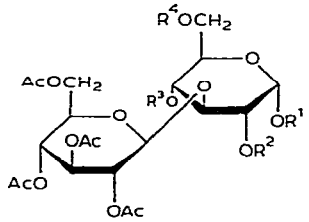
Carbohydrate Research, 95 (1981) 125–131
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

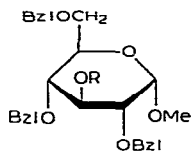
Selective acetolysis of benzyl ethers of methyl D-glucopyranosides*

JUN-ICHI SAKAI, TADAHIRO TAKEDA, AND YUKIO OGIHARA
Faculty of Pharmaceutical Sciences, Nagoya City University, Nagoya (Japan)
(Received November 12th, 1980; accepted for publication in revised form, March 31st, 1981)

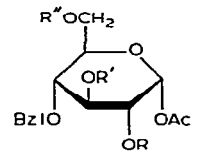
The stepwise synthesis of oligosaccharides requires the preparation of carbohydrate derivatives having both persistent (benzyl, allyl) and temporary (ester) blocking groups[1]. The present note describes the order of cleavage of the benzyl ethers, using, as model compounds, methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**1**), methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**4**), and methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**5**). In addition, we report the synthesis of *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-



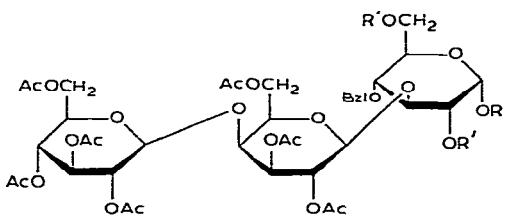
1 R^1 = Me, R^2 = R^3 = R^4 = Bzl
2 R^1 = R^4 = Ac, R^2 = R^3 = Bzl
3 R^1 = R^2 = R^3 = Ac, R^4 = Bzl



4 R = H
5 R = Bzl



6 R = R′ = R″ = Ac
7 R = Bzl, R′ = R″ = Ac
8 R = R′ = Bzl, R″ = Ac



9 R = Me, R′ = Bzl
10 R = R′ = Ac

*Synthesis of oligosaccharides. Part 1.

(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→3)-1,2,6-tri-*O*-acetyl-4-*O*-benzyl-α-D-glucopyranose (**10**). The reactions were monitored by t.l.c., and most of the products were characterized by ^{1}H- and ^{13}C-n.m.r. spectroscopy.

The acetolysis of the benzyl ethers of the hexitols has been studied in detail[2,3]. Ponpipom[4] reported that the order of cleavage by acetolysis of the benzyl ethers of D-mannose is *O*-Bzl-6 > *O*-Bzl-4 > *O*-Bzl-3, and also Eby *et al.*[5] described the selective acetolysis of primary benzyl ethers.

Acetolysis of methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**1**) [which was prepared by the condensation of methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside[6] (**4**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of mercuric cyanide] with 1% sulfuric acid in acetic anhydride at room temperature for 1 h gave two well-separated spots on t.l.c. (**2**: R_F 0.42; and **3**: R_F 0.35) in the ratio of 1:3. Compound **2** was converted into **3** in the course of the reaction. Under these conditions, the glycoside linkage of **1** was not cleaved. The ^{1}H-n.m.r. spectrum of compound **2** shows, in addition to signals for six acetoxyl group, signals for ten aromatic protons that absorb in the range of δ 7.40–7.35. Seven acetoxyl and five aromatic protons signals were present in the spectrum of **3**. The results of methylation analysis of both compounds showed that the former was 1,6,2′,3′,4′,6′-hexa-*O*-acetyl-2,4-di-*O*-benzyllaminarabiose, and the latter was the 4-*O*-benzyl derivative.

Acetolysis of methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside[6] (**4**) for 2 h gave 1,3,6-tri-*O*-acetyl-2,4-di-*O*-benzyl- (**7**) and 1,2,3,6-tetra-*O*-acetyl-4-*O*-benzyl-α-D-glucopyranose (**6**) in the ratio of 1:2, as estimated by t.l.c. When the reaction was continued for 6 h, **6** was obtained as the major product. The ^{1}H-n.m.r. spectrum of **7** shows signals for three acetoxyl group and ten aromatic protons. In the case of **6**, four acetoxyl group and five aromatic-proton signals were present. The signal

