Carbohydrate Research, 211 (1991) 47–57
Elsevier Science Publishers B.V., Amsterdam

Synthesis and mass spectra of 4-*O*-acetyl-1,5-anhydro-2,3,6-tri-*O*-(methoxycarbonylmethyl)-D-glucitol and the positional isomers of 4-*O*-acetyl-1,5-anhydro-di-*O*-(methoxycarbonylmethyl)-*O*-methyl-D-glucitol and 4-*O*-acetyl-1,5-anhydro-*O*-(methoxycarbonylmethyl)-di-*O*-methyl-D-glucitol*

Samuel G. Zeller, George W. Griesgraber, and Gary R. Gray†
The Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455 (U.S.A.)

(Received July 23rd, 1990; accepted for publication, September 4th, 1990)

ABSTRACT

Reductive cleavage of fully methylated, partially *O*-carboxymethylated cellulose had previously been shown to produce 4-*O*-acetyl-1,5-anhydro-2,3,6-tri-*O*-methyl-, -2-*O*-(methoxycarbonylmethyl)-3,6-di-*O*-methyl-, -3-*O*-(methoxycarbonylmethyl)-2,6-di-*O*-methyl-, -6-*O*-(methoxycarbonylmethyl)-2,3-di-*O*-methyl-, -2,3-di-*O*-(methoxycarbonylmethyl)-6-*O*-methyl-, -2,6-di-*O*-(methoxycarbonylmethyl)-3-*O*-methyl-, -3,6-di-*O*-(methoxycarbonylmethyl)-2-*O*-methyl-, and -2,3,6-tri-*O*-(methoxycarbonylmethyl)-D-glucitol. Described herein is the independent synthesis of these derivatives, except for the first, which had been reported. In addition, their ^{1}H-n.m.r. spectra, chemical-ionization (NH_3) mass spectra, and electron-ionization mass spectra are tabulated.

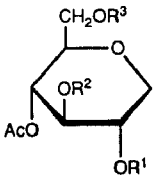
INTRODUCTION

In a previous report[1], the applicability of the reductive-cleavage method[2] for establishing the positions of substitution of *O*-carboxymethyl groups in partially *O*-carboxymethylated cellulose was demonstrated. The strategy employed in these analyses was to fully methylate *O*-carboxymethylcellulose and then carry out reductive cleavage and acetylation in the usual way[3]. Subsequent g.l.c. analysis was expected to reveal the presence of only eight products (**1–8**), and, indeed, all eight products were observed when commercial samples of *O*-carboxymethycellulose were analyzed. The identities of these components were established by comparison to independently synthesized standards by their g.l.c. retention-time and by their electron ionization (e.i.) and chemical ionization (c.i.) mass spectra. Compound **1** was available from previous work[4]; consequently, reported herein is the synthesis of compounds **2–8**. Also reported herein are e.i.- and c.i.-mass spectral data for compounds **2–8**, as an aid to those who may wish to use this method.

* This investigation was supported by Grant GM34710 awarded by the Department of Health and Human Services

† To whom correspondence should be addressed.

0008-6215/91/$03.50

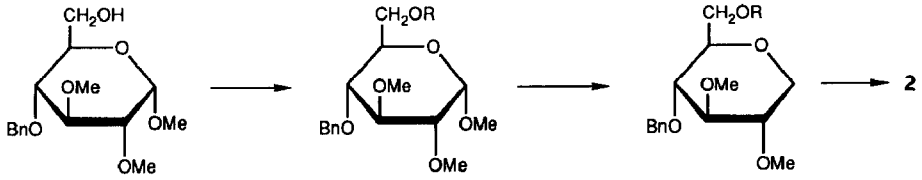


1	$R^1 = R^2 = R^3 = Me$	**5**	$R^1 = R^2 = CH_2CO_2Me$, $R^3 = Me$
2	$R^1 = R^2 = Me$, $R^3 = CH_2CO_2Me$	**6**	$R^1 = R^3 = CH_2CO_2Me$, $R^2 = Me$
3	$R^1 = R^3 = Me$, $R^2 = CH_2CO_2Me$	**7**	$R^1 = Me$, $R^2 = R^3 = CH_2CO_2Me$
4	$R^1 = CH_2CO_2Me$, $R^2 = R^3 = Me$	**8**	$R^1 = R^2 = R^3 = CH_2CO_2Me$

RESULTS AND DISCUSSION

Synthesis. — The various manipulations employed in the syntheses were based upon standard protection and deprotection strategies, and therefore the intermediates were usually not isolated and characterized. The product of each reaction was, however, checked by t.l.c. and/or g.l.c., in addition to ^{1}H-n.m.r. spectroscopy, to ensure completion of the reaction.

