Cimiracemosides I−P, New 9,19-Cyclolanostane Triterpene Glycosides from *Cimicifuga racemosa*

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Eight new and 13 known triterpene glycosides, along with the known compounds glyceryl-1-palmitate and daucosterol-6′-linoleate were isolated from the roots/rhizomes of *Cimicifuga racemosa*. The new compounds, designated as cimiracemosides **I**−**P** (**1**, **3**−**9**), were determined by spectral analysis to be 7-dehydro-23-*epi*-12,26-dideoxyacteol-3-*O*-*β*-D-xylopyranoside (**1**), 12-*O*-acetyl-25-anhydrocimigenol-3-*O*-α-L-arabinopyranoside (**3**), 12-*O*-acetyl-25-anhydrocimigenol-3-*O*-*β*-D-xylopyranoside (**4**), 4′,23-*O*-diacetylshengmanol-3-*O*-*β*-D-xylopyranoside (**5**), 4′,23-*O*-diacetylshengmanol-3-*O*-α-L-arabinopyranoside (**6**), 23-*epi*-acetylacteol-3-*O*-α-L-arabinopyranoside (**7**), 4′-*O*-acetyl-26-deoxyactein (**8**), and 16*β*:23;24:25-diepoxy-12*β*-*O*-acetyl-3*β*-hydroxy-9,19-cyclolanost-23,26-olide-*O*- *β*-D-xylopyranoside (**9**).

Cimicifuga racemosa (L.) Nutt. (Ranunculaceae) or *Actaea racemosa* L.[1,2] is commonly known as black cohosh. It is widely used in the United States as a herbal dietary supplement for the relief of climacteric symptoms related to menopause.[3,4] Studies to date have resulted in the isolation of a number of triterpene glycosides.[5−15]

In our studies on the chemical characterization and standardization of *C. racemosa* extracts to be used in our biological and clinical studies, we previously reported the isolation of a new triterpene glycoside, 26-deoxyactein, and the correction of the existing nomenclature of 27-deoxyactein to 23-*epi*-26-deoxyactein.[16] In a continuation of our chemical investigation, we have isolated 21 additional triterpene glycosides and two other known compounds. In this paper, we describe the isolation and structure elucidation of eight new 9,19-cyclolanostane triterpene glycosides, cimiracemosides **I**−**P** (**1**, **3**−**9**), and the isolation and identification of 13 known triterpene glycosides, including 25-anhydrocimigenol-3-*O*-*β*-D-xyloside,[17] 25-anhydrocimigenol-3-*O*-α-L-arabinoside,[18] cimigenol-3-*O*-*β*-D-xyloside,[18] cimigenol-3-*O*-α-L-arabinoside,[19] 25-*O*-acetylcimigenol- 3-*O*-*β*-D-xyloside[19a] 25-*O*-acetylcimigenol-3-*O*-α-L-arabinoside,[20] 23-*O*-acetyl-shengmanol-3-*O*-α-L-arabinoside,[21] cimicifugoside H-1,[22] cimicifugoside H-2,[23] 24-*O*-acetylshengmanol,[24] 2′-*O*-acetylactein,[25] 23-*O*-acetylshengmanol-3-*O*-α-L-arabinoside,[8] and 26-deoxycimicifugoside (**2**).[26] Additionally, the known compounds glyceryl-1-palmitate[27] and daucosterol-6′-linoleate were also isolated.[28]

Results and Discussion

Cimiracemoside I (**1**) was isolated as a pale yellow powder. In the high-resolution positive HRTOF-ESIMS, it showed a quasi-molecular ion at *m*/*z* 623.3581 $[M + Na]^+$ for a molecular formula of $C_{35}H_{52}O_8$. Its IR spectrum showed absorption at 3420 cm^{-1} for OH. In the ^1H NMR spectrum (Table 1), the characteristic cyclopropane methylene signals at δ_H 0.46 and 0.97 (each 1H, d, $J = 3.5$ Hz); six methyl groups at δ_H 1.04, 1.10, 1.26, 1.35, 1.47, and 1.00 (d, $J = 6.4$ Hz); an anomeric proton at δ_H 4.87 (d, $J = 7.4$ Hz); and an olefinic proton at δ_H 5.08 (1H, d, $J = 6.2$ Hz) were observed. The ^{13}C and DEPT NMR spectra (Table 2) showed signals ascribable to three oxygen-bearing methine carbons at δ_C 88.1 (C-3), 74.9 (C-16), 62.6 (C-24); one oxygen-bearing methylene carbon at δ_C 68.0 (C-26); and two oxygen-bearing quaternary carbons at δ_C 106.2 (C-23) and 62.1 (C-25) for the aglycone moiety. These spectra also showed five oxygenated carbons assignable to a glycosidic moiety [δ_C 107.6 (C-1′), 75.6 (C-2′), 78.7 (C-3′), 71.3 (C-4′), 67.2 (C-5′)]. The $^1H-^1H$ COSY and HMQC spectra disclosed that **1** has partial structures of $-CH_2CH_2CH-$ (due to C_1 to C_3); $-CHCH_2CH(sp^2)-$ (for C_5 to C_7); $-CH_2CH_2-$ (for C_{11} to C_{12}); $-CH_2CHCHCH(CH_3)CH_2-$ (for C_{15} to C_{17}, C_{20} to C_{22}); two pairs of geminal signals for CH_2-19 and CH_2-26; and $-CHCHCHCHCH_2-$ (for C-1′ to C-5′) that were compatible for rings A, B, C, D, and part of E of a 9,19-cyclolanostane-type triterpene skeleton linked to a five-carbon glycoside unit.

The HMBC spectrum showed correlations between H-7 (δ_H 5.08) and a methine signal at δ_C 42.7 (C-5), a methylene signal at δ_C 21.8 (C-6), and signals of two quaternary carbons at δ_C 21.0 (C-9) and 49.8 (C-14); between H_a-15 (δ_H 2.11) and signals of two quaternary carbons at δ_C 44.1 (C-13) and 49.8 (C-14), a methine signal at δ_C 56.9 (C-17), and a methyl signal at δ_C 26.9 (C-28); between H_a-22 (δ_H 1.58) and a quaternary carbon at δ_C 106.2 (C-23), and methine carbons at δ_C 56.9 (C-17), 23.7 (C-20); and between H_b-26 (δ_H 3.61) and two quaternary carbon signals at δ_C 106.2 (C-23) and 62.1 (C-25). Additionally, the methyl signal at δ_H 1.46 (Me-27) showed correlations with a methylene signal at δ_C 68.0 (C-26), a methine signal at δ_C 62.6 (C-24), and a quaternary carbon signal at δ_C 62.1 (C-25). Therefore, the aglycone structure of **1** was elucidated as 7-dehydro-12,26-dideoxyacteol.

