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SYNTHESIS AND REACTIONS OF URONIC ACID DERIVATIVES

PART I. UNAMBIGUOUS SYNTHESES OF METHYL (METHYL α-D-GLUCOPYRANOSID)URONATE 2-, 3-, 4-, 2,3-DI-, 2,4-DI-, AND 3,4-DI-METHYL ETHERS

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ABSTRACT

Oxidation of *O*-benzyl-*O*-methyl derivatives of methyl α-D-glucopyranoside having only HO-6 unsubstituted, with chromium trioxide and dilute sulphuric acid in acetone, followed by esterification, gave high yields of the corresponding methyl (methyl α-D-glucopyranosid)uronates. Removal of the benzyl groups by hydrogenolysis then gave the partially methylated derivatives of methyl (methyl α-D-glucopyranosid)uronate, which were characterized as the amides. In this way, the complete series of partially methylated derivatives was obtained.

INTRODUCTION

Chromium trioxide–sulphuric acid is superior to other reagents[1–4] for the oxidation of the primary hydroxyl group of carbohydrate derivatives[5] that are otherwise fully substituted. The method was used in the synthesis of methyl (benzyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranosid)uronic acid derivatives[5] and 4-*O*-substituted methyl (methyl 2,3-di-*O*-methyl-β-D-glucopyranosid)uronates[6]. Its use in the synthesis of all the theoretically possible, partially methylated derivatives of methyl (methyl α-D-glucopyranosid)uronate is now reported. The title compounds are useful for the identification of the products of methylation analysis of D-glucuronic acid-containing substances.

RESULTS AND DISCUSSION

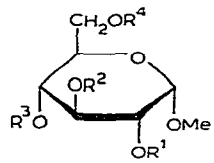
Because degradation by β-elimination takes place simultaneously with the methylation of uronic acid derivatives[6,7], it is advantageous to prepare partially methylated D-glucuronic acid derivatives by oxidation of appropriate derivatives of D-glucose. Moreover, this approach is more flexible synthetically and can be applied to other hexoses.

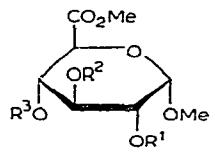
In previous syntheses of partially methylated derivatives of methyl (methyl α-D-glucopyranosid)uronate, the final product obtained, except for the 4-methyl ether[8], was not a pure anomer, because either the starting material was a syrupy mixture of

anomers[9], or esterification of the intermediate methyl glucopyranosiduronic acid derivatives was effected with methanolic hydrogen chloride[10], which caused anomerization.

The fact that oxidation of the primary hydroxyl group of glycosides with oxygen in the presence of rare-metal catalysts does not require blocking of all other hydroxyl groups suggests that the Heyns procedure[1] might be convenient for the synthesis of uronic acid derivatives. Variable results have, however, been reported with this procedure; sometimes the yields were low[9], and occasionally[5,11,12] oxidation was unsuccessful. Permanganate oxidation[2,10] has also been reported[11] not to produce the desired product. An alternative approach involves the application of chromium trioxide–dilute sulphuric acid to methyl *O*-benzyl-*O*-methyl-α-D-glucopyranosides which have HO-6 free. These compounds are either easily crystallizable or have crystalline precursors, so that anomeric purity can be assured. The presence of a benzyl group in these molecules reduces the water solubility and facilitates the isolation of the product acids. The overall yields of the title compounds were ~80%, thus supporting the previous statement[5] that the oxidation procedure described herein is unquestionably superior, as a preparative method, to previous procedures. Since details of the individual syntheses are given in the Experimental, only the following salient points need be noted.

Methyl (methyl α-D-glucopyranosid)uronate 2-(**4**), and 3-methyl ethers (**12**), each containing ~10% of the β-anomer were first prepared by Hashimoto *et al.*[9]. The title 2-methyl ether **4** was synthesised by a similar sequence of reactions, but using, as the key intermediate, anomerically pure[13] methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-methyl-α-D-glucopyranoside. Compound **4** had an $[\alpha]_D$ value (+131.5°) >30° higher than that of the compound described earlier[9].