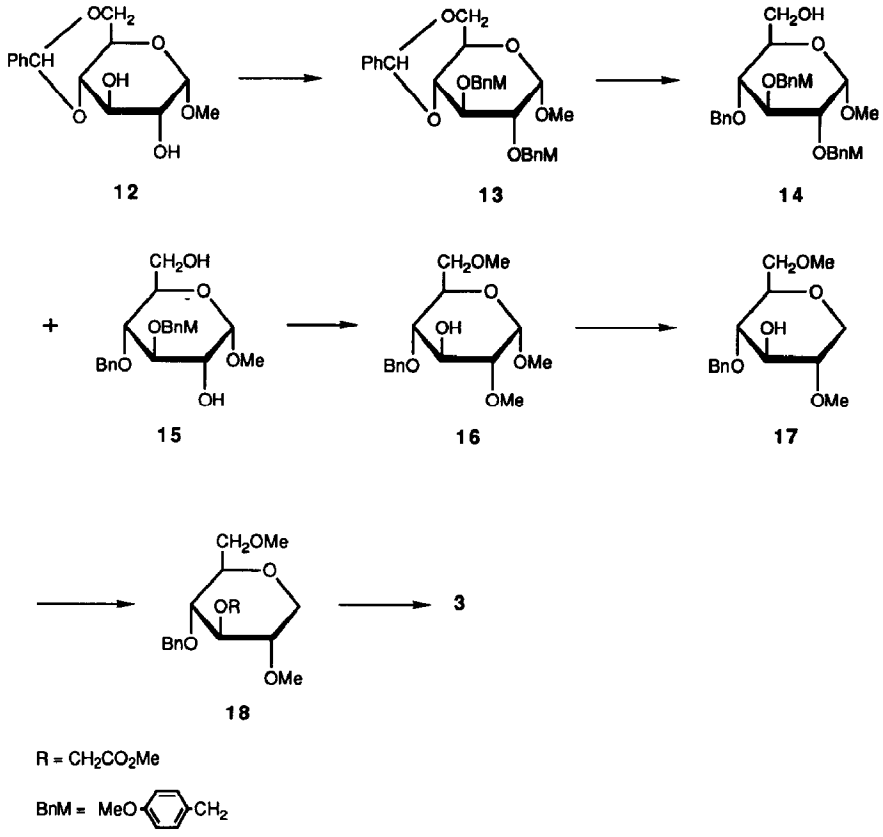
4-*O*-Acetyl-1,5-anhydro-6-*O*-(methoxycarbonylmethyl)-2,3-di-*O*-methyl-D-glucitol (**2**) was prepared as shown in Scheme 1. Methyl 4-*O*-benzyl-2,3-di-*O*-methyl-α-D-



Scheme 1

glucopyranoside (**9**), obtained as previously described[5], was alkylated by sequential treatment with 4 equiv. each of sodium hydride and methyl bromoacetate in tetrahydrofuran to give **10**. The conversion of **10** into **2** was accomplished by reductive cleavage[3] to give **11**, followed by catalytic hydrogenolysis and acetylation.

Compounds **3** and **7** were prepared from methyl 4-*O*-benzyl-3-*O*-*p*-methoxybenzyl-α-D-glucopyranoside (**15**), and compounds **5** and **8** were prepared from methyl 4-*O*-benzyl-2,3-di-*O*-*p*-methoxybenzyl-α-D-glucopyranoside (**14**), which in turn were obtained from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**12**) as shown in Scheme 2. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**12**) was first converted into its di-*O*-*p*-methoxybenzyl ether (**13**), which upon treatment[6] with $LiAlH_4$ and $AlCl_3$ gave a



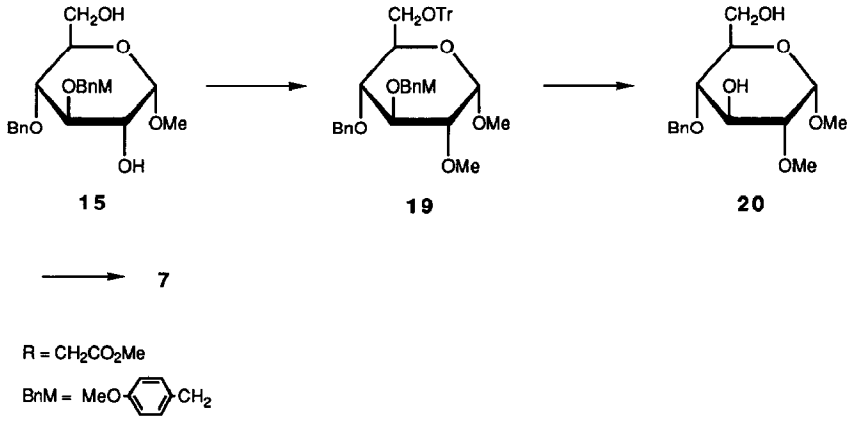
Scheme 2

mixture of products that was fractionated on silica gel to afford pure **14** and **15** in yields of 62 and 25%, respectively. In both compounds, the 4-*O*-benzyl regioisomer was formed by reductive opening of the 4,6-*O*-benzylidene acetal, but in the latter (**15**), removal of the 2-*O*-*p*-methoxybenzyl protecting group also occurred. The structures of **14** and **15** were established by ^{1}H-n.m.r. spectroscopy of their acetates. The spectrum of acetylated **14** displayed a single *O*-acetyl resonance and a complex, two-proton ester methylene resonance at δ 4.23 that was attributed to H-6 and H-6′. In contrast, the spectrum of acetylated **15** displayed two *O*-acetyl resonances, an ester methylene resonance (δ 4.28, complex) for H-6 and H-6′, and, in addition, an ester methine resonance at δ 4.82–4.93 (complex, overlapped with the H-1 resonance). The spectrum of acetylated **15** also contained an upfield triplet (δ 4.02, J 9.3 Hz) for H-3, demonstrating that O-3 was not esterified.

