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SYNTHESIS OF STEROID AND TRITERPENOID GLYCOSIDES BY THE ORTHOESTER METHOD

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ABSTRACT

Lanosteryl D-glucopyranoside, as well as the D-glucopyranosides and maltosides of β-sitosterol, cholesterol, and 16-dehydropregnenolone have been synthesized by means of the orthoester glycosylation method. For the first time, six betulin glycosides have been prepared, including the di-glucoside and di-maltoside. Ethyl and *tert*-butyl orthoacetate derivatives of D-glucose and the methyl orthoacetate of maltose were the glycosylation components. The formation of considerable amounts of acetates and ethers of the alcohols accompanied glycosylation.

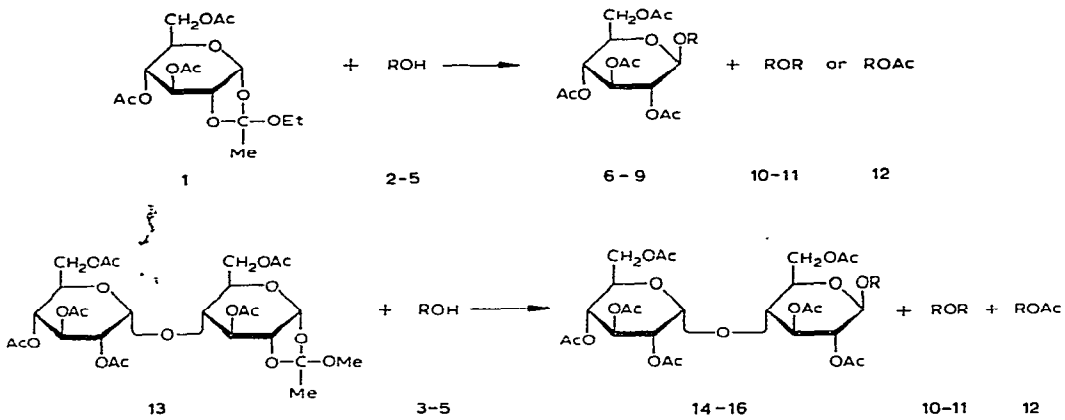
INTRODUCTION

The Koenigs–Knorr reaction and its numerous modifications[1–7] have been the sole means of synthesising glycosides of steroid and triterpene alcohols. With the intention of providing an alternative synthetic procedure, we began a systematic study of the glycosylation of polycyclic alcohols with carbohydrate orthoesters. Kochetkov *et al.* have applied the reaction to synthesize glycosides of cholesterol and oleanolic acid[8–10]. The method is stereospecific in yielding 1,2-*trans* glycosides, gives high yields, and is convenient because of the availability of the orthoester derivatives.

RESULTS AND DISCUSSION

Glycosylation in nitromethane in the presence of mercuric bromide (Method *A*) was used to synthesize the glycosides of lanosterol (**6**), β-sitosterol (**7**), cholesterol (**8**), 16-dehydropregnenolone (**9**), as well as the maltosides of β-sitosterol (**14**), cholesterol (**15**), and 16-dehydropregnenolone (**16**). The glycosylation components were 3,4,6-tri-*O*-acetyl-α-D-glucopyranose 1,2-(ethyl orthoacetate) (**1**) and 3,6,2′,3′4′,6′-hexa-*O*-acetyl-α-maltose 1,2-(methyl orthoacetate) (**13**)[12–13]. The yields of glycosides **6–9** were 29.5–45%[14–15], and those of maltosides **14–16** 29.5–46.9%[16]. T.l.c. of the reaction mixtures showed the absence of the starting orthoesters, their derivatives esterified with starting alcohols, and α-D anomers.

On preparing the glycosides of β-sitosterol and cholesterol with orthoethers **1** and **13**, the formation of acid-stable substances of low polarity was observed together



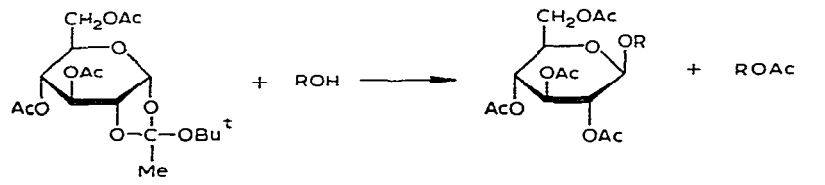
with the main reaction products. For β-sitosterol, the yield of by-product **10** rose from 5 to 17.5% when the catalyst concentration was increased from 8 to 40 μmoles (for orthoester **1**), and up to 35% with increase in reaction temperature to 160°, the yield of **7** being constant. The i.r. spectrum of **10** contains an absorption band in the range 1088–1090 cm^{-1} which, in the absence of other oxygen functions[17-18], unambiguously indicates an ether bond. The stability towards acid and the elemental analysis also indicate **10** to be di-β-sitosteryl ether.

