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SYNTHESIS OF METHYL D-MANNOFURANOSIDES AND OF 5-*O*-METHYL-D-MANNOSE

M. H. RANDALL*
School of Chemistry, The University of New South Wales, Kensington, N. S. W. (Australia)
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ABSTRACT

Kuhn methylation of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose affords a mixture of methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside and methyl 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranoside, in the ratio 99:1. Treatment of the sodio derivative of the di-acetal with methyl iodide gave the same products, but the ratio was reversed and was 10:1 in favour of the β-D anomer. Convenient procedures for the synthesis of methyl α-D-mannofuranoside and methyl β-D-mannofuranoside from the corresponding di-acetals are described, and a synthesis of 5-*O*-methyl-D-mannose is also presented.

INTRODUCTION

The methyl D-mannofuranosides are difficult compounds to prepare and have only been obtained by tedious methods in low yield. For example, methanolysis[1] of D-mannose yields, after extensive chromatography on cellulose powder, both anomers in low yield. Methyl α-D-mannofuranoside[2] has been prepared by Purdie methylation of D-mannofuranose 2,3:5,6-dicarbonate. More recently, derivatives of methyl β-D-mannofuranoside[3] have been obtained by treating 5,6-di-*O*-acetyl-α-D-mannofuranosyl bromide 2,3-carbonate with silver oxide and methanol, whereas the α-D anomer could be obtained by treating the compound with sodium methoxide in benzene.

As part of a programme involving the investigation of the furanoid forms of carbohydrates, some mannofuranosides were required, since, in the β-D anomer, the all *cis* disposition of the hydroxyl groups and the side chain could affect the conformation of the furanoid ring and also the anomeric equilibrium. It was therefore decided to attempt a synthesis of 5-*O*-methyl-D-mannose, since this compound cannot assume a pyranoid form. Perlin[3] obtained 5-*O*-methyl-D-mannose by methylation of 6-*O*-trityl-D-mannose 2,3-carbonate, followed by treatment with base, to yield methyl 5-*O*-methyl-6-*O*-trityl-α-D-mannofuranoside. Acid treatment then gave the required product. An alternative approach is now reported.

*Present address: Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Mass., U. S. A.

RESULTS AND DISCUSSION

Kuhn methylation of the easily obtained 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose[4] gave two products (well separated by g.l.c.) in the ratio *ca.* 99:1. Separation of these products by column chromatography on silicic acid gave first methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside as the main component, followed by methyl 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranoside. Both of these compounds have previously been reported crystalline[5,6], but, in our hands, only the α-D anomer crystallised. The structures of these compounds were confirmed when acid hydrolysis of each di-acetal gave the corresponding methyl D-mannofuranoside. Haworth and co-workers[5] have previously prepared methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside by treating methyl α-D-mannofuranoside with acetone and anhydrous copper sulphate.

Partial, acid hydrolysis of methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside afforded syrupy methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside, characterised as the 5,6-diacetate. Treatment of methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside with 1.1 moles of benzoyl chloride afforded an oily mixture of two components (t.l.c.), presumably the mono- and di-benzoates of methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside. Kuhn methylation of this mixture afforded an oil, which, on treatment with ethanolic sodium hydroxide, gave methyl 2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranoside. From the yield (56%) of this material, the major product of benzoylation was the expected methyl 6-*O*-benzoyl-2,3-*O*-isopropylidene-α-D-mannofuranoside. Acid hydrolysis of methyl 2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranoside gave 5-*O*-methyl-D-mannose which gave a phenylosazone identical with that prepared from 5-*O*-methyl-D-glucose.

Levene and Meyer[7] investigated the Purdie methylation of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose and found that the α-D anomer was the major product; however, they also observed that if the sodio derivative of the diacetal was allowed to react with methyl iodide, the major product was the β-D anomer, together with a small proportion of the α-D anomer. This reversal of product ratios is quite remarkable. It is known that the crystalline starting material exists in the α-D form[8] and mutarotates very slowly, and it would thus be expected that Kuhn or Purdie methylation would afford mainly the α-D anomer. It is difficult to explain why the sodio derivative should give the sterically less-favorable β-D anomer on reaction with methyl iodide, unless some effect is causing the negatively charged oxygen atom to assume the β position.

