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SYNTHESIS OF PANAXATRIOL GLUCOSIDES

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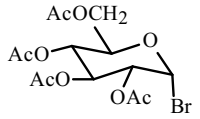
Glycosylation of 3β,6α,12β-trihydroxy-20R,25-epoxydammarane (panaxatriol) and its 3-, 6-, and 3,6-di-O-acetyl derivatives was studied under Koenigs—Knorr conditions. Panaxatriol 3-, 6-, and 12-O-β-D-glucopyranosides were synthesized for the first time.

Key words: dammarane triterpenoids, panaxatriol, glycosylation, *Panax ginseng* C. A. Meyer, panaxatriol 3-*O*-*β*-D-glucopyranoside, panaxatriol 6-*O*-*β*-D-glucopryanoside, panaxatriol 12-*O*-*β*-D-glucopyranoside.

Glycosides of dammarane triterpenoids are components of ginseng (*Panax ginseng* C. A. Meyer) extract and have for many years drawn attention due to the breadth and variety of their physiological activity [1–8]. Although the biological properties of ginseng extract have been studied and active components have been found, the mechanism of action of these compounds is still unknown and the structure–activity relationships have not been established. Observed differences in the properties of ginseng glycosides are often linked to the structuer of their aglycons. For example, the mechanisms of cytotoxicity for B16 melanoma cells differ greatly for ginsenosides Rh2 and Rh1, which have a single glucose on C-3 and C-6 but different aglycons [9, 10].

One of the approaches to studying the structure–activity relationship is to synthesize compounds that are identical to the natural ones and those related to them for subsequent study of their properties using biological tests. Dammarane glycosides from *P. ginseng* are divided into two groups depending on the aglycon structure. These are glycosides of 20*S*-protopanaxadiol and those of 20*S*-protopanaxatriol, which differs from the former by having an additional hydroxyl on C-6. We prepared semi-synthetic glycosides of 20*S*-protopanaxadiol and their analogs by chemical transformation of betulafolientriol, a component of the extract of birch (*Betula*) leaves [11–14]. Then, they were tested biologically [15–20]. Unfortunately, compounds that could be used as starting materials for synthesizing 20*S*-protopanaxatriol glycosides were not found among the many dammarane triterpenoids isolated from *Betula* leaves [21]. The most suitable and relatively available compound for evaluating the reactivity of the C-6 hydroxyl of dammarane triterpenoids for glycosylation compared to the C-3 and C-12 hydroxyls was 3*β*,6*α*,12*β*-trihydroxy-20*R*,25-epoxydammarane (panaxatriol, **1**), one of the acid-hydrolysis products of the total glycoside fraction from *P. ginseng* root [22].



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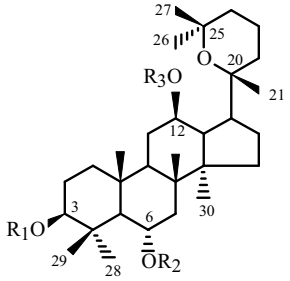

1 - 4, 6 - 20

1: $R_1 = R_2 = R_3 = H$; **2:** $R_1 = R_2 = Ac$, $R_3 = H$; **3:** $R_1 = Ac$, $R_2 = R_3 = H$; **4:** $R_1 = R_3 = H$, $R_2 = Ac$
6: $R_1 = GlcAc_4$, $R_2 = R_3 = H$; **7:** $R_1 = R_2 = H$, $R_3 = GlcAc_4$; **8:** $R_1 = R_2 = Ac$, $R_3 = GlcAc_4$
9: $R_1 = Ac$, $R_2 = GlcAc_4$, $R_3 = H$; **10:** $R_1 = Ac$, $R_2 = H$, $R_3 = GlcAc_4$; **11:** $R_1 = GlcAc_4$, $R_2 = Ac$, $R_3 = H$
12: $R_1 = H$, $R_2 = Ac$, $R_3 = GlcAc_4$; **13:** $R_1 = Glc$, $R_2 = R_3 = H$; **14:** $R_1 = R_2 = H$, $R_3 = Glc$
15: $R_1 = R_2 = Ac$, $R_3 = Glc$; **16:** $R_1 = Ac$, $R_2 = Glc$, $R_3 = H$; **17:** $R_1 = Ac$, $R_2 = H$, $R_3 = Glc$
18: $R_1 = Glc$, $R_2 = Ac$, $R_3 = H$; **19:** $R_1 = H$, $R_2 = Ac$, $R_3 = Glc$; **20:** $R_1 = R_3 = H$, $R_2 = Glc$

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TABLE 1. Condensation Conditions and Results for Compounds **1**–**4** with α-Acetobromoglucose (**5**)

Expt. No.	Starting compound				Reaction product*	Recovery of s.c.*
	Alcohol, mmol	**5**, mmol	Ag_2O, mmol	Mol. sieves 4 Å, g		
1	**1**, 1.0	3.0	3.0	1.0	**6**, 54.9%; **7**, 9.4%	**1**, 16.9%
2	**2**, 0.75	3.0	3.0	1.0	**8**, 18.25%	**2**, 75.3%
3	**3**, 0.37	1.5	1.5	0.7	**9**, 9.9%; **10**, 30.8%	**3**, 38.9%
4	**4**, 0.52	1.5	1.5	0.7	**11**, 58.2%; **12**, 15.1%	**4**, 17.3%

*Yields are given for chromatographically pure compounds.