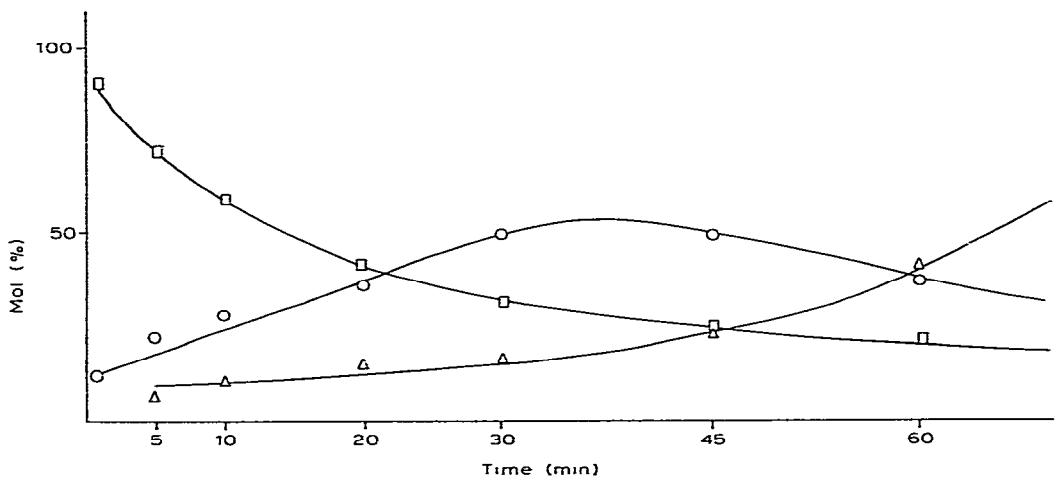


Fig. 1. Variation of the concentration of the products obtained by acetolysis of **6** (△—△), **7** (○—○), and **8** (□—□).

due to H-1 was observed as a one-proton doublet with J 4 Hz. The small coupling constant and the ^{13}C-chemical shift value (δ 89.2) were consistent with the α-D configuration for **6**.

In order to determine the reactivity of the 3-*O*-Bzl group, we acetolyzed methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside[7] (**5**) for 1 h at room temperature. As shown in Fig. 1, the starting material was rapidly converted into the 1,6-di-*O*-acetyl derivative[8] **8**; later 1,3,6-tri-*O*-acetyl-2,4-di-*O*-benzyl-α-D-glucopyranose (**7**) appeared; and then, after 45 min, the 2,4-di-*O*-benzyl derivative **7** disappeared, and **6** appeared. This result shows that the ease of cleavage of the benzyl ethers of D-glucopyranose by acetolysis appears to be in the order of O-Bzl-6 > O-Bzl-3 > O-Bzl-2 > O-Bzl-4.

In the course of the synthesis of oligosaccharides that contain the repeating unit of the lichen polysaccharide lichenan[9], which shows antitumor activity[10], we synthesized the trisaccharide methyl *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**9**) by condensation of methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside

TABLE I

^{13}C-CHEMICAL SHIFTS[a] (δ) OF METHYL D-GLUCOPYRANOSIDES **1**, **4**, **5**, AND **9**, AND THEIR ACETOLYSIS PRODUCTS

Carbon atom	*Compound*											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
C-1	97.3	89.0	89.4	97.6	97.6	89.2	89.2	89.5	97.5	89.1	101.1	89.1
2	79.6	76.5	68.0	79.6	79.9	68.0	75.9	78.9	79.0	67.9	70.9	69.3
3	80.9	79.6	76.5	68.0	82.1	69.7	70.9	81.6	79.0	77.0	71.4	69.9
4	77.2	77.6	77.3	77.6	77.7	75.5	75.5	76.6	76.7	76.3	68.1	68.0
5	71.7	72.7	71.7	69.7	70.1	71.6	72.6	71.0	71.7	72.0	72.5	69.9
6	68.4	61.4	62.0	68.6	68.5	61.6	62.5	62.6	68.0	61.9	61.6	61.5
Ph-CH_2	73.4	73.4	73.3	73.2	73.3	73.0	73.2	73.0	73.0	72.9		
	73.4			73.3	73.4		74.7		73.6			
	74.5	74.5		74.4	74.9			75.0	74.4			
					75.6			75.5				
C-1′	101.5	100.3							100.3	100.3		
2′	69.6	69.8							69.8	69.8		
3′	71.5	71.7							71.7	71.5		
4′	68.3	68.3							81.0	78.9		
5′	72.9	72.9							73.6	73.7		
6′	61.8	61.4							62.4	62.0		
C-1″									100.8	100.7		
2″									72.0	72.0		
3″									72.0	72.0		
4″									68.7	67.7		
5″									72.5	72.9		
6″									61.7	61.5		