Dicholesteryl ether (**11**) was isolated on preparing cholesteryl glycosides with orthoesters **1** and **13**. As with β-sitosterol, the yield of **11** (15–23.8%) in the condensation of cholesterol and **1** depended upon catalyst concentration. Preparation of glycosides from β-sitosterol and cholesterol with the maltose orthoacetate **13** gave the best yields (42.7–46.9%) in the presence of 20 μmoles of mercuric bromide, and the ethers **10–11** were formed simultaneously. Glycosylation of 16-dehydropregnenolone with **1** and **13** gave, together with **9** and **16**, considerable amounts of the acetate **12** (44.0 and 22.5%). The formation of acetates (2.0–4.0%) of the starting alcohol was observed by Conrow in syntheses of steroid phenolic glycosides[3] in the presence of cadmium carbonate. The formation of polycyclic alcohol ethers and acetates in the glycosylation reactions is a complex process which merits further investigation.

Glycosylations in chlorobenzene in the presence of 2,6-dimethylpyridinium perchlorate (Method *B*)[19-20] were also used to synthesize the glucosides **7–9**. Maximum yields were obtained with 20 μmoles of 2,6-dimethylpyridinium perchlorate[21] and were higher than with Method *A* (see Table I). However, acetates (**12**, **18**, or **19**) were formed in each reaction.

A change in catalyst concentration (2, 10, and 30 μmoles), increase in reaction times (2-fold), and introduction of surplus **17** led to lower yields of the main products (**7–9**)[21,22].

The glycosylation of betulin, a triterpene diol of widespread occurrence in plants, was investigated. The only known betulin glycoside is that isolated from *Sophora japonica*[23]. Betulin is an accessible and suitable model for comparing the



17 3-5 7-9 12, 18, 19

TABLE I

COMPARATIVE DATA ON GLYCOSYLATION REACTIONS

Starting alcohol	*Glycosylation agent*	*Yield*[a] (%)	
		Main product	*By-product*
Cholesterol	**1**	**8** 45.0	**11** 23.8
	17	**8** 61.4	**18** 25.0
	13	**15** 42.7	**11** 16.2
β-Sitosterol	**1**	**7** 26.0	**10** 17.5
	17	**7** 37.9	**19** 24.5
	13	**14** 46.9	**10** 13.2
16-Dehydropregnenolone	**1**	**9** 27.38	**12** 44.7
	17	**9** 27.4	**12** 33.7
	13	**16** 29.5	**12** 22.5

[a]The yields are given for crystalline derivatives.

