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Note

A convenient synthesis of 2-deoxy-D-*arabino*-hexose and of its methyl and benzyl glycosides

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2-Deoxy-D-*arabino*-hexose[1] (2-deoxy-D-glucose) (**17**) is a natural sugar of considerable interest in that it not only inhibits yeast fermentation, bacterial growth, and D-glucose utilization in muscle and tumor growth[2], but has also been used as a D-glucose analog in the study of various aspects of carbohydrate transport and metabolism. Numerous synthetic routes have been developed for the synthesis of this important compound and of its methyl glycosides[3–14]. Most start with such transformations of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**1**) as, for example, by hydration[3], methoxymercuration[10,11], addition of hydrochloric acid and methanolysis[12], or addition[6] of bromine followed by introduction of an acetoxyl group at C-1. Activation of the double bond of **1** was also achieved with *N*-haloimides, leading, in the presence of alcohols, to 2-bromo-2-deoxyglycosides in rather good yield[13,14]. However, in contrast with experiments conducted with dihydropyrans[15,16], no attempt was made to introduce directly, at C-1 of a carbohydrate residue, an acetoxyl or a benzyl group by use of acetic acid or benzyl alcohol in the presence of *N*-bromosuccinimide. This would lead, after hydrogenolysis of the C-2–Br bond, to the per-*O*-acetyl derivatives and to the benzyl glycoside of **17** (**12** or **14**, and **15**, respectively). Moreover, these two functional groups are easily removable under alkaline conditions or by hydrogenolysis, thus giving efficient access to **17**.

Before conducting these new experiments, we re-examined the reaction, at 0°, of *N*-bromosuccinimide and methanol with **1**, as this reaction had been reported[13] to give a mixture of methyl α-D-manno- and β-D-glucopyranoside in the ratio of ~4:1 (determined by ^{1}H-n.m.r. studies, but no product being separated). We found that methyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-β-D-glucopyranoside[17] (**2**) could be selectively crystallized in 22% yield from methanol, whereas chromatography of the mother-liquors gave methyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-α-D-mannopyranoside[17] (**7**) in 66% yield. Subsequent hydrogenolysis of **2** or **7** with Raney

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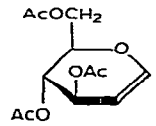

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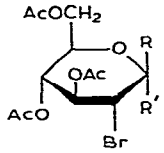
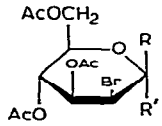
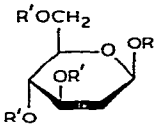


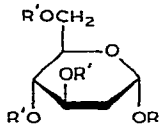
2 R = OMe, R′ = H
3 R, R′ = H, OH
4 R = OAc, R′ = H
5 R = H, R′ = OAc
6 R = OBzl, R′ = H



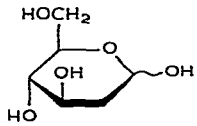
7 R = H, R′ = OMe
8 R = R′ = H, OH
9 R = H, R′ = OAc
10 R = H, R′ = OBzl



11 R = Me, R′ = Ac
12 R = R′ = Ac



13 R = Me, R′ = Ac
14 R = R′ = Ac
15 R = Bzl, R′ = Ac
16 R = Bzl, R′ = H



17

nickel in the presence of triethylamine gave **11** (refs. 10–12 and 18–21) and **13** (ref. 21) in 98% yield. As transesterification of **11** has been reported[12] to occur in a yield higher than 95%, the route of **1** to **2**, or **7** to **11** or **13** constitutes an efficient method for the preparation of methyl glycosides of **17** from readily available D-glucose.

