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SYNTHESIS OF 20*S*-PROTOPANAXADIOL 20-*O*-*β*-D-GLUCOPYRANOSIDE, A METABOLITE OF *Panax ginseng* GLYCOSIDES, AND COMPOUNDS RELATED TO IT

L. N. Atopkina and V. A. Denisenko

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*A preparative semi-synthetic method was developed to prepare 20*S*-protopanaxadiol 20-*O*-β-D-glucopyranoside (**1**), a metabolite of* Panax ginseng *glycosides. The 20-*O*-β-D-glucopyranosides of 20*S*-hydroxydammar-24-en-3,12-dione, 3β,20*S*-dihydroxydammar-24-en-12-one, and 3β,12α,20*S*-trihydroxydammar-24-ene were synthesized for the first time.*

Key words: dammarane triterpenoids; glycosylation; *Betula*; *Panax ginseng* C. A. Meyer; 20*S*-protopanaxadiol 20-*O*-*β*-D-glucopyranoside; 20*S*-hydroxydammar-24-en-3,12-dione 20-*O*-*β*-D-glucopyranoside; 3*β*,20*S*-dihydroxydammar-24-en-12-one 20-*O*-*β*-D-glucopyranoside; 3*β*,12*α*,20*S*-trihydroxydammar-24-ene 20-*O*-*β*-D-glucopyranoside.

Extract of *Panax ginseng* C. A. Meyer root, which is constantly attracting attention to itself owing to the breadth and variety of its biological activity, contains triterpene glycosides, which have been the subject of numerous investigations. Ginseng glycosides are transformed by intestinal microflora in the gastro-intestinal tract into compounds with new biological properties. In the last few years, the properties and mechanism of action of one of the main metabolites of ginseng glycosides, 20*S*-protopanaxadiol 20-*O*-*β*-D-glucopyranoside (**1**) (compound K), have been studied more frequently [1-13]. Glucoside **1** inhibits the growth of tumor cells and induces their apoptosis [3, 9, 10], decreases the toxicity of antitumor preparations [4], possesses antimetastatic and immunomodulating activity [2, 11], and exhibits antiallergic [12] and anti-inflammatory [13] properties. In most of these investigations, **1** was prepared by treating ginseng extract or the enriched glycoside fraction with enzymes, bacteria, or intestinal microflora followed by chromatographic separation of the products of enzymatic hydrolysis.

We previously prepared **1** as one of the condensation products of 20*S*-protopanaxadiol (dammar-24-en-3*β*,12*β*,20*S*-triol) (**2**) with 2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosylbromide (*α*-acetobromoglucose) (**3**) under Koenig—Knorr reaction conditions [14, 15]. Because all three hydroxyls of **3** were glycosylated, the main drawback was the lack of regioselectivity, which led to the formation of a complicated and difficultly separated mixture of mono- and diglucosides. Regioselective glycosylation of the 3,12-diacetate of 20*S*-protopanaxadiol (**4**) with one free hydroxyl on C-20 was unsuccessful [14], apparently because the 20-OH was sterically shielded by the 12*β*-OAc group.

The present article is a continuation of investigations on the synthesis of glycosides based on tetracyclic dammarane triterpenoids. The goal was to develop a preparative semi-synthetic method for preparing 20*S*-protopanaxadiol 20-*O*-*β*-D-glucopyranoside (**1**).

An attempt to synthesize **1** through regio- and stereoselective glycosylation of the tertiary hydroxyl on C-20 of 20*S*-hydroxydammar-24-en-3,12-dione (**5**) with subsequent reduction of both ketones on C-3 and C-12 into the glycosylation product (**6**) did not give the desired result. Reaction of **5** with **3** in the presence of Ag_2O and 4Å molecular sieves in dichloroethane gave the tetraacetate of the diketone 20-*O*-*β*-D-glucopyranoside (**6**) (47% yield), reduction of which with $NaBH_4$ in isopropanol selectively reduced only one ketone on C-3 and formed the tetraacetate of 3*β*,20*S*-dihydroxydammar-24-en-12-one 20-*O*-*β*-D-glucopyranoside (**7**).

Pacific Institute of Bioorganic Chemistry, Far-East Division, Russian Academy of Sciences, 690022, Vladivostok, pr. 100 Let Vladivostoku, 159, fax 7-(4232) 31 40 50, e-mail: atopkina@mail.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 364-369, July-August, 2006. Original article submitted June 9, 2006.