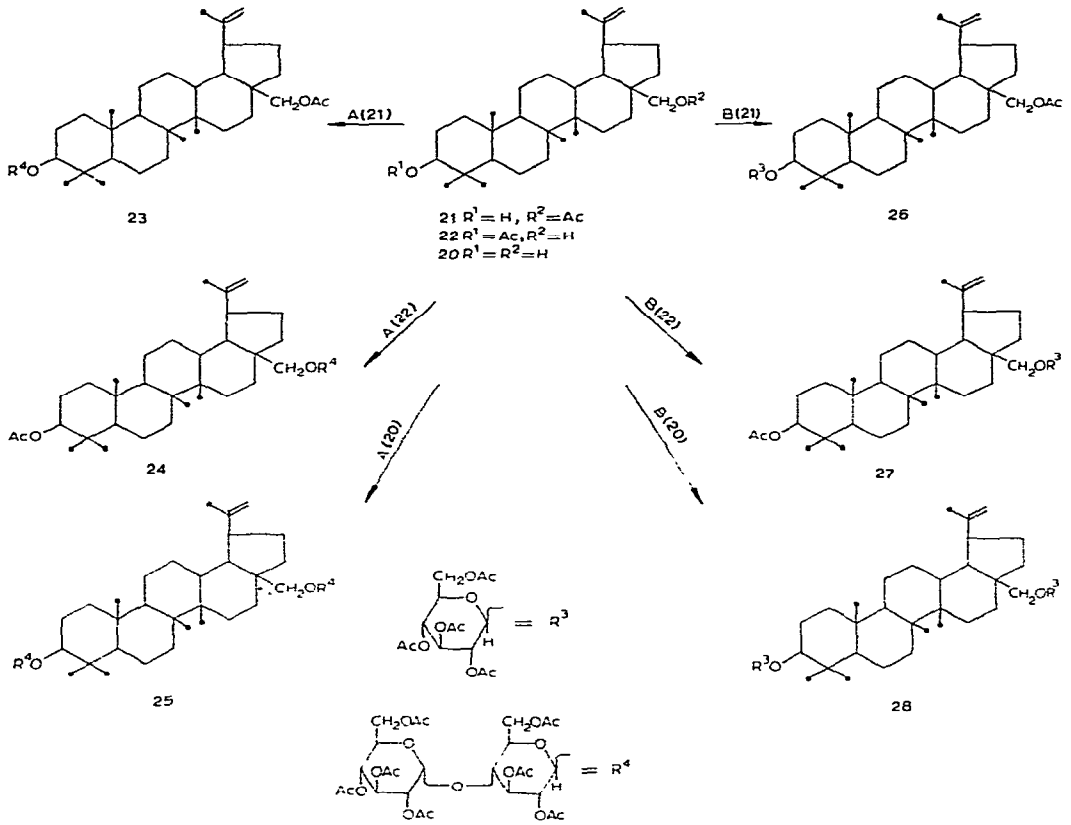
reactivities of triterpenoid primary and secondary hydroxyl groups in the glycosylation reaction. Betulin and the respective mono-acetates[24] were subjected to glycosylation (see Scheme 1).

The formation of betulin diacetate (**29**) as a by-product was observed during glycosylation of the monoacetates **21** and **22**. Glycosylation of betulin gave the diacetate and the **28**-acetate as by-products. The physico-chemical characteristics of the betulin glycosides are given in Table II which show that both the m.p. and polarity are higher for the C-3 glycosides **23** and **26**. The conditions for the synthesis of the

TABLE II

BETULIN GLYCOSIDES

Glycoside	*M.p. (from ethanol) (degrees)*	$[\alpha]_D^{20}$ *(degrees)*	R_F	
			Al_2O_3 *(solvent* a)	$SiO_2/CaSO_4$ *(solvent* b)
23	230–231.5	+62 (*c* 0.22)	0.37	0.41
24	149–151	+75.8 (*c* 0.29)	0.44	0.50
25	200.5–203.5	+66 (*c* 0.45)	0.26	0.32
26	177–179	+41.4 (*c* 0.24)	0.6	0.63
27	140–143	+12 (*c* 0.2)	0.7	0.69
28	230–231	+6.5 (*c* 0.22)	0.5	0.56



Scheme 1. Synthesis of betulin glycoside acetates.

TABLE III

DATA ON SYNTHESIS OF BETULIN GLYCOSIDES

Expt.	*ROH* (*1 mmole*)	*Catalyst* (*mmoles*)	*Reaction times* (*h*)	*Yield*[a] (%)	
				Main product	*By-product*
		$HgBr_2$			
XI	21	0.02	2.5	23 60.74	9 8.9
XII	22	0.02	2.5	24 63.40	–
XIII	20	2×0.02	3.5	25 29.8	–
				24 61.5	
		2,6-Dimethylpyridinium perchlorate			
XIV	21	0.02	0.5	26 44.3	9 25.0
XV	22	0.02	0.5	27 58.12	–
XVI	20	2×0.02	0.75	28 27.1	–
				27 28.7	
				26 8.3	

[a]The by-product yield in Expts. XII–XIII and XV–XVI is not shown, since the reaction mixture was acetylated with a view to convenient separation. The main product yields are given for chromatographically homogeneous substances.

betulin glycosides are given in Table III which shows that the glucoside yield at C-28 is higher than that at C-3 (Expts. XIV–XV). The different reactivities of the primary and secondary hydroxyl groups are also confirmed by the results of Expts. XIII and XVI, in which free betulin was introduced into the reaction, and glycosylation at the primary hydroxyl group was more extensive. A comparison of experiments XI and XII, and XIV and XV, showed that glycosylation with the maltose methyl orthoacetate was more complete than with the glucose *tert*-butyl orthoacetate. The highest utilisation of betulin in the glycosidation reaction was in Expt. XIII, in which **24** and **25** were formed, and in which orthoester **13** (2 mmoles) and mercuric bromide catalyst (40 μmoles) were introduced in two portions with a one-hour interval. Simultaneous introduction of 2 mmoles of orthoesters gave a lower yield of the final products.

