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SYNTHESES OF METHYL ETHERS OF METHYL α-D-MANNOPYRANOSIDE, AND HYDROGEN BONDING IN DIASTEREOISOMERS OF METHYL 4-*O*-(1-ETHOXYETHYL)-α-D-MANNOPYRANOSIDE*

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ABSTRACT

The synthesis of the 4-methyl, the 2,4-dimethyl, and the 2,3,6-trimethyl ethers of methyl α-D-mannopyranoside has been accomplished by the use of selective, benzoyl protecting groups, the 1-ethoxyethyl protecting group, and methylation with diazomethane. Considerable differences were noted in the i.r.- and n.m.r.-spectroscopic and t.l.c. properties of the diastereoisomers of methyl 4-*O*-[1-ethoxyethyl]-α-D-mannopyranoside. A structure, analogous to that of *trans*-decalin, maintained by intramolecular hydrogen-bonding is proposed for these compounds. The differences in physical properties of the two diastereoisomers are interpreted on the basis that the (*R*) isomer has an axially attached methyl group, and, therefore, the ring involved cannot be so stable as that of the (*S*) isomer.

INTRODUCTION

The synthesis of specific methyl ethers of D-mannose has been hampered by the lack of appropriate, selective, protecting groups. However, methyl 3,6-di-*O*-benzoyl-α-D-mannopyranoside (**1**) and methyl 2,3,6-tri-*O*-benzoyl-α-D-mannopyranoside (**4**) have been recommended as starting compounds for synthesis of methyl ethers[1]. Acetyl migration does not occur on methylation of acetates with diazomethane–boron trifluoride[2], and, in 1969, this methylation procedure was used without causing migration of benzoyl protecting groups[3]. Previous use of a selectively benzoylated D-mannopyranoside (the 2,4-diester) involved a series of blocking and deblocking steps to avoid acyl migration[4].

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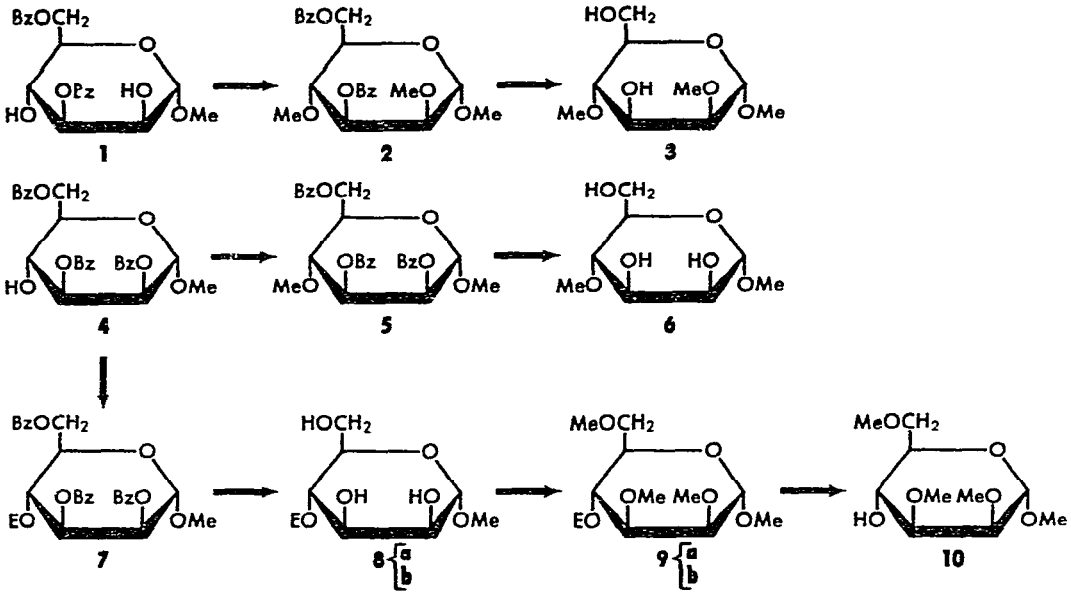

