Heterocyclic Compounds and Aromatic Diglycosides from *Bretschneidera sinensis*

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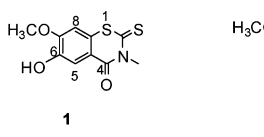
Two new heterocyclic compounds, bretschneiderazines A and B (**1**, **2**), three new aromatic diglycosides, bretschneiderosides A−C (**3**−**5**), and three known aromatic diglycosides, **6**−**8**, were isolated from *Bretschneidera sinensis*. The structure of bretschneiderazine A (**1**) was confirmed by single-crystal X-ray diffraction analysis. Bretschneiderazine A (**1**) showed moderate activity against the NCI-H446 cell line.

The Bretschneideraceae is a monotypic family, containing only one plant assigned the genus *Bretschneidera*, *Bretschneidera sinensis.* As an evergreen tree, *B. sinensis* is distributed only on the southern bank of the Yangtse, China.[1] The bark of this plant, a Chinese folk medicine, has been applied to treat arthralgia and myalgia. However, no phytochemical investigation on this species has been reported. In this paper, we describe the isolation and structure elucidation of two new heterocyclic compounds, bretschneiderazines A and B (**1**, **2**) and three new aromatic diglycosides, bretschneiderosides A−C (**3**−**5**). The known compounds were identified as benzyl 6′ *O*-*β*-D-apiofuranosyl-*β*-D-glucopyranoside (**6**),[2] 3,4,5-trimethoxyphenyl-*β*-D-apiofuranosyl-(1→6)-*β*-D-glucopyranoside (**7**),[3] and canthoside C (**8**),[4] respectively. The cytotoxic activities against the NIC-H446, HL-60, PC-3M, and HCT-116 cell lines were tested.



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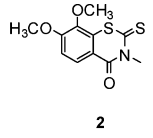

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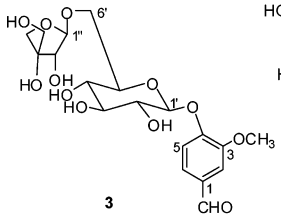

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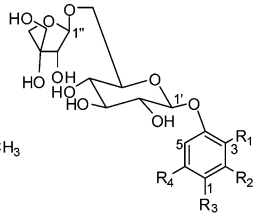
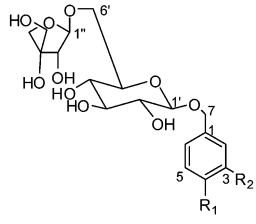


4 R_1 = OH, R_2 = H, R_3 = CHO, R_4 = H

7 R_1 = H, R_2 = OCH_3, R_3 = OCH_3, R_4 = OCH_3

8 R_1 = H, R_2 = OCH_3, R_3 = OH, R_4 = H



5 R_1 = OH, R_2 = OCH_3

6 R_1 = H, R_2 = H

Compound **1** was obtained as pale yellow crystals. Its molecular formula was established as $C_{10}H_9NO_3S_2$ (seven degrees of unsaturation) by negative HRESIMS data [*m*/*z* 253.9935 $[M - H]^-$ (calcd 253.9942)], in combination with the ^1H and ^{13}C NMR data (Table 1). Analysis of the ^1H, ^{13}C, DEPT, and HMQC spectra of **1** revealed the presence of a 1,2,4,5-tetrasubstituted benzene ring [δ_H 6.76 (s) and 7.75 (s); δ_C 152.0, 147.1, 129.3, 111.6, 114.0, and 106.5] and two quaternary carbons [δ_C 191.4 and 159.0]. HMBC correlations of H-5 with C-5a, C-6, C-7, and C-8a revealed the presence of a 1,2,4,5-tetrasubstituted benzene moiety in **1**, while HMBC correlation of H-5 with C-4 (δ_C 159.0) indicated that the carbonyl group was connected to the aromatic ring. Considering the chemical shifts of C-2 (δ_C 191.4, C), C-4 (δ_C 159.0, C), C-5a (δ_C 114.0, C), and C-8a (δ_C 129.3, C), the presence of a nitrogen and two sulfur atoms in **1**, as well as the observation of HMBC correlations from H-8 to C-5a, C-6, C-7, and C-8a and from $-NCH_3$ (δ_H 3.88) to C-2 (δ_C 191.4) and C-4 (δ_C 159.0), the thioxo group was connected to the aromatic ring through a sulfur atom. The structure of **1** was established as shown in Figure 1 by comparing its NMR data with those of the known synthetic compound 3-methyl-2-thioxo-2,3-dihydrobenzo[*e*][1,3]thiazin-4-one.[5] The structure of **1** was further confirmed by single-crystal X-ray diffraction analysis (Figure 2). This type of compound was isolated as a natural product for the first time and named 6-hydroxy-7-methoxy-3-methyl-2-thioxo-2*H*-benzo[*e*][1,3]thiazin-4(3H)-one.