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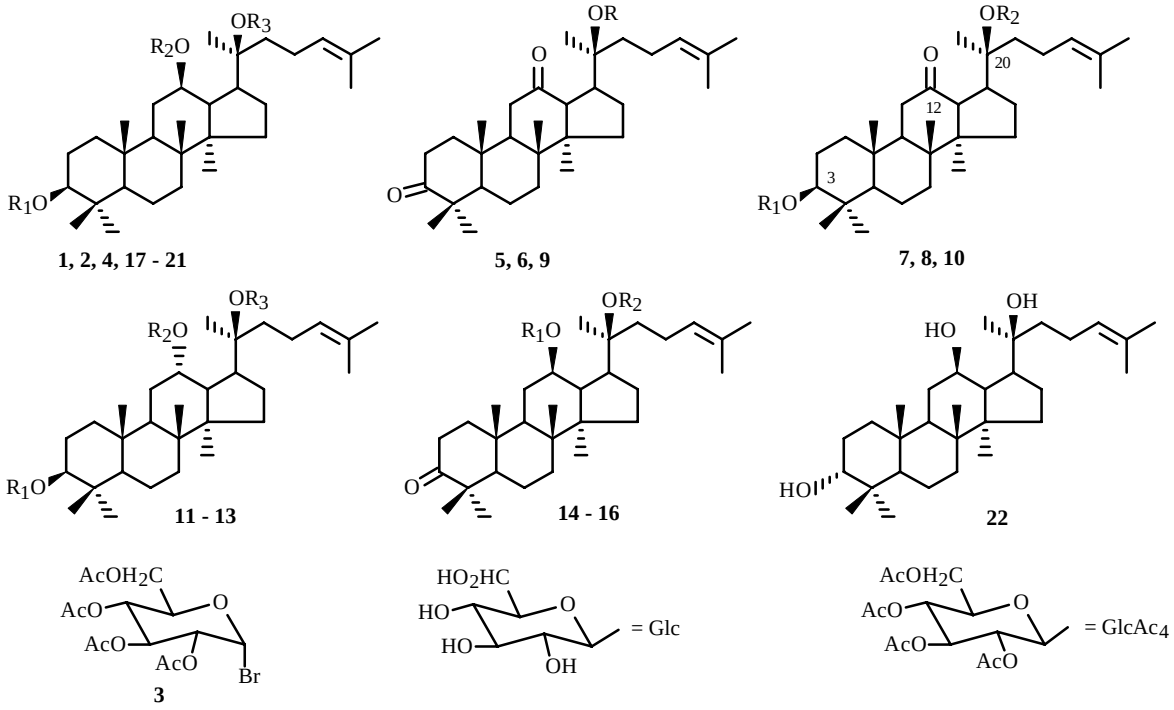

1: $R_1 = R_2 = H$, $R_3 = Glc$; **2:** $R_1 = R_2 = R_3 = H$; **4:** $R_1 = R_2 = Ac$, $R_3 = H$
5: R = H; **6:** R = $GlcAc_4$; **7:** $R_1 = H$, $R_2 = GlcAc_4$; **8:** $R_1 = OAc$, $R_2 = GlcAc_4$; **9:** R = Glc
10: $R_1 = H$, $R_2 = Glc$; **11:** $R_1 = R_2 = H$, $R_3 = Glc$; **12:** $R_1 = Ac$, $R_2 = H$, $R_3 = GlcAc_4$
13: $R_1 = R_2 = Ac$, $R_3 = GlcAc_4$; **14:** $R_1 = R_2 = H$; **15:** $R_1 = GlcAc_4$, $R_2 = H$
16: $R_1 = H$, $R_2 = GlcAc_4$; **17:** $R_1 = R_2 = H$, $R_3 = GlcAc_4$; **18:** $R_1 = R_3 = H$, $R_2 = GlcAc_4$
19: $R_1 = R_2 = Ac$, $R_3 = GlcAc_4$; **20:** $R_1 = Ac$, $R_2 = GlcAc_4$; $R_3 = H$; **21:** $R_1 = R_3 = H$; $R_2 = Glc$

The IR spectrum of **7** contained absorption bands for carbonyl at 1700 cm^{-1} and free hydroxyl at 3612 cm^{-1}. The PMR spectrum of **7** exhibited a signal for the axial proton on C-3 at δ 3.19 ppm, which underwent a low-field shift and appeared at δ 4.47 ppm in the PMR spectrum of **8**, which was obtained by acetylation of **7**. Compared with the ^{13}C NMR spectrum of **6**, that of **7** had one of the two signals for carbonyl C atoms at δ 211.9 ppm, belonging to C-12, whereas the signal for the C-3 carbonyl at δ 216.9 ppm disappeared. Deacetylation of **7** by MeONa (0.1 N) in MeOH gave free 3*β*,20*S*-dihydroxydammar-24-en-12-one 20-*O*-*β*-D-glucopyranoside (**10**), the spectroscopy, elemental analysis, and physicochemical properties of which were identical to the general prosapogenin of natural dammarane glycosides with a 12-ketone in the aglycon [16].

Reduction of free 20*S*-hydroxydammar-24-en-3,12-dione 20-*O*-*β*-D-glucopyranoside (**9**), obtained after removing the protecting groups of **6**, formed 3*β*,12*α*,20*S*-trihydroxydammar-24-ene (the 12-epimer of 20*S*-protopanaxadiol) (**11**) instead of the desired monoglucoside (**1**). Acetylation of **11** by Ac_2O in pyridine at room temperature gave the pentaacetate of 3*β*,12*α*,20*S*-trihydroxydammar-24-ene 20-*O*-*β*-D-glucopyranoside (**12**); at 90°C, its hexaacetate (**13**).