In our hands, the product ratio for the methylation of the sodio derivative was $\beta:\alpha = 10:1$, thus confirming the work of Levene and Meyer. On using the same separation technique as for the Kuhn methylation, we were able to obtain methyl 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranoside. As expected (since all the substituents on the furanose ring are *cis*), the latter compound was very sensitive to acid and underwent partial hydrolysis with acid when stored in daylight in chloroform solution.

A comparison of the acid labilities of the α and β anomers of methyl 2,3:5,6-di-*O*-isopropylidene-D-mannofuranoside was obtained by storing each compound in 0.1N hydrochloric acid for 65 h at 20°, the β anomer gave D-mannose and methyl β-D-mannofuranoside, whereas the α anomer gave methyl α-D-mannofuranoside and methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside. It is therefore clear that the β-D anomer is more acid-labile than the α-D anomer.

As stated previously, methyl mannofuranosides are difficult compounds to synthesise in good yield. However, if the acid hydrolysis of the above diacetals could be stopped at the glycoside stage, an easy route would be obtained for the synthesis of these compounds. Thus, treatment of methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside with 0.05N ethanolic hydrogen chloride for 120 h at 20° afforded a mixture of methyl α-D-mannofuranoside and methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside. Chloroform extraction of the mixture afforded the monoacetal, and concentration of the aqueous solution gave methyl α-D-mannofuranoside. Similarly, mild, acid hydrolysis of methyl 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranoside afforded methyl β-D-mannofuranoside which was characterised as its calcium chloride complex.

EXPERIMENTAL

Melting points were determined on a Kofler microstage apparatus and are uncorrected. Analytical t.l.c. was performed with silica gel G on microscope slides with various solvents. The compounds were detected by treatment with 1:9 chlorosulphonic acid–acetic acid for *ca.* 10 min at 110°.

For g.l.c., a 4-ft. polyester (1.5% LAC-1-R-296 on Celite) column was used in a custom-built instrument. The carrier gas was nitrogen, at a flow rate of 30–40 ml/min. The best operating temperature was 145°, with the injection block at 200°. The retention times of methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside and methyl 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranoside were 4.3 and 9.5 min, respectively.

*Methylation of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose.* — (*a*) The title compound (1 g), *N*,*N*-dimethylformamide (4 ml), methyl iodide (6 ml), and silver oxide (2 g) were stirred together for 14 h at 20°. After the filtered solids had been washed with chloroform, the combined filtrate and washings were concentrated *in vacuo* to yield an oil (1.2 g), which contained (t.l.c., benzene–ether, 7:3) two components (ratio *ca.* 99:1, g.l.c.) with higher mobility than the starting material, and the complete absence of the latter. The compounds were separated by using CC4 100–200 mesh Mallinckrodt silicic acid (15 g) and benzene–ether (7:3) as irrigant; the first component, methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside (0.84 g), b.p. 85°/0.1 mmHg, crystallised completely on storage at 0° and had m.p. 23°, $[\alpha]_D^{25}$ +58.2° (*c*, 3.8, 1,1:2,2-tetrachloroethane), $[\alpha]_D^{25}$ +50.1° (*c* 4.65, chloroform), $[\alpha]_D$ +70.3° (*c*, 1.85, methanol); lit.[5], b.p. 125°/0.04 mmHg (bath temp.), m.p. 24°, $[\alpha]_D^{21}$ +68° (*c* 2.8 in methanol).

Further elution then afforded methyl 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranoside (0.02 g), b.p. 115°/0.5 mmHg, $[\alpha]_D^{25}$ −49.3° (*c* 0.83, 1,1:2,2-tetrachloroethane), $[\alpha]_D^{25}$ −58.9° (*c* 2.0, chloroform); lit.[7] $[\alpha]_D^{20}$ −42.2° (*c* 5.36, 1,1:2,2-tetrachloroethane). P.m.r. data (chloroform-*d*): methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside, δ 1.33 (singlet, 3 protons), 1.38 (singlet, 3 protons), 1.47 (singlet, 6 protons), 3.33 (singlet, OCH_3 protons), 3.8–4.9 (multiplet, 7 protons); methyl 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranoside; δ 1.37 (singlet, 6 protons), 1.43 (singlet, 3 protons), 1.53 (singlet, 3 protons), 3.53 (singlet, OCH_3 protons), 3.55–4.9 (multiplet 7 protons). The two compounds are readily distinguished by the glycosidic methyl signals or the isopropylidene signals.