Me = —CH_3
Bz = C_6H_5CO—
E = CH_3CH_2—O—$\overset{*}{C}H$(—CH_3)
* = asymmetric

RESULTS AND DISCUSSION

In the work presented here, direct methylation of **1** with diazomethane–boron trifluoride quantitatively yielded **2**, which, on debenzoylation, gave the 2,4-dimethyl ether. A similar, high-yielding, two-step synthesis converted the 2,3,6-tribenzoate **4** into the 4-methyl ether **6**. When conditions of incomplete methylation were applied to **1**, a second component, slower-moving in t.l.c., appeared that gave an n.m.r. spectrum equivalent to that for a monomethylated derivative. However, the two absorbances for methoxyl group were present at their expected positions, each showing half the integral for three protons; hence, under these conditions, methylation at the 2- and 4-hydroxyl groups is nonspecific.

The 2,3,6-tribenzoate **4** was converted into its 4-(1-ethoxyethyl) ether (**7**), and this compound was debenzoylated to yield **8**. The resulting 4-(1-ethoxyethyl) ether was methylated to give **9**, which, on hydrolysis with mild acid, afforded the 2,3,6-trimethyl ether **10**.

Each of these methyl ethers (**3**, **6**, and **10**) has already been reported[4–6]. However, the synthetic routes described here give higher yields and are shorter, especially for the 2,4-dimethyl ether.

Although unresolved mixtures of compounds **7**, **8**, and **9** were used in the synthesis of **10**, compound **8** gave two narrowly separated components in t.l.c.

This behavior differs from that of **7** and **9**, whose respective isomers could not be separated under similar conditions. These isomers arise from the asymmetric carbon atom formed by ethyl vinyl ether as it reacts to form the 1-ethoxyethyl substituent. A small sample of **8** was resolved into its diastereoisomers (**8a** and **8b**), and each isomer was separately methylated, to yield **9a** and **9b**. A comparison of the integrals of the acetal protons in the n.m.r. spectrum of the isomeric mixture in chloroform-*d* indicated that **8a** and **8b** are formed in about equal amounts. There were much larger variations in the chemical shifts for **8a** and **8b** than for the respective isomers of **7** or **9**. In fact, **8a**, **9a**, and **9b** have almost equal chemical shifts for comparable protons, as contrasted with **8b**; owing to paramagnetic effects, direct comparison with the isomers of **7** is difficult. The greatest variations in chemical shift for **8b** come from the protons of carbon atoms adjacent to the ethoxyl oxygen atom, with lesser effects on protons that are two carbon atoms away. These shifts are all upfield. Contrasted to a single, hydroxyl resonance of three protons for **8a**, compound **8b** shows two hydroxyl signals, one for a single proton at lower field and one for two protons at higher field. All hydroxyl protons in **8a** and **8b** resonate farther downfield than is usual for protons of free hydroxyl groups[7].

Further studies of the hydroxyl groups of **8a** and **8b** were made by i.r. spectroscopy of the compounds dissolved in carbon tetrachloride and chloroform. The data obtained for each solvent were essentially the same, in agreement with an earlier i.r. comparison of hydroxy episulfides in these solvents[8]. At low concentrations, two hydroxyl bands appear (band I_{CCl_4} at 3590 cm^{-1} and band II_{CCl_4} at 3500 cm^{-1}) whose ratio of band intensities $K(K = A_{II}^a/A_I^a)$ approach 2 at infinite dilution (see Table I for carbon tetrachloride and Fig. 1 for chloroform). At increasing concentrations, K_{8b} remains essentially constant, whereas K_{8a} becomes so large ($K > 10$) at

