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Note

2-Bromoethyl glycosides: synthesis and characterisation

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We recently reported[1] the preparation and use of 2-bromoethyl glycosides in the synthesis of spacer-arm glycosides for coupling to proteins, neoglycolipids, and bidentate glycosides for use as agglutination inhibitors. 2-Bromoethyl glycosides are compatible with most of the standard reactions (including debenzylation) that are used in synthetic carbohydrate chemistry. We now report details of the synthesis and characterisation of 2-bromoethyl glycosides.

The methods normally used for glycoside synthesis can be adopted also for the preparation of 2-bromoethyl glycosides by using 2-bromoethanol. Acetylated sugars were readily converted into the corresponding 1,2-*trans* glycosides (**1–8***; Table I) by the boron trifluoride etherate method[2]. Most of the products were isolated by crystallisation from the crude reaction mixtures, and chromatography of the mother liquors raised the yields substantially. Application of the BF_3-etherate glycosidation method to acetylated 2-deoxy-2-phthalimido sugars[3] gave the corresponding 2-bromoethyl glycosides (**9–11***) in good yields, thus avoiding the sensitive glycosyl halides. In the BF_3-etherate reactions, the starting material and the product often showed similar R_F values in t.l.c. and it was advantageous to use selective detection techniques[2].

Other glycosidation methods (silver triflate, quaternary ammonium halide, oxazoline) were used for the preparation of **12–14***. These methods often show a higher degree of stereoselectivity, and should be used for the preparation of glycosides of higher oligosaccharides because the separation of anomers can be difficult.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. N.m.r. spectra were recorded with a Varian XL-200 spectrometer. Solvents were removed first with a rotary evaporator and then at

*For the names of these compounds, see Experimental.

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TABLE I

DATA FOR ACETYLATED 2-BROMOETHYL GLYCOSIDES **1–12** AND **14**

Compound	*Method*	*Yield (%)*	*M.p. (degrees)*	$[\alpha]_D^{23}$ *(degrees)*	*Molecular formula*	*Analysis (%)*			
						Calc.		*Found*	
						C	*H*	*C*	*H*
1	a	46	114–116	−5 (*c* 1.4, $CDCl_3$)	$C_{16}H_{23}BrO_{10}$	42.21	5.09	42.25	5.09
2	a	42	119–120	−11 (*c* 1.2, $CDCl_3$)	$C_{16}H_{23}BrO_{10}$	42.21	5.09	42.45	5.08
3	a	58	118–119	+45 (*c* 0.6, $CDCl_3$)	$C_{16}H_{23}BrO_{10}$	42.21	5.09	42.12	5.03
4	a	36	142–143	−21 (*c* 0.8, $CDCl_3$)	$C_{15}H_{21}BrO_{10}$	40.83	4.80	41.03	4.82
5	a	53 (**5β**)	syrup	25 (*c* 2.2, $CDCl_3$)					
		16 (**5α**)	syrup	−22 (*c* 0.8, $CDCl_3$)					
6	a	85	144–145	−48 (*c* 1.7, $CDCl_3$)	$C_{13}H_{19}BrO_8$	40.75	5.00	40.76	5.06
7	a	55	amorphous	11 (*c* 1.3, $CHCl_3$)					
8	a	67	amorphous	+6 (*c* 2.4, $CDCl_3$)					
9	b	50	111–114	+21 (*c* 1, $CHCl_3$)	$C_{22}H_{24}BrNO_{10}$	48.72	4.46	48.98	4.49
10	b	80	syrup	−11 (*c* 0.7, $CHCl_3$)					
11	b	55	224–225	+9 (*c* 1, $CHCl_3$)	$C_{34}H_{40}BrNO_{18}$	49.17	4.85	49.65	4.91
12	c	77	174–177	+75 (*c* 2, $CHCl_3$)	$C_{28}H_{39}BrO_{18}$	45.23	5.29	45.13	5.36
14	c	39	174–175	−7 (*c* 1.1, $CDCl_3$)	$C_{16}H_{23}BrNO_9$	42.39	5.11	42.65	5.33

<0.1 Torr. Reactions were monitored by t.l.c., using the technique for selective detection[2] of acetylated sugars and glycosides. Yields, melting points, and optical rotations for the 2-bromoethyl glycosides **1–14** are shown in Table I, and n.m.r. data in Table II. Procedures for the preparations of the starting materials for **8–12** are given variously in refs. 5–8. Compound **1** was recrystallised from ether–light petroleum; **2, 3, 6, 9,** and **14** from ethyl acetate–iso-octane; **4** from ethanol; **11** from ethyl acetate–ether–light petroleum; and **12** from ethyl acetate.

