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STEREOSELECTIVE RING-OPENING OF β-D-MANNOPYRANOSE 1,2-(ALKYL ORTHOACETATES)*

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ABSTRACT

The stability towards alkali of the 3,4,6-tri-*O*-acetyl-β-D-mannose 1,2-(alkyl orthoacetates) provides a route to the corresponding 3,4,6-tri-*O*-benzyl-β-D-mannose 1,2-(alkyl orthoacetates). Alkyl groups that have been incorporated onto the orthoacetate ring include methyl, isopropyl, and cyclohexyl. 3,4,6-Tri-*O*-benzyl-β-D-mannose 1,2-(methyl orthoacetate) (**2**) was hydrolyzed to 3,4,6-tri-*O*-benzyl-D-mannose; periodate oxidation converted this compound into 2,3,5-tri-*O*-benzyl-D-arabinose. Methanolysis of **2** led to methyl 3,4,6-tri-*O*-benzyl-α-D-mannoside (**5**) in high yield; methylation of **5**, followed by debenzylation and acetylation, afforded crystalline methyl 2-*O*-methyl-3,4,6-tri-*O*-acetyl-α-D-mannoside. An acid-catalyzed, stereoselective rearrangement of the 3,4,6-tri-*O*-benzyl-β-D-mannose 1,2-(alkyl orthoacetates) was observed. The resulting products were demonstrated to be the corresponding alkyl 3,4,6-tri-*O*-benzyl-α-D-mannosides.

INTRODUCTION

In the light of unusual rates of periodate oxidation of the carbohydrate group in ovalbumin, attributed to a 2-*O*-substituted D-mannose residue[1], it was of interest to synthesize model D-mannopyranosides that are substituted at O-2. Recent disclosures of simple synthetic routes to 3,4,6-tri-*O*-acetylhexose 1,2-(alkyl orthoacetates)[2,3], and the marked stability of the 1,2-(alkyl orthoacetate) group to base, provided a suitable derivative of D-mannose for the synthesis required. However, the known tendency of *O*-acetyl groups to migrate, particularly the group at O-3 in 3,4,6-tri-*O*-acetyl-D-mannose[4], indicated that a more stable protecting group would be required. *O*-Methyl groups have been used in the synthesis of the 3,4,6-tri-*O*-methyl derivatives of D-glucose[5] and D-mannose[6] 1,2-(alkyl orthoacetates), and this work suggested that benzyl ethers might be used for our purpose.

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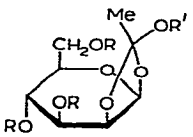
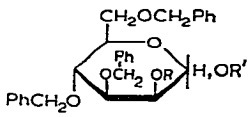
RESULTS AND DISCUSSION

The present report describes the synthesis of methyl 2-*O*-methyl-α-D-mannopyranoside from 3,4,6-tri-*O*-benzyl-β-D-mannose 1,2-(methyl orthoacetate). It is also shown that ring-opening of the 1,2-(alkyl orthoacetates) occurs rapidly with an acid catalyst, and in the absence of an alcohol, to give an almost stereospecific conversion into the corresponding alkyl α-D-mannopyranoside. The benzylation of 3,4,6-tri-*O*-acetyl-β-D-mannose 1,2-(methyl orthoacetate) (**1**) in tetrahydrofuran proceeded smoothly to yield the corresponding 3,4,6-tribenzyl ether (**2**) crystalline, in good yield. The n.m.r. signals of the orthoacetate C-Me and C-OMe protons in **2** had chemical shifts similar to those reported[7] for **1**. A solution of **2** in absolute methanol containing 2% of hydrogen chloride was refluxed to give a syrupy mixture containing more than 90% of methyl 3,4,6-tri-*O*-benzyl-α-D-mannoside (**5**). Compound **5** was obtained as a pure syrup by column chromatography on silica gel. Acetylation of **5** provided syrupy methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannoside (**6**), and the corresponding benzoic ester was also obtained as a syrup.





1 R = Ac; R′ = Me
2 R = $PhCH_2$; R′ = Me
7 R = Ac; R′ = Me_2CH
8 R = $PhCH_2$; R′ = Me_2CH
11 R = Ac; R′ = C_6H_{11}
12 R = $PhCH_2$; R′ = C_6H_{11}

3 R = H; R′ = H
5 R = H; R′ = Me (α-D)
6 R = Ac; R′ = Me (α-D)
9 R = Ac; R′ = Me_2CH (α-D)
10 R = H; R′ = Me_2CH (α-D)
13 R = Me; R′ = Me (α-D)
15 R = Ac; R′ = C_6H_{11}
16 R = H; R′ = C_6H_{11}

Attempts to hydrolyze **2** in acidic methanol–water mixtures gave low yields of crystalline 3,4,6-tri-*O*-benzyl-D-mannose (**3**), contaminated with the corresponding methyl glycosides. Similar difficulties had been reported earlier by Barker and Fletcher[8] in the synthesis of 2,3,5-tri-*O*-benzyl-L-arabinose. Almost quantitative yields of **3** were obtained by heating a solution of **2** in 60% aqueous acetic acid, followed by deacetylation of the resulting syrup.

Support for the structure assigned to **3** was obtained by its oxidation with periodate to form 2,3,5-tri-*O*-benzyl-D-arabinose. The mixture from the oxidation reaction was examined by t.l.c., and a compound, presumably 2,3,5-tri-*O*-benzyl-4-*O*-formyl-D-arabinose, was present which, after catalytic deacylation, was converted into 2,3,5-tri-*O*-benzyl-D-arabinose. Compound **3** was converted into **5** by refluxing it in anhydrous methanol containing 2% of hydrogen chloride.

