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Note

Synthesis of 1,2,3,4-tetra-*O*-acetyl-6-*O*-bromoacetyl-β-D-galactopyranose

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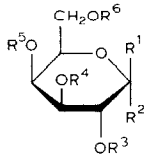
Hydroxyl groups in a sugar molecule blocked by haloacetyl groups[1,2] can be selectively regenerated in the presence of other acyl (*e.g.*, acetyl or benzoyl) substituents. This procedure has been successfully applied in oligosaccharide syntheses[3–8]. *O*-Dehaloacetylation can be effected with thiourea[1,6,7] or hydrazine dithiocarbonate[2]. The advantage of the bromoacetyl over the chloroacetyl group is due to the milder conditions used for the eventual removal of the former[2].

This laboratory has developed a synthesis of (1→6)-β-D-galactooligosaccharides based on the use of 2,3,4-tri-*O*-acetyl-6-*O*-chloroacetyl-α-D-galactopyranosyl bromide[6,8] (**1**). We have now prepared crystalline 1,2,3,4-tetra-*O*-acetyl-6-*O*-bromoacetyl-β-D-galactopyranose (**2**), and describe herein its conversion into a glycosylating reagent (**3**).

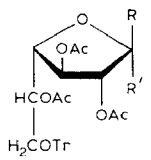
The *O*-chloroacetyl derivative **4** used in previous syntheses of (1→6)-D-galactooligosaccharides was prepared[6] from 6-*O*-trityl-D-galactose (**5**) by sequential acetylation, detritylation, and chloroacetylation of the resulting 1,2,3,4-tetra-*O*-acetyl-D-galactose. The low overall yield[6] in the conversion of **5** into **4** (~35%) can be explained by the acetylation of **5** which yields four isomeric trityl-D-galactose tetraacetates (**6, 7, 12,** and **13**) of which only one, **7**, is the desired intermediate, and by losses in the formation of the next intermediate **8** on account of extensive acyl migration during classical detritylation. During this process, the proportion of **8** may have been further decreased by partial acetylation[9,10] of OH-6 to give **9**.

To minimize these side reactions, the conversion of **5** into **8** was modified as follows. As shown by ^{13}C-n.m.r. spectroscopy, **5** contains a larger proportion of the furanose forms in pyridine than in chloroform. Thus, acetylation[6] of **5** with acetic anhydride in pyridine gave **6, 7, 12,** and **13** (t.l.c.), and the pure α-pyranose **6** and β-furanose **13** were isolated by preparative chromatography. The major zone was a ~10:1 mixture of β-pyranose **7** and α-furanose **12**. Consequently, to avoid extensive formation of furanose forms, and favor the formation of the β-acetate, **5** was acetylated[11] by its addition to a mixture of acetic anhydride and fused sodium acetate (room temperature) and warming to 100°.

To minimize side reactions during detritylation, we used iodotrimethylsilane[12]. This proved to be unquestionably superior to other detritylation



	R^1	R^2	R^3	R^4	R^5	R^6
1	H	Br	Ac	Ac	Ac	$COCH_2Cl$
2	OAc	H	Ac	Ac	Ac	$COCH_2Br$
3	H	Br	Ac	Ac	Ac	$COCH_2Br$
4	OAc	H	Ac	Ac	Ac	$COCH_2Cl$
5	H,OH		H	H	H	Tr
6	H	OAc	Ac	Ac	Ac	Tr
7	OAc	H	Ac	Ac	Ac	Tr
8	OAc	H	Ac	Ac	Ac	H
9	OAc	H	Ac	Ac	Ac	Ac
10	OAc	H	Ac	Ac	H	Ac
11	OAc	H	Ac	H	Ac	Ac



