Copacamphane, Picrotoxane, and Alloaromadendrane Sesquiterpene Glycosides and Phenolic Glycosides from *Dendrobium moniliforme*

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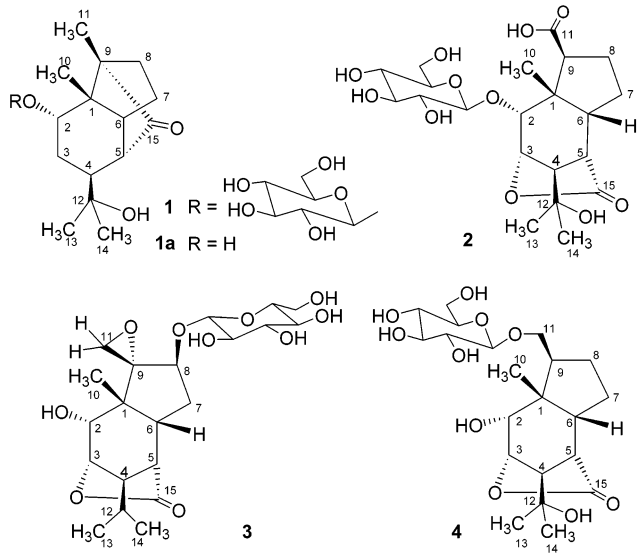
Received April 23, 2003

Seven sesquiterpene glycosides with copacamphane, picrotoxane, and alloaromadendrane sesquiterpene aglyons along with three phenolic glycosides have been isolated from the stems of *Dendrobium moniliforme*. Among them, dendromonilisides A−D (**1**−**4**) were characterized as new compounds, and their structures were determined on the basis of spectral and chemical methods and by X-ray diffraction analysis. The six known compounds were identified as dendrosides A, C, and F, dendromoniliside E, vanilloloside, and acanthoside B. In a preliminary biological test procedure, compounds **1**, **3**, and vanilloloside were found to stimulate the proliferation of B cells and inhibit the proliferation of T cells in vitro.

The stems of *Dendrobium moniliforme* (L.) Sw. (Orchidaceae) are used in traditional Chinese medicine to reduce fever and as a sialogogue.[1,2] Several lipophilic components[3−5] including antiinflammatory phenanthraquinones and a bibenzyl glycoside[6] have been isolated and identified from *D. moniliforme*. In a continuation of our efforts to find new biologically active compounds from *Dendrobium* species,[7−10] a systematic chemical investigation has been undertaken on a polar fraction of *D. moniliforme*. As a result, seven sesquiterpene glycosides and three phenolic glycosides have been obtained, and among them, four new compounds, dendromonilisides A−D (**1**−**4**), were isolated and structurally characterized. In a preliminary biological evaluation, compounds **1** and **3** were found to exhibit immunoregulatory activity in vitro. We report herein the isolation and structural determination of these compounds from *D. moniliforme*.



The stems of *D. moniliforme* were refluxed with 95% EtOH there times. After evaporation of ethanol in vacuo, the aqueous residue was extracted with petroleum ether, ethyl acetate, and *n*-butanol, successively. The *n*-butanol extract was subjected to a series of column chromatographic steps over silica gel, C_{18} silica gel, and Sephadex LH-20 to yield seven sesquiterpenoids and three phenolic glycosides.