A previous synthesis of 2-*O*-methyl-D-mannose had been accomplished through 3,4:5,6-di-*O*-isopropylidene-D-mannose dimethyl dithioacetal[9], or 1,3,4,6-tetra-*O*-acetyl-β-D-mannose[10]. Compounds **5** or **6** provided other intermediates for the

synthesis of derivatives of methyl 2-*O*-methyl-α-D-mannopyranoside. Methylation of **5** with a 1.5 molar excess of sodium methanesulfinyl corbonium[11] and methyl iodide provided syrupy methyl 3,4,6-tri-*O*-benzyl-2-*O*-methyl-α-D-mannoside (**13**) in less than 60% yield, whereas the reaction of **5** with methyl sulfate and potassium hydroxide in tetrahydrofuran gave **13** almost exclusively. Catalytic hydrogenolysis of **13** produced methyl 2-*O*-methyl-α-D-mannopyranoside, from which crystalline methyl 3,4,6-tri-*O*-acetyl-2-*O*-methyl-α-D-mannoside was obtained by acetylation. The n.m.r. signals assigned to the OMe protons in this compound were observed at τ 6.52 and 6.55.

Ring opening of the 1,2-(alkyl orthoacetates) has been studied by using various catalysts. The action of acids on **1** in the presence of alcohols has been investigated by Perlin[4]. The results were in keeping with a mechanism which had been proposed by Pacsu[12] for the acid-catalyzed ring-opening in an excess of methanol. Alternatively, the rearrangement of 3,4,6-tri-*O*-benzoyl-β-D-glucose 1,2-(methyl orthobenzoate), with somewhat more than catalytic amounts of mercuric bromide and anhydrous hydrogen chloride in nitromethane[13], gave crystalline methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucoside in 57% yield. More recently, the catalyzed alcoholysis of 3,4,6-tri-*O*-acetyl-α-D-glucose 1,2-(alkyl orthoacetates) with *p*-toluenesulfonic acid (*p*-TsOH) in dichloromethane has been reported[14], the alcohol being introduced to form the corresponding glycoside, mainly with retention of configuration at the anomeric center. Concomitant loss of the 2-*O*-acetyl group was observed, leading to the postulation of a 1,2-oxirane intermediate product. Kochetkov and co-workers[15–17] have treated 3,4,6-tri-*O*-acetyl-α-D-glucose and -D-galactose 1,2-(ethyl orthoacetates) with a properly protected carbohydrate in the presence of mercuric bromide and *p*-TsOH, or mercuric bromide alone, to yield an oligosaccharide in which the original anomeric configuration in the orthoacetate had been inverted. These reactions proceeded with retention of the 2-*O*-acetyl group.

In the present investigation, the ring opening of **2** in dichloromethane in the presence of *p*-TsOH and methanol was followed in an n.m.r. spectrometer tube by observing the decrease of the C-Me signals at τ 8.35 and 8.56 or the appearance of the *O*-acetyl peak at τ 7.91. A similar technique had been used in a study of the hydrolysis of acyclic orthoacetates[18]. The methanolysis of **2** was complete within 5 min. Chromatography of the resulting syrup on silica gel demonstrated an unexpected stereoselectivity in the opening of the orthoacetate ring, with isolation of 65% of **6** and 18% of **5**. The reaction proceeded similarly, but much less rapidly, when catalyzed with mercuric bromide in nitromethane, with isolation of 66% of **6** and 20% of **5**. Molar ratios of alcohol:orthoacetate of 1:1 and 5:1 effected little change in the stereoselectivity of the reaction; slightly more **5** was recovered with the higher proportion of alcohol, ostensibly due to an acid-catalyzed transacetylation after methanolysis.

Attempts to use anhydrous methanolic hydrogen chloride in dichloromethane for the methanolysis were unsuccessful. The changes in n.m.r. spectrum indicated an increase in the intensity of the *O*-acetyl peak corresponding to the concentration of hydrogen chloride, probably relating to the formation of the corresponding glycosyl chloride.

It was observed that storage of crystalline **2** in the laboratory atmosphere transformed the material into a syrup composed of **5** and **6**, as determined by t.l.c. Compound **2** was stable when stored over sodium hydroxide. This behavior caused speculation as to the ease of cleavage of the orthoacetate ring by acid in the absence of any alcohol. Lemieux[14] had made brief mention of such an experiment, but the result was inconclusive. A solution of **2** in dichloromethane, containing a catalytic amount of *p*-TsOH, was observed by n.m.r. spectroscopy to lose the C-Me signals at τ 8.35 and 8.56 completely in 20–22 min. Chromatography of the reaction product on silica gel gave 83% of **6** and 7% of **5**. The use of mercuric bromide in nitromethane as catalyst led to a slower reaction, but a similar distribution of products was noted.

The stereoselectivity and high yield of product observed in the ring-opening of **2** suggested that this rearrangement might be generally applicable for the synthesis of oligosaccharides, a possibility recognized long ago by Isbell[19]. Replacement of the methoxyl group in the orthoacetate by a suitably protected sugar would be required. As further models for this proposal, 3,4,6-tri-*O*-acetyl-β-D-mannose 1,2-(isopropyl orthoacetate) (**7**) and 1,2-(cyclohexyl orthoacetate) (**11**) were synthesized by the method of Mazurek and Perlin[3] and were obtained crystalline. The signal of the C-Me protons in **7** and **11** occurred at τ 8.22 and 8.26, respectively, in the region associated with the *endo* *C*-alkyl groups observed earlier[3]. Conversion of **7** and **11** into the corresponding crystalline benzyl ethers, **8** and **12**, was straightforward. The n.m.r. spectrum of **8** in the τ 8.5–9.0 region showed that each methyl group of the isopropyl group gave rise to a doublet having $J_{1,2} = 1.8$ Hz.