(*b*) The title compound (1 g) was dissolved in benzene (20 ml), and a few pieces of sodium were added. After storage for 15 h at 20°, the unreacted sodium was removed, and the solution was concentrated to yield an oil, to which methyl iodide (10 ml) was added. After refluxing for 24 h, water (20 ml) was added, and the resulting solution was extracted with benzene (3 × 20 ml). The extract was washed with water (2 × 15 ml), dried (Na_2SO_4), and concentrated to yield an oil (0.7 g) which contained (t.l.c.) the same products as in (*a*), but in the reversed ratio, *viz.* α:β = 10:1 (g.l.c.). The compounds were separated as described in experiment (*a*).

*Comparison of acid lability of anomeric methyl 2,3:5,6-di-*O*-isopropylidene-D-mannofuranosides.* — Each glycoside (0.1 g) was dissolved in 3:1 aqueous ethanol (1.5 ml), which was 0.1N with respect to HCl. After storage for 65 h at 20°, the solutions were neutralized with IRA-400 resin (HCO_3^-) and concentrated to yield, in each case, an oil which was examined by p.m.r. in D_2O with acetone as internal standard.

For the β-D anomer, three resonances were observed in the anomeric region: (*a*) δ 5.1, $J_{1,2}$ 1.5 Hz; (*b*) 4.8, $J_{1,2}$ 1.0 Hz; (*c*) 4.8, $J_{1,2}$ 4.5 Hz. The first two resonances correspond to those reported[9] for D-mannose (δ 5.25, $J_{1,2}$ 1.7 Hz; δ 4.97, $J_{1,2}$ 1.0 Hz), and the latter corresponds to that for methyl β-D-mannofuranoside[10] (δ 4.8, $J_{1,2}$ 4.2 Hz).

For the α-D anomer, no resonances corresponding to mannose were observed, but a strong resonance at δ 4.9, $J_{1,2}$ 4.0 Hz, indicated that the hydrolysis had stopped at the methyl α-D-mannofuranoside stage.

Methyl 2,3-O-isopropylidene-α-D-mannofuranoside. — Methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside (4 g) was dissolved in ethanol (50 ml), and 0.2N HCl (50 ml) was added. After storage for 30 h at 25°, examination of the reaction mixture by t.l.c. [benzene–ether (1:1)] showed traces of starting material, together with a single component of lower mobility. Neutralisation of the mixture with IRA-400 resin (HCO_3^-), followed by concentration of the solution after separation of the resin, gave an oil which was dissolved in benzene and extracted with water (3 × 15 ml). Concentration of the aqueous extract gave syrupy methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (2.5 g, 73%).

Acetylation with pyridine–acetic anhydride gave methyl 5,6-di-*O*-acetyl-2,3-*O*-isopropylidene-α-D-mannofuranoside, which was recrystallised from water or light

petroleum (b.p. 40–60°); m.p. 54–55°, $[\alpha]_D$ +57° (*c* 1.3, chloroform). *Anal.* Calc. for $C_{14}H_{22}O_8$: C, 52.8; H, 7.0. Found: C, 53.1; H, 6.97. P.m.r. data: δ 5.3 (octet, H-5), 3.3 (singlet, 3 protons, OMe), 2.05 (singlet, 6 protons, acetyl groups), 1.44 and 1.33 (singlets, CMe_2).

