Carbohydrate Research, 60 (1978) 200–205

Note

An improved method for selective substitution on *O*-3 of D-mannose. Application to the synthesis of methyl 3-*O*-methyl- and 2-*O*-methyl-α-D-mannopyranosides

MINA A. NASHED*

Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin-Madison, Madison, WI 53706 (U.S.A.)

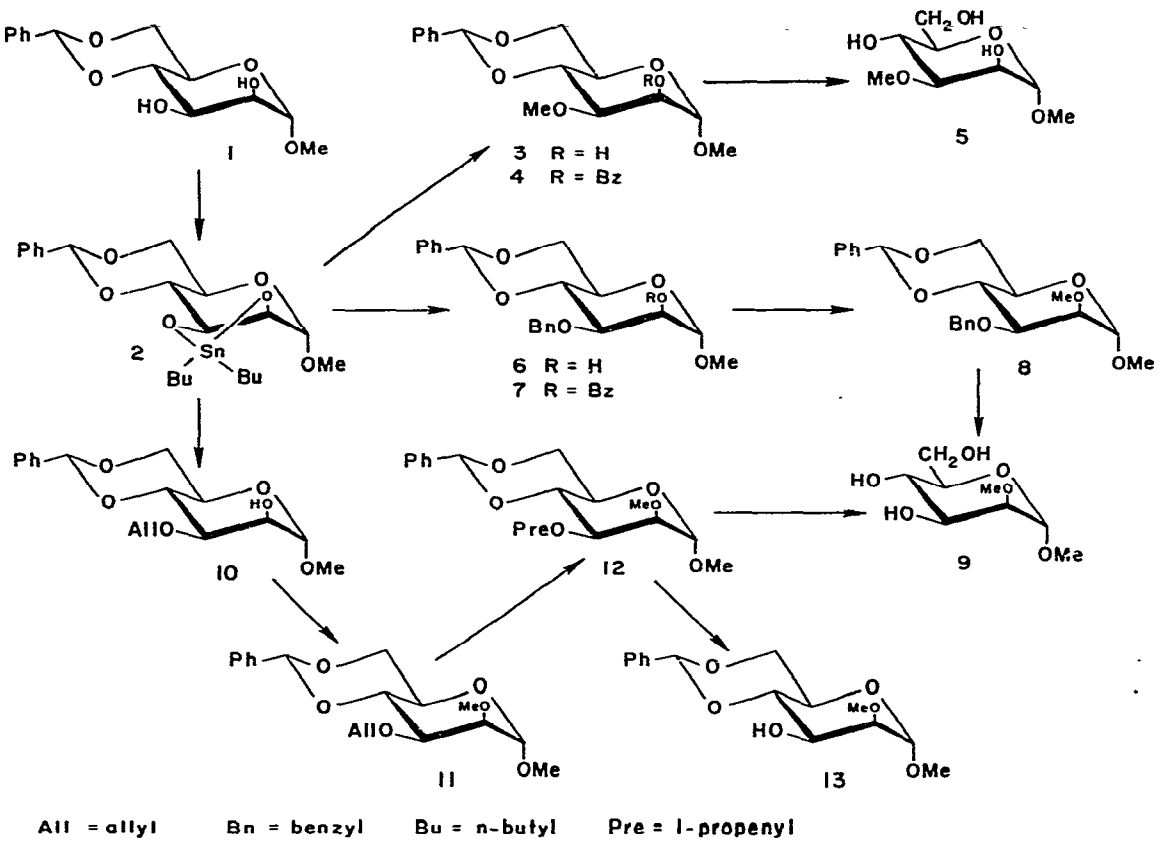
(Received January 24th, 1977; accepted for publication in revised form, April 19th, 1977)

Recent work in this laboratory[1] on the selective alkylation of sugar derivatives showed that methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-mannopyranoside (**2**) reacted with benzyl bromide in the same fashion as other axial–equatorial dibutylstannylene compounds[1,2]: it was benzylated almost exclusively at the equatorial position (O-3). Compound **2** thus appeared to be a promising intermediate for the synthesis of certain methyl ethers of D-mannose. Authentic samples of these compounds are frequently needed as reference substances in studies on the structures of polysaccharides and glycoproteins. The present note describes improved routes to methyl 3-*O*-methyl-(**5**) and 2-*O*-methyl-(**9**)α-D-mannopyranoside, which are the precursors of the respective mono-*O*-methyl-D-mannoses. Simple extensions of the chemistry used would provide effective syntheses of 3,4,6- and 2,4,6-tri-*O*-methyl-D-mannose.

