Antitumor Agents. 180.[1] Chemical Studies and Cytotoxic Evaluation of Cumingianosides and Cumindysoside A, Antileukemic Triterpene Glucosides with a 14,18-Cycloapotirucallane Skeleton

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Treatment of cumingianosides and cumindysoside A, which possess a 14,18-cycloapotirucallane skeleton, with *p*-toluenesulfonic acid in CH_2Cl_2 yielded new triterpene glucosides. Cumingianoside A (**1**) gave **10** and **11**, along with cumingianoside Q (**5**). The structures of **10** and **11** were determined on the basis of spectral examination and contained a dammar-13(17)-ene and a 17(*R*),23(*R*)-epoxydammarane skeleton, respectively. Cumingianoside C (**2**) afforded, together with cumingianoside P (**6**), products **12** and **13**, which were similar to **10** and **11**, respectively. With a short reaction time at room temperature, cumingianoside E (**3**) yielded cumingianoside D (**4**). In contrast, when **3** was treated with *p*-toluenesulfonic acid in CH_2Cl_2 overnight at 5 °C, it gave two products, **9** and **14**. Extensive spectroscopic examination revealed that **9** possessed a dammar-12-ene skeleton, while **14** was a pentacyclic tetranortriterpene glucoside with a novel skeleton. Cumindysoside A (**8**) gave a product (**15**) similar to **14**. The cytotoxicities of **9**−**15** were evaluated against a panel of 58 human tumor cell lines. Compounds **11**−**15** exhibited potent cytotoxicity with log GI_{50} values ranging from −7.11 to −4.94, especially against leukemia and colon-tumor cell lines.

In our search for novel plant antitumor agents active against human tumor cell lines, we previously investigated the MeOH extract of the leaves of *Dysoxylum cumingianum* C. D.C. (Meliaceae) and identified cumingianosides P and Q with an apotirucallane skeleton together with 15 triterpene glucosides, cumingianosides A−O, and trisnor- and tetranortriterpene glucosides, cumindysosides A and B, respectively, with a 14,18-cycloapotirucallane skeleton.[2−5] Among them, cumingianosides A (**1**) and C (**2**) exhibited potent selective cytotoxicity against MOLT-4 human leukemia cells with ED_{50} values of <0.006 25 μM and <0.0045 μM, respectively. In the course of the structure elucidation and semisynthesis of cumingianoside Q (**5**), treatment of cumingianoside A (**1**) with *p*-toluenesulfonic acid in CH_2Cl_2 was found to furnish mainly unknown products (**10** and **11**), along with a small amount of **5**. This finding prompted our structure elucidation of these new products. Similar reactions of cumingianosides C (**2**) and E (**3**) and of cumindysoside A (**7**) were also carried out, and the structures of those products (**9, 12**−**15**) were elucidated. Evaluation of the cytotoxicities of these products was also of interest, insofar as cumingianosides are accumulated in relatively large amounts in the leaves of *Dysoxylum cumingianum* and could be natural sources of new cytotoxic compounds. This paper describes the structure determination of these products and evaluates their cytotoxicities against a panel of 58 human tumor cell lines.

Results and Discussion

Treatment of cumingianoside A (**1**) with *p*-toluenesulfonic acid in CH_2Cl_2 at room temperature overnight furnished **10** and **11**, together with cumingianoside Q (**5**). Compound **10** showed a similar R_f value to that of **1**, while compound **11** had a higher R_f value than that of **1** on Si gel TLC. Compounds **10** and **11** gave the same $[M - H]^-$ ion peak at *m*/*z* 737 using negative FABMS, and the molecular formula was confirmed as $C_{40}H_{66}O_{12}$. ^{1}H- and ^{13}C-NMR data are shown in Tables 1 and 2, respectively.

The ^{1}H-NMR spectrum of **10** exhibited the presence of seven tertiary methyl groups (δ 0.90, 0.91, 0.96, 1.18, 1.52, 1.54, and 1.59) and a secondary methyl group [δ 1.14 (d, J = 7 Hz)]; in contrast, cumingianoside A (**1**) contains only six tertiary methyl groups and a secondary methyl group. At relatively low field, **10** also displayed, along with an anomeric proton signal [δ 4.73 (d, J = 8 Hz)] and deshielded glucosyl H-6 signals [δ 4.70 (dd, J = 5.5, 12 Hz) and 4.94 (br d, J = 12 Hz)], four oxygen-bearing methine signals at δ 3.49 (d, J = 1 Hz), 4.13 (br s), 4.20 (br d, J = 8 Hz), and 4.95 (br s), which were assignable to H-24, H-7, H-23, and H-3, respectively, based on their coupling patterns, which correlated closely with the same signals in **1**. The absence of the cyclopropyl methylene signals seen in **1**, combined with the observation of the additional tertiary methyl, suggested that the cyclopropane moiety of **1** had opened. Although no olefinic proton signal was present in the ^{1}H-NMR spectrum of **10**, the presence of a tetrasubstituted double bond was indicated from ^{13}C-NMR resonances at δ 133.1 and 142.8 (each s). The ^{1}H-NMR

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Table 1. ^{1}H-NMR Data (δ, J in Hz) for Compounds 1 and 9−15 in Pyridine-d_5 (300 MHz)

proton(s)	**1**	**9**	**10**	**11**
H-3	4.94 (br s)	4.95 (br s)	4.95 (br s)	4.94 (br s)
H-5	2.41 (d, 12 Hz)	ca. 2.5	2.47 (d, 12 Hz)	2.41 (d, 12 Hz)
H-7	4.00 (br s)	4.05 (br s)	4.13 (br s)	3.97 (br s)
H-12		5.29 (br s)	2.70 (dd, 4, 13.5 Hz)	
H-15			ca. 2.1	
H-18	0.50, 0.63 (each d, 5.5 Hz)	1.29 (s)	1.52 (s)	1.28 (s)
H-20			3.18 (m)	
H-23	4.53 (br t, 6.5 Hz)	4.08 (m)	4.20 (br d, 8 Hz)	4.40 (dt, 1,9 Hz)
H-24	3.58 (br s)	4.26 (d, 6.5 Hz)	3.49 (d, 1 Hz)	3.45 (s)
CH_3-19	0.90 (s)	0.99 (s)	0.91 (s)	0.88 (s)
CH_3-21	1.11 (d, 6.5 Hz)	1.32 (d, 7 Hz)	1.14 (d, 7 Hz)	0.93 (d, 6.5 Hz)
CH_3-25, 26 or CH_3-25 and H-26	1.60, 1.65 (s)	4.95, 5.19 (each br s) 1.98 (s)	1.54, 1.59 (s)	1.50, 1.52 (s)
CH_3-28	1.19 (s)	1.19 (s)	1.18 (s)	1.16 (s)
CH_3-29	0.83 (s)	0.92 (s)	0.90 (s)	0.90 (s)
CH_3-30	1.08 (s)	0.83 (s)	0.96 (s)	0.95 (s)
glycosyl				
H-1	4.76 (d, 7.5 Hz)	4.77 (d, 8 Hz)	4.73 (d, 8 Hz)	4.72 (d, 8 Hz)
H-6	4.72 (dd, 5.5, 11.5 Hz)	4.73 (dd, 5.5, 11.5 Hz)	4.70 (dd, 5.5, 12 Hz)	4.73 (dd, 5.5, 12 Hz)
	4.94 (dd, 2, 11.5 Hz)	4.95 (br d, 11.5 Hz)	4.94 (br d, 12 Hz)	4.85 (dd, 1, 12 Hz)
Ac	1.93, 2.05 (each s)	1.75, 2.08 (each s)	1.82, 2.10 (each s)	1.95, 2.06 (each s)
OMe				

proton	**12**	**13**	**14**[a]	**15**[a]
H-3	4.97 (br s)	4.98 (br s)	4.91 (br s)	4.92 (br s)
H-5	2.50 (d, 12 Hz)	2.45 (d, 12 Hz)	2.47 (d, 11.5 Hz)	2.45 (d, 11.5 Hz)
H-7	4.15 (br s)	4.00 (br s)	4.27 (br s)	4.24 (br s)
H-12	2.70 (dd, 4, 13.5 Hz)			
H-15	ca. 1.95		5.77 (d, 1.5 Hz)	5.76 (br s)
H-18	1.55 (s)	1.29 (s)	ca. 1.6 and 2.5	ca. 1.8 and 2.59 (dd, 3.5, 13 Hz)
H-20	3.20 (m)			
H-23	4.05 (br d, 9 Hz)	4.31 (br d, 9 Hz)	3.95 (m)	4.50 (dd, 3.5, 12 Hz)
H-24	3.51 (d, 2 Hz)	3.53 (s)		4.88, 5.62 (each br s)
CH_3-28	1.20 (s)	1.18 (s)	1.15 (s)[a]	1.15 (s)[a]
CH_3-29	0.90 (s)	0.91 (s)	0.91 (s)[a]	0.91 (s)[a]
CH_3-30	0.97 (s)	0.96 (s)	1.21 (s)[a]	1.21 (s)[a]
CH_3-19	0.91 (s)	0.89 (s)	0.94 (s)	0.95 (s)
CH_3-21	1.15 (d, 7 Hz)	0.92 (d, 6.5 Hz)	0.87 (d, 6.5 Hz)	1.06 (d, 6.5 Hz)
CH_3-25,26	1.37 (6H) (s)	1.34, 1.43 (s)		
glucosyl				
H-1	4.76 (d, 8 Hz)	4.75 (d, 8 Hz)	4.79 (d, 8 Hz)	4.76 (d, 8 Hz)
H-6	4.74 (dd, 5.5, 12 Hz)	4.75 (dd, 5.5, 12 Hz)	4.71 (dd, 5.5, 11.5 Hz)	4.67 (dd, 5.5, 11.5 Hz)
	4.97 (br d, J = 12 Hz)	4.97 (dd, 1, 12 Hz)	4.99 (dd, 1.5, 11.5 Hz)	5.02 (dd, 2, 11.5 Hz)
Ac	1.78, 2.10 (each s)	1.92, 2.05 (each s)	1.79, 2.08 (each s)	1.71, 2.09 (each s)
OMe	3.18 (s)	3.16 (s)		

[a] Assignments are for methyls in equivalent positions (compounds **14** and **15** have only 26 and 27 carbons, respectively).

spectrum also exhibited characteristic methine signals at δ 2.70 (dd, J = 4, 13.5 Hz) and 3.18 (m), which could be assigned to H-12 and H-20, respectively, by ^{1}H−^{1}H COSY examination. This observation suggested that the double bond was present at C-13(17), and thus an additional tertiary methyl group was presumed to be at C-14. The locations of the double bond and the additional tertiary methyl group were confirmed to be at C-13(17) and C-14, respectively, by ^{1}H−^{13}C long-range COSY examinations; the ^{1}H−^{13}C long-range correlations are shown in Table 3. On the basis of the spectral evidence described above, the structure of **10** was assigned as 3-*O*-acetyl-3α,7α,23(*R*),24(*S*),25-pentahydroxy-20(*S*)-dammar-13(17)-ene 7-*O*-*β*-D-(6′-*O*-acetyl)-glucopyranoside (**10**).