Methyl 2,3-O-isopropylidene-5-O-methyl-α-D-mannofuranoside. — A cooled solution of methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (1.35 g) in pyridine (40 ml) was treated with benzoyl chloride (0.84 ml). After storage for 3 days at 0°, the solution was concentrated under diminished pressure at 60°, and water (25 ml) was added. After extraction of the aqueous solution with chloroform (3 × 20 ml), the organic extract was washed with dilute HCl until the washings were acid, and then with dilute, aqueous sodium hydrogen carbonate and water. The dried ($MgSO_4$) extract was concentrated to yield an oil (1.97 g) which was shaken for 14 h with *N,N*-dimethylformamide (15 ml), methyl iodide (30 ml), and silver oxide (5 g). The solids were filtered off and well washed with chloroform, and the resulting filtrate and washings were concentrated to yield an oil (1.9 g) which was dissolved in ethanol (15 ml), and 20% sodium hydroxide solution (5 ml) was then added. After heating on the steam bath for 4 h, the solution was neutralised with carbon dioxide and extracted with chloroform (3 × 20 ml). The dried ($MgSO_4$) extract was concentrated to yield an oil (1 g) which crystallised spontaneously. Examination of the material by t.l.c. [benzene–ether (3:2)] showed the presence of two components, the minor of which corresponded to methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside. The material was fractionated by using CC7 100–200 mesh Mallinckrodt silicic acid as absorbent and ethyl acetate as irrigant. Fractionation was monitored by t.l.c., and the initial fraction (0.8 g) crystallised upon evaporation of the solvent and was recrystallised from light petroleum (b.p. 40–60°) to yield methyl 2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranoside (0.55 g, 56%), m.p. 54°, $[\alpha]_D^{24}$ +76° (*c*, 0.25 chloroform).

Anal. Calc. for $C_{11}H_{20}O_6$: C, 53.2; H, 8.1. Found: C, 53.5; H, 8.2.

Methyl α-D-mannofuranoside. — Methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside (0.67 g) was dissolved in absolute ethanol (4 ml), and 0.1N hydrochloric acid (4 ml) added. After storage for 5 days at 20°, the solution was neutralised with IRA-400 resin (HCO_3^-), filtered, and extracted continuously with chloroform to yield, on concentration, an oil (0.41 g). Concentration of the aqueous solution gave an oil (0.12 g) which crystallised spontaneously; recrystallisation from propyl alcohol yielded methyl α-D-mannofuranoside (0.1 g), m.p. 119°, $[\alpha]_D^{20}$ +114.4° (*c* 0.7, water); lit.[11], m.p. 120–121°, $[\alpha]_D^{24}$ +109° (*c* 1.0, water). Investigation of the chloroform-soluble component showed it to be homogeneous and to have the same mobility as methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside.

Methyl β-D-mannofuranoside. — Methyl 2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranoside (1.79 g) was dissolved in absolute ethanol (20 ml), and 0.033N hydrochloric acid (50 ml) was added. The reaction mixture was stored at 25° and monitored by t.l.c. [ethyl acetate–methanol (24:1), detection with iodine vapour]. After 22.5 h, the starting material had disappeared, and three components, all having lower mobility than the starting material, had appeared. The reaction mixture

was neutralised with IRA-400 resin (HCO_3^-) and then extracted continuously with chloroform for 1.5 h. Concentration of the extract yielded an oil (0.12 g), which was shown by t.l.c. to contain the more-mobile components of the hydrolysate and none of the slow-moving material. The aqueous extract was concentrated *in vacuo* at 50° to yield crude methyl β-D-mannofuranoside (1.06 g), $[\alpha]_D^{20}$ −80.6° (*c* 2.2, water). The p.m.r. spectrum in D_2O showed a doublet at δ 5.0, $J_{1,2}$ 4.2 Hz.

Preparation of the calcium chloride complex of methyl β-D-mannofuranoside. — Crude methyl β-D-mannofuranoside (0.94 g) was mixed with 70% calcium chloride solution (3 ml), whereupon precipitation began almost immediately. After addition of cold propyl alcohol (2 ml), the mixture was stored overnight at 0° and then filtered, and the crystals were washed with absolute ethanol and dried *in vacuo* over anhydrous calcium chloride to give the complex (1.31 g), $[\alpha]_D^{20}$ −54.7° (*c* 1.35, water); lit.[12] $[\alpha]_D^{20}$ −58.5° (*c* 1.71, water).

5-O-Methyl-D-mannose. — Methyl 2,3-*O*-isopropylidene-5-*O*-methyl-α-D-mannofuranoside (0.25 g) was dissolved in 0.2N HCl and heated for 1.5 h at 80–90°. The hydrolysate was then neutralised with IRA-400 resin (HCO_3^-) and concentrated to yield syrupy 5-*O*-methyl-D-mannose (0.18 g) which, on treatment with phenylhydrazine hydrochloride and sodium acetate, gave 5-*O*-methyl-D-*arabino*-hexose phenylosazone, m.p. 131°; in admixture with the phenylosazone formed from 5-*O*-methyl-D-glucose, the product had m.p. 130–131°.

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