12 R = H,R′ = OAc
13 R = OAc,R′ = H

methods[13–15], and losses due to the acetylation of the primary position were eliminated. Acyl migration became unimportant when detritylation was carried out at 0°. The amorphous product of detritylation (**8**) was not fully characterized, as it contained traces of the product of acetyl migration (t.l.c.). Lee *et al.*[16] claimed to have obtained crystalline 1,2,3,4-tetra-*O*-acetyl-β-D-galactopyranose, m.p. 142–143°. Their m.p. and ^{1}H-n.m.r. data agree with those found by us for the tetra-*O*-acetyl-β-D-galactopyranose, here unambiguously shown to be the 1,2,3,6-tetra-acetate **10**. The incorrect assignment of structure by Lee *et al.*[16] was suggested to us by the n.m.r. data reported by Libert *et al.*[17]. Our proof of the position of the acetyl groups in **8, 10,** and **11** is based on the comparison of ^{1}H- and ^{13}C-n.m.r. data (Tables I and II). Consistent with the downfield shift of a signal of a proton that is part of a HCOCOR group, the H-4 signal in the spectrum of **8** appeared at δ 5.42. Conversely, the position of the signal at δ 4.13 in the spectrum of **10** was indicative of that proton (H-4) not being a part of an HCOCOR group. Also, the chemical shift of the signal at δ 4.30 indicated that H-6 and -6′ are proximal to an electron withdrawing group, whereas H-6 and -6′ in **8**, appearing in the ^{1}H-n.m.r. spectrum as a multiplet at δ 3.81–3.45, are not. Therefore, the compound to which Lee *et al.*[16] assigned structure **8** is in fact the 1,2,3,6-tetraacetate **10** resulting (as in the present case) from acetyl group migration. In a similar manner, **11** was readily recognized as a 1,2,4,6-tetraacetate, since, among the signals of ring protons in its ^{1}H-n.m.r. spectrum, the one that appeared furthermost upfield was that of H-3. The same conclusion could be derived from the ^{13}C-chemical shifts observed in the spectra of **8, 10,** and **11**. Except for the differences that can be due to different conditions of measurement, the ^{13}C-n.m.r. chemical shifts reported herein for **10** agree with those reported recently by Lee *et al.*[18] for 1,2,3,6-tetra-*O*-acetyl-β-D-

TABLE I

^{1}H-N.M R. DATA FOR COMPOUNDS **2–4, 8, 10,** AND **11**

Data	*Compound*					
	2	**3**	**4**	**8**	**10**	**11**
Chemical shifts (δ)						
H-1	5.70d	6.69d	5.70d	5.70d	5.71d	5.68d
H-2	5.33dd	5.05dd	5.33dd	5.34dd	5.45dd	5.16dd
H-3	5.09dd	5.38dd	5.09dd	5.10dd	5.00dd	3.94dd
H-4	5.43dd	5.54dd	5.43dd	5.42dd	4.13dd	5.38dd
H-5	4.10m	4.54m	4.10m	3.90m	3.94m	from 4.35m
H-6,6′	4.24d	4.22m	4.26d	3.63m	4.35m	to 4.00m
CH_2X[a]	3.82s	3.84s	4.06s			
OAc	2.00, 2.04, 2.11, 2.18	2.02, 2.12, 2.17	2.00, 2.04, 2.13, 2.18	2.00, 2.04, 2.11, 2.13	2.04, 2.09, 2.11[b]	2.06,2.13, 2.20, 2.25
Coupling constants (Hz)						
$J_{1,2}$	8.0	3.7	8.0	8.0	8.0	8.0
$J_{2,3}$	10.0	10.5	10.0	10.0	10.0	10.0
$J_{3,4}$	3.5	3.4	3.5	3.5	3.5	3.5
$J_{4,5}$	1.0	1.0	1.0	1.0	1.0	1.0
$J_{5,6}$	7.5	6.5	7.0	7.0	6.0	[c]

[a]Methylene protons of the haloacetyl groups. [b]Six-proton singlet. [c]Not determined.

TABLE II

^{13}C-N.M R. CHEMICAL SHIFTS (δ) FOR COMPOUNDS **2–4, 8, 10,** AND **11**

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-X*[a]
2	92.1	67.7	71.4	66.8	70.7	62.7	25.2
3	87.8	67.6	67.9	66.9	71.4	62.4	25.1
4	92.2	67.7	71.4	66.8	70.7	62.6	40.5
8	92.4	67.6	71.0	68.2	74.5	60.4	
10	92.2	68.2	73.3	66.8	73.3	62.6	
11[b]	92.0	71.3	71.1	69.5	72.0	61.7	

[a]The methylene carbon atom of the haloacetyl group is denoted C-X. [b]Assignment confirmed by 2D, heteronuclear proton–carbon correlation spectroscopy recorded with a Nicolet 270 spectrometer.

galactopyranose. Thus, compound **8** has yet to be obtained in crystalline form.