	R¹	R²	R³	R⁴		R¹	R²	R³
1	Me	Bn	Bn	Tr	3	Me	Bn	Bn
2	Me	Bn	Bn	H	4	Me	H	H
5	Bn	Me	–C(Ph,H)–		11	Bn	Me	Bn
6	Bn	Me	H	H	12	H	Me	H
7	Bn	Me	H	Tr	14	Bn	Bn	Me
8	Bn	Me	Ac	Tr	15	H	H	Me
9	Bn	Me	Bn	Tr	17	Me	Me	Bn
10	Bn	Me	Bn	H	18	Me	Me	H
13	Bn	Bn	Me	H	20	Me	Bn	Me
16	Me	Me	Bn	H	21	Me	H	Me
19	Me	Bn	Me	H	24	Bn	Me	Me
22	Bn	Me	Me	Tr	25	H	Me	Me
23	Bn	Me	Me	H				

Bn = benzyl

The 3-*O*-methyl derivative **12** was synthesized from methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside[14]. The previous procedure[15] for making this starting compound (treatment of 3-*O*-methyl-D-glucose with methanolic hydrogen chloride followed by benzylidenation and fractional crystallization) did not give an anomerically pure product. Methyl (methyl 3-*O*-methyl-α-D-glucopyranosid)uronate (**12**) had an $[\alpha]_D$ value (+150°) which was >50° higher than that of the previously described substance[9].

Methyl (methyl 4-*O*-methyl-α-D-glucopyranosid)uronate (**15**) was synthesized by Wacek *et al.*[8], and the compound was also obtained, albeit in a very low yield, as an intermediate in the synthesis[11] of 4-*O*-methyl-D-glucuronic acid. The yield of **15** obtained *via* oxidation of methyl 2,3-di-*O*-benzyl-4-*O*-methyl-α-D-glucopyranoside (**13**), now obtained crystalline, compared well with that obtained by catalytic oxidation.

Of the title dimethyl ethers, only the 2,3 compound was previously obtained by a specific synthesis[10]. The $[\alpha]_D$ value (+137°) of methyl (methyl 2,3-di-*O*-methyl-α-D-glucopyranosid)uronate (**18**) described herein shows that, probably, neither the synthetic product[10] ($[\alpha]_D$ +111°) nor the compound ($[\alpha]_D$ +70°) isolated from natural sources[16] was anomerically pure.

The logical starting-material for the synthesis of the title 2,4-dimethyl ether **21** was methyl 3-*O*-benzyl-2,4-di-*O*-methyl-6-*O*-trityl-α-D-glucopyranoside[17]. The crystalline, hitherto unknown, detritylated product **19** was oxidized and then esterified to give, after hydrogenolysis, methyl (methyl 2,4-di-*O*-methyl-α-D-glucopyranosid)uronate (**21**).

Derivatives of 3,4-di-*O*-methyl-D-glucuronic acid were first isolated during a study[18] of the structure of glycyrrhizic acid, and the crystalline, free acid was isolated[19] from another natural source. The corresponding amides described by these authors[18,19] were probably anomeric mixtures, as indicated by the physical constants of the amide derived from crystalline methyl (methyl 3,4-di-*O*-methyl-α-D-glucopyranosid)uronate (**25**) described herein.

EXPERIMENTAL

General methods. — M.p.s. were determined on a Kofler hot-stage. Optical rotations were measured with a Bendix–Ericsson automatic polarimeter. N.m.r. spectra were recorded at 80 MHz for solutions in deuteriochloroform, with tetramethylsilane as internal standard. Thin-layer chromatography (t.l.c.) was carried out on Silica gel G, and column chromatography on silica gel (0.05–0.1 mm); detection was by charring with 5% sulphuric acid in ethanol. 1,2-Dimethoxyethane was dried as described by Perrin *et al.*[20] and stored over sodium hydride. Solvents were removed under diminished pressure at <40°. All reactions were monitored by t.l.c.