Compounds **8** and **12** both rearranged in dichloromethane containing *p*-TsOH, under the conditions used for **2**. In the case of **8**, the rearrangement required approximately 70 min, and gave isopropyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannoside (**9**) in 74% yield. In addition, 11% of isopropyl 3,4,6-tri-*O*-benzyl-α-D-mannoside was also obtained. Compound **12** required approximately 100 minutes to rearrange; 79% of cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannoside was isolated, together with 8% of cyclohexyl 3,4,6-tri-*O*-benzyl-α-D-mannoside.

It is interesting to note that the ring-opening of **1** proceeded at a much lower rate, and n.m.r. spectroscopy showed a greater diversity of products, indicating that the benzyl residues have a special role. The difference is being studied further.

This rearrangement appears to be general for the benzyl ethers of D-mannose 1,2-(alkyl orthoacetates). It provides a high degree of stereoselectivity, especially where the OR group of the orthoacetate is that of a secondary alcohol, in which case, no β-D anomer was detected in the products. The ease of rearrangement would demand stringent choice of conditions in using these orthoacetate derivatives as precursors for oligosaccharides by glycosidation reactions.

The mechanism of the ring-opening rearrangement appears to be essentially that proposed by Kochetkov and co-workers[17]. In the case of the methyl orthoacetate (**2**), which is principally in the *endo*-CMe form (see Fig. 1), it was observed that, although the total concentration of **2** quickly decreased, with over 90% disappearing in 15 min at 46.5°, there was an initial increase in the concentration of the *exo*-CMe

form (**2a**) to a maximum at about 6 min. There was, therefore, a preferential reaction of the *endo*-CMe form (**2b**) to give the methyl α-D-glycoside (**6**). It would seem that, by the mechanism shown, the rate of attack of methanol at the anomeric carbon atom is more rapid than at the carbon atom of the ortho ester group, but that, in the latter

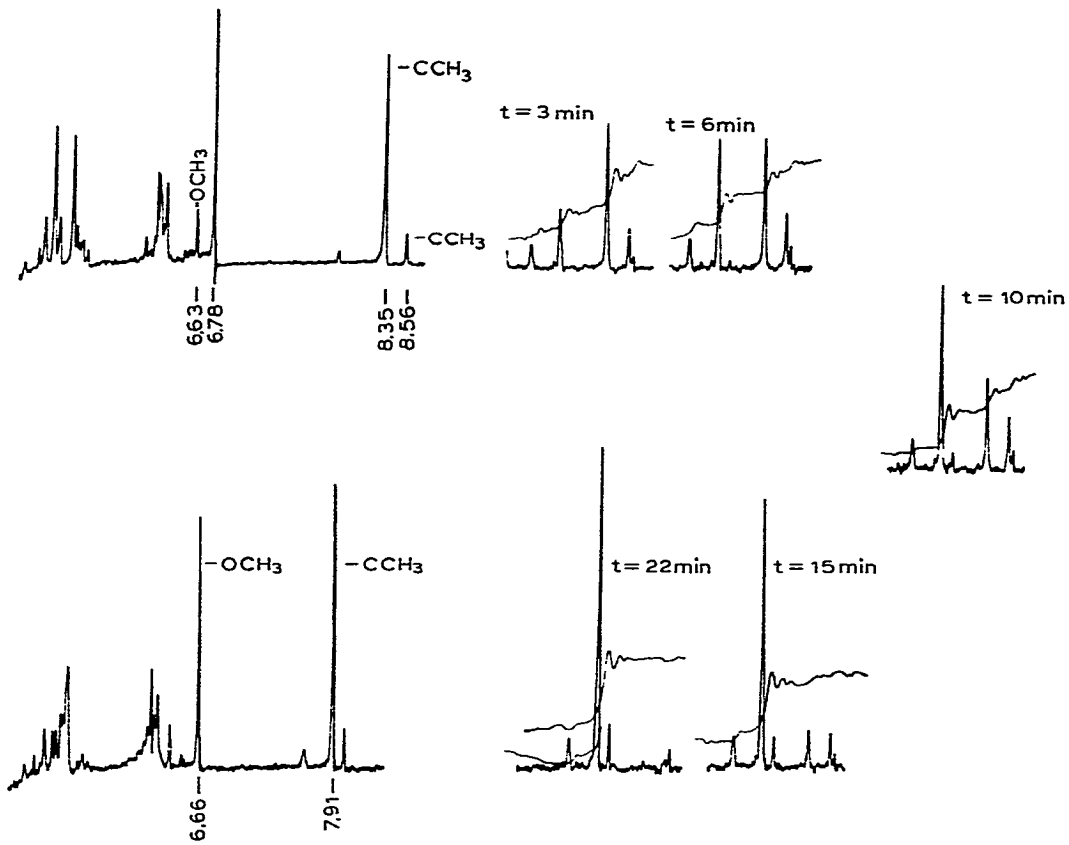


Fig. 1. Acid-catalyzed rearrangement (0.037M *p*-toluenesulfonic acid) of tri-*O*-benzyl-β-D-mannose 1,2-(methyl orthoacetate). The n.m.r. spectra (τ in p.p.m.) in dichloromethane at 60 MHz are shown, to be read clockwise from top to bottom.