As in **10**, the ^{1}H-NMR signals of **11** correlated closely with those of **1**, except for the absence of a cyclopropyl methylene group and the presence of seven tertiary methyl groups. Also, like that of **10**, the ^{1}H-NMR spectrum of **11** exhibited no olefinic proton signals; however, in contrast to **10**, the ^{13}C-NMR spectrum of **11** showed no double bond, but did show a distinct carbon resonance at δ 92.4 (s). The assignment of this carbon resonance and the location of the additional methyl group were achieved from ^{1}H−^{13}C long-range COSY correlations, which are summarized in Table 3. The additional methyl signal at δ 1.28 (s) showed long-range correlations with C-8, C-13, C-14, and C-15, indicating the location of this methyl group to be at C-14. On the other hand, the methyl proton signal at δ 0.93 (d, J = 6.5 Hz), assignable to CH_3-21, exhibited a long-range correlation with the carbon resonance at δ 92.4 through a three-bond coupling. Therefore, this carbon signal could be assigned to C-17. By taking the molecular formula into account, the presence of a cyclic ether epoxy group either at C-17 and C-23 or at C-17 and C-24 was suggested.

On acetylation, **11** yielded a hexaacetate (**11a**), which gave an $[M - H]^-$ ion peak at m/z 905 in the negative FABMS. The ^{1}H-NMR spectrum of **11a** displayed H-23 and H-24 signals at δ 4.45 (1H, br d, J = 7 Hz) and 4.74 (1H, d, J = 2 Hz), respectively; the latter showed a downfield shift (+1.37 ppm) as compared with that [δ 3.37 (1H, d, J = 1.5 Hz) in $CDCl_3$] of **11**. Therefore, the position of the cyclic ether group was concluded to be at C-17 and C-23.

The configurations of C-13 and C-17 were determined fron NOE examination. Observation of NOE correlation

Table 2. ^{13}C-NMR Data (δ) for Cumingianosides A (1) and Q (5), and 9−15 in Pyridine-d_5

	1	5	9	10	11	12	13	14	15
carbon									
1	34.4 t	34.2 t	34.2 t	34.8 t	34.7 t	34.7 t	34.7 t	34.1 t	34.1 t
2	23.3 t	23.4 t	23.3 t	23.8 t	23.6 t	23.6 t	23.5 t	23.3 t	23.3 t
3	77.9 d	78.2 d	78.3 d	78.3 d	78.2 d	78.5 d	78.2 d	78.1 d	77.9 d
4	36.9 s	37.0 s	36.8 s	37.1 s	37.0 s	36.9 s	37.0 s	36.9 s	36.9 s
5	41.4 d	42.1 d	42.2 d	41.6 d	42.0 d	41.5 d	42.0 d	41.9 d	41.9 d
6	20.6 t	21.1 t	23.3 t	22.1 t	21.8 t	22.0 t	21.8 t	21.1 t	21.2 t
7	78.6 d	77.6 d	78.2 d	78.8 d	78.2 d	78.6 d	78.3 d	77.8 d	77.8 d
8	35.4 s	43.3 s	42.5 s	45.5 s	44.9 s	45.4 s	44.9 s	43.2 s	43.1 s
9	45.3 d	43.5 d	45.2 d	47.7 d	47.3 d	47.6 d	47.3 d	44.1 d	44.1 d
10	37.6 s	37.8 s	38.2 s	38.0 s	37.7 s	37.8 s	37.7 s	37.8 s	37.8 s
11	17.3 t	17.5 t	24.1 t	21.9 t	21.2 t	21.8 t	21.3 t	17.3 t	17.3 t
12	28.1 t	36.4 t	114.1 d	23.1 d	21.5 t	23.0 t	21.5 t	30.5 t	30.3 t
13	30.5 s	46.9 s	152.7 s	142.8 s	48.4 d	142.5 s	48.5 d	48.4 s	47.6 s
14	39.3 s	158.7 s	52.0 s	57.7 s	49.4 s	57.6 s	49.2 s	159.9 s	159.0 s
15	25.4 t	120.4 d	30.7 t	31.2 t	31.8 t	31.1 t	31.8 t	120.0 d	119.9 d
16	26.0 t	36.1 t	26.1 t	30.3 t	31.4 t	30.2 t	31.4 t	29.9 t	30.5 t
17	53.4 d	62.1 d	51.2 d	133.1 s	92.4 s	133.0 s	92.1 s	56.2 d	59.5 d
18	17.4 t	19.4 q	25.5 q	28.3 q	20.8 q	28.1 q	20.3 q	42.2 t	43.8 t
19	16.2 q	16.1 q	15.6 q	16.3 q	16.1 q	16.2 q	16.0 q	15.9 q	15.9 q
20	33.0 d	32.2 d	33.1 d	29.1 d	39.4 d	28.9 d	39.3 d	29.3 d	34.6 d
21	19.7 q	20.1 q	20.6 q	21.0 q	14.1 q	20.8 q	14.1 q	20.4 q	16.2 q
22	39.6 t	42.0 t	37.0 t	42.2 t	36.6 t	42.8 t	37.6 t	40.2 t	155.5 s
23	69.5 d	69.4 d	74.7 d	69.8 d	75.2 d	68.3 d	78.7 d	67.4 d	69.9 d
24	77.0 d	76.9 d	80.3 d	79.2 d	78.9 d	78.4 d	77.7 d		102.7 t
25	73.6 s	73.8 s	147.5 s	73.9 s	73.0 s	78.6 s	73.5 s		
26	27.7 q	27.7 q	112.9 t	27.7 q	28.1 q	22.6 q	22.4 q		
27	27.1 q	27.1 q	18.4 q	27.4 q	26.4 q	20.8 q	21.1 q		
28	27.1 q	27.7 q	28.0 q	28.1 q	28.0 q	27.9 q	27.9 q	27.7 q[a]	27.6 q[a]
29	22.2 q	22.3 q	22.5 q	22.7 q	22.4 q	22.6 q	22.8 q	22.3 q[a]	22.3 q[a]
30	20.3 q	28.5 q	19.0 q	18.1 q	17.2 q	17.9 q	17.1 q	28.7 q[a]	28.8 q[a]
glycosyl									
1	100.1 d	100.3 d	100.7 d	100.9 d	100.5 d	100.8 d	100.4 d	100.7 d	100.9 d
2	74.9 d	74.7 d	74.7 d	74.8 d	74.9 d	74.8 d	74.9 d	74.9 d	74.7 d
3	78.2 d	78.5 d	78.3 d	78.4 d	78.2 d	78.0 d	78.1 d	78.6 d	78.7 d
4	71.5 d	71.3 d	71.6 d	71.9 d	71.7 d	71.9 d	71.7 d	71.4 d	71.3 d
5	74.6 d	74.6 d	74.0 d	74.7 d	74.7 d	74.7 d	74.7 d	74.5 d	74.9 d
6	64.6 t	64.5 t	64.6 t	65.0 t	64.6 t	64.9 t	64.6 t	64.7 t	64.6 t
Ac	20.8 q	21.0 q	20.9 q	21.0 q	20.9 q	20.8 q	20.7 q	20.9 q	20.9 (2C) q
	21.0 q	21.1 q	21.0 q	21.2 q	21.8 q	20.9 q	20.8 q	21.0 q	
	169.4 s	170.9 s	170.7 s	171.0 s	170.8 s	170.6 s	170.6 s	170.8 s	170.6 s
	169.2 s	171.1 s	170.9 s	171.2 s	170.9 s	170.8 s	170.8 s	170.9 s	170.8 s
OMe						49.2 q	49.3 q		

[a] Assignments are for methyls in equivalent positions (compounds **14** and **15** have only 26 and 27 carbons, respectively). q = CH_3, t = CH_2, d = CH, s = C.

between CH_3-30 and H-13 indicated that the configuration of H-13 was β. On the other hand, CH_3-18 showed NOE enhancements with H-20 and Hα-12, and thus, the configuration of the C-17 side chain was concluded to be α. Based on the spectral evidence described above, the structure of **11** was characterized as 3-*O*-acetyl-3α,7α,24(*S*),25-tetrahydroxy-17(*R*),23(*R*)-epoxy-20(*S*)-dammarane 7-*O*-β-D-(6′-*O*-acetyl)glucopyranoside.

Treatment of cumingianoside C (**2**) with *p*-toluenesulfonic acid in CH_2Cl_2 furnished, along with cumingianoside P (**6**), compounds **12** and **13**, which gave the same $[M - H]^-$ ion peak at *m*/*z* 751 in the negative FABMS. This peak was 14 mass units greater than the analogous data for **10** and **11**. The ^{1}H- and ^{13}C-NMR spectra of **12** and **13** resembled those of **10** and **11**, respectively, except for the presence of a methoxy group. Therefore, the structures of **12** and **13** can be represented by formulas **12**, 3-*O*-acetyl-3α,7α,23(*R*),24(*S*)-tetrahydroxy-25-methoxy-20(*S*)-dammar-13(17)-ene 7-*O*-β-D-(6′-*O*-acetyl)glucopyranoside, and **13**, 3-*O*-acetyl-3α,7α,24(*S*),25-tetrahydroxy-25-methoxy-17(*R*),23(*R*)-epoxy-20(*S*)-dammarane 7-*O*-β-D-(6′-*O*-acetyl)glucopyranoside, respectively.

