and polysaccharides.[9,10] In a continuation of the studies on the bioactive principles of crude Korean drugs, we have conducted a chemical study of *G. applanatum*. Four new lanostane-type triterpenoids (**1**−**4**) were isolated from the MeOH extract of the fruiting bodies of *G. applanatum*. We describe here the isolation and structure elucidation of **1**−**4** by spectroscopic methods.



Results and Discussion

The dichloromethane layer of the MeOH extract of *G. applanatum* was chromatographed on silica gel to separate it into several fractions. Some of them were subjected to silica gel column chromatography to give four triterpenoids (**1**−**4**).

A molecular formula of $C_{30}H_{46}O_8$ was assigned to compound **1** on the basis of its HRFABMS (*m*/*z* 539.2982, calcd for $C_{30}H_{44}O_7Na$ [M + Na − H_2O]$^+$, 539.2985). The UV absorption at 252 nm (log ϵ 4.34) suggested the presence of an α,*β*-unsaturated C=O group. The IR spectrum suggested the presence of hydroxyls (3430 cm^{-1}), a five-membered ring C=O (1773 cm^{-1}), a carboxylic C=O (1711 cm^{-1}), and an α,*β*-unsaturated C=O (1647 cm^{-1}).[11] The ^{1}H NMR spectrum of **1**, analyzed with the aid of ^{1}H−^{1}H COSY and HMQC experiments (Table 1), exhibited six tertiary methyl groups, at *δ* 0.87, 1.06, 1.17, 1.24, 1.36, and 1.47 (3H each, s), a secondary methyl group at *δ* 1.33 (3H, d, *J* = 7.5 Hz), and three oxygenated methine protons [*δ* 3.23 (1H, dd, *J* = 5.5, 11.0 Hz), 4.81 (1H, dd, *J* = 8.0, 9.0 Hz), 4.85 (m)]. The ^{13}C NMR spectrum displayed signals characteristic of six methyl groups, an oxygen-bearing quaternary carbon at δ_C 73.4, three hydroxy-bearing methine carbons at δ_C 78.6, 67.1, and 74.8, an α,*β*-unsaturated C=O at δ_C 156.9, 142.7, and 198.0, a ketone carbon at δ_C 217.9, and a carboxylic carbonyl at δ_C 178.8. These data suggested a polyoxygenated lanostane-type triterpene with a structure similar to ganoderic acid I,[12] with the exception of C-22 to C-27. The presence of two hydroxyl groups together with a carboxylic acid group in the side chain was supported by the fragment ions at *m*/*z* 358 and 175, corresponding to a loss of the side chain in the EIMS spectrum.[11−14] The high-field shifts of C-22, -23, and -24 by 4.2, 135.6, and 10.9 ppm, respectively, compared with those of methyl ganoderate I, suggested that two hydroxyl groups may be located at C-20 and -23 in the side chain.

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Table 1. ^{1}H and ^{13}C NMR Data (δ in ppm, J in Hz) for Compounds **1**−**4** in $CDCl_3$