Table 1. NMR Data for Compounds **1** and **2**

	1[a]		**2**[b]	
position	δ_H (*J* in Hz)	δ_C, mult.	δ_H (*J* in Hz)	δ_C, mult.
2		191.4, s		193.4, s
4		159.0, s		160.2, s
5	7.75, s	111.6, d	8.10, d (8.0)	128.7, d
5a		114.0, s		115.7, s
6		147.1, s	7.01, d (8.0)	111.6, d
7		152.0, s		156.1, s
8	6.76, s	106.5, d		139.3, s
8a		129.3, s		131.1, s
NCH_3	3.88, s	33.9, q	3.92, s	34.6, q
OCH_3	3.98, s	54.9, q	3.92, s	60.8, q
OCH_3			3.97, s	56.1, q

[a] Acetone-d_6, ^1H NMR at 600 MHz, ^{13}C NMR at 150 MHz. [b] $CDCl_3$, ^1H NMR at 600 MHz, ^{13}C NMR at 150 MHz.

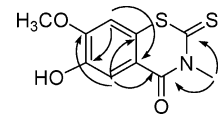


Figure 1. Selected HMBC correlations for bretschneiderazine A (**1**).

The molecular formula of compound **2** was established as $C_{11}H_{11}NO_3S_2$ (seven degrees of unsaturation) by analysis of its HRESIMS [*m*/*z* 270.0242 $[M + H]^+$ (calcd for $C_{11}H_{12}NO_3S_2$,

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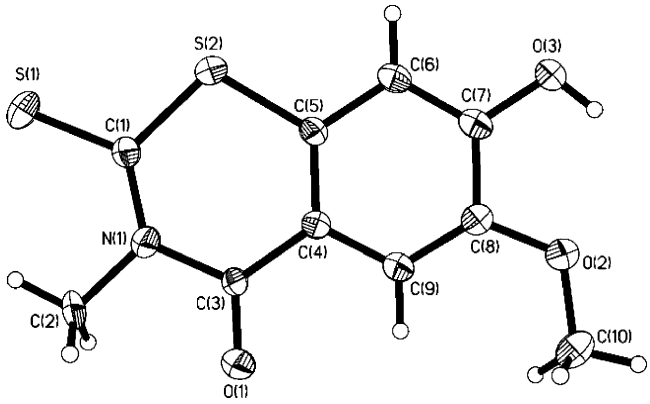

Figure 2. Molecular structure of bretschneiderazine A (**1**) obtained by X-ray analysis [Flack parameter: $x = 0.2(3)$].

270.0253)] and NMR data. The ^{1}H and ^{13}C NMR data of **2** were analogous to those of **1** except for one more methoxy group. The two methoxy groups were placed at C-7 and C-8, respectively, on the basis of strong HMBC correlations of one methoxy group (δ_H 3.97) with the aromatic quaternary carbon (C-7) and the other methoxy group (δ_H 3.92) with the aromatic quaternary carbon (C-8). Compound **2** is named bretschneiderazine B.