In the HMBC spectrum, a correlation was also observed between the proton signal at δ_H 4.87 (H-1′, 1H, d, $J = 7.4$ Hz) and the methine signal at δ_C 88.1 (C-3), suggesting that the sugar moiety was attached at the C-3 position (see Figure 1). The coupling constants ($J_{H1'-H2'} = 7.4$ Hz, $J_{H2'-H3'} = 6.9$ Hz, and $J_{H5'a-H4'} = 4.1$ Hz, $J_{H5'b-H4'} = 10.3$ Hz) indicated that the protons at C-1′, C-2′, C-3′, and C-4′ are in the *axial*-, *equatorial*-, *axial*-, *equatorial* direction, which means the hydroxyl groups at C-2′, C-3′, and C-4′ are in the α-, *β*-, and α-positions, as found in *β*-D-xylopyranoside.[29] The relative configuration of H-3 was assigned to an *axial*

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Table 1. ^{1}H NMR Data of Cimiracemoside **I**−**P** (**1**, **3**−**9**) in Pyridine-d_5[a]

proton	**1**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1	1.70 (m)	1.58 (brd. 12.2)	1.56 (brt, 12.4)	1.62 (overlapped)	1.60 (overlapped)	1.49 (overlapped)	1.51 (overlapped)	1.57 (overlapped)
	1.30 (m)	1.11 (brd. 14.4)	1.08 (brd. 14.4)	1.28 (overlapped)	1.28 (overlapped)	1.12 (overlapped)	1.12 (overlapped)	1.14 (overlapped)
2	2.33 (m, overlapped)	2.32 (m)	2.30 (m)	2.42 (m)	2.31 (m)	2.28 (m)	2.24 (m)	2.32 (m)
	1.30 (m, overlapped)	1.33 (m)	1.90 (m)	1.35 (m)	1.95 (m)	1.83 (m)	1.85 (m)	1.88 (m)
3	3.48 (brd, 7.5)	3.49 (dd, 3.1, 7.9)	3.49 (dd, 3.5, 10.8)	3.53 (dd, 4.3, 11.7)	3.55 (dd, 4.0, 12.8)	3.44 (dd, 4.2, 13.0)	3.43 (dd, 4.0, 11.4)	3.48 (brd, 7.0)
5	1.24 (overlapped)	1.77 (brd,12.4)	1.76 (brd, 12.2)	1.39 (overlapped)	1.39 (overlapped)	1.22 (overlapped)	1.21 (overlapped)	1.27 (overlapped)
6	1.80 (m)	1.56 (m)	1.53 (m)	1.60 (m)	1.59 (m)	1.38 (m)	1.27 (m)	1.43 (overlapped)
	1.46 (m)	0.75 (m)	0.73 (m)	0.76 (m)	0.79 (m)	0.63 (m)	0.67 (m)	0.70 (m)
7	5.08 (d, 7.2)	2.22 (m)	2.19 (m)	1.30 (overlapped)	2.10 (overlapped)	1.29 (overlapped)	1.25 (overlapped)	1.25 (overlapped)
		1.12 (m)	1.10 (m)	1.14 (overlapped)	1.18 (overlapped)	0.89 (overlapped)	0.89 (overlapped)	0.95 (overlapped)
8		1.29 (overlapped)	1.30 (overlapped)	1.88 (dd, 4.4, 12.4)	1.88 (dd, 4.6, 11.5)	1.60 (m)	1.62 (m)	1.63 (m)
11	2.09 (m)	2.29 (m)	2.26 (m)	2.10 (m)	2.10 (m)	2.71 (dd, 8.8, 15.4)	2.71 (m)	2.75 (m)
	1.11 (m)	1.03 (m)	1.02 (m)	1.15 (m)	1.15 (m)	1.16 (overlapped)	1.21 (overlapped)	1.21 (overlapped)
12	1.66 (2H) (m)	5.27 (brd, 7.8)	5.28 (brd, 7.6)	1.80 (2H) (m)	1.82 (2H) (m)	5.12 (overlapped)	5.10 (brd, 6.0)	5.11 (brd 6.8)
15	2.11 (brt, 8.6)	4.42 (s)	4.42 s	4.35 s	4.39 s	1.88 (m)	1.75 (m)	1.90 (overlapped)
	1.96 (dd, 6.3, 11.4)					1.76 (m)	1.55 (m)	1.64 (overlapped)
16	4.31 (dd, 6.7, 12.0)					4.24 (brt, 6.9)	4.62 (dd, 7.1, 14.3)	4.05 (brt, 7.7)
17	1.56 (t, 13.5)	1.65 (overlapped)	1.64 (overlapped)	2.35 (d, 6.5)	2.39 (d, 6.5)	1.79 (overlapped)	1.78 (overlapped)	1.86 (overlapped)
18	1.26 s	1.37 s	1.32 s	1.38 s	1.38 s	1.42 s	1.37 s	1.33 s
19	0.97 (d, 3.5)	0.61 (d, 4)	0.60 (d, 3.4)	0.59 (d, 3.7)	0.60 (d, 3.6)	0.54 (d, 3.6)	0.57 (d, 4.5)	0.57 (d, 3.8)
	0.46 (d, 3.5)	0.32 (d, 4)	0.32 (d, 3.4)	0.32 (d, 3.7)	0.33 (d, 3.6)	0.19 (d, 3.6)	0.23 (d, 4.5)	0.26 (d, 3.8)
20	2.26 (overlapped)	1.64 (overlapped)	1.64 (overlapped)	2.14 (overlapped)	2.13 (overlapped)	2.23 (overlapped)	1.80 (overlapped)	1.85 (overlapped)
21	1.00 (d, 6.4)	0.94 (d, 6.5)	0.95 (d, 6.5)	1.27 (d, 6.9)	1.27 (d, 6.8)	1.02 (d, 6.3)	0.98 (d, 6.5)	0.93 (d, 5.0)
22	1.58 (brd. 13.5)	2.94 (dd, 9.6, 15.4)	2.94 (dd, 9.5, 16.1)	2.69 (brt 12.2)	2.69 (brt, 12.8)	1.58 (overlapped)	2.24 (overlapped)	2.21 (overlapped)
	1.40 (brt, 14.7)	1.17 (brd, 15.3)	1.16 (brd, 16.1)	1.77 (m)	1.78 (m)	1.45 (overlapped)	1.70 (dd, 6.5, 18.0)	1.67 (overlapped)
23		4.31 (overlap)	4.30 (d, 8.5)	5.42 (brt, 8.4)	5.39 (brt, 8.4)			
24	3.70 s	4.12 (brs)	4.18 (brs)	3.05 (d, 8.4)	3.05 (d, 8.4)	3.68 s	3.95 s	4.41 s
26	4.04 (d, 10.2)	5.36 (brs)	5.35 (brs)	1.26 s	1.26 s	4.07 (d, 10.5)	5.76 s	
	3.61 (d, 10.2)	4.89 (brs)	4.89 (brs)			3.63 (d, 10.5)		
27	1.46 s	1.85 s	1.85 s	1.40 s	1.41 s	1.48 s	1.79 s	1.65 s
28	1.10 s	1.20 s	1.20 s	1.22 s	1.22 s	0.85 s	0.80 s	0.85 s
29	1.35 s	1.28 s	1.31 s	1.31 s	1.34 s	1.27 s	1.79 s	1.33 s
30	1.04 s	1.01 s	1.04 s	1.06 s	1.07 s	0.96 s	0.98 s	1.02 s
1′	4.87 (d, 7.4)	4.79 (d, 6.8)	4.84 (d, 7.4)	4.82 (d, 7.1)	4.90 (d, 7.2)	4.78 (d, 6.8)	4.85 (d, 7.3)	4.87 (d, 7.1)
2′	4.05 (overlapped)	4.44 (t, 7.8)	4.03 (dd, 8.0, 15.4)	4.48 (brt, 8.1)	4.29 (t, 8.6)	4.45 (t, 14.5)	4.04 (dd, 8.5, 8.3)	4.05 (m)
3′	4.18 (t, 6.9)	4.17 (overlapped)	4.15 (t, 8.4)	4.21 (d, 7.3)	4.08 (t, 6.7)	4.24 (d, 6.9)	4.28 (dd, 9.1,9.2)	4.20 (t, 8.6)
4′	4.24 (dd, 6.0, 9.0)	4.32 (overlapped)	4.21 (m)	5.61 brs	5.41 (overlapped)	4.33 (brs)	5.41 (ddd, 5.4, 9.7, 9.7)	4.22 (m)
5′	4.38 (dd, 4.5, 10.5)	4.31 (overlapped)	4.34 (dd, 4.8, 9.8)	4.28 (d, 12.6)	4.38 (overlapped)	4.31 (d, 11.0.2)	4.34 (dd, 5.5,11.4)	4.38 (m)
	3.76 (t, 10.3)	3.79 (brd, 11.3)	3.72 (dd, 9.8, 9.1)	3.85 (d, 12.6)	3.63 (t, 10.5)	3.80 (d, 11.0.2)	3.61 (dd, 10.9, 11.4)	3.76 (9.8, 10.1)
OAc		2.13 s	2.12 s	2.06 s	1.99 s	2.14 s	2.16 s	2.16 s
				2.12 s	2.07 s		1.99 s	