Compound **1** was obtained as a white amorphous powder, with an elemental formula of $C_{21}H_{34}O_8$ determined by HRESIMS (*m*/*z* 437.2124, $[M + Na]^+$) and NMR analysis. In the IR spectrum, there was evidence of hydroxyl absorption at 3407 cm^{-1}, and carbonyl absorption was observed at 1726 cm^{-1}. In the ^{13}C NMR spectrum (Table 1), 21 carbon atom signals were observed as four methyls, four methylenes, nine methines, and four quaternary carbons. Enzymatic hydrolysis of **1** yielded the aglycon **1a** and glucose. In the ^1H NMR spectrum (Table 2), an anomeric proton signal was found at δ_H 4.93 (1H, d, J = 7.7 Hz), so the glucose unit was deduced to be connected to the aglycon in a β-glycosidic linkage. Analysis of the $^1H-^1H$ COSY and HMQC spectra of **1** enabled deduction of the fragment $-CH-CH_2-CH-CH-CH-CH_2-CH_2-$ in its structure. In the HMBC spectrum of **1**, $^{13}C-^1H$ long-range correlation signals were observed for C-1/H-2, H-6, H-10, H-11; C-9/H-8, H-10, H-11; C-15/H-5, H-6, H-11; C-12/H-4, H-13, H-14; and C-2/H-3, H-10, which enabled establishment of the planar structure of **1a**. In the NOESY spectrum of **1**, correlation signals were found between H-2 and H-6, H-10; and H-6 and H-10, H-13, H-14. All chiral carbons except C-9 in **1a** could be established on the basis of the above NOE information. To elucidate the relative configuration of **1**, X-ray diffraction analysis was performed on **1a**, with CH_3-10 and CH_3-11 determined to be in a *cis* orientation; so the relative configuration of **1** was accordingly fully established. A copacamphane-type sesqueterpene skeleton was therefore assigned to **1a**. To our best knowledge, compound **1a** is a new compound. The glucose moiety was determined to connect to C-2 of the aglycon according to the $^{13}C-^1H$ long-range correlation signal between C-2 and H_{glc-1} in the HMBC spectrum. Compound **1** (dendromoniliside A) was finally established as 2α,12-dihydroxycopacamphan-15-one 2-*O*-β-D-glucopyranoside.

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10.1021/np0301801 CCC: $25.00 © 2003 American Chemical Society and American Society of Pharmacognosy
Published on Web 08/01/2003

Table 1. ^{13}C NMR Data of **1**−**4** and **1a** (**1**−**3** in C_5D_5N, **4** in CD_3OD, and **1a** in $CDCl_3$, 100 MHz)

position	1	1a	2	3	4
1	52.9, C	52.9, C	51.6, C	43.3, C	50.9, C
2	81.0, CH	74.2, CH	78.9, CH	75.4, CH	74.7, CH
3	27.7, CH_2	30.2, CH_2	79.6, CH	83.8, CH	86.7, CH
4	45.8, CH	44.9, CH	53.8, CH	52.2, CH	55.1, CH
5	55.0, CH	54.3, CH	45.8, CH	45.9, CH	47.8, CH
6	43.8, CH	43.2, CH	43.6, CH	43.1, CH	46.2, CH
7	25.5, CH_2	24.8, CH_2	26.1, CH_2	34.4, CH_2	27.3, CH_2
8	33.4, CH_2	32.5, CH_2	28.6, CH_2	82.5, CH	29.9, CH_2
9	58.2, C	57.4, C	50.1, CH	75.0, C	44.9, CH
10	16.0, CH_3	15.1, CH_3	23.8, CH_3	27.0, CH_3	23.0, CH_3
11	12.2, CH_3	11.3, CH_3	178.7, C	51.0, CH_2	74.9, CH_2
12	71.9, C	73.2, C	68.5, C	25.0, CH	70.1, C
13	29.0, CH_3	28.7, CH_3	30.0, CH_3	19.7, CH_3	30.5, CH_3
14	30.0, CH_3	30.1, CH_3	30.3, CH_3	20.5, CH_3	30.6, CH_3
15	223.0, C	223.5, C	178.8, C	179.1, C	182.1, C
Glc-1	102.7, CH		101.5, CH	103.5, CH	104.8, CH
Glc-2	75.3, CH		74.7, CH	75.0, CH	75.4, CH
Glc-3	78.8, CH		77.5, CH	78.5, CH	78.5, CH
Glc-4	72.1, CH		71.0, CH	71.2, CH	71.9, CH
Glc-5	78.0, CH		78.0, CH	78.3, CH	78.3, CH
Glc-6	63.1, CH_2		62.3, CH_2	62.1, CH_2	63.1, CH_2