It is known that the orthoester method is highly stereospecific and leads to the formation of 1,2-*trans* glycosides. This configuration for all the glycosides reported was corroborated by means of n.m.r. spectroscopy, the results of which are reported in the following Note.

EXPERIMENTAL

Nitromethane, chlorobenzene, 1,2-dichloroethane, chloroform, and *tert*-butyl alcohol were purified according to the procedures of Bochkov *et al.*[11] and Kochetkov *et al.*[19,20]. The latter authors' technique[19,20] was also used to prepare 2,6-dimethylpyridinium perchlorate. Sugar orthoesters **1**, **13**, and **17** were synthesised by means of procedures described previously[11,19,20]. The bark of *Betula daurica* served as the betulin source. Melting points were determined on Koffler hot-stage, and specific rotations were determined on solutions in chloroform with an SPU-M instrument (U.S.S.R.). Evaporations were carried out *in vacuo* at 40–50°. Chromatography, both thin-layer and column, was performed on alumina (neutral, Brockman III), and in a fixed Silica Gel layer, using (*a*) chloroform–butanone (98.5:1.5), (*b*) benzene–ethyl acetate (5:2), and (*c*) light petroleum–ethyl ether (95:5). In Expts. I–X, 1 mmole of alcohol and orthoester, respectively, were used in the synthesis. The final and by-product yields (%) are shown in Table I. In Expts. VIII–X, 2,6-dimethylpyridinium perchlorate (20 μmoles) was introduced in 1,2-dichloroethane (1.5 ml). The synthesis conditions and constants for the glycosides obtained in Expts. XI–XVI are given in Tables II and III.

The analyses were carried out by Dr. L. I. Glebko, Laboratory of Microanalysis, Institute of Biologically Active Substances, Vladivostok, U.S.S.R.

Betulin 28-acetate (**21**). — Betulin (1.31 g) was acetylated at 0° for 40 min with a mixture of acetic anhydride in pyridine in the usual manner. The crude product was eluted from alumina with light petroleum–benzene–chloroform to give **21** (0.92 g), m.p. 216–218° (from ethanol), $[\alpha]_D^{20}$ +14.6° (*c* 0.12).

The n.m.r. spectrum of betulin has a C-3 methine proton signal at δ 3.24 and C-28 methylene proton signals at δ 3.67 (quartet), whereas in that of **21**, the position

of the methine proton signal does not change, and the methylene proton signals are shifted to low field by up to 3.93 Hz, thereby confirming the location of the acetate residue.

Lanosteryl β-D-glucopyranoside tetra-acetate (**6**) (Expt. I). — A mixture of **1**, **2**, and nitromethane (8 ml) was distilled at atmospheric pressure. Nitromethane was added to the mixture so that the volume remained constant. After distilling off 3 ml of the solvent, 26 μmoles of mercuric bromide dissolved in benzene were added, and the mixture was boiled for 2.5 h and then cooled. The precipitate was collected and washed with hot methanol. Several drops of pyridine were then added to the filtrate, and the mixture was evaporated *in vacuo*. Recrystallisation of the precipitate from ethanol gave **6** (0.24 g), m.p. 203–204.5° (from ethanol), $[\alpha]_D^{20}$ +17° (*c* 1.73). A further amount (0.06 g) of **6** was obtained from the filtrate. Total yield 40%. Lit.[27] m.p. 186–189°, $[\alpha]_D^{20}$ +19° (chloroform).

β-Sitosteryl β-D-glucopyranoside tetra-acetate (**7**) (Expt. II). — Cooling of the reaction mixture obtained from **1**, **3**, and mercuric bromide (40 μmoles), under conditions similar to those in Expt. I, gave a precipitate (60 mg) which was collected, washed with hot nitromethane, and crystallized from chloroform–methanol to give di-β-sitosteryl ether (**10**), m.p. 190–192°, $[\alpha]_D^{20}$ −22.2° (*c* 0.58).

Anal. Calc. for $C_{58}H_{98}O$: C, 85.85; H, 12.17. Found: C, 85.62; H, 12.17.

The above filtrate and washings were concentrated, and the residue was twice crystallized from ethanol to give **7** (0.19 g), m.p. 167–168.5° (from chloroform–methanol), $[\alpha]_D^{20}$ −22.6° (*c* 0.22); lit.[28] m.p. 167–168.5°, $[\alpha]_D^{20}$ −24.2°.