In order to obtain **17** with a large-scale method that avoids acid hydrolysis[3] of the methyl glycosides, direct introduction of an acetyl or benzyl group at C-1 was attempted. Conditions similar to those previously reported by Dalton *et al.*[22] (*N*-bromosuccinimide–1,4-dioxane–water) allowed the preparation in excellent yield (95–97%) of a mixture of 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-D-glucose (**3**) and -D-mannose (**8**). Acetylation of this mixture in the presence of pyridine led to three compounds, two isomers having a D-*gluco* (**4** and **5**) and one a D-*manno* configuration **9** (55%). In contrast, when the acetylation was performed in the presence of perchloric acid[23], the exclusive formation of **4** (24%) and **9** (44%) was observed. The latter two derivatives could be obtained directly from **1** with *N*-bromosuccinimide in the presence of acetic acid with a total yield of 74% after purification. Hydrogenolysis of **4** and **9**, under the conditions previously used for **2** and **7**, afforded the corresponding 1,3,4,6-tetra-*O*-acetyl-2-deoxy-β- (**12**) and -α-D-*arabino*-hexopyranose[24] (**14**). *O*-Deacetylation of **12** or **14** gave 2-deoxy-D-*arabino*-hexose (**17**) in quantitative yield. Synthesis of **17** could be conducted without purification of the first step, and further without chromatography, since the 2-deoxy derivative **14** could be isolated by crystallization from hexane–acetone in ~35–36% yield after hydrogenolysis of the mixture of unpurified **4** and **9**.

TABLE I

^{1}H-N.M.R. SPECTRAL DATA AT 240 MHz FOR COMPOUNDS **2**, **4**, **5–7**, AND **9–16**

Compound[a]	*Chemical shifts (δ)*[b]										*Coupling constants*[b] *(Hz)*								
	H-1	*H-2a*	*H-2e*	*H-3*	*H-4*	*H-5*	*CH_2-6*		*OMe*	*OAc*	$J_{1,2e}$	$J_{1,2a}$	$J_{2a,2e}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
							A(q)	*B(q)*											
2	4.50(d)	3.78		5.30(t)	5(t)	3.84–3.68(m)	4.31	4.12	3.58	2.03, 2.09, 2.10		8.5		9.5	9.5	10	4.5	2	12.5
4	5.82(d)	3.94–3.86		5.02(t)	5.35(t)	3.94–3.86(m)	4.30	4.10		2.02, 2.08, 2.10, 2.17		9		10	9	10	4.5	2	12.5
5	6.35(s)			←5.08–5.51(t)—→		4.16–4(m)	4.29	4.04		2.04, 2.08, 2.10, 2.23		3.5		10	9.5	10	4	2	12.5
6[c]	4.61(d)	3.82(q)		←4.98–5.24(t)—→		3.70(m)	4.28	4.14		2.01, 2.08, 2.10		8.5		10	10	10	5	2.5	12.5
7	4.98(s)		4.44(q)	5.20(q)	5.39(t)	4(m)	4.26	4.15	3.43	2.06, 2.10, 2.12	1			4	10	10	5	2.5	12.5
9	6.31(s)		4.44(q)	5.20(q)	5.49(t)	4.16–4.08(m)	4.14	4.16–4.08		2.07, 2.11, 2.12, 2.13	1.5			4	4.5	10			13
10[d]	5.15(s)	4.47(q)		5.26(q)	5.43(t)	4.05–3.98(m)	4.45	4.08		2.05, 2.08, 2.12	1			4	9	9	4.5	2	12.5
11	4.48(q)	←2.38–1.70(m)→		←5.08–4.95(m)→			4.31	4.12	3.51	2.04, 2.05, 2.09	1.5	9.5					4.5	2	12.5
12	5.80(q)	1.88(m)	2.32(m)	←5.10–5(m) —→		3.75(m)	4.33	4.10		2.04, 2.05, 2.10, 2.13	2	10	13.5		10	10	4.5	2	12.5
13	4.84(d)	1.81(m)	2.26(m)	5.29(m)	5(t)	3.94(m)	4.30	4.06	3.35	2, 2.04, 2.10	<1	3	13.5	5.5 9.5	9.5	9.5	4.5	2	12.5
14	6.25(d)	1.96(m)	2.20(m)	5.31(m)	5.07(t)	4.10–4(m)	4.30	4.04		2.03, 2.04, 2.08, 2.13	1.5	3.5	13	11.5 5	10	10	4.5	2	12.5
15[e]	5.13(d)	1.84(m)	2.27(m)	5.36(m)	5.02(t)	4.02–3.94(m)	4.30	4.04		2, 2.03, 2.10	<1	3.5	13.5	9 5	10	10	5	1	12.5
16[f]	4.93	1.30(m)	2.02(m)			←—— 3.60(m) ——→													

