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SYNTHESIS OF SOME ARYL 2,3,4,6-TETRA-*O*-ACETYL-L-IDOPYRANOSIDES AND OF 4-METHYLCOUMARIN-7-YL α-L-IDOPYRANOSIDURONIC ACID

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ABSTRACT

Several routes for synthesis of 3,5,6-tri-*O*-acetyl-1,2-*O*-isopropylidene-β-L-idofuranose have been evaluated. Previously described routes, which involved selective sulphonylation, were not reproducible on a 100-g scale. To overcome this difficulty, a new variation was developed, involving complete tosylation of 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone followed by reduction and acetylation. The idofuranose derivative was converted into the desired 1,2,3,4,6-penta-*O*-acetyl-α-L-idopyranose *via* 1,6-anhydro-β-L-idopyranose. Fusion of 1,2,3,4,6-penta-*O*-acetyl-α-L-idopyranose with 4-nitrophenol, 1- or 2-naphthol, or 4-methylcoumarin-7-ol, using freshly fused zinc chloride as catalyst, gave an anomeric mixture of glycosides, with the α anomer being preponderant. The major 4-methylcoumarin-7-yl glycoside was deacetylated and converted, by catalytic oxidation, into 4-methylcoumarin-7-yl α-L-idopyranosiduronic acid, a fluorogenic substrate for α-L-iduronidase.

INTRODUCTION

For detection of Hurler and Scheie syndromes, by assay of α-L-iduronidase (EC 3.2.1.76) activity, 4-methylcoumarin-7-yl α-L-idopyranosiduronic acid (**1**) is a sensitive and convenient substrate[1–3]. Two general strategies are available for the synthesis of aryl hexopyranosiduronic acids, either by glycosidation of a suitable hexopyranuronic acid derivative or by selective oxidation of the corresponding hexopyranoside. No available derivative of L-iduronic acid is suitable for use in the former strategy. Two syntheses of aryl α-L-idopyranosiduronic acids using the latter strategy have been reported[4,5] and difficulty was noted in the formation of the intermediate blocked idopyranosides. We now report syntheses of aryl idopyranosides, in moderate yield, by conventional Helferich synthesis in which no difficulties were experienced, and conversion of 4-methylcoumarin-7-yl α-L-idopyranoside (**2**) into the corresponding uronic acid **1**, in low yield, by catalytic oxidation.

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DISCUSSION

The Helferich[6] method for synthesis of glycosides, involving fusion of a peracetylated sugar with a phenol in the presence of a Lewis acid catalyst, has been successfully applied in a number of cases[7], but has been reported to be unsatisfactory for synthesis of aryl idopyranosides[4,5]. For this synthesis, use of a high-boiling solvent such as 1,2-diacetoxyethane was recommended, and gave moderate but variable yields. Other potential routes to L-idopyranosides may involve the corresponding glycosyl halide, but this is made[8] from the sugar penta-acetate.

The key intermediate penta-*O*-acetyl-α-L-idopyranose can be prepared[8] from 3,5,6-tri-*O*-acetyl-1,2-*O*-isopropylidene-β-L-idofuranose (**3**). Several routes to **3**, starting from readily available materials, were explored. The principal difficulty in the route introduced by Vargha[9] was the selective sulphonylation[10] of 1,2-*O*-isopropylidene-α-D-glucofuranose to give the 5,6-ditosylate. In relatively large-scale reactions, ~6% overall yields based on D-glucose were achieved. In an earlier synthesis of a suitable intermediate, Ohle *et al.*[11] were unable to obtain either a good yield or a pure product from toluene-*p*-sulphonylation of 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**4**) because of acetyl migration or displacement by chloride ion[12]. These difficulties were overcome[13] by cooling the reaction mixture, when a 91% yield was obtained in this step. In our hands, when working with larger (~200 g) quantities of **4**, such high yields could not be obtained and the reaction was less reproducible; nevertheless, in some experiments, the overall yield of **3** could be increased (~10%). The use of an anion-exchange (AcO^-) resin in acetic anhydride[13] for the nucleophilic displacement step gave a further improvement to 16% overall yield.

In order to circumvent these difficulties, we have developed an alternative route which gave a reasonable yield and good reproducibility on scale-up. Thus, D-glucofuranurono-6,3-lactone was converted into 1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-D-glucofuranurono-6,3-lactone[14], which was reduced with sodium borohydride in 1,4-dioxane to the corresponding glucofuranose[15]. Acetylation and inversion of configuration with an anion-exchange (AcO^-) resin in acetic anhydride gave **3** in 27% overall yield from the starting lactone.

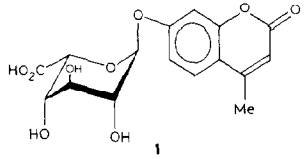
There are discrepancies between our physical constants for **3** and those previously reported; the melting point (91–92°) was close to one reported value[9], but higher than others[12,16], and the specific rotation ($[\alpha]_D$ −20°) was significantly different from reported values[9,12] (0°, −2°). The $[\alpha]_D$ value obtained in this work remained unchanged on recrystallisation and the material was homogeneous by t.l.c.

In contrast to earlier reports[4,5], we have found that the unmodified Helferich reaction can be applied for the synthesis of aryl L-idopyranosides. This work is part of a programme aimed at synthesis of artificial chromogenic and fluorogenic substrates for use in enzyme assays and, for this purpose, 4-nitrophenyl, 1- and 2-naphthyl, and 4-methylcoumarin-7-yl moieties are most suitable as aglycons.