Therefore, the optimal version of the preparative synthesis of **1** was, in our opinion, glycosylation of 12*β*,20*S*-dihdyroxydammar-24-en-3-one (**14**) by **3** with subsequent reduction by $NaBH_4$ in isopropanol of the reaction products (**15** and **16**) to form a mixture of the two tetraacetates 20*S*-protopanaxadiol 20- and 12-*O*-*β*-D-glucopyranosides (**17** and **18**). In order to simplify the chromatographic separation of **17** and **18**, the resulting mixture of **17** and **18** was treated with Ac_2O in pyridine at 90°C for 2-3 h. Because the tertiary OH on C-20 in **18** was not acetylated, the treatment produced a mixture of the hexaacetate of 20*S*-protopanaxadiol 20-*O*-*β*-D-glucopyranoside (**19**) and the pentaacetate of 20*S*-protopanaxadiol 12-*O*-*β*-D-glucopyranoside (**20**), the chromatographic separation of which was facile. Deacetylation of **19** and **20** was effected using KOH solution (10%) in MeOH and produced free **1** and **21**, respectively, in quantitative yields.

TABLE 1. ^{13}C NMR Chemical Shifts of **1**, **5-7**, **9-12**, and **21** (δ, ppm, TMS = 0)

C atom	**1**	**5**	**6**	**7**	**9**	**10**	**11**	**12**	**21**
1	39.19	39.03	39.26	38.60	39.16	38.82	39.26	38.51	38.83
2	28.05	33.77	33.79	27.16	33.97	27.89	28.08	24.05	28.02
3	77.83	216.75	216.91	78.61	215.97	77.53	77.86	80.87	77.79
4	39.34	47.37	47.36	38.93	47.26	39.31	39.40	37.91	39.32
5	56.14	55.13	55.17	55.76	54.79	55.94	56.40	55.96	56.13
6	18.55	19.66	19.77	18.36	19.86	18.64	18.62	18.17	18.47
7	34.95	33.27	33.76	34.40	33.83	34.61	35.80	35.21	34.77
8	39.86	40.12	40.45	40.50	40.55	40.70	40.71	40.40	39.76
9	50.09	52.74	53.88	54.57	53.94	54.73	45.98	45.28	50.06
10	37.14	37.13	37.30	37.63	37.26	37.67	37.00	36.72	37.25
11	30.56	39.27	39.87	39.76	39.16	39.93	30.33	29.25	27.71
12	69.96	213.22	211.19	211.88	210.76	211.06	67.51	68.22	77.38
13	49.30	56.27	55.62	55.53	56.41	56.24	45.80	45.35	46.54
14	51.21	54.79	56.25	56.25	56.16	56.05	49.21	48.97	52.01
15	30.74	30.86	31.69	31.67	32.23	32.12	31.77	31.52	31.10
16	26.42	24.61	23.77	23.73	24.46	24.39	25.02	23.70	26.96
17	51.39	45.90	41.07	40.99	42.48	42.38	46.60	45.48	53.91
18	15.81	15.57	15.24	15.56	15.41	15.77	15.40	15.08	15.50
19	16.14	15.53	15.83	16.13	15.78	16.14	16.45	16.25	16.14
20	83.08	73.17	82.17	82.18	81.25	81.15	82.87	83.44	72.82
21	22.13	26.38	23.45	23.33	22.44	22.26	21.58	22.59	26.68
22	35.96	37.96	38.77	38.80	40.07	40.38	37.00	37.08	36.29
23	22.98	22.46	23.53	23.52	23.90	23.76	22.77	23.33	22.76
24	125.75	124.80	124.26	124.28	125.67	125.56	126.07	124.55	126.37
25	130.69	131.57	131.68	131.63	130.80	130.63	130.58	131.55	130.36
26	25.54	25.73	25.65	25.67	25.71	25.57	25.57	25.71	25.59
27	17.54	17.68	17.67	17.67	17.70	17.56	17.60	17.79	17.50
28	28.47	26.57	26.70	27.98	26.63	28.38	28.48	28.01	28.49
29	16.14	21.05	20.99	15.27	21.00	15.98	16.17	16.61	16.06
30	17.18	17.34	16.73	16.77	16.80	16.79	19.84	19.18	17.14
$CH_3\underline{C}O$			170.58	170.63				170.95	
			170.17	170.22				170.74	
			169.55	169.55				170.32	
			169.06	169.04				169.54	
								169.47	
$\underline{C}H_3CO$			20.84	20.82				21.35	
			20.60	20.61				20.88	
			20.60	20.61				20.72	
			20.58	20.61				20.65	
								20.65	

The structures of all prepared compounds were proved by IR, PMR, and ^{13}C NMR spectroscopy. Doublets for anomeric protons of the sugars of acetylated glucosides (**6-8**, **12**, **13**, **19**, and **20**) appeared in PMR spectra in $CDCl_3$ at δ 4.60-4.73 ppm ($J_{1',2'}$ = 7.8-8.0 Hz). Doublets for anomeric glucose protons in PMR spectra in C_5D_5N of free glucosides (**1**, **9-11**, and **21**) were observed at δ 5.09-5.27 ppm ($J_{1',2'}$ = 7.6-7.8 Hz). Chemical shifts and spin—spin coupling constants for anomeric glucose protons were consistent with the *trans*-configuration of the glycoside bond in all glycosides. The site of attachment of the glucose was confirmed by comparing ^{13}C NMR spectra of **1**, **5-7**, **9-12**, and **21** (Tables 1 and 2).