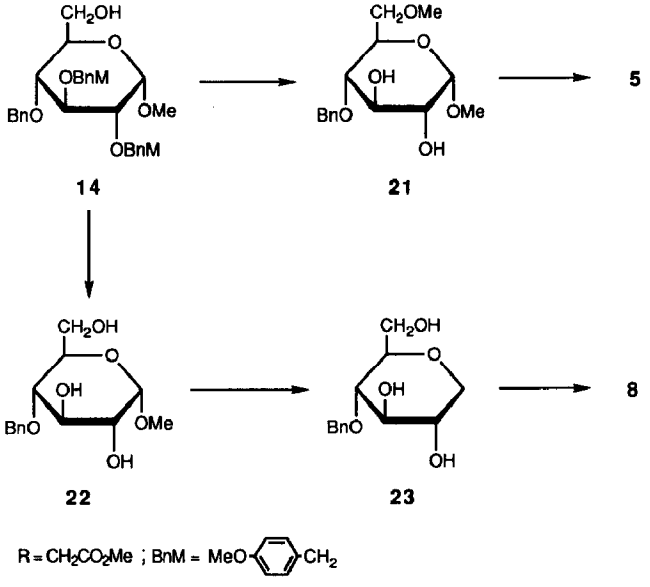
The conversion of **15** into 4-*O*-acetyl-1,5-anhydro-3-*O*-(methoxycarbonylmethyl)-2,6-di-*O*-methyl-D-glucitol (**3**) was accomplished as shown in Scheme 2. Methylation[7] of **15** and selective hydrolysis of the 3-*O*-*p*-methoxybenzyl group afforded **16**. The conversion of **16** into 1,5-anhydro-4-*O*-benzyl-3-*O*-(methoxycarbonylmethyl)-2,6-di-*O*-methyl-D-glucitol (**18**) could be accomplished either by sequential alkylation

(sodium hydride, followed by methyl bromoacetate) and reductive cleavage[3] or by sequential silylation and reductive cleavage[8], to afford **17**, and alkylation. The latter sequence was the method of choice due to increased yield and the higher purity of the product. Debenzylation of **18** and acetylation of the product afforded **3**.

4-*O*-Acetyl-1,5-anhydro-3,6-di-*O*-(methoxycarbonylmethyl)-2-*O*-methyl-D-glucitol (**7**) was also prepared from **15** as outlined in Scheme 3. Compound **15** was first tritylated, and the product was methylated to yield **19**. Removal of the trityl and *p*-methoxybenzyl protecting groups of **19** by acid hydrolysis afforded **20**, which was converted into **7** as described for the conversion of **9** into **2**.



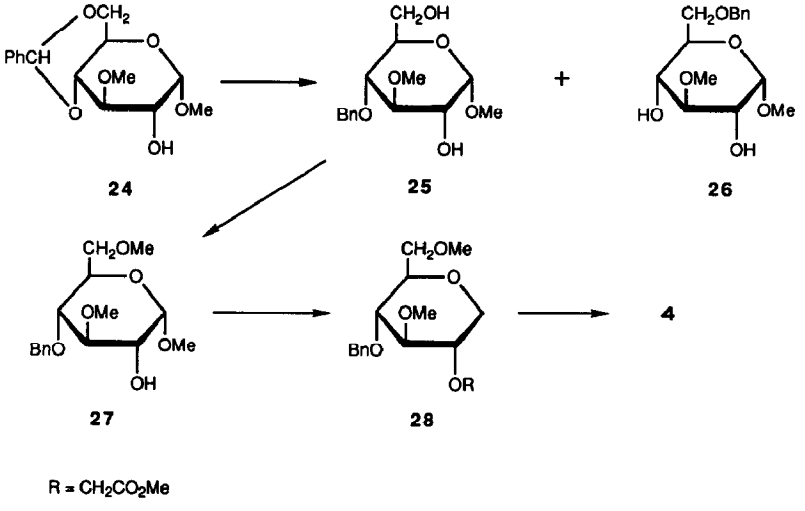
Scheme 3



Scheme 4

4-*O*-Acetyl-1,5-anhydro-2,3-di-*O*-(methoxycarbonylmethyl)-6-*O*-methyl-D-glucitol (**5**) and 4-*O*-acetyl-1,5-anhydro-2,3,6-tri-*O*-(methoxycarbonylmethyl)-D-glucitol (**8**) were both prepared from compound **14**, prepared as outlined in Scheme 2. For the synthesis of **5** (Scheme 4), compound **14** was methylated prior to removal of the *p*-methoxybenzyl protecting groups by mild acid hydrolysis. The product (**21**) was then converted into **5** as described previously for the conversion of **16** into **3** (see Scheme 2). For the synthesis of **8** (Scheme 4), the *p*-methoxybenzyl groups of **14** were first removed by mild acid hydrolysis, and the product (**22**) was reductively cleaved[8] to produce 1,5-anhydro-4-*O*-benzyl-D-glucitol (**23**). The conversion of **23** into **8** was accomplished by sequential alkylation (sodium hydride and methyl bromoacetate), debenzylation, and acetylation.

The remaining compounds (**4** and **6**) were prepared from methyl 4-*O*-benzyl-3-*O*-methyl-α-D-glucopyranoside (**25**). Treatment of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside **24** (ref. 5) with a mixture of lithium aluminum hydride and aluminum trichloride as described by Lipták, *et al.*[6] gave **25** and the corresponding 6-*O*-benzyl regioisomer (**26**) in a ratio of 7:3, respectively (Scheme 5). Chromatography



Scheme 5

of the mixture of **25** and **26** on silica gel afforded the pure compounds, which were easily distinguished by the ^{1}H-n.m.r. spectra of their acetates. For the conversion of **25** into **4**, compound **25** was selectively methylated at the 6-position by sequential mesylation and treatment with sodium methoxide in methanol to yield **27**. The conversion of **27** into **4** was accomplished as previously described for the conversion of **9** into **2**. Compound **25** was used directly in the synthesis of 4-*O*-acetyl-1,5-anhydro-2,6-di-*O*-(methoxycarbonylmethyl)-3-*O*-methyl-D-glucitol (**6**), however, by the sequence of reactions used in the conversion of **9** into **2** (see Scheme 1).