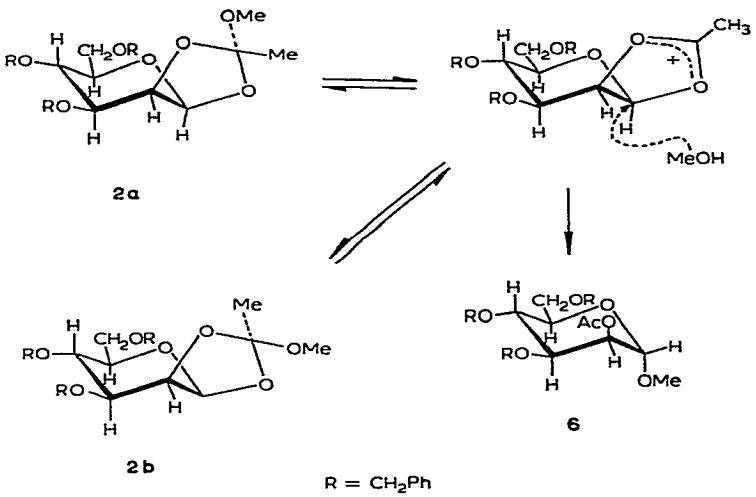
event, the favored approach of the entering methoxyl group is from the side of the ring-oxygen atom. Alternative mechanisms that would account for these results are being considered further.

EXPERIMENTAL

General. — Reagents were used without further purification, except for lutidine and benzyl chloride. Lutidine was distilled from barium oxide, and benzyl chloride was distilled to remove extraneous color. The powdered potassium hydroxide was

commercially available*. *p*-Toluenesulfonic acid monohydrate was dried overnight at 100° *in vacuo*.

Solutions were concentrated *in vacuo* with bath temperatures generally no higher than 50°. Melting points (Fisher-Johns apparatus) are uncorrected. All optical rotations were measured in dichloromethane.



The n.m.r. spectra were obtained with a Varian A-60 spectrometer. The solvent was chloroform and tetramethylsilane was used as an external standard. The proton resonance of chloroform, obscured the signal of the phenyl group. For rearrangement studies, the n.m.r. sample-tubes were cleaned with chromic acid, rinsed successively with water and dilute ammonium hydroxide, and dried at 120°.

T.l.c. was effected on Silica Gel G (E. Merck, Darmstadt, Germany) with 1:1 chloroform–ethyl acetate as eluent; zones were detected by spraying with sulfuric acid and heating the plates for 20 min at 110–120°. Dry-column chromatography[20] was used, with silica gel (0.05–0.20 mm) (E. Merck, Darmstadt, Germany) in a column loaded with no more than 1 g of compound per 50 g of adsorbent. The absorbent was poured into the column in a continuous stream and was then packed by light tapping of the column with a cork ring. Better separations were achieved if the sample to be chromatographed was evaporated onto a small amount of adsorbent and this was placed at the top of an already packed column. Elution was with dichloromethane, followed by dichloromethane–ethyl acetate (3:1 v/v), and finally with dichloromethane–ethyl acetate (1:1 v/v). Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

*Preparation of 3,4,6-tri-*O*-acetyl-β-*D*-mannose 1,2-(methyl orthoacetate)* (**1**). — The preparation was essentially that described by Mazurek and Perlin[3]. Syrupy tetra-*O*-acetyl-α-D-mannosyl bromide, prepared from 10 g of D-mannose, was dissolved in chloroform (88 ml). To this solution was added 2,6-lutidine (11.5 ml) in

*Hooker Chemical Company, Buffalo, New York.

absolute methanol (88 ml). A slight warming was observed during the addition. After the solution had been kept overnight at room temperature, chloroform (100 ml) was added, and the solution was washed with ice-cold, 3% aqueous sodium hydrogen carbonate. The aqueous solution was extracted with chloroform (50 ml) and this extract was combined with the chloroform extract. The combined chloroform extracts were washed once with ice–water and dried with anhydrous sodium sulfate. After addition of several grams of Darco G-60, the mixture was filtered, and the filtrate was evaporated *in vacuo*; yield after azeotropic distillation with toluene (20 ml), 16.3 g. The product was crystallized from methanol–water (some excess lutidine present is desirable) to yield 14 g of crystalline **1**, m.p. 109–110° (lit.[3] m.p. 111–113°).

Synthesis of 3,4,6-tri-O-benzyl-β-D-mannose 1,2-(methyl orthoacetate) (**2**). — A solution of **1** (25 g) in benzyl chloride (140 ml) and tetrahydrofuran (50 ml) in a 3-necked, round-bottomed flask (equipped with a stirrer and a reflux condenser) was heated under anhydrous conditions to reflux. External heat was removed and potassium hydroxide (50 g) was added in portions such that the exothermic reaction maintained the solution at reflux. Efficient stirring was mandatory, since the reaction mixture became quite viscous after the initial addition.

When all of the potassium hydroxide had been added, the reaction mixture was stirred for an additional 3–4 h at reflux, and then cooled to room temperature. Water (200 ml) was added, and the mixture was extracted with dichloromethane (150 ml). The extract was washed several times with concentrated, aqueous sodium hydrogen carbonate, dried with sodium sulfate, decolorized with Darco G-60, filtered, and concentrated *in vacuo* at $\leq 50°$. The residual syrup was then heated slowly to 100° at 0.1 torr to remove dibenzyl ether. To the residue was added ethyl ether (20 ml) followed by hexane (50 ml). Crystallization, induced by seeding, was continued overnight at 5°, and the crystals, separated by decantation of the mother liquors, were triturated with hexane and filtered off. The product was dried *in vacuo* over paraffin wax and sodium hydroxide; yield 29.3 g, m.p. 76–78°, $[\alpha]_D^{23.5}$ +12.1° (*c* 1.65).