[a]In chloroform-*d*, except **16** in dimethyl sulfoxide-d_6. [b]First order couplings. Signal multiplicities: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. [c]CH_2Ph, A 4.92, B 4.68. [d]CH_2Ph, A 4.73, B 4.57. [e]CH_2Ph, A 4.64, B 4.50. [f]CH_2Ph, A 4.60, B 4.40.

Use of benzyl alcohol instead of methanol or acetic acid gave, in 58% yield after chromatography, the benzyl glycosides **6** and **10** in the ratio of 1:6. Hydrogenolysis of benzyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-α-D-mannopyranoside (**10**) afforded **15** and, after transesterification, the benzyl α-D-glycoside[25,26] **16** of **17** in 80% overall yield from **10**.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi melting-point apparatus and are uncorrected. Specific rotations were measured with a Perkin–Elmer Model 141 MC polarimeter for solution in a 1-dm tube. I.r. spectra were recorded with a Perkin–Elmer Model 257. Kieselgel G (type 60 Merck) was the support for t.l.c. and Kieselgel H (type 60, Merck) for column chromatography. Microanalyses were performed by the Service Central de Microanalyses du C.N.R.S.

General procedure for the preparation of **2**, **4**, **6**, *and* **10**. — To a solution of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**1**) in alcohol, 1,4-dioxane–water, or acetic acid was added *N*-bromosuccinimide (1.1 to 1.5 equiv.). After being stirred for 3 h at room temperature (except for methanol, where the temperature was 5°), the mixture was extracted with ether in the usual manner.

*Methyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-β-*D*-glucopyranoside* (**2**) *and* -α-D-*mannopyranoside* (**7**). — These compounds were obtained from **1** (5 g), *N*-bromosuccinimide (4.4 g), and methanol (50 mL). The crude product (7 g, 98%) was crystallized from methanol to give **2** (1.6 g, 22%). The mother liquors (5.4 g) were chromatographied on silica gel, and elution with 3:1 (v/v) hexane–ethyl acetate gave 7 (4.7 g, 66%).

Compound **2**: m.p. 136–137°, $[\alpha]_D^{20}$ +54° (*c* 1.8, chloroform); ν_{max}^{Nujol} 1730, 1250, and 1025 cm^{-1} (ester).

Anal. Calc. for $C_{13}H_{19}BrO_8$: C, 40.75; H, 5.00; Br, 20.85; O, 33.40. Found: C, 40.46; H, 4.97; Br, 21.13; O, 33.17.

Compound **7**: syrup, $[\alpha]_D^{20}$ +190° (*c* 1.35, chloroform); ν_{max}^{Nujol}, see compound **2**.

Anal. Calc. for $C_{13}H_{19}BrO_8$: C, 40.75; H, 5.00; Br, 20.85; O, 33.40. Found: 40.81; H, 5.07; Br, 20.85; O, 33.07.

*Mixture of 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-*D*-glucopyranose* (**3**) *and* D-*mannopyranose* (**8**). — This mixture was obtained from **1** (1 g), *N*-bromosuccinimide (0.7 g), and 1:1 (v/v) 1,4-dioxane–water (15 mL); ν_{max}^{film} 3340 (OH), 1750, 1240, and 1050 cm^{-1} (ester). A part was purified by distillation under vacuum (4 kPa, 2 h, and 140°), and no decomposition, as observed for some 2-acetoxy-3-bromopyrans[27], took place.

Anal. Calc. for $C_{12}H_{17}BrO_8$: C, 39.04; H, 4.63; Br, 21.64. Found: C, 39.02; H, 5.01; Br, 21.65.