TABLE 2. ^{13}C NMR Chemical Shifts of Sugars in **1**, **6**, **7**, **9-12**, and **21** (δ, ppm, TMS = 0)

Compound	C atom					
	1′	2′	3′	4′	5′	6′
1	98.05	74.92	79.10	71.45	78.07	62.68
6	94.61	72.01	73.22	69.00	71.59	62.66
7	94.57	71.93	73.21	68.94	71.53	62.64
9	98.42	75.67	79.20	71.83	77.98	62.88
10	98.31	75.53	79.06	71.72	77.83	62.78
11	98.19	75.11	78.77	71.78	77.47	62.96
12	95.15	71.90	72.59	68.83	71.65	62.47
21	100.23	75.08	78.23	70.99	78.18	62.40

EXPERIMENTAL

PMR and ^{13}C NMR spectra of **1**, **9-11**, and **21** were recorded on a Bruker Avance-500 spectrometer at working frequency 500 MHz for ^{1}H and 125 MHz for ^{13}C at 30°C in C_5D_5N; for **5-8**, **12**, **13**, **19**, and **20**, in $CDCl_3$. Chemical shifts are given on the δ scale relative to TMS. The multiplicity of the ^{13}C signals was established using DEPT-135 experiments by the standard method. Homonuclear 2D proton—proton correlation COSY-45 spectra and 2D heteronuclear HSQC and HMBC correlation spectra were also recorded using standard methods. HMBC experiments were optimized for $^{n}J_{HC} \approx 10$ Hz. IR spectra were recorded on a Bruker Vector 22 spectrophotometer in $CHCl_3$ solution. Optical rotation was determined on a Perkin—Elmer 141 instrument in 10-cm cuvettes at 20°C. Melting points were measured on a Boetius stage. Column chromatography was performed over KSK silica gel (120-150 mesh) using solvent systems hexane:acetone (15:1, 15:1→6:1, 10:1). The purity of compounds was monitored using TLC on Sorbfil plates (Russia) and hexane:acetone (3:2) and C_6H_6:$CHCl_3$:CH_3OH (6:4:1, 3:2:1, 2:1:1). Development used H_2SO_4 (10%) in ethanol with heating at 100-200°C. Elemental analyses of all newly prepared compounds agreed with those calculated.

Betulafolientriol (3*α*,12*β*,20*S*-trihydroxydammar-24-ene, **22**) was isolated from an extract of *Betula pendula* leaves according to the literature method [14, 15], mp 195-196°C (acetone).

12*β*,20*S*-Dihydroxydammar-24-ene-3-one (**14**) was prepared on [14, 15], mp 196-198°C (acetone).

Oxidation of Betulafolientriol (22) into Diketone 5. Cooled absolute pyridine (25 mL) was stirred and treated with CrO_3 (3.4 g). After the yellowish-orange complex formed, a solution of **22** (1.67 g) in pyridine (12 mL) was added. The mixture was stirred at room temperature for 20 h. The course of the reaction was monitored by TLC. The reaction mixture was diluted with $CHCl_3$ and passed through a layer of silica gel. Solvent was evaporated at reduced pressure. The solid was dried and chromatographed over a column of silica gel with elution by hexane:acetone (15:1) to afford diketone **5** (1.17 g, 70.3%) and monoketone **14** (0.33 g, 19.7%).

20*S*-Hydroxydammar-24-en-3,12-dione (5), mp 151-152°C (MeOH), $[\alpha]_D^{20}$ +63.3° (*c* 0.9, $CHCl_3$), lit. mp 152-153.5°C [17]. PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.812 (3H, s, Me-30), 1.039 (3H, s, Me-19), 1.072 (3H, s, Me-29), 1.106 (3H, s, Me-28), 1.119 (3H, s, Me-21), 1.228 (3H, s, Me-18), 1.621 (3H, s, Me-27), 1.688 (3H, s, Me-26), 2.29 (2H, d, J = 8.6, 2H-11), 2.49 (3H, m, 2H-2, H-17), 2.90 (1H, d, J = 10.2, H-13), 5.11 (1H, t, J = 7.1, 7.1, H-24).

Condensation of 5 with 3 in the Presence of Silver Oxide and 4Å Molecular Sieves. A mixture of **5** (2.4 g, 5 mmol), **3** (4.11 g, 10 mmol), Ag_2O (2.34 g, 10 mmol), and 4Å molecular sieves (2 g) in dichloroethane (30 mL) was stirred at room temperature for 1 h; treated twice at 1-h intervals with additional portions of **3** (2.06 g, 5 mmol), Ag_2O (1.17 g, 5 mmol), and 4Å molecular sieves (1 g); stirred for 3 h until **3** disappeared in the reaction mixture (TLC monitoring); and filtered to remove insoluble silver compounds and molecular sieves. Solvent was removed at reduced pressure. The solid was dried, washed three times with hot water, dried, and chromatographed over a silica-gel column with elution by hexane:acetone (15:1→6;1) to isolate diketone **5** (0.97 g, 40.4%) and glycoside **6** (1.86 g, 47.2%).