Compound **2** was obtained as a white amorphous powder, with an elemental formula of $C_{21}H_{32}O_{11}$ determined by HRESIMS (*m*/*z* 483.1816 $[M + Na]^+$) and NMR analysis. In the ^{13}C NMR spectrum of **2** (Table 1), 21 carbon atom signals including three methyls, three methylenes, 11 methines, and four quaternary carbons were observed. Enzymatic hydrolysis of **2** yielded glucose as the sugar moiety by co-TLC with an authentic sample. The ^1H NMR spectrum of **2** revealed an anomeric proton signal at δ_H 5.15 (1H, d, $J = 7.4$ Hz), which indicated the glucose unit to be in a β-glycosidic linkage to the aglycon. Analysis of the $^1H-^1H$ COSY and HMQC spectra of **2** led to the deduction of the fragment $-CH-CH-CH-CH-CH-CH_2-CH_2-CH-$ in the structure. In the HMBC spectrum of **2**, $^{13}C-^1H$ long-range correlation signals were observed for C-1/H-2, H-6, H-9, and H-10; C-11/H-1 and H-9; C-15/H-3 and H-5; and C-12/H-4, H-13, and H-14. In the NOESY spectrum of **2**, correlation signals were found between H-2 and H-6; H-2 and H-10; H-2 and H-13; H-2 and H_{glc-1}; and H-6 and H-10. Therefore, the relative configuration of all chiral carbons in the structure of **2** could be determined except for C-9. To elucidate the stereochemistry of the molecule, X-ray diffraction analysis was performed using a single crystal of **2**. As a result, CH_3-10 and COOH-11 were determined to be in a *cis* orientation. The structure of **2** was thus established to be 2α,3α,12-trihydroxypicrotoxane-3(15α)-olid-11-oic acid 2-*O*-β-D-glucopyranoside.[11] Compound **2** is a new natural glycoside and has been assigned the trivial name dendromoniliside B.

Compound **3** was obtained as a white amorphous powder, with an elemental formula of $C_{21}H_{32}O_{10}$ determined by HRESIMS (*m*/*z* 467.1897, $[M + Na]^+$). An IR hydroxyl peak at 3361 cm^{-1} and a carbonyl absorption peak at 1726 cm^{-1} were both observed. In the ^{13}C NMR spectrum of **3** (Table 1), 21 carbon signals including three methyls, three methylenes, 12 methines, and three quaternary carbon signals were apparent. Enzymatic hydrolysis of **3** yielded glucose as its sugar component. Analysis of the $^1H-^1H$ COSY and HMQC spectra of **3** led to the deduction of the fragment $-C-2-C-3-C-4[-C-12(-C-13)-C-14]-C-5-C-6-C-7-C-8-$ in its aglycon. In the HMBC spectrum of **3**, $^{13}C-^1H$ long-range correlation signals were observed for C-1/H-2, H-6, H-10; C-9/H-8, H-10, H-11; C-15/H-3, H-5; and C-8/H-7, H_{glc-1}. A picrotoxane-type sesquiterpene skeleton was derived for the aglycon of **3**,[11] and the glucose unit was linked to C-8 of the aglycon in a β-glycosidic linkage from the above-mentioned $^{13}C-^1H$ long-range correlation information and the coupling constant of the anomeric proton signal ($J = 7.7$ Hz). The relative configuration of **3** was established according to the NOESY spectrum, in which NOE signals were found between H-10 and H-2, H-6, H-11; H-3 and H-5, H-13, H-14; and H-8 and H-7α. The structure of **3** was finally determined to be 2α,3α,8β-trihydroxy-9α-(11)-epoxypicrotoxan-3(15α)-olide 8-*O*-β-D-glucopyranoside. Compound **3** is a new sesquiterpene glycoside and has been given the trivial name dendromoniliside C.