Debenzylation was effected by hydrogenolysis at atmospheric pressure and room temperature over 5% palladium-on-charcoal (0.1 g/g, Koch–Light Laboratories Ltd.).

Detritylation and debenzylidenation were achieved with warm, dilute acetic acid. The 6-acetate, formed on concentration of solutions in aqueous acetic acid[5,21], was deacetylated (Zemplén) with sodium methoxide in methanol.

Etherification (methylation and benzylation). — Sodium hydride (3 equiv./OH group) was added, with stirring and exclusion of atmospheric moisture and carbon dioxide, to a chilled solution of the substrate in 1,2-dimethoxyethane (10 or 20 ml/g for methylation and benzylation, respectively). Methyl iodide or benzyl bromide (2 equiv./OH group) was added and the mixture was stirred (with gentle reflux for benzylation of tritylated compounds) until t.l.c. showed that the reaction was complete (15 min–2 h). The excess of the etherification agent was destroyed by the addition of methanol and, after the addition of water, the organic solvents were removed. The mixture was partitioned between chloroform and water, and the chloroform solution was washed with water until neutral. Evaporation of the dried (Na_2SO_4) chloroform solution gave the product, from which pure compounds were isolated by crystallization or column chromatography.

Oxidation. — A solution of chromium trioxide (1.2 g/g of the substrate) in 3.5M sulphuric acid (2.7 ml/g of chromium trioxide) was added with stirring to a solution of the substrate in acetone (16 ml/g) at ~0°. Cooling was terminated after 10 min, and the mixture was stirred for an additional 60 min and then filtered through a sintered-glass filter-funnel of medium porosity on to crushed ice (50 g/g of substrate). The solids were washed with acetone, and the combined filtrate and washings were concentrated to remove the organic solvent. The aqueous phase, from which some oily product started to separate, was washed with chloroform which was then washed with water. The chloroform solution was dried (Na_2SO_4) and evaporated to dryness, and a solution of the residue in a little methanol was added to the top of a column of freshly prepared, methanol-washed Amberlite IRA-402 (HO^-) resin (twofold excess). Elution with methanol removed unreacted starting material and oxidation by-products (monitoring of fractions by t.l.c.), and the free acid was obtained by elution with methanol–acetic acid–water (45:45:10, 5–10 bed volumes). The eluate was concentrated with co-distillation with water to remove acetic acid, the residue was dissolved in methanol (5 ml/g), and excess 1–2% diazomethane in ether was added. The resulting methyl ester was purified by column chromatography on silica gel and then distilled.

Preparation of amides. — A mixture of liquid ammonia and dry methanol (1:1, 30 ml) was added to a solution of a methyl ester (200 mg) in methanol (10 ml), and the solution was left overnight under a potassium hydroxide drying-tube. T.l.c. then showed that the reaction was complete and that a single, slower-moving product was formed. The solution was concentrated and the solid residue was crystallized.

Methyl (methyl 2-O-methyl-α-D-glucopyranosid)uronate (**4**). — Methyl 3-*O*-benzyl-2-*O*-methyl-α-D-glucopyranoside[13] (5.9 g) was tritylated and acetylated to give the known 4-acetate[22] (9.5 g, 81.6%), m.p. 124–125°; lit.[22] m.p. 125–126°. Deacetylation[17] and subsequent benzylation of HO-4 afforded methyl 3,4-di-*O*-benzyl-2-*O*-methyl-6-*O*-trityl-α-D-glucopyranoside (**1**; 9.8 g, 94.2%), m.p. 112–113°

(from ethanol), $[\alpha]_D^{24}$ +45° (*c* 1.07, chloroform) (Found: C, 78.14; H, 6.84; OMe, 10.00. $C_{41}H_{42}O_6$ calc.: C, 78.07; H, 6.71; OMe, 9.84%).