^{1}H-N.m.r. spectra. — The ^{1}H-n.m.r. spectra of compounds **2–8** were compared to the previously reported[4] spectrum of **1**. All spectra displayed the expected triplet (*J*

9.1–9.3 Hz for **1–7**; *J* 8.7 Hz for **8**) for H-4, which is characteristic[4,5,9,10] of 4-*O*-acetyl-1,5-anhydro-D-glucitol derivatives. The chemical shift of the H-4 resonance was dependent upon the type of substituent at O-3; for compounds (**1, 2, 4,** and **6**) containing a 3-*O*-methyl group, the H-4 triplet was observed at δ 4.80 $\pm$ 0.01, whereas for compounds (**3, 5, 7,** and **8**) containing a 3-*O*-(methoxycarbonylmethyl) group, the H-4 triplet was observed downfield at δ 4.89 $\pm$ 0.01. Likewise, the chemical shift of the *O*-acetyl resonance was also dependent upon the identity of the *O*-3 substituent; *i.e.*, in 3-*O*-(methoxycarbonylmethyl) derivatives (**3, 5, 7,** and **8**), the acetyl resonance was observed at δ 2.133 $\pm$ 0.003, whereas in 3-*O*-methyl derivatives (**1, 2, 4,** and **6**) the acetyl resonance was observed upfield at δ 2.105 $\pm$ 0.066. Similarly, the H-1e resonance (dd, *J* 5 and 11 Hz) of compounds (**4, 5, 6,** and **8**) containing a 2-*O*-(methoxycarbonylmethyl) group was observed downfield (δ 4.171 $\pm$ 0.003) compared to those containing a 2-*O*-methyl group, at least for those compounds (**1** and **3**) for which the chemical shift (δ 4.12 $\pm$ 0.01) of H-1e could be measured. Thus, the spectra of these derivatives are fully in accord with the expected positions of substitution of *O*-acetyl, *O*-methyl, and *O*-(methoxycarbonylmethyl) groups.

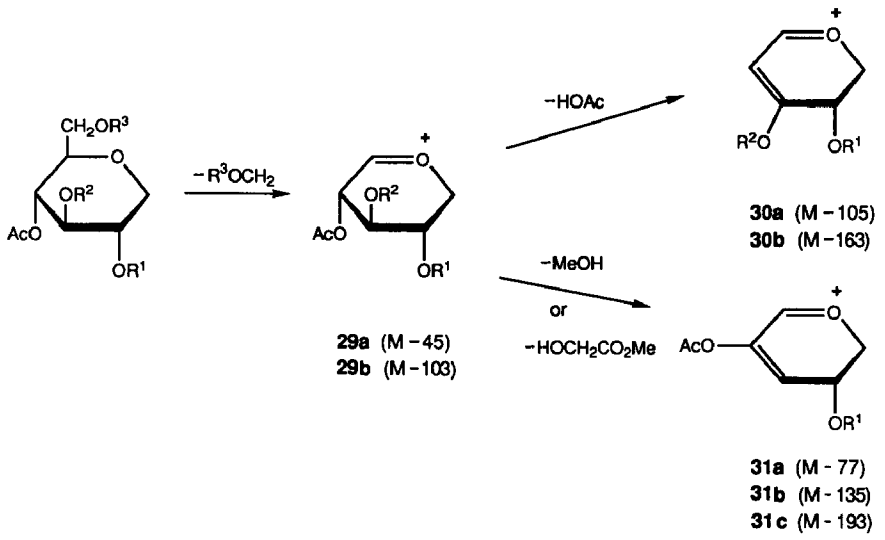
Mass spectra. — Inspection of the e.i. mass spectra of compounds **2–8** revealed the presence of a fragmentation pathway (Scheme 6) similar to that previously reported[5] for the corresponding *O*-methyl and *O*-ethyl positional isomers. Loss[11] of the exocyclic methoxymethyl group ($MeOCH_2$, M − 45) or (methoxycarbonylmethoxy)methyl group ($MeO_2CCH_2OCH_2$, M − 103) gives fragment ions **29a** and **29b**, respectively. The further loss of acetic acid from the (M − 45) ion (**29a**) and (M − 103) ion (**29b**) gives rise to fragment ions **30a** (M − 105) and **30b** (M − 163), respectively, whereas the elimination of methanol or methyl 2-hydroxyacetate ($HOCH_2CO_2Me$) from the (M − 45) ion (**29b**) gives rise to fragment ions **31a** (M − 77) and **31b** (M − 135), respectively. A fragment ion (**31b**) at (M − 135) is also formed by elimination of methanol from the (M − 103) ion (**29b**), but elimination of methyl 2-hydroxyacetate from the (M − 103) ion (**29b**) gives a fragment ion (**31c**) at (M − 193).

TABLE I

Selected fragments observed in the electron-impact mass spectra of compounds **1–8**

Compound	*Mol. wt*	*(M − 45)*	*(M − 77)*	*(M − 103)*	*(M − 105)*	*(M − 135)*	*(M − 163)*	*(M − 193)*
1[a]	248	+	+	−	+	−	−	−
2	306	−	−	+	−	+	+	−
3	306	+	−	−	+	+	+[b]	−
4	306	+	+	−	+	−	−	−
5	364	+	−	−	+	+	−	−
6	364	−	−	+	−	+	+	−
7	364	−	−	+	−	−	+	+
8	422	−	−	+	−	−	+	+

[a] Data from ref. 4. [b] An ion of low intensity at *m/z* 143 was unexpectedly observed in the mass spectrum. It apparently originates from a fragmentation pathway other then that depicted in Scheme 6.