Cholesteryl β-D-glucopyranoside tetra-acetate (**8**) (Expt. III). — On cooling, unreacted **4** and the by-product were precipitated from the reaction mixture obtained from **1**, **4**, and mercuric bromide (40 μmoles) as described in Expt. I. The mixture was filtered, the filtrate was evaporated and the residue was crystallized from methanol to yield **8** (0.31 g), m.p. 157–159°, $[\alpha]_D^{20}$ −20° (*c* 1.94); lit.[8] m.p. 157–159°, $[\alpha]_D^{20}$ −25° (chloroform). The cholesterol–by-product mixture was extracted with hot nitromethane, and the insoluble portion was crystallized from chloroform–methanol to give dicholesteryl ether (**11**, 0.08 g), m.p. 200–202°, $[\alpha]_D^{20}$ −45° (*c* 1.76); lit.[29] m.p. 201–202°, $[\alpha]_D^{20}$ −10° (light petroleum).

16-Dehydropregnenonyl β-D-glucopyranoside tetra-acetate (**9**) (Expt. IV). — Treatment of mercuric bromide, **1**, and **5** as in Expt. I, followed by evaporation of the reaction mixture and elution of the residue from alumina with the solvent sequence light petroleum→benzene→chloroform, gave **12** (0.16 g), m.p. 174–175° (from acetone), $[\alpha]_D^{20}$ −27.5° (*c* 0.98); lit.[30] m.p. 176°, $[\alpha]_D^{20}$ −33° (ethanol); and **9** (0.17 g), m.p. 230–232° (from ethanol), $[\alpha]_D^{20}$ −20.3° (*c* 0.3); lit.[31] m.p. 234–237°, $[\alpha]_D^{20}$ −24° (chloroform).

β-Sitosteryl β-maltoside hepta-acetate (**14**) (Expt. V). — A reaction mixture from **3** and **13** was treated as in Expt. II to give **10** (60 mg) and **14** (0.41 g), m.p. 172–174° (from ethanol), $[\alpha]_D^{20}$ +0.6° (*c* 0.24).

Anal. Calc. for $C_{53}H_{84}O_{18}$: C, 64.09; H, 8.19. Found: C, 63.85; H, 8.34.

Cholesteryl β-maltoside hepta-acetate (**15**) (Expt. VI). — Compounds **11**

(60 mg) and **15** (0.43 g) were obtained from **4** and **13** under conditions similar to those in Expt. I: **15** had m.p. 179–182.5° (from ethanol), $[\alpha]_D^{20}$ +36.6° (*c* 0.24).

Anal. Calc. for $C_{53}H_{80}O_{18}$: C, 63.33; H, 8.02. Found: C, 63.35; H, 8.20.

16-Dehydropregnenonyl β-maltoside hepta-acetate (**16**) (Expt. VII). — Compounds **12** (80 mg) and **16** (0.26 g) were obtained from **5** and **13** by the procedures described in Expt. I: **16** had m.p. 229.5–231° (from ethanol), $[\alpha]_D^{20}$ +8.9° (*c* 0.17).

Anal. Calc. for $C_{47}H_{65}O_{19}$: C, 60.43; H, 7.01. Found: C, 60.36; H, 7.33.

Cholesteryl β-D-glucopyranoside tetra-acetate (**8**) (Expt. VIII). — Compounds **1** and **4** were boiled in 10 ml of chlorobenzene, using the procedure described in Expt. I. After distilling off 3 ml of the solvent, the catalyst was introduced and boiling was continued for 30 min. The chlorobenzene was then evaporated, and the dry residue was extracted with hot nitromethane and crystallized from methanol to yield **18** (0.11 g), m.p. 113–114°, $[\alpha]_D^{20}$ −40.3° (*c* 0.12); lit.[32] m.p. 114.5–114.8°, $[\alpha]_D^{20}$ −47.4° (chloroform). The filtrate was evaporated and the residue was crystallised to give **8** (0.44 g), m.p. 156–157.5°.

β-Sitosteryl β-D-glucopyranoside tetra-acetate (**7**) (Expt. IX). — A reaction mixture obtained from **3** and **17**, as in Expt. VIII, was evaporated and the residue was eluted from alumina with light petroleum to give **19** (0.16 g), m.p. 123–124° (from methanol), $[\alpha]_D^{20}$ −36° (*c* 0.09); lit.[28] m.p. 130–132°, $[\alpha]_D^{20}$ −42.5°. Subsequently, **7** was eluted with chloroform to give, after crystallization, material (0.28 g) having m.p. 165–167°, $[\alpha]_D^{20}$ −17.6° (*c* 0.09).