[a]For solutions in chloroform-*d*.

with 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-D-cellobiosyl bromide[11] in the presence of mercuric cyanide. Acetolysis of this trisaccharide tribenzyl ether with 1% sulfuric acid in acetic anhydride for 1 h gave, at room temperature, *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-*O*-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→3)-1,2,6-tri-*O*-acetyl-4-*O*-benzyl-α-D-glucopyranose (**10**) in good yield. The acetolyzed trisaccharide **10** was *O*-deacetylated and converted into a deca-*O*-methyl derivative by methylation, and the resulting decamethyl ether was subjected to hydrogenation with palladium–carbon in acetic acid, followed by methanolysis. The methanolyzate gave three methylated sugars that were identified by g.l.c. as the methyl pyranosides of 2,3,4,6-tetra-*O*-methyl-, 2,4,6-tri-*O*-methyl-, and 2,6-di-*O*-methyl-D-glucose in the ratios 1:1:1. Under these acetolysis conditions, *O*-Bzl-2 and -6 and also CH_3-1 were replaced by an acetyl group.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto micro-apparatus and are uncorrected. ^{1}H-N.m.r. spectra were recorded with a JNM MH-100 spectrometer, and ^{13}C-n.m.r. spectra with a FX-100 instrument, tetramethylsilane being the internal standard in both cases. Optical rotations were recorded with a Union Giken PM-201 automatic digital polarimeter. T.l.c. was conducted on pre-coated silica gel plates (Merck GF-254), and column chromatography on silica gel (Merck Kieselgel 60). T.l.c. scanning was performed with a Shimadzu Dual-wavelength TLC Zig-zag Scanner CS-910.

General acetolysis procedure. — The carbohydrate derivative was dissolved in acetic anhydride at room temperature, and 1% sulfuric acid in acetic anhydride was added. The reaction mixture was poured into ice–water. The product was extracted with chloroform, and the extract was washed with water, saturated sodium hydrogencarbonate solution, and water, dried with sodium sulfate, and evaporated to a syrup. The syrup was chromatographed on silica gel with chloroform and 10:1 (v/v) benzene–acetone as eluents.

Materials. — Methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**4**) was prepared by the method of Koto *et al.*[6]. Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**5**) was prepared by the method of Tate and Bishop[7].

*Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside* (**1**). — A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.5 g, 1.22 mmol) in nitromethane (1 mL) was added to a mixture of methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (0.5 g, 1.08 mmol) and mercuric cyanide (0.25 g) in the same solvent (1 mL). After being stirred for 4 h at 60°, the mixture was cooled, washed successively with saturated aqueous sodium hydrogencarbonate, saturated aqueous sodium chloride, and water, dried (sodium sulfate), and evaporated to a syrup that was chromatographed on a column of silica gel. Elution with 4:1 (v/v) benzene–acetone gave **1** (0.82 g, 86.4%), $[\alpha]_D^{21}$ +8.8° (*c* 4.5, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.36–7.31 (m, 15 H, arom.), 4.82 (d, 1 H, *J* 3.8 Hz, H-1),

4.54 (d, 1 H, *J* 8 Hz, H-1'), 3.47 (s, 3 H, OMe), 2.06 (s, 3 H, OAc), 1.99 (s, 6 H, 2 OAc), and 1.92 (s, 3 H, OAc).

Anal. Calc. for $C_{42}H_{50}O_{15}$: C, 63.47; H, 6.34. Found: C, 63.36; H, 6.29.

1,6-Di-O-acetyl-2,4-di-O-benzyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-glucopyranose (**2**), and *1,2,6-tri-O-acetyl-4-O-benzyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-glucopyranose* (**3**). — Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**1**) (223 mg) was dissolved in acetic anhydride (0.5 mL) and acetolyzed with 1% sulfuric acid in acetic anhydride (1 mL) for 1 h at room temperature. After the usual processing, the mixture was chromatographed on silica gel with the same solvent as that used for t.l.c. (4:1, v/v, benzene–acetone) to give **2**, $[\alpha]_D^{21}$ +50.3° (*c* 7.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.40–7.35 (m, 10 H, arom.), 6.36 (d, 1 H, *J* 4 Hz, H-1), 1.99 (s, 6 H, 2 OAc), 1.96 (s, 3 H, OAc), and 1.92 (s, 9 H, 3 OAc).