Anal. Calc. for $C_{30}H_{34}O_7$: C, 71.13; H, 6.77. Found: C, 71.10; H, 6.81.

3,4,6-Tri-O-benzyl-D-mannose (**3**) *from 3,4,6-tri-O-benzyl-β-D-mannose 1,2-(methyl orthoacetate)*. — A solution of **2** (3.43 g) in glacial acetic acid (41 ml) and water (27 ml) was heated for 2 h on a steam bath, and then concentrated *in vacuo*. Residual acetic acid was removed by dissolving the syrup in dichloromethane and washing several times with saturated, aqueous sodium hydrogen carbonate. The dichloromethane solution was dried (sodium sulfate), filtered, and concentrated *in vacuo* to a syrup, which was deacetylated overnight with a catalytic amount of sodium methoxide in methanol. The solution was neutralized with glacial acetic acid, and the methanol was removed *in vacuo*. The product was kept for several h in a vacuum desiccator over sodium hydroxide, and it was then extracted with ethyl ether (25 ml). The ether extract was treated with Darco G-60, and filtered. Cyclohexane was added to the filtrate to incipient opalescence, and the solution was then refrigerated, to give a total of 2.9 g of **3**, m.p. 98–99°, $[\alpha]_D^{24}$ +22.7° (*c* 1.92).

Anal. Calc. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.91; H, 6.73.

Periodate oxidation of 3,4,6-tri-O-benzyl-D-mannose to form 2,3,5-tri-O-benzyl-D-arabinose. — 3,4,6-Tri-*O*-benzyl-D-mannose (**3**) (0.7 g) was added to a well-stirred mixture of methanol (70 ml) and 0.769M sodium periodate (17 ml) at room temperature. Sodium iodate began to crystallize from the solution almost immediately. Progress of the reaction could be followed by t.l.c. Starting material (R_F 0.19) was, for the most part, converted into a second compound (R_F 0.68), demonstrably different from authentic 2,3,5-tri-*O*-benzyl-D-arabinofuranose (R_F 0.56).

After 22 h, saturated aqueous sodium hydrogen carbonate (5 ml) was added to the mixture; this was filtered, and the precipitate was washed with additional methanol. The methanol was removed *in vacuo*, and the product was extracted with dichloromethane. The combined extracts were washed twice with equal volumes of water, dried (sodium sulfate), and concentrated to a syrup (R_F 0.68) which was probably 2,3,5-tri-*O*-benzyl-4-*O*-formyl-D-arabinose. Attempts to crystallize this material were unsuccessful. The syrup was deacylated, as usual, with methanolic sodium methoxide to give **4** (R_F 0.56) as a syrup, which was extracted with dichloromethane. The extract was washed with water, dried (sodium sulfate), and concentrated *in vacuo* to a syrup, which crystallized on being kept in a vacuum desiccator over sodium hydroxide. Recrystallization from ether–hexane yielded crystalline **4**, 299 mg, m.p. 72–85°, undepressed on admixture with an authentic sample. A further amount of **4** (167 mg) was obtained by recrystallizing the residual mother liquor from isopropyl ether–petroleum ether[8].

Anal. Calc. for $C_{26}H_{28}O_5$: C, 74.26; H, 6.71. Found: C, 74.55; H, 6.88.

Synthesis of 3,4,6-tri-O-acetyl-β-D-mannose 1,2-(isopropyl orthoacetate) (**7**). — To syrupy tetra-*O*-acetyl-α-D-mannopyranosyl bromide (from 25 g of D-mannose) in dichloromethane (175 ml) was added, with shaking, lutidine (40 ml), and 2-propanol (30 ml). After 2 days at room temperature, the reaction mixture was treated in the same manner as for **1**, with crystallization from methanol–water (buffered with small amounts of lutidine), yield 31.5 g, m.p. 104.5–106°, $[\alpha]_D^{21}$ −13° (*c* 2.38). One preparation, crystallized from ethyl ether–petroleum ether, exhibited a melting point from 87–89°, followed by solidification, and remelting at 104.5–106°.

Anal. Calc. for $C_{17}H_{26}H_{10}$: C, 52.30; H, 6.71. Found: C, 51.82; H, 6.71.

3,4,6-Tri-O-benzyl-β-D-mannose 1,2-(isopropyl orthoacetate) (**8**). — A solution of benzyl chloride (28 ml), benzene (25 ml), and **7** (5 g) was heated to reflux with vigorous stirring. Powdered potassium hydroxide (10 g) was added in portions, and the source of external heat was removed. The potassium hydroxide was added at such a rate that reflux was maintained. Additional benzene (25 ml) was added when the solution became extremely viscous. After the addition of base was complete, heating was resumed, and the reaction mixture was refluxed with continuous stirring for an additional 3 h. The mixture was then allowed to cool, and water (50 ml) was added to dissolve the solids. The aqueous layer was removed, and extracted with benzene (20 ml), and the extracts were combined, washed with saturated, aqueous sodium hydrogen carbonate (3 × 100 ml), and dried (sodium sulfate). Concentration of the solution was conducted as in the preparation of **2**. The resulting syrup was dissolved

in ethyl ether (25 ml), and the solution was treated with Darco G-60, the suspension filtered, and the residue washed with additional ether (25 ml). The product began to crystallize out at this point. The solution was, therefore, warmed, petroleum ether (50 ml) was added, and the mixture was kept overnight in the refrigerator; yield 3.5 g, m.p. 97–100°, $[\alpha]_D^{29}$ +13° (*c* 1.73).