[a] TMS was used as internal standard; chemical shifts are in δ scale with J values in parentheses.

Table 2. ^{13}C NMR Data of Cimiracemosides **I**−**P** (**1**, **3**−**9**) in Pyridine-d_5[a]

C	1	3	4	5	6	7	8	9
1	30.9 t	32.4 t	32.4 t	32.2 t	32.2 t	31.9 t	31.9 t	31.9 t
2	29.6 t	30.1 t	30.0 t	30.1 t	30.0 t	29.8 t	29.5 t	29.9 t
3	88.1 d	88.3 d	88.3 d	88.8 d	88.5 d	88.1 d	88.2 d	88.1 d
4	40.4 s	41.3 s	41.3 s	41.4 s	41.4 s	41.2 s	41.2 s	41.2 s
5	42.7 d	47.2 d	47.2 d	47.5 d	47.4 d	47.0 d	46.9 d	45.7 d
6	21.8 t	20.8 t	20.8 t	21.0 t	21.1 t	20.3 t	20.4 t	20.4 t
7	113.5 d	26.0 t	26.0 t	26.7 t	26.4 t	25.6 t	25.6 t	25.7 t
8	149.2 s	47.2 d	47.2 d	48.3 d	48.3 d	45.6 d	45.7 d	47.0 d
9	21.0 s	20.1 s	20.1 s	20.1 s	20.1 s	20.1 s	20.1 s	20.1 s
10	23.7 s	26.8 s	26.8 s	26.8 s	26.8 s	26.7 s	26.7 s	26.8 s
11	25.3 t	38.5 t	38.5 t	26.0 t	26.7 t	36.6 t	36.7 t	36.6 t
12	32.9 t	77.3 d	77.3 d	33.1 t	33.1 t	77.1 d	77.0 d	76.8 d
13	44.1 s	48.4 s	48.4 s	41.6 s	41.6 s	48.8 s	48.7 s	48.8 s
14	49.8 s	46.1 s	46.1 s	46.1 s	46.1 s	47.8 s	47.8 s	48.0 s
15	43.0 t	79.3 d	79.3 d	83.0 d	83.0 d	44.1 t	43.5 t	43.2 t
16	74.9 d	112.3 s	112.3 s	220.0 s	220.0 s	74.7 d	73.0 d	75.6 d
17	56.9 d	59.6 d	59.6 d	60.0 d	60.0 d	56.2 d	56.4 d	55.6 d
18	22.9 q	12.7 q	12.7 q	19.8 q	19.8 q	13.5 q	13.5 q	13.5 q
19	28.3 t	30.9 t	30.9 t	30.5 t	30.0 t	29.5 t	29.8 t	29.6 t
20	23.7 d	23.9 d	23.9 d	28.0 d	28.0 d	23.3 d	26.0 d	25.3 d
21	20.8 q	19.8 q	19.8 q	20.4 q	20.4 q	21.3 q	21.0 q	20.7 q
22	37.5 t	37.5 t	37.5 t	37.0 t	37.0 t	37.5 t	37.6 t	35.6 t
23	106.2 s	74.7 d	74.6 d	72.1 d	72.1 d	105.9 s	105.8 s	106.2 s
24	62.6 d	86.5 d	86.5 d	65.2 d	65.2 d	62.5 d	63.4 d	62.7 d
25	62.1 s	145.8 s	145.8 s	58.6 s	58.6 s	62.2 s	65.8 s	58.6 s
26	68.0 t	113.2 t	113.2 t	24.7 q	24.7 q	68.1 t	98.4 d	172.4 s
27	14.3 q	18.1 q	18.1 q	19.4 q	19.4 q	14.3 q	13.1 q	11.1 q
28	26.9 q	12.0 q	12.0 q	12.0 q	12.0 q	19.6 q	19.5 q	19.5 q
29	25.8 q	25.7 q	25.7 q	25.7 q	25.7 q	25.7 q	25.6 q	25.7 q
30	14.3 q	15.4 q	15.4 q	15.5 q	15.4 q	15.3 q	15.3 q	15.3 q
1′	107.6 d	107.4 d	107.5 d	107.6 d	107.4 d	107.5 d	107.3 d	107.6 d
2′	75.6 d	73.0 d	75.6 d	73.2 d	75.0 d	72.9 d	75.7 d	75.4 d
3′	78.7 d	74.7 d	78.6 d	72.6 d	75.8 d	74.5 d	75.0 d	78.7 d
4′	71.3 d	69.5 d	71.6 d	72.1 d	73.2 d	69.6 d	73.1 d	71.3 d
5′	67.2 t	66.7 t	67.1 t	64.4 t	63.2 t	66.8 t	63.2 t	67.2 t
OAc		170.6 s	170.6 s	170.9 s	170.5 s	170.7 s	170.6 s	170.5 s
		21.7 q	21.7 q	170.7 s	170.5 s	21.7 q	170.6 s	21.6 q
				21.0 q	20.9 q		21.6 q	
				21.2 q	21.0 q		20.9 q	