TABLE I

RELATIVE INTENSITIES OF THE I.R. HYDROXYL BANDS, AND THEIR DEPENDENCE ON CONCENTRATION IN CARBON TETRACHLORIDE

Concentration (mM)	A[a] *band I* (*3590 cm*$^{-1}$)	A[a] *band II* (*3500 cm*$^{-1}$)	K (A_{II}^a/A_I^a)
Compound **8a**			
48.6	80.9	222	2.75
34.9	58.9	137	2.33
17.5	32.2	73.8	2.28
8.9	18.4	39.8	2.16
4.4	11.6	23.9	2.04
Compound **8b**			
45.7	62.4	129.5	2.06
25.1	36.3	72.1	1.98
12.5	19.2	41.8	2.14
6.3	12.0	22.2	1.85
3.1	6.4	14.4	2.14

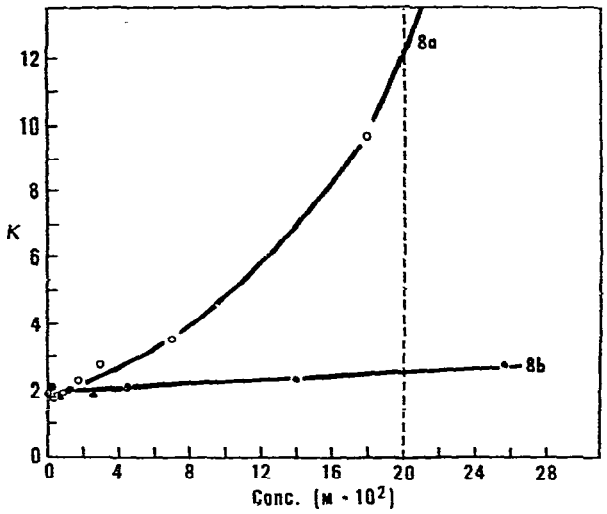

Fig. 1. Change in concentration *vs.* *K* (the ratio of the intensity of the i.r. band at 3500 cm^{-1} to that at 3590 cm^{-1}) for the two isomers of methyl 4-*O*-(1-ethoxyethyl)-α-D-mannopyranoside (**8**) in chloroform.

~0.2M that the ratio of the areas of the bands can no longer be accurately estimated. The n.m.r. spectra of both isomers were recorded for ~0.2M solutions.

In interpreting the experimental data, hydrogen bonding must be considered. The methyl ethers (**9a** and **9b**) of **8a** and **8b** show little difference in R_F values (in t.l.c.) and in n.m.r. spectra; also, the final product from both is **10**, indicating that the fundamental difference between **8a** and **8b** lies in the position of the ethoxyethyl group. The separation of the n.m.r. hydroxyl absorptions for **8b**, contrasted with that for **8a**, and their radically different curves for *K vs.* concentration both indicate hydrogen-bonding differences. In fact, the i.r. spectra suggest that both intra- and inter-molecular bonding occur. For O–H stretching in carbon tetrachloride solution, the absorption wavenumbers expected are: free hydroxyl group (3639–3605 cm^{-1}), intramolecular-bonded hydroxyl group (3602–3540 cm^{-1}), and intermolecular-bonded hydroxyl group (3500 cm^{-1} and lower)[9]. The two isomers differ only by the asymmetric carbon atom in the 1-ethoxyethyl group, and this difference must, in some way, affect hydrogen bonding. Lastly, although the mobility in t.l.c. depends on a number of factors, for sugars it is greatly dependent on the number of hydroxyl groups present[10]. The relatively large difference in R_F of these two isomers (as contrasted with their precursors and successors) suggests a different number of effective or "functional" hydroxyl groups for the two compounds.

Structures in agreement with the experimental data are shown in Fig. 2. The compounds assume a form analogous to that of *trans*-decalin, being held by an O–H···O bond system that replaces a C–C bond in decalin. This ring system appears to be much more plausible than a similar one, formed through the 6-hydroxyl group, that would require a larger, less-favored ring. An O···H distance of 1.85 Å was

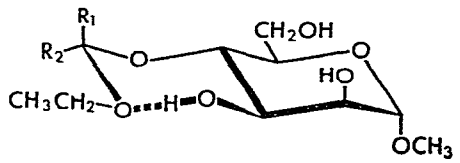

Fig. 2. Structure I: $R_1 = CH_3$; $R_2 = H$. Methyl 4-*O*-[R(−)-1-ethoxyethyl]-α-D-mannopyranoside, the structure proposed for **8a**. Structure II: $R_1 = H$; $R_2 = CH_3$. Methyl 4-*O*-[S(+)-1-ethoxyethyl]-α-D-mannopyranoside, the structure proposed for **8b**.