carbon no.	**1**		**2**		**3**		**4**	
	δ_H[a]	δ_C[b]	δ_H[c]	δ_C[b]	δ_H[c]	δ_C[d]	δ_H[c]	δ_C[d]
1	1.00 br d (10.0, 15.0) 2.86 m	35.1	1.42−1.53 m 2.95 ddd (5.4, 7.5, 13.7)	35.9	1.49 dt (8.5, 14.0) 2.94−2.99 m	35.9	1.42−1.52 m 2.9−3.0 m	35.6
2	1.68 m	28.0	2.4−2.6 m	34.5	2.4−2.6 m	34.5	2.50 m	34.2
3	3.23 dd (5.5, 11.0)	78.6		216.8		216.7		216.4
4		39.1		47.0		47.0		46.7
5	0.89 dd (1.0, 13.0)	49.4	1.58 dd (1.0, 12.8)	49.2	1.59 dd (1.5, 13.5)	49.2	1.60 m	48.8
6	2.21 ddd (1.5, 8.0, 13.0) 1.64 ddd (9.0, 13.5, 13.5)	26.9	2.12 ddd (1.2, 9.0, 13.5) 1.70 ddd (9.6, 13.5, 13.0)	27.9	2.13 ddd (1.5, 7.5, 13.0) 1.69 ddd (9.5, 13.0, 13.3)	27.9	2.12 br dd (7.2, 12.6) 1.65 br dt (8.1, 11.4)	27.6
7	4.81 dd (8.0, 9.0)	67.1	4.85 m	66.5	4.88 ddd (4.5, 9.5, 7.6)	66.5	4.88 dd (7.8, 8.7)	66.2
8		156.9		157.9		157.8		157.3
9		142.7		141.3		141.4		141.2
10		38.9		38.5		38.6		38.3
11		198.0		197.8		197.5		196.8
12	2.79 d (17.4) 2.86 d (17.4)	51.1	2.78 d (17.4) 2.87 d (17.4)	50.9	2.80 dd (1.0, 17.5) 2.59 d (17.5)	49.2	2.62 d (16.8) 2.85 d (16.8)	48.9
13		46.0		45.7		45.9		45.9
14		59.8		59.8		58.8		58.6
15		217.9		218.0		217.3		216.6
16	2.57 dd (8.0, 19.5) 2.81 dd (10.0, 19.5)	36.2	2.56 dd (8.4, 19.5) 2.82 dd (10.5, 19.5)	36.4	2.6 m	38.1	2.65 m	37.8
17	2.27 dd (8.0, 10.0)	50.2	2.24 dd (9.0, 9.6)	50.4	3.02 br t (9.5)	48.3	3.08 br t (9.6)	49.7
18	1.17 s	19.1	1.18 s	19.4	0.91 s	19.2	0.89 s	19.0
19	1.24 s	18.6	1.26 s	18.4	1.28 s	18.4	1.25 s	18.1
20		73.4		73.3		138.5		153.3
21	1.47 s	26.4	1.46 s	26.3	1.83 d (1.0)	18.3	2.16 br s	21.0
22	1.68 dd (3.0, 14.5) 1.90 dd (10.5, 14.5)	48.5	1.65 dd (2.4, 14.7) 1.88 dd (10.5, 14.7)	48.5	5.36 br d (8.0)	126.9	6.04 br s	124.7
23	4.85 m	74.8	4.82 m	74.8	5.30 ddd (2.5, 7.5, 13.5)	74.5		197.9
24	2.10 dd (6.5, 7.5)	36.8	2.08 dd (6.6, 7.8)	36.8	2.18 m	37.2	2.53 m 2.94 m	47.7
25	2.72 dd (7.5, 15.5)	33.8	2.70 dd (7.2, 15.3)	33.7	2.76 dd (7.0, 15.5)	34.5	2.98 m	34.8
26		178.8		178.8		179.8		176.3
27	1.33 d (7.5)	16.1	1.31 d (7.2)	16.1	1.32 d (7.0)	16.0	1.20 d (6.9)	17.2
28	1.06 s	28.4	1.12 s	27.2	1.15 s	27.3	1.13 s	27.0
29	0.87 s	15.7	1.10 s	21.0	1.13 s	21.0	1.11 s	20.8
30	1.36 s	25.1	1.34 s	25.3	1.40 s	24.8	1.40 s	24.7
7-OH	NO[e]		4.09 d (4.5)		3.95 d (4.5)		NO[e]	
OCH_3							3.69 s	51.9

[a] 500 MHz. [b] 125 MHz. [c] 300 MHz. [d] 75.5 MHz. [e] Not observed.

The connectivities of **1** were established by interpretation of the significant HMBC spectrum (Figure 1). The connectivity of the hydroxyl group at C-23 in the side chain and C-24, C-25, and CH_3-27 was revealed by the ^{1}H−^{1}H correlations between H-22 and -23, H-23 and -24, H-24 and -25, and H-25 and CH_3-27 in the ^{1}H−^{1}H COSY spectrum. This was further supported by long-range correlations between H-22 and C-20/21/23 and H-25 and C-23/24/26/27 in the HMBC spectrum. The relative configuration of **1** was confirmed on the basis of a NOESY experiment, with the exceptions of C-23 and C-25. Two equatorial hydroxyl groups at C-3 and C-7 were deduced from the multiplicities of H-3 (δ_H 3.23, dd, J = 5.5, 11.0 Hz) and H-7 (δ_H 4.81, dd, J = 8.0, 9.0 Hz), which were further supported by the NOE correlations observed from H-5 to H-3 and H-7 and from H-7 to CH_3-30 (Figure 1). The presence of a cross-peak between H-17 and CH_3-30 in the NOESY experiment provided evidence that the C-17 side chain was in a β-position. Consequently, the structure of **1** was determined as 3β,7β,20,23ξ-tetrahydroxy-11,15-dioxolanosta-8-en-26-oic acid, i.e., 23-dihydroganoderic acid I.

