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SYNTHESIS OF METHYL 6″-DEOXY-6′-FLUORO-α-ISOMALTOSIDE AND OF THE CORRESPONDING TRISACCHARIDE*

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ABSTRACT

Methyl 6-*O*-(6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**5**) was formed with high stereoselectivity when the condensation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl (**1**) with 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl chloride in ether was promoted with silver perchlorate in the presence of 2,4,6-trimethylpyridine. O-Deacetylation of **5**, followed by treatment of the formed **6**, containing only HO-6′ unsubstituted, with diethylaminosulfur trifluoride (DAST) or dimethylaminosulfur trifluoride (methyl DAST) gave the per-*O*-benzyl derivative (**9**) of methyl 6′-deoxy-6′-fluoro-α-isomaltoside. Compound **9** was also obtained by condensation of **1** with 2,3,4-tri-*O*-benzyl-6-deoxy-6-fluoro-β-D-glucopyranosyl fluoride (**4**) in the presence of silver perchlorate and anhydrous stannous chloride. The fully benzylated methyl α-glycoside (**15**) of 6-deoxy-6-fluoro-isomaltotriose, was obtained by condensation of **6** with **4**. Hydrogenolysis of **9** and **15** gave the methyl α-glycosides of isomaltose and isomaltotriose fluorinated at C-6 of their (nonreducing) D-glucosyl group. Fluoride-ion displacements involving DAST and methyl DAST gave practically identical results, but mixtures arising from reactions involving the latter reagent were lighter-colored and easier to resolve by chromatography. The isolation of methyl α-glycosides of 6′-deoxy-6′-fluorogentiobiose and of 6′-*O*-(6-deoxy-6-fluoro-β-D-glucopyranosyl) isomaltose is also described.

INTRODUCTION

We have, in the past, used galacto-oligosaccharides containing deoxyfluoro groups at defined positions as probes to reveal the subsite location of galactopyranan-binding monoclonal antibodies[1]. Since then, our attention was again[2] drawn to an antidextran monoclonal antibody which is unique in that it only binds to its

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polysaccharide antigen by contacting the nonreducing terminal five sugar residues[2,3]. In order to evaluate the binding pattern of this antibody, we needed a series of saccharides having deoxyfluoro groups in defined positions. We now report the synthesis of two specifically fluorinated isomalto-oligosaccharides.

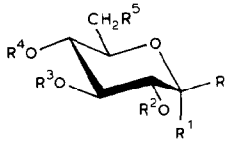
RESULTS AND DISCUSSION

Methyl α-isomaltoside was first obtained by Jones *et al.*[4] by the action of the enzyme dextransucrase on a solution of methyl α-D-glucopyranoside and sucrose. Highly stereoselective, chemical construction of (1,2-*cis*)-linked oliogosaccharides having an α-(1→6) linkage involving D-glucosyl residues is a difficult task. In addition to the known difficulties associated with the synthesis of 1,2-*cis*-glycosides, glycosidations involving primary hydroxyl groups of sugars suffer from a decreased stereoselectivity[5]. Consequently, numerous approaches to the chemical synthesis of isomaltose and its derivatives have been described[6–14]. Most recently, methyl α-isomaltoside was obtained[15], in admixture with methyl α-gentiobioside, by applying the methodology of halide-ion catalysis[16].

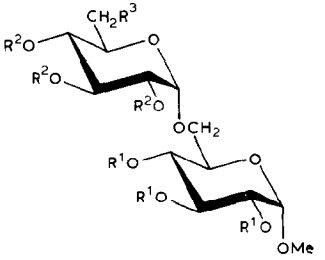
Our strategy for the assembly of the desired, fluorinated glycosides **10** and **16** could essentially follow two pathways. In the first, a fully substituted methyl α-glycoside of isomaltose and isomaltotriose containing a selectively removable blocking group at the position to be fluorinated could first be synthesized. After partial deblocking, the free hydroxyl group at the designated position would be transformed into the deoxyfluoro function by one of the many methods available[17]. Alternatively, a glycosyl donor derived from 6-deoxy-6-fluoro-D-glucose could be condensed with a suitable derivative of methyl α-D-glucopyranoside. We have explored both approaches.

Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[18,19] (**1**) and the corresponding benzoyl derivative[20,21] (**3**) have been the glycosyl acceptors most frequently used in previous chemical syntheses of derivatives of methyl α-isomaltoside. Crystalline compounds **1** and **3** are readily obtainable from methyl α-D-glucopyranoside *via* the corresponding 6-*O*-trityl derivative. They have now been characterized by ^{1}H- and ^{13}C-n.m.r. data, and these data were used as an aid in the assignments of spectra of more-complex structures.

In pursuing the approach whereby the fluorine atom would be introduced into previously assembled oligosaccharides, a suitable derivative of methyl α-isomaltoside had to be synthesized. In view of the simplicity of its preparation, we chose 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl chloride[22] (**2**) as the glycosyl donor, and examined its reaction with **1** under various conditions. The preparation of **5** from **1** plus **2** was conducted under conditions ranging from halide-ion catalysis[16], to those using silver perchlorate as the promoter[14], as well as by applying the original conditions for the preparation[7] of **5**. To evaluate the individual procedures in terms of yields and stereoselectivity, the resulting mixtures were resolved by chromatography, the zone containing disaccharides **5** and **11** (inseparable by t.l.c.) was



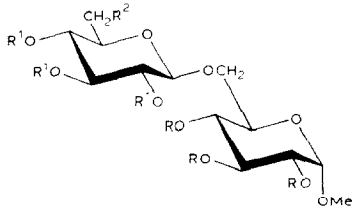
	R	R^1	R^2	R^3	R^4	R^5
1	H	OMe	Bn	Bn	Bn	OH
2	H	Cl	Bn	Bn	Bn	OAc
3	H	OMe	Bz	Bz	Bz	OH
4	F	H	Bn	Bn	Bn	F



