GLYCOSYLATION OF TRITERPENOIDS OF THE DAMMARANE SERIES.

VI. 3-MONO- AND 3,12-DI-O-β-D-GLUCOPYRANOSIDES OF PYXINOL

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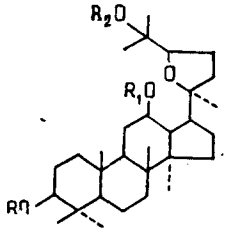
UDC 547.917+547.918+547.597

The condensation of 20(S),24(R)-epoxydammarane-3β,12β,25-triol with α-acetobromoglucose in the presence of silver oxide, silver zeolite, and silver oxide with 4 Å molecular sieves has been studied. It has been established that the reaction takes place nonregioselectively and leads to a mixture of acetylated mono-, di-, and triglucosides with a predominance of the 3-O-mono- and 3,12-di-O-glucosides. The structures of the newly obtained 3-O-mono- and 3,12-di-O-glucosides have been established on the basis of the results of IR and ^1H and ^{13}C NMR spectroscopy.

In order to study the biological activity of dammarane glycosides, we have performed the synthesis of the 3-O-mono- and 3,12-di-O-β-D-glucopyranosides from pyxinol – 20(S),24(R)-epoxydammarane-3β,12β,25-triol (1) – one of the components of extracts of the leaves of the Siberian birches Betula humilis Schrank and B. fusca [1], which was first isolated by Japanese workers [2]. The exhaustive glycosylation of (1) under the conditions of Helferich's modification and of the orthoester method led to the 3,12,25-tri-O-glucoside (2) (53.6%) [3]. The 12,25-di-O-glucoside (3) was obtained by the catalytic rearrangement of the corresponding 3,12-di-O-orthoester [4]. In addition, the optimum conditions have been found for the regio- and stereoselective preparation of the 12-O-monoglucoside (4) [5, 6]. For the synthesis of the 3-O-mono- and 3,12-di-O-glucosides of pyxinol (5 and 6, respectively) we used conditions under which 3-O-mono- and 3,12-di-O-glucosides have been obtained previously from betulafolienetriol oxide [7], which differs from (1) only by the orientation of the hydroxy group at C^3.



(1) R=R$_1$=R$_2$=H
(2) R=R$_1$=R$_2$=Glc(Ac)$_4$
(3) R=H, R$_1$=R$_2$=Glc(Ac)$_4$
(4) R=R$_2$=H, R$_1$=Glc(Ac)$_4$
(5) R$_1$=R$_2$=H, R=Glc(Ac)$_4$
(6) R=R$_1$=Glc(Ac)$_4$, R$_2$=H
(7) R=Glc, R$_1$=R$_2$=H
(8) R=R$_1$=Glc, R$_2$=H

The condensation of the triol (1) with α-acetobromoglucose was carried out in the presence of silver oxide, of silver zeolite, and of silver oxide with 4 Å molecular sieves. The results of the experiments are presented in Table 1. Under all the conditions considered, the reaction led to multicomponent mixtures of mono-, di-, and tri-O-glucosides. The absence of regioselectivity, and, as a consequence, the multicomponent nature of the reaction mixture was not an obstacle to the separation of the glucosides because of the considerable differences in their polarities.

The structures of the 3-O-mono- and 3,12-di-O-glucosides (5) and (6) were established on the basis of the results of IR and of ^1H and ^{13}C spectroscopy and elementary analysis, and those of the known glucosides (2), (3), and (4) by comparison with authentic samples. The doublet signal of the anomeric proton of glucose at C^3 in the ^1H spectra of the monoglucoside (5) and the diglucoside (6) appeared at 4.53-4.56 ppm ($J_{1',2'}$ = 8.0 Hz), and of that at C^{12} of the diglucoside (6) at 4.60 ppm ($J_{1',2'}$ = 8.0 Hz). The chemical shifts and spin–spin coupling constants of the anomeric protons of the glucose residues showed the trans

Pacific Ocean Institute of Bioorganic Chemistry, Far Eastern Scientific Center, Academy of Sciences of the USSR, Vladivostok. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 451-455, July-August, 1986. Original article submitted January 28, 1986; revision submitted April 23, 1986.