*1,3,4,6-Tetra-*O*-acetyl-2-bromo-2-deoxy-β-*D*-glucopyranose* (**4**) *and* -α-D-*mannopyranose* (**9**). — The treatment of **1** (0.5 g) with *N*-bromosuccinimide (0.4 g) and acetic acid (5 mL), followed by neutralization, after the reaction, with a cooled

solution of 10% (v/v) sodium hydroxide and extraction with ether, afforded a syrup (0.75 g, 98%). Column chromatography (3 : 1, v/v, hexane–ethyl acetate) gave, successively, **4** (172 mg, 22%), a mixture of **4** and **9** (50 mg, 6%), and **9** (352 mg, 46%).

Compound **4**: m.p. 95–96° (methanol), $[\alpha]_D^{20}$ +61° (*c* 1, chloroform); ν_{max}^{Nujol} 1760, 1740, and 1225 cm^{-1}.

Anal. Calc. for $C_{14}H_{19}BrO_9$: C, 40.89; H, 4.65; Br, 19.43. Found: C, 40.96; H, 4.62; Br, 19.66.

Compound **9**: syrup $[\alpha]_D^{20}$ +24° (*c* 2.8, chloroform); ν_{max}^{Nujol} 1740 and 1225 cm^{-1}.

Anal. Calc. for $C_{14}H_{19}BrO_9$: C, 40.89; H, 4.65; Br, 19.43. Found: C, 40.87; H, 4.56; Br, 19.85.

*Benzyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-β-*D*-glucopyranoside* (**6**) *and* -α-D-*mannopyranoside* (**10**). — These compounds were obtained by treatment of **1** (4 g) with benzyl alcohol (4 mL), acetonitrile (20 mL), and *N*-bromosuccinimide (3 g). Column chromatography (2 : 1, v/v, hexane–ethyl acetate) gave successively **6** (2.82 g, 44%), a mixture of **6** and **10** (0.54 g, 8%), and **10** (0.37 g, 6%).

Compound **6**: m.p. 108–110° (methanol), $[\alpha]_D^{20}$ +6° (*c* 1, chloroform); ν_{max}^{film} 1745, 1230, and 1040 cm^{-1}.

Anal. Calc. for $C_{19}H_{23}BrO_8$: C, 49.68; H, 5.04; Br, 17.39. Found: C, 49.87; H, 5.22; Br, 18.02.

Compound **10**: syrup, $[\alpha]_D^{20}$ +43° (*c* 2, chloroform); ν_{max}^{film} 1745, 1230, and 1080 cm^{-1}.

Anal. Calc. for $C_{19}H_{23}BrO_8$: C, 49.68; H, 5.04; Br, 17.39. Found: C, 50.02; H, 5.12; Br, 17.60.

General procedure for the preparation of **11–15**. — To a solution of bromo compound (1 mmol) in ethyl acetate (10 mL) were added triethylamine (0.5 mL) and Raney nickel (2 mL). The mixture was stirred overnight under a hydrogen atmosphere (1 bar). The catalyst was removed by filtration and washed with ethyl acetate. The filtrate was washed with water, dried, and evaporated *in vacuo*.

*Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-*arabino*-hexopyranoside* (**11**). — This compound was obtained as a crystalline residue (98%) from **2**, m.p. 94–95° (hexane–ethyl acetate), $[\alpha]_D^{20}$ −25° (*c* 1, chloroform); lit.[10] m.p. 95–97° (water), $[\alpha]_D$ −22° (*c* 1, chloroform); lit.[12] m.p. 96–97°, $[\alpha]_D$ −24° (*c* 1, chloroform); lit.[18] m.p. 98–100.5° (ether–petroleum ether), $[\alpha]_D^{22}$ −31.2° ±2 (*c* 0.9, 1,1,2,2-tetrachloroethane); lit.[20] m.p. 99–101°, $[\alpha]_D$ −23.6° (*c* 1, chloroform); lit.[21] m.p. 99–99.5°, $[\alpha]_D^{22}$ −27.4° (*c* 1, chloroform); ν_{max}^{Nujol} 1740, 1225, 1070, and 1050 cm^{-1}.

*Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-*arabino*-hexopyranoside* (**13**). — Syrup, $[\alpha]_D^{20}$ +108° (*c* 2.34, chloroform); lit.[21] syrup, $[\alpha]_D^{20}$ +100.5° (*c* 1, chloroform); ν_{max}^{film}, identical with i.r. of **11**.

*1,3,4,6-Tetra-*O*-acetyl-2-deoxy-β-*D*-arabino-hexopyranose* (**12**). — This compound was obtained in 72% yield from **4**, m.p. 90–91° (hexane–acetone), $[\alpha]_D^{20}$ −2° (*c* 1, chloroform); lit.[24] m.p. 92–93°, $[\alpha]_D^{20}$ −3° (*c* 1, chloroform).

*1,3,4,6-Tetra-*O*-acetyl-2-deoxy-α-*D*-arabino-hexopyranose* (**14**). — This compound was obtained in 74% yield from **9**, m.p. 109–110° (hexane–acetone), $[\alpha]_D^{20}$

+96° (*c* 1, chloroform); lit.[24] m.p. 110–111° (ethanol–ligroin or propanol), $[\alpha]_D$ +108° (*c* 1.13, chloroform).

*Benzyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-*arabino*-hexopyranoside* (**15**). — This compound was obtained in 84% yield from **10**, syrup, $[\alpha]_D^{20}$ +132° (*c* 1.4, chloroform); ν_{max}^{film} 1740 and 1230 cm^{-1}.

Anal. Calc. for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36; O, 33.65. Found: C, 60.03; H, 6.30; O, 33.52.

Acetylation of the mixture of **3** *and* **8**. — (*a*) *In the presence of pyridine.* The mixture (2.6 g) was acetylated with pyridine (15 mL) and acetic anhydride (10 mL) to give a crude product (2.7 g) and, after chromatography, **4** (195 mg, 7%), **5** (185 mg, 6%), and **9** (1.6 g, 55%).

(*b*) *In the presence of perchloric acid.* The mixture (0.62 g) was treated with acetic anhydride (20 mL) and perchloric acid (0.15 mL) according to the procedure described[23]. Chromatography of the crude product (633 mg) afforded **4** (163 mg, 24%) and **9** (303 mg, 44%).

*1,3,4,6-Tetra-*O*-acetyl-2-bromo-2-deoxy-α-*D*-glucopyranose* (**5**). — M.p. 111° (methanol), $[\alpha]_D^{20}$ +150° (*c* 1, chloroform); ν_{max}^{Nujol}, same i.r. spectrum as **6**.

Anal. Calc. for $C_{14}H_{19}BrO_9$: C, 40.89; H, 4.65; Br, 19.43. Found: C, 40.96; H, 4.62; Br, 19.66.

Preparation of **16** *and* **17**. — A solution of **12**, **14**, or **15** (1 mmol) in methanol (4 mL) and M sodium methoxide (0.4 mL) was stirred for 3 h at room temperature. After filtration through Amberlite IR-120 (H^+) ion-exchange resin, the solvent was removed *in vacuo* to give a crystalline residue (yield 95–100%).

*Benzyl 2-deoxy-α-*D*-arabino-hexopyranoside* (**16**). — This compound was obtained from **15**, m.p. 129–130° (ethyl acetate), $[\alpha]_D^{20}$ +111° (*c* 1, methanol); lit.[25] m.p. 131–133° (ethyl acetate–ether), $[\alpha]_D^{20}$ +73° (*c* 1.7, water); lit.[26] m.p. 129° (ethyl acetate), $[\alpha]_D^{20}$ +93° (*c* 1, water).

*2-Deoxy-*D*-arabino-hexose* (**17**). — This compound was obtained either from **12** or **14** in 95% yield, and identified with an authentic sample after crystallization from acetone.

Direct preparation of **14** *from* **1**. — Compound **1** (2 g) was treated with *N*-bromosuccinimide and acetic acid as previously described. Hydrogenolysis of the crude product (3 g) afforded a syrup (2.7 g) which crystallized from 1:1 (v/v), hexane–acetone, and gave pure **14** (900 mg, ~35–36% yield).

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