When cumingianoside E (**3**) was treated with *p*-toluenesulfonic acid as for **1**, no identifiable compound could be separated from the complex product mixture. In contrast, **3** yielded cumingianoside D (**4**) in a shorter time reaction (2 h). When **3** was treated with *p*-toluenesulfonic acid in CH_2Cl_2 overnight at 5 °C, the reaction gave **9** (as the main product) and **14** (as a minor product).

The negative FABMS of **9** gave an $[M - H]^-$ ion peak at *m*/*z* 719, and the molecular formula was established as $C_{40}H_{64}O_{11}$ by HRFABMS. The ^{1}H-NMR spectrum of **9** showed the absence of a cyclopropyl methylene moiety. The presence of an exomethylene group was revealed by two one-proton olefinic signals at δ 4.95 and 5.29 (br s each) in the ^{1}H-NMR spectrum, and by carbon resonances at δ 112.9 (t) and 147.5 (s), which were similar to those of cumingianoside D (**4**). An additional tertiary methyl signal and an olefinic proton signal [δ 5.29 (br s)] in the ^{1}H-NMR spectrum combined with the absence of the cyclopropyl methylene signals found in cumingianoside D (**4**) implied that the cyclopropyl methylene group had opened, forming an additional tertiary methyl group and a double bond. The locations of these groups were assigned at C-14 and C-12(13), respectively, by ^{1}H−^{13}C long-range COSY examinations; the long-range correlations in **9** are shown in Table 3. Accordingly, the structure of **9**, 3-*O*-acetyl-3α,7α,24(*S*),-

Table 3. $^1H-^{13}C$ Long-range Correlations for 9, 10, 11, and 14 (J_{C-H} = 10 Hz)

carbon	**9**	**10**	**11**	**14**
C-1	H_3-19	H-2, H_3-19	H-2, H_3-19	H_3-19
C-2				
C-3	H_3-28, 29	H_3-28, 29		H_3-28, 29
C-4	H-5, H_3-28, 29	H-5, 28, 29	H_3-28, 29	H-5
C-5	H-3, 7, H_3-28, 29	H-3, 7, H_3-28, 29	H-7, H_3-28	H-3, 7
C-6				
C-7	H_3-30	H_3-30		H_3-30
C-8	H-6, H_3-18, 30	H-9, H_3-18, 30	H-6, 11, H_3-18, 30	H-6, H_3-30
C-9	H-7, H-12, H_3-19, 30	H-7, 12, H_3-19	H-7, H_3-19, 30	H_3-19, 30
C-10	H-2, 6, H_3-19	H-6, 9, 11, H_3-19	H-2, H_3-19	H-6, H_3-19
C-11				
C-12				H-18
C-13	H_3-18	H-12, H_3-18	H_3-18	H-15
C-14	H-13, H_3-18, 30	H-12, H_3-18	H-13, H_3-18, 30	H_3-30
C-15	H_3-18	H_3-18	H_3-18	
C-16				H-15
C-17	H_3-21	H-16, H_3-21	H_3-21[a]	H-15, 18
C-18				
C-19				H-5
C-20				
C-21			H-22[a]	
C-22				
C-23				
C-24			H_3-26[a]	
C-25	H_3-27	H_3-26, 27	H_3-26, 27	
C-26				
C-27	H-26			
C-28				
C-29				
C-30				
C-1′	H-7	H-7	H-7	H-7

[a] Correlation was observed in J_{C-H} = 10 Hz.

25-tetrahydroxy-20(*S*)-dammar-12,24-diene 7-*O*-*β*-D-(6′-*O*-acetyl)glucopyranoside, can be represented by the formula shown.

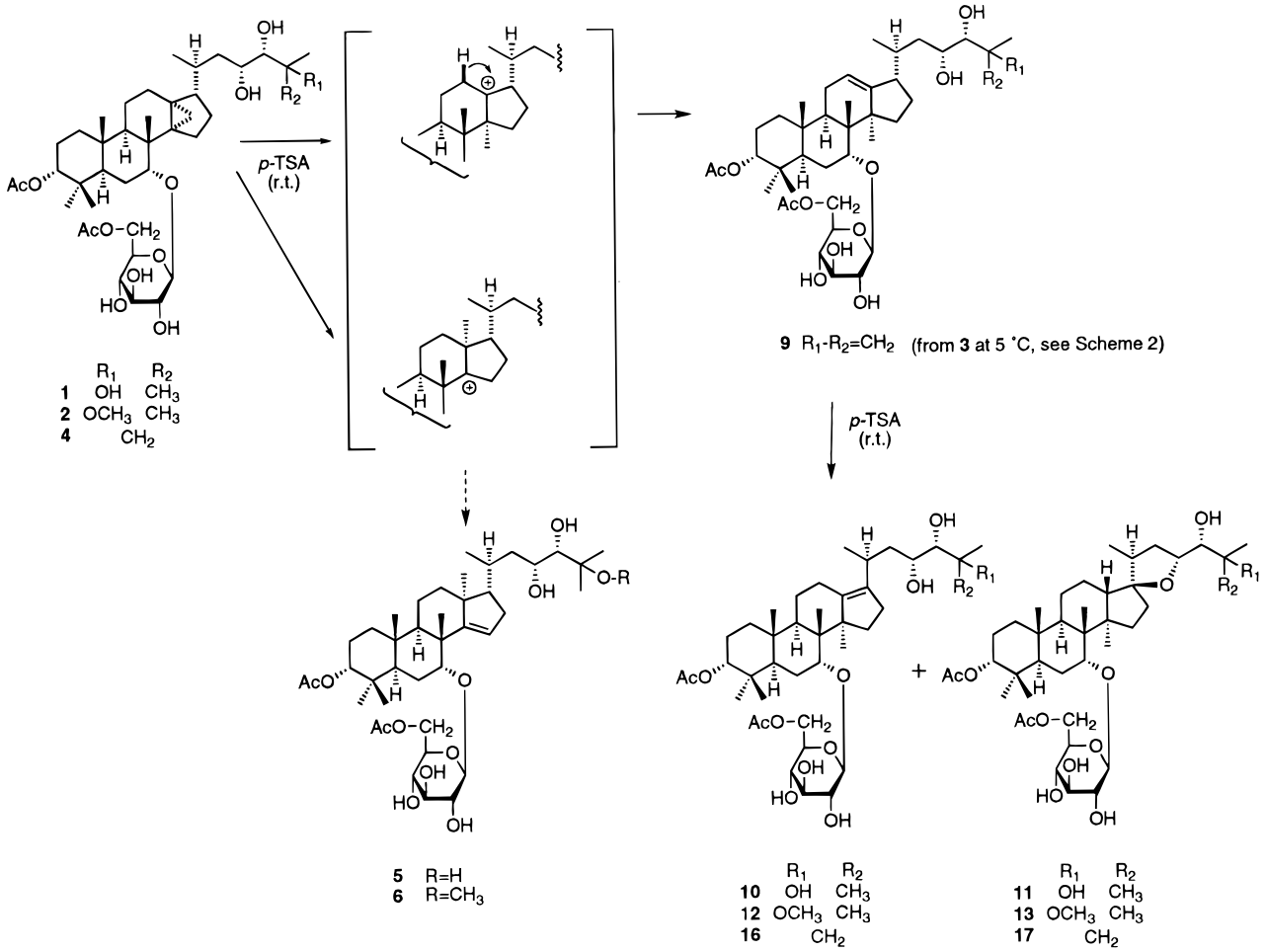
The negative FABMS of **14** gave an $[M - H]^-$ ion peak at *m/z* 647. Using HRFABMS, the molecular formula was confirmed as $C_{36}H_{56}O_{10}$, which differed from that of **3** by C_4H_8O. The ^{1}H-NMR spectrum of **14** showed the presence of four tertiary methyl groups [*δ* 0.91, 0.94, 1.15, and 1.21 (each s)], a secondary methyl group [*δ* 0.87 (d, *J* = 6.5 Hz)], and two acetyl groups [*δ* 1.79 and 2.08 (each s)]. At low field, the spectrum showed two methine signals [*δ* 4.27 and 4.91 (each br s)] ascribable to H-7 and H-3, respectively, an anomeric proton signal [*δ* 4.79 (d, *J* = 8 Hz)], deshielded glucosyl H-6 signals [*δ* 4.71 (dd, *J* = 5.5, 11.5 Hz) and 4.99 (dd, *J* = 1.5, 11.5 Hz)], a methine proton signal [*δ* 3.95 (m)], and an olefinic proton signal [*δ* 5.77 (d, *J* = 1.5 Hz)]. In the $^1H-^{13}C$ long-range COSY spectrum, the four tertiary methyl signals at *δ* 0.91, 0.94, 1.15, and 1.21 exhibited long-range correlations to quaternary, methine, and/or methylene carbons through a three- or a two-bond coupling as shown in Table 3, confirming the assignments of these methyl signals to be CH_3-29, CH_3-10, CH_3-28, and CH_3-30, respectively. NOE enhancements between an olefinic signal at *δ* 5.77 and CH_3-30 and H-7 were similar to those found in cumingianoside Q (**5**) and indicated the location of the double bond at C-14(15). Extensive $^1H-^{13}C$ long-range COSY examinations suggested that **14** contained the same partial structure found in cumingianoside Q (**5**), but lacked the 13-CH_3 and the C-17 side chain moiety.

