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Note

Practical synthesis of methyl 2,4-di-*O*-methyl-β-L-arabinopyranoside*

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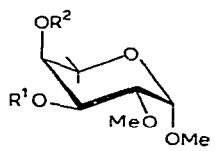
Methyl ethers of L-arabinose are useful reference compounds in the elucidation of the structure of plant polysaccharides, saponins, and other L-arabinose-containing substances by methylation analysis. Although some derivatives of 2,4-di-*O*-methyl-L-arabinose are known[2,3], methyl pyranosides of the sugar have not been prepared because of the difficulties involved in the synthesis of suitable intermediates.

The lower reactivity of axial as compared with equatorial hydroxyl groups of carbohydrates was demonstrated by partial benzoylation of methyl α-D-galactopyranoside[4] and methyl β-L-arabinopyranoside[5,6], which gave good yields of the corresponding benzoates having the axial HO-4 unsubstituted. It therefore seemed reasonable to expect that methyl 2-*O*-methyl-β-L-arabinopyranoside (**1**) should undergo selective benzoylation at the equatorial HO-3. Accordingly, **1** was treated with 1.1 mol. of benzoyl chloride in pyridine, and methyl 3-*O*-benzoyl-2-*O*-methyl-β-L-arabinopyranoside (**2**) was the major product. Although **2** was not obtained crystalline, the minor product, namely, the isomeric 4-benzoate **3**, crystallized after purification by column chromatography on silica gel.



	R^1	R^2		R^1	R^2
1	H	H	7	NBz	Me
2	Bz	H	8	H	Me
3	H	Bz	9	Me	Bz
4	NBz	H	10	Me	NBz
5	H	NBz	11	Me	H
6	Bz	Me			

NBz = *p*-nitrobenzoyl

*Alternative syntheses of methylated sugars: Part XII[1].

TABLE I

FIRST-ORDER CHEMICAL SHIFTS AND COUPLING CONSTANTS OF **2–11**

Compound	*Chemical shift*[a] (δ)									*Coupling constants (Hz)*					
	H-1	*H-2*	*H-3*	*H-4*	*H-5*[b]	*H-5'*[b]	*Aromatic*	*Methyl*	*OH*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$[f]	$J_{4,5}$[f]	$J_{4,5'}$[f]	$J_{5,5'}$
2	4.91d	3.88q	5.38q	4.20m	3.86q	3.65q	7.25–8.13m	3.45; 3.44	2.55	3.4	9.8	3.3	0.8	2.3	−12.5
3	4.99d	3.65q	4.20q	5.43m	3.89q	3.80q	7.25–8.13m	3.55; 3.45	2.58	3.4	9.9	3.4	0.7	3.2	−13.0
4	4.98d	3.90q	5.41q	4.26m	3.94q	3.70q	8.25s	3.46[c]	2.41	3.5	10.0	3.2	1.5	2.1	−12.5
5	5.00d	3.63q	4.21q	5.45m	3.91q	3.80q	8.25s	3.54; 3.45	2.60	3.3	9.9	3.4	1.6	2.4	−12.5
6	4.93d	3.89q	5.43q	———	3.80[d]	———	7.25–8.13m	3.51; 3.46; 3.40	—	3.5	9.9	3.1	g	g	g
7	4.96d	3.90q	5.43q	———	3.80[d]	———	8.25s	3.51; 3.46; 4.41	—	3.4	10.0	3.1	g	g	g
8	4.86d	3.45q	3.96q	3.53m	3.79m	3.64q	—	3.54; 3.50; 3.40	2.79	3.5	10.0	3.4	2.6	1.4	−13.0
9	4.93m[h]	——	3.69t[e]	——	5.56m	3.86q	3.79q	7.25–8.13m	3.54; 3.44[c]	—	g	g	g	1.2	1.8	−13.0
10	4.95d	3.54q	3.76q	5.56m	3.93q	3.80q	8.25s	3.55; 3.46; 3.45	—	3.1	10.0	2.6	1.6	2.4	−12.5
11	4.85m[h]	——	3.56t[e]	——	4.06m	——	3.73d[e]	——	—	3.50[c]; 3.41	3.00	g	g	g	g	g	g