Compound **1** was detritylated to give, in almost theoretical yield, methyl 3,4-di-*O*-benzyl-2-*O*-methyl-α-D-glucopyranoside (**2**), b.p. 260–280° (bath)/0.1 torr, $[\alpha]_D^{25}$ +77° (*c* 1.03, chloroform) (Found: C, 67.87; H, 7.12; OMe, 16.00. $C_{22}H_{28}O_6$ calc.: C, 68.02; H, 7.26; OMe, 15.79%).

Oxidation of **2** (4.6 g) and esterification gave methyl (methyl 3,4-di-*O*-benzyl-2-*O*-methyl-α-D-glucopyranosid)uronate (**3**; 3.5 g, 71.2%), b.p. 260–280° (bath)/0.1 torr, $[\alpha]_D^{25}$ +69° (*c* 1.3, chloroform) (Found: C, 66.35; H, 6.99; OMe, 22.41. $C_{23}H_{28}O_7$ calc.: C, 66.34; H, 6.78; OMe, 22.36%). The derived amide had m.p. 168.5–169.5° (from ethyl acetate), $[\alpha]_D^{25}$ +34.5° (*c* 1.04, acetone) (Found: C, 65.85; H, 6.58; N, 3.31; OMe, 15.15. $C_{22}H_{27}NO_6$ calc.: C, 65.83; H, 6.78; N, 3.49; OMe, 15.46%).

Hydrogenolysis of **3** gave **4**, b.p. 180° (bath)/0.1 torr, $[\alpha]_D^{25}$ +131.5° (*c* 1.04, methanol); lit.[9] $[\alpha]_D^{23}$ +98° (*c* 1, methanol). N.m.r. data: τ 5.07 (1-proton doublet, $J_{1,2}$ 3.5 Hz, H-1), 6.19 (3-proton singlet, COOMe), 6.50 and 6.56 (3-proton singlets, 2 OMe) (Found: C, 45.55; H, 6.90; OMe, 39.68. $C_9H_{16}O_7$ calc.: C, 45.80; H, 6.83; OMe, 39.41%). The corresponding amide had m.p. 155–155.5° (from 2-propanol or acetone), $[\alpha]_D^{25}$ +138° (*c* 1.03, water) (Found: C, 43.40; H, 6.99; N, 6.13; OMe, 28.29. $C_8H_{15}NO_6$ calc.: C, 43.44; H, 6.83; N, 6.33; OMe, 28.06%).

Methyl (methyl 3-O-methyl-α-D-glucopyranosid)uronate (**12**). — Methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside[14] (15 g) was converted into the 2-*O*-benzyl derivative **5** (18.5 g, 94%), m.p. 97–98° (from ethanol), $[\alpha]_D^{24}$ +21° (*c* 0.98, chloroform) (Found: C, 68.64; H, 6.84; OMe, 15.98. $C_{22}H_{26}O_6$ calc.: C, 68.37; H, 6.78; OMe, 16.06%). Debenzylidenation of **5** (14.5 g) gave methyl 2-*O*-benzyl-3-*O*-methyl-α-D-glucopyranoside (**6**; 11 g, 91.7%), b.p. 210° (bath)/0.02 torr, $[\alpha]_D^{24}$ +59° (*c* 0.98, chloroform) (Found: C, 60.24; H, 7.27; OMe, 20.74. $C_{15}H_{22}O_6$ calc.: C, 60.39; H, 7.43; OMe, 20.81%). Methyl 2-*O*-benzyl-3-*O*-methyl-6-*O*-trityl-α-D-glucopyranoside (**7**) {m.p. 146–147° (from chloroform–ether), $[\alpha]_D^{24}$ +37° (*c* 1, chloroform) (Found: C, 75.49; H, 6.67; OMe, 12.18%. $C_{34}H_{36}O_6$ calc.: C, 75.53; H, 6.71; OMe, 12.48%)} was obtained (82%) from **6** most conveniently through the 4-acetate **8** {m.p. 121–122° (from chloroform–ethanol), $[\alpha]_D^{24}$ +45° (*c* 0.98, chloroform)}. Benzylation of **7** (18 g) afforded methyl 2,4-di-*O*-benzyl-3-*O*-methyl-6-*O*-trityl-α-D-glucopyranoside (**9**; 18 g, 85.8%), $[\alpha]_D^{25}$ +43° (*c* 1.19, chloroform), as a glassy solid (Found: C, 78.07; H, 6.97; OMe, 10.10%). Compound **9** (17 g) was detritylated to give methyl 2,4-di-*O*-benzyl-3-*O*-methyl-α-D-glucopyranoside (**10**; 8 g, 76.6%), m.p. 60–61° (from ether–hexane), $[\alpha]_D^{24}$ +62° (*c* 1.2, chloroform) (Found: C, 68.07; H, 7.24; OMe, 16.04%).