During bromoacetylation of **8** with bromoacetyl chloride, halogen exchange took place leading to the formation of both **2** and **4** (^{13}C- and ^{1}H-n.m.r.). That **4** was indeed present was proved unambiguously by treatment of the mixture with thiourea under conditions previously shown to completely regenerate the primary hydroxyl group in **2**. The material that remained unchanged under these conditions was isolated in crystalline form and found to be identical (m.p., n.m.r.) with an authentic[6] sample of **4**. To avoid such difficulties bromoacetyl bromide was used as the reagent.

Without isolation of the intermediates, **2** was obtained from **5** in an overall yield of ~50%. Compound **2** could be readily converted into the α-glycosyl halide **3**, which was isolated as an oil. Its use as a glycosyl donor in oligosaccharide syntheses is demonstrated in the next publication[19].

EXPERIMENTAL

General methods. — See ref. 8 with the following changes. T.l.c. was performed with (*A*) 10:1 carbon tetrachloride–acetone, (*B*) 5:2 carbon tetrachloride–acetone, and (C) 10:1 toluene–acetone. ^{1}H-N.m.r. spectra for solution in $CDCl_3$ (internal standard Me_4Si) were recorded at 220 MHz with a Varian HR-220 spectrometer. Solutions in organic solvents were dried (Na_2SO_4) and evaporated at 40° and 2 kPa.

*1,2,3,4-Tetra-O-acetyl-6-O-bromoacetyl- (**2**) and -6-O-chloroacetyl-β-D-galactopyranose* (**4**). — (*a*) Crystalline 6-*O*-trityl-D-galactose[6] (**5**; 5 g, 11.8 mmol) was added at 20° to a suspension of acetic anhydride (25 mL, 240 mmol) and fused sodium acetate (5 g), and the mixture was stirred while the temperature was raised within 1 h to 100°. After an additional 2 h at ~100°, t.l.c. (*A*) showed the reaction to be complete. The mixture was processed conventionally and the crude product was obtained as a colorless foam; t.l.c. showed one major (R_F 0.7) and two minor (R_F 0.75 and 0.65) spots. Chlorotrimethylsilane (4.5 mL) was added under anhydrous conditions and at 0° to a solution of this product and NaI (5.3 g) in dry acetonitrile (12 mL); I_2 evolved immediately, as indicated by strong discoloration, and after 2 min ice–water (30–50 mL) was added. After 15 min at 0°, the mixture was filtered onto solid NaS_2O_4 (~3 g), the precipitate was washed with water, and the filtrate, combined with the washings, was thoroughly extracted with dichloromethane; t.l.c. (*B*) of the solution and precipitate showed that the reaction was complete and that the solution contained mainly **8** (R_F 0.35, *B*). After concentration to ~30 mL, the solution was cooled to −40°, and 2,6-dimethylpyridine (2.47 mL, 21.2 mmol) added to the stirred solution, followed by bromoacetyl chloride (1.46 mL, 17.7 mmol). The coolant was removed and, after 15 min while the solution was still very cold, t.l.c. (*C*) showed that the reaction was complete, indicating one major (R_F 0.6) and two minor components (R_F 0.65 and 0.55). After the usual processing, crystallization from ethanol gave a chromatographically homogeneous, crystalline, crude product (2.27 g, ~41%), m.p. 117–119°; ^{13}C-n.m.r.: ring-carbon region identical with that of **2** or **4** (no noticeable line-broadening), δ 25.3 (CH_2Br) and 40.5 (CH_2Cl) in ratio of ~3:1; ^{1}H-n.m.r.: very similar to that of pure **2** with an additional singlet at δ 4.06 (~0.5 H) indicating CH_2Cl (~25% of **4** in the mixture). Several recrystallizations gave the pure bromoacetate **2**, m.p. 114–115°, $[\alpha]_D^{25}$ +18.7° (*c* 1.9, chloroform).

Anal. Calc. for $C_{16}H_{21}BrO_{11}$: C, 40.95; H, 4.51; Br, 17.02. Found: C, 40.98; H, 4.46; Br, 17.19.