Scheme 6

There was excellent correlation between the presence or absence of fragment ions at (M − 45), (M − 77), (M − 103), (M − 105), (M − 135), (M − 163), and (M − 193) and the positions of substitution of *O*-(methoxycarbonylmethyl) groups (see Table I). For example, in the mono-*O*-(methoxycarbonylmethyl)-substituted positional isomers (**2, 3,** and **4**), loss of the exocyclic methoxymethyl group of **3** and **4** gives an (M − 45) ion (**29a**) at *m/z* 261, whereas loss of the exocyclic $MeO_2CCH_2OCH_2$ group of **2** gives an (M − 103) ion (**29b**) at *m/z* 203. Compounds **3** and **4** can in turn be differentiated by observing fragment ions **31a** (M − 77) and **31b** (M − 135) at *m/z* 229 and *m/z* 171, respectively. The former ion is present only in the mass spectrum of **4**, whereas the latter is present only in the mass spectrum of **3**. In the di-*O*-(methoxycarbonylmethyl)-substituted positional isomers (**5, 6,** and **7**), loss of the exocyclic methoxymethyl group of **5** gives an (M − 45) ion at *m/z* 319, whereas loss of the exocyclic $MeO_2CCH_2OCH_2$ group of **6** and **7** gives an (M − 103) ion at *m/z* 261. Compounds **6** and **7** can in turn be distinguished by observing fragment ions **31b** (M − 135) and **31c** (M − 193); *i.e.*, further loss of methanol from the *m/z* 261 fragment ion gives a characteristic ion (**31b**) for **6** at *m/z* 229 (M − 135), whereas loss of methyl 2-hydroxyacetate from the *m/z* 261 fragment ion gives a characteristic fragment ion (**31c**) for **7** at *m/z* 171 (M − 193).

EXPERIMENTAL

General. — Methylations were conducted as described by Blakeney and Stone[7]. Benzylidenations were performed as described by Evans[12]. Reductive cleavages were achieved with triethylsilane as the reducing agent and a mixture of trimethylsilyl methanesulfonate and boron trifluoride etherate as the catalyst, as described by Jun and Gray[3]. Silylation–reductive cleavage was performed as described by Bennek and Gray[8]. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was obtained from Sigma Chemical

Company. Elemental analyses were performed by M-H-W Laboratories, Inc., Phoenix, Arizona.

^{1}H-N.m.r. spectra were recorded with an IBM NR-300 or IBM NR-200 AF n.m.r. spectrometer for solutions in $CDCl_3$ and were referenced to internal tetramethylsilane ($CHCl_3$ resonance at δ 7.262). G.l.c.–m.s. analyses were performed by using either a Finnigan 4000 mass spectrometer equipped with a VG Multispec data system or a VG Analytical Ltd. Model VG 7070E-HF high-resolution, double-focusing mass spectrometer. Column effluents were analyzed by c.i.-m.s. with ammonia as the reagent gas, and by e.i.-m.s. In c.i.-mass spectra, *m/z* values are reported for characteristic $(M + H)^+$ and $(M + NH_4)^+$ ions, along with their percent intensity (in parenthesis) relative to the base peak. In e.i.-mass spectra, *m/z* values are reported for ions below *m/z* 150 that comprise 10% or more of the intensity of the base peak and for ions above *m/z* 150 that are prominent regardless of their absolute intensity. Medium-pressure liquid chromatography (m.p.l.c.) was carried out in an instrument consisting of a Rheodyne 7125 injector, Eldex model B-100-S4 pump, Scientific Systems model LP-21 pulse dampener, Waters Associates differential refractometer, and ChiraTech Scientific Instruments, Inc. ultraviolet absorption monitor. Chromatography was conducted on glass columns packed with 40 Å silica gel (35–70 mesh) from E. Merck. High performance liquid chromatography (h.p.l.c.) was performed using a Beckman model 338 System Gold chromatograph.

4-O-Acetyl-1,5-anhydro-6-O-(methoxycarbonylmethyl)-2,3-di-O-methyl-D-glucitol (**2**). — Alkylation of **9** (ref. 5) was performed by heating under reflux a sample of **9** (500 mg) in tetrahydrofuran (20 mL) in the presence of sodium hydride (4 equiv.) for 4 h, followed by the addition of methyl bromoacetate (4 equiv.) at 0°. After 15 min, the excess hydride was destroyed by the addition of H_2O (15 mL), and the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, dried over sodium sulfate, and concentrated, and the residue was purified by m.p.l.c. on a column (0.8 × 25 cm) of silica gel. Elution with 1:1 (v/v) hexane–ethyl acetate afforded **10** in 59% yield. Compound **10** was converted into **11** in 73% yield by reductive cleavage[3] in the presence of triethylsilane (5 equiv.) and trimethylsilyl methanesulfonate (5 equiv.) and boron trifluoride etherate (1 equiv.). Debenzylation of **11** in EtOH with H_2 at 101 kPa in the presence of Pd for 18 h, and acetylation of the product, yielded **2** as an oil: ^{1}H-n.m.r.: δ 2.109 (s, 3 H, AcO), 3.478 (s, 3 H, MeO-2), 3.528 (s, 3 H, MeO-3), 3.735 (s, 3 H, CO_2Me), 3.09–3.65 (complex, 6 H, H-1*a*,2,3,5,6,6′), 4.06–4.13 (complex, 1 H, H-1*e*), 4.072, 4.175 (two d, 2 H, *J* 16.6 Hz, $-CH_2CO_2Me$), and 4.798 (t, 1 H, *J* 9.1 Hz, H-4); g.l.c.–c.i.-m.s. (NH_3, positive): *m/z* 307 (10) and 324 (100); g.l.c.–e.i.-m.s.: *m/z* 43 (100), 45 (42), 58 (41), 59 (20), 71 (15), 73 (11), 74 (13), 85 (12), 97 (13), 111 (7), 129 (7), 143 (8), 171 (6), and 203 (2).