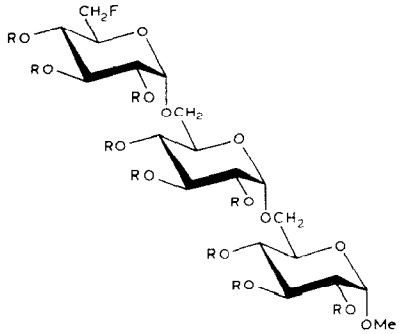
	R^1	R^2	R^3
5	Bn	Bn	OAc
6	Bn	Bn	OH
7	Bz	Bn	OAc
8	Bz	Bn	OH
9	Bn	Bn	F
10	H	H	F

isolated, and the stereoselectivity of the reaction was deduced from the intensities, in the ^{1}H-n.m.r. spectrum, of the signals due to the OMe groups in these compounds. Judging by the yields obtained, the observed stereoselectivity, and the number of by-products formed, as well as the simplicity of execution, we found the procedure by Igarashi *et al.*[14] to be far superior.

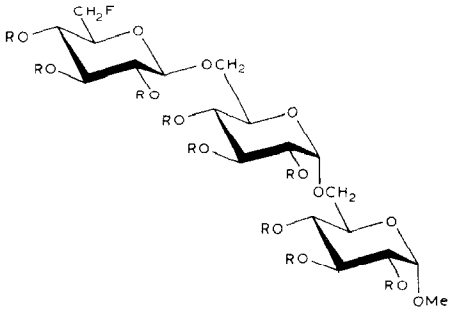
Under those conditions, using a 20% excess of **2**, the nucleophile **1** was completely consumed within 15 min, and the disaccharides **5** and **11** were obtained in an almost theoretical (combined) yield. The proportion of the β-linked disaccharide **11** formed was <5%, as found by ^{1}H-n.m.r. spectroscopy. The only other product formed was a small amount of a mixture of compounds, eluted from the silica-gel column as one zone, the ^{1}H-n.m.r. spectrum of which indicated that these were nonreducing, trehalose-type disaccharides resulting from the reaction of **2** with the product of its hydrolysis. In the preparative run (only this experiment is described in the Experimental section), a large proportion of the desired disaccharide **5** crystallized directly from the processed mixture. Chromatography of the material that remained in the mother liquor yielded an additional crop of **5** (total yield, 88%), as well as the β-linked disaccharide **11**. The latter compound, previously obtained[12] amorphous, is here described crystalline. It is noteworthy that the m.p. originally found[7] for **5**, and which is in excellent agreement with that found by us, is higher by ~30° than the one recently reported[12]. *O*-Deacetylation of **5** then readily afforded **6**. In anticipation that a mixture of **7** and **12** might be easier to resolve by chromatography than in the case with **5** and **11**, synthons **2** and **3** were coupled, using silver perchlorate as promoter. The yield of **7** and **12**, and the stereoselectivity of their formation, were comparable to those in the glycosidation of **1** with **2**. The **7** and **12** formed were resolved by t.l.c., but were only poorly separated. The pure isomaltose derivative **7**, isolated by column chromatography, could be deacetylated[23,24] without affecting the other ester groups present in the molecule and, thus, the synthetic



	R	R^1	R^2
11	Bn	Bn	OAc
12	Bz	Bn	OAc
13	Bn	Bn	F
14	H	H	F



15 R = Bn
16 R = H



17 R = Bn
18 R = H

pathway involving **7** as an intermediate constitutes an alternative route to oligosaccharides in this and related series.

Since its inception by Middleton[25], fluorination by diethylaminosulfur trifluoride (DAST) has also been succesfully carried out in carbohydrate chemistry (*c.f.*, ref. 17). Although the original paper[25] was clear, in that DAST and dimethylaminosulfur trifluoride (methyl DAST) work equally well in replacing hydroxyl groups with fluorine, the latter reagent does not appear to have been used in the carbohydrate field. Methyl DAST is more stable and less expensive than its ethyl analog. It is commercially available as an almost colorless liquid which has a long shelf-life, whereas DAST is invariably supplied more or less discolored. Because conversions with DAST are commonly followed by isolation of the products by chromatography, it seemed important to examine whether the use of methyl DAST would give rise to less-colored reaction-mixtures which might be easier to resolve. For this purpose, we treated 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside, and 2,3,4-tri-*O*-benzyl-D-glucose with methyl DAST (these reactions are not described in the Experimental section), conversions originally[26-28]

carried out with DAST. The results showed that, although the yields of products were comparable to those obtained by employing DAST, the mixtures involving methyl DAST were indeed less colored. This manifested itself especially in cases wherein the conversion was effected at ambient or sub-ambient temperature, such as that 2,3,4,6-tetra-*O*-benzyl-D-glucose. Accordingly, the disaccharide **6** was separately treated with both reagents, to give, in both cases, a good yield of **9**. When an unresolved mixture of **5** and **11** was *O*-deacetylated, and the product treated with methyl DAST, the resulting mixture of **9** and **13** was readily separable by t.l.c. and, after separation by column chromatography, both compounds were obtained crystalline.