Anal. Calc. for $C_{32}H_{38}O_7$: C, 71.89; H, 7.16. Found: C, 72.07 H, 7.29.

3,4,6-Tri-O-acetyl-β-D-mannose 1,2-(cyclohexyl orthoacetate) (**11**). — A solution of syrupy tetra-*O*-acetyl-α-D-mannopyranosyl bromide (from 25 g of D-mannose) in dichloromethane (175 ml) containing lutidine (40 ml) and cyclohexanol (30 ml) was agitated briefly, and kept at room temperature for 2 days. The isolation and crystallization procedure was that described for **7**; yield 23.3 g, m.p. 129–141°, $[\alpha]_D^{24}$ −11.4° (*c* 1.97).

Anal. Calc. for $C_{20}H_{30}O_{10}$: C, 55.80; H, 7.03. Found: C, 55.10; H, 7.00,

Microanalysis of material that had been dried *in vacuo* over phosphorus pentaoxide at 100° provided analytical figures quite different from those above (Found: C, 51.62; H, 6.39).

3,4,6-Tri-O-benzyl-β-D-mannose 1,2-(cyclohexyl orthoacetate) (**12**). — The benzylation of **11** was performed exactly as described for the synthesis of **8**; yield 1.83 g, m.p. 87.5–90°, $[\alpha]_D^{29}$ +13.6° (*c* 1.84).

Anal. Calc. for $C_{35}H_{42}O_7$: C, 73.14; H, 7.37. Found: C, 73.28; H, 7.38.

Methyl 3,4,6-tri-O-benzyl-α-D-mannoside (**5**). — (*a*) Freshly prepared **2** (19.65 g) was dissolved in absolute methanol (400 ml) with stirring, and the solution was heated almost to reflux. Acetyl chloride (12 ml) was added dropwise, with continued stirring, and the solution was refluxed under anhydrous conditions for 18 h; t.l.c. then indicated that over 90% of the material present had R_F 0.47, the next most-intense zone (probably methyl 3,4,6-tri-*O*-benzyl-β-D-mannoside) having R_F 0.42. The methanol was removed *in vacuo*, the resulting syrup was dissolved in chloroform, and the solution was washed several times with equal volumes of saturated aqueous sodium hydrogen carbonate, dried (sodium sulfate), and concentrated *in vacuo*. The residual syrup was kept for an additional 24 h in a vacuum desiccator over sodium hydroxide; yield 17.7 g. Some of this syrup was subjected to dry-column chromatography, and the resulting, pure (by t.l.c.) material had $[\alpha]_D^{21}$ +59.7° (*c* 1.85).

Anal. Calc. for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 71.90; H, 6.94.

(*b*) Acetyl chloride (0.6 ml) was added dropwise to a solution of **3** (1.0 g) in absolute methanol (50 ml), and the solution was refluxed for 19 h under anhydrous conditions; t.l.c. then indicated that virtually all of the starting material (R_F 0.2) had been converted, principally into **5** (R_F 0.46). Refluxing was continued for an additional 24 h, the methanol was removed *in vacuo*, and the product was treated as in (*a*). The yield of syrupy material was 0.97 g, $[\alpha]_D^{25}$ +53.5° (*c* 1.94), which amounts to a purity of over 90%, based on Hudson's rules of isorotation. This syrup was chromatographed on silica gel by the dry-column method, to yield **5**, identical (by t.l.c.) with that prepared by method (*a*). A small amount of transesterification evidently catalyzed by the

silica gel, occurred between **5** and the ethyl acetate used as the eluent, to give the corresponding 2-*O*-acetyl derivative (**6**).

Methyl 2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannoside (**6**). — Several grams of the crude methanolysis product containing **5** was acetylated with acetic anhydride–pyridine in the usual way. A portion of this product (0.7 g) was chromatographed on silica gel by the dry-column technique, to provide **6** (0.55 g) as a pure syrup (n.m.r. and t.l.c.); $[\alpha]_D^{27}$ +27.9° (*c* 2.24).

Anal. Calc. for $C_{30}H_{34}O_7$: C, 71.13; H, 6.77. Found: C, 70.57; H, 6.97.

Methyl 3,4,6-tri-O-acetyl-2-O-methyl-α-D-mannoside (**14**). — Syrupy **5** (approx. 10.5 g, from the methanolysis with hydrogen chloride) was dissolved in tetrahydrofuran, and powdered potassium hydroxide (7.4 g) was added, with stirring, to this solution. Stirring was continued, and methyl sulfate (4.1 ml) was added dropwise. The slurry initially became warm, and then it cooled. Stirring was continued at room temperature for another 18 h, the mixture being protected from atmospheric moisture. Water (60 ml) was added to dissolve the solids, and the resulting mixture was heated at 60° with stirring. The tetrahydrofuran was evaporated off in a stream of nitrogen, and heating was continued for 30 min after completion of the evaporation. The mixture was cooled, and adjusted to pH 8 with sulfuric acid. The product was extracted with chloroform, and the extract was washed with saturated aqueous sodium hydrogen carbonate, dried (sodium sulfate), decolorized, and concentrated *in vacuo* to a syrup (10.4 g). T.l.c. showed one major zone, at R_F 0.56. A small amount of this methylated material was chromatographed on silica gel (dry column), and the resulting syrup had $[\alpha]_D^{25}$ +50.3° (*c* 2.11).