TABLE 2. ^{13}C NMR Chemical Shifts for Compounds **1**–**4**, **6**, **7** (δ, ppm relative to TMS)

C atom	**1**	**2**	**3**	**4**	**6**	**7**
1	38.66	38.18	38.31	38.56	38.60	38.95
2	27.07	23.27	23.37	27.07	25.71	26.94
3	78.58	80.29	80.66	78.28	90.60	78.58
4	39.23	37.69	38.16	38.79	39.42	39.36
5	61.13	58.70	61.18	58.67	61.36	61.30
6	68.72	70.66	68.48	70.93	68.49	68.65
7	47.07	42.51	47.11	42.56	47.16	46.92
8	40.99	40.72	40.95	40.77	40.96	40.78
9	49.38	49.29	49.28	49.38	49.42	50.10
10	39.16	39.27	39.01	39.41	38.76	39.12
11	30.86	30.32	30.37	30.34	30.50	28.58
12	69.78	69.62	69.70	69.68	69.80	78.50
13	48.75	48.73	48.74	48.74	48.79	45.99
14	51.01	51.02	50.96	51.05	51.02	52.47
15	31.09	31.07	31.06	31.10	31.11	32.74
16	25.12	25.08	25.09	25.11	25.14	26.82
17	54.64	54.61	54.63	54.62	54.69	51.27
18	17.14	16.81	16.54	16.81	17.19	17.11
19	17.14	17.13	17.22	17.02	17.05	17.31
20	76.61	76.61	76.60	76.62	76.64	76.52
21	19.37	19.38	19.36	19.39	19.39	27.20
22	35.70	35.68	35.68	35.69	35.73	31.73
23	16.22	16.22	16.22	16.24	16.24	16.52
24	36.41	36.40	36.39	36.42	36.44	37.02
25	73.13	73.14	73.13	73.14	73.16	70.81
26	33.00	33.00	32.99	33.01	33.02	33.60
27	27.12	27.12	27.12	27.12	27.15	27.65
28	30.38	30.28	30.63	30.43	30.44	30.80
29	15.46	16.72	16.97	15.58	16.24	15.42
30	17.02	16.98	17.14	17.06	17.03	18.93
$\underline{C}H_3CO$		21.99	21.29	22.04	20.72	20.72
		21.26			20.66	20.65
					20.60	20.59
					20.57	20.59
$CH_3\underline{C}O$		170.97	171.03	170.23	170.57	170.53
		170.18			170.31	170.27
					169.39	169.47
					169.18	169.01

Herein we continue research on the synthesis of glycosides based on dammarane tetracyclic triterpenoids with the goal of studying glycosylation of **1** and its acetyl derivatives **2**–**4** under Koenigs–Knorr reaction conditions.

TABLE 3. ^{13}C NMR Chemical Shifts for Compounds **8**–**12** (δ, ppm relative to TMS)

C atom	**8**	**9**	**10**	**11**	**12**
1	38.46	38.32	38.53	38.47	38.84
2	23.19	23.10	23.25	25.53	26.94
3	80.15	80.91	80.49	90.10	78.24
4	37.79	37.74	38.22	38.95	38.89
5	58.89	59.97	61.31	58.96	58.84
6	70.42	79.96	68.37	70.78	70.69
7	42.35	44.47	46.87	42.62	42.39
8	40.53	40.81	40.69	40.76	40.56
9	50.00	49.23	49.94	49.45	50.06
10	39.26	39.31	38.92	39.05	39.39
11	28.48	30.39	28.52	30.40	28.48
12	78.16	69.67	78.27	69.72	78.31
13	45.96	48.84	45.92	48.78	45.96
14	52.45	51.01	52.38	51.06	52.49
15	32.74	30.94	32.69	31.12	32.74
16	26.81	25.05	26.79	25.12	26.82
17	51.21	54.61	51.19	54.65	51.23
18	16.85	17.17	17.07	16.83	16.84
19	17.28	17.28	17.36	16.98	17.21
20	76.46	76.58	76.50	76.64	76.48
21	27.18	19.41	27.16	19.40	27.19
22	31.80	35.69	31.64	35.73	31.74
23	16.52	16.22	16.49	16.24	16.51
24	37.00	36.40	36.98	36.45	37.00
25	70.81	73.16	70.77	73.16	70.83
26	33.57	32.99	33.57	33.02	33.57
27	27.63	27.17	27.60	27.14	27.63
28	30.22	29.88	30.56	29.96	30.35
29	16.71	16.73	16.49	16.39	15.56
30	18.87	16.91	18.86	17.02	18.89
$\underline{C}H_3CO$	21.94	21.27	21.29	21.99	22.00
	21.24	20.96	20.72	20.71	20.72
	20.71	20.76	20.66	20.67	20.66
	20.66	20.58	20.59	20.59	20.58
	20.58	20.58	20.59	20.57	20.58
	20.58				
$CH_3\underline{C}O$	170.92	170.85	170.02	170.55	170.53
	170.52	170.60	170.56	170.32	170.28
	170.26	170.36	170.27	169.99	170.14
	170.08	169.36	169.49	169.38	169.45
	169.47	169.25	169.02	169.08	168.98
	168.97				

We used **1** and its partially protected derivatives such as the 3,6-diacetate (**2**) and the 3- (**3**) and 6-monoacetates (**4**) in order to achieve a high degree of selectivity upon the glycosylation. Diacetate **2** was prepared by acetylating **1** with acetic anhydride in pyridine at room temperature. The C-12 hydroxyl, the proton of which is involved in an intramolecular H-bond with the O atom of the tetrahydropyran ring, was not actylated under these conditions. Monoacetates **3** and **4** were prepared by treating **1** with acetic anhydride in pyridine at –8°C with subsequent chromatographic separation of the product mixture. Preparation of one of **3** or **4** by partial deacetylation of **2** was unsuccessful. Treatment of **2** with sodium methoxide in MeOH at room temperature gave a mixture of **3** and **4** in addition to unreacted **2** and **1**.

