9,19-Cyclolanostane Derivatives from the Roots of Actaea pachypoda

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9,19-Cyclolanostane Derivatives from the Roots of *Actaea pachypoda*

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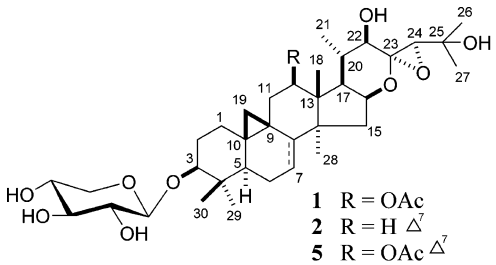
Phytochemical investigation of the chemical constituents of the roots of *Actaea pachypoda* afforded 12 9,19-cyclolanostane type triterpenoids, including the new 7,8-dihydroactaeaepoxide 3-*O*-*β*-D-xylopyranoside (**1**), 12-deacetoxyactaeaepoxide 3-*O*-*β*-D-xylopyranoside (**2**), and 12*β*-acetoxycimigenol (**3**). Their structures were determined by spectroscopic and chemical methods.

The genus *Actaea* (Ranunculaceae) was first described by Von Linné in 1735.[1] Owing to a lack of understanding of the delimitation of the genus and closely related genera, e.g., *Cimicifuga* and *Souliea*, and the species within the genus itself, the taxonomic debate is continuing. Some *Actaea* species were previously classified under the genus *Cimicifuga*, creating more taxonomical discord among closely related genera. Morphological and molecular analyses have also revealed supraspecific groupings within the genus.[1] Updated and concise taxonomic classification of *Actaea* versus *Cimicifuga* and *Souliea* was done via utilization of morphological and molecular data.[1] Accordingly, *Actaea* consists of 28 species distributed throughout East Asia, Europe, and North America.

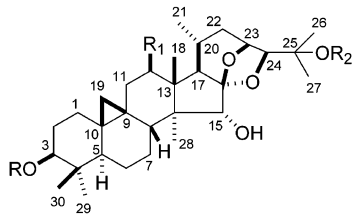
Actaea racemosa L. [syn. *Cimicifuga racemosa* L. (Nutt.)], commonly known as black cohosh, is a well-known dietary supplement for women's health in alleviating menstrual pain and menopausal disorders. The roots of *A. pachypoda* are used to ease pain during childbirth.[2] Black cohosh has been investigated extensively and found to contain cycloartane type triterpenes[3−7] and phenylpropanoid derivatives.[8,9] It is usually collected from the wild in North America, where it often coexists with the closely related *A. pachypoda* (white cohosh).[10]

In order to differentiate *A. pachypoda* and black cohosh, we undertook a phytochemical investigation of the largely unexplored constituents of white cohosh. This paper describes the identification of three new 9,19-cyclolanostane triterpene derivatives, 7,8-dihydroactaeaepoxide 3-*O*-*β*-D-xylopyranoside (**1**), 12-deacetoxy-actaeaepoxide 3-*O*-*β*-D-xylopyranoside (**2**), and 12*β*-acetoxy-cimigenol (**3**), and nine known compounds from the MeOH extract of the roots of *A. pachypoda*. The structures of **1**−**3** were determined on the basis of spectroscopic and chemical methods.