16-Dehydropregnenonyl β-D-glucopyranoside tetra-acetate (**9**) (Expt. X). — Compounds **12** (0.12 g), m.p. 173–175°, and **9** (0.16 g), m.p. 231–233°, were obtained from **5** and **17** by following the procedure of Expt. IX.

Betulin-3-yl β-maltoside octa-acetate (**23**) (Expt. XI). — Glycosylation of **21** as in Expt. VI gave **23**, **21**, and **29** (detected by t.l.c.). The product mixture was eluted from alumina with light petroleum–benzene (1:1) to give betulin diacetate (**29**, 47 mg, 8.7%), m.p. 217–219° (from ethanol), $[\alpha]_D^{20}$ +32° (*c* 0.23); lit.[33] m.p. 217–219°, $[\alpha]_D^{20}$ +23°. The column was then eluted with chloroform to give a product which was acetylated and then chromatographed on alumina (benzene→chloroform→methanol) to give **29** (0.147 g, 27.1%) and **23** (0.67 g), m.p. 230–231.5°, $[\alpha]_D^{20}$ +62° (*c* 0.22).

Anal. Calc. for $C_{58}H_{86}O_{20}$: C, 63.14; H, 7.85. Found: C, 62.92; H, 8.11.

Betulin-28-yl β-maltoside octa-acetate (**24**) (Expt. XII). — A reaction mixture from **13** and **22**, obtained as in Expt. VI, was evaporated and the residue was acetylated. Elution of the product from alumina (benzene→chloroform→methanol) gave **29** (0.19 g, 35.3%) and **24** (0.7 g), m.p. 149–151° (from ethanol), $[\alpha]_D^{20}$ +75.8° (*c* 0.29).

Anal. Calc. for $C_{58}H_{86}O_{20}$: C, 63.14; H, 7.85. Found: C, 63.07; H, 8.17.

Betulin-3,28-diyl di(β-maltoside) tetradeca-acetate (**25**) (Expt. XIII). — The experimental conditions are given in Table III. The reaction product from **13** and **20** was acetylated and then eluted from alumina, using the solvent sequence benzene→chloroform→methanol, to give **29** (0.05 g), **24** (0.68 g), and **25** (0.5 g), m.p. 200.5–203.5° (from ethanol), $[\alpha]_D^{20}$ +66° (*c* 0.45), as well as 0.17 g of a mixture of **24** and **25**.

Anal. Calc. for $C_{82}H_{118}O_{36}$: C, 58.63; H, 7.08. Found: C, 58.64; H, 7.22.

Betulin-3-yl β-D-glucopyranoside penta-acetate (**26**) (Expt. XIV). — Under conditions given in Table III, **29** (105 mg, 19.4%) and **26** (0.37 g), m.p. 177–179°, $[\alpha]_D^{20}$ +41.4° (*c* 0.24), were obtained from **21** and **17**.

Anal. Calc. for $C_{46}H_{70}O_{12}$: C, 67.78; H, 8.67. Found: C, 68.03; H, 8.83.

Betulin-28-yl β-D-glucopyranoside penta-acetate (**27**) (Expt. XV). — A reaction mixture obtained from **22** and **17**, in accord with Table III, was acetylated, and the residue was eluted from alumina (benzene→chloroform→methanol) to give **29** (0.21 g, 39.7%) and **27** (0.48 g), m.p. 140–143° (from ethanol), $[\alpha]_D^{20}$ +12° (*c* 0.2).

Anal. Calc. for $C_{46}H_{70}O_{12}$: C, 67.78; H, 8.67. Found: C, 67.59; H, 8.83.

Betulin-3,28-diyl di(β-D-glucopyranoside) octa-acetate (**28**) (Expt. XVI). — A reaction mixture, treated as in Expt. VI, gave a product which was eluted from alumina [(light petroleum–benzene, 1:9)→benzene→chloroform] to yield **29** (0.14 g, 26.5%), **27** (0.24 g), **26** (0.07 g), a mixture (0.21 g) of **27**, **26**, and **28**, and **28** (0.29 g), m.p. 230–231° (from ethanol), $[\alpha]_D^{20}$ +6.5° (*c* 0.22).

Anal. Calc. for $C_{58}H_{86}O_{20}$: C, 63.14; H, 7.85. Found: C, 63.22; H, 8.12.

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