To synthesize the title oligosaccharides by using glycosyl donors already fluorinated at the desired position, we applied the methodology developed by Mukaiyama *et al.*[9], whereby glycosyl fluorides, following activation with stannous chloride, can be used as glycosyl donors in stereoselective synthesis of 1,2-*cis*-oligosaccharides. Accordingly, compound **1** was condensed with 2,3,4-tri-*O*-benzyl-6-deoxy-6-fluoro-β-D-glucopyranosyl fluoride[26] (**4**). The disaccharides formed were isolated by chromatography, and showed to be identical with the independently prepared **9** and **13**. Catalytic hydrogenolysis of **9** and **13** readily yielded methyl α-glycosides of isomaltose and gentiobiose fluorinated at C-6 of their D-glucosyl group. To obtain the 6″-fluorinated methyl α-isomaltotrioside **16**, the nucleophile **6** was coupled with **4**, and the trisaccharides **15** and **17** formed were resolved by column chromatography. Subsequent catalytic hydrogenolysis afforded **16** as an amorphous solid. The ^{13}C-n.m.r. spectra of **16**, as well as those of **10**, **14**, and **18**, fully supported the expected structures.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler hot-stage. Unless otherwise stated, optical rotations were measured at 25° for solutions in chloroform, using a Perkin–Elmer automatic polarimeter, Model 241 MC. Preparative chromatography was performed by gradient elution from columns of Silica Gel 60 (Merck, Cat. No. 9385). Thin-layer chromatography (t.l.c.) was performed on silica gel-coated glass slides (Analtech or Whatman). Elutions were conducted with solvent mixtures of appropriately adjusted polarity, consisting of *A*, carbon tetrachloride–ethyl acetate; *B*, toluene–acetone, and *C*, ethyl acetate–1-propanol–water. One-dimensional, ^{13}C- and ^{1}H-n.m.r. spectra were routinely recorded at 25° by using a Jeol XL 300 and a Varian HR 220 spectrometer, respectively. In this case, proton-signal assignments were made by first-order analysis of the spectra, supported by selective homonuclear decoupling experiments, and carbon-signal assignments were made by intercomparison of the spectra, by comparison of the spectra with those of related compounds[26], and the signals of secondary carbon atoms were assigned by DEPT experiments. Two-dimensional (2 D) proton–proton and proton–^{13}C correlation n.m.r. spectra of **1**, **3**, **6**, **7**, **9**, and **13** were recorded for

solutions in $CDCl_3$, with a Nicolet spectrometer operated at 500 and 125 MHz for ^1H and ^{13}C nuclei, respectively. The standard COSY experiment[29] for ^1H–^1H correlation, and the proton-detected, multiple quantum method[30] for ^1H–^{13}C correlation, were applied. Solvents for other measurements are listed as required. ^{13}C-N.m.r. chemical shifts found in the spectra recorded for solutions in chloroform-*d* and D_2O are reported using Me_4Si and methanol as internal standards (δ_{MeOH} *vs.* δ_{Me_4Si} 49.0 p.p.m.). DAST and methyl DAST were purchased from Aldrich Chemical Company, Alfa Chemical Company, or Carbolabs, Inc., and used as supplied. Palladium-on-charcoal (5%) catalyst was a product of Engelhard Industries. Anhydrous silver perchlorate was prepared as previously described[31]. To obtain anhydrous stannous chloride, the commercial product (Aldrich Chemical Co.) was dried for 8 h at 190°/133 Pa. Powdered molecular sieves 4A (Fluka Chemical Company) were activated by heating for 8 h at 150°/133 Pa. Solutions in organic solvents were dried with anhydrous sodium sulfate and evaporated at 40°/2 kPa.

Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (**1**). — This compound was prepared as described[19], except that iodotrimethylsilane[32,33] was used to detritylate the intermediate 6-*O*-trityl derivative, as detailed for the preparation of **3**. For compound **1**, ^1H-n.m.r. (500 MHz, $CDCl_3$): δ 7.36–7.26 (m, 15 H, aromatic protons), 5.00–4.61 (6 d, 6 H, ^2J ~11 Hz, CH_2 benzylic protons), 4.55 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.02 (t, $J_{4,5}$ ~9.5 Hz, H-3), 3.85–3.73 (m, 1 H, H-6a), 3.71–3.62 (m, 2 H, H-5,6b), 3.52 (t, 1 H, $J_{3,4}$ ~9.5 Hz, H-4), 3.49 (dd, 1 H, $J_{2,3}$ 9.5 Hz, H-2), 3.34 (s, 3 H, Me), and 1.77 (m, 1 H, disappears on deuteration, OH); ^{13}C-n.m.r. (125 MHz, $CDCl_3$): δ 98.06 (C-1), 81.86 (C-3), 79.95 (C-2), 77.49 (C-4), 75.67, 74.93, 73.33 (CH_2 benzylic carbons), 70.83 (C-5), 61.41 (C-6), and 55.02 (Me).

6-O-Acetyl-2,3,4-tri-O-benzyl-α-D-glucopyranosyl chloride (**2**). — A solution of 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranose[26] (1 g) in ether (2 mL) was treated with ethereal hydrogen chloride (0.2 g/mL, 5 mL) for 48 h at room temperature. The product could not be crystallized (*c.f.*, ref. 22, m.p. 63–64°). It was eluted from a column of silica gel (solvent A), and obtained as a chromatographically homogeneous, thick oil, 0.75 g (78%). For compound **2**, ^1H-n.m.r. (300 MHz, $CDCl_3$): δ 7.40–7.20 (m, 15 H, aromatic protons), 6.02 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.02–4.56 (4 d, 4 H, ^2J ~11 Hz; and s, 2 H, 3 CH_2-benzylic protons), 4.33–4.23 (m, 2 H, H-6a,6b), 4.15 (dt, 1 H, $J_{5,6a} = J_{5,6b} =$ ~3 Hz, H-5), 4.06 (t, 1 H, $J_{4,5}$ ~9.3 Hz, H-3), 3.70 (dd, 1 H, $J_{2,3}$ 9.2 Hz, H-2), 3.53 (dd, 1 H, $J_{4,5}$ 10 Hz, H-4), and 1.99 (s, 3 H, OAc); ^{13}C-n.m.r. (75 MHz; in $CDCl_3$): δ 92.86 (C-1), 81.27 (C-3), 79.83 (C-2), 76.06 (C-4), 75.85, 75.15, 72.89 (3 CH_2-benzylic carbons), 71.82 (C-5), and 62.29 (C-6).