Fusion of 1,2,3,4,6-penta-*O*-acetyl-α-L-idopyranose (**5**; prepared[8] from **3**) at

140° for 0.5 h with 4-nitrophenol, using freshly fused zinc chloride as catalyst, gave a mixture of glycosides which was resolved by column chromatography on silica gel, to yield the α-glycoside **6** ($[\alpha]_D$ −126.4°) in 44% yield, and the β-glycoside **7** ($[\alpha]_D$ +72.5°) in 7% yield. The configurations of **6** and **7** were assigned on the basis of their optical rotations, the α configuration being assigned to that with the high negative rotation[4,5].

For reaction with 1-naphthol, the lower melting point of the phenol allowed a lower reaction temperature (120° for 1 h), and this gave the α-glycoside **8** in 20% yield, and the β-glycoside **9** in 2% yield. Similarly, reaction with 2-naphthol gave both glycosides (**10** and **11**), with the α-glycoside **10** (28%) as the major product.



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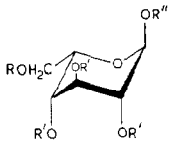

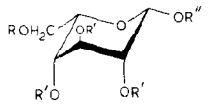

7 R = R′ = Ac, R″ = 4-nitrophenyl
9 R = R′ = Ac, R″ = 1-naphthyl
11 R = R′ = Ac, R″ = 2-naphthyl
13 R = R′ = Ac, R″ = 4-methylcoumarin-7-yl

2 R = R′ = H, R″ = 4-methylcoumarin-7-yl
5 R = R′ = R″ = Ac
6 R = R′ = Ac, R″ = 4-nitrophenyl
8 R = R′ = Ac, R″ = 1-naphthyl
10 R = R′ = Ac, R″ = 2-naphthyl
12 R = R′ = Ac, R″ = 4-methylcoumarin-7-yl
14 R = Ph_3C, R′ = Ac, R″ = 4-methylcoumarin-7-yl
15 R = R′ = H, R″ = 4-nitrophenyl
16 R = R′ = H, R″ = 1-naphthyl
17 R = R′ = H, R″ = 2-naphthyl

Because of the high melting point of 4-methylcoumarin-7-ol, the fusion reaction with this phenol was first carried out at 165° and the reaction time was reduced to 5 min. This gave the α-glycoside (**12**) in 25% yield, and the β-glycoside (**13**) in 5% yield, after chromatography. The principal objective of this work was to develop an efficient synthesis of the 4-methylcoumarin-7-yl glycoside **2** for oxidation to the corresponding iduronide. Consequently, the reaction conditions were optimised, and the α-glycoside could then be obtained by direct crystallisation without recourse to chromatography. The conditions and yields of α-glycoside obtained by crystallisation are summarised in Table I, from which it can be seen that the best yield of 38% was obtained when the reaction was carried out at ~150° for 45 min.

In each of the above investigations, the specific rotation was used to assign configuration to the glycosides; the anomer with strongly negative rotation was as-

TABLE I

SYNTHESIS OF 4-METHYLCOUMARIN-7-YL 2,3,4,6-TETRA-*O*-ACETYL-α-L-IDOPYRANOSIDE FROM **5** (5 g)

4-Methylcoumarin-7-ol (g)	*Zinc chloride (g)*	*Temperature (degrees)*	*Time (min)*	*Yield (%)*
3.35	0.60	145	30	23
3.35	0.60	165	5	20
3.35	0.60	135–140	60	20
3.35	1.50	145	30	10
4.0	0.75	140–150	45	17
4.0	0.85	140–150	45	16
3.67	0.83	140–150	40	20
3.35	0.70	150–155	45	31
3.33	0.60	150–155	45	38
3.5	0.60	150–155	45	35.5

signed the α-L configuration in each case. These assignments parallel other configurational assignments for aryl L-idopyranosides[4,5]

The preferred conformations of these aryl tetra-*O*-acetylidopyranosides were deduced by n.m.r. spectroscopy. The small difference (<0.1 p.p.m.) in chemical shifts for H-1 of anomeric pairs of glycosides indicated that the anomers were not in the same conformation, because an equatorial anomeric proton gives rise to a signal to lower field than that of the corresponding axial proton if the conformation remains the same[17]. For the α-glycosides, the observed small coupling-constants ($J_{1,2}$ <1, $J_{3,4}$ 4, and $J_{4,5}$ 1.5 Hz) suggest the $^1C_4$(L) conformation[18,19]. The values for the β-glycosides ($J_{1,2}$ 2.5, $J_{2,3}$ 6, $J_{3,4}$ 6, and $J_{4,5}$ 4 Hz) suggest that the $^4C_1$(L) conformation is significantly populated in addition to the $^1C_4$(L) conformation[19].

The aryl tetra-*O*-acetyl-α-L-idopyranosides **6, 8, 10,** and **12** were deacetylated with sodium methoxide in dry methanol, to give the respective free glycosides (**15, 16, 17,** and **2**). Satisfactory elemental analyses were obtained for the 4-nitrophenyl (**15**) and 4-methylcoumarin-7-yl (**2**) glycosides, but not for the isomeric naphthyl glycosides **16** and **17**.

Catalytic oxidation[20] of **2** using platinum black, prepared by hydrogenation of platinum oxide, was carried out at ~95° with periodic addition of sodium hydrogencarbonate. The resulting mixture was subjected to chromatography, to give the iduronide **1** (19%), which was used as a substrate in convenient, sensitive assays for α-L-iduronidase[1,2], together with the corresponding glucuronide. Epimerisation was also observed during oxidation of phenyl α-L-idopyranoside[4,5], but not during oxidation of L-idopyranosyl phosphate[8], benzyl 2,3-di-*O*-benzyl-α- or -β-L-idopyranoside[21], or 4-methylcoumarin-7-yl β-D-glucopyranoside[22].