Anal. Calc. for $C_{13}H_{22}O_8$: C, 50.98; H, 7.24. Found: C, 51.20; H, 7.39.

4-O-Acetyl-1,5-anhydro-3-O-(methoxycarbonylmethyl)-2,6-di-O-methyl-D-glucitol (**3**). — Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (1 equiv.) was reacted with NaH (4 equiv.) and of *p*-methoxybenzyl chloride (2.2 equiv.) in DMF for 2 h at 110°. The solution was cooled to room temperature, and methanol was added to decompose the excess hydride. The reaction mixture was then added to ethyl acetate, and the ethyl

acetate layer was separated and extracted with water (3 ×). The organic solution was dried over sodium sulfate, filtered, and evaporated leaving crystalline **13**, which was recrystallized from EtOH (75% yield). The 4,6-*O*-benzylidene group of **13** was reductively opened using a modification of the Lipták[6] method. Compound **13** (7.58 g) was dissolved in freshly distilled Et_2O (150 mL), and freshly distilled CH_2Cl_2 (150 mL), and $LiAlH_4$ (5 equiv.) were slowly added. The solution was heated under reflux for 15 min, then $AlCl_3$ (5 equiv., anhydrous) in Et_2O (150 mL) was added to the reaction dropwise over a period of 15 min. The reaction was heated under reflux for an additional 10 min, cooled to 0°, and the excess hydride was decomposed by the successive addition of EtOAc (30 mL) and water (100 mL). The reaction mixture was extracted with Et_2O (3 × 200 mL), and the combined Et_2O extracts were re-extracted with water (200 mL). The ether layer was dried over sodium sulfate and concentrated to give a mixture of **14** and **15** which later crystallized. Chromatography (m.p.l.c.) of the mixture on a column (2.1 × 30 cm) of silica gel, and elution with 1:1 (v/v) hexane–ethyl acetate afforded pure **14** (m.p. 89–94°) and **15** (m.p. 144–152°) in yields of 62 and 25%, respectively. Successive methylation[6] of **15** and removal of the *p*-methoxybenzyl group (50% glacial acetic acid for 21 h at 75°) gave impure **16**, which was obtained in pure form (69%) by m.p.l.c. on a column (4 × 35 cm) of silica gel and elution with 1:99 (v/v) MeOH–CH_2Cl_2. Silylation–reductive cleavage[7] of **16** afforded the corresponding anhydroalditol **17** which was alkylated with methyl bromoacetate in the usual way to yield **18**. Debenzylation of **18** as already described, and acetylation of the product gave **3** as an oil: ^{1}H-n.m.r.: δ 2.135 (s, 3 H, AcO), 3.355 (s, 3 H, MeO-6), 3.424 (s, 3 H, MeO-2), 3.731 (s, 3 H, CO_2Me), 3.09–3.50 (complex, 6 H, H-1*a*,2,3,5,6,6′), 4.128 (dd, 1 H, *J* 4.3, 11.5 Hz, H-1*e*), 4.359 (s, 2 H, $-CH_2CO_2Me$), and 4.890 (broadened t, 1 H, *J* 9.2 Hz, H-4); g.l.c.–c.i.-m.s. (NH_3, positive): *m/z* 307 (26) and 324 (100); g.l.c.–e.i.-m.s.: *m/z* 43 (100), 45 (59), 58 (42), 59 (23), 69 (20), 71 (24), 73 (14), 81 (12), 87 (26), 97 (61), 111 (18), 129 (33), 143 (16), 169 (14), 171 (43), 201 (10), and 261 (2).

Anal. Calc. for $C_{13}H_{22}O_8$: C, 50.98; H, 7.24. Found: C, 50.87; H, 7.23.

4-O-Acetyl-1,5-anhydro-2-O-(methoxycarbonylmethyl)-3,6-di-O-methyl-D-glucitol (**4**). — Methyl 3-*O*-methyl-α-D-glucopyranoside[13] was benzylidenated as described by Evans[12] to give **24**, which upon treatment with of $LiAlH_4$ (5 equiv.) and $AlCl_3$ (5 equiv.), as described by Lipták, *et al.*[6], resulted in a 7:3 mixture of **25** and **26** (58% yield). Separation of the product (m.p.l.c.) on a column (2.1 × 30 cm) of silica gel, and elution with 1:2 (v/v) hexane–ethyl acetate gave pure **25** in 37% yield. Compound **25** was treated with methanesulfonyl chloride (10 equiv.) in pyridine for 24 h to give the 2,6-di-*O*-mesylate (96% yield), which in turn was reacted with sodium methoxide in methanol[14] (prepared by addition of metallic sodium to dry methanol) to give **27** in 63% yield. Alkylation of **27** as described for **9** and reductive cleavage[3] of the product gave **28**, which was purified by m.p.l.c. on a column (0.8 × 25 cm) of silica gel in 1:1 (v/v) hexane–ethyl acetate (38% yield). Debenzylation of **28** as already described, and acetylation of the product yielded **4** as an oil: ^{1}H-n.m.r.: δ 2.100 (s, 3 H, AcO), 3.338 (s, 3 H, MeO-6), 3.524 (s, 3 H, MeO-3), 3.738 (s, 3 H, CO_2Me), 3.21–3.50 (complex, 6 H, H-1*a*,2,3,5,6,6′), 4.171 (dd, 1 H, *J* 5.0, 11.0 Hz, H-1*e*), 4.303 (s, 2 H, $-CH_2CO_2Me$), and 4.805 (t, 1 H, *J* 9.2 Hz,