20*S*-(2′,3′,4′,6′-Tetra-*O*-acetyl-*β*-D-glucopyransoyloxy)dammar-24-en-3,12-dione (6). $C_{44}H_{66}O_{12}$, mp 200-202°C (EtOH), $[\alpha]_D^{20}$ +32.6° (*c* 0.7, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1704 (C=O), 1753 (CH_3C=O). PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.741 (3H, s, Me-30), 1.034 (3H, s, Me-21), 1.038 (3H, s, Me-19), 1.067 (3H, s, Me-29), 1.096 (3H, s,

Me-28), 1.251 (3H, s, Me-18), 1.612 (3H, s, Me-27), 1.657 (3H, s, Me-26), 1.988 (6H, s, 2OAc), 2.028 (3H, s, OAc), 2.056 (3H, s, OAc), 2.15 (1H, dd, J = 12.6, 4.1, H-11α), 2.23 (1H, t, J = 12.9, 12.9, H-11β), 2.47 (3H, m, 2H-2, H-17), 3.06 (1H, d, J = 9.7, H-13), 3.66 (1H, ddd, J = 10.0, 6.8, 2.4, H-5′), 4.09 (1H, dd, J = 12.1, 2.5, H-6′), 4.16 (1H, dd, J = 12.1, 6.8, H-6′), 4.61 (1H, d, $J_{1',2'}$ = 7.8, H-1′), 4.94 (1H, dd, J = 9.5, 7.8, H-2′), 4.98 (1H, t, J = 9.6, 9.6, H-4′), 5.05 (1H, t, J = 7.1, 7.1, H-24), 5.19 (1H, t, J = 9.5, 9.5, H-3′).

Reduction of 6. A suspension of $NaBH_4$ (180 mg) in isopropanol (10 mL) was treated at room terperature with a solution of **6** (680 mg) in isopropanol (35 mL), stirred for 30 min until the starting **5** disappeared in the reaction mixture (TLC monitoring), treated dropwise with dilute (1:1) acetic acid, and poured onto ice. The resulting solid was filtered off and dried to afford **7** (570 mg, 83.6%).

3β-Hydroxy-20*S*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)dammar-24-en-12-one (7). $C_{44}H_{68}O_{12}$, mp 199-200.5°C (MeOH), $[\alpha]_D^{20}$ +21.3° (*c* 0.7, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1701 (C=O), 1752 (CH_3C=O), 3612 (OH). PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.724 (3H, s, Me-30), 0.796 (3H, s, Me-29), 0.935 (3H, s, Me-19), 0.981 (3H, s, Me-28), 1.028 (3H, s, Me-21), 1.197 (3H, s, Me-18), 1.604 (3H, s, Me-27), 1.651 (3H, s, Me-26), 1.977 (3H, s, OAc), 1.981 (3H, s, OAc), 2.020 (3H, s, OAc), 2.049 (3H, s, OAc), 2.15 (2H, d, J = 8.6, 2H-11), 2.45 (1H, td, J = 10.4, 10.4, 5.4, H-17), 3.01 (1H, d, J = 9.6, H-13), 3.19 (1H, dd, J = 11.1, 4.7, H-3α), 3.66 (1H, ddd, J = 10.1, 6.9, 2.5, H-5′), 4.07 (1H, dd, J = 12.1, 2.5, H-6′), 4.15 (1H, dd, J = 12.1, 6.9, H-6′), 4.60 (1H, d, $J_{1',2'}$ = 7.9, H-1′), 4.93 (1H, dd, J = 9.4, 7.9, H-2′), 4.98 (1H, t, J = 9.4, 9.4, H-4′), 5.04 (1H, t, J = 7.0, 7.0, H-24), 5.18 (1H, t, J = 9.4, 9.4, H-3′).

Acetylation of 7. Glucoside **7** (200 mg) in absolute pyridine (2 mL) was treated with absolute acetic anhydride (1 mL) and left at room temperature for 1 d. The reaction mixture was poured into a cylinder with ground ice. The resulting precipitate was filtered off, washed with icewater, and dried to afford **8**.

3β-Acetoxy-20*S*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)dammar-24-en-12-one (8). $C_{46}H_{70}O_{13}$, mp 241-243°C (EtOH), lit. mp [16] 242-244°C, $[\alpha]_D^{20}$ +25.4° (*c* 0.6, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1708 (C=O), 1730 (CH_3C=O), 1753 (CH_3C=O). PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.727 (3H, s), 0.864 (3H, s), 0.876 (3H, s), 0.966 (3H, s), 1.033 (3H, s), 1.204 (3H, s), 1.609 (3H, s), 1.657 (3H, s), 1.974 (3H, s, OAc), 1.980 (3H, s, OAc), 2.019 (3H, s, OAc), 2.038 (3H, s, OAc), 2.048 (3H, s, OAc), 2.15 (2H, m, 2H-11), 2.46 (1H, td, J = 10.2, 10.2, 5.5, H-17), 3.01 (1H, d, J = 9.6, H-13), 3.66 (1H, ddd, J = 10.1, 6.6, 2.5, H-5′), 4.08 (1H, dd, J = 12.1, 2.5, H-6′), 4.15 (1H, dd, J = 12.1, 6.6, H-6′), 4.47 (1H, dd, J = 11.2, 4.9, H-3α), 4.60 (1H, d, $J_{1',2'}$ = 7.7, H-1′), 4.93 (1H, dd, J = 9.6, 8.0, H-2′), 4.98 (1H, t, J = 9.6, 9.6, H-4′), 5.04 (1H, t, J = 7.1, 7.1, H-24), 5.18 (1H, t, J = 9.3, 9.3, H-3′).