In an effort to increase the rate of the oxidation and thereby minimise epimerisation, residual hydrogen gas was removed from the catalyst under vacuum[23]. Also, platinum-on-carbon, prepared by absorption of platinum chloride onto charcoal in alkaline medium followed by reduction with formaldehyde, was

used as catalyst. Neither variation gave significant improvement. Palladium-on-carbon catalyst prepared in the above way has been recommended for oxidation of aldoses to aldonic acids with minimal base-promoted isomerisation[24].

In view of the difficulties experienced during catalytic oxidation of **2**, alternative synthetic strategies, involving selective blocking and chemical oxidation, were considered. Thus, in an attempt to block only the secondary hydroxyl groups, **2** was treated with triphenylmethyl chloride and then acetic anhydride to give 4-methylcoumarin-7-yl 2,3,4-tri-*O*-acetyl-6-*O*-triphenylmethyl-α-L-idopyranoside (**14**). When the trityl group was removed from this compound, by brief treatment with hydrogen bromide in acetic acid, a crystalline triacetate was obtained after chromatography. It was clear from the p.m.r. spectrum that acetyl migration had occurred, because of the presence of a doublet, rather than a triplet, for the hydroxyl group at δ 2.68, which disappeared on treatment with D_2O. The triacetate was assigned the 4-methylcoumarin-7-yl 2,3,6-tri-*O*-acetyl-α-L-idopyranoside structure because its p.m.r. spectrum was very similar to that reported[25] for 1,2,3,6-tetra-*O*-acetyl-α-D-idopyranose and because migration from O-4 to O-6 is expected to be facile as a result of the *cis*-relationship of these groups. Other migrations would involve *trans*-related groups and should be less facile[26].

An alternative approach would be to achieve selective blocking at an earlier stage in the reaction sequence. Thus, 1,6-anhydro-β-L-idopyranose was benzylated to give 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-L-idopyranose which was acetolysed under conditions reported[27] for the corresponding *gluco* isomer. The resulting syrupy product appeared, by n.m.r. spectroscopy, to be 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α,β-L-idopyranose. The syrup could not be crystallised or fractionated into individual anomers, and the approach was not further explored.

EXPERIMENTAL

General methods. — Melting points are uncorrected. 1,4-Dioxane was dried over calcium hydride, chloroform was dried over anhydrous calcium chloride, pyridine was distilled from phosphorus pentaoxide and stored over potassium hydroxide, and methanol was dried by distillation from magnesium methoxide. Zinc chloride was fused, cooled, and powdered just before use.

T.l.c. was performed on silica gel (Merck, 7731), and detection effected by iodine vapour or vanillin–sulphuric acid. Column chromatography was carried out on silica gel (Merck, 7734). ^{1}H-N.m.r. spectra were recorded with a Perkin–Elmer R-14 or Varian XL 100 spectrometer for solutions in $CDCl_3$ (internal Me_4Si) unless otherwise specified. Coupling constants are measured splittings. Optical rotations were determined with a Perkin–Elmer 141 polarimeter (1-dm tube).

*1,2-O-Isopropylidene-5-O-toluene-*p*-sulphonyl-α-*D*-glucofuranurono-6,3-lactone* (**18**). — D-Glucofuranurono-6,3-lactone (50 g) was dissolved in acetone (2.5 L) containing conc. sulphuric acid (30 mL), and the mixture was stored overnight, stirred with anhydrous sodium carbonate (100 g) until neutral, filtered, and concen-

trated. The residue was recrystallised from propan-2-ol, to yield the 1,2-*O*-isopropylidene derivative (57 g, 93%), m.p. 119–121°; lit.[28] (65%), m.p. 120°.

To a solution of the foregoing compound (75 g) in acetone (1 L) and pyridine (100 mL) was added, portionwise with stirring, toluene-*p*-sulphonyl chloride (107 g). The mixture was stored overnight at room temperature, and then poured onto ice and water. The crystalline product was collected, and recrystallised from aqueous acetone, to give **18** (96.3 g, 75%), m.p. 182–183°; lit.[14] m.p. 189–194°.

*3,6-Di-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-*D*-glucofuranose.* — (*a*) To a stirred solution of **18** (3 g) in 1,4-dioxane (90 mL), cooled in an ice-bath, was added acetic acid (9 mL) followed by sodium borohydride (3 g) portionwise during 0.5 h. The mixture was kept at 0° overnight, and then poured onto ice and water (100 mL). The product was extracted with chloroform (3 × 100 mL), the extract was washed with water, dried ($MgSO_4$), and concentrated, and the residue was crystallised from chloroform–light petroleum, to give 1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose (2.2 g, 73%), m.p. 118–120°; lit.[15] m.p. 124–125.5°.

A solution of the foregoing product (7.3 g) in dry pyridine (20 mL) and acetic anhydride (60 mL) was stored overnight at room temperature and then concentrated. Toluene was distilled several times from the residue, which crystallised from methanol to give the title product (8.4 g, 94%), m.p. 129–130°, $[\alpha]_D$ −15° (*c* 1, chloroform). N.m.r. data: δ 7.75–7.30 (q, 4 H, Ph), 5.85 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.15 (d, 1 H, $J_{3,4}$ 5 Hz, H-3), 5.0 (m, 1 H, H-5), 5.5 (d, 1 H, $J_{4,5}$ 3 Hz, H-4), 4.45–4.15 (m, 3 H, H-2,6,6'), 2.40 (s, 3 H, PhMe), 2.10, 1.94 (2 s, 6 H, 2 Ac), 1.42, and 1.25 (2 s, 6 H, CMe_2) (Found: C, 52.3; H, 5.9; S, 7.1. $C_{20}H_{26}O_{10}S$ calc.: C, 52.4; H, 5.7; S, 7.0%).