[a] TMS was used as internal standard.

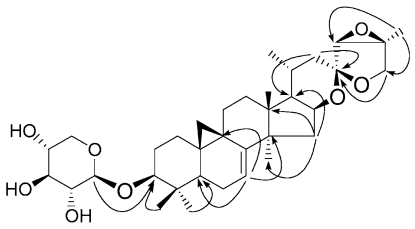
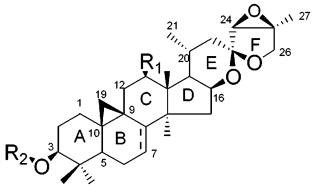


Figure 1. Major long-distance $^1H-^{13}C$ correlations of **1** observed by HMBC (300 MHz, pyridine-d_5).

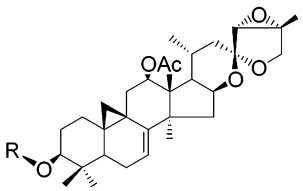
direction, i.e., the α-position on the basis of the coupling constants of H-3 with two protons at C-2 (brd, J_{H3-H2} = 7.5 Hz).

A comparison of the above data with those of **2** showed that, structurally, **1** closely resembles that of the known compound 26-deoxycimicifugoside (**2**),[26] except for the absence of an acetyl group at C-12 and the other differences between them at C-16 and C-20, which are very similar to the differences between 26-deoxyactein and 23-*epi*-26-deoxyactein.[16] By comparing the ^{13}C and ^1H chemical shifts of **1** with those of 26-deoxyactein and 23-*epi*-26-deoxyactein, the relative configurations of H-16 and H-24 were both determined to be in the α-position. The structure of **1** was thus elucidated as (23*S*)-16*β*,23:23*β*,26:24*β*:25-triepoxy-9, 19-cyclolanost-7-en-3*β*-*O*-*β*-D-xylopyranoside.

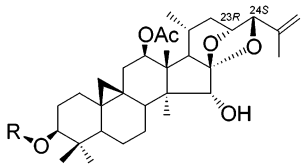
The spectral features of cimiracemosides J (**3**) and K (**4**) were very similar to each other. The HRTOF-ESIMS of both compounds exhibited a sodiated molecular ion at *m*/*z* 683.37 $[M + Na]^+$ (**3**, *m*/*z* 683.3763; **4**, *m*/*z* 683.3745) for the same molecular formula of $C_{37}H_{56}O_{10}Na$, which is 58 Da more than those of 25-anhydrocimigenol glycosides.[17,18] The IR spectrum of each compound showed hydroxyl and carbonyl absorptions at 3468, 1731 cm^{-1} (**3**) and 3425, 1732 cm^{-1} (**4**), respectively. The ^1H NMR spectra (Table 1) of **3** and **4** indicated the presence of the characteristic cyclopropane methylene signals [**3**, δ_H 0.32, 0.61 (each 1H, d, J = 4.0 Hz); **4**, δ_H 0.32, 0.59 (each 1H, d, J = 4.0 Hz)]; six methyl groups at δ_H 1.01, 1.20, 1.28, 1.37, 1.85, and 0.94 (d, J = 6.5 Hz) for **3**; δ_H 1.04, 1.20, 1.31, 1.32, 1.85, and 0.95 (d, J = 6.5 Hz) for **4**; an acetyl methyl (**3**, δ_H 2.13; **4**, δ_H 2.12); an anomeric proton (**3**, δ_H 4.79; **4**, δ_H 4.84); an oxygen-bearing methine proton (**3**, δ_H 5.27; **4**, δ_H 5.28); and two olefinic protons (**3**, δ_H 5.36, 4.89; **4**, δ_H 5.35, 4.89), suggesting both compounds are similar to 25-anhydrocimigenol glycoside and with an acetyl substituent group. In the ^{13}C NMR spectrum (Table 2) of both compounds, 37 carbons were evident, which represent two resonance signals more than those of 25-anhydrocimigenol glycosides. The DEPT resonance signals at δ_C 107.6 (d), 73.0 (d), 74.7 (d), 69.5 (d), and 66.7 (t) in **3** and at δ_C 107.6 (d), 75.6 (d), 78.6 (d), 71.6 (d), and 67.1 (t) in **4** indicated the presence of an arabinose and a xylose moiety, respectively.[17,18] The remaining 32 carbon signals were identified as the aglycone signals of an acetyl-containing 25-anhydrocimigenol.[17,18] The acetyl group was assigned to C-12 on the basis of the correlation of H-12 (**3**, δ_H 5.57; **4**, δ_H 5.58) with the acetyl at δ_C 170.6 in the HMBC spectrum and the correlation of H-12 with H_2-11 (**3**, δ_H 1.03, 2.29; **4**, δ_H 1.02, 2.26) in the