Methyl 2,3,4-tri-O-benzoyl-α-D-glucopyranoside (**3**). This compound was prepared by a slightly modified procedure[17,18]. Thus, methyl α-D-glucopyranoside (19.4 g, 0.1 mol) was tritylated, and the ether benzoylated conventionally. Chlorotrimethylsilane (38 mL, 0.3 mol) was added at 0° (inside) to a solution of the crude product and sodium iodide (45 g, 0.3 mol) in acetonitrile (~800 mL). The mixture was stirred for 3 min at 10°, and, after addition of water (150 mL) and of aqueous

sodium thiosulfate (until a colorless solution was obtained), was concentrated. The residue was partitioned between water and dichloromethane; the organic phase was dried, concentrated, and eluted from a column of silica gel (solvent B), to give **3** (40 g, ~80%); m.p. 148–149° (from ethanol, twice), $[\alpha]_D$ +58° (*c* 1.4); lit.[21] m.p. 141–143°, $[\alpha]_D$ +54.5°; ^{1}H-n.m.r. (220 MHz, C_6D_6 containing a drop of CD_3OD): δ 8.18–6.75 (m, 15 H, aromatic protons), 6.59 (t, 1 H, $J_{3,4}$ ~10 Hz, H-3), 5.80 (t, 1 H, $J_{4,5}$ ~10 Hz, H-4), 5.50 (dd, 1 H, $J_{2,3}$ 10 Hz, H-2), 5.25 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.01 (ddd, 1 H, $J_{5,6a}$ 2.5, $J_{5,6b}$ 4.5 Hz, H-5), 3.75 (dd, 1 H, $J_{5a,6b}$ 12 Hz, H-6a), 3.65 (dd, 1 H, H-6b), and 3.10 (s, 3 H, OMe); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 97.19 (C-1), 72.08 (C-2), 70.70 (C-3), 69.84 (C-5), 69.59 (C-4), 61.12 (C-6), and 55.65 (Me).

Anal. Calc. for $C_{28}H_{26}O_9$: C, 66.39; H, 5.17. Found: C, 66.37; H, 5.18.

Methyl O-*(6-*O-*acetyl-2,3,4-tri-*O-*benzyl-*α-D-*glucopyranosyl)-(1→*6)-2,3,4-tri-O-*benzyl-*α-D-*glucopyranoside* (**11**). — Ethereal silver perchlorate (0.08M, 20 mL, 1.6 mmol) was added with stirring at −30° to a solution of **1** (0.542 g, 1.17 mmol), **2** (0.75 g, 1.46 mmol), and 2,4,6-trimethylpyridine (0.21 mL, 1.6 mmol) in ether (5 mL). Silver chloride was immediately precipitated, and, after 10 min, t.l.c. showed the absence of both **1** and **2**. Two products were formed, the one with the higher mobility greatly preponderating. The mixture was filtered through a Celite pad, the solids were washed with ether, the filtrate was concentrated, and a solution of the residue in dichloromethane was washed successively with aqueous sodium thiosulfate and water, dried, and concentrated; crystallization from methanol (twice) gave 0.66 g of pure **5**, m.p. 109–110°; lit.[7] m.p. 109–109.5°, lit.[12] m.p. 80–82°; ^{1}H-n.m.r. (220 MHz, $CDCl_3$): δ 7.43–7.15 (m, 30 H, aromatic protons), 5.02–4.51 (m, 14 H, 6 CH_2-benzylic protons, H-1,1′), 4.24–4.16 (m, 2 H, H-6a′, 6b′), 4.05–3.93 (2 t, $J_{3,4} = J_{3',4'} = 9$ Hz, H-3,3′), 3.90–3.40 (m, 8 H, H-2,2′,4,4′,5, 5′,6a,6b), 3.35 (s, 3 H, Me), and 1.96 (s, 3 H, Ac); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 98.01 (C-1), 97.04 (C-1′), 82.14 (C-3), 81.62 (C-3′), 80.15, 80.02 (C-2,2′), 77.99 (C-4), 77.14 (C-4′), 75.75, 75.59, 75.02, 74.88, 73.37, 72.40 (6 CH_2-benzylic carbons), 70.38 (C-5), 68.75 (C-5′), 66.07 (C-6), 63.06 (C-6′), and 55.18 (Me).

The material remaining in the combined mother liquors was chromatographed, and fractions constituting the front of the main zone gave a further crop of **5** (0.31 g; total yield, 88%).

The last fractions eluted from the main zone were enriched in the β-linked isomer **11**, as shown by ^{1}H-n.m.r. spectroscopy. Crystallisation from methanol (twice) gave **11**, m.p. 125–126°, $[\alpha]_D$ +33° (*c* 0.8); lit.[12], $[\alpha]_D$ +29°, for the amorphous material. Diagnostically significant signals in the ^{1}H-n.m.r. spectrum (300 MHz, $CDCl_3$) were at δ 4.60 (d, 1 H, $J_{1,2}$ 4.4 Hz, H-1), 4.33 (d, partially overlapped, $J_{1',2'}$ 7.5 Hz, H-1′), 3.98 (t, 1 H, $J_{3,4}$ 9 Hz, H-3), 3.22 (s, 3 H, Me), and 1.98 (s, 3 H, OAc); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 103.79 (C-1′), 98.10 (C-1), 84.78 (C-3′), 81.98 (2 C, C-3,2′), 79.88 (C-2), 78.04 (C-4), 77.43 (C-4′), 75.72, 75.67, 75.00, 74.91, 73.36 (3 C, 2 C, 1 C, 6 CH_2-benzylic carbons), 72.91 (C-5′), 69.84 (C-5), 68.68 (C-6), 63.08 (C-6′), and 55.23 (Me).

Anal. Calc. for $C_{57}H_{62}O_{12}$: C, 72.90; H, 6.66. Found: C, 73.04; H, 6.70.

The mother liquor was combined with the unresolved mixture of **5** and **11**, and processed as described in the preparation of **9** and **13**.

The minor, slower-moving material was examined by ^{1}H-n.m.r. spectroscopy. The general features of the spectrum, not containing signals of OMe protons, indicated that it was a mixture of nonreducing disaccharides, resulting from the reaction of **2** with the products of its hydrolysis.