(*b*) The lactone **18** (27 g) was reduced as described above, and a solution of the residue (from the chloroform extraction) in pyridine (90 mL) and acetic anhydride (180 mL) was stored overnight at room temperature and then concentrated, and toluene was distilled from the residue. Crystallisation from methanol gave the title product (21 g, 63%), m.p. 125–126°.

*3,5,6-Tri-*O*-acetyl-1,2-*O*-isopropylidene-β-*L*-idofuranose* (**3**). — (*a*) By the method of Vargha[9], 3-*O*-acetyl-1,2-*O*-isopropylidene-5,6-di-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose (210 g) was treated with anhydrous potassium acetate (200 g) in acetic anhydride (1 L), followed by a second treatment with potassium acetate (150 g) in acetic anhydride (1 L), to give **3** (42.6 g, 33%), m.p. 92–93° (from ethanol), $[\alpha]_D^{19}$ −21° (*c* 1.9, chloroform); lit.[9] m.p. 95–96°, $[\alpha]_D$ 0° (chloroform); lit.[12] m.p. 82–84°, $[\alpha]_D$ −2° (chloroform); lit.[16] m.p. 82–84°. N.m.r. data: δ 5.95 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.4 (m, 1 H, H-5), 5.25 (d, 1 H, H-3), 4.4 (m, 3 H, H-2,4,6), 3.95 (m, 1 H, H-6'), 2.09, 2.07, 2.0 (3 s, 9 H, 3 Ac), 1.5, and 1.3 (2 s, 6 H, 2 CMe_2).

(*b*) A mixture of 3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose (40 g), anhydrous potassium acetate (38 g), and acetic anhydride (400 mL) was boiled under reflux for 55 h and then worked-up as described above, to give **3** (16.5 g, 55%), m.p. 91–92°, $[\alpha]_D$ −21° (*c* 1, chloroform).

(*c*) Dry Amberlite IRA-400 (AcO^-) resin (70 g) was added to acetic anhydride (150 mL), followed by 3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-5-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose (5 g), and the mixture was boiled under reflux for 48 h. The mixture was filtered hot, the resin was washed with acetic anhydride (150 mL), and the combined filtrate and washings were concentrated. A solution of the syrupy residue in chloroform was washed with water (3×), dried ($MgSO_4$), filtered, and concentrated. The residue crystallised from ethanol, to yield **3** (2.5 g, 67%), m.p. 88–90°.

(*d*) The lactone **18** (27 g) was reduced as described above. To a solution of the residue from the chloroform extraction in acetic anhydride (100 mL) was added a suspension of dry Amberlite IRA-400 (AcO^-) resin (200 g) in acetic anhydride (600 mL). The mixture was boiled under reflux for 48 h and then worked-up as in (*c*), to give **3** (9.5 g, 38% overall), m.p. 87–89°.

2,3,4-Tri-O-acetyl-1,6-anhydro-β-L-idopyranose. — A solution of 3,5,6-tri-*O*-acetyl-1,2-*O*-isopropylidene-β-L-idofuranose (20 g) in methanolic sodium methoxide [from sodium (0.3 g) and dry methanol (400 mL)] was stored overnight at room temperature, neutralised with dilute hydrochloric acid, and concentrated. A solution of the solid residue in water (280 mL) containing conc. hydrochloric acid (15 mL) was boiled under reflux for 6 h and then concentrated, and the resulting syrup was treated with acetic anhydride (120 mL) and dry pyridine (200 mL) at room temperature overnight. The solvents were evaporated, and toluene was distilled several times from the residue, which crystallised from ethanol to give the title product (10.4 g, 62%), m.p. 85–87°; lit.[29] m.p. 85.5–87°, 67–68°.

4-Nitrophenyl 2,3,4,6-tetra-O-acetyl-α- (**6**) *and -β-L-idopyranoside* (**7**). — A mixture of 4-nitrophenol (4.0 g) and 1,2,3,4,6-penta-*O*-acetyl-α-L-idopyranose **5** (4.0 g) was melted under high vacuum with stirring. The vacuum was released and fused zinc chloride (0.4 g) was added. The mixture was stirred and the temperature was raised to 140° for 0.5 h. The cooled mixture was mixed with chloroform (100 mL), washed with 0.2M sodium hydroxide (3 × 100 mL) and water (2 × 100 mL), dried, and concentrated. The syrupy residue (3.9 g) was subjected to column chromatography. Gradient elution with chloroform–ethyl acetate gave, first, **6** (2.02 g, 44%), m.p. 118° (from ether), $[\alpha]_D^{25}$ −126° (*c* 0.5, chloroform). ^{1}H-N.m.r. data: δ 8.28–7.13 (m, 4 H, aromatic protons), 5.66 (d, 1 H, $J_{1,2}$ 1 Hz, H-1), 5.12 (m, 2 H, H-2,3), 4.98 (m, 1 H, H-4), 4.51 (m, 1 H, H-5), 4.20 (m, 2 H, H-6,6′), 2.17, 2.14, and 1.90 (3 s, 3, 6, and 3 H, 4 Ac) (Found: C, 50.9; H, 4.9; N, 3.3. $C_{20}H_{23}NO_{12}$ calc.: C, 51.2; H, 4.9; N, 3.0%).