Both 2-*O*-methyl- and 3-*O*-methyl-D-mannose and their methyl glycosides (**9** and **5**) have been made from methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) or its ethylidene analog. However, previous techniques did not permit the selective methylation of either the 2- or the 3-position in these compounds. Hence, for the synthesis of the 3-*O*-methyl compounds in particular, complex sequences of blocking and deblocking steps were required[3–5]. A possible alternative route to the 3-*O*-methyl derivatives would proceed via the β anomer of **3**, obtained[6] by the reduction of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-*arabino*-hexopyranosid-2-ulose, but this route is also lengthy. The preparation of the glycosidulose[6] from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose is a multi-step process.

In the present synthesis of methyl 3-*O*-methyl-α-D-mannopyranoside (**5**) from **1**, no selective blocking is required. The dibutylstannylene compound **2** is prepared from **1** and immediately methylated in high yield to the intermediate **3**. Mild, acid

*On leave of absence from the Department of Chemistry, Alexandria University, Alexandria, Egypt.



hydrolysis removes the benzylidene group from **3** to give **5**; more vigorous conditions should give 3-*O*-methyl-D-mannose directly.

As the properties of the 3-*O*-methyl mannoside **5** and its 2-*O*-methyl isomer **9** are quite similar, it was important to characterize the precursor **3** rigorously. The identification of **3** as methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside is based on the correspondence of its optical rotation with the value reported for the product of an independent synthesis[7], and on the p.m.r. spectrum of its benzoyl derivative **4** (see Experimental). The 2-*O*-methyl isomer (**13**) of **3** is distinguishable from it by t.l.c., but no **13** was detected in the product of the methylation reaction.

All syntheses of 2-*O*-methyl-D-mannose or its methyl glycoside **9** from methyl 4,6-*O*-alkylidene-α-D-mannopyranosides involve the introduction of a protecting group at position 3 prior to the methylation step*†. The *p*-tolylsulfonyl[3] and the 2,6-

*2-*O*-Methyl-D-mannose was originally prepared via the methylation of 3,4:5,6-di-*O*-isopropylidene-D-mannose dibenzyl dithioacetal[8].

†A very short synthesis of 2-*O*-methyl-D-mannose, employing a quite different approach, has been described by Deferrari *et al.*[9]. 1,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranose, made from D-mannose by a "one-pot" procedure, is methylated with diazomethane–boron trifluoride, and the product is deacetylated. Because the preparation of the tetraacetate is evidently tricky, the utility of this three-step synthesis remains to be established.

dimethoxybenzoyl[10] groups have been used. Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**6**) has also been made[11], and converted[12], without purification of intermediates, into **9**.

The synthesis of methyl 2-*O*-methyl-α-D-mannopyranoside (**9**) reported here makes use of the superior qualities of the benzyl ether group for protecting position 3. The alkali stability of the *O*-benzyl group permits methylation at position 2 by an efficient method[13]. One deblocking step is saved at the end of the sequence, as both the 3-*O*-benzyl and the 4,6-*O*-benzylidene groups are removed in a single operation, by hydrogenolysis over palladium on charcoal. On the basis of yield and regiospecificity, the preparation of the 3-*O*-benzyl intermediate **6** by the alkylation of **2** is to be preferred over the earlier described[11] lithium aluminum hydride–aluminum chloride reduction of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside.