TABLE 4. ^{13}C NMR Chemical Shifts for Compounds **13**–**20** (δ, ppm relative to TMS)

C atom	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
1	38.94	38.87	37.80	38.33	38.16	38.69	38.65	39.41
2	26.42	27.96	23.49	23.47	23.79	26.31	27.82	27.88
3	89.23	78.22	80.16	81.13	81.14	88.31	77.45	78.55
4	40.34	40.17	37.98	39.23	38.77	39.69	39.53	40.29
5	61.65	61.77	58.94	60.85	61.56	59.19	59.30	61.38
6	67.38	67.61	70.49	79.41	67.34	70.74	70.97	80.05
7	47.37	47.24	42.85	45.00	47.05	43.12	42.99	45.20
8	40.94	40.86	40.91	40.85	40.92	41.06	40.96	41.07
9	49.57	50.36	50.15	49.48	50.31	49.53	50.33	49.91
10	38.68	39.16	39.37	38.58	38.99	39.15	39.62	39.66
11	30.97	28.97	28.86	30.92	28.97	30.95	28.99	31.14
12	70.05	77.13	76.73	69.91	76.93	69.94	77.05	70.20
13	49.31	46.55	46.63	49.24	46.67	49.41	46.64	49.45
14	51.06	52.63	52.64	50.98	52.73	51.13	52.67	51.21
15	31.10	32.99	33.04	30.97	33.10	31.17	33.08	31.18
16	25.19	27.16	27.23	25.12	27.27	25.23	27.24	25.32
17	54.72	51.65	51.61	54.62	51.76	54.76	51.63	54.80
18	17.25	17.22	17.05	17.08	17.29	17.04	17.09	17.32
19	17.09	17.48	17.26	17.23	17.51	17.15	17.37	17.55
20	76.69	76.76	76.82	76.64	76.87	76.79	76.81	76.84
21	19.40	27.55	27.60	19.36	27.68	19.51	27.60	19.54
22	35.60	31.93	32.15	35.53	32.04	35.70	32.20	35.71
23	16.29	16.75	16.87	16.23	16.88	16.39	16.88	16.41
24	36.34	36.96	37.05	36.29	37.08	36.46	37.06	36.46
25	72.82	70.46	70.62	72.74	70.59	72.96	70.61	72.91
26	32.96	33.74	33.86	32.88	33.87	33.08	33.87	33.06
27	27.16	27.65	27.74	27.12	27.77	27.28	27.75	27.32
28	31.25	31.72	30.34	30.72	31.14	30.70	31.07	31.66
29	16.80	16.21	16.82	16.67	16.77	16.98	16.43	16.31
30	17.21	19.11	19.15	16.74	19.26	17.15	19.14	16.95
$\underline{C}H_3CO$			21.76 21.03	20.90	21.10	21.79	21.86	
$CH_3\underline{C}O$			170.01 170.57	170.92	170.65	170.00	170.08	

Compounds **1**–**4** were glycosylated using 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosylbromide (α-acetobromoglucose) (**5**) in the classical version of the Koenigs–Knorr reaction. Table 1 lists the experimental results. Condensation of **1** with **5** in dichloroethane in the presence of silver oxide and molecular sieves (4 Å) at room temperature formed the 3-*O*-β-D-glucopyranoside (**6**, 54.9%) and a small quantity of the 12-*O*-β-D-glucopyranoside (**7**, 9.4%) (Table 1, expt. 1). Starting with the diacetate (**2**) gave under the same conditions panaxatriol 12-*O*-β-D-glucopyranoside (**8**) in low yield (18%) (Table 1, expt. 2). Use of monoacetate **3** for the glycosylation formed a mixture of monoglucosides **9** and **10** with predominance of the latter (9.9 and 30.8% yields, respectively (Table 1, expt. 3); of monoacetate **4**, the corresponding 3-*O*-β-D-glucopyranoside (**11**, 58.2%) and a small quantity of the 12-*O*-β-D-glucopyranoside (**12**, 15.1%) (Table 1, expt. 4).

Deacetylation of **6** and **7** by NaOMe (0.1 M) in MeOH at room temperature for 1–2 h formed the corresponding free 3- and 12-*O*-β-D-glucopyranosides **13** and **14** in quantitative yields; **8**–**12** gave corresponding glycosides **15**–**19**, the aglycons of which retained the acetate groups. Increasing the reaction time to 7 d completely removed the protecting groups in **15**–**19** and produced free 3-, 12-, and 6-*O*-β-D-glucopyranosides **13**, **14**, and **20**.

TABLE 5. ^{13}C NMR Chemical Shifts for Sugar Components of Compounds **6**–**20** (δ, ppm relative to TMS)

Compound	C atom					
	1′	2′	3′	4′	5′	6′
6	103.30	71.65	72.87	68.90	71.57	62.37
7	98.16	71.39	73.02	68.76	71.39	62.06
8	98.04	71.39	73.04	68.70	71.43	62.02
9	101.51	71.92	73.51	68.37	71.85	62.47
10	98.01	71.34	72.98	68.59	71.33	61.97
11	103.04	71.68	72.89	68.86	71.60	62.36
12	98.10	71.38	73.00	68.76	71.39	62.05
13	106.99	75.72	78.59	71.72	78.10	62.93
14	101.36	75.07	78.65	72.18	77.94	63.12
15	101.37	75.17	78.83	72.32	78.18	63.25
16	105.84	75.17	79.34	71.60	77.94	62.86
17	101.34	75.20	78.85	72.36	78.17	63.27
18	107.15	75.75	78.73	71.82	78.33	63.04
19	101.55	75.20	78.78	72.30	78.11	63.26
20	105.96	75.40	79.57	71.85	78.05	63.09

Structures of all compounds were established using IR, PMR, and ^{13}C NMR spectroscopy. Doublets of anomeric protons of the sugar components of acetylated glucosides **6**–**12** appeared in PMR spectra in $CDCl_3$ at δ 4.50–4.69 ppm ($J_{1',2'}$ = 7.8-8.1 Hz). Doublets of anomeric glucose protons for **13**–**20** were observed in PMR spectra in deuteropyridine at δ 4.98-5.07 ppm ($J_{1',2'}$ = 7.6-7.8 Hz). Chemical shifts and spin–spin coupling constants of anomeric glucose protons indicated that the glycoside bond has the *trans*-configuration in all glycosides. The site of glucose attachment was confirmed by comparing ^{13}C NMR spectra of **1**–**4** and **6–20** (Tables 2-5). The results were consistent with decreasing reactivity of the hydroxyls of 3*β*,6*α*,12*β*-trihydroxy-20*R*,25-epoxydammarane upon Koenigs–Knorr glycosylation in the order 3*β*-OH > 12*β*-OH > 6*α*-OH.