TABLE II

^{1}H-N.M.R. DATA FOR COMPOUNDS **1–12** AND **14**

Compound	*H-1, δ ($J_{1,2}$ in Hz)*	*Compound*	*H-1, δ ($J_{1,2}$ in Hz)*
1	4.55 (7.8)	**7**	4.54 (8.0)
2	4.58 (7.8)	**8**	4.49 (7.8)
3	4.88 (1.5)	**9**	5.43 (8.4)
4	4.63 (7.6)	**10**	5.37 (8.5)
5α	5.14 (0)	**11**	5.42 (8.5)
5β	4.49 (7.9)	**12**	4.54 (8.0)
6	4.56 (6.7)	**14**	4.77 (8.0)

Synthesis of 2-bromoethyl glycosides. — (*a*) (*Cf.* ref. 2). To a cooled solution of acetylated sugar (5 mmol; α,β-mixture) and 2-bromoethanol (6 mmol) in dry dichloromethane (10 mL) was added, dropwise (~15 min), boron trifluoride etherate (25 mmol). The ice-bath was removed after 1 h and the reaction was continued at room temperature until the starting material had been consumed (t.l.c.; 2–20 h).

The 1,2-*trans* glycosides were formed first. At the end of the reaction period, a small proportion of the 1,2-*cis* glycoside could usually be detected. Prolonged reaction time usually gave small proportions of deacetylated compounds.

Each reaction mixture was poured into ice–water (10 mL), the aqueous phase was extracted with dichloromethane (5 mL), and the combined dichloromethane solutions were washed (water, aqueous sodium hydrogencarbonate, water), dried (Na_2SO_4), filtered, and concentrated. The resulting syrup was crystallised from ether (or ethyl acetate) and light petroleum, or isolated by silica gel chromatography (ethyl acetate–iso-octane). Chromatography of the mother liquors raised the yields considerably.

The following compounds were synthesised by this method: 2-bromoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**1**), 2-bromoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[4] (**2**), 2-bromoethyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**3**), methyl (2-bromoethyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (**4**), 2-bromoethyl 2,3,4-tri-*O*-acetyl-L-fucopyranoside (**5**), 2-bromoethyl 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside (**6**), 2-bromoethyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**7**), and 2-bromoethyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (**8**). See Tables I and II.

(*b*) (*Cf.* ref. 3). To a cooled solution of acetylated 2-deoxy-2-phthalimido sugar (5 mmol; α,β-mixture) and 2-bromoethanol (6 mmol) in dry dichloromethane (10 mL) was added, dropwise (~15 min), boron trifluoride etherate (25 mmol). The ice-bath was removed after ~1 h and the reaction was continued at room temperature until the starting material had been consumed (t.l.c.; 16–24 h). 1,2-*cis* Glycosides were not detected as products. Work-up as in (*a*) gave the pure product.

The following compounds were synthesised by this method: 2-bromoethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**9**), 2-bromoethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranoside (**10**), and 2-bromoethyl 3,6-di-*O*-acetyl-2-deoxy-2-phthalimido-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**11**). See Tables I and II.