Anal. Calc. for $C_{38}H_{46}O_{17}$: C, 58.91; H, 5.98. Found: C, 58.96; H, 6.04.

Further elution gave **3**, $[\alpha]_D^{21}$ +33.3° (*c* 9.9, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.36–7.31 (m, 5 H, arom.), 6.30 (d, 1 H, *J* 4 Hz, H-1), 2.05 (s, 9 H, 3 OAc), 2.01 (s, 3 H, OAc), and 2.00 (s, 9 H, 3 OAc).

Anal. Calc. for $C_{33}H_{42}O_{18}$: C, 54.54; H, 5.83. Found: C, 54.64; H, 5.85.

1,3,6-Tri-O-acetyl-2,4-di-O-benzyl-α-D-glucopyranose (**7**) *and 1,2,3,6-tetra-O-acetyl-4-O-benzyl-α-D-glucopyranose* (**6**). — Methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**4**) (500 mg) was acetolyzed for 2 h at room temperature. After the usual processing, column chromatography on silica gel with chloroform as the solvent gave **7**, $[\alpha]_D^{21}$ +51.5° (*c* 1.1, chloroform); t.l.c. (4:1, v/v, benzene–acetone): R_F 0.56; ^{1}H-n.m.r. ($CDCl_3$): δ 7.32–7.28 (m, 10 H, arom.), 6.31 (d, 1 H, *J* 4 Hz, H-1), 5.50 (t, 1 H, *J* 8 Hz, H-3), 2.04, 2.02, and 1.96 (s, each 3 H, 3 OAc).

Anal. Calc. for $C_{26}H_{30}O_9$: C, 64.19; H, 6.22. Found: C, 64.02: H, 6.16.

Further elution gave **6**, $[\alpha]_D^{21}$ +58.0° (*c* 1.2, chloroform); t.l.c. (4:1, v/v, benzene–acetone): R_F 0.46; ^{1}H-n.m.r. ($CDCl_3$): δ 7.36–7.31 (m, 5 H, arom.), 6.36 (d, 1 H, *J* 4 Hz, H-1), 5.42 (t, 1 H, *J* 8 Hz, H-3), 2.17, 2.06, 2.01, and 2.00 (s, each 3 H, 4 OAc).

Anal. Calc. for $C_{21}H_{26}O_{10}$: C, 57.53; H, 5.98. Found: C, 57.43; H, 5.89.

Acetolysis of methyl 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside. — Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside[7] (**5**) (720 mg) was dissolved in acetic anhydride (6.3 mL) and acetolyzed for 1 h at room temperature. Aliquots of the mixture were examined at time intervals by t.l.c. on silica gel plates in 4:1 (v/v) benzene–acetone. The developed plates were examined with a scanner at the following wave lengths: sample, 260 nm (λ_S); and reference compound, 450 nm (λ_R). Three well-separated spots corresponding to **8** (R_F 0.62), **7** (R_F 0.56), and **6** (R_F 0.46) were observed. The intensity of the spots was plotted against time (see Fig. 1). 1,6-Di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranose[8] (**8**): $[\alpha]_D^{21}$ +59.2° (*c* 3.1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.28–7.20 (m, 15 H, arom.), 6.32 (d, 1 H, *J* 4 Hz, H-1), 2.05, and 1.97 (s, each 3 H, 2 OAc).

Methyl O-*(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-(1→4)-O-(2,3,6-tri-O-*

acetyl-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-O-benzyl-α-D-glucopyranoside (**9**). — A solution of 2,3,4,6,2′,3′,6′-hepta-*O*-acetyl-α-D-cellobiosyl bromide[11] (5 g, 7.2 mmol) in nitromethane (10 mL) was added to a mixture of methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**4**) (3 g, 6.5 mL), mercuric cyanide (1.7 g), and molecular sieve 4 A (1 g) in the same solvent (10 mL). After being stirred for 2 h at 60°, the mixture was cooled, washed successively with saturated aqueous sodium hydrogencarbonate, saturated aqueous sodium chloride, and water, dried (sodium sulfate), and evaporated to a syrup that contained, as shown by t.l.c. in 4:1 (v/v) benzene–acetone, a major product (R_F 0.46) and a hydrolysis product of the bromide (R_F 0.32). The residue was chromatographed on a column of silica gel. The product eluted with 4:1 (v/v) benzene–acetone crystallized from methanol to give **9** (yield 4.97 g, 71%), m.p. 65–66°, $[\alpha]_D^{21}$ +16.0° (*c* 0.5, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.21–7.06 (m, 15 H, arom.), 4.98 (d, 1 H, *J* 4.4 Hz), 4.72 (d, 1 H, *J* 9 Hz), 4.52 (d, 1 H, *J* 8 Hz), 3.21 (s, 3 H, OMe), 2.02 (s, 3 H, OAc), 1.96 (s, 9 H, 3 OAc), and 1.94, 1.91, 1.87 (s, each 3 H, 3 OAc).