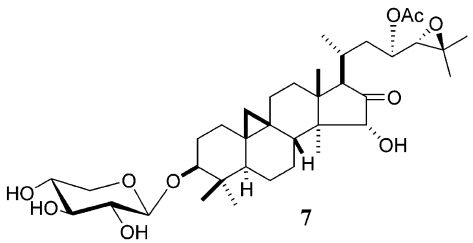
Compound **1** showed a pseudomolecular ion in the positive ESIMS at *m*/*z* 701 $[M + Na]^+$. When considered in conjunction with its ^{13}C NMR data, it indicated a molecular formula of $C_{35}H_{54}O_9$. The assignment of ^1H and ^{13}C NMR spectroscopic data of **1** (Table 1) was based on HMQC, HMBC (Figure 1), and $^1H-^1H$ COSY spectra. The ^{13}C NMR spectrum showed 37 resonances, of which 30 were attributed to a triterpene skeleton, five to a pentose unit, and two to an acetyl group. A DEPT NMR experiment permitted differentiation of the 37 ^{13}C NMR resonances into eight methyl, eight methylene, 13 methine, and eight quaternary carbons. Characteristic resonances in the ^1H and ^{13}C NMR spectra (Table 1) for an isolated cyclopropane methylene [$\delta_{H/C}$ 0.20, 0.54/30.0 (C-19)], six tertiary methyls [$\delta_{H/C}$ 0.85/ 20.0 (C-28), 0.99/ 15.6 (C-30), 1.30/ 26.0 (C-29), 1.34/ 14.0 (C-18), 1.67/ 25.1 (C-26), and 1.73/ 28.1 (C-27)], and a secondary methyl [$\delta_{H/C}$ 1.30/ 17.7 (C-21)] indicated a 9,19-cyclolanostane type triterpene architecture.[3−7] Several resonances due to oxygenated carbons in the ^{13}C NMR spectrum of **1** at δ_C 88.4 (C-3), 77.3 (C-12), 72.4 (C-16), 87.0 (C-22), 105.9 (C-23), 83.6 (C-24), 83.9 (C-25), and 170.8 (C-*O*C*O*Me) and the resonances of a pentosyl moiety at δ_C 107.7 (C-1′), 75.8 (C-2′), 78.8 (C-3′), 71.5 (C-4′), and 67.3 (C-6′) indicated a significant degree of *O*-decoration. The correlations of H-12 (δ_H 5.12) and a methyl resonance at δ_H 2.07 with a carbonyl carbon at δ_C 170.8 in the HMBC spectrum (Figure 1) indicated an *O*-acetyl group at C-12. Similarly, the correlations of an anomeric proton at



1 R = OAc
2 R = H Δ^7
5 R = OAc Δ^7



3 R = H, R_1 = OAc, R_2 = H
4 R = β-D-xylopyranose, R_1 = OAc, R_2 = H
6 R = β-D-xylopyranose, R_1 = H, R_2 = H



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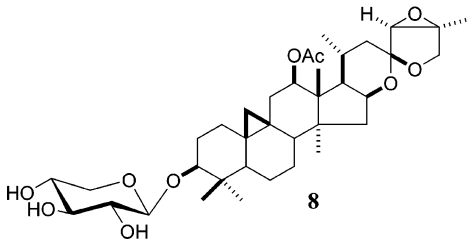

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Table 1. ^{1}H and ^{13}CNMR Data for Compounds **1**−**4**