The crude syrupy material (**13**, 10.3 g) was dissolved in absolute methanol (100 ml), and the solution was refluxed with several g of decolorizing carbon for 20 min. The suspension was filtered, and the filtrate was shaken overnight in an atmosphere of hydrogen (Parr apparatus) with a catalyst (1 g) of 10% palladium chloride on carbon. The catalyst was filtered off, and the methanol was removed *in vacuo*. The syrup was acetylated overnight with pyridine (10 ml) and acetic anhydride (20 ml).

Excess of acetic anhydride was destroyed by pouring the mixture over cracked ice, and, after 30 min, the product was extracted from the mixture with chloroform. The extract was washed with saturated, aqueous hydrogen carbonate, dried (sodium sulfate), filtered, and concentrated *in vacuo* to yield a syrup (6.53 g). Some difficulty was encountered in crystallizing this material; seed crystals were obtained by dry-column chromatography of a small amount of the syrup. Once nucleated, the substance crystallized readily from ethyl ether–petroleum ether. The yield from 5.5 g of syrupy material was 3.36 g, m.p. 59–61°, $[\alpha]_D^{27}$ +53° (*c* 2.09). The n.m.r. spectrum was in accord with the values expected for **14**.

Anal. Calc. for $C_{14}H_{22}O_9$: C, 50.27; H, 6.63. Found: C, 50.24; H, 6.51.

Methanolysis of **2**. — A solution of **2** (0.202 g, 0.4 mmole), anhydrous methanol (0.013 g, 0.4 mmole), and *p*-toluenesulfonic acid (0.014 g, 0.008 mmole) in dichloromethane (1.2 ml), contained in an n.m.r. spectrometer tube, was observed at 46.5°. A scan made 5 minutes after addition of the *p*-toluenesulfonic acid indicated that the

characteristic, orthoacetate C-Me peaks at τ 8.35 and 8.56 had disappeared, and, in their place, an *O*-acetyl peak had appeared at τ 7.91. A small peak at τ 8.03 also appeared, and was assigned to a small amount of acetic acid that had evidently been formed by hydrolysis during the reaction. No further change was observed after an additional hour.

The resulting syrup was placed on a column (1.2 × 42 cm) of dry silica gel, the column was developed as described earlier, and 2-ml fractions were collected. Three distinct zones were found. The most abundant (132 mg, 65%) and fastest-moving material was determined to be **6**, on the basis of n.m.r. and t.l.c. data. Deacetylation with methanol and sodium methoxide yielded material having an R_F value identical with that of **5**. The next largest amount (36 mg, 18%) was **5**, and the slowest-moving material (11 mg, 5%) had a t.l.c. mobility slightly less than that of **5**. On this basis, this compound was tentatively assumed to be methyl 3,4,6-tri-*O*-benzyl-β-D-mannoside.

A solution of 0.202 g (0.4 mmole) of **2**, 0.013 g (0.4 mmole) of anhydrous methanol, and 0.0043 g (0.012 mmole) of mercuric bromide in nitromethane (1 ml) in an n.m.r. spectrometer tube was observed as before. The n.m.r. spectrum was much more complicated than that observed in dichloromethane. It was observed that, after the sample had been kept overnight at 40°, there was no further reaction. Removal of the nitromethane *in vacuo*, dissolution of the sample in dichloromethane, and observation of the n.m.r. spectrum, demonstrated that the product had a composition quite similar to that of the crude mixture obtained in (*a*) above. Silica-column chromatography yielded 134 mg (66%) of **6**, and 40 mg (20%) of **5**.

Experiments with an orthoacetate: alcohol ratio of 1:5 gave comparable results.

Acid-catalyzed rearrangement of **2**. — (*a*) A solution of **2** (202 mg, 0.4 mmole) and 7 mg (0.04 mmole) of *p*-toluenesulfonic acid (7 mg, 0.04 mmole) in dichloromethane (1 ml), contained in an n.m.r. spectrometer tube, was observed at 46.5° at intervals, as described for the preceding experiment. Disappearance of the orthoacetate C-Me signals at τ 8.35 and 8.56, and the concomitant appearrance of the *O*-acetyl peak at τ 7.91, were used as guides to indicate the progress of the reaction. Less than 10% of the orthoacetate remained after 15 min. During the rearrangement, the n.m.r. peak at τ 8.56 (representing the *exo*-orthoacetate C-Me) appeared to increase with respect to the peak τ 8.35 representing the *endo*-orthoacetate C-Me group. After 6 min, the *exo* C-Me peak still represented only 12–13% of the total acetyl orthoacetate present.

The reaction mixture was chromatographed on silica gel, and three components were isolated. The first compound eluted was **6**, $[\alpha]_D^{21.5}$ +28° (*c* 3.36); a recovery of 168 mg (83%) was obtained. The second component (14 mg, 7%) was assumed to be **5** on the basis of its t.l.c. mobility. A small amount (2 mg) of a compound (R_F 0.42), presumably methyl 3,4,6-tri-*O*-benzyl-β-D-mannoside, was eluted as the third component.

(*b*) A solution of **2** (202 mg, 0.4 mmole) and mercuric bromide (4.3 mg, 0.012 mmole) in nitromethane (1 ml) was observed at 46.5° in a spectrometer tube. The rearrangement was much less rapid than in (*a*). After 48 h, there was no further

change in the spectrum observed. The nitromethane was removed *in vacuo*, and the sample was kept overnight in a vacuum desiccator over sodium hydroxide. The n.m.r. spectrum of this mixture, in dichloromethane, demonstrated that the orthoacetate C-Me peaks had been converted into an *O*-acetyl peak at τ 7.91.