Compound **3** was obtained as a colorless oil. Its molecular formula, $C_{19}H_{26}O_{12}$, was established on the basis of HRESIMS (*m/z* 469.1336 $[M + Na]^+$, calcd for $C_{19}H_{26}O_{12}Na$, 469.1330). The ^{1}H NMR spectrum indicated the presence of a trisubstituted benzene ring (AMX system) from the signals at δ_H 7.27 (d, $J = 8.4$ Hz), 7.41 (d, $J = 1.8$ Hz), and 7.52 (dd, $J = 8.4$, 1.8 Hz), a methoxy signal at δ_H 3.87, a formyl proton at δ_H 9.79, and two anomeric proton signals at δ_H 5.05 (d, $J = 7.2$ Hz) and 4.99 (d, $J = 2.4$ Hz). The ^{13}C NMR spectrum exhibited signals for six aromatic carbons (δ_C 153.8, 151.5, 132.3, 127.8, 116.2, and 112.0), one methoxy group (δ_C 57.4), one formyl group (δ_C 194.1), and 11 sugar-derived carbons (δ_C 102.2, 75.6, 78.2, 72.0, 77.7, 69.3, 111.5, 78.7, 81.2, 75.2, and 66.1). Six carbon signals were characteristic for a glucopyranosyl moiety. In addition, an apiofuranosyl unit in **3** was also determined from the characteristic NMR signals [δ_H 4.99 (1H, d, $J = 2.4$ Hz, H-1″), 3.93 (1H, d, $J = 2.4$ Hz, H-2″), 3.94 (1H, d, $J = 9.6$ Hz, H_a-4″), 3.78 (1H, d, $J = 9.6$ Hz, H_b-4″), and 3.60 (2H, s, H-5″); δ_C 111.5, 81.2, 78.7, 75.2, and 66.1].[6−8] The ^{13}C NMR data of the sugar moiety was consistent with those of the β-D-apiofuranosyl-(1→6)-β-D-glucopyranosyl portions of known compound **6**.[2] The glycosidic linkage position was unambiguously determined by a HMBC correlation between the anomeric proton H-1″ (δ_H 4.99) and the nonequivalent oxymethylene resonance at δ_C 69.3 (C-6′), which confirmed a terminal apiofuranosyl unit and an inner glucopyranosyl unit with a (1→6) linkage. The additional HMBC correlation between the anomeric proton H-1′ (δ_H 5.05) and C-4 (δ_C 153.8) indicated that this diglycoside moiety was attached to C-4. The coupling constant of the anomeric proton H-1′ ($J = 7.2$ Hz) was characteristic for a β-glycosidic linkage in a glucopyranosyl unit; similarly, the coupling constant of H-1″ ($J = 2.4$ Hz) was characteristic for a β-glycosidic linkage in an apiofuranosyl unit.[9] The D-configuration of the glucopyranosyl and apiofuranosyl moieties was confirmed via acid hydrolysis (see Experimental Section). Therefore, the structure of compound **3** was established as 3-methoxy-4-[*O*-β-D-apiofuranosyl-(1→6)-*O*-β-D-glucopyranosyloxy]benzaldehyde and named bretschneideroside A.

Compound **4**, a colorless oil, had the molecular formula $C_{18}H_{24}O_{12}$ as deduced from the HRESIMS spectrum. The ^{1}H and ^{13}C NMR spectra suggested the presence of a 1,2,4-trisubstituted benzene ring [δ_H 7.26 (d, $J = 8.4$ Hz), 7.35 (d, $J = 2.0$ Hz), and 7.43 (dd, $J = 8.4$, 2.0 Hz); δ_C 153.2 (C), 151.0 (C), 110.6 (CH), 132 (C), 125.2 (CH), and 115.8 (CH)], a carbonyl group, and a β-D-apiofuranosyl-(1→6)-*O*-β-D-glucopyranosyl unit (two anomeric proton signals at δ_H 5.09 and 5.04). The ^{1}H and ^{13}C NMR data of **4** indicated that this compound had the same molecular skeleton as **3**, except that the methoxy group at C-3 in **3** was replaced by a hydroxy group in **4**. HMBC correlations from H-1″ to C-6′ and from H-1′, H-2, and H-6 to C-4 established that a carbonyl group was attached to C-1 and a β-D-apiofuranosyl-(1→6)-*O*-β-D-glucopyranosyl unit was substituted at C-4. On the basis of the above evidence, compound **4** was characterized as 3-hydroxy-4-[*O*-β-D-apiofuranosyl-(1→6)-*O*-β-D-glucopyranosyloxy]benzaldehyde and named bretschneideroside B.