Methyl O-(2,3,4-tri-O-benzyl-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**6**). — Compound **5** (0.92 g) was dissolved in hot toluene (5 mL), and methanol (20 mL) was added, followed by a few drops of M methanolic sodium methoxide. The solution was allowed to cool to room temperature and, after 2 h, made neutral with Amberlite IR 120 (H^+) resin, filtered, and concentrated, to give the desired product in virtually theoretical yield. Crystallization from isopropyl ether afforded pure **6**, m.p. 112–113°, $[\alpha]_D$ +74° (*c* 0.7); lit.[34], m.p. 104–106°, $[\alpha]_D$ +62.9° (*c* 1) for the independently synthesized compound; ^{1}H-n.m.r. (500 MHz, in $CDCl_3$): δ 7.38–7.20 (m, 30 H, aromatic protons), 4.99–4.56 (m, partially overlapped with signals of anomeric protons, 6 CH_2-benzylic protons, 4.94, 4.53 (2 d, partially overlapped with signals of benzylic protons, $J_{1,2} = J_{1',2'} = \sim 3$ Hz, H-1,1'), 4.01–3.96 (2 overlapping triplets, 2 H, $J_{3,4} = J_{3',4'} \sim 9.5$ Hz, H-3,3'), 3.82–3.76 (m, 2 H, H-5,6a), 3.71–3.60 (m, 5 H, H-4,5',6b,6'a,6'b), 3.51 (t, partially overlapped with signals of H-2', $J_{4',5'}$ 9 Hz, H-4'), 3.47 (dd, partially overlapped with signals of H-4', $J_{1',2'}$ 3.5, $J_{2',3'}$ 9.5 Hz, H-2'), 3.44 (dd, 1 H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.5 Hz, H-2), and 3.35 (s, 3 H, Me); ^{13}C-n.m.r. (75 MHz, in $CDCl_3$): δ 98.06 (C-1), 97.17 (C-1'), 82.12 (C-3), 81.51 (C-3'), 80.18 (2 C, C-2,2'), 79.79 (C-4), 77.44 (C-4'), 75.71, 75.48, 75.00, 74.94, 73.40, 72.46 (6 CH_2-benzylic carbons), 70.92 (C-5'), 70.46 (C-5), 66.04 (C-6), 61.89 (C-6'), and 55.19 (Me).

Methyl O-(6-O-acetyl-2,3,4-tri-O-benzyl-α-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzoyl-α-D-glucopyranoside (**7**). — A solution of **2** (0.613 g, 1.2 mmol) in ether (2 mL) was added at −20° to a stirred mixture of **3** (0.506 g, 1 mmol) and 2,4,6-trimethylpyridine (165 μL, 1.35 mmol) in 0.08M silver perchlorate (18.75 mL, 1.5 mmol). Cooling was discontinued and, after 15 min, t.l.c. (solvent A) showed that the reaction was complete. According to t.l.c., the mixture closely resembled the one formed in the preparation of **5** except that, here, the major zone appeared to contain two poorly resolved components, the slower-moving of which largely preponderated. After work-up, the crude product was chromatographed, to give, first, material (15 mg) whose n.m.r. spectra showed that it was the β-linked product **12**. Definite signals in the ^{1}H-n.m.r. spectrum (300 MHz, $CDCl_3$) were at δ 8.00–7.20 (m, 30 H, aromatic protons), 6.17 (t, 1 H, $J_{3,4}$ 9.8 Hz, H-3), 5.46 (t, 1 H, $J_{4,5}$ 10 Hz, H-4), 5.27–5.21 (m, 2 H, H-1,2), 5.09–4.51 (6 d, $^2J \sim 11$ Hz, 3 CH_2-benzylic protons), 4.48 (d, 1 H, $J_{1',2'}$ 7.5 Hz, H-1'), 3.87 (bt, 1 H, H-5), 4.07 (bd, 1 H, $J_{6a,6b}$ 10.7 Hz, H-6a), 3.81 (dd, 1 H, $J_{5,6}$ 6.7, $J_{6a,6b}$ 10.7 Hz, H-6b), 3.39 (s, 3 H, Me), and 1.91 (s, 3 H, OAc); ^{13}C-n.m.r. (75 MHz, in $CDCl_3$): δ 104.06 (C-1'), 96.87 (C-1), 84.53 (C-3'), 82.23 (C-2'), 77.46 (C-4'), 75.70, 75.00, 74.83 (3 CH_2-benzylic car-

bons), 72.84 (C-5′), 72.10 (C-2), 70.45 (C-3), 69.93 (C-4), 69.11 (C-6), 68.92 (C-5), 63.24 (C-6′), and 55.63 (Me).

Eluted subsequently was pure **7** (0.75 g, 76%); $[\alpha]_D$ +81° (*c* 1.3); ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 8.00–7.20 (m, 30 H, aromatic protons), 6.12–6.20 (m, 1 H, H-3), 5.56 (t, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 5.26–5.21 (m, 2 H, H-1,2), 4.97–4.53 (6 d, 6 H, ^2J ~11.3 Hz, 3 CH_2-benzylic protons), 4.71 (d, 1 H, $J_{1',2'}$ 3.4 Hz, H-1′), 4.32–4.31 (m, 1 H, H-5), 4.20–4.10 (m, 2 H, H-6′a,6′b), 4.01 (t, 1 H, $J_{3',4'}$ ~9 Hz, H-3′), 3.98–3.91 (m, 1 H, H-5′), 3.84 (dd, 1 H, $J_{5,6a}$ 6.3, $J_{6a,6b}$ 11 Hz, H-6a), 3.60 (dd, 1 H, $J_{5,6b}$ 2 Hz, H-6b), 3.51 (dd, partially overlapped with the signal of the OMe group, $J_{2',3'}$ ~9.5 Hz, H-2′), 3.46 (s, partially overlapping the signals of H-2′ and H-4′, OMe), 3.44 (t, partially overlapped with the signal of OMe protons, H-4′), and 1.97 (s, 3 H, OAc). In the ^{1}H-n.m.r. spectrum of **7** in a solution in benzene-d_6, at 220 MHz, the signals of H-1 and H-2 were well resolved: δ 5.44 (dd, 1 H, $J_{2,3}$ 10 Hz, H-2), and 5.31 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1); ^{13}C-n.m.r. (75 MHz, in $CDCl_3$): δ 97.07 (C-1′), 96.89 (C-1), 81.67 (C-3′), 80.14 (C-2′), 77.35 (C-4′), 75.62, 74.80, 73.10 (3 CH_2-benzylic carbons), 72.23 (C-2), 70.63 (C-3), 69.60 (C-4), 68.83 (C-5′), 68.65 (C-5), 66.75 (C-6), 63.05 (C-6′), and 55.63 (Me).