Oxidation of **10** (6.3 g), followed by esterification, gave methyl (methyl 2,4-di-*O*-benzyl-3-*O*-methyl-α-D-glucopyranosid)uronate (**11**; 5.5. g, 81.2%), b.p. 166–167°/0.01 torr, $[\alpha]_D^{25}$ +54° (*c* 1.02, chloroform) (Found: C, 65.95; H, 6.78; OMe, 22 55%), which gave an amide, m.p. 173–173.5° (from methanol or 2-propanol), $[\alpha]_D^{24}$ +62° (*c* 1, acetone) (Found: C, 65.72; H, 6.92; N, 3.52; OMe, 15.43%).

The ester **11** was hydrogenolyzed to give **12**, b.p. 180–190° (bath)/0.02 torr, as a viscous syrup that crystallized on standing, m.p. 85–90°, but which could not be recrystallized. Trituration with ether–hexane and hexane, gradually raised the m.p. to a constant value of 88.5–89°, $[\alpha]_D^{25}$ +150° (*c* 1, methanol), lit.[9] $[\alpha]_D^{23}$ +98.5°. N.m.r. data: τ 5.15 (1-proton doublet, $J_{1,2}$ 3 Hz, H-1), 6.12 (3-proton singlet, COOMe), 6.35 and 6.45 (3-proton singlets, 2OMe) (Found: C, 45.85; H, 6.84; OMe, 39.20%). Methyl 3-*O*-methyl-α-D-glucopyranosiduronamide, when crystallized from methanol, had $[\alpha]_D^{25}$ +144° (*c* 1.04, water) and sublimed above 245° (Found: C, 43.40; H, 6.90; N, 6.30; OMe, 27.77%).

*Methyl (methyl 4-*O*-methyl-α-*D*-glucopyranosid)uronate* (**15**). — Methyl 2,3-di-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside[23] (30 g) was methylated and detritylated to give methyl 2,3-di-*O*-benzyl-4-*O*-methyl-α-D-glucopyranoside (**13**; 16.8 g, 89%), m.p. 52–53° (from isopropyl ether at −5°), $[\alpha]_D^{25}$ +46° (*c* 1.15, chloroform); lit.[23] for amorphous **13**, $[\alpha]_D^{25}$ +43° (*c* 1, chloroform).

Oxidation of **13** (5 g), followed by esterification, gave methyl (methyl 2,3-di-*O*-benzyl-4-*O*-methyl-α-D-glucopyranosid)uronate (**14**; 4.5 g, 84.2%), which gave an amide having m.p. 182–183°, $[\alpha]_D^{24}$ +86° (*c* 1, acetone); lit.[8] m.p. 179°, $[\alpha]_D^{18}$ +79°.