	1		**2**		**3**		**4**	
position	δ_C, mult.	δ_H mult. (*J* in Hz)	δ_C, mult.	δ_H mult. (*J* in Hz)	δ_C, mult.	δ_H mult. (*J* in Hz)	δ_C, mult.	δ_H mult. (*J* in Hz)
1	32.3 t	1.07	30.7 t	1.17	32.9 t	1.07	32.7 t	1.10
		1.47		1.57		1.47		1.56
2	30.2 t	1.27	29.9 t	1.92	31.5 t	1.83	30.4 t	1.89
		2.23		2.24		1.94		2.28
3	88.4 d	3.34 brd (10.4)	88.5 d	3.48 dd (11.2, 4.0)	78.1 d	3.51 dd (11.6, 4.4)	88.6 d	3.48 dd (11.6, 4.0)
4	41.5 s		40.7 s		41.3 s		41.6 s	
5	47.3 d	1.25	43.0 d	1.28	47.4 d	1.25 dd (13.0, 4.8)	47.5 d	1.27
6	20.8 t	0.72	22.2 t	1.56	21.3 t	0.80	21.0 t	0.74
		1.43		1.87		1.55		1.49
7	26.1 t	0.97	113.6 d	5.12 brd (6.0)	26.5 t	1.22	26.3 t	1.10
		1.25				2.16		2.07
8	45.9 d	1.54	150.0 s		47.8 d	1.78 dd (12.8, 5.2)	47.5 d	1.76 dd (12.8, 4.8)
9	20.3 s		21.4 s		20.4 s		20.5 s	
10	27.0 s		28.6 s		27.4 s		27.1 s	
11	37.1 t	1.13	25.6 t	1.11	38.0 t	1.16	37.8 t	1.18
		2.71 dd (9.2, 16.0)		2.07		2.97 dd (16.0, 9.6)		2.94 dd (16.0, 9.2)
12	77.3 d	5.12 d (8.4)	33.5 d	1.32	77.7 d	5.29 dd (9.3, 2.4)	77.6 d	5.27 brd (7.2)
				1.71				
13	49.7 s		45.0 s		46.6 s		46.6 s	
14	48.5 s		50.7 s		48.8 s		48.8 s	
15	43.3 t	1.70	42.3 t	1.93	79.5 d	4.41 s	79.5 d	4.38 s
		1.91		2.12 dd (12.0, 7.6)				
16	72.4 d	5.01	72.9 d	5.07 q (7.6)	112.3 s		112.3 s	
17	52.8 d	1.81	53.2 d	1.61	59.6 d	1.70 brs	59.5 d	1.68 brs
18	14.0 q	1.34 s	23.3 q	1.21 s	13.0 q	1.36 s	13.0 q	1.33 s
19	30.0 t	0.20 brs	28.7 t	0.97 d (3.6)	31.4 t	0.34 d (4.4)	31.2 t	0.30 d (3.2)
		0.54 brs		0.45 d (3.6)		0.64 d (4.4)		0.60 d (3.2)
20	34.7 d	2.21	35.0 d	2.23	24.4 d	1.66	24.4 d	1.66
21	17.7 q	1.30 brs	17.8 q	1.25 d (6.0)	20.3 q	0.96 d (6.0)	20.3 q	0.95 brs
22	87.0 d	3.85 d (10.4)	87.1 d	3.91 d (10.8)	38.9 t	1.08	38.9 t	1.03
						2.32		2.31
23	105.9 s		106.4 s		71.8 d	4.76 d (8.8)	71.8 d	4.74 d (9.2)
24	83.6 d	4.19 s	83.6 d	4.19 s	90.3 d	3.78 s	90.2 d	3.77 s
25	83.9 s		83.9 s		71.3 s		71.3 s	
[a]26	25.1 q	1.67 s	25.2 q	1.67 s	25.8 q	1.48 s	25.8 q	1.47 s
[a]27	28.1 q	1.73 s	28.2 q	1.78 s	27.4 q	1.50 s	27.3 q	1.49 s
28	20.0 q	0.85 s	27.1 q	1.08 s	12.3 q	1.23 s	12.2 q	1.21 s
29	26.0 q	1.30 s	26.1 q	1.35 s	26.4 q	1.85 s	26.0 q	1.29 s
30	15.6 q	0.99 s	14.6 q	1.05 s	15.2 q	1.06 s	15.7 q	1.02 s
OAc	170.8 s	2.07 s			170.9 s	2.14 s	170.8 s	2.12 s
	21.9 q				22.0 q		22.0 q	
1′	107.7 d	4.82 d (7.9)	107.8 d	4.85 d (8.0)			107.8 d	4.83 d (8.0)
2′	75.8 d	3.99 t (7.9)	75.9 d	4.03 t (8.0)			75.9 d	4.01 t (8.0)
3′	78.8 d	4.13 t (7.9)	78.9 d	4.15 t (8.0)			78.9 d	4.14 t (8.0)
4′	71.5 d	4.17 (overlapped)	71.6 d	4.22 (overlapped)			71.5 d	4.19 dd (9.6, 4.8)
5′	67.3 t	3.70 t (10.8)	67.4 t	3.73 t (10.8)			67.4 t	3.71 t (10.8)
		4.33 dd (10.8, 4.8)		4.36 dd (10.8, 4.8)				4.33 dd (10.8, 4.8)

[a] May be interchanged.

δ_H 4.82 (^3J = 7.9 Hz) with C-3 (δ_C 88.4) and that of H-3 (δ_H 3.34) with C-1′ (δ_C 107.7) located the sugar moiety at C-3. The NMR spectroscopic data of compound **1** showed close resemblance with those of actaeaepoxide 3-*O*-β-D-xylopyranoside[6] except for significant changes at or around the C-7−C-8 bond. This reflected the presence of a C-7−C-8 single bond in **1** instead of the olefinic bond in actaeaepoxide 3-*O*-β-D-xylopyranoside.[6] The sugar obtained after acid hydrolysis was identified as D-xylose by comparing its TLC and specific rotation with a D-xylose authentic sample. The relative configuration of **1** was assigned on the basis of coupling constants, molecular models, and a NOESY experiment (Figure 2). The NOESY associations of H-3 with H-5; H-12 with H-17 and Me-28; H-17 with H-12, H-16, Me-21, H-22, and Me-28; and Me-21 with H-17 and H-22 suggested a β-orientation of the substituents at C-3, C-12, C-16, and C-22 (Figure 2), similar to actaeaepoxide 3-*O*-β-D-xylopyranoside.[6] Under the constraints of the β-oriented *O*-substitution at C-16 and C-22, a Dreiding model was consistent only with an α-oriented C-23−C-24 oxirane functionality. Compound **1** is thus 7,8-dihydroactaeaepoxide 3-*O*-β-D-xylopyranoside.