EXPERIMENTAL

PMR and ^{13}C NMR spectra in $CDCl_3$ at 30°C of **1–4**, **9**, and **10** were recorded on a Bruker Avance-300 spectrometer at operating frequency 300 MHz for ^1H and 75 MHz for ^{13}C; of **6–8**, **11**, and **12**, on a Bruker Avance-500 spectrometer at operating frequency 500 MHz for ^1H and 125 MHz for ^{13}C; of **13–20**, in deuteropyridine. Chemical shifts are given on the δ scale relative to TMS. The multiplicity of ^{13}C resonances was established by DEPT-135 experiments using standard method. Homonuclear 2D H–H COSY-45 spectra and heteronuclear 2D HSQC and HMBC correlation spectra were also recorded using standard methods. HMBC experiments were optimized for $^nJ_{HC} \approx 10$ Hz. IR spectra were recorded in $CHCl_3$ on a Bruker Vector 22 spectrophotometer. Optical rotation was determined on a Perkin–Elmer 141 instrument in a 10 cm cuvette at 20°C. Melting points were measured on a Boetius stage. Column chromatography was performed over KSK silica gel (120–150 mesh) using hexane:acetone (20:1→10:1) and benzene:methanol (200:1→40:1). The purity of compounds was monitored by TLC on Sorbfil plates (Russia) using C_6H_6:$CHCl_3$:CH_3OH (6:4:1, 3:2:1, 2:1:1) and hexane:acetone (3:2). Detection used H_2SO_4 in EtOH (10%) and heating at 100-200°C. Elemental analyses of all newly prepared compounds agreed with those calculated.

Panaxatriol (3*β*,6*α*,12*β*-trihydroxy-20*R*,25-epoxydammarane, 1) was prepared by acid hydrolysis of the total glycoside fraction of *P. ginseng* root extract according to the literature method [23, 24] followed by chromatography over a column of silica gel and crystallization from EtOAc, mp 225–228°C, lit. mp 238–239°C [22]. IR spectrum (ν, cm^{-1}): 3584 (OH), 3269 (OH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.908 (3H, s, Me-30), 0.936 (3H, s, Me-19), 0.987 (3H, s, Me-29), 1.061 (3H, s, Me-18), 1.181 (3H, s, Me-21), 1.219 (3H, s, Me-26), 1.265 (3H, s, Me-27), 1.318 (3H, s, Me-28), 3.18 (1H, dd, J = 11.1, 5.2, H-3*α*), 3.53 (1H, td, J = 10.3, 10.3, 5.3, H-12*α*), 4.11 (1H, m, H-6*β*), 6.26 (1H, s, OH).

Acetylation of 1. a. Triol **1** (307 mg) in anhydrous pyridine (3 mL) was treated with acetic anhydride (1.5 mL), left at room temperature for 1 d, and poured into a beaker with ground ice. The resulting precipitate was filtered off, washed thoroughly with icewater, and dried to afford **2** (354 mg, 98%);

b. Triol **1** (640 mg) in anhydrous pyridine (6 mL) was treated with acetic anhydride (3 mL), left at –8°C for 5 h, and poured into a beaker with ground ice. The resulting precipitate was filtered off, washed thoroughly with icewater and dried. The dry solid (730 mg) was chromatographed over a column of silica gel with elution by hexane:acetone (20:1, TLC monitoring) to afford **2** (160 mg, 21.2%), **3** (137 mg, 19.7%), **4** (198 mg, 28.4%), and **1** (174 mg, 27.2%).

3*β*,6*α*-Diacetoxy-12*β*-hydroxy-20*R*,25-epoxydammarane (2), mp 288–289°C (acetone), $[\alpha]_D^{20}$ +31.8° (*c* 1.0, $CHCl_3$), lit. mp 268–269°C [22]. IR spectrum (ν, cm^{-1}): 3277 (OH), 1723 (CH_3C=O).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.896 (3H, s, Me-30), 0.916 (3H, s, Me-29), 1.016 (3H, s, Me-19), 1.023 (3H, s, Me-28), 1.113 (3H, s, Me-18), 1.179 (3H, s, Me-21), 1.217 (3H, s, Me-26), 1.263 (3H, s, Me-27), 2.037 (3H, s, OAc), 2.054 (3H, s, OAc), 3.53 (1H, td, J = 10.3, 10.3, 5.1, H-12*α*), 4.46 (1H, dd, J = 11.0, 5.6, H-3*α*), 5.35 (1H, m, H-6*β*), 6.26 (1H, s, OH).

3*β*-Acetoxy-6*α*,12*β*-dihydroxy-20*R*,25-epoxydammarane (3), $C_{32}H_{54}O_5$, mp 228–231°C (hexane:acetone), $[\alpha]_D^{20}$ +27.8° (*c* 0.6, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3596 (OH), 3284 (OH), 1723 (CH_3C=O).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.904 (3H, s, Me-30), 0.962 (3H, s, Me-19), 1.063 (6H, s, Me-18,29), 1.170 (3H, s, Me-28), 1.180 (3H, s, Me-21), 1.219 (3H, s, Me-26), 1.264 (3H, s, Me-27), 2.06 (3H, s, OAc), 3.53 (1H, td, J = 10.3, 10.3, 5.2, H-12*α*), 4.10 (1H, m, H-6*β*), 4.44 (1H, dd, J = 10.4, 6.2, H-3*α*), 6.27 (1H, s, OH).