Anal. Calc. for $C_{57}H_{56}O_{15}$: C, 69.78; H, 5.75. Found: C, 69.54; H, 5.70.

Methyl O-*(2,3,4-tri-*O*-benzyl-*α-D-*glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-*α-D-*glucopyranoside* (**8**). — Compound **7** (0.5 g) was dissolved in chloroform (1 mL) and methanolic hydrogen chloride (2.5 mL, prepared by adding 1 mL of acetyl chloride to 20 mL of methanol, and adjusting the volume to 25 mL) was added, and the solution was kept at room temperature while the course of the reaction was periodically checked by t.l.c. (solvent A). After 2.5 h, t.l.c. showed that, while the reaction was almost complete and one major product, **8**, was present, compounds more polar than **8** were starting to form. The mixture was made neutral with solid sodium hydrogencarbonate, diluted with dichloromethane, filtered, concentrated and the residue chromatographed, to give the major product **8** (0.36 g, 75%) as an amorphous solid; $[\alpha]_D$ +81° (*c* 1); ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 8.00–7.20 (m, 30 H, aromatic protons), 6.15 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 5.56 (t, 1 H, $J_{4,5}$ 10 Hz, H-4), 4.95–4.61 (6 d, ^2J ~11 Hz, 6 CH_2-benzylic protons), 4.36–4.28 (m, 1 H, H-5), 4.00 (t, 1 H, $J_{3',4'}$ 9.3 Hz, H-3′), 3.83 (dd, 1 H, $J_{5,6a}$ 6.4 Hz, H-6a), 3.78–3.71 (m, 1 H, H-5′), 3.69–3.49 (m, partially overlapped with the signals of the OMe protons, H-6b,2′,4′,6′a,6′b), and 3.47 (s, partially overlapping the signals of the ring protons, Me). The spectrum at 220 MHz of **8** in benzene-d_6 containing a drop of methanol-d_4 showed the signal of H-2 as a well resolved dd at δ 5.50 $J_{2,3}$ 10.3 Hz, and the doublet of H-1 appeared at δ 5.31, $J_{1,2}$ 3.7 Hz; ^{13}C-n.m.r. (75 MHz, in $CDCl_3$): δ 97.28 (C-1′), 96.87 (C-1), 81.58 (C-3′), 80.22 (C-2′), 77.39 (C-4′), 75.52, 74.83, 73.15 (3 CH_2-benzylic carbons), 72.21 (C-2), 71.01 (C-5′), 70.64 (C-3), 69.73 (C-4), 68.68 (C-5), 66.90 (C-6), 61.79 (C-6′), and 55.64 (Me).

Anal. Calc. for $C_{55}H_{54}O_{14}$: C, 70.34; H, 5.79. Found: C, 70.24; H, 5.85.

Methyl O-*(2,3,4-tri-*O*-benzyl-6-deoxy-6-fluoro-*α- (**9**) *and* β-D-*glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-*α-D-*glucopyranoside* (**13**). — (*a*) A solution of silver

perchlorate (0.08M, 15 mL, 1.2 mmol) was added at −20° to a stirred solution of **1** (0.46 g, 1 mmol), **4** (0.45 g, 1 mmol), and stannous chloride (190 mg, 1 mmol) in ether (5 mL) containing molecular sieves 4 A (2 g). The mixture was stirred for 30 min, while it was allowed to warm. T.l.c. (solvent A) showed that two main products were formed, that showing the higher chromatographic mobility largely preponderating. After neutralization with 2,4,6-trimethylpyridine, and filtration through a Celite pad, the resulting filtrate was concentrated and chromatographed, to give **9** (560 mg, 62%); m.p. 129–130° (from isopropyl ether–ethanol), $[\alpha]_D$ +70.3° (*c* 0.6); ^{1}H-n.m.r. (500 MHz, $CDCl_3$): δ 7.35–7.22 (m, 30 H, aromatic protons), 4.98–4.59 (m, partially overlapped with signals of anomeric protons and H-6'a, 6 CH_2-benzylic protons), 4.96 (d, partially overlapped with the signals of benzylic protons, $J_{1',2'}$ ~3 Hz, H-1'), 4.55 (d, partially overlapped with signals of benzylic protons and H-6'a, $J_{1,2}$ 3.5 Hz, H-1), 4.51–4.50 (m, $J_{F,6b}$ 49 Hz, H-6b and a portion of signals of H-6a), 3.99 (2 t, 2 H, $J_{3,4}$ ~9.5, $J_{3',4'}$ ~9 Hz, H-3,3'), 3.82–3.76 (m, 2 H, H-5,6a), 3.73–3.62 (m, 5 H, H-4,5 6a,6b,5'), 3.54 (bt, partially overlapped with the signals of H-2', $J_{4',5'}$ ~9.5 Hz, H-4'), 3.52 (dd, partially overlapped with the signals of H-4', $J_{2,3}$ 10, $J_{1',2'}$ ~3.5 Hz, H-2), 3.45 (dd, 1 H, $J_{2,3}$ 10.5, $J_{1,2}$ ~3 Hz, H-2), and 3.35 (s, 3 H, Me); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 98.03 (C-1), 97.27 (C-1'), 82.15 (C-3), 81.92 ($J_{F,C}$ 172.9 Hz, C-6'), 81.42 (C-3'), 80.21, 79.97 (C-2,2'), 77.81 (C-4), 76.72 ($J_{F,C}$ 5.9 Hz, C-4'), 75.72, 75.48, 75.08, 74.96, 73.38, 72.49 (6 CH_2-benzylic carbons), 70.39 (C-5), 69.96 ($J_{F,C}$ 18.7 Hz, C-5'), 66.18 (C-6), and 55.17 (Me).