Eluted second was syrupy **7** (0.3 g, 7%), $[\alpha]_D^{25}$ +72.5° (*c* 0.7, chloroform). ^{1}H-N.m.r. data: δ 8.30–7.13 (m, 4 H, aromatic protons), 5.70 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.52 (t, 1 H, $J_{3,2}$ 6, $J_{3,4}$ 6 Hz, H-3), 5.18 (q, 1 H, $J_{2,1}$ 2.5, $J_{2,3}$ 6 Hz, H-2), 5.09 (q, 1 H, $J_{4,3}$ 6, $J_{4,5}$ 4 Hz, H-4), 4.64–4.44 (m, 1 H, H-5), 4.28 (m, 2 H, H-6,6′), 2.08, 2.06, and 1.90 (3 s, 6, 3, and 3 H, 4 Ac) (Found: C, 50.9; H, 5.1; N, 3.2%).

1-Naphthyl 2,3,4,6-tetra-O-acetyl-α- (**8**) *and -β-L-idopyranoside* (**9**). — A mixture of **5** (6.0 g), 1-naphthol (6.0 g), and zinc chloride (0.6 g) was fused at 120°

for 1 h and then processed as described above, to give a syrup (5.8 g) which was purified by column chromatography (chloroform–ethyl acetate gradient). The resulting chromatographically homogeneous syrup (3.1 g) crystallised from methanol, to give **8** (1.48 g, 20%), m.p. 169°, $[\alpha]_D^{23}$ −86° (*c* 0.7, chloroform). ^{1}H-N.m.r. data: δ 8.26–7.12 (m, 7 H, aromatic protons), 5.75 (s, 1 H, H-1), 5.25 (m, 2 H, H-2,3), 5.02 (m, 1 H, H-4), 4.60 (m, 1 H, H-5), 4.19 (m, 2 H, H-6,6′), 2.28, 2.16, and 1.84 (3 s, 3, 6, and 3 H, 4 Ac) (Found: C, 60.5; H, 5.6. $C_{24}H_{26}O_{10}$ calc.: C, 60.8; H, 5.5%).

Further crystallisation of the mother liquor gave **9** (0.13 g, 2%), m.p. 158°, $[\alpha]_D^{23}$ +82° (*c* 0.5, chloroform). ^{1}H-N.m.r. data : δ 8.28–7.14 (m, 7 H, aromatic protons), 5.69 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.64 (t, 1 H, $J_{3,2}$ 6, $J_{3,4}$ 6 Hz, H-3), 5.25 (q, 1 H, $J_{2,1}$ 2.5, $J_{2,3}$ 6 Hz, H-2), 5.08 (q, 1 H, $J_{4,3}$ 6, $J_{4,5}$ 4 Hz, H-4), 4.68–4.23 (m, 3 H, H-5,6,6′), 2.08, 2.07, and 1.87 (3 s, 6, 3, and 3 H, 4 Ac) (Found: C, 60.6; H, 5.5%).

*2-Naphthyl 2,3,4,6-tetra-*O*-acetyl-α-* (**10**) *and -β-*L*-idopyranoside* (**11**). — A mixture of 2-naphthol (6.0 g), **5** (6.0 g), and zinc chloride (0.6 g) was fused at 120° for 1 h and then processed as described above, to give **10** (2.03 g, 28%), m.p. 98°, $[\alpha]_D^{23}$ −144° (*c* 0.6, chloroform). ^{1}H-N.m.r. data: δ 7.83–7.09 (m, 7 H, aromatic protons), 5.66 (s, 1 H, H-1), 5.11 (m, 2 H, H-2,3), 4.96 (q, 1 H, $J_{4,3}$ 4, $J_{4,5}$ 1.5 Hz, H-4), 4.58 (m, 1 H, H-5), 4.17 (m, 2 H, H-6,6′), 2.17, 2.12, and 1.70 (3 s, 3, 6, and 3 H, 4 Ac) (Found: C, 60.5; H, 5.2. $C_{24}H_{26}O_{10}$ calc.: C, 60.8; H, 5.5%).

Further chromatography of the mother liquor gave syrupy **11** (89 mg, 1%), $[\alpha]_D^{23}$ +49° (*c* 0.9, chloroform). ^{1}H-N.m.r. data: δ 7.86–7.14 (m, 7 H, aromatic protons), 5.71 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.55 (t, 1 H, $J_{3,2}$ 6, $J_{3,4}$ 6 Hz, H-3), 5.16 (q, 1 H, $J_{2,1}$ 2.5, $J_{2,3}$ 6 Hz, H-2), 5.08 (q, 1 H, $J_{4,3}$ 6, $J_{4,5}$ 4 Hz, H-4), 4.63–4.14 (m, 3 H, H-5,6,6′), 2.08, 2.06, and 1.78 (3 s, 6, 3, and 3 H, 4 Ac), together with signals due to the α anomer (~15%).

*4-Methylcoumarin-7-yl 2,3,4,6-tetra-*O*-acetyl-α-* (**12**) *and -β-*L*-idopyranoside* (**13**). — (*a*) A mixture of 4-methylcoumarin-7-ol (4.0 g), **5** (6.0 g), and zinc chloride (0.8 g) was fused at 165° for 5 min and then processed as described above, to give **12** (1.95 g, 25%), m.p. 140–141° (from methanol), $[\alpha]_D^{23}$ −135° (*c* 0.5, chloroform); lit.[5] m.p. 137–138°, $[\alpha]_D^{23}$ −125° (chloroform). ^{1}H-N.m.r. data: δ 7.50–6.09 (m, 4 H, aromatic protons), 5.51 (s, 1 H, H-1), 5.02 (m, 2 H, H-2,3), 4.90 (m, 1 H, H-4), 4.46 (m, 1 H, H-5), 4.13 (m, 2 H, H-6,6′), 2.38 (s, 3 H, C=CMe), 2.13, 2.11, and 1.89 (3 s, 3, 6, and 3 H, 4 Ac) (Found: C, 56.8; H, 5.5. $C_{24}H_{26}O_{12}$ calc.: C, 56.9; H, 5.2%).