6*α*-Acetoxy-3*β*,12*β*-dihydroxy-20*R*,25-epoxydammarane (4), $C_{32}H_{54}O_5$, mp 296–298°C (acetone), $[\alpha]_D^{20}$ +36.0° (*c* 0.75, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3605 (OH), 3279 (OH), 1723 (CH_3C=O).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.838 (3H, s, Me-29), 0.898 (3H, s, Me-30), 0.990 (3H, s, Me-19), 1.112 (3H, s, Me-18), 1.173 (3H, s, Me-28), 1.179 (3H, s, Me-21), 1.216 (3H, s, Me-26), 1.264 (3H, s, Me-27), 2.05 (3H, s, OAc), 3.18 (1H, dd, J = 11.0, 5.4, H-3*α*), 3.52 (1H, td, J = 10.3, 10.3, 5.2, H-12*α*), 5.35 (1H, ddd, J = 11.3, 9.4, 5.2, H-6*β*), 6.26 (1H, s, OH).

Deacetylation of 2. Diacetate **2** (164 mg) in anhydrous MeOH (5 mL) was treated with several drops of NaOMe solution (1 N) in MeOH, left at 10°C for 10 d until the appearance of triol **1** in the mixture (TLC monitoring), diluted with MeOH, and neutralized with KU-2 (H^+-form). The MeOH was vacuum distilled. The dry solid (147 mg) was chromatographed over a column of silica gel with elution by hexane:acetone (20:1) to afford **2** (43 mg, 26.2%), **3** (10 mg, 6.6%), **4** (44 mg, 29.0%), and **1** (15 mg, 10.8%).

General Method for Condensing 1-4 with 2,3,4,6-Tetra-*O*-acetyl-*α*-D-glucopyranosylbromide (5) in the Presence of Silver Oxide and 4Å Molecular Sieves. A solution of glycosylated compound in dichloroethane (10–20 mL) was stirred, treated with the required amount of silver oxide and 4Å molecular sieves and then **5**, stirred continuously at room temperature (20–22°C) for 5–8 h until **5** disappeared (TLC monitoring), diluted with $CHCl_3$, and filtered to remove insoluble silver compounds and molecular sieves. The solvent was distilled at reduced pressure. The solid was worked up three times with hot water to remove water-soluble glucose derivatives, dried, and chromatographed over a column of silica gel with elution by C_6H_6:CH_3OH (200:1→40:1).

6*α*,12*β*-Dihydroxy-3*β*-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (6), $C_{44}H_{70}O_{13}$, mp 221–223°C (MeOH), $[\alpha]_D^{20}$ +10.0° (*c* 1.0, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3596 (OH), 3284 (OH), 1756 (CH_3C=O).

PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.897 (3H, s, Me-30), 0.930 (3H, s, Me-19), 0.945 (3H, s, Me-29), 1.053 (3H, s, Me-18), 1.178 (3H, s, Me-21), 1.216 (3H, s, Me-26), 1.234 (3H, s, Me-28), 1.264 (3H, s, Me-27), 2.003 (3H, s, OAc), 2.024 (6H, s, 2OAc), 2.069 (3H, s, OAc), 3.05 (1H, dd, J = 11.8, 4.8, H-3*α*), 3.52 (1H, td, J = 10.3, 10.3, 5.3, H-12*α*), 3.69 (1H, ddd, J = 10.1, 5.8, 2.5, H-5′), 4.10 (1H, dd, J = 12.1, 2.5, H-6′), 4.11 (1H, m, H-6*β*), 4.25 (1H, dd, J = 12.1, 6.0, H-6′), 4.53 (1H, d, $J_{1',2'}$ = 8.1, H-1′), 5.02 (1H, t, J = 9.8, 9.8, H-4′), 5.05 (1H, dd, J = 9.8, 8.1, H-2′), 5.21 (1H, t, J = 9.6, 9.6, H-3′), 6.27 (1H, s, OH).

3*β*,6*α*-Dihydroxy-12*β*-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (7), $C_{44}H_{70}O_{13}$, amorph., $[\alpha]_D^{20}$ +9.1° (*c* 0.7, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3596 (OH), 3284 (OH), 1756 (CH_3C=O).

PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.887 (3H, s, Me-30), 0.918 (3H, s, Me-19), 0.988 (3H, s, Me-29), 1.022 (3H, s, Me-18), 1.098 (3H, s, Me-26), 1.201 (3H, s, Me-27), 1.302 (3H, s, Me-21), 1.322 (3H, s, Me-28), 1.998 (3H, s, OAc), 2.026 (3H, s, OAc), 2.029 (3H, s, OAc), 2.063 (3H, s, OAc), 3.20 (1H, dd, J = 11.8, 4.8, H-3*α*), 3.56 (1H, td, J = 10.8,

10.8, 4.8, H-12α), 3.63 (1H, ddd, J = 10.1, 4.5, 2.8, H-5′), 4.11 (1H, m, H-6β), 4.14 (1H, dd, J = 12.1, 3.0, H-6′), 4.18 (1H, dd, J = 12.1, 4.5, H-6′), 4.50 (1H, d, $J_{1',2'}$ = 8.1, H-1′), 4.88 (1H, dd, J = 9.8, 8.0, H-2′), 5.05 (1H, t, J = 9.8, 9.8, H-4′), 5.17 (1H, t, J = 9.6, 9.6, H-3′).

3β,6α-Diacetoxy-12β-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (8), $C_{48}H_{74}O_{15}$, mp 154–156°C (MeOH), $[\alpha]_D^{20}$ +9.6° (*c* 1.0, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1755 (CH_3C=O), 1730 (CH_3C=O).

PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.875 (3H, s, Me-30), 0.923 (3H, s, Me-29), 0.999 (3H, s, Me-19), 1.022 (3H, s, Me-28), 1.079 (3H, s, Me-18), 1.088 (3H, s, Me-26), 1.195 (3H, s, Me-27), 1.294 (3H, s, Me-21), 1.996 (3H, s, OAc), 2.026 (6H, s, 2OAc), 2.034 (3H, s, OAc), 2.065 (6H, s, 2OAc), 3.58 (1H, td, J = 10.6, 10.6, 4.5, H-12α), 3.63 (1H, ddd, J = 9.8, 4.5, 2.8, H-5′), 4.15 (1H, dd, J = 12.1, 2.8, H-6′), 4.19 (1H, dd, J = 12.1, 4.5, H-6′), 4.47 (1H, dd, J = 11.8, 4.8, H-3α), 4.52 (1H, d, $J_{1',2'}$ = 7.8, H-1′), 4.89 (1H, dd, J = 9.8, 8.0, H-2′), 5.05 (1H, t, J = 9.8, 9.8, H-4′), 5.17 (1H, t, J = 9.6, 9.6, H-3′), 5.35 (1H, td, J = 10.8, 10.8, 3.8, H-6β).

3β-Acetoxy-12β-hydroxy-6α-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (9), $C_{46}H_{72}O_{14}$, mp 255–257°C (EtOH), $[\alpha]_D^{20}$ +15.1° (*c* 1.0, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3284 (OH), 1756 (CH_3C=O), 1723 (CH_3C=O).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.893 (3H, s, Me-30), 0.963 (3H, s, Me-29), 0.971 (3H, s, Me-19), 1.021 (3H, s, Me-28), 1.046 (3H, s, Me-18), 1.176 (3H, s, Me-21), 1.215 (3H, s, Me-26), 1.258 (3H, s, Me-27), 1.992 (3H, s, OAc), 2.008 (3H, s, OAc), 2.025 (3H, s, OAc), 2.040 (3H, s, OAc), 2.064 (3H, s, OAc), 3.53 (1H, td, J = 10.1, 10.1, 5.0, H-12α), 3.70 (1H, m, H-5′), 4.01 (1H, td, J = 10.5, 10.5, 3.5, H-6β), 4.15 (2H, m, 2H-6′), 4.41 (1H, dd, J = 11.3, 5.3, H-3α), 4.69 (1H, d, $J_{1',2'}$ = 7.8, H-1′), 5.00 (1H, dd, J = 9.3, 8.0, H-2′), 5.06 (1H, t, J = 9.8, 9.8, H-4′), 5.17 (1H, t, J = 9.4, 9.4, H-3′), 6.31 (1H, s, OH).

3β-Acetoxy-6α-hydroxy-12β-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (10), $C_{46}H_{72}O_{14}$, amorph., $[\alpha]_D^{20}$ +7.8° (*c* 0.9, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3596 (OH), 1755 (CH_3C=O), 1723 (CH_3C=O).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.883 (3H, s, Me-30), 0.942 (3H, s, Me-19), 1.022 (3H, s, Me-18), 1.063 (3H, s, Me-29), 1.098 (3H, s, Me-26), 1.175 (3H, s, Me-28), 1.201 (3H, s, Me-27), 1.302 (3H, s, Me-21), 1.997 (3H, s, OAc), 2.026 (3H, s, OAc), 2.028 (3H, s, OAc), 2.068 (3H, s, OAc), 2.073 (3H, s, OAc), 3.57 (1H, td, J = 10.5, 10.5, 4.7, H-12α), 3.64 (1H, m, H-5′), 4.10 (1H, m, H-6β), 4.14 (1H, dd, J = 12.0, 2.8, H-6′), 4.20 (1H, dd, J = 12.0, 4.5, H-6′), 4.46 (1H, dd, J = 11.2, 5.6, H-3α), 4.52 (1H, d, $J_{1',2'}$ = 8.0, H-1′), 4.89 (1H, dd, J = 9.6, 8.0, H-2′), 5.05 (1H, t, J = 9.7, 9.7, H-4′), 5.17 (1H, t, J = 9.5, 9.5, H-3′).

6α-Acetoxy-12β-hydroxy-3β-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (11), $C_{46}H_{72}O_{14}$, mp 188–191°C (MeOH), $[\alpha]_D^{20}$ +14.7° (*c* 1.0, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3279 (OH), 1755 (CH_3C=O), 1730 (CH_3C=O).

PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.802 (3H, s, Me-29), 0.886 (3H, s, Me-30), 0.986 (3H, s, Me-19), 1.088 (3H, s, Me-28), 1.104 (3H, s, Me-18), 1.176 (3H, s, Me-21), 1.213 (3H, s, Me-26), 1.263 (3H, s, Me-27), 2.003 (3H, s, OAc), 2.021 (3H, s, OAc), 2.024 (3H, s, OAc), 2.028 (3H, s, OAc), 2.068 (3H, s, OAc), 3.06 (1H, dd, J = 11.8, 5.0, H-3α), 3.52 (1H, td, J = 10.3, 10.3, 5.3, H-12α), 3.69 (1H, ddd, J = 10.1, 6.0, 2.5, H-5′), 4.10 (1H, dd, J = 12.1, 2.5, H-6′), 4.24 (1H, dd, J = 12.1, 6.0, H-6′), 4.53 (1H, d, $J_{1',2'}$ = 8.0, H-1′), 5.02 (1H, t, J = 9.8, 9.8, H-4′), 5.04 (1H, dd, J = 9.8, 8.0, H-2′), 5.20 (1H, t, J = 9.6, 9.6, H-3′), 5.31 (1H, ddd, J = 11.1, 8.8, 5.8, H-6β), 6.27 (1H, s, OH).