Compound **2** showed a molecular $[M + Na]^+$ ion at *m*/*z* 641.3670 in the positive HRESIMS, indicative of a molecular formula of $C_{35}H_{54}O_9$. When its ^{1}H and ^{13}C NMR data (Table 1) were compared with those of actaeaepoxide 3-*O*-β-D-xylopyranoside,[6] the resonances of an *O*-acetyl group were absent in **2**, showing instead a methylene functionality at C-12. The assignments of the ^{1}H and ^{13}C NMR data were facilitated by comparison with those of actaeaepoxide 3-*O*-β-D-xylopyranoside[6] and confirmed by HMQC, HMBC (Figure 1), and ^{1}H−^{1}H COSY data. The relative configuration of **2** was determined in a similar manner to that of 7,8-dihydroactaeaepoxide 3-*O*-β-D-xylopyranoside (**1**). Accordingly, compound **2** was characterized as 12-deacetoxyactaeaepoxide 3-*O*-β-D-xylopyranoside.

The positive ESIMS of compound **3** showed an $[M + Na]^+$ molecular ion at *m*/*z* 569, which, in conjunction with ^{13}C NMR data, established the molecular formula $C_{32}H_{50}O_7$. The 32 resonances in the ^{13}C NMR spectrum of **3** indicated a triterpenoid backbone bearing an *O*-acetyl group. Assignment of ^{1}H and ^{13}C NMR data (Table 1) in the usual manner (Figures 1 and 2) indicated that compound **3** comprised the unreported aglycon of 12β-acetoxycimigenol 3-*O*-β-D-xylopyranoside (**4**)[11] and cimiracemoside D.[5] Significant NOESY correlations (Figure 2) of H-12 with H-17 and Me-28; H-17 with H-12, Me-21, H-24, and Me-28; and H-3 with H-5 indicated their α-orientation, whereas the associations of

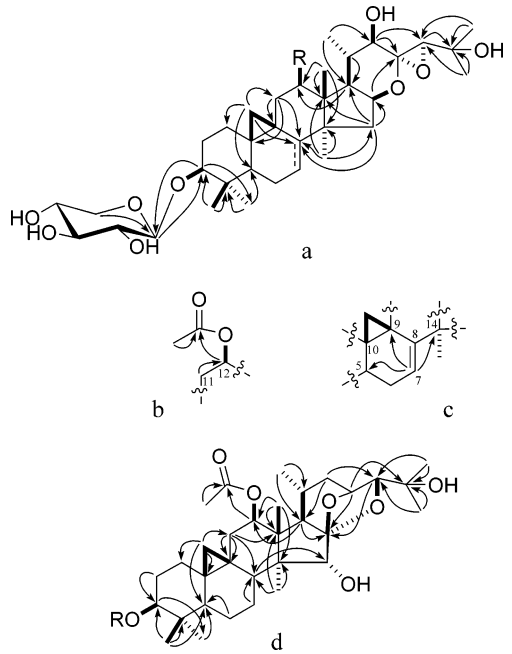

Figure 1. HMBC correlations of (a) compounds **1** and **2**, (b) compound **1**, (c) compound **2**, and (d) compounds **3** and **4**.