A solution of the material having m.p. 117–119° (1 g) in dichloromethane (20

mL) was treated with a solution of thiourea (0.46 g) and 2,6-dimethylpyridine (0.22 mL) in methanol (20 mL) for 20 min. The mixture was poured into a saturated NaCl solution and extracted several times with dichloromethane, and the dried solution was concentrated. The residue was chromatographed to give **4**, m.p. 132–133° (lit.[6] m.p. 129–131°); ^{13}C- and ^{1}H-n.m.r.: identical with those of authentic[6] **4**. Subsequently **8** was eluted together with traces of **10**, detectable by t.l.c. but not by n.m.r. spectroscopy, which could not be removed.

(*b*) 6-*O*-Trityl-D-galactose (**5**; 5 g) was treated as just described, but with bromoacetyl bromide, for the conversion of **8** into **2**. Chromatography and crystallization gave **2** (2.75 g, 49.4%), m.p. 114–115°.

1,2,3,6-Tetra-O-*acetyl-* (**10**) *and 1,2,4,6-tetra-O*-acetyl-*β*-D-*galactopyranose* (**11**). — 6-*O*-Trityl-D-galactose (**5**; 5 g) was acetylated as just described and detritylated at 20–25°. After being processed, the crude product showed (t.l.c.) two components (R_F 0.4 and 0.35, *B*) in the ratio of ~1:4. Chromatography first gave pure **10** (430 mg, 10.4%), m.p. 142–143° (dichloromethane–ether), $[\alpha]_D^{25}$ +38.5° (*c* 0.9, chloroform); lit.[20] 139–140°, $[\alpha]_D$ +38.1°; Lee *et al.*[16] reported m.p. 142–143° and $[\alpha]_D$ +33° for a compound described as the isomeric 1,2,3,4-tetraacetate **8**; the present ^{1}H-n.m.r. data (Table I) agreed with those reported by Libert *et al.*[17] for **10** and by Lee *et al.*[16] for the compound described as **8**. The ^{13}C-n.m.r. data (Table II) agree with those subsequently reported by Lee *et al.*[18] for **10**.

Anal. Calc. for $C_{14}H_{20}O_{10}$: C, 48.27; H, 5.78. Found: C, 48.33; H, 5.80.

Subsequently, a mixture of **8** and **10** with **8** largely preponderating was eluted. T.l.c. revealed the presence of a third component in the last fractions. This compound crystallized from chloroform–isopropyl ether (210 mg, 5%), m.p. 146–147°, $[\alpha]_D^{25}$ +24° (*c* 0.8, chloroform), and was shown by n.m.r. (Tables I and II) to be **11**.

Anal. Calc. for $C_{14}H_{20}O_{10}$: C, 48.27; H, 5.78. Found: C, 47.97; H, 6.01.

2,3,4-Tri-O-*acetyl-6*-O-*bromoacetyl-α*-D-*galactoprepanosyl bromide* (**3**). — A solution of **2** (1.5 g) in dry dichloromethane (5 mL) was treated with hydrogen bromide in acetic acid (33%, 5 mL). After 1 h at room temperature, t.l.c. (*C*) showed that all starting material (R_F 0.6) had been converted into a single, faster-moving product. The solution was concentrated and the residual solvent coevaporated with toluene to remove acetic acid. Passage through a short silica gel column gave, after concentration, amorphous **3**. The chromatographically homogeneous oil tenaciously trapped solvents, but produced n.m.r. spectral data (Tables I and II) confirming its purity and expected structure.

O-*Debromoacetylation*. — A solution of 2,6-dimethylpyridine (11 μL, 50 μmol) and thiourea (23 mg, 0.3 mmol) in methanol (2 mL), was added dropwise to a solution of **2** (47 mg, 0.1 mmol) in dichloromethane (1 mL). Monitoring of the reaction by t.l.c. (*B*) showed that, after 15 min, only traces of the starting material remained. The solution was concentrated and the solid residue extracted with dichloromethane. The dichloromethane solution was washed with water, dried, and evaporated. ^{1}H-N.m.r. spectrum of the residue showed it to be **8**, sufficiently pure for further conversions.

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