Compound **4** was obtained as a white amorphous powder, with an elemental formula of $C_{21}H_{34}O_{10}$ determined by HRESIMS (*m*/*z* 469.2060 $[M + Na]^+$). In the ^{13}C NMR spectrum of **4**, 21 carbon signals including three methyls, four methylenes, 11 methines, and three quaternary carbons were observed. Enzymatic hydrolysis of **4** yielded glucose as the only sugar component. The ^1H NMR spectrum of **4** exhibited one anomeric proton signal at δ_H 4.08 (1H, d, $J = 7.8$ Hz), which indicated the glucose unit in a β-glycosidic linkage to the aglycon. Analysis of $^1H-^1H$ COSY and HMQC spectra of **4** led to the deduction of the fragment $-C-2-C-3-C-4-C-5-C-6-C-7-C-8-C-9-$ in its aglycon. In the HMBC spectra of **4**, $^{13}C-^1H$ long-range correlation signals were observed between C-1 and H-2, H-6, H-9, and H-10; between C-12 and H-4, H-13, and H-14; between C-15 and H-3 and H-5; and between C-11 and H_{glc-1}. A picrotoxane-type sesquiterpene was deduced for the aglycon of **4**,[11] and the glucose unit should link to C-11 of the aglycon in a β-glycosidic linkage from the above-mentioned $^{13}C-^1H$ long-range correlation information and the coupling constant of the anomeric proton signal ($J = 7.8$ Hz). The relative configuration of **4** was established according to its NOESY spectrum, in which correlation signals were found between H-2 and H-6, H-10; H-5 and H-7β, H-13, H-14; and H-10 and H-6, H-11a, H-11b. The structure of **4** was finally identified as 2α,3α,11,12-tetrahydroxypicrotoxan-3(15α)-olide 11-*O*-β-D-glucopyranoside. This is a new sesquiterpene glycoside and has been given the trivial name dendromoniliside D.

Six known compounds were identified as the alloaromadendrane-type sesquiterpene glycosides, dendrosides A[8] and C;[9] a picrotoxane-type sesquiterpene glycoside, dendroside F;[10] and phenolic glycosides, dendromoniliside E,[6] vanilloloside,[12] and acanthoside B,[13] respectively, by comparing their NMR data with those reported in the literature and by co-TLC with authentic samples.

In a preliminary test procedure using a previously described method,[14,15] dendromonilisides A (**1**) and C (**3**) and vanilloloside were found to stimulate the proliferation of B cells at 10^{-5} M ($p < 0.05$) and to inhibit the proliferation of T cells at 10^{-7} M ($p < 0.05$) in vitro, without any obvious cytotoxic effects. Other isolates were not submitted to the bioassay. The regulatory effects on the proliferation of B and T lymphocytes of these tested compounds were evaluated by comparison with negative control groups and positive control groups. Con A and LPS were used as positive control for T and B cells, respectively. Independent two-tailed Student *t*-tests were performed.

Experimental Section

General Experimental Procedures. Melting points (uncorrected) were determined on a Kofler apparatus. Optical rotations were measured with a Horiba Sepa-300 polarimeter. IR spectra were recorded using a Perkin-Elmer 577 spectrometer. NMR spectra were run in C_5D_5N, $CDCl_3$, or CD_3OD on a Bruker AM-400 spectrometer with TMS as internal standard. LRESIMS were measured using a Finnigan LCQ-DECA instrument, and HRESIMS data were obtained on a Micro

Table 2. ^{1}H NMR Data of **1**−**4** and **1a** (**1**−**3** in C_5D_5N, **4** in CD_3OD, and **1a** in $CDCl_3$, 400 MHz)