Hydrogenolysis of **14** gave syrupy **15**, $[\alpha]_D^{25}$ +143.5–147° (*c* 1, methanol); lit.[8] $[\alpha]_D$ +145.5°. N.m.r. data: τ 5.20 (1-proton doublet, $J_{1,2}$ 3.25 Hz, H-1), 6.18 (3-proton singlet, COOMe), 6.50 and 6.56 (3-proton singlets, 2 OMe).
The derived amide had m.p. 236–237°, $[\alpha]_D^{24}$ +142° (*c* 1, water); lit.[8,24] m.p. 235–236° (dec.), $[\alpha]_D^{17}$ +150°.

*Methyl (methyl 2,3-di-*O*-methyl-α-*D*-glucopyranosid)uronate* (**18**). — Methyl 2,3-di-*O*-methyl-6-*O*-trityl-α-D-glucopyranoside[25] (25.6 g) was benzylated and detritylated to give methyl 4-*O*-benzyl-2,3-di-*O*-methyl-α-D-glucopyranoside (**16**; 15.9 g, 92.2%), m.p. 94–95° (from ether–hexane), $[\alpha]_D^{24}$ +142° (*c* 1.2, chloroform) (Found: C, 61.70; H, 7.62; OMe, 29.84. $C_{16}H_{24}O_6$ calc.: C, 61.52; H, 7.74; OMe, 29.80%).

Oxidation of **16** (10 g), followed by esterification, gave methyl (methyl 4-*O*-benzyl-2,3-di-*O*-methyl-α-D-glucopyranosid)uronate (**17**; 8.5 g, 78.2%), b.p. 136–138°/0.01 torr, $[\alpha]_D^{25}$ +131° (*c* 1.4, chloroform) (Found: C, 59.80; H, 7.20; OMe, 36.49. $C_{17}H_{24}O_7$ calc.: C, 59.99; H, 7.10; OMe, 36.47%). The derived amide had m.p. 184.5–185.5° (from ethanol), $[\alpha]_D^{24}$ +101° (*c* 1, acetone) (Found: C, 58.94; H, 7.06; N, 4.45; OMe, 28.48. $C_{16}H_{23}NO_6$ calc.: C, 59.06; H, 7.12; N, 4.30; OMe, 28.61%).

Hydrogenolysis of **17** gave **18**, b.p. 86–87°/0.03 torr, $[\alpha]_D^{25}$ +137° (*c* 1.08, methanol); lit.[10] $[\alpha]_D^{18}$ +111°. N.m.r. data: τ 5.05 (1-proton doublet, $J_{1,2}$ 3 Hz, H-1), 6.14 (3-proton singlet, COOMe), 6.29 (3-proton singlet, OMe), 6.37 (6-proton singlet, 2 OMe) (Found: C, 47.62; H, 7.25; OMe, 49.97. $C_{10}H_{18}O_7$ calc.: C, 48.00; H, 7.25; OMe, 49.61%). The derived 4-*p*-nitrobenzoate had m.p. 161° (from ethanol), $[\alpha]_D^{25}$ +69° (*c* 1, chloroform); lit.[10,16] m.p. 156–158°, $[\alpha]_D$ +69°. Methyl 2,3-di-*O*-methyl-α-D-glucopyranosiduronamide had m.p. 109–110° (from ethyl acetate–ether), $[\alpha]_D^{25}$ +98° (*c* 1.02, methanol) (Found: C, 46.19; H, 7.40; N, 5.67; OMe, 39.94. $C_9H_{17}NO_6$ calc.: C, 45.95; H, 7.29; N, 5.95; OMe, 39.58%).

Methyl (methyl 2,4-di-O-methyl-α-D-glucopyranosid)uronate (**21**). — Methyl 3-*O*-benzyl-2,4-di-*O*-methyl-α-D-glucopyranoside (**19**; 7 g, 88.5%), obtained by detritylation of methyl 3-*O*-benzyl-2,4-di-*O*-methyl-6-*O*-trityl-α-D-glucopyranoside[17] (14 g) and crystallized from isopropyl ether or isopropyl acetate–hexane, had m.p. 49–51°, $[\alpha]_D^{25}$ +116° (*c* 1.5, chloroform) (Found: C, 61.22; H, 7.22; OMe, 30.08%).