chosen from the literature[11] as an average value; this value is in agreement with one for similar, intramolecular bond-lengths determined by neutron-diffraction studies[12]. When the C–C bond (1.54 Å) was replaced by an O–H bond (0.96 Å) and the O···H bond (1.85 Å) in Dreiding models[13], the conformation of the pyranoside was not altered. Due to the rigidity of the *C1*(D) conformation, the substituent acetal carbon atom would be expected to maintain a chair conformation, even when the O–H···O length is allowed considerable variation. Structure II, then, would be expected to be stable, and structure I to be much less so, because attachment of a methyl group by an axial bond is sterically unfavored[14].

The structures in Fig. 2 offer an explanation of the data. In dilute solutions, both of the intramolecular, hydrogen-bonded structures (I and II) can exist in small aggregates (possibly dimers), explaining the similar spectra in dilute solutions. Those hydroxyl groups not participating in intramolecular bonding would be intermolecularly bonded to other hydrogen atoms in the small aggregate. This aggregation of alcohols in dilute solutions has been widely observed[15]. At higher concentrations, the unpaired electrons of the carbohydrate oxygen atoms enter into competition with the intramolecular hydrogen-bonding of the 1-ethoxyethyl groups. The tendency of these ring-oxygen atoms to form hydrogen bonds has been observed[12]. The freed, donor 1-ethoxyethyl groups no longer are bonded to a hydrogen atom, and this change in electron distribution is reflected in the chemical shifts of protons adjacent to the bonding site. This tendency toward rupture of the intramolecular bonds is much greater for structure I, with its ring destabilized by an axially attached methyl group; therefore, structure I represents compound **8a**, because its intramolecular hydrogen-bonding disappears rapidly with increasing concentration, as shown by the (i.r.) *K vs.* concentration curve. According to this argument, **8a** has structure I, which is the (*R*) isomer[16]; and **8b** is the (*S*) isomer. This structure is also in agreement with the R_F values observed in t.l.c. At the higher concentrations used for t.l.c., **8b** would still be in the *trans*-decalin shape, have one fewer effective hydroxyl groups than **8a**, and, therefore, have a larger R_F value than **8a**.

Although this explanation is in agreement with the data, it is surprising that the relative C–H shifts for **8b** (which differ significantly from those for **8a**, **9a**, and **9b**) are upfield. The nature of the electron density–charge distribution during hydrogen-bonding is still unclear[17–19], but certain relevant observations have been made. During hydrogen-bonding, protons attached to the species providing the hydrogen

atom have been observed to show upfield shifts of their resonances[20]. In like manner, resonances of protons attached to carbon atoms adjacent to oxygen atoms (as an alcohol or ether) reportedly shift downfield ($\tau \sim -0.4$), because of involvement of this oxygen atom in a hydrogen bond[21]; however, these values were obtained by taking the difference of the chemical shifts for a given compound measured first in carbon tetrachloride and then in trifluoroacetic acid. That solvent effects, other than hydrogen-bonding, were involved was indicated in a study[22] that showed that the change in chemical shifts was much less ($\tau \sim -0.03$) when chloroform-*d* and perdeuterioacetic acid were compared as solvents for similar compounds. What the effect would be when all other solvent-effects are eliminated appears, as yet, to be unknown. However, a structure in which a hydrogen atom from the 1-ethoxyethyl group is donated to a ring-oxygen atom appears impossible. This bound hydrogen atom would display a chemical shift displaced downfield from the normal position, a situation that is not observed.

The i.r. data given in Table I and Fig. 2 closely parallel those in a study on the concentration-dependent relationship of intra- to inter-molecular hydrogen-bonding for 1-methoxy-2-propanol[23]. Both the band wavelengths and the disappearance of a band on changing the concentration were identical. Hirano and Tsuruta[23] also showed changes in the n.m.r. spectra on dilution; such measurements were not made in the present work, owing to the complexity of the spectra of the sugars and to the relatively low concentration of sugar necessary for observation of such effects.