position	1	1a	2	3	4
2	4.88, m	4.20, dd (10.6, 6.4)	5.18, br s	3.78, br s	4.21, d (1.8)
3	2.70 (a), m, 2.02 (b), m	2.15 (a), m, 1.38 (b), m	5.46, br d (4.9)	4.70, br d (5.1)	4.51, dd (5.1, 1.8)
4	2.24, m	1.87, m	2.46, m	2.01, m	2.18, dd (5.1, 4.4)
5	2.58, br d (3.0)	2.26, br d (2.3)	2.72, m	2.54, dd (6.6, 4.0)	2.29, dd (4.4, 3.7)
6	2.92, br d (4.4)	2.45, d (4.5)	3.28, m	2.31, dd (9.2, 2.9)	2.70, m
7	1.29 (a), m, 1.86 (b), m	1.91 (a), m, 1.29 (b), m	2.18 (a), m, 2.18 (b), m	2.70 (α), m 2.46 (β), m	1.87 (α), m, 1.61 (β), m
8	1.80 (a), m, 1.38 (b), m	1.84 (a), m, 1.33 (b), m	2.24 (a), m, 2.24 (b), m	5.08, dd (8.4, 8.1)	1.87 (α), m, 1.30 (β), m
9			3.92, m		2.53, m
10	1.39, s	1.15, s	1.84, s	1.40, s	0.93, s
11	1.46, s	1.15, s		3.47 (a), d (5.5), 3.06 (b), d (5.5)	3.78 (a), dd (8.8, 5.1), 3.58 (b), dd (8.8, 8.4)
12				1.59, m	
13	1.44, s	1.26, s	1.47, s	0.77, d (6.6)	1.14, s
14	1.43, s	1.26, s	1.39, s	0.77, d (6.6)	1.15, s
Glc-1	4.93, d (7.7)		5.15, d (7.4)	4.80, d (7.7)	4.08, d (7.8)
Glc-2	4.00, dd (8.0, 7.7)		4.04, m	3.88, dd (7.7, 8.2)	2.98, m
Glc-3	4.24, m		4.19, m	4.18, dd (8.2, 9.4)	3.16, m
Glc-4	4.25, m		4.06, m	4.30, m	3.14, m
Glc-5	3.79, m		3.79, m	3.73, m	3.09, m
Glc-6	4.52, dd (11.6, 2.8), 4.38, dd (11.6, 5.4)		4.35, br d (11.3), 4.22, m	4.35, m, 4.35, m	3.50, m, 3.69, m

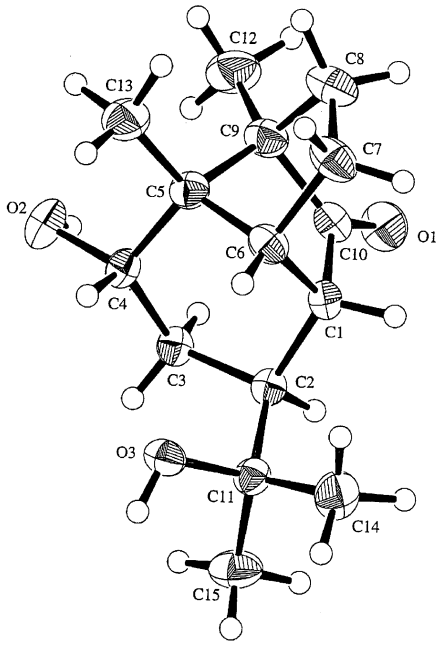

Figure 1. Perspective view of the molecule of **1a**.

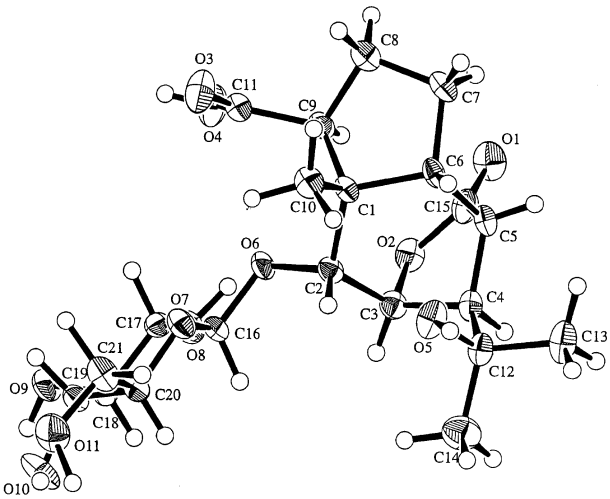

Figure 2. Perspective view of the molecule of **2**.

mass LTC instrument. X-ray diffraction analysis was performed on a Rigaku AFC7R diffractometer with graphite-monochromated Mo Kα radiation and 12 kW rotating anode generator. Silica gel H60 (Qingdao Haiyang Chemical Group Corp., Qingdao, People's Republic of China), RP-18 silica gel (100−200 mesh, Tianjin No. 2 Chemical Reagent Factory, Tianjin, People's Republic of China), and Sephadex LH-20 (Pharmacia Biotech AB, Uppsala, Sweden) were used for column chromatography. HSGF254 silica gel TLC plates (Yantai Chemical Industrial Institute, Yantai, People's Republic of China) were used for analytical TLC. β-Cellulase was produced by Lizhu Donfeng Bio-Tech Co. Ltd., Shanghai, People's Republic of China.