On the other hand, in the $^1H-^1H$ COSY spectrum, the methine signal at *δ* 3.95 showed correlations with methylene signals at H-18 and H-22. Although further noticeable correlations of these methylene signals were not discerned in the $^1H-^1H$ COSY spectrum, in the homonuclear Hartman Hahn (HOHAHA) spectrum of **14**, the methine signal at *δ* 3.95 clearly exhibited further correlations with the methine signal at *δ* ca. 1.8 and with the secondary methyl signal at *δ* 0.87, assignable to H-20 and CH_3-21, respectively. Therefore, the assignment of the signals at *δ* ca. 1.4 and 1.95 in the long-range $^1H-^{13}C$ COSY spectrum, and at *δ* 3.95 were established as H_2-22 and H-23, respectively. Furthermore, the methylene proton signal at *δ* ca. 1.6 showed a long-range correlation to C-12, while the signal at *δ* ca. 2.5 displayed a long-range (three-bond) coupling with C-17. The HMBC spectrum also exhibited correlation between the methylene signal at *δ* ca. 1.6 and C-13 through a two-bond coupling. This spectral evidence indicated that this methylene group was connected to C-13, thus establishing the entire carbon framework for compound **14**. The configuration of H-23 was concluded to be *β*, based on the observation of NOE with H-20 and with Hα-12. The spectral evidence of **14** described above led us to conclude that the structure of this compound can be represented by formula **14**, 3-*O*-acetyl-3α,7α,23α(*R*)-trihydroxy-24,25,26,27-tetranor-18,23-cycloapotirucallane 7-*O*-*β*-D-(6′-*O*-acetyl)glucopyranoside. Compound **14** is a pentacyclic tetranortriterpene glucoside with a novel skeleton.

As with **3**, treatment of cumindysoside A (**8**) with *p*-toluenesulfonic acid in CH_2Cl_2 gave a complicated product mixture; however, one product (**15**) could be isolated. The negative FABMS of **15** exhibited an $[M - H]^-$ ion peak at *m/z* 659. The ^{1}H- and ^{13}C-NMR spectra of **15** resembled those of **14**, suggesting the existence of a carbon framework similar to that of **14**. The appearance of two one-proton olefinic signals at *δ* 4.88 and 5.62 (each br s) as well as the downfield shifts of the CH_3-20 [*δ* 1.06 (d, *J* = 6.5 Hz), +0.19 ppm] and H-23 [*δ* 4.50 (dd, *J* = 3.5, 12 Hz), +0.45 ppm] signals as compared with those of **14** suggested the presence of an exomethylene group at C-22. As with **4**, the cyclopropyl methylene group in **8** would open under acidic conditions and form a methylene cation, which could easily condense with the aldehyde group in **8** (Scheme 2). Thus, compound **15** was presumed to contain a skeleton similar to that of **14**, which was supported by extensive 2D-NMR examinations. The configuration of H-23 was confirmed to be *β* by NOE examination (Figure 1). H-23, which possesses an axial orientation based on its large coupling constant (dd, *J* = 3.5, 12 Hz), exhibited an NOE correlation with Hα-12, indicating the configuration at H-23 to be *β*. In addition, H-23 also showed NOE enhancement with H-20, suggesting that the configuration of H-20 in cumindysoside A (**8**), which has not been determined previously, to be the same as that seen in the cumingianosides. Based on the spectral evidence described above, the structure **15** was concluded to be represented by formula **15**, 3-*O*-acetyl-3α,7α,23α(*S*)-trihydroxy 22-methylene-24,25,26,27-tetranor-18,23-cycloapotirucallane 7-*O*-*β*-D-(6′-*O*-acetyl)glucopyranoside.

In summary, as described above, 14,18-cycloapotirucallanes **1** and **2** yielded a dammar-13(17)-ene-type

Scheme 1



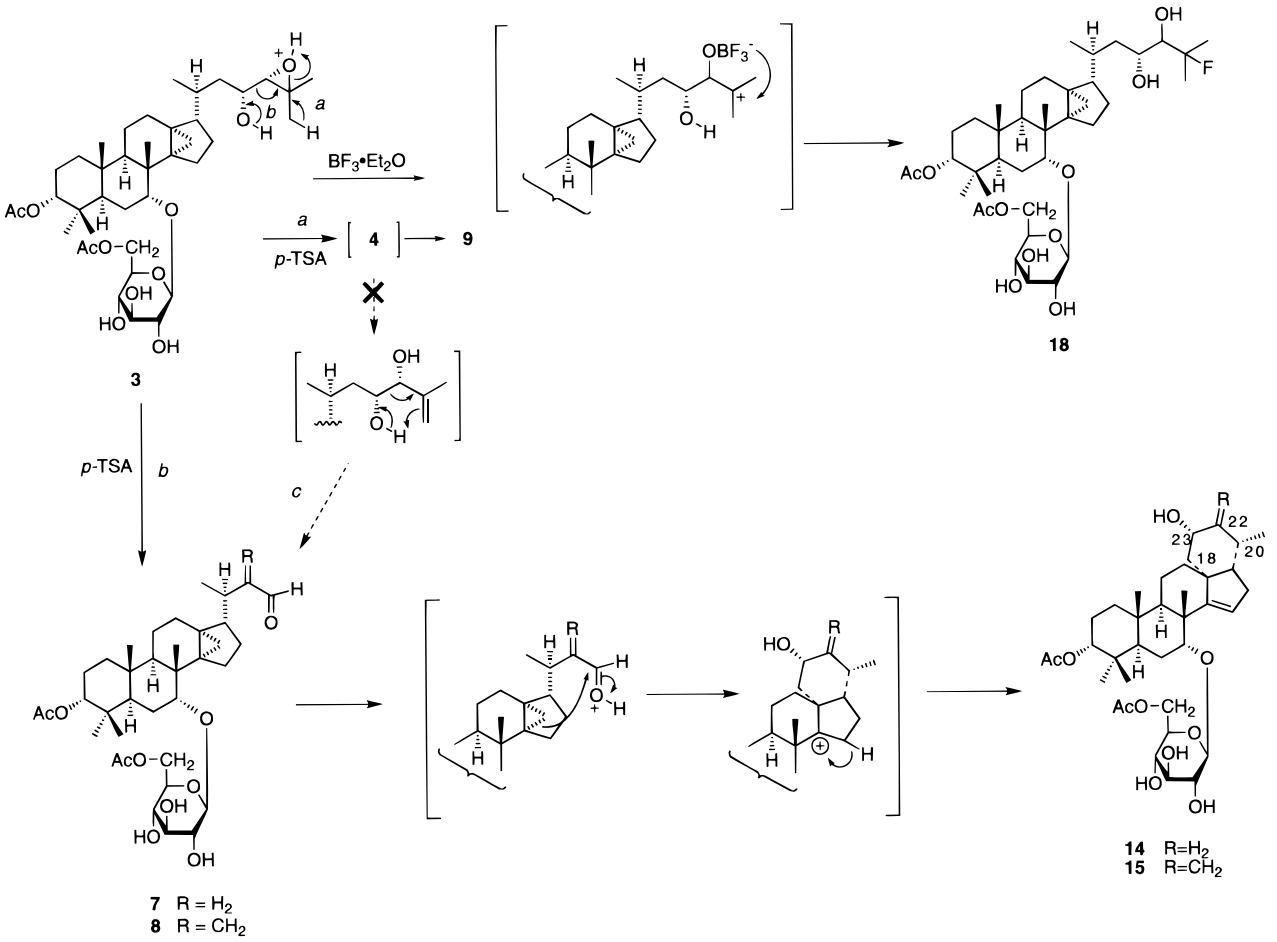
compound (**10** and **12**, respectively), along with a 17,23-epoxydammarane-type compound (**11** and **13**, respectively) and an apotirucallane-type compound (**5** and **6**, respectively), on treatment with *p*-toluenesulfonic acid at room temperature (Scheme 1). In contrast, similar acid treatment of the 14,18-cycloapotirucallanes **3** at 5 °C gave a dammar-12(13)-ene-type compound (**9**), together with **14** (Scheme 2). These results suggested that 14,18-cycloapotirucallanes predominantly furnish an intermediate with a cation at C-13 (see Scheme 1), which gives a dammar-12(13)-ene-type compound at lower temperature (5 °C) but subsequently yields a more stable dammar-13(17)-ene-type compound at room temperature (Scheme 1). The production of a C-14 cation is probably quite slow because production of apotirucallane-type compounds (**5** and **6**) was very low. In support of the above hypothesis, treating the dammar-12(13)-ene type-compound **9** with *p*-toluenesulfonic acid in CH_2Cl_2 at room temperature gave a dammar-13(17)-ene-type compound (**16**), together with a 17,23-epoxydammarane-type compound (**17**). Production of **17** from **9** suggested that a dammar-12(13)-ene and a dammar-13(17)-ene might exist as an equilibrium mixture in the acidic solution at room temperature, and upon transformation of the 12(13)-ene to the 13(17)-ene, the C17-C23 cyclic ether bond was formed to afford a 17,23-epoxydammarane. Scheme 1 summarizes the possible pathways for the production of **10**−**13**, **16**, and **17** from cuminginosides A (**1**), C (**2**), and D (**4**).

Production of compound **14** from cumingianoside E (**3**) suggested that cumindysoside B (**7**) was an intermediate under acidic conditions. This was supported by the fact that, in a similar reaction, cumindyoside A (**8**) gave **15**, which contains the same skeleton as **14**. There are two possible pathways for production of **7** from **3**: through pathway c (a *retro*-ene type reaction via **4**) or through pathway b (a Grob-type fragmentation) as shown in Scheme 2. Because treatment of **4** with *p*-toluenesulfonic acid did not afford **14**, it is likely that **7** was produced from **3** through pathway b.[6] Because the initial stage for the fission of the C23−C24 bond is probably opening of the epoxide ring at C24−C25, BF_3 was used instead of *p*-toluenesulfonic acid in an effort to improve the yield of **14**. Unexpectedly, however, production of the fluorinated **18** was predominant with this reagent. In a similar fashion, treatment of lanosterol 24,25-epoxide acetate with BF_3 gave a fluorohydrin.[7]

The 9,19-cycloartenols are known to give mainly their isomeric lanost-9(11)-ene counterparts on acid treatment, while the corresponding products from the 14,18-cycloapotirucallanes had not been known previously due to their limited availability from plants belonging to the Meliaceae, Rutaceae, and Simaroubaceae families. Our present study has now provided some examples of the products of 14,18-cycloapotirucallanes on acid treatment.