Glucosides **6** and **7** were deacetylated using MeONa (0.1 N) in MeOH at room temperature for 1-2 h.

20-*O*-β-D-Glucopyranosyl-20*S*-hydroxydammar-24-en-3,12-dione (9). $C_{36}H_{58}O_8$, amorph., $[\alpha]_D^{20}$ +30.5° (*c* 0.9, C_5H_5N). PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.877 (3H, s, Me-30), 0.889 (3H, s, Me-19), 1.044 (3H, s, Me-29), 1.133 (3H, s, Me-28), 1.333 (3H, s, Me-18), 1.592 (3H, s, Me-21), 1.624 (3H, s, Me-26), 1.640 (3H, s, Me-27), 3.67 (1H, d, J = 9.3, H-13), 3.92 (1H, m, H-5′), 4.03 (1H, t, J = 8.2, 8.2, H-2′), 4.24 (2H, m, H-3′, H-4′), 4.36 (1H, dd, J = 11.5, 5.3, H-6′), 4.51 (1H, dd, J = 11.8, 2.8, H-6′), 5.12 (1H, d, $J_{1',2'}$ = 7.6, H-1′), 5.22 (1H, m, H-24).

20-*O*-β-D-Glucopyranosyl-3β,20*S*-dihydroxydammar-24-en-12-one (10). $C_{36}H_{60}O_8$, amorph., $[\alpha]_D^{20}$ +27.3° (*c* 1.2, C_5H_5N). PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.891 (3H, s, Me-19), 0.910 (3H, s, Me-30), 1.041 (3H, s, Me-29), 1.225 (3H, s, Me-28), 1.340 (3H, s, Me-18), 1.594 (3H, s, Me-21), 1.621 (3H, s, Me-26), 1.640 (3H, s, Me-27), 2.96 (1H, td, J = 9.4, 9.4, 4.6, H-17), 3.41 (1H, dd, J = 10.7, 5.4, H-3α), 3.65 (1H, d, J = 9.5, H-13), 3.92 (1H, m, H-5′), 4.03 (1H, t, J = 8.1, 8.1, H-2′), 4.23 (1H, t, J = 8.8, 8.8, H-4′), 4.26 (1H, t, J = 8.8, 8.8, H-3′), 4.36 (1H, dd, J = 11.5, 5.1, H-6′), 4.51 (1H, dd, J = 11.5, 2.7, H-6′), 5.12 (1H, d, $J_{1',2'}$ = 7.7, H-1′), 5.22 (1H, t, J = 7.1, 7.1, H-24).

Reduction of 9. A suspension of $NaBH_4$ (70 mg) in isopropanol (10 mL) at room temperature was treated dropwise with a solution of **9** (35 mg) in isorpopanol (7 mL) and stirred for 20 h. The excess of $NaBH_4$ was destroyed by adding dropwise dilute (1:1) acetic acid. The reaction mixture was poured onto ice and extracted with $CHCl_3$. The solvent was distilled off. The solid was dried to afford **11** (30 mg, 85.3%).

20-*O*-β-D-Glucopyranosyl-3β,12α,20*S*-trihydroxydammar-24-ene (11). $C_{36}H_{62}O_8$, amorph., $[\alpha]_D^{20}$ +24° (*c* 1.5, C_5H_5N). PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.934 (3H, s, Me-19), 1.007 (3H, s, Me-18), 1.078 (3H, s, Me-29), 1.252 (3H, s, Me-28), 1.432 (3H, s, Me-30), 1.604 (3H, s, Me-21), 1.643 (3H, s, Me-26), 1.655 (3H, s, Me-27), 3.43 (1H, dd, J = 11.4, 4.7, H-3α), 3.92 (1H, ddd, J = 9.4, 5.2, 2.7, H-5′), 3.99 (1H, t, J = 8.0, 8.0, H-2′), 4.20 (1H, t, J = 8.9, 8.9, H-4′), 4.24 (1H, t, J = 8.9, 8.9, H-3′), 4.35 (1H, dd, J = 11.4, 5.5, H-6′), 4.53 (1H, dd, J = 11.4, 2.7, H-6′), 4.88 (1H, dd, J = 5.7, 2.9, H-12β), 5.09 (1H, d, $J_{1',2'}$ = 7.7, H-1′), 5.29 (1H, t, J = 7.1, 7.1, H-24).

Acetylation of 11. a) Glucoside **11** (30 mg) in absolute pyridine (1 mL) was treated with absolute acetic anhdyride (0.7 mL) and left at room temperatrure for 1 d. The reaction mixture was poured into a cylinder with ground ice and extracted with $CHCl_3$. The solvent was distilled off. The solid was dried to afford **12**.

b) A solution of **11** (30 mg) in absolute pyridine (1 mL) was treated with absolute acetic anhdyride (0.7 mL) and left at 80-90°C for 5 h. The reaction mixture was poured into a cylinder with ground ice. The resulting precipitate was filtered off, washed with icewater, dried, and crystallized from EtOH to afford **13**.