H-4); g.l.c.–c.i.-m.s. (NH_3, positive): *m/z* 307 (51) and 324 (100); g.l.c.–e.i.-m.s.: *m/z* 43 (100, 45 (51), 59 (15), 69 (11), 71 (32), 73 (10), 74 (13), 85 (18), 87 (20), 97 (24), 103 (11), 111 (20), 116 (13), 117 (10), 129 (11), 145 (15), 159 (8), 169 (31), 187 (47), 201 (38), 229 (28), and 261 (16).

Anal. Calc. for $C_{13}H_{22}O_8$: C, 50.98; H, 7.24. Found: C, 50.72; H, 7.09.

4-O-Acetyl-1,5-anhydro-2,3-di-O-(methoxycarbonylmethyl)-6-O-methyl-D-glucitol (**5**). — Compound **14**, isolated as described for the synthesis of **3**, was methylated[7] (90%), and the *p*-methoxybenzyl groups of the product were removed by stirring in 50% acetic acid at 70° for 18 h. The solvent was evaporated, and the product was purified by m.p.l.c. on a column (2.1 × 30 cm) of silica gel. Elution with 3:97 (v/v) MeOH–CH_2Cl_2 afforded pure **21** in 65% yield. Compound **21** was then converted into **5** as described for the conversion of **16** into **3**. For **5**: ^{1}H-n.m.r.: δ 2.133 (s, 3 H, AcO), 3.349 (s, 3 H, MeO-6), 3.723, 3.743 (two s, 6 H, CO_2Me), 3.17–3.77 (complex, 6 H, H-1*a*,2,3,5,6,6'), 4.174 (dd 1 H, *J* 4.4, 11.3 Hz, H-1*e*), 4.287 (s, 2 H, $-CH_2CO_2Me$), 4.386 (s, 2 H, $-CH_2CO_2Me$), and 4.895 (broadened t, 1 H, *J* 9.3 Hz, H-4); g.l.c.–c.i.-m.s. (NH_3, positive): *m/z* 365 (16) and 382 (100); g.l.c.–e.i.-m.s.: *m/z* 43 (100), 45 (65), 59 (14), 69 (12), 71 (18), 73 (13), 97 (18), 111 (3), 169 (15), 187 (9), 229 (6), 259 (2), and 319 (0.1).

Anal. Calc. for $C_{15}H_{24}O_{10}$: C, 49.45, H, 6.64. Found: C, 49.50; H, 6.74.

4-O-Acetyl-1,5-anhydro-2,6-di-O-(methoxycarbonylmethyl)-3-O-methyl-D-glucitol (**6**). — Compound **25**, obtained as described in the synthesis of **4**, was subjected to the same sequence of reactions used in the conversion of **9** into **2**, to afford **6** as an oil: ^{1}H-n.m.r.: δ 2.111 (s, 3 H, AcO), 3.531 (s, 3 H, MeO-3), 3.732, 3.746 (two s, 6 H, CO_2Me), 3.21–3.63 (complex, 6 H, H-1*a*,2,3,5,6,6'), 4.062, 4.163 (two d, 2 H, *J* 16.6 Hz, $-CH_2CO_2Me$), 4.169 (dd, 1 H, *J* 5.0, 11.0 Hz, H-1*e*), 4.312 (s, 2 H, $-CH_2CO_2Me$), and 4.802 (t, 1 H, *J* 9.3 Hz, H-4); g.l.c.–c.i.-m.s. (NH_3, positive): *m/z* 365 (19) and 382 (100); g.l.c.–e.i.-m.s.: *m/z* 43 (100), 45 (50), 57 (12), 59 (20), 69 (13), 71 (36), 73 (25), 74 (18), 85 (23), 87 (14), 97 (17), 103 (13), 111 (28), 116 (14), 145 (19), 169 (17), 187 (18), 201 (17), 229 (7), and 261 (2).

Anal. Calc. for $C_{15}H_{24}O_{10}$: C, 49.45; H, 6.64. Found: C, 49.61; H, 6.57.

4-O-Acetyl-1,5-anhydro-3,6-di-O-(methoxycarbonylmethyl)-2-O-methyl-D-glucitol (**7**). — Compound **15**, isolated as described for the synthesis of **3**, was reacted with triphenylmethyl chloride (1.1 equiv.) in pyridine to give the 6-*O*-trityl ether, which was isolated in 44% yield following chromatography (m.p.l.c.) on a column (2.1 × 30 cm) of silica gel and elution with 3:1 (v/v) hexane–ethyl acetate. Subsequent methylation[7] of the product gave **19** in 95% yield. The *p*-methoxybenzyl and trityl groups of **19** were removed by heating (70°) in 50% acetic acid for 18 h. The product **20** was purified (m.p.l.c.) on a silica gel column (2.1 × 30 cm) using 3:97 (v/v) MeOH–CH_2Cl_2 as the eluent. Alkylation of **20** was performed by refluxing with NaH (20 equiv.) in THF for 2 h, followed by the addition of methyl bromoacetate (20 equiv.) at 0°. The solution was stirred at room temperature for 18 h and processed as described for the synthesis of **2**. The product was purified (m.p.l.c.) on a silica gel column using 5:1 (v/v) hexane–ethyl acetate as the eluent. Sequential reductive cleavage[3] (80%), debenzylation, and acetylation gave **7** as an oil: ^{1}H-n.m.r.: δ 2.131 (s, 3 H, AcO), 3.427 (s, 3 H, MeO-2), 3.732, 3.737