[a]Observed multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. [b]C-5 proton resonating at lower field is denoted H-5. [c]6-Proton singlet. [d]Broad, 3-proton singlet. [e]Deceptively simple, second-order spectrum. [f]Coupling constants calculated by ABX analysis of the spectrum. [g]First-order coupling constants were not observed. [h]The large $J_{2,3}$ coupling constant together with small chemical shifts of H-2 and H-3 are responsible for further splitting of the H-1 signal.

When **1** was treated with 1.1 mol. of *p*-nitrobenzoyl chloride, methyl 2-*O*-methyl-3-*O*-*p*-nitrobenzoyl-β-L-arabinopyranoside (**4**) could be crystallized directly. Chromatography of the mother liquor gave crystalline methyl 2-*O*-methyl-4-*O*-*p*-nitrobenzoyl-β-L-arabinopyranoside (**5**).

The location of the benzoyl and *p*-nitrobenzoyl groups in **2**–**5** was based on n.m.r. spectral data (Table I) which clearly showed the downfield position of the signal for the proton in the HCOCOR group.

Methylation of **2** and **4** under conditions known not to cause migration of the base-labile substituents[7] gave the corresponding di-*O*-methyl derivatives **6** and **7** in good yield, and the latter was crystalline. Thus, **7**, apart from being an accessible intermediate in the synthesis of the title glycoside, is a suitable substance for identification of methyl 2,4-di-*O*-methyl-β-L-arabinopyranoside. Deacylation of **6** and **7** with methanolic sodium methoxide afforded methyl 2,4-di-*O*-methyl-β-L-arabinopyranoside (**8**).

Using a reaction sequence similar to that for the synthesis of **8**, the by-products **3** and **5** of the partial acylation of **1** were converted into syrupy 2,3-di-*O*-methyl-β-L-arabinopyranoside (**11**), which was hitherto unknown. The intermediate 4-*p*-nitrobenzoate **10** is crystalline and is a good derivative for the identification of **11**.

EXPERIMENTAL

M.p.s. were determined on a Kofler hot-stage. Optical rotations were measured with a Perkin–Elmer automatic polarimeter Model 141. N.m.r. spectra were measured at 80 MHz in chloroform-*d* (internal Me_4Si) with a Tesla BS-487-B spectrometer. The proton-signal assignments were made by the INDOR technique. G.l.c. was carried out at 130° with a Hewlett–Packard Research Chromatograph Model 5750 G on a column (180 × 0.3 cm) packed with 3% OV-17 on Gas Chrom Q (100–120 mesh). Nitrogen (26 ml/min) was used as a carrier gas. T.l.c. was performed on Silica gel G, and preparative chromatography on columns of dry-packed silica gel (0.05–0.1 mm), using benzene–acetone mixtures: *A* (6:1), *B* (10:1), *C* (8:1), and *D* (15:1), and *E* chloroform–acetone (10:1). During the preparative separation of **2**–**5**, the flow rate was 1–1.5 ml/min, and the ratio of the amount of the separated material/adsorbent was that recommended for mixtures very difficult to separate[8]; a clean-cut separation was achieved.

Chromatographically homogeneous, anhydrous **1** was prepared by an improved procedure in 70% overall yield by isopropylidenation of methyl β-L-arabinopyranoside[9] with acetone–methanol (10:1, 22 ml/g) containing 1% of toluene-*p*-sulphonic acid, followed by methylation[10], deisopropylidenation at 50° with 6M acetic acid (4 ml/g), and purification by chromatography on silica gel. It had $[\alpha]_D^{24}$ +225° (*c* 2.2, methanol); lit.[9] $[\alpha]_D$ +208° (methanol). When prepared by the original procedure[9], **1** was not chromatographically homogeneous.