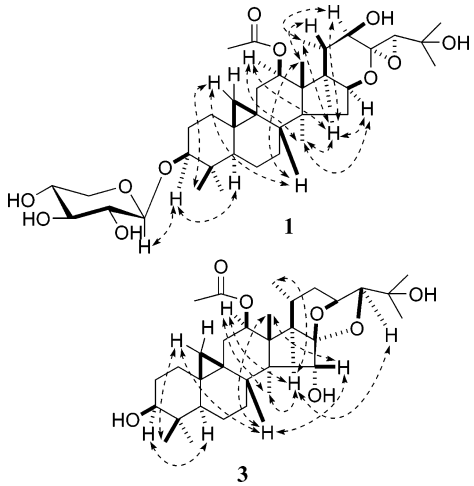

Figure 2. NOESY correlations of compounds **1** and **3**.

H-19 with H-8 and Me-30; H-8 with H-15, Me-18, and H-19; and H-15 with H-8 and Me-18, revealed their β-orientation. Thus, compound **3** is 12β-acetoxycimigenol.

12β-Acetoxycimigenol 3-*O*-β-D-xylopyranoside (**4**)[11] and similar compounds[5,7] were reported earlier. According to these reports, the ^{13}C NMR chemical shifts of C-13 and C-14 were assigned at δ_C 48.4 (48.5) and 46.1 (46.3), respectively. We have assigned the chemical shifts of C-13 and C-14 in both **3** and **4** at δ_C 46.6 and 48.8, respectively, on the basis of the HMBC correlation of H-11 (δ_H 2.94) to C-13 (δ_C 46.6) (Figures 1 and S1, Supporting Information).

Known compounds were characterized as 12β-acetoxycimigenol 3-*O*-β-D-xylopyranoside (**4**),[11] actaeaepoxide 3-*O*-β-D-xylopyranoside (**5**),[6] cimigenol 3-*O*-β-D-xylopyranoside (**6**),[6] 23-acetylshengmanol 3-*O*-β-D-xylopyranoside (**7**),[4] 23-*epi*-26-deoxyactein (**8**),[3] 25-*O*-acetylcimigenol 3-*O*-β-D-xylopyranoside,[12] 25-*O*-methylcimigenol 3-*O*-β-D-xylopyranoside,[12] cimigenol,[13] and 24-*O*-acetylhydroshengmanol 3-*O*-β-D-xylopyranoside.[14]

Compounds **1**−**8** did not show cytotoxic, estrogenic, antioxidant, and anticomplement activity, except 12β-acetoxycimigenol (**3**), which exhibited moderate anticomplement activity (see Supporting Information).

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Rudolph Research Auto Pol IV polarimeter. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. NMR spectra were recorded on a Varian AS 400 NMR spectrometer in pyridine-d_5. ESIMS data were obtained on an Agilent Series 1100 SL mass spectrometer. Gravity column chromatography was performed using silica gel (J.T.Baker, 40 μm for flash chromatography) and reversed-phase RP-18 silica (Polarbond, J.T.Baker). TLC was carried out on silica gel 60 F_{254} plates (Merck, Germany).

Plant Material. The roots of *A. pachypoda* Elliott were collected in Madison County, NC (August 2004), and identified by Mr. G. Gust, William L. Brown Center, Missouri Botanical Garden, St. Louis, MO. A voucher specimen (FDA #4) has been deposited at the Missouri Botanical Garden.