Plant Material. The plant material was collected in Pingbian County of Yunnan Province in November 2000 and was idendtified by Professor Yuqing Ye of Shanghai Traditional Medicine Institute. A voucher specimen has been deposited at the Herbarium of the Shanghai Institute of Materia Medica, Chinese Academy of Sciences (No. WZ20001101).

Extraction and Isolation. Powdered, air-dried stems of *Dendrobium moniliforme* (5.0 kg) were refluxed with 95% ethanol three times. After evaporation of ethanol in vacuo, the aqueous residue was extracted with petroleum ether, ethyl acetate, and *n*-butanol, successively, yielding a petroleum ether fraction (150.0 g), an ethyl acetate fraction (10.0 g), and a *n*-butanol fraction (40.0 g). The *n*-butanol extract (40.0 g) was first chromatographed on a silica gel column eluted with $CHCl_3$−MeOH (6:1 → 0:1) to give fractions I (10.3 g), II (10.6 g), and III (19 g). Fraction I (10.3 g) was subjected to further column chromatography on silica gel with $CHCl_3$−MeOH (8:1 → 0:1) to give fractions I-1 (2.0 g), I-2 (4.0 g), and I-3 (4.0 g). Fraction I-1 (2.0 g) was passed over a Sephadex LH-20 column with 95% ethanol as eluent to give acanthoside B (100 mg). Fraction I-2 (4.0 g) was passed over a Sephadex LH-20 column with 95% ethanol and then chromatographed over a RP-18 silica gel column, eluted with ethanol−water (1:1), to afford dendromoniliside B (15 mg). Fr. I-3 (4.0 g) was passed over a Sephadex LH-20 column with 95% ethanol and then subjected to chromatography over silica gel with a mixture of chloroform−methanol (3:1) as eluent to yield dendroside F (8 mg). Fraction II (10.6 g) was initially eluted over a Sephadex LH-20 column, using 95% ethanol, to give two subfractions, fraction II-1 (1.1 g) and fraction II-2 (9.4 g). Fraction II-1 (1.1 g) was further subjected to column chromatography over silica gel washed with a $CHCl_3$−MeOH gradient (6:1 → 0:1) and then separated over a RP-18 column with ethanol−water (1:4 → 1:1) as eluent to give dendromonilisides A (35 mg), C (35 mg), and E (6 mg) and dendrosides A (8 mg) and C (10 mg). Fraction II-2 (10.6 g) was passed over a Sephadex LH-20 column, eluted with 95% ethanol, and then chromatographed over silica gel with a

$CHCl_3$−MeOH gradient (6:1 → 0:1) as eluent to give dendromoniliside D (15 mg) and vanilloloside (15 mg).

Dendromoniliside A (1): white amorphous powder; mp 215−216 °C (dec); $[\alpha]_D^{20}$ 0.6° (*c* 0.4, H_2O); IR (KBr) ν_{max} 3407, 2976, 1726, 1623, 1384, 1119, 605 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m/z* 453.3 $[M + K]^+$, 437.3 $[M + Na]^+$; HRESIMS (positive-ion mode) *m/z* 437.2124 $[M + Na]^+$ (calcd for $C_{21}H_{34}O_8Na$, 437.2124).

Enzymatic Hydrolysis of Dendromoniliside A (1). Compound **1** (15 mg) and *β*-cellulase (20 mg) were dissolved in 5 mL of H_2O and kept at 37 °C for 72 h. The product that hydrolyzed was compared with an authentic standard glucose by co-TLC (EtOAc−MeOH−H_2O−HOAc, 13:3:3:4, R_f 0.46). The aqueous solution was extracted with EtOAc to give **1a** (10 mg), and prismatic crystals were obtained from EtOAc.