The UV, IR, and ^{1}H and ^{13}C NMR spectra of **2** were similar to those of **1**. However, the ^{13}C NMR spectrum of **2** showed a downfield shift at δ 216.8 and lacked one of the oxygenated methine carbons at δ 78.6 present in the spectrum of **1**. This suggested that **2** has a carbonyl function at C-3 (δ 216.8) instead of a hydroxyl group in **1**. The connectivity of the carbonyl group was confirmed by HMBC correlations observed between H-1 and C-3 and between CH_3-29 and C-3, which led to the conclusion that the structure of **2** was 7β,20,23ξ-trihydroxy-3,11,15-trioxolanosta-8-en-26-oic acid, i.e., 23-dihydroganoderic acid N.[15]

A molecular formula of $C_{30}H_{42}O_7$ was assigned to compound **3** on the basis of its HRFABMS (m/z 497.2913 [M + H − H_2O]$^+$, $C_{30}H_{41}O_6$, calcd 497.2903). The IR spectrum exhibited absorption bands due to the presence of a hydroxyl (3437 cm^{-1}), carbonyls (1761 and 1719 cm^{-1}), and α,β-unsaturated C=O (1655 cm^{-1}), and the UV spectrum indicated an α,β-unsaturated carbonyl absorption at 254 nm, as in **1** and **2**. The ^{1}H NMR spectrum of **3** exhibited five methyl singlets at δ 0.91, 1.13, 1.15, 1.28, and 1.40, two methyl doublets at δ 1.83 (d, 1.0) and 1.32 (d, 7.0), two oxymethines at δ 4.88 and 5.30, and an olefinic proton at δ 5.36 (br d, 8.0). These data resembled those of **2**, with the exception of signals for a vinylic methyl at δ 1.83 (d, 1.0) and a trisubstituted olefinic proton at δ 5.36 (br d, 8.0). Allylic couplings were observed between an olefinic proton at C-22 and a vinylic methyl group at C-21 and a methine proton at C-17 (δ 3.02) in the ^{1}H−^{1}H COSY spectrum. This

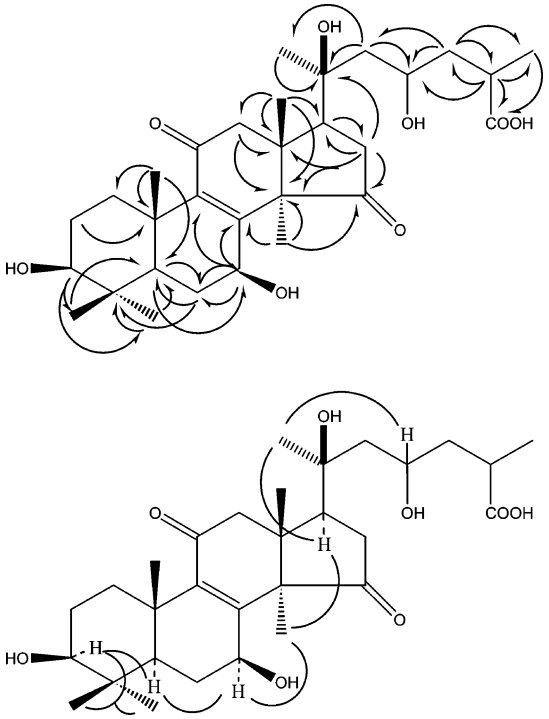

Figure 1. HMBC (upper) and NOESY (lower) correlations observed for **1**.

spectrum also showed mutual long-range coupling between CH_3-21 and H-17. Analysis of the HMBC spectrum (Figure 2) confirmed the positions of unsaturation ($\Delta^{20,22}$), a hydroxyl at C-23 and a carboxylic acid at C-26. The NOE between CH_3-21 and H-23, as well as H-22 and H-17, indicated the *E* configuration of the C-20 double bond, as in applanoxidic acids A and B[7] and ganoderenic acids B and D.[16] Therefore, the structure of **3** was determined as 7*β*,23*ξ*-dihydroxy-3,11,15-trioxolanosta-8,20*E*(22)-dien-26-oic acid, i.e., 23-dihydroganoderenic acid D.

The molecular formula, $C_{31}H_{42}O_7$, of compound **4** was deduced from the ^{13}C NMR and FABMS data, which showed a quasi-molecular peak ion $[M + H]^+$ at *m*/*z* 527 (HRFABMS *m*/*z* 527.3008, $C_{31}H_{43}O_7$, calcd 527.3009). The ^{13}C NMR data were similar to those of ganoderenic acid D,[16] except for the absence of the signal for a carboxylic acid being replaced by peaks at δ_C 176.3 and 51.9 (δ_H 3.69) of a carbomethoxy group. Unambiguous assignments for all the carbons (Table 1) could be made based on the correlations observed in the $^1H-^1H$ COSY, NOESY, and HMBC spectra. Comparison of our results, with the earlier ^{13}C NMR assignments, indicated that two pairs of carbonyl carbons (C-3/C-15 and C-11/C-23) were incorrectly assigned in the earlier work.[16] Therefore, the structure of **4** was determined as 7*β*-hydroxy-3,11,15,23-tetraoxolanosta-8,-20*E*(22)-dien-26-oic acid methyl ester, i.e., methyl ganoderenate D.