An alternative, slightly longer synthesis of **9**, which also yielded the needed reference compound **13**, was realized via the *O*-allyl derivative **10**. The allylation of **2**, like other alkylations of this intermediate, proceeded in high yield and with essentially complete regioselectivity. The evidence for the structure of **10** is its conversion, via the 1-propenyl ether **12**, into the methyl 4,6-*O*-benzylidene-*O*-methyl-α-D-mannopyranoside **13**. Since, as noted above, compound **13** can be distinguished from the 3-methyl ether **3**, **13** must be the 2-*O*-methyl isomer. Hence the allyl protecting group in its precursor must be at position 3. The simultaneous removal of the propenyl and benzylidene groups from **12**, by mild acidic hydrolysis, gave **9**.

EXPERIMENTAL

General methods. — Instrumental and chromatographic procedures were as described in earlier papers of the series[14]. The following solvent combinations (v/v) were utilized for thin layer and column chromatography: A, 19:1 chloroform–acetone; B, 97:3 chloroform–ethyl acetate; and C, 17:3 chloroform–methanol. P.m.r. spectra at 270 MHz (specifically noted) were recorded with a Bruker WH-270 instrument. Elemental analyses were performed by the Micro-Tech Laboratories, Skokie, IL.

Methyl 4,6-O-benzylidene-3-O-methyl-α-D-mannopyranoside (**3**). — A suspension of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[15] (**1**, 0.2 g, 0.7 mmol) and dibutyltin oxide (0.18 g, 0.7 mmol) in methanol (25 ml) was heated under reflux for ~1 h (clear solution), and then the solvent was removed under diminished pressure. The resulting *methyl 4,6-O-benzylidene-2,3-O-dibutylstannylene-α-D-mannopyranoside*[1] (**2**) was dried under oil-pump vacuum, taken up in *N*,*N*-dimethylformamide (5 ml), and treated with methyl iodide (0.3 ml, 4.8 mmol). After the mixture had been heated for ~4 h at 45°, t.l.c. (solvent A) showed complete disappearance of the starting material. There was no trace of the 2-*O*-methyl isomer **13**. Following evaporation of the solvent under diminished pressure, the material was chromatographed on a column of silica gel (solvent A) to afford 1.6 g (76%) of **3**, $[\alpha]_D^{25}$ +73.6°, $[\alpha]_{436}^{25}$ +143° (*c* 0.5, chloroform). This compares with lit.[7] $[\alpha]_D^{27}$ +76° and lit.[5] $[\alpha]_D^{20}$

+72°. The p.m.r. spectrum ($CDCl_3$) (lit.[7]) showed δ 3.53 and 3.38 (2 s, 3 each, OCH_3).

Methyl 2-O-benzoyl-4,6-O-benzylidene-3-O-methyl-α-D-mannopyranoside (**4**). — This compound was prepared from **3** (100 mg) by treatment with benzoyl chloride in pyridine in the conventional way. The chromatographically pure (silica gel, solvent B), amorphous compound showed $[\alpha]_D^{27}$ −32.2° and $[\alpha]_{436}^{27}$ −80° (*c* 1.5, chloroform). The value at the D-line is substantially different from the $[\alpha]_D^{27}$ of −48° (chloroform) reported by Miljković, Gligorijević, and Glišin[7]. The p.m.r. spectrum in $CDCl_3$ was as described by these authors, but at 270 MHz had improved resolution at δ 5.58 (dd, 1, *J* 1.8 and 3.3 Hz, H-2, collapsed to d on irradiation of H-1) and 4.83 (d, 1, $J_{1,2}$ 1.8 Hz, H-1). The coupling to H-1 and the two small *J* values identify the doublet of doublets as belonging to the proton at C-2, which from the low-field position of the signal must be the location of the benzoyl group. Found: C, 66.34; H, 5.99. $C_{22}H_{24}O_7$ (400.43) requires C, 65.99; H, 6.04.