The cytotoxicities of **9**−**15** against a panel of 58 human tumor cell lines in vitro were evaluated at the National Cancer Institute (NCI). The log GI_{50} values, which represent the log molar drug concentration required to cause 50% inhibition, are shown in Table 4

Scheme 2



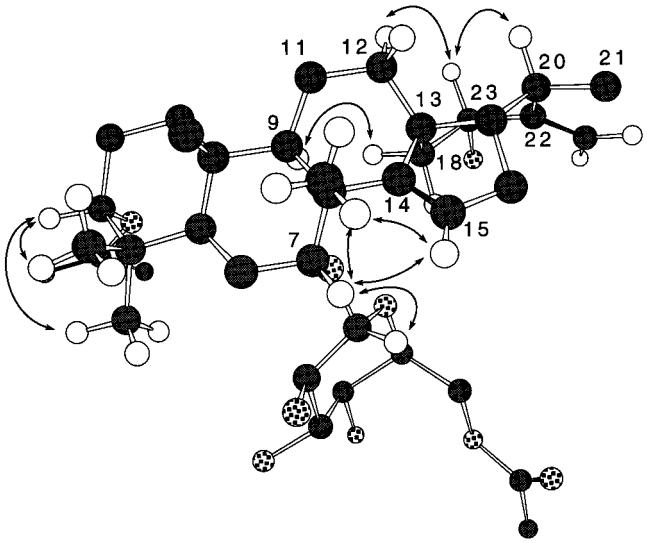


Figure 1. Possible conformation of **15** and NOE correlations in **15**.

for representative cell lines. Table 5 summarizes the average TGI values [total growth inhibitory concentration (μM)] for compounds **1**−**4** and **8**−**15** in eight disease types (leukemia, non-small-cell lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast cancers). The TGI values for each colon-cancer cell line are also included.

In our previous study, cumingianosides A (**1**) and C (**2**) demonstrated potent cytotoxicities against the MOLT-4 human leukemia cell line with log GI_{50} values of <-8.20 and <-8.35, respectively. However, they did not show significant cytotoxicities against the other tumor cell lines, indicating sensitivity only against the MOLT-4 cell line. Moreover, the dose−response curves of **1** and **2** against MOLT-4 did not reach 0% cell growth even at 10^{-4} M, resulting in low cytotoxicities with TGI values of 45.0 and 26.7 μM, respectively.

Treatment of **1** and **2** with *p*-toluenesulfonic acid in CH_2Cl_2 yielded two types of compounds, possessing a dammar-13(17)-ene skeleton (**10** and **12**, respectively) and a 17(*R*),23(*R*)-epoxydammarane skeleton (**11** and **13**, respectively) in each case. Compounds **10** and **12** did not show significant cytotoxicity in any cell line. In contrast, significant selective cytotoxicity was observed with compound **13** for the HCC2998 cell line with a log GI_{50} value of −6.69. In addition, **13** demonstrated selectivity for the colon subpanel, as shown by the small TGI concentrations for the colon tumor cell lines compared to the TGI concentrations for the other tumor subpanels and the full panel average (Table 5). Compound **11** also exhibited a weak but less significant selectivity against the colon subpanel.

On the other hand, cumingianoside E (**3**), which exhibited selective cytotoxicities against leukemia and colon cancer subpanels, furnished **9** and **14** on treatment with *p*-toluenesulfonic acid in CH_2Cl_2. Compound **9** did not display selectivity for the leukemia subpanel, but was selective for the melanoma and colon subpanels, with the highest cytotoxicity against HCC2998 (TGI 0.908). The double bond at C-12(13) might be important for the selectivity against the melanoma subpanel, since

Table 4. Cytotoxicity (log GI_{50} in M[a]) of Compounds 9−15 Against Human Cancer Cell Lines In Vitro

disease type and cell line	9	10	11	12	13	14	15
Leukemia							
CCRF-CEM	−5.65	−4.80	−5.50	−5.27	−5.51	−5.67	−5.59
HL60TB	−5.68	−4.89	−5.53	−5.44	−5.63	−5.68	−5.56
K-562	−5.72	−4.90	−5.35	−5.22	−5.51	−5.53	−5.51
MOLT-4	−5.64	−4.88	−5.50	−5.29	−5.64	−5.67	−5.71
RPMI8226	−5.72	−4.98	−5.47	−5.38	−5.62	−5.55	−5.53
SR	−5.72	−4.91	−5.51	−5.51	−5.66	−5.74	−5.63
Non-Small Cell Lung Cancer							
A549/ATCC	−5.49	−4.72	−5.29	−5.11	−5.41	−5.32	−5.32
EKVX	−5.50	−4.77	−5.02	−4.89	−5.26	−5.15	−5.00
HOP-62	−5.58	−4.79	−4.85	−4.84	−4.94	−4.95	−4.89
HOP-92	−5.63	−4.84	−5.00	−4.89	−5.29	−5.31	−4.97
NCI-H226	−5.52	−4.76	−4.97	−4.88	−5.32	−5.31	−5.22
NCI-H23	−5.38	−4.78	−4.89	−4.84	−5.03	−5.41	−5.02
NCI-H322M	−5.73	−4.76	−5.77	−4.89	−5.72	−5.18	−4.89
NCI-H460	−5.61	−4.80	−5.18	−5.04	−5.42	−5.48	−5.37
NCI-H522	−5.74	−4.88	−5.15	−4.91	−5.34	−5.51	−5.13
Colon Cancer							
COLO205	−5.69	−4.80	−5.39	−4.97	−5.67	−5.74	−5.75
HCC2998	−7.11	−4.92	−5.44	−5.40	−6.69	−5.68	−5.80
HCT116	−5.73	−4.85	−5.42	−5.22	−5.57	−5.75	−5.46
HCT15	−5.53	−4.77	−5.66	−4.96	−5.62	−5.05	−4.94
HT29	−5.72	−4.78	−5.74	−5.29	−5.73	−5.77	−5.63
KM112	−5.80	−4.65	−5.70	−5.45	−5.88	−5.62	−5.81
SW620	−5.52	−4.77	−4.98	−4.80	−5.19	−5.34	−5.14
CNS Cancer							
SF-268	−5.55	−4.78	−5.03	−4.99	−5.22	−5.39	−5.18
SF-295	−5.66	−4.76	−5.19	−4.94	−5.36	−5.41	−5.38
SNB-19	−5.41	−4.84	−4.90	−4.91	−5.00	−5.41	−5.26
SNB-75	−5.73	−4.88	−5.29	−5.06	−5.41	−5.45	−5.43
U251	−5.66	−4.84	−5.22	−4.97	−5.27	−5.47	−5.55
Melanoma							
LOXIMVI	−5.79	−4.90	−5.44	−5.20	−5.32	−5.74	−5.40
MALME-3M	−5.80	−4.78	−4.99	−4.82	−4.95	−5.03	−4.94
Ml4	−5.68	−4.76	−5.30	−4.91	−5.35	−5.41	−5.45
SK-MEL-2	−5.70	−4.79	−5.22	−4.88	−5.21	−5.61	−5.68
SK-MEL-28	−5.63	−4.77	−4.99	−4.93	−5.20	−5.08	−5.08
SK-MEL-5	−5.72	−4.79	−4.97	−4.84	−5.08	−5.41	−5.22
UACC-257	−5.56	−4.79	−4.94	−4.90	−5.23	−5.47	−4.99
UACC-62	−5.82	−4.90	−5.20	−5.06	−5.28	−5.36	−5.15
Ovarian Cancer							
IGR-OV1	−5.63	−4.79	−5.02	−4.88	−5.36	−5.50	−5.32
OVCAR3	−5.73	−4.84	−5.15	−5.13	−5.32	−5.41	−5.55
OVCAR4	−5.53	−4.77	−5.47	−4.97	−5.53	−5.36	−5.40
OVCAR5	−5.72	−4.75	−5.29	−4.83	−5.50	−5.63	−5.68
OCCAR8	−5.44	−4.80	−5.03	−4.89	−5.28	−5.35	−5.18
SK-OV-3	−5.54	−4.75	−5.10	−4.82	−5.32	−5.22	−4.93
Renal Cancer							
786-0	−5.43	−4.74	−5.06	−4.84	−5.28	−5.36	−5.28
A498	−5.41	−4.76	−4.93	−4.85	−4.88	−4.85	−4.83
ACHN	−5.72	−4.75	−5.03	−4.98	−5.28	−5.29	−5.15
CAKI-1	−5.58	−4.81	−5.49	−5.39	−5.27	−5.02	−4.88
RKF-393	−5.68	−4.83	−5.39	−5.16	−5.50	−5.58	−5.40
SN12C	−5.51	−4.79	−4.95	−4.87	−5.38	−5.40	−5.22
UO-31	−5.41	−4.74	−5.11	−4.87	−5.28	−4.83	−4.86
Prostate Cancer							
PC-3	−5.67	−4.84	−5.42	−5.25	−5.55	−5.50	−5.46
DU-145	−5.59	−4.75	−4.97	−4.82	−5.35	−4.98	−4.97
Breast Cancer							
MCF7	−5.56	−5.54	−5.97	−5.58	−5.67	−5.35	−5.82
MCF7/ADR-RES	−4.79	−4.69	−4.79	−4.82	−5.13	−4.82	−4.75
MDA-MB-232/ATCC	−5.73	−4.94	−4.99	−4.94	−4.96	−5.69	−5.11
HS 578T	−5.63	−4.82	−5.03	−4.93	−5.39	−5.39	−5.31
MDA-MR-435	−5.71	−4.80	−5.08	−4.91	−5.44	−5.43	−5.32
MDA-N	−5.63	−4.77	−5.15	−4.93	−5.28	−5.37	−5.29
BT-549	−5.47	−4.81	−4.92	−4.82	−4.90	−4.96	−4.94
T-47D	−5.59	−4.78	−5.25	−4.90	−5.38	−5.36	−5.14
MG-MID[a]	−5.64	−4.82	−5.22	−5.02	−5.38	−5.38	−5.28
Delta[b]	1.47	0.72	0.76	0.56	1.32	0.39	0.53
Range[c]	2.31	0.89	1.19	0.78	1.81	0.95	1.07

[a] Calculated mean panel logGI_{50}. [b] The number of log units by which the logGI_{50} of the most sensitive line(s) of the panel differs from the corresponding MG-MID. [c] The number of log units by which the logGI_{50} of the most sensitive line(s) of the panel differs from the logGI_{50} of the least sensitive line(s).