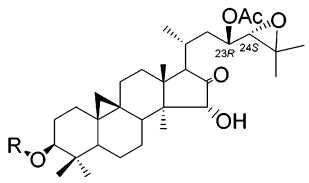
1. R_1 = H, R_2 = β-D-xyloside, Δ^7, 23*S*
7. R_1 = OAc, R_2 = α-L-arabinoside, 23*S*



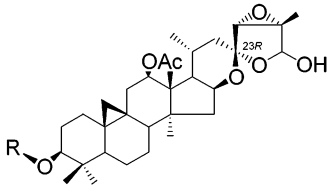
2. 26-deoxycimicifugoside



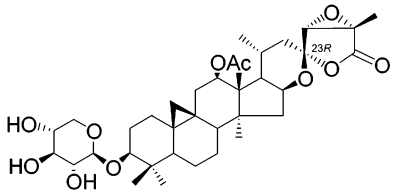
3. R = α-L-arabinoside, 23*R*, 24*S*
4. R = β-D-xyloside, 23*R*, 24*S*



5. R = 4'-O-acetyl-α-L-arabinoside, 23*R*, 24*S*
6. R = 4'-O-acetyl-β-D-xyloside, 23*R*, 24*S*



8. R = 4'-O-acetyl-β-D-xyloside, 23*R*



9. 23*R*

^{1}H−^{1}H COSY spectrum. The configurations of C-23 and C-24 were assigned as *R* and *S*, respectively, by comparing the coupling constants of the C-23 and C-24 proton signals of **3** and **4** with those of known 9,19-cyclolanostane triterpene glycosides.[7] Therefore, **3** and **4** were elucidated as (23*R*,24*S*)-16*β*,23:16α,24-diepoxy-12*β*-acetyoxyl-15α-hydroxy-9,19-cyclolanost-25-en-3*β*-*O*-α-L-arabinopyranoside (**3**) and (23*R*,24*S*)-16*β*,23:16α,24-diepoxy-12*β*-acetyoxyl-15α-hydroxy-9,19-cyclolanost-25-en-3*β*-*O*-*β*-D-xylopyranoside (**4**), respectively.

Cimiracemoside L (**5**) was isolated as a white powder. The high-resolution positive TOF-ESIMS established the molecular formula of **5** as $C_{39}H_{60}O_{11}$. The IR spectrum showed absorptions of hydroxyl and carbonyl groups at 3466 and at 1737 cm^{-1}, respectively. The ^{1}H NMR spectrum (Table 1) displayed cyclopropane methylene signals at δ_H 0.32 and 0.59 (each 1H, d, J = 3.7 Hz); seven methyl groups at δ_H 1.06, 1.22, 1.26, 1.31, 1.38, 1.40, and 1.27 (d, J = 6.9 Hz); two acetyl methyls at δ_H 2.06 and 2.12; and an anomeric proton at δ_H 4.82 (d, J = 7.1 Hz), suggesting **5** to be a 9,19-cyclolanostane triterpene glycoside with two acetyl groups. Furthermore, two significant downfield signals were observed at δ_H 5.61 (brs) and 5.42 (brt, J = 8.4 Hz) in the ^{1}H−^{1}H COSY spectrum. The proton at δ_H 5.61 showed correlations with the methine signal at δ_H 4.21 (H-3′) and with the methylene signals at δ_H 4.28 and 3.85 (H_2-5′). The methine signal at δ_H 4.21 showed correlations with a second methine signal at δ_H 4.48 (H-2′), which, in turn, showed a correlation with an anomeric proton at δ_H 4.82. From this evidence, we can deduce that an acetyl group is attached at C-4′. This conclusion was also supported by an analysis of the HMBC spectrum, which showed correlation between the H-4′ and the acetyl group signal at δ_C 170.7. The signal at δ_H 5.42 showed correlations with a methine signal at δ_H 3.04 (H-24) and methylene signals at δ_H 2.69 and 1.77 (H_2-22), indicating an acetyl group being attached to C-23. Significant HMBC correlations were observed between the quaternary carbon signal at δ_C 220.0 (C-16) and H-15 (δ_H 4.35) and between the methine signal at δ_C 83.0 (C-15) and H-17 (δ_H 2.35), C-15 and Me-28 (δ_H 1.22). The configurations of C-23 and C-24 were assigned as *R* and *S*, respectively, by comparing the coupling constants of the C-23 and C-24 proton signals of **5** with those of known 9,19-cyclolanostane triterpene glycosides.[22] The aglycone, therefore, was identified as 23-*O*-acetylshengmanol,[22] and the structure of **5** was elucidated as (23*R*,24*S*)-23,4′-*O*-diacetyloxy-24α,25-epoxy-3*β*-*O*-(α-L-arabinopyranosyloxy)-1α-hydroxy-9,19-cyclolanostan-16-one.

The molecular formula of cimiracemoside M (**6**) was determined as $C_{39}H_{60}O_{11}$, which is identical to **5** by high-resolution positive TOF-ESIMS. The IR and NMR data of **6** were also very similar to those of **5**. The major difference in the ^{1}H NMR of the two compounds involves the anomeric proton. The signals at δ_H 4.82 (d, J = 7.1 Hz) in **5** was shifted downfield to δ_H 4.90 (d, J = 7.2 Hz) in **6**; δ_H 4.48 for H-2′ in **5** was shifted to δ_H 4.29 in **6**; and δ_H 4.21 for H-3′ in **5** shifted upfield to δ_H 4.09 in **6**. In the ^{13}C and DEPT NMR spectra (Table 2), **6** exhibited signals very similar to those of **5**, except for the sugar moiety. The signals at δ_C 107.4 (d), 75.0 (d), 75.8 (d), 73.2 (d), and 63.2 (t) are assignable to a xyloside with an acetyl group attached at C-4′. The signals of the other 32 carbon signals were identical to the aglycone signals of **5**. Therefore, **6** was deduced to be (23*R*,24*S*)-23,4′-*O*-diacetyloxy-24α,25-epoxy-15α-hydroxy-3*β*-*O*-(*β*-D-xylopyranosyloxy)-9,19-cyclolanostan-16-one.