Oxidation of **19** (8 g), followed by esterification, gave methyl (methyl 3-*O*-benzyl-2,4-di-*O*-methyl-α-D-glucopyranosid)uronate (**20**; 8 g, 91.7%), b.p. 127–128°/0.01 torr, $[\alpha]_D^{25}$ +94° (*c* 1.27, chloroform) (Found: C, 59.63; H, 7.06; OMe, 36.36%). The corresponding amide had m.p. 175–176°, $[\alpha]_D^{25}$ +104.5° (*c* 1.02, acetone) (Found: C, 59.23; H, 7.08; N, 4.31; OMe, 28.9%).

Catalytic hydrogenolysis of **20** gave **21**, b.p. 85–86°/0.03 torr, $[\alpha]_D^{25}$ +140° (*c* 1.05, methanol). N.m.r. data: τ 5.04 (1-proton doublet, $J_{1,2}$ 3.25 Hz, H-1), 6.16 (3-proton singlet, COOMe), 6.45 (6-proton singlet, 2 OMe), 6.55 (3-proton singlet, OMe) (Found: C, 47.91; H, 7.18; OMe, 49.22%). The derived amide had m.p. 240° (from ethanol), $[\alpha]_D^{25}$ +150° (*c* 0.98, methanol) (Found: 45.86; H, 7.36; N, 5.92; OMe, 39.40%).

Methyl (methyl 3,4-di-O-methyl-α-D-glucopyranosid)uronate (**25**). — Compound **7** (15 g) was methylated to give methyl 2-*O*-benzyl-3,4-di-*O*-methyl-6-*O*-trityl-α-D-glucopyranoside (**22**; 15.5 g, ~100%), which was crystallized from ether–hexane. Recrystallization from ether afforded material (12.5 g, 81.4%) having m.p. 115–116°, $[\alpha]_D^{25}$ +50° (*c* 0.96, chloroform) (Found: C, 75.77; H, 6.80; OMe, 16.97. $C_{35}H_{38}O_6$ calc.: C, 75.78; H, 6.91; OMe, 16.79%). Detritylation of **22** (11 g) gave methyl 2-*O*-benzyl-3,4-di-*O*-methyl-α-D-glucopyranoside (**23**; 5.5 g, 88.5%), b.p. 135–136°/0.01 torr, $[\alpha]_D^{25}$ +67.5° (*c* 1.22, chloroform) (Found: C, 61.59; H, 7.95; OMe, 29.73%).

Oxidation of **23** (7.1 g) and subsequent esterification gave methyl (methyl 2-*O*-benzyl-3,4-di-*O*-methyl-α-D-glucopyranosid)uronate (**24**; 5.7 g, 73.7%), b.p. 131–132°/0.02 torr, $[\alpha]_D^{25}$ +51° (*c* 1.05, chloroform) (Found: C, 60.15; H, 7.13; OMe, 36.40%). The derived amide had m.p. 191–192° (from methanol), $[\alpha]_D^{25}$ +100° (*c* 1, acetone)(Found: C, 60.13; H, 7.20; N, 4.48; OMe, 29.01%).

Catalytic hydrogenolysis of **24** produced **25**, m.p. 67.5–68.5° (from isopropyl ether), $[\alpha]_D^{25}$ +158° (*c* 1, chloroform); lit.[18,19] syrup, $[\alpha]_D$ not given. N.m.r. data: τ 5.20 (1-proton doublet, $J_{1,2}$ 3.25 Hz, H-1), 6.19 (3-proton singlet, COOMe), 6.38 (3-proton singlet, OMe), 6.53 (6-proton singlet, 2 OMe) (Found: C, 47.77; H, 7.26; OMe, 49.43%). The derived amide had m.p. 208–209°, $[\alpha]_D^{25}$ +163.5° (*c* 1.01, methanol); lit.[18,19] m.p. 191–193°, $[\alpha]_D^{17}$ +100°.

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