Extraction and Isolation. The freeze-dried roots of *A. pachypoda* were ground, and the resultant powder (382 g) was extracted with MeOH (0.75 L × 24 h × 5). The combined extract was evaporated under reduced pressure to afford a brown powder (28 g). A portion of this powder (22.0 g) was subjected to column chromatography on flash silica gel (40 μm) and eluted with mixtures of EtOAc−$CHCl_3$−MeOH−H_2O (15:8:4:1) to obtain fractions F1 (1.1 g) and F2 (6.7 g). Elution with a 12:8:8:2 mixture afforded fractions F3 (0.78 g) and F4 (4.1 g), followed by fraction F5 (2.2 g) on elution with MeOH. Fraction F2 (6.0 g) was resolved into 13 subfractions (F2A−F2M) by column chromatography over reversed-phase silica gel (RP-18, MeOH−H_2O, 7:3). Actaeaepoxide 3-*O*-β-D-xylopyranoside (**5**, 41 mg) was purified from fraction F2D (130 mg) by column chromatography (silica gel, EtOAc−$CHCl_3$−MeOH−H_2O, 15:8:4:1). Fraction F2E (1.0 g) was subjected to further column chromatography, initially over silica gel (EtOAc−$CHCl_3$−MeOH, 12:6:1) and then over octadecylsilyl silica gel (MeOH−H_2O, 7:3) to yield 7,8-dihydroactaeaepoxide 3-*O*-β-D-xylopyranoside (**1**, 117 mg) and actaeaepoxide 3-*O*-β-D-xylopyranoside (**5**, 169 mg). 23-*epi*-26-Deoxyactein (**8**, 52 mg) was obtained from fraction F2F (173 mg) via column chromatography (silica gel, $CHCl_3$−MeOH, 16:1). 23-Acetylshengmanol 3-*O*-β-D-xylopyranoside (**7**, 128 mg) and 12β-acetoxycimigenol 3-*O*-β-D-xylopyranoside (**4**, 170 mg) were purified from fraction F2H (1.1 g) by column chromatography over silica gel ($CHCl_3$−MeOH−H_2O, 9:1:0.7, and EtOAc−$CHCl_3$−MeOH, 12:6:1). Purification of fraction F2J (365 mg) on silica gel (EtOAc−$CHCl_3$−MeOH, 12:6:1) afforded 12β-acetoxycimigenol (**3**, 14 mg), 24-*O*-acetylhydroshengmanol 3-*O*-β-D-xylopyranoside (87.9 mg), and impure deacetoxyactaeaepoxide 3-*O*-β-D-xylopyranoside. 12-Deacetoxyactaeaepoxide 3-*O*-β-D-xylopyranoside (**2**) was purified (41 mg) by column chromatography over reversed-phase silica gel (MeOH−H_2O, 8:2). Cimigenol 3-*O*-β-D-xylopyranoside (**6**, 72 mg), 25-*O*-acetylcimigenol 3-*O*-β-D-xylopyranoside, 25-*O*-methylcimigenol 3-*O*-β-D-xylopyranoside (75 mg), and cimigenol (12 mg) were obtained from fraction F2M (871 mg) by column chromatography over silica gel (EtOAc−$CHCl_3$−MeOH, 12:6:1).

7,8-Dihydroactaeaepoxide 3-*O*-β-D-xylopyranoside (1): white powder; $[\alpha]^{25}_D$ −55.3 (*c* 0.13, MeOH); IR (KBr) ν_{max} 3415, 2949, 1728, 1638 cm^{-1}; ^{1}H and ^{13}C NMR, Table 1; positive ESIMS *m*/*z* 701 [M + Na]$^+$; HRESIMS *m*/*z* 701.3883 (calcd for $C_{37}H_{58}NaO_{11}$, 701.3877).

12-Deacetoxyactaeaepoxide 3-*O*-β-D-xylopyranoside (2): white powder; $[\alpha]^{27}_D$ −26.5 (*c* 0.40, MeOH); IR (KBr) ν_{max} 3416, 2926, 1645 cm^{-1}; ^{1}H and ^{13}C NMR, Table 1; positive ESIMS *m*/*z* 641 [M + Na]$^+$; HRESIMS *m*/*z* 641.3670 (calcd for $C_{35}H_{54}NaO_9$, 641.3666).

12β-Acetoxycimigenol (3): white powder; $[\alpha]^{29}_D$ −16.7 (*c* 1.2, MeOH); IR (KBr) ν_{max} 3428, 2929, 1731, 1652 cm^{-1}; ^{1}H and ^{13}C NMR, Table 1; positive ESIMS *m*/*z* 569 [M + Na]$^+$; HRESIMS *m*/*z* 569.3445 (calcd for $C_{32}H_{50}NaO_7$, 569.3454).

Acid Hydrolysis and Identification of the Sugar Moieties in Compounds 1 and 2. Compounds **1** and **2** (15 mg) were separately refluxed with 0.5 N HCl (3 mL) for 2 h. Each reaction mixture was diluted with water and extracted with $CHCl_3$. The water layer was evaporated to dryness under reduced pressure to give a monosaccharide, which had an R_f (EtOAc−$CHCl_3$−MeOH−H_2O, 12:8:8:4) and specific rotation $[\alpha]^{29}_D$ +20.7 (*c* 0.5, H_2O) comparable to those of D-xylose (Sigma-Aldrich).

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Supporting Information Available: Biological testing results, protocols, and figure showing the HMBC NMR spectrum of compound **4**. This information is available free of charge via the Internet at http://pubs.acs.org.

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