Methyl 3-O-methyl-α-D-mannopyranoside (**5**). — The debenzylidenation of **3** was effected by heating 0.5 g of the compound for 15 min at reflux in a mixture of methanol (15 ml) and 0.5M hydrochloric acid (3 ml). An excess of sodium hydrogencarbonate was added to the cooled solution, the solvents were evaporated off, and the residue was extracted with hot chloroform (3 × 5 ml). After chromatography on silica gel (solvent C) the product **5** was a syrup, $[\alpha]_D^{25}$ +59.6°, $[\alpha]_{436}^{25}$ +117° (*c* 1.8, chloroform) (lit.[5] $[\alpha]_D^{20}$ +53.6° in ethanol); p.m.r. ($CDCl_3$): δ 3.60 and 3.48 (2 s, OCH_3).

Methyl 4,6-O-benzylidene-3-O-benzyl-α-D-mannopyranoside (**6**). — The dibutylstannylene derivative **2** from 0.5 g (1.8 mmol) of **1** was dissolved in *N,N*-dimethylformamide (5 ml). Benzyl bromide (0.3 ml, 2.5 mmol) was added and the solution was brought to 100°. After 20 min, t.l.c. (solvent A) showed complete disappearance of the starting material. Processing of the mixture as already described for compound **3** afforded 0.56 g (85%) of syrupy **6**, $[\alpha]_D^{25}$ +51°, $[\alpha]_{436}^{25}$ +96.5° (*c* 1.5, chloroform), $[\alpha]_D^{25}$ +38.3°, (*c* 1, ethanol) (lit.[11] $[\alpha]_D$ +38° in ethanol); p.m.r. ($CDCl_3$) at 270 MHz: δ 7.5–7.25 (Ph-H) now 10 H, 4.86 and 4.70 (q_{AB}, 2, *J* 11.7 Hz, $PhCH_2$), and 3.37 (s, 3, OCH_3).

Methyl 2-O-benzoyl-3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (**7**). — To a solution of **6** (0.32 g, 0.86 mmol) in 5 ml of pyridine, benzoyl chloride (0.25 ml, 2.2 mmol) was added. The mixture was kept for 1 h at room temperature, and then poured into 20 ml of cold water. Recovery of the product by conventional extraction with chloroform, followed by chromatography on silica gel (solvent B), afforded pure **7** (0.36 g, 88%) as an amorphous solid, $[\alpha]_D^{25}$ −52.9°, $[\alpha]_{436}^{25}$ −123° (*c* 1, chloroform); p.m.r. ($CDCl_3$) at 270 MHz: δ 8.12–8.01 (m, 2 H of PhCO), 7.5–7.25 now ~13 H, 5.59 (dd, 1, $J_{1,2}$ 1.5 and $J_{2,3}$ 3.4 Hz, H-2, collapsed to d on irradiation of H-1), and 4.82 (d, 1, $J_{1,2}$ 1.5 Hz, H-1). Found: C, 70.78; H, 5.85. $C_{28}H_{28}O_7$ (476.53) requires C, 70.58; H, 5.92.

Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl-α-D-mannopyranoside (**8**). — Compound **6** (1.75 g, 4.7 mmol), methyl iodide (3 ml), and sodium hydride (0.25 g)

in dry benzene (10 ml) were heated for 20 h under reflux. T.l.c. (solvent B) showed the methylation to be almost complete. After the mixture had cooled, the excess of sodium hydride was decomposed by the cautious addition of methanol, and water was added. The organic layer was separated, washed with water, dried, and evaporated. Chromatography of the crude product on silica gel (solvent B) gave 1.36 g (75%) of pure **8**, $[\alpha]_D^{25}$ +65.4°, $[\alpha]_{436}^{25}$ +130° (*c* 1.7, chloroform); p.m.r. ($CDCl_3$) at 90 MHz, similar to that of **6**, except for the loss of O*H* and the addition of OCH_3 at δ 3.52. Found: C, 68.25; H, 6.88. $C_{22}H_{26}O_6$ (386.44) requires C, 68.38; H, 6.78.