Cimiracemoside N (**7**) was isolated as a pale yellow powder. In the high-resolution positive TOF-ESIMS, it showed a quasi-molecular ion at m/z 661.3962 [M + H]$^+$ for a molecular formula of $C_{37}H_{56}O_{10}$, which is identical to 26-deoxyactein.[15] The IR spectrum indicated the presence

of hydroxyl and ester carbonyl groups at 3454 and 1729 cm^{-1}, respectively. The NMR spectra of **7** resemble those of 26-deoxyactein, with the main difference being that the anomeric proton at δ_H 4.86 (d, J = 7.6 Hz) was shifted upfield to δ_H 4.78 (d, J = 6.8 Hz) and the H-2′ signal shifted downfield from δ_H 4.05 (t, J = 7.8 Hz) in 26-deoxyactein to δ 4.45 in **7**, respectively.

Comparative analysis of the ^1H, ^{13}C, and DEPT NMR spectra of **7** with those of 26-deoxyactein and 23-*epi*-26-deoxyactein showed them to be similar except for the glycoside signals, which at δ_C 107.6 (d), 72.9 (d), 74.5 (d), 69.6 (d), and 66.8 (t) indicated the presence of arabinose instead of the xylose moiety found in 23-*epi*-26-deoxyactein. Therefore, the structure of **7** was established as (23*S*)-16β,-23:23β,26:24β,25-triepoxy-12β-acetyloxy-9,19-cyclolanostan-3β-*O*-β-D-xylopyranoside.

Cimiracemoside O (**8**) (a pale yellow powder) gave a quasi-molecular ion at *m/z* 701.3889 $[M - H_2O + H]^+$ (HR TOF-ESIMS, molecular formula, $C_{39}H_{58}O_{12}$). Its IR and NMR spectra were very similar to those of **7**. The ^1H NMR spectrum of **8** differed from **7** in that the anomeric proton of **7** at δ_H 4.78 (d, J = 6.8 Hz) was shifted downfield to δ_H 4.85 (d, J = 7.3 Hz) in **8**. At the same time, the signal for H-2′ was shifted upfield to δ_H 4.04 (dd, J = 7.4, 15.4 Hz) and the signal for H-4′ was shifted downfield to δ_H 5.41 (ddd, J = 5.4, 9.7, 9.7 Hz) in **8**. The downfield shift of H-4′ in **8** can be explained by the presence of an acetyl group being attached to it. Moreover, the glycosidic signals observed at δ_C 107.3 (d), 75.7 (d), 75.0 (d), 73.1 (d), and 63.2 (t) are assignable to a xyloside containing an acetyl at C-4′.[19] Supportive evidence was obtained from the HMBC spectrum, which showed a correlation between the H-4′ signal and acetyl group signal at δ_C 170.7. Comparison of the NMR data of **8** with those of actein indicated that the signals were identical except for those of the sugar moiety. Thus, the configuration of **8** should be the same as actein, and the structure of **8** was assigned as (23*R*)-16β,23:23α,26:24α,25-triepoxy-12,4′-26-hydroxydiacetyloxy-9,19-cyclolanost-7-en-3β-*O*-β-D-xylopyranoside.

Cimiracemoside P (**9**), isolated as a pale yellow powder, gave a molecular formula ($C_{37}H_{54}O_{11}$, HRTOF-ESIMS at *m/z* 675.3758 $[M + H]^+$) that is 2 Da less than that of **7**. Its IR spectrum was very similar to that of **7** except for the presence of a lactone absorption at 1787 cm^{-1}. The NMR data of **9** were also very similar to those of **7**, except for the presence of two proton signals at δ_H 3.63 and 4.07 that were not observed in **9**. The anomeric proton of the glycone moiety at δ_H 4.79 (d, J = 6.8 Hz) in **7** was shifted downfield to δ_H 4.87 (d, J = 7.1 Hz) in **9**. The signal at δ 4.05 for H-2′ in **9** was shifted upfield from δ_H 4.45 in **7**. The ^{13}C and DEPT NMR spectra of **9** (Table 2) were also very similar to those of **7** except for the sugar signals and the absence of the methylene signal at δ_C 68.1 found in **7**. The ^{13}C signals at δ_C 107.6 (d), 75.4 (d), 78.7 (d), 71.3 (d), and 67.2 (t) belonged to a xyloside. In the HMBC spectrum, the Me-27 (δ_H 1.65) showed a correlation with the ester carbonyl signal at δ_C 172.4 (C-26), which in turn showed a correlation with a methine signal at δ_C 62.7 (C-24), and a quaternary carbon signal at δ_C 58.6 (C-25). The aglycone of **9** was therefore identified as 26-oxo-acetylacteol. The relative configuration of **9** was determined by analysis of its NMR data and those of actein. The structure of **9** was elucidated as (23*R*)-16β,23:24α,25-diepoxy-12β-acetyloxy-9,19-cyclolanost-23α,26-olide-3-*O*-β-D-xylopyranoside.

In addition to the above eight triterpene glycosides being described for the first time from nature, 13 known compounds of previous known structures were identified as 25-anhydrocimigenol-3-*O*-β-D-xyloside,[17] 25-anhydrocimigenol-3-*O*-α-L-arabinoside,[18] cimigenol-3-*O*-β-D-xyloside,[18] cimigenol-3-*O*-α-L-arabinoside,[19] 25-*O*-acetylcimigenol- 3-*O*-β-D-xyloside,[20] 25-*O*-acetylcimigenol-3-*O*-α-L-arabinoside,[19a] 23-*O*-acetylshengmanol-3-*O*-α-L-arabinoside,[21] cimicifugoside H-1,[22] cimicifugoside H-2,[23] 24-*O*-acetylshengmanol,[24] 2′-*O*-acetylactein,[25] 23-*O*-acetylshengmanol-3-*O*-α-L-arabinoside,[8] 26-deoxycimicifugoside (**2**),[26] glyceryl-1-palmitate,[27] and daucosterol-6′-linoleate[28] by comparing their NMR data to the literature.