Notwithstanding the "anomalous" direction of some chemical shifts, structures I and II appear to be consistent with the data, and are proposed as corresponding to compounds **8a** and **8b**, respectively.

EXPERIMENTAL

General. — N.m.r. spectra in chloroform-*d* were obtained at 100 MHz with a Varian HA-100 spectrometer, with tetramethylsilane ($\tau = 10.0$) as the internal standard. Only pertinent parts of the n.m.r. spectra are presented, the remainder being in accord with the presumed structures. The i.r. spectra were recorded with a Perkin–Elmer Model 337 grating spectrophometer. A 1.0-mm, sodium chloride cell was used for solutions having concentrations less than 0.05M, and a 0.1-mm sodium chloride cell for higher concentrations. Matching reference-cells were used. Frequency measurements are considered to be correct within ± 5 cm^{-1}. Spectrograde chloroform was washed by shaking with water, dried with sodium sulfate, and passed through a column of silicic acid. Spectrograde carbon tetrachloride was untreated. Optical rotations were determined with a Bendix NPL polarimeter. All measurements (n.m.r. and i.r. spectra, and optical rotation) were made at $\sim 25°$. The intensities of the i.r. bands were estimated from the apparent band-areas by the method of Krueger and Mettee[24].

Solutions were evaporated below 60° under diminished pressure. Precoated plates of Silica Gel F-254 (E. Merck, Darmstadt) were used for t.l.c. Sulfuric acid

(10%) in methanol was the spray reagent. The *p*-dioxane was boiled under reflux with sodium hydride for 2 h, and then distilled. The solutions of diazomethane were prepared as described by Dick[25]; it should be emphasized that at no time were these solutions distilled. The acetal resonance reported in the n.m.r. data is, for each compound, that of the 4-(1-ethoxyethyl) group, the anomeric proton always being a doublet at τ 5.2.

The composition of all mixed solvents is expressed in terms of volume/volume.

*Methyl 3,6-di-*O*-benzoyl-2,4-di-*O*-methyl-α-*D*-mannopyranoside* (**2**). — Methyl 3,6-di-O-benzoyl-α-D-mannopyranoside[1] (**1**, 1.00 g) in dichloromethane (100 ml) was cooled in a bath of acetone–Dry Ice, with stirring. A solution of boron trifluoride etherate [1.5 ml, 4% (v/v) in dichloromethane] was added, and then diazomethane–dichloromethane solution (130 ml) was quickly added. The mixture was stirred for 2 min, pyridine was added, and the mixture was successively washed with ice-cold M hydrochloric acid (2 × 100 ml), 10% potassium hydrogen carbonate (30 ml), and water (30 ml), dried (sodium carbonate), and evaporated to dryness, to yield 0.98 g (97% yield); R_F 0.6 (1:49 methanol–chloroform); $[\alpha]_D$ +24° (*c* 1.0, chloroform); n.m.r. data: τ 1.9 (m, 4 H, *o*-Ar-*H*), 3.1 (m, 6 H, *m*- and *p*-Ar-*H*), 5.21 (d, 1 H, *J* 4 Hz), 5.44 (m, 1 H, H-6 and H-3), 6.51 (s, 3 H), and 6.56 (s, 6 H, CH_3O).

Anal. Calc. for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09. Found: C, 64.11; H, 5.97.

*Methyl 2,4-di-*O*-methyl-α-*D*-mannopyranoside* (**3**). — A solution of **2** (0.80 g) in boiling methanol (30 ml) was treated with barium oxide (100 mg) under reflux for 1 h, cooled, filtered, and evaporated to a syrup. Methanol (5 × 30 ml) was successively added to and evaporated from the syrup to yield 0.35 g (84% yield); R_F 0.2 (1:10 methanol–chloroform), $[\alpha]_D$ +51° (*c* 1.1, water); n.m.r. data: τ 6.45 (s, 3 H), 6.54 (s, 3 H), and 6.67 (s, 3 H, CH_3O).

*Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-methyl-α-*D*-mannopyranoside* (**5**). — By the same procedure as for the conversion of **1** into **2**, methyl 2,3,6-tri-*O*-benzoyl-α-D-mannopyranoside[1] (**4**) (1.10 g) reacted to yield, on crystallization from methanol, 1.05 g (90% yield), R_F 0.7 (1:49 methanol–chloroform), m.p. 174–175°, $[\alpha]_D$ −43° (*c* 1.0, water); n.m.r. data: τ 2.0 (m, 6 H, *o*-Ar-*H*), 2.64 (m, 9 H, *m*- and *p*-Ar-*H*), 4.32 (m, 2 H), 5.11 (d, 1 H, *J* 2.0 Hz), 5.32 (d, 1 H, *J* 3.0 Hz, H-6, H-3, and H-2), 6.50 (s, 3 H), and 6.52 (s, 3 H, CH_3O).

Anal. Calc. for $C_{29}H_{28}O_9$: C, 66.91; H, 5.42. Found: C, 66.77; H, 5.51.

*Methyl 4-*O*-methyl-α-*D*-mannopyranoside* (**6**). — By the same procedure as for the conversion of **2** into **3**, compound **5** (0.90 g) reacted to yield 0.32 g (87% yield), $[\alpha]_D$ +64° (*c* 0.8, water) {lit.[4] $[\alpha]_D$ +60.5° (*c* 1.8, water)}, R_F 0.3 (1:5 methanol–chloroform); n.m.r. data (deuterium oxide); τ 6.18 (s, 3 H) and 6.33 (s, 3 H, CH_3O).

*Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(1-ethoxyethyl)-α-*D*-mannopyranoside* (**7**). — Ethyl vinyl ether (5 ml) and then dichloromethane (1.5 ml) presaturated with hydrogen chloride were added to a solution of the tribenzoate[1] **4** (3.7 g) in dichloromethane (50 ml). After 20 h at room temperature, the solution was made neutral with solid potassium carbonate, washed with 5% potassium hydrogen carbonate (aq. solution), dried (sodium sulfate), and evaporated to a syrup, 3.84 g (92% yield), R_F 0.7 compared

to R_F 0.5 for **4** (3:97 methanol–chloroform). On standing, the neat syrup crystallized, giving needles, m.p. 135–136°; n.m.r. data: τ 1.98 (q, 6 H, J 9 Hz, *o*-Ar-*H*), 2.61 (m, 9 H, *m*- and *p*-Ar-*H*), 4.32 (m, 1 H, the acetal proton), and 8.9 (m, 6 H, CH_3CHO and CH_3CH_2O).

Anal. Calc. for $C_{32}H_{34}O_{10}$: C, 66.42; H, 5.92. Found: C, 66.29; H, 5.96.

Methyl 4-O-(1-ethoxyethyl)-α-D-mannopyranoside (**8**). — A solution of **7** (4.60 g) in boiling methanol (100 ml) was treated with barium oxide (200 mg) under reflux for 1 h; the mixture was then filtered, and the filtrate was evaporated to a syrup. Methanol (5 × 30 ml) was successively added to and evaporated from the syrup, to give 2.10 g (99% yield), R_F 0.35, 0.40 (1:10 methanol–chloroform).

Part of **8** was separated by preparative chromatography on a 2-mm, preparative plate of silica gel (E. Merck, Darmstadt) with 7:93 methanol–chloroform (two developments, visibilized with iodine vapor) to give fractions *a* and *b*, plus a central, overlapping fraction of unresolved material.

Compound **8a**. — This weighed 40 mg and had R_F 0.35 (1:10 methanol–chloroform), $[\alpha]_D$ +59° (*c* 2.5, chloroform); n.m.r. data: τ 5.04 (q, 1 H, J 5.0 Hz, acetal proton), 5.76 (s, 3 H, O*H*), 6.17 (d, 2 H, J 7.0 Hz, CH_3CH_2O), 8.65 (d, 3 H, J 5.0 Hz, CH_3CHO), and 8.79 (t, 3 H, J 7.0 Hz, CH_3CH_2O).