The second component obtained was syrupy **13** (0.35 g, 5%), $[\alpha]_D^{23}$ +71° (*c* 0.5, chloroform). ^{1}H-N.m.r. data: δ 7.45–6.08 (m, 4 H, aromatic protons), 5.51 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.38 (t, 1 H, $J_{3,2}$ 6, $J_{3,4}$ 6 Hz, H-3), 5.07 (q, 1 H, $J_{2,1}$ 2.5, $J_{2,3}$ 6 Hz, H-2), 4.98 (q, 1 H, $J_{4,3}$ 6, $J_{4,5}$ 4 Hz, H-4), 4.52–4.32 (m, 1 H, H-5), 4.20 (m, 2 H, H-6,6′), 2.37 (s, 3 H, C=CMe), 2.10, 2.07, and 1.96 (3 s, 6, 3, and 3 H, 4 Ac) (Found: C, 57.0; H, 5.4%).

(*b*) The fusion was repeated with 4-methylcoumarin-7-ol (6.7 g), **5** (10 g), and

zinc chloride (1.2 g) at 150–155° for 0.75 h. The reaction mixture was processed as described above and the product was crystallised from methanol, to give **12** (4.96 g, 38%), m.p. 140–141°, $[\alpha]_D^{23}$ −134° (*c* 1, chloroform).

(*c*) The experiment in (*b*) was repeated, but with the variations shown in Table I.

4-Nitrophenyl α-L-idopyranoside (**15**). — A solution of **6** (1.73 g) in methanolic 0.02M sodium methoxide (20 mL) was left overnight at room temperature, neutralised with IR-120 (H^+) resin, and concentrated. The residue was recrystallised from methanol, to give **15** (0.68 g, 52%), m.p. 184°, $[\alpha]_D^{24}$ −154° (*c* 0.5, chloroform). ^{1}H-N.m.r. data (Me_2SO-d_6): δ 8.28–7.25 (m, 4 H, aromatic protons), 5.49 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), and 5.35 (d, 1 H, $J_{H,OH}$ 5 Hz, OH) (Found: C, 47.8; H, 5.2; N, 4.4. $C_{12}H_{15}NO_8$ calc.: C, 47.8; H, 5.0; N, 4.6%).

1-Naphthyl α-L-idopyranoside (**16**). — To a solution of **8** (1.0 g) in dry methanol (50 mL) and dry 1,4-dioxane (20 mL) was added methanolic sodium methoxide [from sodium (8 mg) and dry methanol (5 mL)]. The mixture was stored at ambient temperature overnight, neutralised with Amberlite IR-120 (H^+) resin, and concentrated, to yield syrupy **16** (512 mg, 79%), $[\alpha]_D^{18}$ −74° (*c* 0.55, pyridine). N.m.r. data (Me_2SO-d_6): δ 8.40–7.18 (m, 7 H, aromatic protons), 5.53 (s, 1 H, H-1), 4.80–4.37 (m, 4 H, OH), 4.18–3.92 (m, 1 H), and 3.80–3.35 (m, 5 H) (Found: C, 58.4; H, 6.1. $C_{16}H_{18}O_6 \cdot H_2O$ calc.: C, 59.3; H, 6.2%).

2-Naphthyl α-L-idopyranoside (**17**). — As for **8**, **10** (1.5 g) was deacetylated to give syrupy **17** (537 mg, 55%), $[\alpha]_D^{19}$ −103° (*c* 0.7, pyridine). N.m.r. data (Me_2SO-d_6): δ 7.98–7.20 (m, 7 H, aromatic protons), 5.46 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.18–4.20 (m, 4 H, OH), 4.18–4.00 (m, 1 H), and 3.80–3.53 (m, 5 H) (Found: C, 61.3; H, 6.3. $C_{16}H_{18}O_6 \cdot 0.5\,H_2O$ calc.: C, 61.0; H, 6.1%).

4-Methylcoumarin-7-yl α-L-idopyranoside (**2**). — To a solution of **12** (6.5 g) in dry methanol (100 mL) was added methanolic sodium methoxide [from sodium (50 mg) and dry methanol (20 mL)]. The solution was stored overnight at room temperature, and the resulting crystals were collected and recrystallised from methanol, to give **2** (3.5 g, 81%), m.p. 211°, $[\alpha]_D^{27}$ −143° (*c* 0.5, pyridine); lit.[5] m.p. 208–209°, $[\alpha]_D^{25}$ −132° (pyridine). N.m.r. data (Me_2SO-d_6): δ 7.83–6.25 (m, 4 H, aromatic protons), 5.46 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.36 (d, 1 H, $^3J_{H,H}$ 5 Hz, OH), 5.12 (d, 1 H, $^3J_{H,H}$ 4 Hz, OH), 4.93 (d, 1 H, $^3J_{H,H}$ 5 Hz, OH), 4.71 (t, 1 H, $^3J_{H,H}$ 5 Hz, CH_2OH), 4.17 (m, 1 H), 3.80–3.53 (m, 5 H), and 2.40 (s, 3 H, C=CMe); the signals at δ 5.36, 5.12, 4.93, and 4.71 disappeared on the addition of D_2O (Found: C, 56.6; H, 5.3. $C_{16}H_{28}O_8$ calc.: C, 56.8; H, 5.4%).