Anal. Calc. for $C_{55}H_{59}FO_{10}$: C, 73.47; H, 6.61; F, 2.11. Found: C, 73.49; H, 6.49; F, 2.08.

Continued elution gave **13** (145 mg, 16%); m.p. 162–164° (from acetone–methanol), $[\alpha]_D$ +18° (*c* 0.9); ^{1}H-n.m.r. (500 MHz, $CDCl_3$): δ 7.38–7.18 (m, 30 H, aromatic protons), 4.99–4.48 (m, partially overlapping the signals of H-1 and H-6a,6b, 6 CH_2-benzylic protons), 4.60 (d, partially overlapped by signals of CH_2-benzylic protons, $J_{1,2}$ 3.5 Hz, H-1), 4.36 (d, 1 H, $J_{1',2}$ 7.5 Hz, H-1'), 4.17 (bd, 1 H, $J_{6a,6b}$ ~11 Hz, H-6a), 4.0 (t, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 3.84 (bdd, 1 H, H-5), 3.68 (dd, partially overlapped by signals of H-3', $J_{5,6a}$ 5 Hz, H-6b), 3.65 (t, partially overlapped by signals of H-6b, $J_{3',4'}$ 11 Hz, H-3'), 3.56–3.48 (m, 4 H, H-2,4,2',4'), 3.40 (bddd, $J_{F,5'}$ ~25 Hz, H-5'), and 3.24 (s, 3 H, Me); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 103.79 (C-1'), 98.02 (C-1), 84.56 (C-3'), 81.94 (2 C, C-3,2'), 81.81 ($J_{F,C}$ 173.8 Hz, C-6'), 79.86 (C-2), 78.05 (C-4), 76.71 ($J_{F,C}$ 6.3 Hz, C-4'), 75.64, 75.05, 74.86, 74.8, 73.31 (2 C, 1 C, 2 C, 1 C, 6 CH_2-benzylic carbons), 74.86 ($J_{F,C}$ 18.5 Hz, C-5'), 69.86 (C-5), 68.71 (C-6), and 55.19 (Me).

Anal. Calc. for $C_{55}H_{59}FO_{10}$: C, 73.47; H, 6.61; F, 2.11. Found: C, 73.32; H, 6.55; F, 2.19.

(*b*) To a solution of **6** (225 mg, 0.25 mmol) in 1,2-dimethoxyethane (1.5 mL) was added, at −20°, DAST or methyl DAST (0.75 mmol), and the mixture was stirred at 60°. T.l.c. (solvent B) showed that the reaction was complete after ~30 min. The mixture was cooled to −10°, methanol was added, and, after concent-

ration, the residue was partitioned between dichloromethane and a mixture of saturated aqueous solution of sodium chloride and sodium hydrogencarbonate. The organic phase was dried and concentrated, and the crude product was chromatographed, to give **9** (185 mg, 82%).

(*c*) An unresolved mixture of **5** and **11** (2.0 g) was *O*-deacetylated as described for the preparation of **6**. The crude product was dissolved in 1,2-dimethoxyethane (15 mL) and treated as described in (*b*). Chromatography (solvent A) yielded **9** (1.05 g) and **13** (0.3 g). An intermediate, mixed fraction (0.2 g; total yield, 77.5%) was also obtained.

Methyl O-*(2,3,4-tri*-O-*benzyl-6-deoxy-6-fluoro*-α- (**15**) *and* β-D-*glucopyranosyl)-(1→6)-2,3,4-tri*-O-*benzyl*-α-D-*glucopyranosyl)-(1→6)-2,3,4-tri*-O-*benzyl*-α-D-*glucopyranoside* (**17**). — A solution of silver perchlorate (0.08M, 32.5 mL, 2.6 mmol) was added at −20° to a solution of **6** (1.8 g, 2 mmol) and **4** (refs 23,26; 1.136 g, 2.5 mmol) in ether (20 mL) containing powdered molecular sieves 4A (5 g) and anhydrous stannous chloride (0.5 g, 2.6 mmol). Cooling was discontinued, and the mixture was stirred for 1 h. A considerable amount of unchanged **6** was still present, as shown by t.l.c. (solvent A), and a further portion of the reagents (0.3 mmol) was added. After 30 min, the mixture was processed as described for preparation (*a*) of **9**, and chromatographed to yield the two main components of the mixture. The one showing the higher chromatographic mobility (major) was the desired α-linked product **15** (1.8 g, 67.6%); $[\alpha]_D$ +76° (*c* 0.6); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 98.00 (C-1), 97.10, 97.04 (C-1′,1″), 82.08 (C-3), 81.86 ($J_{F,C}$ 172.8 Hz, C-6″), 81.61, 81.37 (C-3′,3″), 80.30, 80.20, 80.03 (C-2,2′,2″), 77.46, 77.37 (C-4,4′), 76.67 ($J_{F,C}$ 6.0 Hz, C-4″), 75.64, 75.40, 75.07, 74.96, 74.82, 73.32, 72.36, 72.27 (1 C, 2 C, 6×C, 9 CH_2-benzylic carbons), 70.60, 70.48 (C-5,5′), 69.89 ($J_{F,C}$ 18.9 Hz, H-5″), 65.84 (2 C, C-6,6′), and 55.10 (Me).

Anal. Calc. for $C_{82}H_{87}FO_{15}$: C, 73.96; H, 6.58; F, 1.42. Found: C, 74.06; H, 6.63; F, 1.49.