Anal. Calc. for $C_{11}H_{22}O_7$: C, 49.61; H, 8.33. Found: C, 49.46; H, 8.44.

Compound **8b**. — This weighed 125 mg and had R_F 0.40 (1:10 methanol–chloroform), $[\alpha]_D$ +73° (*c* 2.5, chloroform); n.m.r. data: τ 5.34 (q, 1 H, J 5.0 Hz, acetal proton), 5.3 (1 H), 7.05 (s, 2 H, O*H*), 6.46 (d, 2 H, J 7.0 Hz, CH_3CH_2O), 8.70 (d, 3 H, J 5.0 Hz, CH_3CHO), and 8.77 (t, 3 H, J 7.0 Hz, CH_3CH_2O). On addition of deuterium oxide, all of the alcohol peaks disappeared.

Anal. Calc. for $C_{11}H_{22}O_7$: C, 49.61; H, 8.33. Found: C, 49.56; H, 8.26.

Methyl 4-O-(1-ethoxyethyl)-2,3,6-tri-O-methyl-α-D-mannopyranoside (**9**). — To freshly distilled *p*-dioxane (100 ml) were added **8** (1.60 g), powdered sodium hydroxide (10 g), and methyl sulfate (7 ml), and the mixture was stirred overnight at 60°, and filtered. The filtrate was evaporated to a syrup (1.30 g, 52% yield), R_F 0.7 (3:97 methanol–chloroform).

This procedure was repeated on a smaller scale, but with the pure isomers **8a** and **8b**. The isomeric mixture **9** (compared to **9a** and **9b**) gave identical R_F values with methanol–chloroform.

Compound **9a**. — On methylation, compound **8a** (40 mg) gave **9a** (29 mg, 49% yield) $[\alpha]_D$ +62.9° (*c* 1.6, chloroform); n.m.r. data: τ 5.10 (q, 1 H, J 5.0 Hz, acetal proton), 6.53 (s, 3 H), 6.57 (s, 3 H), 6.61 (s, 3 H), 6.62 (s, 3 H, CH_3O, 8.72 (d, 3 H, J 5.0 Hz, CH_3CHO), and 8.81 (t, 3 H, J 7.0 Hz, CH_3CH_2O).

Anal. Calc. for $C_{14}H_{28}O_7$: C, 54.53; H, 9.15. Found: C, 54.57; H, 8.62.

Compound **9b**. — On methylation, compound **8b** (100 mg) gave **9b** (81 mg, 50% yield), $[\alpha]_D$ +72.4° (*c* 2.2, chloroform); n.m.r. data: τ 5.06 (q, 1 H, J 5.0 Hz, acetal proton), 6.52 (s, 3 H), 6.53 (s, 3 H), 6.63 (s, 6 H, CH_3O), 8.72 (d, 3 H, J 5.0 Hz, CH_3CHO), and 8.81 (t, 3 H, J 7.0 Hz, CH_3CH_2O).

Anal. Calc. for $C_{14}H_{28}O_7$: C, 54.53; H, 9.15. Found: C, 54.41; H, 8.62.

Methyl 2,3,6-tri-O-methyl-α-D-mannopyranoside (**10**). — A mixture of compound **9** (0.90 g) with acetic acid (50 ml) and water (10 ml) was stirred for 1.5 h at 100°. Evaporation, with successive addition and evaporation of water (3 × 10 ml), gave a pure syrup (0.72 g, 96%), R_F 0.2 (3:20 methanol–chloroform), $[\alpha]_D$ +31° (*c* 2.4, chloroform) {lit.[5] $[\alpha]_D$ +32° (*c* 2.8, chloroform)}; n.m.r. data: τ 6.55 (s, 6 H), 6.61 (s, 3 H), and 6.62 (s, 3 H, CH_3O).

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