Column chromatography of this mixture yielded 146 mg (72%) of **6**. Compound **5** (31 mg, 15%) was also recovered.

Rearrangement of 3,4,6-tri-O-benzyl-β-D-mannose 1,2-(isopropyl orthoacetate) (**8**).—A solution of **8** (214 mg, 0.4 mmole) in 0.037M *p*-toluenesulfonic acid in dichloromethane (1 ml), contained in a spectrometer tube at 46.5°, was monitored by observing the disappearance of the orthoacetate C-Me peak at τ 8.32 and the appearance of the *O*-acetyl peak at τ 7.91. The reaction was complete in 65–70 min.

Column chromatography demonstrated the presence of two components, obtained as syrups. The faster-moving product (159 mg, 74%) was isopropyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannoside (**9**), $[\alpha]_D^{26}$ +24.5° (*c* 1.59). A 3-proton singlet at τ 7.96 (in $CHCl_3$) was still observed in the n.m.r. spectrum of this compound after silica-gel chromatography.

Anal. Calc. for $C_{32}H_{38}O_7$: C, 71.89; H, 7.16. Found: C, 72.16; H, 7.45.

The second, slower-moving product (24 mg, 11%) was isopropyl 3,4,6-tri-*O*-benzyl-α-D-mannoside (**10**). Deacetylation of **9** with a catalytic amount of sodium methoxide in methanol yielded **10**, $[\alpha]_D^{22}$ +49.9° (*c* 2.02).

Anal. Calc. for $C_{30}H_{26}O_6$: C, 73.14; H, 7.37. Found: C, 72.42; H, 7.51.

Rearrangement of 3,4,6-tri-O-benzyl-β-D-mannose 1,2-(cyclohexyl orthoacetate) (**12**). — A solution of **12** (230 mg, 0.4 mmole) in 0.037M *p*-toluenesulfonic acid in dichloromethane (1 ml) was treated as described for **8**. The reaction was complete in 95–100 min, as judged by change in the *O*-acetyl peak at τ 7.91.

T.l.c. demonstrated the presence of two compounds, R_F 0.72 and 0.62; these materials were separated by column chromatography. A syrup (132 mg, 79%) appeared as the faster-moving zone, $[\alpha]_D^{20}$ +28.2° (*c* 1.77). This compound was cyclohexyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannoside (**15**).

Anal. Calc. for $C_{35}H_{42}O_7$: C, 73.14; H, 7.37. Found: C, 73.33; H, 7.28.

The second syrupy material (19 mg, 8%) was identified as cyclohexyl 3,4,6-tri-*O*-benzyl-α-D-mannoside (**16**), since this compound could also be obtained by deacetylation of **15** with methanolic sodium methoxide; $[\alpha]_D^{23}$ +52.8° (*c* 1.83).

Anal. Calc. for $C_{33}H_{40}O_6$: C, 74.40; H, 7.51. Found: C, 74.53; H, 7.68.

REFERENCES

1 R. MONTGOMERY, Y.-C. WU, and Y. C. LEE, *Biochemistry*, 4 (1965) 578.
2 R. U. LEMIEUX AND A. R. MORGAN, *Can. J. Chem.*, 43 (1965) 2199.
3 M. MAZUREK AND A. S. PERLIN, *Can. J. Chem.*, 43 (1965) 1918.
4 A. S. PERLIN, *Can. J. Chem.*, 41 (1963) 555.
5 R. U. LEMIEUX AND J. D. T. CIPERA, *Can. J. Chem.*, 34 (1956) 906.
6 H. G. BOTT, W. N. HAWORTH, AND E. L. HIRST, *J. Chem. Soc.*, (1930) 1395.
7 A. S. PERLIN, *Can. J. Chem.*, 41 (1963) 399.
8 R. BARKER AND H. G. FLETCHER, JR., *J. Org. Chem.*, 26 (1961) 4605.

9 E. J. C. CURTIS AND J. K. N. JONES, *Can. J. Chem.*, 38 (1960) 890.
10 J. O. DEFERRARI, E. G. GROS, AND I. O. MASTRONARDI, *Carbohyd. Res.*, 4 (1967) 432.
11 S. HAKAMORI, *J. Biochem.* (Tokyo), 55 (1964) 205.
12 E. PACSU, *Advan. Carbohydrate Chem.*, 1 (1945) 77.
13 B. HELFERICH AND K. WEIS, *Chem. Ber.*, 89 (1956) 314.
14 R. U. LEMIEUX, *Chem. Can.*, 16 (10) (1964) 14.
15 N. K. KOCHETKOV, A. J. KHORLIN, AND A. F. BOCHKOV, *Tetrahedron Lett.*, (1964) 289.
16 N. K. KOCHETKOV, A. J. KHORLIN, AND A. F. BOCHKOV, *Dokl. Akad. Nauk SSSR*, 162 (1965) 104; *Chem. Abstr.*, 63 (1965) 8467.
17 N. K. KOCHETKOV, A. J. KHORLIN, AND A. F. BOCHKOV, *Tetrahedron*, 23 (1967) 693.
18 A. M. WENTHES AND E. H. CORDES, *J. Am. Chem. Soc.*, 87 (1965) 3173.
19 H. S. ISBELL, *Bur. Std. J. Res.*, 7 (1931) 1115, footnote 15.
20 B. LOEV AND K. M. SNADER, *Chem. Ind.* (London), (1965) 15.