Methyl 2-O-methyl-α-D-mannopyranoside (**9**). — *A. From* **8**. To a solution of **8** (0.95 g, 2.5 mmol) in methanol (25 ml), 0.08 g of 10% palladium-on-charcoal was added, and the mixture was stirred under hydrogen at ambient temperature and pressure. Twenty h sufficed to complete the hydrogenolysis (t.l.c., solvent C). The residue obtained by removal of the catalyst and evaporation of the solvent was chromatographed on a column of silica gel (solvent C) to afford 0.42 g (82%) of the syrupy, title compound, $[\alpha]_D^{25}$ +51.2°, $[\alpha]_{436}^{25}$ +99.9° (*c* 2.9, chloroform) (lit.[10] $[\alpha]_D^{25}$ +51°); p.m.r. (CD_3COCD_3): δ 4.70 (d, 1, $J_{1,2}$ ~1.3 Hz, H-1), 3.42 and 3.33 (2 s, 3 each, OCH_3).

B. From the propenyl ether **12**. The crude propenyl derivative (see under **13**, later) from 0.6 g (1.8 mmol) of **11** was dissolved in 0.5M hydrochloric acid (3 ml) and methanol (15 ml), and the solution was boiled under reflux. After 15 min, all of the starting material had disappeared (t.l.c., solvent C). Isolation and purification as already described for compound **5** gave 0.28 g (75%) of **9**. The material was identical (t.l.c., $[\alpha]_D$, and p.m.r.) with that prepared by method A.

Methyl 3-O-allyl-4,6-O-benzylidene-α-D-mannopyranoside (**10**). — The dibutylstannylene derivative from 0.4 g (1.4 mmol) of **1** was dissolved in *N,N*-dimethylformamide (10 ml) and allyl iodide (0.5 ml, 5.5 mmol) was added. The solution was heated for 0.5 h at 100°, at which time t.l.c. (solvent A) showed disappearance of the starting material. Following evaporation of the solvent, the material was chromatographed on a column of silica gel (solvent A) to afford 0.36 g (79%) of the syrupy, title compound, $[\alpha]_D^{25}$ +63.5°, $[\alpha]_{436}^{25}$ +122° (*c* 1.5, chloroform); p.m.r. ($CDCl_3$): δ 6.23–5.53 (m, 1, -C*H*=), 5.40–4.92 (m, 2, =CH_2), 4.30–3.79 now 8 H (addition of OCH_2CH=), 3.35 (s, 3, OCH_3), and 2.85 (bs, 1, D_2O exchangeable, O*H*). Found: C, 63.21; H, 7.03. $C_{17}H_{22}O_6$ (322.36) requires C, 63.34; H, 6.88.

Methyl 3-O-allyl-4,6-O-benzylidene-2-O-methyl-α-D-mannopyranoside (**11**). — The procedure for the methylation of **10** (0.25 g, 0.8 mmol) was the same as that used for compound **6**. Chromatography of the product on silica gel (solvent B) gave 0.19 g (73%) of the syrupy title compound, $[\alpha]_D^{25}$ +66.6°, $[\alpha]_{436}^{25}$ +128° (*c* 0.6, chloroform); p.m.r. ($CDCl_3$): as for **10**, except for the addition of OCH_3 at δ 3.51 and the loss of O*H*. Found: C, 64.52; H, 7.31. $C_{18}H_{24}O_6$ (336.38) requires C, 64.27; H, 7.19.

Methyl 4,6-O-benzylidene-2-O-methyl-α-D-mannopyranoside (**13**). — Methyl 3-*O*-allyl-4,6-*O*-benzylidene-2-*O*-methyl-α-D-mannopyranoside (**11**) (1 g, 3 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in dry methyl sulfoxide (5 ml) were

heated under dry nitrogen[16] for 20 min at 100°. The solution was cooled, diluted with water, and extracted with ether. Evaporation of the dried ether extract gave a syrup which, in view of its ready hydrolysis to **9** and **13**, must have been *methyl 4,6-O-benzylidene-2-O-methyl-3-O-(1-propenyl)-α-D-mannopyranoside* (**12**).