Experimental Section

General Experimental Procedures. The optical rotations were determined on a JASCO P-1020 polarimeter. The IR spectra were obtained on a JASCO FT/IR-5300 spectrometer. The EI mass spectra were obtained on a Hewlett-Packard 5989B spectrometer. The EIMS was performed on a Hewlett-Packard 5989B mass spectrometer. The FAB mass spectrum was obtained in a 3-nitrobenzyl alcohol matrix in positive ion mode on a JEOL-700 spectrometer. The NMR spectra were measured on a Varian Gemmi 2000 instrument (300 MHz) or a Bruker AM-500 (500 MHz), and the chemical shifts were referenced to TMS. The TLC was performed on silica gel $60F_{254}$ (Merck).

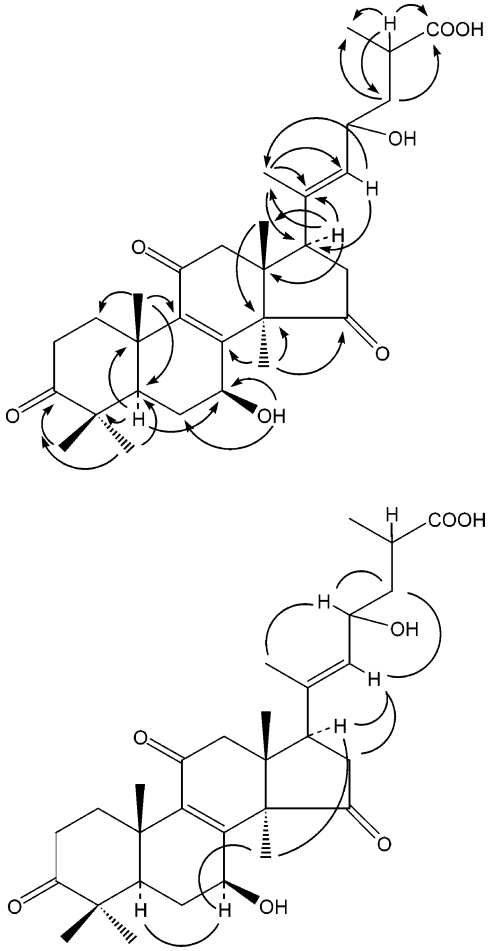

Figure 2. HMBC (upper) and NOESY (lower) correlations observed for **3**.

Plant Material. The fruiting bodies of *G. applanatum* were provided by St. Clair Milk and Grocery (Niagara Falls, Canada) in March 2002. The botanical identification was made by Mr. Gregory J. Belmore (Ministry of Natural Resources, Ontario, Canada). A voucher specimen (No. 2002-02) was deposited in the Herbarium of our Institute.

Extraction and Isolation. The ground fruiting bodies (2.1 kg) of *G. applanatum* were extracted five times, with MeOH under reflux, to give an extract (85 g). The MeOH extract was suspended in water and successively partitioned with *n*-hexane, dichloromethane, EtOAc, and *n*-BuOH, to yield 15, 25, 30, and 15 g fractions, respectively. The dichloromethane fraction (25 g) was separated by silica gel column chromatography with $CHCl_3$ containing increasing amounts of MeOH (1, 2, 3, 5, 10, 50, and 100%), as the eluent, to give 16 fractions (MC01−MC16). Fraction MC09 was subjected to silica gel column chromatography, with increasing amounts of hexane−Me_2CO (5, 10, 15, 20, 30, and 50%) as the eluent, to yield 13 fractions (MC09-01−MC09-13). Fraction MC09-08 was further purified by crystallization from MeOH to yield **3** (12 mg). Fractions MC09-07, MC10, and MC11 were further purified on a silica gel column, with hexane−EtOAc (10:1, 8:5, 5:8, 1:10) as the eluent, to yield **4** (10 mg), **1** (120 mg), and **2** (150 mg), respectively.