Compound **5** was isolated as a colorless oil, with the molecular formula $C_{19}H_{28}O_{12}$ as determined by HRESIMS at *m/z* 471.1479 $[M + Na]^+$ (calcd 471.1473). Its IR and ^{1}H and ^{13}C NMR data were similar to those of **3**, with the exception that signals for a benzylic oxymethylene [δ_H 4.55 (2H, s); δ_C 65.0] were apparent. The HMBC correlations of δ_C 65.0 (the benzylic oxymethylene, C-7) and δ_H 4.94 (H-1′), 7.03 (H-2), 6.93 (H-6) and of δ_C 68.9 (C-6′) and δ_H 5.00 (H-1″) showed that a β-D-apiofuranosyl-(1→6)-*O*-β-D-glucopyranosyl unit was located at C-7. Consequently, the structure of compound **5** was identified as 4-hydroxy-3-methoxybenzyl-*O*-β-D-apiofuranosyl-(1→6)-*O*-β-D-glucopyranoside and named bretschneideroside C.

Experimental Section

General Experimental Procedures. Optical rotations were acquired with a Perkin-Elmer 341 polarimeter. Melting points were determined on a Yanaco MP instrument. IR spectra were recorded on a Bruker Vector-22 spectrometer with KBr pellets. NMR spectra were recorded on a Bruker Avance 600 NMR spectrometer. HRESIMS was determined on a Q-TOF micro mass spectrometer. Materials for column chromatography were silica gel (100−200, 300−400 mesh, 10−40 μm; Huiyou Silica Gel Development Co. Ltd., Yantai, China) and Sephadex LH-20 (40−70 μm, GE Healthcare Biosciences AB, Uppsala, Sweden). Semipreparative HPLC was performed on a Waters liquid chromatograph 510 instrument with a PDA UV detector at 208 or 254 nm using an ODS column (Kromasil, 5 μm, 300 × 10 mm). Preparative TLC (0.4−0.5 mm, 20 × 20 cm) was conducted with glass precoated silica gel GF_{254} (Huiyou Silical Gel Development Co. Ltd., Yantai, China). Spots were visualized under UV light (254 nm) or by spraying with 5% H_2SO_4 in 95% EtOH followed by heating. The cell lines NIC-H446, HL-60, PC-3M, and HCT-116 were purchased from Shanghai Institute of Pharmaceutical Industry (Shanghai, China). MTT was purchased from Sigma Chemical Co. (St Louis, MO), DMSO from Merck, Sharp & Dohme Ltd. (Beijing, China), and doxorubicin hydrochloride from Shanghai New Asiatic Pharmaceuticals Co., Ltd.

Plant Material. *B. sinensis* was collected in Jiujiang, Jiangxi Province, in August 2008 and was identified by Prof. Han-Ming Zhang in the Department of Pharmacognosy, Second Military Medical University. A voucher specimen (20080823) was deposited at the Herbarium of School of Pharmacy, Second Military Medical University, Shanghai, China.

Extraction and Isolation. The air-dried stems of *B. sinensis* (10.0 kg) were powdered and extracted three times (3 × 4 h) with 80% ethanol. Evaporation of the solvent *in vacuo* afforded a brown residue (510.0 g), which was suspended in H_2O and then partitioned with petroleum ether, EtOAc, and *n*-BuOH, respectively. The EtOAc fraction (30.0 g) was chromatographed on a normal-phase preparative MPLC column eluted with a petroleum ether−EtOAc gradient system (from 90:10 to 0:100) to give eight fractions (A−H). Fraction B (1.9 g) was purified by Sephadex LH-20 column chromatography, using petroleum ether−CH_2Cl_2−MeOH (5:5:1) as eluant, then purified by preparative TLC with petroleum ether−acetone (3:1) to obtain **1** (6.0 mg). Fraction C (1.4 g) was purified by Sephadex LH-20 column chromatography, eluted with acetone, to give **2** (3.0 mg).

The *n*-BuOH fraction (310.0 g) was subjected to column chromatography over MCI gel, eluting with a gradient system of H_2O−MeOH (100:0, 70:30, and 30:70), to give three fractions (1−3). Fraction 1 (116.0 g) was submitted to ODS-AQ [gradient MeOH−H_2O (from 0:100 to 40:60)], yielding three subfractions (1.1−1.3) on the basis of TLC analysis. Fraction 1.2 (28.0 g) was submitted to MPLC (RP-18, gradient MeOH−H_2O, 10:90→100:0), yielding nine subfractions (1.2.1−1.2.9). Fraction 1.2.5 (2.1 g) was subjected to column (4.5 ×