3β-Acetoxy-12α-hydroxy-20*S*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)dammar-24-ene (12). $C_{46}H_{72}O_{13}$, mp 193-195°C (EtOH), $[\alpha]_D^{20}$ +48.5° (*c* 0.4, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1726 (CH_3C=O), 1753 (CH_3C=O), 3469 (OH). PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.852 (3H, s, Me-29), 0.856 (3H, s, Me-28), 0.895 (3H, s, Me-19), 0.939 (3H, s, Me-18), 1.077 (3H, s, Me-30), 1.198 (3H, s, Me-21), 1.598 (3H, s, Me-27), 1.665 (3H, s, Me-26), 1.990 (3H, s, OAc), 2.017 (3H, s, OAc), 2.043 (3H, s, OAc), 2.046 (3H, s, OAc), 2.064 (3H, s, OAc), 3.65 (1H, ddd, J = 10.1, 5.7, 2.4, H-5′), 4.08 (1H, dd, J = 12.2, 2.4, H-6′), 4.14 (1H, dd, J = 12.1, 5.7, H-6′), 4.28 (1H, m, H-12β), 4.49 (1H, dd, J = 11.1, 5.3, H-3α), 4.69 (1H, d, $J_{1',2'}$ = 7.9, H-1′), 4.92 (1H, dd, J = 9.8, 7.9, H-2′), 5.00 (1H, t, J = 9.8, 9.8, H-4′), 5.04 (1H, t, J = 6.9, 6.9, H-24), 5.23 (1H, t, J = 9.6, 9.6, H-3′).

3β,12α-Diacetoxy-20*S*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)dammar-24-ene (13). $C_{48}H_{74}O_{14}$, mp 174-176°C (EtOH), $[\alpha]_D^{20}$ +49.9° (*c* 0.4, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1726 (CH_3C=O), 1753 (CH_3C=O). PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.854 (3H, s, Me-29), 0.862 (3H, s, Me-28), 0.886 (3H, s, Me-19), 0.974 (3H, s, Me-18), 1.036 (3H, s, Me-30), 1.170 (3H, s, Me-21), 1.599 (3H, s, Me-27), 1.653 (3H, s, Me-26), 1.980 (3H, s, OAc), 2.014 (3H, s, OAc), 2.038 (3H, s, OAc), 2.041 (3H, s, OAc), 2.046 (3H, s, OAc), 2.074 (3H, s, OAc), 3.65 (1H, ddd, J = 10.1, 6.6, 2.5, H-5′), 4.08 (1H, dd, J = 12.1, 2.5, H-6′), 4.15 (1H, dd, J = 12.1, 6.6, H-6′), 4.47 (1H, dd, 1H, J = 10.4, 5.8, H-3α), 4.63 (1H, d, $J_{1',2'}$ = 8.0, H-1′), 4.95 (1H, dd, J = 9.6, 8.0, H-2′), 4.98 (1H, t, J = 9.6, 9.6, H-4′), 5.03 (1H, t, J = 6.9, 6.9, H-24), 5.16 (1H, dd, J = 6.0, 3.0, H-12β), 5.19 (1H, t, J = 9.6, 9.6, H-3′).

Synthesis of 20*S*-Protopanaxadiol 20- and 12-*O*-β-D-Glucopyranosides (1 and 21). A mixture of **14** (1.15 g, 2.5 mmol), **3** (2.06 g, 5 mmol), Ag_2O (1.17 g, 5 mmol), and 4Å molecular sieves (1 g) in dichloroethane (30 mL) was stirred at room temperature for 1 h; treated twice at 1-h intervals with additional portions of **3** (2.06 g, 5 mmol), Ag_2O (1.17 g, 5 mmol), and 4Å molecular sieves (1 g); stirred for 3 h until **3** disappeared in the reaction mixture (TLC monitoring); and filtered to remove insoluble silver compounds and molecular sieves. Solvent was removed at reduced pressure. The solid was dried, washed three times with hot water to remove the excess of glucose derivatives, and dried to afford the crude product (1.9 g). A suspension of $NaBH_4$ (200 mg) in isopropanol (15 mL) was treated dropwise with a solution of the crude product (1.9 g) in isopropanol (10 mL) and stirred at room temperature for 3 h until the reaction was complete (TLC monitoring). The excess of $NaBH_4$ was decomposed by adding dropwise dilute (1:1) acetic acid. The reaction mixture was poured into a cylinder with ground ice and extracted with $CHCl_3$. The extracts were evaporated and dried. The solid was dissolved in absolute pyridine (10 mL), treated with acetic anhydride (7 mL), held at 90°C for 3 h (TLC monitoring), and poured onto ice. The resulting precipitate was filtered off, washed with cold water, and dried. The solid (1.48 g) was chromatographed over a silica-gel column with elution by hexane:acetone (10:1) to afford **19** (0.32 g, 14.5%) and **20** (0.98 g, 45.7%).