2α, 12-Dihydroxycopacamphan-15-one (1a): colorless prismatic crystals (EtOAc); mp 153−154 °C; $[\alpha]_D^{20}$ 73.0° (*c* 0.1, MeOH); IR (KBr) ν_{max} 3437, 2970, 1738, 1726, 1631, 1471, 1379, 1138, 1057, 1041, 858 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; EIMS *m/z* 252 $[M^+]$.

Dendromoniliside B (2): colorless prismatic crystals (MeOH−H_2O, 1:1); mp 225−227 °C; $[\alpha]_D^{20}$ −18.3° (*c* 0.5, MeOH); IR (KBr) ν_{max} 3384, 2972, 1743, 1628, 1423, 1387, 1294, 1202, 1078, 798 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m/z* 453.3 $[M + K]^+$, 437.3 $[M + Na]^+$; HRESIMS (positive-ion mode) *m/z* 483.1816 $[M + Na]^+$ (calcd for $C_{21}H_{32}O_{11}Na$, 483.1842).

X-ray Diffraction Analysis of Crystals of Compounds 1a and 2. The X-ray measurements were made on a Rigaku AFC7R diffractometer with graphite-monochromated Mo Kα radiation and a 12 kW rotating anode generator. The data were collected at 20 ± 1 °C using the $\omega-2\theta$ scan technique to a maximum 2θ value of 55.0°. A total of 3682 reflections were collected for **1a** and 3052 reflections for **2**. The intensities of three representative reflections were measured after every 200 reflections. Over the course of data collection, the standards decreased by −1.0% for **1a** and increased by 3.0% for **2**. The space group was $P2_12_12_1$ with unit cell parameters $a = 11.868(4)$ Å, $b = 23.064(4)$ Å, $c = 10.344(5)$ Å, $V = 2831(1)$ Å^3 for **1a**; and $a = 9.068(2)$ Å, $b = 32.437(3)$ Å, $c = 7.801(2)$ Å, $V = 2294.5(9)$ Å^3 for **2**. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinements was based on 2462 observed reflections with $I > 2.50\sigma(I)$ for **1a** and 1864 observed reflections with $I > 3.00\sigma(I)$ for **2**. The structures were solved by direct methods[16] and expanded using Fourier techniques.[17] The crystallographic data of compounds **1a** and **2** have been deposited at the Cambridge Crystallographic Data Center, Cambridge, U.K., under the reference numbers CCDC-212592 and CCDC-212593, respectively.[18]

Dendromoniliside C (3): white amorphous powder; mp 170−172 °C; $[\alpha]_D^{20}$ 0.5° (*c* 0.4, H_2O); IR (KBr) ν_{max} 3361, 2962, 1755, 1591, 1369, 1167, 1074, 1036, 756 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m/z* 467.4 $[M + Na]^+$; HRESIMS (positive-ion mode) *m/z* 467.1897 $[M + Na]^+$ (calcd for $C_{21}H_{34}O_8Na$, 467.1891).

Dendromoniliside D (4): white amorphous powder; mp 205−207 °C; $[\alpha]_D^{20}$ −0.4° (*c* 1.2, H_2O); IR (KBr) ν_{max} 3396, 2970, 1755, 1635, 1363, 1161, 1078, 962, 644 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m/z* 469.4 $[M + Na]^+$; HRESIMS (positove-ion mode) *m/z* 469.2060 $[M + Na]^+$(calcd for $C_{21}H_{34}O_8Na$, 429.2050).

Acknowledgment. The authors wish to thank Shanghai Municipal Committee of Science and Technology, Shanghai, People's Republic of China, for partial financial support of the work (No. 01JC14049).

References and Notes

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(18) Crystallographic data of compounds **1a** and **2** have been deposited at the Cambridge Crystallographic Data Center, Cambridge U.K. These data may be obtained on application to the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-(0)1223−336033 or e-mail: deposit@ccdc.cam.ac.uk).

NP0301801