(two s, 6 H, 2 CO_2Me), 3.07–3.66 (complex, 6 H, H-1*a*,2,3,5,6,6'), 4.03–4.21 (complex, 3 H, H-1*e*, $-CH_2CO_2Me$), 4.352 (s, 2 H, $-CH_2CO_2Me$), and 4.881 (broadened t, 1 H, *J* 9.3 Hz, H-4); g.l.c.–c.i.-m.s. (NH_3, positive): *m/z* 365 (2) and 382 (100); g.l.c.–e.i.-m.s.: *m/z* 43 (100), 45 (43), 58 (37), 59 (19), 69 (12), 71 (14), 73 (15), 87 (11), 97 (28), 111 (10), 129 (12), 169 (8), 171 (14), 201 (5), and 261 (0.4).

Anal. Calc. for $C_{15}H_{24}O_{10}$: C, 49.45; H, 6.64. Found: C, 49.60; H, 6.70.

4-O-Acetyl-1,5-anhydro-2,3,6-tri-O-(methoxycarbonylmethyl)-D-glucitol (**8**). — Compound **14**, isolated as described for the synthesis of **3**, was reacted with 50% acetic acid for 23 h at 75° to remove the *p*-methoxybenzyl groups. Following purification (m.p.l.c.) on a column of silica gel, and elution with 5:95 (v/v) MeOH–CH_2Cl_2, compound **22** was isolated in 42% yield. Sequential silylation and reductive cleavage of **22**, as described for **3**, gave crystalline **23** (m.p. 141–143°) in 75% yield. Alkylation with methyl bromoacetate as already described gave 1,5-anhydro-4-*O*-benzyl-2,3,6-tri-*O*-(methoxycarbonylmethyl)-D-glucitol which was isolated in pure form by reversed-phase h.p.l.c. on a column (9.4 mm × 25 cm) of DuPont Zorbax ODS, eluted over 20 min with a linear gradient from 40% acetonitrile in water to 80% acetonitrile in water at a flow rate of 3 mL/min. Debenzylation and acetylation as already described gave **8** as an oil: ^{1}H-n.m.r.: δ 2.130 (s, 3 H, AcO), 3.21–3.72 (complex, 6 H, H-1*a*,2,3,5,6,6'), 3.725. 3.736, 3.745 (three s, 9 H, 3 CO_2Me), 4.075, 4.157 (two d, 2 H, *J* 17.6 Hz, $-CH_2CO_2Me$), 4.174 (dd, 1 H, *J* 5.5, 11.2 Hz, H-1*e*), 4.288 (s, 2 H, $-CH_2CO_2Me$), 4.374 (s, 2 H, $-CH_2CO_2Me$), and 4.885 (broadened t, 1 H, *J* 8.7 Hz, H-4); g.l.c.–c.i.-m.s. (NH_3, positive): *m/z* 440 (8); g.l.c.–e.i.-m.s.: *m/z* 43 (100), 45 (49), 57 (10), 69 (15), 71 (19), 73 (25), 74 (12), 75 (11), 81 (12), 97 (25), 103 (10), 111 (11), 129 (11), 143 (13), 145 (15), 169 (50), 183 (21), 187 (32), 229 (19), 259 (10), 319 (0.6), and 333 (6).

REFERENCES

1 S. G. Zeller, G. W. Griesgraber, and G. R. Gray, *Carbohydr. Res.*, 211 (1991) 41–45.
2 D. Rolf and G. R. Gray, *J. Am. Chem. Soc.*, 104 (1982) 3539–3541.
3 J. -G. Jun and G. R. Gray, *Carbohydr. Res.*, 163 (1987) 247–261.
4 D. Rolf, J. A. Bennek, and G. R. Gray, *Carbohydr. Res.*, 137 (1985) 183–196.
5 S. G. Zeller, A. J. D'Ambra, M. J. Rice, and G. R. Gray, *Carbohydr. Res.*, 182 (1988) 53–62.
6 A. Lipták, I. Jodál, and P. Nánási, *Carbohydr. Res.*, 44 (1975) 1–11.
7 A. B. Blakeney and B. A. Stone, *Carbohydr. Res.*, 140 (1985) 319–324.
8 J. A. Bennek and G. R. Gray, *J. Org. Chem.*, 52 (1987) 892–897.
9 D. Rolf and G. R. Gray, *Carbohydr. Res.*, 152 (1986) 343–349.
10 S. A. Vodonik and G. R. Gray, *Carbohydr. Res.*, 175 (1988) 93–102.
11 N. K. Kochetkov and D. S. Chizhov, *Adv. Carbohydr. Chem.*, 21 (1966) 39–93.
12 M. E. Evans, *Carbohydr. Res.*, 21 (1972) 473–475.
13 R. W. Jeanloz and M. Gut, *J. Am. Chem. Soc.*, 76 (1954) 5793–5794.
14 A. K. Mitra, D. H. Ball, and L. Long, Jr., *J. Org. Chem.*, 27 (1962) 160–162.