4, which has the same C-17 substituent but no C-12-(13) double bond did not display selectivity against the melanoma subpanel. Compound **14** exhibited selectivity only for the colon subpanel, while the cytotoxicities for

Table 5. The Average TGI Concentrations (in μM) of Compounds 1−4 and 8−15 for the Tumor Subpanels and the TGI Concentrations Against All Colon Cancer Cell Lines

disease type and cell line	**1**	**10**	**11**	**2**	**12**	**13**	**3**	**4**	**9**	**14**	**8**	**15**
leukemia	18.5	32.2	17.3	11.3	20.9	32.1	1.8	8.2	5.1	7.0	4.0	8.7
non-small cell lung cancer	13.1	30.3	21.8	12.4	25.6	17.8	14.5	11.7	9.0	18.1	12.5	23.4
colon cancer	13.9	30.2	12.3	7.9	20.7	6.9	4.2	11.0	5.0	8.8	5.0	11.3
COLO205	14.0	30.2	14.3	11.3	22.8	4.7	1.8	12.6	3.5	3.2	1.4	3.3
HCC2998	12.9	25.2	15.9	4.9	13.4	1.8	2.7	12.4	0.9	3.8	1.4	3.5
HCT116	13.8	27.2	15.1	8.7	19.2	10.0	3.5	9.27	3.5	3.5	1.4	9.8
HCT15	13.9	30.8	5.9	6.3	23.8	5.6	6.0	10.4	10.0	22.3	7.5	27.5
HT29	14.3	30.1	4.3	2.5	16.9	4.0	1.7	8.77	3.8	3.3	11.9	5.9
KM12	14.2	37.1	7.7	7.6	18.9	2.6	3.8	11.3	3.0	7.6	9.5	4.8
SW620	14.4	30.7	22.9	13.7	30.1	19.8	10.0	12.0	10.4	18.1	1.4	24.2
CNS cancer	13.3	28.2	22.2	11.6	23.8	18.7	7.9	10.9	9.5	15.0	1.4	16.9
melanoma	13.7	29.1	20.7	12.6	29.9	20.2	15.4	12.2	4.2	14.4	6.9	19.1
ovarian cancer	13.6	30.4	20.1	12.0	25.6	15.8	5.9	12.7	7.4	13.5	10.4	17.6
renal cancer	13.5	30.8	20.5	13.2	23.6	17.9	10.0	12.7	9.7	18.8	10.8	22.1
prostate cancer		29.9	18.5		23.5	13.1			7.0	16.7		18.3
breast cancer		28.9	21.3		24.8	18.6			10.7	17.9		21.5
full panel average	14.0	29.9	19.7	11.6	23.7	17.7	9.0	11.8	7.6	14.5	8.9	18.0

the other tumor subpanels were decreased compared to those of **3** and **9**. Compound **15**, which has the same novel skeleton as **14**, exhibited a similar cytoxic profile to that of **14**, with weak selectivities against colon tumor cell lines.

Overall, with the exception of **9**, the products **10**, **11**; **12**, **13**; **4**, **14**; and **15** of *p*-toluenesulfonic acid treatment were less toxic than the original compounds **1**, **2**, **3**, and **8**, respectively, as shown by the larger full panel TGI values. In addition, compounds **11** and **13**−**15** displayed selectivity for the colon tumor subpanels. Interestingly, the selectivity shown by **11** and **13**, which contain a cyclic ether epoxy group, was absent in **10** and **12**, which have a 13,17 double bond. These results suggested that moieties other than the cyclopropane ring found in cumingianosides and cumindysoside A might be essential for selectivity for the colon tumor cell lines.

Experimental Section

General Experimental Procedures. NMR spectra were obtained at 300, 400, and 500 MHz for ^{1}H and 75, 100, and 125 MHz for ^{13}C, with tetramethylsilane as an internal standard. Chemical shift values are given in δ (ppm).

General Procedure for Treatment with *p*-Toluenesulfonic Acid in CH_2Cl_2. A mixture of the sample (20−1050 mg) and *p*-toluenesulfonic acid (2−50 mg) in CH_2Cl_2 (3−50 mL) was kept standing at room temperature or at 5 °C for 2 h to overnight. The reaction mixture was diluted with CH_2Cl_2, washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure to a syrup, which was purified by Si gel chromatography.

Compound 10: yield 38.6% (starting with 1050 mg of **1**); white amorphous powder; $[\alpha]^{27}_D$ −78.0° (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, C_5H_5N-d_5 + D_2O), see Table 1; ^{13}C NMR (75 MHz, C_5H_5N-d_5 + D_2O), see Table 2; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.9 (C-19), 17.3 (2C) (C-21, C-30), 20.2 (Ac), 20.8 (C-11), 21.3 (Ac), 21.4 (C-6), 22.1 (C-29), 22.2 (C-12), 22.9 (C-2), 26.1 (C-27), 27.2 (C-26), 27.7 (C-20), 28.1 (2C)(C-18, C-28), 29.6 (C-16), 30.4 (C-15), 34.3 (C-1), 36.4 (C-4), 37.5 (C-10), 40.1 (C-22), 41.3 (C-5), 44.9 (C-8), 46.9 (C-9), 46.9 (C-13), 57.0 (C-14), 63.5 (glucosyl C-6), 69.7 (glucosyl C-4), 70.5 (C-23), 74.4 (glucosyl C-2), 74.0 (C-25), 74.1 (glucosyl C-5), 76.1 (glucosyl C-3), 77.5 (C-24), 78.2 (C-3), 78.3 (C-7), 98.7 (glucosyl C-1), 132.1 (C-17), 142.4 (C-13), 170.7, 171.4 (COO); negative FABMS *m/z* 737 $(M - H)^-$, 695 $(M - Ac - H)^-$; positive FABMS *m/z* 761 $(M + Na)^+$; HRFABMS *m/z* calcd for $C_{40}H_{66}O_{12}Na$ 761.4452, found 761.4450.

Compound 11: yield 13.7% (starting with 1050 mg of **1**); white amorphous powder; $[\alpha]^{27}_D$ −59.0° (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75, 0.82, 0.85, 1.15, 1.20, 1.22 (each 3H, s, *t*-CH_3), 0.85 (3H, d, J = 6.5 Hz, CH_3-20), 2.02, 2.11 (each 3H, s, OAc), 3.37 (1H, d, J = 1.5 Hz, H-24), 3.71 (1H, br s, H-7), 4.12 (1H, br d, J = 8.5 Hz, H-23), 4.22 (1H, d, J = 7.5 Hz, anomeric H), 4.27 (1H, dd, J = 1.5, 12 Hz, glucosyl H-6), 4.30 (1H, dd, J = 4, 12 Hz, glucosyl H-6′), 4.59 (1H, br s, H-3); (C_5H_5N-d_5 + D_2O), see Table 1; ^{13}C NMR (75.5 MHz, C_5H_5N-d_5 + D_2O), see Table 2; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8 (C-30), 15.4 (C-19), 16.8 (C-21), 20.7 (C-18), 20.8 (Ac), 20.9 (C-2), 21.1 (C-12), 21.3 (C-11), 21.4 (Ac), 22.0 (C-29), 22.8 (C-6), 26.5 (C-27), 26.7 (C-26), 27.7 (C-28), 30.9 (C-16), 31.2 (C-15), 34.2 (C-1), 35.5 (C-22), 36.4 (C-4), 37.4 (C-10), 39.2 (C-20), 42.0 (C-5), 44.4 (C-8), 46.9 (C-9), 47.8 (C-13), 48.9 (C-14), 63.1 (glucosyl C-6), 70.2 (glucosyl C-4), 73.1 (C-25), 73.4 (glucosyl C-2), 74.1 (glucosyl C-5), 75.5 (C-23), 76.0 (glucosyl C-3), 77.1 (C-24), 78.1 (C-3), 78.2 (C-7), 92.3 (C-17), 98.7 (glucosyl C-1), 170.7, 171.3 (COO); negative FABMS *m/z* 737 $(M - H)^-$, 695 $(M - Ac - H)^-$; positive FABMS *m/z* 761 $(M + Na)^+$; HRFABMS *m/z* calcd for $C_{40}H_{66}O_{12}Na$ 761.4452; found 761.4449.