Anal. Calc. for $C_{54}H_{66}O_{23}$: C, 59.88; H, 6.14. Found: C, 59.65; H, 6.14.

O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-(1→4)-O-(2,3,6-tri-O-acetyl-β-D-glucopyranosyl)-(1→3)-1,2,6-tri-O-acetyl-4-O-benzyl-α-D-glucopyranose (**10**). — Compound **9** (11.68 g) was dissolved in acetic anhydride (26.5 mL) and acetolyzed with 1% sulfuric acid in acetic anhydride (53 mL) to give **10** (9.38 g) as a white powder, in 78.4% yield, m.p. 100–101°, $[\alpha]_D^{21}$ +20.0° (*c* 0.5, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.40–7.29 (m, 5 H, arom.), 6.30 (d, 1 H, *J* 4 Hz, H-1), 5.12 (d, 1 H, *J* 7 Hz), 4.48 (d, 1 H, *J* 7 Hz), 2.12, 2.10 (s, each 3 H, 2 OAc), 2.08 (s, 6 H, 2 OAc), 2.06 (s, 3 H, OAc), 2.01 (s, 12 H, 4 OAc), and 1.97 (s, 3 H, OAc).

Anal. Calc. for $C_{45}H_{58}O_{26}$: C, 53.25; H, 5.76. Found: C, 53.48; H, 5.72.

Methylation analysis of compound **10**. — Compound **10** was *O*-deacetylated with triethylamine in 50% methanolic solution, followed by methylation by Hakomori's method[12]. The decamethyl ether obtained was hydrogenated with palladium–carbon in acetic acid, and then methanolyzed with 5% hydrogen chloride in methanol. The resulting mixture was analyzed by g.l.c.: methyl 2,3,4,6-tetra-*O*-methyl-α,β-D-glucopyranosides (*t* of β anomer 1.00, of α anomer 2.07), methyl 2,3,6-tri-*O*-methyl-α,β-D-glucopyranosides (*t* of β anomer 2.70, of α anomer 3.68), and methyl 2,6-di-*O*-methyl-α,β-D-glucopyranosides (*t* of β anomer 5.18, of α anomer 6,72) were identified by comparison with the corresponding authentic samples and were present in the ratios 1:1:1.

ACKNOWLEDGMENT

We thank Miss T. Kumagai for the ^{1}H-n.m.r. and ^{13}C-n.m.r. spectral measurements.

REFERENCES

1 P. J. Pfäffli, S. H. Hixson, and L. Anderson, *Carbohydr. Res.*, 23 (1972) 195–206.
2 R. Allerton and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, 76 (1954) 1757–1760.

3 C. M. McCloskey, *Adv. Carbohydr. Chem.*, 12 (1957) 137–156.
4 M. M. Ponpipom, *Carbohydr. Res.*, 59 (1977) 311–317.
5 R. Eby, S. J. Sondheimer, and C. Schuerch, *Carbohydr. Res.*, 73 (1979) 273–276.
6 S. Koto, Y. Takebe, and S. Zen, *Bull. Chem. Soc. Jpn.*, 45 (1972) 291–293.
7 M. E. Tate and C. T. Bishop, *Can. J. Chem.*, 41 (1963) 1801–1806.
8 N. Pravdić and D. Keglević, *Tetrahedron*, 21 (1965) 1897–1901.
9 M. Fleming and D. J. Manners, *Biochem. J.*, 100 (1966) 4p–5p.
10 F. Fukuoka, M. Nakanishi, S. Shibata, Y. Nishikawa, T. Takeda, and M. Tanaka, *Gann*, 59 (1968) 421–432.
11 M. L. Wolfrom and A. Thompson, *Methods Carbohydr. Chem.*, 2 (1963) 211–214.
12 S. Hakomori, *J. Biochem. (Tokyo)*, 55 (1964) 205–208.