3β,12β-Diacetoxy-20*S*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)dammar-24-ene (19), mp 176-177°C (EtOH), lit. mp [1] 177-178°C. PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.849 (6H, s), 0.878 (3H, s), 0.927 (3H, s), 0.968 (3H, s), 1.177 (3H, s), 1.595 (3H, s), 1.653 (3H, s), 1.977 (3H, s, OAc), 1.991 (3H, s, OAc), 2.023 (3H, s, OAc), 2.035 (3H, s, OAc), 2.049 (3H, s, OAc), 2.056 (3H, s, OAc), 3.65 (1H, ddd, J = 10.2, 5.3, 3.2, H-5′), 4.10 (1H, dd, J = 12.0, 3.2, H-6′), 4.13 (1H, dd, J = 12.2, 5.5, H-6′), 4.48 (1H, dd, J = 11.0, 5.00, H-3α), 4.67 (1H, d, $J_{1',2'}$ = 7.7, H-1′), 4.83 (1H, td, J = 10.7, 10.7, 5.2, H-12α), 4.92 (1H, dd, J = 9.7, 8.0, H-2′), 4.99 (1H, t, J = 9.7, 9.7, H-4′), 5.01 (1H, m, H-24), 5.19 (1H, t, J = 9.5, 9.5, H-3′).

3β-Acetoxy-20*S*-hydroxy-12β-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)dammar-24-ene (20), mp 137-140°C (EtOH), lit. mp [15] 137-140°C. PMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.867 (6H, s), 0.886 (3H, s), 0.898 (3H, s), 0.970 (3H, s), 1.110 (3H, s), 1.643 (3H, s), 1.706 (3H, s), 1.989 (3H, s, OAc), 2.014 (3H, s, OAc), 2.034 (3H, s, OAc), 2.061 (3H, s, OAc), 2.093 (3H, s, OAc), 3.67 (1H, dt, J = 10.0, 3.7, 3.7, H-5′), 3.81 (1H, td, J = 10.7, 10.7, 5.00, H-12α), 3.95 (1H, s, OH), 4.21 (2H, d, J = 4.00, 2H-6′), 4.49 (1H, dd, J = 11.5, 4.7, H-3α), 4.73 (1H, d, $J_{1',2'}$ = 8.0, H-1′), 4.91 (1H, dd, J = 9.7, 8.0, H-2′), 5.09 (1H, t, J = 9.7, 9.7, H-4′), 5.17 (1H, m, H-24), 5.21 (1H, t, J = 9.5, 9.5, H-3′).

Compounds **19** and **20** were deacetylated by KOH (10%) in methanol at room temperature.

20-*O*-β-D-Glucopyranosyl-3β,12β,20*S*-trihydroxydammar-24-ene (1). $C_{36}H_{62}O_8 \cdot 1.5\ H_2O$, amorph., $[\alpha]_D^{20}$ +31° (*c* 0.5, C_5H_5N). PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.900 (3H, s, Me-19), 0.956 (3H, s, Me-30), 0.997 (3H, s, Me-18), 1.049 (3H, s, Me-29), 1.239 (3H, s, Me-28), 1.604 (3H, s, Me-27), 1.607 (3H, s, Me-26), 1.640 (3H, s, Me-21), 3.43 (1H, m, H-3α), 3.94 (1H, ddd, J = 9.15, 5.53, 2.64, H-5′), 4.02 (1H, t, J = 8.2, 8.2, H-2′), 4.18 (1H, t, J = 8.9, 8.9, H-4′), 4.18 (1H, m, H-12α), 4.25 (1H, t, J = 8.7, 8.7, H-3′), 4.34 (1H, dd, J = 11.7, 5.2, H-6′), 4.51 (1H, dd, J = 11.7. 2.4, H-6′), 5.21 (1H, d, $J_{1',2'}$ = 7.8, H-1′), 5.26 (1H, t, J = 6.8, 6.8, H-24).

12-*O*-β-D-Glucopyranosyl-3β,12β,20*S*-trihydroxydammar-24-ene (21). $C_{36}H_{62}O_8 \cdot H_2O$, amorph., $[\alpha]_D^{20}$ -6.5° (*c* 0.75, C_5H_5N). PMR spectrum (500 MHz, C_5D_5N, δ, ppm, J/Hz): 0.770 (3H, s, Me-19), 0.827 (3H, s, Me-18), 0.842 (3H, s, Me-30), 1.019 (3H, s, Me-29), 1.223 (3H, s, Me-28), 1.343 (3H, s, Me-21), 1.643 (3H, s, Me-26), 1.649 (3H, s, Me-27), 3.42 (1H, dd, J = 10.7, 5.6, H-3α), 4.00 (1H, ddd, J = 9.6, 5.0, 2.6, H-5′), 4.09 (1H, dd, J = 9.0, 7.8, H-2′), 4.21 (1H, t, J = 9.2, 9.2, H-4′), 4.29 (1H, t, J = 8.8, 8.8, H-3′), 4.30 (1H, m, H-12α), 4.32 (1H, dd, J = 11.6, 5.0, H-6′), 4.47 (1H, dd, J = 11.6, 2.6, H-6′), 5.27 (1H, d, $J_{1',2'}$ = 7.6, H-1′), 5.34 (1H, m, H-24).

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