0009-3130/86/2204-0421$12.50

TABLE 1. Conditions* and Results of Glycosylation of the Triol (1) with α-Acetobromoglucose (ABG) in the Presence of Certain Silver Compounds

Expt. No.	Initial substances			Solvent, ml	Reaction products, %†					Recovery† of the initial substance, %
	alcohol, mmole	α-ABG, mmole × n (times)	HBr acceptor. g × n (times)		monoglucosides		diglucosides		triglucosides	
					3-O-(5)	12-O-(4)	3,12-(6)	12,25-(3)		
1	(1),1	1×4	Ag_2O, 0,234×4	CH_2Cl_2, 10	44 0	15,9	30,8	2,2	2,9	—
2			Ag_2O, 0,234×4	CH_2Cl_2—CH_3NO_2 10 (1:1)	66.1	13,0	6,3	2.5	1,5	6,3
3			Ag zeolite 1,5×4	CH_2Cl_2, 10	52,2	18,7	13,1	1,7	1,5	8,2
4			Ag zeolite 1 5×4	CH_2Cl_2—CH_3NO_2 10 (1:1)	46,6	10 5	32,7	3,2	4,5	—
5			Ag_2O, 0,234×4 4 Å mol. sieves 2×4	CH_2Cl_2, 10	14,6	16,4	44,3	6,7	12,9	—
6			Ag_2O, 0 234×4 4 Å mol. sieves 2×4	CH_2Cl_2—CH_3NO_2 10 (1:1)	29,5	10,3	36,1	3,2	7,9	6,9

*The reaction time for all the experiments was 4 h.
†The yields are given on the chromatographically homogeneous substances.

TABLE 2. ^{13}C Chemical Shifts of Triol (1) and its Glucosides (5) and (6) (δ, ppm relative to TMS)

C atom	Compound			C atom	Compound		
	(1)	(5)	(6)		(1)	(5)	(6)
1	39,1	39,0	39,0	16	28,6	28,5	26,9
2	27,6	25,9	25,9	17	49,4	49,3	50,1
3	78,5	90,4	90,0	18	16,3	16,2	16,2
4	38,9	39,0	39,0	19	15,4	15,4	15,6
5	56,1	56,3	56,3	20	86,4	86,4	86,5
6	18,3	18,2	18,2	21	26,1	26,1	22,0
7	34,9	34,9	34,7	22	32,6	32,6	39,0
8	39,8	39,8	39,8	23	25,0	24,9	26,2
9	50,6	50,6	50,1	24	85,4	85,3	83,5
10	37,2	36,9	37,0	25	70,1	70,0	71,3
11	31,2	31,1	27,6	26	27,8	27,9	27,7
12	71,0	70,9	77,5	27	27,5	27,6	24,2
13	48,0	48,0	48,0	28	28,1	27,6	27,7
14	52,0	51,9	52,1	29	15,4	16,0	16,2
15	31,4	31,4	31,7	30	18,1	18,0	17,8

TABLE 3. ^{13}C Chemical Shifts of the Sugar Components of Glucosides (5) and (6) (δ, ppm relative to TMS)*

C atom	Compound					
	1′	2′	3′	4′	5′	6′
(5)	102,7	71,5	72,9	68,4	71,7	62,3
(6)	102,8	71,6	73,0	68,8	71,8	62,0
	97,1	71,6	72,9	68,8	71,6	62,0

*Signals of nuclear ^{13}C acetate groups of the sugar components of glucosides (5) and (6) are found in the 170.0-170.6 and 20.8-21.6 ppm regions.

configuration of the glycosidic bonds both in the monoglucoside (5) and in the diglucoside (6). The positions of attachment of the glucose residues were established by comparing the ^{13}C spectra of the initial alcohol (1) and of the newly obtained glucosides (5) and (6) (Tables 2 and 3).

The use of silver oxide (Table 1, experiments 1 and 2) in the glycosylation of (1) led to the production of a complex mixture of glucosides with a predominance of the 3-O-monoglucoside (5). The use of silver zeolite (Table 1, experiments 3 and 4), and also the addition of 4 Å molecular sieves to silver oxide (Table 1, experiments 5 and 6) directed the reaction towards the formation of diglucoside. Furthermore, the use of nitromethane in admixture with methylene chloride changes the ratio of monoglucosides in the direction of the formation of the 3-O-monoglucoside (5) and that of the diglucosides towards the 3,12-di-O-glucoside (6) (Table 1, experiments 2, 4, and 6). The results obtained show that the ratio of the glucosides depends directly on the conditions of performing the experiment, while the total yield, the number of glucosides, and their structures scarcely change.

EXPERIMENTAL

IR spectra were recorded on a Specord 75 IR spectrophotometer in chloroform solution, and ^{1}H and ^{13}C NMR spectra were measured on a Bruker WM-250 spectrometer with a working frequency of 250 MHz for ^{1}H and 62.9 MHz for ^{13}C at 30°C in deuterochloroform with tetramethylsilane as internal standard. Optical rotations were determined on a Perkin-Elmer 141 polarimeter in a cell 10 cm long at 20°C, and the melting points of the substances on a Boëtius stage. Column chromatography was performed on KSK silica gel (120-150 mesh) in the hexane–acetone (30:1) → (4:1) system. The individuality of the substances was checked with the aid of TLC in a fixed layer of silica gel in the hexane–acetone (2:1) and (3:2) and benzene–chloroform–methanol (6:4:1) and (3:2:1) systems. The spots were revealed with 10% H_2SO_4 in ethanol with heating at 100-200°C. The elementary analyses of the newly obtained glucosides agreed with the calculated figures.