4-Methylcoumarin-7-yl α-L-idopyranosiduronic acid (**1**). — (*a*) Oxygen was passed into a pear-shaped flask through a glass sinter set into the base, and then water (60 mL), **2** (1 g), and platinum black catalyst[20] (0.3 g) were added. The apparatus was immersed in a water bath at 95°. The oxygen flow was adjusted to give vigorous mixing, and a solution of sodium hydrogencarbonate (0.25 g) in water (10 mL) was added dropwise to maintain pH 7–8. After 3 h, when all of the base had been used, the mixture was filtered through a Celite pad, adjusted to pH 4 with di-

lute hydrochloric acid, and freeze-dried. The residue was partially fractionated on a column of silica gel (70 g) with acetone–water (19:1), to give a mixture (0.71 g) comprising (t.l.c.; cellulose; ethyl acetate–pyridine–water, 12:5:4) mainly the title compound (R_F 0.38) and 4-methylcoumarin-7-yl β-D-glucopyranosiduronic acid[30] (R_F 0.29). Rechromatography on silica gel with ethyl acetate–methanol–acetic acid (18:2:1) gave a chromatographically homogeneous product (0.4 g) that crystallised from methanol–2-propanol to give **1** (0.22 g, 21%), m.p. 200–203° (dec.), $[\alpha]_D$ −48° (*c* 0.5, water). N.m.r. data (Me_2SO-d_6): δ 7.7–6.9 (m, 3 H, aromatic protons), 6.12 (s, 1 H, C=C-H), 5.53 (d, 1 H, $J_{1,2}$ 5 Hz, H-1), 5.3 (bs, 4 H, OH), 4.14 (d, 1 H, $J_{4,5}$ 4 Hz, H-5), 4.0–3.2 (m, 3 H, H-2,3,4), and 2.34 (s, 3 H, Me) (Found: C, 48.6; H, 4.2. $C_{16}H_{15}O_9Na \cdot H_2O$ calc.: C, 49.0; H, 4.4%).

(*b*) The experiment in (*a*) was repeated, except that the suspension of platinum black catalyst was degasssed in a rotary evaporator for 40 min before use. The reaction required 3 h. The product contained both **1** and glucuronide[30], and was fractionated as in (*a*) to give **1** (0.25 g).

(*c*) The experiment in (*a*) was repeated, except that the catalyst was 10% Pt/C (1 g) prepared by reduction with formaldehyde essentially as described[24] for Pd/C. The product contained both **1** and the *gluco* isomer.

*4-Methylcoumarin-7-yl 2,3,4-tri-*O*-acetyl-6-*O*-triphenylmethyl-α-*L*-idopyranoside* (**14**). — (*a*) To a solution of **2** (0.3 g) in dry pyridine (6 mL) was added, with swirling, recrystallised triphenylmethyl chloride (0.5 g). The solution was stored for 2 days, and then acetic anhydride (10 mL) was added. After a further 24 h, the mixture was poured into ice and water, and the product was recovered by chloroform extraction and subjected to chromatography on silica gel (50 g). Elution with chloroform–methanol (19:1) gave triphenylmethanol, and elution with chloroform–methanol (9:1) gave **14** (0.33 g, 55%), m.p. 196–197°. N.m.r. data: δ 7.15 (m, 21 H, aromatic protons), 6.05 (s, 1 H, Me-C=C*H*), 5.50 (d, 1 H, H-1), 5.05 (m, 2 H, H-2,4), 4.85 (t, 1 H, H-3), 4.15 (s, 3 H, C=CMe), 2.15, 2.10, and 1.90 (3 s, 9 H, 3 Ac) (Found: C, 69.6; H, 5.4. $C_{41}H_{38}O_{11}$ calc.: C, 69.8; H, 5.4%).

(*b*) The reaction was repeated as in (*a*), using **2** (0.5 g). The crude product crystallised from methanol to give triphenylmethanol. Concentration of the mother liquor to dryness and crystallisation of the residue from 2-propanol gave **14** (0.51 g, 50%), m.p. 196–197°.

*4-Methylcoumarin-7-yl 2,3,6-tri-*O*-acetyl-α-*L*-idopyranoside.* — To a solution of **14** (0.98 g) in acetic acid (25 mL) was added hydrogen bromide in acetic acid (20%, 6 mL). After 1 min, the mixture was filtered into aqueous sodium hydrogencarbonate. The product was extracted with chloroform and subjected to chromatography on silica gel (40 g). Elution with tetrachloromethane–ethyl acetate (1:1) gave the title product (0.22 g, 33%), m.p. 183–184°, $[\alpha]_D^{20}$ −136° (*c* 0.5, methanol). N.m.r.data: δ 7.75–7.30 (m, 3 H, aromatic protons), 6.4 (s, 1 H, C=CH), 5.78 (s, 1 H, H-1), 5.30 (m, 2 H, H-2,3), 4.33 (m, 3 H, H-5,6,6'), 3.78 (m, 1 H, H-4), 2.88 (d, 1 H, OH), 2.40 (s, 3 H, C=CMe), 2.2, and 1.9 (2 s, 9 H, 3 Ac) (Found: C, 56.85; H, 5.0. $C_{22}H_{24}O_{11}$ calc.: C, 56.8; H, 5.3%).

1,6-Anhydro-2,3,4-tri-O-*benzyl*-β-L-idopyranose. — To a solution of 1,6-anhydro-β-L-idopyranose (5.0 g) in ice-cooled, dry *N,N*-dimethylformamide (60 mL) was added sodium hydride (2.8 g) followed slowly by benzyl bromide (35 mL) with stirring. After 2 h, dry methanol (2 mL) was added, and the mixture was poured into water and extracted with chloroform. After evaporation of the solvent, crystallisation of the residue from ether–light petroleum gave the title product (4.55 g, 72%), m.p. 67°, $[\alpha]_D^{23}$ +32° (*c* 0.53, chloroform). N.m.r. data: δ 7.29 (s, 15 H, 3 Ph), 5.29 (d, 1 H, $J_{1,2}$ 1 Hz, H-1), 4.82, 4.67 (2 s, 4 H, 2 OCH_2Ph), 4.66 (q, 2 H, J_{gem} 6 Hz, OCH_2Ph), and 4.38 (t, $J_{5,4}$ 4.5, $J_{5,6}$ 4.5 Hz, H-5) (Found: C, 75.0; H, 6.3. $C_{27}H_{28}O_5$ calc.: C, 75.0; H, 6.5%).