Eluted next was **17** (415 mg, 15.5%); $[\alpha]_D$ +49.5° (*c* 0.6); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 103.57 (C-1″), 97.73 (C-1′), 96.83 (C-1), 84.40 (C-3″), 81.97, 81.74 (C-3,2″), 81.65 ($J_{F,C}$ 172.9 Hz, C-6″), 81.32 (C-3′), 79.94, 79.77 (C-2,2′), 77.74, 77.56 (C-4,4′), 76.53 ($J_{F,C}$ 4.9 Hz, C-4″), 75.55, 75.26, 74.95, 74.84, 74.80, 74.62, 73.23, 72.17 (2 C, 7×C, 9 CH_2-benzylic carbons), 74.38 ($J_{F,C}$ 18.6 Hz, C-5″), 70.29 (C-5), 69.74 (C-5′), 68.52 (C-6′), 65.68 (C-6), and 54.98 (Me).

Anal. Calc. for $C_{82}H_{87}FO_{15}$: C, 73.96; H, 6.58; F, 1.42. Found: C, 74.05; H, 6.64; F, 1.34.

Methyl O-*(6-deoxy-6-fluoro*-α-D-*glucopyranosyl)-(1→6)*-α-D-*glucopyranoside (methyl 6′-deoxy-6′-fluoro-α-isomaltoside)* (**10**). — A solution of **9** (0.85 g) in 2-methoxyethanol (50 mL) was stirred in a hydrogen atmosphere at room temperature and atmospheric pressure in the presence of 5% palladium-on-charcoal catalyst (0.3 g) until the consumption of hydrogen ceased (~2 h). A single product was formed, as shown by t.l.c. (R_F 0.5, in 5:5:1 ethyl acetate–1-propanol–water). The mixture was processed conventionally, to give chromatographically pure **10** in

essentially theoretical yield. The crude product was eluted from a small column of silica gel (solvent C) to remove some colored material, as well as catalyst debris. After drying at 105°/133 Pa, the amorphous **10** showed $[\alpha]_D$ +166° (*c* 0.9, water): ^{13}C-n.m.r. (75 MHz, D_2O): δ 99.48 (C-1), 98.09 (C-1'), 82.28 ($J_{F,C}$ 168.0 Hz, C-6'), 73.51 (C-3), 73.04 (C-3'), 71.48, 71.32 (C-2,2'), 70.22 ($J_{F,C}$ 17.6 Hz, C-5'), 70.12 (C-5), 69.60 (C-4), 68.59 ($J_{F,C}$ 5.8 Hz, C-4'), 65.87 (C-6), and 55.26 (Me).

Anal. Calc. for $C_{13}H_{23}FO_{10}$: C, 43.57; H, 6.46; F, 5.30. Found: C, 43.69; H, 6.09; F, 5.35.

Methyl O-*(6-deoxy-6-fluoro-β-*D*-glucopyranosyl)-(1→6)-α-*D*-glucopyranoside (methyl 6'-deoxy-6'-fluoro-α-gentiobioside)* (**14**). — Compound **13** (260 mg) was treated as described for the preparation of **10**, to give **14** as an amorphous solid; $[\alpha]_D$ +58° (*c* 0.5, water); ^{13}C-n.m.r. (75 MHz, D_2O): δ 103.21 (C-1'), 99.47 (C-1), 82.15 ($J_{F,C}$ 168.9 Hz, C-6'), 75.59 (C-3'), 74.49 ($J_{F,C}$ 17.6 Hz, C-5'), 73.18, 73.12 (C-3,2'), 71.28 (C-2), 70.73 (C-5), 69.58 (C-4), 69.12 (C-6), 68.47 ($J_{F,C}$ 5.7 Hz, C-4), and 55.37 (Me).

Anal. Calc. for $C_{13}H_{23}FO_{10}$: C, 43.57; H, 6.46; F, 5.30. Found: C, 44.12; H, 6.56; F, 5.01.

Methyl O-*(6-deoxy-6-fluoro-α-*D*-glucopyranosyl)-(1→6)-(α-*D*-glucopyranosyl)-(1→6)-α-*D*-glucopyranoside (methyl 6''-deoxy-6''-fluoro-α-isomaltotrioside)* (**16**). — Hydrogenolysis of **15** as already described gave amorphous **16** in almost theoretical yield; $[\alpha]_D$ +176° (*c* 1, water); ^{13}C-n.m.r. (75 MHz, in D_2O): 99.43 (C-1), 97.98 (2 C, C-1',1''), 82.26 ($J_{F,C}$ 168.0 Hz, C-6''), 73.45 (2 C, C-3,3'), 73.03 (C-3''), 71.46 (2 C, C-2',2''), 71.28 (C-2), 70.69 ($J_{F,C}$ 16.6 Hz, C-5''), 70.27, 70.05 (C-5,5'), 69.66, 69.58 (C-4,4'), 68.53 ($J_{F,C}$ 6.1 Hz, C-4''), 65.88, 65.67 (C-6,6'), and 55.24 (Me).

Methyl O-*(6-deoxy-6-fluoro-β-*D*-glucopyranosyl)-(1→6)-(α-*D*-glucopyranosyl)-(1→6)-α-*D*-glucopyranoside* (**18**). — Hydrogenolysis of **17** (~200 mg) as already described gave amorphous **18** in virtually theoretical yield; $[\alpha]_D$ +86.2° (*c* 0.7, water); ^{13}C-n.m.r. (75 MHz, D_2O): δ 103.03 (C-1''), 99.47 (C-1), 98.03 (C-1'), 82.05 ($J_{F,C}$ 167.7 Hz, C-6''), 75.56 (C-3''), 74.49 ($J_{F,C}$ 17.5 Hz, C-5''), 73.46 (C-2''), 73.17, 73.08 (C-3,3'), 71.51, 71.30 (C-2,2''), 70.97 (C-5'), 70.14 (C-5), 69.58, 69.50 (C-4,4'), 68.69 (C-6'), 68.45 ($J_{F,C}$ 6.1 Hz, C-4''), 65.85 (C-6), and 55.28 (Me).

Anal. Calc. for $C_{19}H_{33}FO_{15}$: C, 43.84; H, 6.39; F, 3.65. Found: C, 43.31; H, 6.71; F, 3.57.

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