Boron trifluoride etherate was freshly distilled from calcium hydride. *p*-Nitrobenzoyl chloride was freshly recrystallised from hexane and dried at 15 Torr at room temperature for 5 h. Solutions were concentrated under diminished pressure at <40°.

Methyl 3-O-benzoyl- (**2**) *and 4-O-benzoyl-2-O-methyl-β-L-arabinopyranoside* (**3**). — Benzoyl chloride (1.45 ml) was added at −20° and 6–10 drops/min to a solution of **1** (2 g) in dry pyridine (50 ml). After a further 30 min, the reaction mixture, which contained only traces of the starting material, was worked up in the usual manner. The two major reaction products (R_F 0.3 and 0.4; t.l.c., solvent *A*) were isolated by elution of the crude product (3.1 g) from a column of silica gel with solvent *B*.

The faster-moving product was **2** (2.3 g, 72.5%), which could not be crystallized, and, after drying at 40°/15 Torr, it had $[\alpha]_D^{24}$ +200° (*c* 1.48, chloroform) (Found: C, 59.82; H, 6.35; OMe, 21.86%. $C_{14}H_{18}O_6$ calc.: C, 59.56; H, 6.43; OMe, 21.99%).

When chromatographically homogeneous **2** was distilled at 160–180°/0.05 Torr, the product gave a satisfactory analysis for a methyl *O*-benzoyl-*O*-methylpentoside, but t.l.c. (solvent *A*) revealed two components (R_F 0.3 and 0.4) in the ratio ~1:2 consistent with partial migration of BzO-3 to HO-4 during distillation. Whereas the n.m.r. spectrum of **2** contained a quartet at δ 5.38 for H-3, that of the distilled material contained in this region overlapping signals for H-3 of **2** and H-4 of **3**. Therefore, chromatographically homogeneous, undistilled **2** was subsequently used.

The slower-moving product was **3** (0.35 g, 10.5%), m.p. 109–110° (from isopropyl ether), $[\alpha]_D^{24}$ +209° (*c* 1.03, chloroform) (Found: C, 59.78; H, 6.33; OMe, 22.10%).

Methyl 2-O-methyl-3-O-p-nitrobenzoyl- (**4**) *and -4-O-p-nitrobenzoyl-β-L-arabinopyranoside* (**5**). — To a cold (−20°) solution of **1** (3 g) in dry pyridine (75 ml), a solution of *p*-nitrobenzoyl chloride (3.45 g) in dry pyridine (45 ml) was added at ~15 drops/min. The solid residue obtained after the usual work-up of the reaction mixture was recrystallized from ethanol to give **4** (3.1 g), m.p. 161.5–162.5°, $[\alpha]_D^{24}$ +185° (*c* 1.04, chloroform). Chromatography of the mother liquor on a column of silica gel with solvent *C* afforded, as the faster-moving product, more **4** (0.9 g; total yield, 72%) (Found: C, 51.65; H, 5.44; N, 4.42%. $C_{14}H_{17}NO_8$ calc.: C, 51.37; H, 5.24; N, 4.28%).

Eluted second was **5** (0.5 g, 9.5%), m.p. 99–101° (from ether), $[\alpha]_D^{24}$ +187° (*c* 1, chloroform) (Found: C, 51.30; H, 5.18; N, 4.22%).