Experimental Section

General Experimental Procedures. Melting points were determined on a Fisher-Johns melting point apparatus. Optical rotations were obtained with a Perkin-Elmer 241 polarimeter (Perkin-Elmer, Inc., MA). ^1H and ^{13}C NMR were measured on a Bruker Avance 500 or 300 MHz instrument (Bruker, Zürich, Switzerland) using TMS as internal standard for chemical shifts. Chemical shifts (δ) were expressed in ppm with reference to the TMS signal. HR-ESI data were recorded on a Micromass (Manchester, UK) Q-TOF-2 system. Infrared spectra were recorded on an ATI Mattson Genesis Series FTIR (ATI Mattson Instruments Inc., WI) by using liquid layer on NaCl. Thin-layer chromatography was performed on precoated TLC plates (250 μm thickness, K6F Si gel 60 and K6F RP-18 Si gel 60, EM Science, Germany) with compounds visualized by spraying the dried plates with 5% H_2SO_4 in 1-BuOH and followed by heating until dryness. Semipreparative HPLC was carried out on a Waters Delta 600 system with a Waters 996 photodiode array detector, Waters 717 plus autosampler, and Millennium^{32} Chromatography Manager (Waters Co, MA) on a GROM-Sil 120 ODS-4 HE (Watrex-International, Inc., NY) semipreparative column (5 μm, 300 × 20 mm) with a flow rate of 6 mL/min. Reversed-phase column chromatography was carried out on Merck Lobar Lichroprep RP-18 columns (EM Science, Germany) with a Fluid pump (FMI, Fluid Metering, Inc., NY) and fraction collector (Spectrum, Spectrum Chromatography, TX). Silica gel (230−400 mesh, Davsil, W.R. Grace & Co., MD) was used for column chromatography.

Plant Material. *Cimicifuga racemosa* (L.) Nutt. roots/rhizomes were collected in Rockbridge County, Virginia (June 1999), GPS coordinates 37 48.27 N × 79 18.67 W, and identified by Dr. G. Ramsey, Department of Biology, Lynchburg College, Lynchburg, VA. Voucher specimens have been deposited at the Ramsey-Freer Herbarium at Lynchburg College, Lynchburg, VA, and at the Field Museum of Natural History Herbarium, Chicago, IL.

Extraction and Isolation. The dried, milled roots/rhizomes of *C. racemosa* (8 kg) were extracted with MeOH and fractionated by successive partitions with EtOAc and 1-BuOH. The EtOAc-soluble fraction was chromatographed on a silica gel (2kg) column to give eight fractions as described previously.[16] Fraction IV (2.3 g) was subjected to normal-phase silica gel column chromatography (100 g) and gradient elution with a solvent system of chloroform−MeOH (40:1 in increasing polarity to 20:1) to afford five fractions (CR-4-SF-I to CR-4-SF-V). The fraction CR-4-SF-I (1.2 g) was subjected to Sephadex LH-20 column chromatography (30 g) and eluted by MeOH to yield the fractions CR-4-SF-I-A to CR-4-SF-I-E (100 mL each). Chromatography of fraction CR-4-SF-I-B (1.0 g) on a silica gel column (100 g), eluting with a petroleum ether−ethyl acetate mixture (gradient of increasing polarity from 2:1 to 1:1), yielded seven major subfractions, CR-4-SF-I-B-1 to CR-4-SF-I-B-7. Separation of CR-4-SF-I-B-1 (450 mg) on a Lichroprep RP-18 column (Lobar, 310 × 25 mm, ACN−H_2O, 70:30) yielded glyceryl-1-palmitate (5 mg, 0.0013% of dried plant material); elution with 100% ACN led to 430 mg of crude daucosterol-6′-linoleate, which was purified on a silica gel column (60 g, elution with $CHCl_3$−acetone, 3:1) to yield daucosterol-6′-linoleate (400 mg, 0.05%). Chromatography of CR-4-SF-I-B-2 (90 mg), first on a Lichroprep RP-18 column (Lobar, 240 × 10 mm, ACN−H_2O, 70:30), followed by a silica

gel (30 g) column, eluting with petroleum ether−EtOAc−MeOH (10.0:4.0:0.5) gave 24-*O*-acetylshengmanol (4.5 mg, 0.0012%). Compounds **6** (6.1 mg, 0.0016%), **8** (5.0 mg, 0.0013%), and **5** (7.0 mg, 0.0018%) were separately obtained by successive chromatographic separation of the respective subfractions, CR-4-SF-I-B-3 (90 mg), CR-4-SF-I-B-4 (85 mg), and CR-4-SF-I-B-5 (100 mg), under the same conditions on a Lichroprep RP-18 column (Lobar 240 × 10 mm, ACN−H_2O, 65:35), followed by a silica gel (30 g) column (eluting with petroleum ether−EtOAc−MeOH, 10.0:4.0:0.5). Separation of CR-4-SF-I-B-7 (90 mg) in a similar manner (Lichroprep RP-18 column: Lobar 240 × 10 mm, ACN−H_2O, 55:45; silica gel: 30 g, petroleum ether−EtOAc−MeOH, 10.0:4.0:0.5) yielded 2′-*O*-acetylactein (7.0 mg, 0.0022%).