Acetolysis of 1,6-anhydro-2,3,4-tri-O-*benzyl*-β-L-*idopyranose*. — To a solution of the title compound (0.75 g) in acetic anhydride (3 mL) was added a 0.8% solution of conc. sulphuric acid in acetic anhydride (1 mL). After 3 min, the solution was poured into ice–water (50 mL), and the mixture was stirred overnight. The product was extracted into chloroform (50 mL), and the extract was washed with water (25 mL), dried, and concentrated. Column chromatography of the syrupy residue (0.78 g), with gradient elution using chloroform–ethyl acetate, gave the product as a syrup (0.63 g), $[\alpha]_D^{20}$ −4° (*c* 1.9, chloroform). N.m.r. data: δ 7.3 (s, 15 H, 3 Ph), 6.12 (m, 1 H, H-1), 4.80–4.23 (m, 9 H), 4.00–3.52 (m, 3 H), and 2.10–2.00 (3 s, 6 H, 2 Ac).

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REFERENCES

1 J. L. STIRLING, D. ROBINSON, A. H. FENSOM, P. F. BENSON, AND J. E. BAKER, *Lancet*, (1978) 147.
2 J. J. HOPWOOD, V. MULLER, A. SMITHSON, AND N. BAGGETT, *Clin. Chim. Acta*, 92 (1979) 257–265.
3 B. WEISSMANN, *Methods Enzymol.*, 50 (1978) 141–150; L. H. ROMA, *ibid.*, 83 (1982) 578–582.
4 R. B. FRIEDMANN AND B. WEISSMANN, *Carbohydr. Res.*, 24 (1972) 123–131.
5 R. M. SRIVASTAVA, N. HUDSON, F. R. SEYMOUR, AND B. WEISSMANN, *Carbohydr. Res.*, 60 (1978) 315–326.
6 B. HELFERICH AND E. SCHMITZ-HILLEBRECHT, *Ber.*, 66 (1933) 378–383.
7 E. M. MONTGOMERY, N. K. RICHTMYER, AND C. S. HUDSON, *J. Am. Chem. Soc.*, 64 (1942) 690–694; W. E. TREVELYAN, *Carbohydr. Res.*, 2 (1966) 418–420.
8 P. PERCHEMLIDES, T. OSAWA, E. A. DAVIDSON, AND R. W. JEANLOZ, *Carbohydr. Res.*, 3 (1967) 463–477.
9 L. VARGHA, *Chem. Ber.*, 87 (1954) 1351–1356.
10 H. OHLE AND E. DICKHAUSER, *Ber.*, 58 (1925) 2593–2606.
11 H. OHLE, E. EULER, AND R. LICHTENSTEIN, *Ber.*, 62 (1929) 2885–2893.
12 R. C. CHALK, D. H. BALL, AND L. LONG, JR., *Carbohydr. Res.*, 20 (1971) 151–164.
13 M. A. MILJKOVIC AND E. A. DAVIDSON, *Carbohydr. Res.*, 13 (1970) 444–446.
14 J. K. N. JONES, *Can. J. Chem.*, 34 (1956) 310–312.
15 M. BLANC-MUESSER AND J. DEFAYE, *Synthesis*, (1977) 568–569.
16 D. H. BUSS, L. D. HALL, AND L. HOUGH, *J. Chem. Soc.*, (1965) 1616–1619.

17 R. U. LEMIEUX AND J. D. STEVENS, *Can. J. Chem.*, 43 (1965) 2059–2070.
18 P. LUGER AND H. PAULSEN, *Carbohydr. Res.*, 51 (1976) 169–178.
19 H. PAULSEN AND M. FRIEDMANN, *Chem. Ber.*, 105 (1972) 705–717.
20 K. HEYNS AND H. PAULSEN, *Adv. Carbohydr. Chem* ,17 (1962) 169–221; R. ADAMS AND R. L. SHRINER, *J. Am. Chem. Soc.*, 46 (1924) 1683–1693.
21 J. KISS AND P. C. WYSS, *Tetrahedron*, 32 (1976) 1399–1402.
22 C. A. MARSH AND G. A. LEVVY, *Nature (London)*, 178 (1956) 589–590.
23 K. C. TSOU AND A. M. SELIGMAN, *J. Am. Chem. Soc.*, 75 (1953) 1042–1044.
24 Brit. Pat. 1,527,571 (1977).
25 H. PAULSEN, W.-P. TRAUTWEIN, F. G. ESPINOSA, AND K. HEYNS, *Chem. Ber.*, 100 (1967) 2822–2836.
26 W. A. BONNER, *J. Org. Chem.*, 24 (1959) 1388–1390.
27 G. ZEMPLÉN, Z. CSUROS, AND S. ANGYAL, *Ber.*, 70 (1937) 1848–1856.
28 L. N. OWEN, S. PEAT, AND W. J. G. JONES, *J. Chem. Soc.*, (1941) 339–344.
29 P. J. STOFFYN AND R. W. JEANLOZ, *J. Biol. Chem.*, 235 (1960) 2507–2510, A. S. PERLIN AND G. R. SANDERSON, *Carbohydr. Res.*, 12 (1970) 183–192.
30 J. A. R. MEAD, J. N. SMITH, AND R. T. WILLIAMS, *Biochem., J.*, 61 (1955) 569–574.