Methyl 2,4-di-O-methyl-β-L-arabinopyranoside (**8**). — (*a*) Compound **2** (1 g) was dissolved in dichloromethane (20 ml), and boron trifluoride etherate (0.05 ml) was added with stirring at −20° and exclusion of moisture. An ~1% solution of diazomethane in dichloromethane was then added slowly until a yellow colour persisted, the temperature of the mixture being kept below −15°. The conversion of the starting material (R_F 0.2), which was then ~60% (t.l.c., solvent *D*), into one product (R_F 0.5) could be increased to ~90% by periodical addition of the catalyst (0.01 ml) and the solution of diazomethane. The filtered mixture was washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and concentrated. The crude product was eluted from a column of silica gel with solvent *D* to give methyl 3-*O*-benzoyl-2,4-di-*O*-methyl-β-L-arabinopyranoside (**6**; 0.81 g, 77%), b.p. 135° (bath)/0.01 Torr, $[\alpha]_D^{24}$ +185° (*c* 1, chloroform) (Found: C, 60.82; H, 6.77; OMe, 31.35%. $C_{15}H_{20}O_6$ calc.: C, 60.80; H, 6.80; OMe, 31.42%).

A solution of **6** (0.5 g) in dry methanol (10 ml) was treated with a few drops of methanolic M sodium methoxide, and when t.l.c. showed that the debenzoylation was complete the mixture was deionized with Amberlite IR-120(H^+) resin, filtered, and concentrated. The syrupy residue was partitioned between ether and water to give, after concentration of the aqueous solution, crude **8** still containing some methyl benzoate. Elution from a column of silica gel with solvent *E* yielded **8** (0.27 g, 83.5%), b.p. 110–120° (bath)/0.1 Torr, $[\alpha]_D^{22}$ +220° (*c* 1, methanol) (Found C, 49.80; H, 8.52; OMe, 48.0%. $C_8H_{16}O_5$ calc.: C, 49.98; H, 8.39; OMe, 48.43%). On g.l.c., **8** gave a single peak (*T* 5.8 min).

(*b*) The *p*-nitrobenzoate **4** (2 g) was methylated, as described in (*a*), to give methyl 2,4-di-*O*-methyl-3-*O*-*p*-nitrobenzoyl-β-L-arabinopyranoside **7** (1.6 g, 76.3%), m.p. 94–95° (from isopropyl ether), $[\alpha]_D^{23}$ +179° (*c* 1, chloroform) (Found: C, 52.50; H, 5.91; N, 3.75%. $C_{15}H_{19}NO_8$ calc.: C, 52.78; H, 5.60; N, 4.09%).

Deacylation of **7** (1 g), as described in (*a*), gave **8** (0.5 g, 89%) which was identical with the compound obtained from **6**.

*Methyl 2,3-di-*O*-methyl-β-*L*-arabinopyranoside* (**11**). — (*a*) Crystalline **3** (0.85 g) was methylated in dichloromethane (15 ml) as described above, and the crude product was chromatographed to give methyl 4-*O*-benzoyl-2,3-di-*O*-methyl-β-L-arabinopyranoside **9** (0.62 g, 70%), b.p. 140° (bath)/0.02 Torr, $[\alpha]_D^{23}$ +212° (*c* 1, chloroform) (Found: C, 60.59; H, 6.78; OMe, 31.29%).

Compound **9** (0.35 g) was debenzoylated to give, after purification by chromatography, **11** (0.2 g, 88.2%), b.p. 120°/0.1 Torr, $[\alpha]_D^{23}$ +221° (*c* 1.3, methanol), which on g.l.c. gave a single peak (*T* 4.9 min) (Found: C, 50.1; H, 8.50; OMe, 48.12%).

(*b*) Purification by chromatography of the crude product obtained on methylation of **5** (0.4 g) gave methyl 2,3-di-*O*-methyl-4-*O*-*p*-nitrobenzoyl-β-L-arabinopyranoside **10** (0.3 g, 71.6%), m.p. 85–86° (from isopropyl ether), $[\alpha]_D^{23}$ +200° (*c* 1, chloroform) (Found: C, 52.78; H, 5.55; N, 4.28%).

De-*p*-nitrobenzoylation of **10** (0.35 g), with purification of the crude product as described in (*a*), gave **11** (0.15 g, 77%) identical in all respects with the compound obtained from **9**.

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