(*c*) A solution of hydrogen bromide in acetic acid (45%, 30 mL) was added dropwise (~25 min) to a solution of 1,2,3,6-tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-α-D-galactopyranose[8] (20.0 g, 29.5 mmol) in acetic acid–acetic anhydride (2:1, 20 mL) at 0°. The reaction mixture was kept at 0° for 4 h and then at room temperature for 1.5 h, diluted with dichloromethane (400 mL), and poured into ice-cold, saturated, aqueous sodium hydrogencarbonate (400 mL). The aqueous phase was extracted with dichloromethane (150 mL), and the combined organic solutions were washed with aqueous sodium hydrogencarbonate (300 mL), dried (Na_2SO_4), filtered, and concentrated to give 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-α-D-galactopyranosyl bromide (20.8 g; pure by t.l.c.). Recrystallisation from ethyl acetate–ether gave material having m.p. 97–99°, $[\alpha]_D^{23}$ +219° (*c* 0.8, chloroform). ^{1}H-N.m.r. data ($CDCl_3$, Me_4Si): δ 6.73 (d, 1 H, $J_{1,2}$ 4 Hz, H-1).

Anal. Calc. for $C_{26}H_{35}BrO_{16}$: C, 45.69; H, 5.16; Br, 11.69. Found: C, 45.51, H, 5.10; Br, 11.21.

A solution of the crude acetobromo sugar (20.5 g, 29.3 mmol) in dry dichloromethane (100 mL) was added dropwise (~20 min) to a cold (−78°) solution of silver trifluoromethanesulfonate (commercial material; 10.3 g, 40 mmol), 2,4,6-trimethylpyridine (3.6 g, 30 mmol), and 2-bromoethanol (17.5 g, 140 mmol) in dichloromethane (250 mL) under nitrogen. The mixture was stirred in the dark for 23 h, during which time it had reached room temperature. The yellowish-white precipitate was removed, and the colorless filtrate was washed consecutively with M hydrochloric acid, water, saturated aqueous sodium hydrogencarbonate, and water, dried (Na_2SO_4), filtered, and concentrated. Recrystallisation of the residue from ethyl acetate, followed by evaporation of the mother liquor and recrystallisation of the residue from methanol, gave 2-bromoethyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-β-D-galactopyranoside (**12**; 16.6 g, 77%). See Tables I and II.

(*d*) Bromotrimethylsilane (7.96 g, 6.78 mL, 52 mmol) was added with a syringe to a mixture of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (28 g, 52 mmol), 2-bromoethanol (4.46 mL, 40.0 mmol), dry cobalt(II) bromide (11.4 g, 52.0

mmol), tetraethylammonium bromide (10.9 g, 52.0 mmol), and molecular sieves (4Å, 41 g) in dichloromethane (138 mL) under nitrogen with protection from light. The mixture was stirred at room temperature overnight and then filtered, and insoluble material was washed with dichloromethane (100 mL). The combined filtrate and washings were concentrated under reduced pressure, and the product (25.8 g) was subjected to chromatography (SiO_2; iso-octane–ethyl acetate, 3:2) to give, first, 2-bromoethyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside (**13**) as a syrup (6.0 g), $[\alpha]_D^{23}$ +30.5° (*c* 1.4, chloroform), and then an α,β-mixture (10.0 g). Total yield of glycosides, 16 g (48%). This procedure is a slight modification of that of Koto *et al.*[9]. N.m.r. data for **13** ($CDCl_3$, Me_4Si): ^1H, δ 7.30 (m, 20 H, 4 Ph), 4.97–4.42 (m, 9 H), 4.0–3.8 (m, 6 H), and 3.52 (t, 4 H, *inter alia* CH_2Br); ^{13}C, δ 103.3 (d, C-1, $J_{C,H}$ 168 Hz), 84.2, 81.6, 80.2, 75.0 (C-2,3,4,5), 80.0, 78.7, 78.6, 78.5, 74.2, 73.5 (C-6, benzylic CH_2, and aglycon O-CH_2), and 35.5 (CH_2Br).

(*e*) A solution of acetylated D-glucose oxazoline[10] (4.62 g, 14.0 mmol), 2-bromoethanol (8.49 g, 67.9 mmol), and toluene-*p*-sulfonic acid (81 mg) in toluene and nitromethane (1:1; 80 mL) was left at 110° for ~10 min and then cooled. T.l.c. (SiO_2; toluene–ether–methanol, 7:7:1) showed that all of the oxazoline had reacted. Pyridine (0.2 mL) was added and the mixture was concentrated to dryness. Preparative chromatography of the residue gave 2-bromoethyl-2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (**14**). See Tables I and II.

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