Fraction V (23 g) was subjected to a normal-phase silica gel (250 g) column eluted by a gradient solvent system of increasing polarity of petroleum ether−ethyl acetate from 3:1 to 1:2 to afford 10 subfractions (CRSF-I to CRSF-X). Chromatographic separation of subfraction CR-SF-I (1.8 g) on successive columns of Lichroprep RP-18 (Lobar, 310 × 25 mm), eluted by MeOH−H_2O, 70:30, and ACN−H_2O, 55:45, respectively, followed by separation on a column of silica gel (100 g) using petroleum ether−EtOAc−MeOH (10.0:4.5:0.5) led to the isolation of 23-*O*-acetylshengmanol-3-*O*-α-L-arabinoside (8.1 mg, 0.0021%) and 23-*O*-acetylshengmanol-3-*O*-β-D-xyloside (7.3 mg, 0.0019%). Chromatographic treatment of subfraction CR-SF-II (2.8 g) in the same manner as for CR-SF-I afforded cimigenol-3-*O*-β-D-xyloside (24 mg, 0.0063%), cimigenol-3-*O*-α-L-arabinoside (7.1 mg, 0.0019%), and 26-deoxyactein (4 mg). Cimigenol-3-*O*-β-D-xyloside (6 mg, 0.0016%) was obtained from the post 26-deoxyactein mother liquor[16] of subfraction CR-SF-III by successive column chromatography on Lichroprep RP-18 (Lobar, 240 × 10 mm, first with ACN−H_2O, 45:55, then by MeOH−H_2O, 60:40) and a silica gel column (30 g, elution by petroleum ether−EtOAc−MeOH, 10.0:5.0:0.5). Separation of subfraction CR-SF-IV (1.9 g) by Lichroprep RP-18 column (Lobar, 310 × 25 mm, initially with ACN−H_2O, 40:60, followed by MeOH−H_2O, 60:40) and a silica gel column (80 g, petroleum ether−EtOAc−MeOH, 10.0:5.0:0.5) led to 26-deoxycimicifugoside (**2**, 3.0 mg 0.00079%) and the novel isolates **3** (7.3 mg, 0.0019%), **4** (9.4 mg, 0.0025%), and **9** (5.1 mg, 0.0013%). Successive Lichroprep RP-18 (Lobar, 310 × 25 mm) chromatography of subfraction CR-SF-VI (1.8 g) on columns eluted by MeOH−H_2O, 50:50, and ACN−H_2O, 35:65, respectively, followed by silica gel (100 g) column chromatography, eluting with petroleum ether−EtOAc−MeOH (10.0:6.5:0.5), yielded 25-anhydrocimigenol-3-*O*-β-D-xyloside (30 mg, 0.0039%), 25-anhydrocimigenol-3-*O*-α-L-arabinoside (5.1 mg, 0.0013%), and an additional quantity of 23-*epi*-26-deoxyactein (5.1 mg). Workup of subfraction CR-SF-VII (0.9 g) on silica gel (petroleum ether−EtOAc−MeOH, 10.0:7.0:0.5), Lichroprep RP-18 (Lobar, 310 × 25 mm, MeOH−H_2O, 40:60), and semipreparative HPLC on a C-18 column (linear gradient from 30% to 70% ACN in water over 40 min) gave **1** (3.2 mg, 0.0008%). Chromatography of subfraction CR-SF-VIII (1.9 g) on two successive Lichroprep RP-18 columns (Lobar, 310 × 25 mm; solvent for column 1: MeOH−H_2O, 25:75; solvent for column 2: ACN−H_2O, 25:75) and a silica gel column (100 g, petroleum ether−EtOAC−MeOH, 10.0:4.5:0.5) led to 25-*O*-acetylcimigenol-3-*O*-β-D-xyloside (40 mg, 0.01%), 25-*O*-acetylcimigenol-3-*O*-α-L-arabinoside (30 mg, 0.0079%), and **7** (30 mg, 0.0079%). Under identical conditions, subfractions CR-SF-IX (1.7 g) and CR-SF-X (0.9 g) gave respectively cimicifugoside H-2 (8 mg, 0.0021%) and cimicifugoside H-1 (13 mg, 0.0034%).

Cimiracemoside I (1): pale yellow powder, mp >300 °C (began decomposing at 250 °C), $[\alpha]^{20}_D$ −13.13° (*c* 0.267, $CHCl_3$); ^1H, ^{13}C NMR, Tables 1 and 2; IR ν_{max} (cm^{-1}) 3485, 3409, 2923, 1454, 1379, 1038, 966; HRESIMS *m/z* 623.3581 (calc 623.3560 for $C_{35}H_{52}O_8Na$).

Cimiracemoside J (3): pale yellow powder, mp 138−140 °C, $[\alpha]^{20}_D$ −14.23° (*c* 0.260, $CHCl_3$); ^1H, ^{13}C NMR, Tables 1 and 2; IR ν_{max} (cm^{-1}) 3468, 2933, 2869, 1731, 1454, 1377, 1240, 1067, 755; HRESIMS *m/z* 683.3763 (calc 683.3771 for $C_{37}H_{56}O_{10}Na$).

Cimiracemoside K (4): pale yellow powder, mp 142−143 °C, $[\alpha]^{20}_D$ −59.32° (*c* 0.147, $CHCl_3$); ^1H, ^{13}C NMR, Tables 1 and 2; IR ν_{max} (cm^{-1}) 3425, 2935, 2869, 1732, 1456, 1376, 1233, 1042, 760; HRESIMS *m/z* 683.3745 (calc 683.3771 for $C_{37}H_{56}O_{10}Na$).

Cimiracemoside L (5): white powder, mp 125−128 °C, $[\alpha]^{20}_D$ −41.11° (*c* 0.450, $CHCl_3$); ^1H, ^{13}C NMR, Tables 1 and 2; IR ν_{max} (cm^{-1}) 3466, 2937, 2871, 1737, 1455, 1376, 1241, 1089, 757; HRESIMS *m/z* 705.4205 (calc 705.4214 for $C_{39}H_{61}O_{11}$).

Cimiracemoside M (6): white powder, mp 107−109 °C, $[\alpha]^{20}_D$ −19.00° (*c* 0.30, $CHCl_3$); ^1H, ^{13}C NMR, Tables 1 and 2; IR ν_{max} (cm^{-1}) 3465, 2933, 2866, 1732, 1370, 1235, 1041, 750; HRESIMS *m/z* 727.4041 (calc 727.4033 for $C_{39}H_{60}O_{11}Na$).

Cimiracemoside N (7): pale yellow powder, mp 172−174 °C, $[\alpha]^{20}_D$ −70.36° (*c* 0.367, $CHCl_3$); ^1H, ^{13}C NMR, Tables 1 and 2; IR ν_{max} (cm^{-1}) 3454, 2935, 2871, 1729, 1455, 1372, 1244, 1070, 1030, 754; HRESIMS 661.3962 (calc 661.3952 for $C_{37}H_{57}O_{11}$).

Cimiracemoside O (8): pale yellow powder, mp 143−145 °C, $[\alpha]^{20}_D$ −60.00° (*c* 0.160, $CHCl_3$); ^1H, ^{13}C NMR, Tables 1 and 2; IR ν_{max} (cm^{-1}) 3449, 2940, 2869, 1732, 1455, 1371, 1241, 1048, 983, 755; HRESIMS *m/z* 701.3889 (calc 701.3901 for $C_{39}H_{57}O_{11}$ [M − H_2O + H]$^+$).

Cimiracemoside P (9): pale yellow powder, mp 151−153 °C, $[\alpha]^{20}_D$ −69.77° (*c* 0.440, $CHCl_3$); ^1H, ^{13}C NMR, Tables 1 and 2; IR ν_{max} (cm^{-1}) 3423, 2956, 2934, 2870, 1787, 1731, 1454, 1362, 1243, 1041, 968, 753; HRESIMS *m/z* 675.3758 (calc 675.3744 for $C_{37}H_{55}O_{11}$).

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