3*β*,7*β*,20,23*ξ*-Tetrahydroxy-11,15-dioxolanosta-8-en-26-oic acid (1): colorless amorphous solid; $[\alpha]^{26}_D$ +117.5° (*c* 0.211, $CHCl_3$), UV (MeOH) λ_{max} (log ϵ) 252 nm (4.34); IR ν_{max} 3430 (OH), 1773 (five-membered ring C=O), 1711 (COOH), 1647 (α,β-unsaturated C=O), 1458 (CH_2), 1377 (CH_3), 1181, 1034 (OH), 926 cm^{-1}; EIMS *m*/*z* (rel int, %) 516 $[M - H_2O]^+$ (2.5), 498 $[M - 2H_2O]^+$ (0.8), 470 $[M - (2H_2O + CO)]^+$ (5.8), 358 [M − side chain (SC) − H]$^+$ (1.7), 313 $[M - SC - (CO + H_2O)]^+$ (0.8), 175 $[C_8H_{15}O_4, SC]^+$ (8.3), 157 $[SC - H_2O]^+$ (8.3), 99 (45.5), 69 (100), 55 (100); (+)-FABMS *m*/*z* 539 $[M + Na - H_2O]^+$; (+)-HRFABMS *m*/*z* 539.2982 (calcd for $C_{30}H_{44}O_7Na$, 539.2985).

7*β*,20,23*ξ*-Trihydroxy-3,11,15-trioxolanosta-8-en-26-oic acid (2): colorless amorphous solid; $[\alpha]^{26}_D$ +225.5° (*c* 0.216, $CHCl_3$), UV (MeOH) λ_{max} (log ϵ) 250 nm (4.07); IR ν_{max} 3569 and 3491 (OH), 1767 (five-membered ring C=O), 1734 (six-membered ring C=O), 1699 (COOH), 1661 (α,*β*-unsaturated C=O), 1458 (CH_2), 1377 (CH_3), 1171 and 1069 (OH), 924 cm^{-1}; EIMS *m*/*z* (rel int, %) 514 $[M - H_2O]^+$ (43.8), 468 $[M - (2H_2O + CO)]^+$ (100), 376 (20.8), 329 $[M - (SC + CO)]^+$ (6.9), 175 $[C_8H_{15}O_4, SC]^+$ (8.5), 157 $[SC - H_2O]^+$ (8.3), 99 (13.8), 69 (13.5); (+)-FABMS *m*/*z* 537 $[M + Na - H_2O]^+$; (+)-HRFABMS *m*/*z* 537.2807 (calcd for $C_{30}H_{42}O_7Na$, 537.2828).

7*β*,23*ξ*-Dihydroxy-3,11,15-trioxolanosta-8,20*E*(22)-dien-26-oic acid (3): colorless amorphous solid; $[\alpha]^{27}_D$ +95.4° (*c* 0.2, MeOH), UV (MeOH) λ_{max} (log ϵ) 254 nm (3.94); IR ν_{max} 3437 (OH), 1761 (five-membered ring C=O), 1719 (six-membered ring C=O), 1655 (α,*β*-unsaturated C=O), 1458 (CH_2), 1377 (CH_3) cm^{-1}; EIMS *m*/*z* (rel int, %) 496 $[M - H_2O]^+$ (7.3), 468 $[M - H_2O - CO]^+$ (9.8), 450 $[M - 2H_2O - CO]^+$ (1.6), 435 $[M - 2H_2O - CO - CH_3]^+$ (1.6), 395 (7.3), 358 $[M - SC + H]^+$ (16.3), 273 (13.0), 175 (39.0), 157 $[C_8H_{13}O_3, SC]^+$ (12.2), 149 (42.3), 121 (59.3), 93 (87.8), 69 (74.8), 55 (100); (+)-FABMS *m*/*z* 497 $[M + H - H_2O]^+$, 479 $[M + H - 2H_2O]^+$; (+)-HRFABMS *m*/*z* 497.2913 (calcd for $C_{30}H_{41}O_6$, 497.2903).

7*β*-Hydroxy-3,11,15,23-tetraoxolanosta-8,20*E*(22)-dien-26-oic acid methyl ester (4): colorless amorphous solid; $[\alpha]^{27}_D$ +106.8° (*c* 0.5, MeOH), UV (MeOH) λ_{max} (log ϵ) 245 nm (3.74); IR ν_{max} 3429 (OH), 1736 (five-membered ring C=O), 1730 (six-membered ring C=O), 1710 ($COOCH_3$), 1657 (α,*β*-unsaturated C=O), 1385 (CH_3), 1170 and 833 cm^{-1}; (+)-FABMS *m*/*z* 527 $[M + H]^+$; (+)-HRFABMS *m*/*z* 527.3008 (calcd for $C_{31}H_{43}O_7$, 527.3009).

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