Acetylation of Compound 11 (11a). Compound **11** (28 mg) was treated with Ac_2O (1 mL) and dry pyridine (C_5H_5N) (1 mL) at room temperature overnight. After the usual workup, the mixture was chromatographed on Si gel [hexane (C_6H_6)−Me_2CO (3:1 → 2:1)] to furnish a hexaacetate (**11a**) (16.2 mg) as a white amorphous powder; $[\alpha]^{27}_D$ −56.8° (*c* 0.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, s, CH_3-4α), 0.86 (3H, s, CH_3-10), 0.89 (3H, s, CH_3-4β), 0.90 (3H, s, CH_3-8), 0.90 (3H, d, J = 6.5 Hz, CH_3-20), 1.09, 1.33 (each 3H, s, CH_3-25), 1.26 (3H, s, CH_3-14), 2.00, 2.03, 2.04, 2.07, 2.10, 2.15 (each 3H, s, OAc), 3.63 (1H, dt, J = 3.5, 9.5 Hz, glucosyl H-5), 3.81 (1H, br s, H-7), 4.18 (2H, d, J = 3.5 Hz, glucosyl H_2-6), 4.45 (1H, br d, J = 7 Hz, H-23), 4.57 (1H, d, J = 7.5 Hz, anomeric H), 4.63 (1H, br s, H-3), 4.74 (1H, d, J = 2 Hz, H-24), 5.04−5.23 (3H, m, glucosyl H-2, 3, and 4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6 (C-30), 15.5

(C-19), 17.4 (C-21), 20.6, 20.7, 20.8, 21.0, 21.2, 21.6 (Ac), 21.1 (C-18), 22.1 (C-29), 22.8 (C-6), 26.9 (C-27), 27.6 (C-26), 27.7 (C-28), 31.0 (C-16), 31.5 (C-15), 33.6 (C-1), 35.1 (C-22), 36.0 (C-4), 37.1 (C-10), 38.9 (C-20), 42.7 (C-5), 44.6 (C-8), 47.1 (C-9), 47.8 (C-13), 48.8 (C-14), 61.8 (glucosyl C-6), 68.8 (glucosyl C-4), 71.3 (glucosyl C-5), 71.6 (glucosyl C-2), 72.6 (C-25), 73.5 (glucosyl C-3), 74.9 (C-23), 77.6 (C-7), 77.8 (C-24), 78.5 (C-3), 92.3 (C-17), 96.2 (glucosyl C-1), 168.9, 169.0, 170.3, 170.5, 170.7, 171.3 (COO); negative FABMS *m/z* 905 $(M - H)^-$; positive FABMS *m/z* 929 $(M + Na)^+$; HRFABMS *m/z* calcd for $C_{48}H_{74}O_{16}Na$ 929.4874; found 929.4872.

Compound 12: yield 39.5% (starting with 100 mg of **2**); white amorphous powder; $[\alpha]^{17}_D$ −83.0° (*c* 0.44, $CHCl_3$); ^1H NMR (300 MHz, C_5H_5N-d_5 + D_2O), see Table 1; ^{13}C NMR, see Table 2; negative FABMS *m/z* 751 $(M - H)^-$, 709 $(M - Ac - H)^-$; positive FABMS *m/z* 775 $(M + Na)^+$; HRFABMS *m/z* calcd for $C_{41}H_{68}O_{12}Na$ 775.4609, found 775.4611.

Compound 13: yield 24.8% (starting with 100 mg of **3**); white amorphous powder; $[\alpha]^{17}_D$ −66.2° (*c* 0.45, $CHCl_3$); ^1H NMR (300 MHz, C_5H_5N-d_5 + D_2O), see Table 1; ^{13}C NMR, see Table 2; negative FABMS *m/z* 751 $(M - H)^-$, 709 $(M - Ac - H)^-$; positive FABMS *m/z* 775 $(M + Na)^+$; HRFABMS *m/z* calcd for $C_{40}H_{66}O_{12}Na$ 775.4609, found 775.4611.

Compound 9: yield 26.8% (starting with 581 mg of **3**); white amorphous powder; $[\alpha]^{27}_D$ −59.0° (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.72, 0.84, 0.91, 0.94, 1.13 (each 3H, s, *t*-CH_3), 1.04 (3H, d, J = 6.5 Hz, CH_3-20), 1.73 (3H, s, CH_3-25), 2.08, 2.09 (each 3H, s, OAc), 3.35−3.58 (4H, m, glucosyl H-2−5), 3.67 (1H, m, H-23), 3.85 (1H, br s, H-7), 3.86 (1H, d, J = 5 Hz, H-24), 4.31 (1H, d, J = 7.5 Hz, anomeric H), 4.36 (2H, br s, glucosyl H2-6), 4.68 (1H, br s, H-3), 4.96, 5.03 (each 1H, br s, H-26), 5.10 (1H, t, J = 1.5 Hz, H-12); ^1H NMR (300 MHz, C_5H_5N-d_5 + D_2O), see Table 1; ^{13}C NMR, see Table 2; negative FABMS *m/z* 719 $(M - H)^-$, 677 $(M - Ac - H)^-$; positive FABMS *m/z* 743 $(M + Na)^+$; HRFABMS *m/z* calcd for $C_{40}H_{64}O_{11}Na$ 743.4342, found 743.4346.

Treatment of 9 with *p*-Toluenesulfonic Acid in Me_2CO (Formation of Acetonide 9a). A solution of compound **9** (45 mg) in Me_2CO (10 mL) was stirred for 3 h at room temperature in the presence of *p*-toluenesulfonic acid (3.5 mg). The reaction mixture was concentrated under reduced pressure to give a syrup, which was subjected to chromatography over Si gel. Elution with $CHCl_3$−MeOH (40:1) furnished **12a** (30 mg) as a white amorphous powder; $[\alpha]^{25}_D$ −78.7° (*c* 0.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.72, 0.84, 0.91, 0.95, 1.13 (each 3H, s, *t*-CH_3), 1.00 (3H, d, J = 6.5 Hz, CH_{3-20}), 1.41 (6H, s, isopro-pyridine−CH_3), 1.77 (3H, s, CH_{3-25}) 2.08, 2.10 (each 3H, s, OAc), 3.36−3.50 (3H, m, glucosyl H-2, 4, and 5), 3.58 (1H, t, glucosyl H-3), 3.84 (1H, m, H-23), 3.85 (1H, br s, H-7), 3.96 (1H, d, J = 8 Hz, H-24), 4.32 (1H, d, J = 7.5 Hz, anomeric H), 4.34 (1H, dd, J = 2, 12 Hz, glucosyl H-6), 4.42 (1H, dd, J = 3.5, 12 Hz, glucosyl H-6′), 4.68 (1H, br s, H-3), 4.96, 5.05 (each 1H, br s, H-25), 5.06 (1H, m, H-12); positive FABMS *m/z* 783 $(M + Na)^+$; HRFABMS *m/z* calcd for $C_{43}H_{68}O_{11}Na$ 783.4659, found 783.4657.

Compound 14: yield 9.5% (starting with 581 mg of **3**); white amorphous powder; $[\alpha]^{25}_D$ −104.1° (*c* 0.75, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (3H, s, CH_3-4α), 0.92 (3H, d, J = 6.5 Hz, CH_3-20), 0.92 (6H, s, CH_3-4β and 10), 1.11 (3H, s, CH_3-8), 2.08, 2.10 (each 3H, s, OAc), 3.30 (1H, dd, J = 7.5, 9.5 Hz, glucosyl H-2), 3.39 (1H, dt, J = 3.5, 9.5 Hz, glucosyl H-5), 3.43 (1H, t, J = 9.5 Hz, glucosyl H-4), 3.53 (1H, t, J = 9.5 Hz, glucosyl H-3), 3.68 (1H, tt, J = 4, 11.5 Hz, H-23), 4.00 (1H, br s, H-7), 4.30 (1H, d, J = 7.5 Hz, anomeric H), 4.34 (1H, dd, J = 1.5, 10 Hz, glucosyl H-6), 4.37 (1H, d, J = 10 Hz, glucosyl H-6′), 4.68 (1H, t, J = 2.5 Hz, H-3), 5.32 (1H, d, J = 2 Hz); (300 MHz, C_5H_5N-d_5 + D_2O), see Table 1; ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9 (C-19), 16.9 (C-11), 20.0 (C-21), 20.6 (C-6), 20.9, 21.4 (Ac), 21.8 (C-29), 22.8 (C-2), 27.4 (C-28), 27.5 (C-30), 28.6 (C-20), 29.3 (C-16), 31.0 (C-12), 33.8 (C-1), 36.5 (C-4), 37.5 (C-10), 39.5 (C-22), 42.2 (C-5), 42.2 (C-18), 42.8 (C-8), 44.1 (C-9), 47.8 (C-13), 55.5 (C-17), 63.3 (glucosyl C-6), 68.4 (C-23), 70.2 (glucosyl C-4), 73.5 (glucosyl C-5), 73.9 (glucosyl C-2), 76.3 (glucosyl C-3), 77.5 (C-7), 78.2 (C-3), 98.5 (glucosyl C-1), 120.3 (C-15), 158.9 (C-14), 170.8, 171.4 (COO); ^{13}C NMR (75 MHz, C_5H_5N-d_5 + D_2O), see Table 2; negative FABMS *m/z* 647 $(M - H)^-$, 605 $(M - Ac - H)^-$; positive FABMS *m/z* 671 $(M + Na)^+$; HRFABMS *m/z* calcd for $C_{36}H_{56}O_{10}Na$ 671.3771, found 671.3769.

Acetylation of Compound 14. Compound **14** (15 mg) was treated with Ac_2O (0.5 mL) and dry C_5H_5N (0.5 mL) at room temperature overnight. The usual workup as for **11** afforded a pentaacetate (**14a**) (13 mg) as a white amorphous powder; $[\alpha]^{25}_D$ −72.1° (*c* 0.24, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, s, CH_3-4α), 0.91 (6H, s, CH_3-4β and 10), 0.91 (3H, d, J = 6.5 Hz, CH_3-20), 1.09 (3H, s, CH_3-8), 1.96, 2.02, 2.04, 2.05, 2.07, 2.10 (each 3H, s, OAc), 2.18 (1H, dd, J = 12, 15 Hz, H-16), 3.62 (1H, dt, J = 4, 9.5 Hz, glucosyl H-5), 4.05 (1H, br s, H-7), 4.19 (2H, m, glucosyl H_2-6), 4.58 (1H, d, J = 8 Hz, anomeric H), 4.70 (1H, br s, H-3), 4.74 (1H, tt, J = 4, 11 Hz, H-23), 4.92 (1H, dd, J = 8, 9.5 Hz, glucosyl H-2), 5.09 (1H, t, J = 9.5 Hz, glucosyl H-4), 5.16 (1H, t, J = 9.5 Hz, glucosyl H-3), 5.27 (1H, br s, H-15); ^1M NMR (300 MHz, C_5H_5N-d_5 + D_2O), see Table 1; ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.7 (C-19), 16.9 (C-11), 19.9 (C-21), 20.1 (C-6), 20.6, 20.6, 20.7, 20.9, 21.6, 21.6 (Ac), 22.1 (C-29), 23.0 C-2), 27.5 (C-28), 28.2 (C-30), 28.4 (C-20), 29.3 (C-16), 30.3 (C-12), 33.5 (C-1), 35.1 (C-22), 36.3 (C-4), 37.4 (C-10), 37.6 (C-18), 42.7 (C-5), 42.8 (C-8), 43.7 (C-9), 47.8 (C-13), 55.5 (C-17), 62.1 (glucosyl C-6), 69.0 (glucosyl C-4), 71.4 (C-23), 71.7 (glucosyl C-2 and C-5), 73.5 (glucosyl C-3), 76.6 (C-7), 78.0 (C-3), 95.9 (glucosyl C-1), 120.2 (C-15), 159.0 (C-14), 168.5, 169.4, 170.4, 170.6, 170.7, 171.1 (COO); negative FABMS *m/z* 815 $(M - H)^-$, 773 $(M - Ac - H)^-$, 731 $(M - Ac \times 2\text{-}H)^-$; positive FABMS *m/z* 839 $(M + Na)^+$; HRFABMS *m/z* calcd for $C_{44}H_{64}O_{14}Na$ 839.4194, found 839.4195.