6α-Acetoxy-3β-hydroxy-12β-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (12), $C_{46}H_{72}O_{14}$, amorph., $[\alpha]_D^{20}$ +12.5° (*c* 1.0, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3602 (OH), 1755 (CH_3C=O), 1730 (CH_3C=O).

PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.844 (3H, s, Me-29), 0.878 (3H, s, Me-30), 0.972 (3H, s, Me-19), 1.076 (3H, s, Me-18), 1.090 (3H, s, Me-26), 1.169 (3H, s, Me-28), 1.197 (3H, s, Me-27), 1.297 (3H, s, Me-21), 2.000 (3H, s, OAc), 2.028 (3H, s, OAc), 2.032 (3H, s, OAc), 2.049 (3H, s, OAc), 2.064 (3H, s, OAc), 3.21 (1H, dd, J = 11.3, 4.5, H-3α), 3.57 (1H, td, J = 10.6, 10.6, 4.5, H-12α), 3.63 (1H, m, H-5′), 4.14 (1H, dd, J = 12.1, 2.8, H-6′), 4.18 (1H, dd, J = 12.1, 4.5, H-6′), 4.51 (1H, d, $J_{1',2'}$ = 7.8, H-1′), 4.88 (1H, dd, J = 9.6, 8.0, H-2′), 5.05 (1H, t, J = 9.8, 9.8, H-4′), 5.17 (1H, t, J = 9.6, 9.6, H-3′), 5.35 (1H, td, J = 10.8, 10.8, 3.8, H-6β).

Deacetylation of **6**–**12** used NaOMe solution (0.1 N) in MeOH at room temperature for 1–2 h and 7 d.

6α,12β-Dihydroxy-3β-(β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (13), $C_{36}H_{62}O_9$, mp 232–233°C (MeOH), $[\alpha]_D^{20}$ +6.6° (*c* 1.0, C_5H_5N).

PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.946 (6H, s, Me-19,30), 1.076 (3H, s, Me-18), 1.201 (3H, s, Me-21), 1.212 (3H, s, Me-27), 1.258 (3H, s, Me-26), 1.406 (3H, s, Me-29), 2.053 (3H, s, Me-28), 3.46 (1H, dd, J = 12.1, 4.4, H-3α), 3.78 (1H, td, J = 9.9, 9.9, 5.2, H-12α), 3.99 (1H, m, H-5′), 4.06 (1H, t, J = 8.0, 8.0, H-2′), 4.21 (1H, t, J = 8.5, 8.5, H-4′), 4.24 (1H, t, J = 8.5, 8.5, H-3′), 4.34 (1H, td, J = 10.4, 10.4, 3.6, H-6β), 4.40 (1H, dd, J = 11.8, 5.2, H-6′), 4.58 (1H, dd, $J_{1',2'}$ = 11.8, 2.5, H-6′), 4.98 (1H, d, J = 7.7, H-1′).

3β,6α-Dihydroxy-12β-(β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (14), $C_{36}H_{62}O_9$, amorph., $[\alpha]_D^{20}$ +2.3° (*c* 1.0, C_5H_5N).

PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.933 (3H, s, Me-30), 0.948 (3H, s, Me-19), 1.129 (3H, s, Me-18), 1.178 (3H, s, Me-26), 1.181 (3H, s, Me-27), 1.415 (3H, s, Me-29), 1.513 (3H, s, Me-21), 1.959 (3H, s, Me-28), 3.51 (1H, m, H-3α), 3.98 (1H, ddd, J = 9.6, 5.6, 2.7, H-5′), 4.02 (1H, t, J = 8.1, 8.1, H-2′), 4.12 (1H, td, J = 10.7, 10.7, 4.4, H-12α), 4.15 (1H, t, J = 9.1, 9.1, H-4′), 4.28 (1H, t, J = 9.0, 9.0, H-3′), 4.30 (1H, dd, J = 11.6, 5.5, H-6′), 4.39 (1H, m, H-6β), 4.53 (1H, m, H-6′), 5.05 (1H, d, $J_{1',2'}$ = 7.8, H-1′).

3β,6α-Diacetoxy-12β-(β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (15), $C_{40}H_{66}O_{11}$, amorph., $[\alpha]_D^{20}$ +5.7° (*c* 0.75, C_5H_5N).

PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.861 (3H, s, Me-19), 0.943 (3H, s, Me-30), 1.006 (3H, s, Me-29), 1.158 (3H, s, Me-18), 1.173 (9H, s, Me-26,27,28), 1.488 (3H, s, Me-21), 2.061 (3H, s, OAc), 2.069 (3H, s, OAc), 4.03 (2H, m, H-2′,5′), 4.12 (1H, td, J = 10.9, 10.9, 4.6, H-12α), 4.16 (1H, t, J = 9.0, 9.0, H-4′), 4.29 (1H, t, J = 9.0, 9.0, H-3′), 4.32 (1H, dd, J = 11.6, 5.8, H-6′), 4.57 (1H, dd, J = 11.6, 2.6, H-6′), 4.65 (1H, dd, J = 11.7, 4.6, H-3α), 5.05 (1H, d, $J_{1',2'}$ = 7.6, H-1′), 5.58 (1H, td, J = 11.0, 11.0, 3.7, H-6β).

3β-Acetoxy-12β-hydroxy-6α-(β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (16), $C_{38}H_{64}O_{10}$, amorph., $[\alpha]_D^{20}$ +4.7° (*c* 0.85, C_5H_5N).

PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.786 (3H, s, Me-30), 0.984 (3H, s, Me-19), 1.164 (3H, s, Me-18), 1.191 (3H, s, Me-21), 1.202 (3H, s, Me-27), 1.247 (3H, s, Me-26), 1.456 (3H, s, Me-29), 1.727 (3H, s, Me-28), 2.038 (3H, s, OAc), 3.73 (1H, td, J = 10.1, 10.1, 5.3, H-12α), 3.93 (1H, ddd, J = 9.0, 5.4, 2.7, H-5′), 4.03 (1H, t, J = 8.1, 8.1, H-2′), 4.18 (1H, t, J = 8.8, 8.8, H-4′), 4.22 (1H, t, J = 8.8, 8.8, H-3′), 4.35 (2H, m, H-6β, H-6′), 4.51 (1H, dd, J = 11.5, 2.7, H-6′), 4.75 (1H, dd, J = 9.7, 7.0, H-3α), 4.99 (1H, d, $J_{1',2'}$ = 7.8, H-1′), 5.98 (1H, s, OH).

3β-Acetoxy-6α-hydroxy-12β-(β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (17), $C_{38}H_{64}O_{10}$, amorph., $[\alpha]_D^{20}$ +4.5° (*c* 0.29, C_5H_5N).

PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.894 (3H, s, Me-19), 0.944 (3H, s, Me-30), 1.108 (3H, s, Me-18), 1.175 (3H, s, Me-26), 1.181 (3H, s, Me-27), 1.285 (3H, s, Me-29), 1.513 (3H, s, Me-21), 1.623 (3H, s, Me-28), 2.071 (3H, s, OAc), 4.04 (2H, m, H-2′,5′), 4.13 (1H, td, J = 10.7, 10.7, 4.6, H-12α), 4.17 (1H, t, J = 9.0, 9.0, H-4′), 4.30 (1H, t, J = 9.0, 9.0, H-3′), 4.33 (2H, m, H-6β, H-6′), 4.57 (1H, dd, J = 11.5, 2.7, H-6′), 4.73 (1H, dd, J = 10.8, 5.8, H-3α), 5.07 (1H, d, $J_{1',2'}$ = 7.6, H-1′).

6α-Acetoxy-12β-hydroxy-3β-(β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (18), $C_{38}H_{64}O_{10}$, amorph., $[\alpha]_D^{20}$ +4.4° (*c* 1.0, C_5H_5N).

PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.917 (3H, s, Me-19), 0.938 (3H, s, Me-30), 1.137 (3H, s, Me-29), 1.146 (3H, s, Me-18), 1.175 (3H, s, Me-21), 1.205 (3H, s, Me-27), 1.253 (3H, s, Me-26), 1.636 (3H, s, Me-28), 2.031 (3H, s, OAc), 3.39 (1H, dd, J = 11.8, 4.5, H-3α), 3.76 (1H, td, J = 10.2, 10.2, 5.2, H-12α), 4.00 (1H, m, H-5′), 4.05 (1H, t, J = 8.0, 8.0, H-2′), 4.20 (1H, t, J = 8.8, 8.8, H-4′), 4.24 (1H, t, J = 8.7, 8.7, H-3′), 4.40 (1H, dd, J = 11.5, 5.7, H-6′), 4.58 (1H, dd, J = 11.7, 2.4, H-6′), 4.96 (1H, d, $J_{1',2'}$ = 7.7, H-1′), 5.61 (1H, td, J = 10.7, 10.7, 3.6, H-6β), 6.00 (1H, s, OH).

6α-Acetoxy-3β-hydroxy-12β-(β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (19), $C_{38}H_{64}O_{10}$, amorph., $[\alpha]_D^{20}$ +8.8° (*c* 0.25, C_5H_5N).

PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.935 (3H, s, Me-19), 0.942 (3H, s, Me-30), 1.174 (3H, s, Me-29), 1.193 (6H, s, Me-26,27), 1.199 (3H, s, Me-18), 1.506 (3H, s, Me-21), 1.523 (3H, s, Me-28), 2.096 (3H, s, OAc), 3.47 (1H, dd, J = 10.5, 5.9, H-3α), 3.97 (1H, m, H-5′), 4.04 (1H, t, J = 8.3, 8.3, H-2′), 4.12 (1H, td, J = 10.0, 10.0, 4.6, H-12α), 4.18 (1H, t, J = 9.0, 9.0, H-4′), 4.30 (1H, t, J = 9.0, 9.0, H-3′), 4.33 (1H, dd, J = 11.5, 5.8, H-6′), 4.57 (1H, dd, J = 11.5, 2.4, H-6′), 5.06 (1H, d, $J_{1',2'}$ = 7.6, H-1′), 5.68 (1H, td, J = 11.0, 11.0, 3.7, H-6β).

3β,12β-Dihydroxy-6α-(β-D-glucopyranosyloxy)-20*R*,25-epoxydammarane (20), $C_{36}H_{62}O_9$, amorph., $[\alpha]_D^{20}$ +12.8° (*c* 0.63, C_5H_5N).

PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.784 (3H, s, Me-30), 1.048 (3H, s, Me-19), 1.185 (3H, s, Me-18), 1.197 (3H, s Me-21), 1.207 (3H, s, Me-27), 1.249 (3H, s, Me-26), 1.588 (3H, s, Me-29), 2.054 (3H, s, Me-28), 3.51 (1H, dd, J = 11.7, 4.6, H-3α), 3.74 (1H, m, H-12α), 3.94 (1H, ddd, J = 8.6, 5.6, 2.7, H-5′), 4.08 (1H, t, J = 8.3, 8.3, H-2′), 4.19 (1H, t, J = 9.0, 9.0, H-4′), 4.24 (1H, t, J = 8.8, 8.8, H-3′), 4.35 (1H, dd, J = 11.5, 5.6, H-6′), 4.42 (1H, td, J = 10.5, 10.5, 2.7, H-6β), 4.51 (1H, dd, J = 11.5, 2.7, H-6′), 5.02 (1H, d, $J_{1',2'}$ = 7.8, H-1′), 6.00 (1H, s, OH).

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