Table 2. NMR Data for Compounds **3**−**5** in Methanol-d_4

	3[a]		**4**[a]		**5**[a]	
position	δ_H (J in Hz)	δ_C, mult.	δ_H (J in Hz)	δ_C, mult.	δ_H (J in Hz)	δ_C, mult.
1		132.3, s		132.9, s		137.6, s
2	7.41, d (1.8)	112.0, d	7.35, d (2.0)	110.6, d	7.03, d (1.8)	113.0, d
3		151.5, s		151.0, s		150.2, s
4		153.8, s		153.2, s		146.6, s
5	7.27, d (8.4)	116.2, d	7.26, d (8.4)	115.8, d	7.11, d (8.4)	117.5, d
6	7.52, dd (8.4, 1.8)	127.8, d	7.43, dd (8.4, 2.0)	125.2, d	6.93, dd (8.4, 1.8)	121.4, d
7	9.79, s	194.1, d	9.73, s	196.1, d	4.55, s	65.0, t
1′	5.05, d (7.2)	102.2, d	5.09, d (7.4)	101.8, d	4.94, d (7.4)	102.4, d
2′	3.68, dd (9.0, 7.2)	75.6, d	3.74, overlapped	74.3, d	3.68, dd (7.4, 7.0)	75.0, d
3′	3.57, overlapped	78.2, d	3.62, overlapped	78.0, d	3.57, overlapped	77.1, d
4′	3.41, dd (9.4, 8.7)	72.0, d	3.51, t (9.0)	71.0, d	3.46, dd (9.2, 9.0)	71.3, d
5′	3.57, overlapped	77.7, d	3.62, overlapped	76.8, d	3.57, overlapped	76.6, d
6′a	4.02, brd (11.0)	69.3, t	4.04, brd (11.0)	68.4, t	3.98, brd (11.0)	68.9, t
6′b	3.63, dd (11.0, 4.7)		3.74,	overlapped	3.68, dd	(11.0, 6.0)
1″	4.99, d (2.4)	111.5 d	5.04, d (3.0)	110.6, d	5.00, d (2.6)	110.7, d
2″	3.93, d (2.4)	78.7 d	3.96, d (3.0)	78.1, d	3.94, d (3.0)	78.1, d
3″		81.2 s		80.7, s		80.7, s
4″a	3.94, d (9.6)	75.2 t	4.01, d (10.1) 74.3, t		3.95, d (10.4)	74.3, t
4″b	3.78, d (9.6)		3.83, d (10.1)		3.81, d	(10.4)
5″	3.60, s	66.1 t	3.62, s 65.0 t		3.60, s	65.3, t
OCH_3	3.87, s	57.4 q			3.85, s	57.1, q

[a] ^{1}H NMR at 600 MHz, ^{13}C NMR at 150 MHz.

150 cm) chromatography over Sephadex LH-20 using MeOH−H_2O (8:2) as the eluting solvent to afford **6** (9.0 mg) and **8** (5.2 mg). Fraction 1.2.6 (1.4 g) was chromatographed on Sephadex LH-20 using MeOH−H_2O (1:1) as eluant to give **5** (11.0 mg). Fraction 1.2.7 (4.1 g) was purified by Sephadex LH-20 column chromatography eluted with MeOH−H_2O (5:5) to give **3** (11.5 mg) and **7** (6.6 mg). Compound **4** (17.0 mg) was purified by a silica gel column ($CHCl_3$−MeOH−H_2O, 7:3:0.5) from fraction 2 (1.2 g).

Bretschneiderazine A (1): pale yellow crystals ($CHCl_3$); mp 202−204 °C (dec); IR (KBr) ν_{max} 3422, 2924, 2853, 1737, 1655, 1384 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m*/*z* 253.9935 $[M - H]^-$ (calcd for $C_{10}H_8NO_3S_2$, 253.9942).

Bretschneiderazine B (2): pale yellow, amorphous solid; IR (KBr) ν_{max} 2955, 2935, 1737, 1633, 1591, 1515 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m*/*z* 270.0242 $[M + H]^+$ (calcd for $C_{11}H_{12}NO_3S_2$, 270.0253).

Bretschneideroside A (3): colorless oil; $[\alpha]^{21}_D$ −79.3 (*c* 2.70, CH_3OH); IR (KBr) ν_{max} 3375, 2927, 2882, 1681, 1591, 1508, 1269, 1069 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2; HRESIMS *m*/*z* 469.1336 $[M + Na]^+$ (calcd for $C_{19}H_{26}O_{12}Na$, 469.1330).