Compound 15: yield 23.8% (starting with 150 mg of **8**); white amorphous powder; $[\alpha]^{17}_D$ −111.9° (*c* 0.45, $CHCl_3$); ^1H NMR (300 MHz, C_5H_5N-d_5 + D_2O), see Table 1; ^{13}C NMR, see Table 2; negative FABMS *m/z* 659 $(M - H)^-$, 617 $(M - Ac - H)^-$; positive FABMS *m/z* 683 $(M + Na)^+$; HRFABMS *m/z* calcd for $C_{37}H_{56}O_{10}Na$ 683.3771, found 683.3769.

Compound 16: yield 35% (starting with 20 mg of **9**); a white amorphous powder; $[\alpha]^{21}_D$ −67.5° (*c* 0.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.83, 0.86, 0.89, 0.90, 1.26, 1.36 (each 3H, s, *tert*-CH_3), 1.00 (3H, d, J = 7 Hz, CH_3-20), 1.68 (3H, s, CH_3-25), 2.08, 2.09 (each 3H, s, OAc), 2.43 (1H, dd, J = 5, 12.5 Hz, H-16), 2.80 (1H,

m, H-20), 3.36−3.60 (5H, m, glucosyl H-2,3,4,5 and H-23), 3.80 (1H, d, J = 6 Hz, H-24), 3.91 (1H, br s, H-7), 4.30 (1H, d, J = 7.5 Hz, anomeric H), 4.34 (1H, d, J = 11.5 Hz, glucosyl H-6), 4.41 (1H, dd, J = 2.5, 11.5 Hz, glucosyl H-6), 4.67 (1H, br s, H-3), 4.95, 4.99 (each 1H, s, H-26); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (C-19), 17.2 (C-30), 17.9 (C-21), 20.3 (Ac), 20.7 (C-11), 21.3 (C-6), 21.4 (Ac), 22.1 (C-29), 22.2 (C-12), 22.9 (C-2), 27.7 (C-20), 28.1 (C-28), 28.3 (C-18), 29.6 (C-27), 29.7 (C-16), 30.4 (C-15), 34.4 (C-1), 36.5 (C-4), 37.5 (C-10), 38.5 (C-22), 41.4 (C-5), 45.0 (C-8), 47.0 (C-9), 46.9 (C-13), 57.0 (C-14), 63.3 (glucosyl C-6), 70.4 (glucosyl C-4), 70.8 (C-23), 73.5 (glucosyl C-2), 74.2 (glucosyl C-5), 76.0 (glucosyl C-3), 78.2 (C-3), 78.3 (C-7), 79.6 (C-24), 98.8 (glucosyl C-1), 113.9 (C-26), 132.0 (C-17), 142.7 (C-13), 144.6 (C-25), 170.6, 171.4 (COO); positive FABMS m/z 743 $(M + Na)^+$; negative FABMS m/z 719 $(M - H)^-$; HRFABMS m/z calcd for $C_{40}H_{46}O_{11}Na$ 743.4346, found 743.4330.

Compound 17: yield 36% (starting with 20 mg of **9**); a white amorphous powder; $[\alpha]^{21}_D$ − 58.3° (c 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, s, *tert*-CH_3), 0.91 (6H, s, *tert*-CH_3), 0.93, 1.26, 1.31 (each 3H, s, *tert*-CH_3), 0.93 (3H, d, J = 7 Hz, CH_3-20), 1.74 (3H, s, CH_3-25), 2.07, 2.09 (each 3H, s, OAc), 3.37−3.60 (4H, m, glucosyl H-2,3,4,5), 3.71 (1H, d, J = 6.5 Hz, H-24), 3.79 (1H, br s, H-7), 3.86 (1H, m, H-23), 4.30 (1H, d, J = 7.5 Hz, anomeric H), 4.33 (1H, dd, J = 2.5, 11.5 Hz, glucosyl H-6), 4.40 (1H, dd, J = 5.5, 11.5 Hz, glucosyl H-6), 4.67 (1H, br s, H-3), 4.88, 4.92 (each 1H, s, H-26); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (C-30), 15.8 (C-19), 16.9 (C-21), 20.7 (C-18), 20.8 (Ac), 21.0 (C-2), 21.1 (C-12), 21.3 (C-11), 21.4 (Ac), 22.0 (C-29), 22.8 (C-6), 27.7 (C-27), 29.7 (C-28), 31.4 (C-16), 31.8 (C-15), 34.4 (C-1), 35.2 (C-22), 36.5 (C-4), 37.5 (C-10), 39.1 (C-20), 42.1 (C-5), 44.5 (C-8), 46.9 (C-9), 48.3 (C-13), 48.9 (C-14), 62.9 (glucosyl C-6), 70.2 (glucosyl C-4), 73.5 (glucosyl C-2), 74.2 (glucosyl C-5), 75.9 (glucosyl C-3), 76.8 (C-24), 77.2 (C-23), 78.2 (C-3), 78.9 (C-7), 92.2 (C-17), 98.7 (glucosyl C-1), 113.3 (C-26), 145.0 (C-25), 170.7, 171.5 (COO); positive FABMS m/z 743 $(M + Na)^+$; negative FABMS m/z 719 $(M - H)^-$; HRFABMS m/z calcd for $C_{40}H_{64}O_{11}$-Na 743.4346, found 743.4330.

Treatment of Compound 3 with BF_3·Et_2O. A solution of **3** (440 mg) in CH_2Cl_2 (10 mL) was treated with 0.1 M BF_3 (0.8 mL) at room temperature overnight with stirring. The reaction mixture was diluted with $CHCl_3$; washed successively with 5% $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4; and concentrated under reduced pressure. The residue was chromatographed over Si gel [EtOAc−MeOH (30:1 → 20:1)] to give two fractions (fractions 1 and 2). Subsequently, Si gel chromatography with C_6H_6−Me_2CO (3:2) gave **14** (46 mg) as a white amorphous powder. Fraction 1 was further chromatographed over Si gel [hexane−EtOAc (2:1)] to yield **18** (184 mg) as a white amorphous powder. The structure of **18** was assigned by spectral examination, although the configuration at C-24 remains to be determined.

Compound 18; a white amorphous powder; $[\alpha]^{21}_D$ −56.1° (c 0.41, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.48, 0.57 (each 1H, d, J = 5.5 Hz, H-18), 0.88 (3H, s, CH_3-4β), 0.90 (3H, s, CH_3-10), 1.08 (3H, s, CH_3-8), 1.09 (3H, d, J = 6.5 Hz, CH_3-20), 1.11 (3H, s, CH_3-4α), 1.63, 1.71 (each 3H, d, J = 22 Hz, CH_3-25), 1.91, 2.03 (each 3H, s, OAc), 2.39 (1H, d, J = 12 Hz, H-5), 3.80 (1H, d, J = 11.5 Hz, H-24), 3.86 (1H, t, J = 8 Hz, glucosyl H-2), 3.95 (1H, m, glucosyl H-5), 3.99 (1H, t, J = 8 Hz, glucosyl H-4), 4.00 (1H, br s, H-7), 4.16 (1H, t, J = 8 Hz, glucosyl H-3), 4.25 (1H, t, J = 6.5 Hz, H-23), 4.68 (1H, dd, J = 5.5, 11.5 Hz, glucosyl H-6), 4.73 (1H, d, J = 7 Hz, anomeric H), 4.91 (1H, dd, J = 2, 11.5 Hz, glucosyl H-6), 4.93 (1H, br s, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (C-19), 17.2 (C-18), 17.4 (C-11), 19.8 (C-21), 20.3 (C-30), 20.6 (C-6), 20.8, 21.0 (Ac), 22.2 (C-29), 23.4 (C-2), 23.6 (d, J = 24 Hz, C-27), 24.9 (d, J = 24 Hz, C-26), 25.4 (C-15), 26.0 (C-16), 27.1 (C-28), 27.7 (C-13), 28.0 (C-12), 33.1 (C-20), 34.4 (C-1), 35.4 (C-8), 36.9 (C-4), 37.6 (C-10), 39.3 (C-14), 40.0 (C-22), 41.4 (C-5), 45.3 (C-9), 53.3 (C-17), 64.6 (glucosyl C-6), 68.5 (d, J = 5 Hz, C-23), 71.5 (glucosyl C-4), 74.6 (glucosyl C-2), 74.9 (glucosyl C-5), 76.6 (d, J = 25 Hz, C-24), 78.0 (C-7), 78.1 (glucosyl C-3), 78.2 (C-3), 98.4 (d, J = 165 Hz, C-25), 100.2 (glucosyl C-1), 170.8, 170.9 (COO); positive FABMS m/z 763 $(M + Na)^+$; negative FABMS m/z 739 $(M - H)^-$; HRFABMS m/z calcd for $C_{40}H_{65}O_{11}FNa$ 763.4409, found 763.4417.

Cytotoxicity Assays. The in vitro cytotoxicity assays were carried out at the National Cancer Institute. Details of the assay procedures have been reported.[8,9]

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Supporting Information Available: ^{1}H- and ^{13}C-NMR spectra of **9**−**15** (7 pages). Ordering information is given on any current masthead page.

References and Notes

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