The crude propenyl ether was cleaved by treatment with mercuric oxide and mercuric chloride in acetone–water as described by Gigg and Warren[17]. Crystallization and recrystallization from ether–Skellysolve B gave 0.72 g (82%) of **13**, m.p. 111.5–112°, $[\alpha]_D^{25}$ +32.7°, $[\alpha]_{436}^{25}$ +60.9° (*c* 0.4, chloroform); p.m.r. ($CDCl_3$): δ 7.77–7.05 (m, 5, Ph-H), 5.53 (s, 1, PhC*H*), 4.77 (narrow d, 1, H-1), 4.60–3.63 (m, 6, H-2,3,4,5,6,6'), 3.50 and 3.38 (2 s, 3 each, OCH_3), and 2.47 (bs, 1, D_2O exchangeable, O*H*). Found: C, 61.09; H, 7.01. $C_{15}H_{20}O_6$ (296.32) requires C, 60.80; H, 6.80.

ACKNOWLEDGMENTS

This work was supported by the College of Agricultural and Life Sciences, University of Wisconsin–Madison, and by Grant No. AM-10588 (to Prof. Laurens Anderson) from the National Institute of Arthritis, Metabolism, and Digestive Diseases, N.I.H. I thank Prof. Anderson for the facilities of his laboratory and for invaluable advice and encouragement.

The Biochemistry 270-MHz n.m.r. Facility was made possible by grants from the Graduate School and The National Science Foundation (No. BMS74-23826). I thank Prof. W. A. Gibbons for making this facility available, and Mr. Sean Hehir for skillfully recording the spectra.

REFERENCES

1 M. A. Nashed and L. Anderson, *Tetrahedron Lett.*, (1976) 3503–3506.
2 C. Augé, S. David, and A. Veyrières, *J. Chem. Soc., Chem. Commun.*, (1976) 375–376.
3 G. O. Aspinall and G. Zweifel, *J. Chem. Soc.*, (1957) 2271–2278.
4 F. R. Seymour, *Carbohydr. Res.*, 34 (1974) 65–70.
5 A. I. Usov, S. V. Yarotskii, and L. K. Vasyanina, *Bioorgan. Khim.*, 1 (1975) 1583–1588.
6 M. Miljković, M. Gligorijević, and D. Miljković, *J. Org. Chem.*, 39 (1974) 2118–2120, and references cited therein.
7 M. Miljković, M. Gligorijević, and D. Glišin, *J. Org. Chem.*, 39 (1974) 3223–3226.
8 E. Pacsu and S. M. Trister, *J. Am. Chem. Soc.*, 63 (1941) 925–928.
9 J. O. Deferrari, E. G. Gros, and I. O. Mastronardi, *Carbohydr. Res.*, 4 (1967) 432–434; J. O. Deferrari, E. G. Gros, and I. M. E. Thiel, *Methods Carbohydr. Chem.*, 6 (1972) 365–367.
10 S. Abbas and A. H. Haines, *Carbohydr. Res.*, 41 (1975) 298–303.
11 S. S. Bhattacharjee and P. A. J. Gorin, *Can. J. Chem.*, 47 (1969) 1195–1206.
12 S. S. Bhattacharjee and P. A. J. Gorin, *Can. J. Chem.*, 47 (1969) 1207–1215.
13 P. A. Gent, R. Gigg, and R. Conant, *J. Chem. Soc. Perkin. Trans. I*, (1972) 1535–1542.
14 P. J. Pfäffli, S. H. Hixson, and L. Anderson, *Carbohydr. Res.*, 23 (1972) 195–206; S. A. Holick and L. Anderson, *ibid.*, 34 (1974) 208–213; S. A. Holick, S.-H. L. Chiu, and L. Anderson, *ibid.*, 50 (1976) 215–225.
15 J. G. Buchanan and J. C. P. Schwarz, *J. Chem. Soc.*, (1962) 4770–4777.
16 J. Gigg and R. Gigg, *J. Chem. Soc. C*, (1966) 82–86.
17 R. Gigg and C. D. Warren, *J. Chem. Soc. C*, (1968) 1903–1911.