Bretschneideroside B (4): colorless oil; $[\alpha]^{21}_D$ −19.2 (*c* 0.70, CH_3OH); IR (KBr) ν_{max} 3395, 2926, 2882, 1680, 1593, 1506, 1383, 1280, 1067 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2; HRESIMS *m*/*z* 455.1153 $[M + Na]^+$ (calcd for $C_{18}H_{24}O_{12}Na$, 455.1160).

Bretschneideroside C (5): colorless oil; $[\alpha]^{21}_D$ −106.8 (*c* 0.40, CH_3OH); IR (KBr) ν_{max} 3385, 2926, 2881, 1513, 1384, 1267, 1069 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2; HRESIMS *m*/*z* 471.1479 $[M + Na]^+$ (calcd for $C_{19}H_{28}O_{12}Na$, 471.1473).

Single-Crystal X-ray Analysis. Bretschneiderazine A (**1**) was crystallized from $CHCl_3$−acetone to give colorless platelets, space group *Pc*, $a = 3.985(5)$ Å, $b = 11.542(14)$ Å, $c = 11.205(14)$ Å, $\beta = 91.985(17)°$, $V = 515.1(11)$ Å^3, $Z = 2$, $D_{calc} = 1.646$ mg/m^3. Data collection was carried out on a Bruker Smart APEX CCD diffractometer equipped with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) at 293(2) K. The structure was solved by direct methods and refined with full-matrix least-squares calculations of F^2 using SHELX-97.[10] The collected data were reduced by using the program SAINT, and empirical absorption correction was made by using the SADABS program. All the hydrogen atoms were located from difference maps and included in the refinements as riding. The numbers of measured, independent, and observed parameters were 2051, 1201, and 1061, respectively. The refined structural model converged to a final $R = 0.0910$ for observed reflections and $R_1 = 0.0840$, $wR_2 = 0.2262$, $S = 1.045$ for all data with 145 parameters. The Flack parameter was 0.2(3).

Cytotoxicity Assay. The bioassay for cytotoxic activity against human cell cultures *in vitro* was performed by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylterazolium bromide] colorimetric method. Doxorubicin hydrochloride (DOX) was used as a postive control. The samples (purity >95%) were dissolved in DMSO separately and used for the *in vitro* cytotoxicity assay, and diluted with phosphate-buffered saline (PBS) to a final concentration 1000 μg mL^{-1}. The solutions were serially diluted with PBS to obtain the lower dilutions, 100−3.125 μg mL^{-1}. The cells were incubated in a 96-well microtiter plate (Nunc and Tarson) at a density of (4−6) × 10^4 cell mL^{-1}. The samples of different concentrations, 10 μL/well, were added after 24 h seeding. The microtiter plates were incubated for 72 h in a humidified atmosphere of 5% CO_2 at 37 °C. The cellular viability was determined using the standard MTT method.[11] The optical densities were read on an enzyme-labeled detector (Denley MK-2) at a wavelength of 570 nm.

Acid Hydrolysis of Compounds 3−5 and Sugar Analysis. Each compound (8.0 mg) was hydrolyzed with 1 N HCl (1 mL) for 3 h at 85 °C. The solution was evaporated under a stream of N_2. The residue was dissolved in 0.3 mL of Tri-Sil Z (*N*-trimethylsilylimidazole−pyridine, 1:4, Pierce Biotechnology, Rockford, IL), and the mixture was allowed to react at 60 °C for 15 min. After drying under a stream of N_2, the residue was dissolved in 2 mL of H_2O and partitioned with 2 mL of CH_2Cl_2. The CH_2Cl_2 layer was analyzed by GC-MS (Agilent 7890A/5973N, DB-5 GC column: 60 m × 0.25 μm × 0.25 mm, temperatures for inlet injection 200 °C; temperature gradient system for the oven, 150 °C for 1 min and then raised to 280 °C at rate of 6 °C/min). D-Glucose and D-apiose were identified for **3**−**5** by comparison with retention times of standard samples [D-glucose ($t_R = 24.03$ min) and D-apiose ($t_R = 14.51$ min)] after treatment in the same manner with Tri-Sil Z.

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Supporting Information Available: NMR spectra, cytotoxic activity of the new compounds **1**−**5**, and CIF data for the crystal structure of **1** are available free of charge via the Internet at http://pubs.acs.org.

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