The deacetylation of compounds (5) and (6) with a 0.1 N solution of sodium methanolate in methanol led to the formation of the corresponding free glucosides (7) and (8) with yields of 95-97%. Pyxinol (1) was obtained as described in [3].

General Procedure for Performing Condensation in the Presence of Silver Compounds. A mixture of 1 mmole of the triol (1), 1 mmole of α-acetobromoglucose, a hydrogen bromide acceptor, and an appropriate solvent (Table 1) was stirred at room temperature for 1 h. Then 1 mmole each of α-acetobromoglucose and the corresponding amount of hydrogen bromide acceptor was added in three portions at one-hour intervals. After 4 h, the reaction mixture was eluted with methylene chloride and filtered from the insoluble silver compounds. The filtrate was evaporated and the residue was dried. The dry residue was chromatographed on a column of silica gel.

3β-(2',3',4',6'-Tetra-O-acetyl-β-D-glucopyranosyloxy)-20(S),24(R)-epoxydammarane-12β,25-diol (5). mp 126-136°C (hexane); $[\alpha]_D^{20}$ −12.2° (c 1.0; chloroform). IR spectrum (ν, cm^{-1}): 1750, 3398. ^1H spectrum (δ, ppm): 0.73 (s, 3H), 0.84 (s, 3H), 0.89 (s, 6H), 0.97 (s, 3H), 1.09 (s, 3H), 1.27 (s, 3H), 1.28 (s, 3H), 2.00 (s, 3H, OAc), 2.03 (s, 6H, 2 × OAc), 2.07 (s, 3H, OAc), 3.08 (d-d, 1H, J = 4.9 and 10.8 Hz, H_a^3); 3.49 (t-d, 1H, $J_{a,a} = J_{a,a} = 10.0$ and $J_{a,e} = 5.0$ Hz, H_a^{12}), 3.65 (m, 1H $H^{5'}$), 3.85(t, 1H, J = 6.8 Hz, H^{24}), 4.12 (d-d, 1H, J = 2.6 Hz, J = −12.0 Hz, $H^{6'}$), 4.22 (d-d, 1H, J = 4.7 Hz, J = −120.0 Hz, $H^{6'}$), 4.53 (d, 1H, J = 8.0 Hz, $H^{1'}$), 5.00 (d-d, 1H, J = 7.5 Hz, J = 9.0 Hz, $H^{2'}$), 5.08 (t, 1H, J = 9.5 Hz, $H^{4'}$), 5.23 (t, 1H, J = 9.5 Hz, J = 9.5 Hz, $H^{3'}$).

3β,12β-Di(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyloxy-20(S),24(R)-epoxydammaran-25-ol (6). mp 208-210°C (ethanol), $[\alpha]_D^{20}$ −3.8° (c 1.0; chloroform). IR spectrum (ν, cm^{-1}): 1750, 3543. ^1H spectrum (δ, ppm): 0.74 (s, 3H), 0.85 (s, 3H), 0.86 (s, 3H), 0.91 (s, 3H), 0.94 (s, 3H), 1.07 (s, 3H), 1.09 (s, 3H), 1.19 (s, 3H), 2.00 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.03 (s, 12H, 4 × OAc), 2.07 (s, 3H, OAc), 2.11 (s, 3H, OAc), 3.08 (d-d, 1H, J = 4.9 Hz, J = 10.8 Hz, H_a^3), 3.49 (t-d, 1H, J = 10.0 Hz, J = 10.0 Hz, J = 5.0 Hz, H_a^{12}), 3.70 (m, 3H, H^{24}, 2 × $H^{5'}$), 4.12-4.22 (m, 4H, 2 × $H^{6'}$), 4.56 (d, 1H, J = 8.0 Hz, $H^{1'}$ at C^3), 4.60 (d, 1H, J = 8.0 Hz, $H^{1'}$ at C^{12}), 4.90-5.22 (m, 2 × $H^{2'}$, 2 × $H^{3'}$, 2 × $H^{4'}$).

SUMMARY

1. The condensation of 20(S),24(R)-epoxydammarane-3β,12β,25-triol with α-acetobromoglucose in the presence of insoluble silver compounds has been studied.

2. The 3-mono- and 3,12-di-O-β-D-glucopyranosides of 20(S),24(R)-epoxydammarane-3β,12β,25-triol have been obtained for the first time.

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