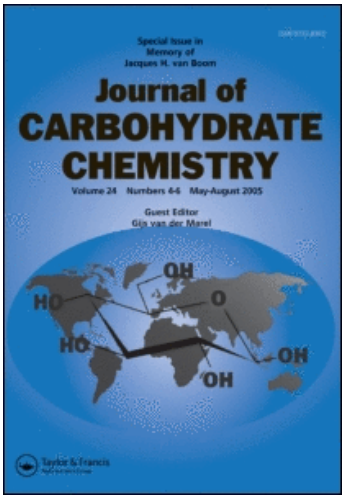

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SYNTHESIS OF THE 4-DEOXY-2-DEUTERO-4-FLUORO ANALOG OF METHYL O-β-D-GALACTOPYRANOSYL-(1→6)-β-D-GALACTOPYRANOSIDE

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ABSTRACT

Methyl 4-deoxy-4-fluoro-6-*O*-(β-D-galactopyranosyl)-(2-^{2}H)-β-D-galactopyranoside was prepared by the condensation of 2,3,4,6-tetra-O-benzoyl-α-D-galactopyranosyl bromide and methyl 2-*O*-benzoyl-3-*O*-benzyl-4-deoxy-4-fluoro-(2-^{2}H)-β-D-galactopyranoside (**17**), followed by deprotection. The introduction of deuterium at *C*-2 in an intermediate methylhexopyranoside was achieved by a double inversion, brought about by oxidation of C-2 of a derivative of methyl α-D-glucopyranoside, to give the corresponding ketone, and subsequent reduction thereof with $NaBD_4$, to give a derivative with the D-*manno* configuration (**8**). Inversion of the configuration at C-2 of the latter was achieved by displacement with sodium benzoate of the *O*-trifluoromethanesulfonyl (triflyl) group in the 2-*O*-triflyl derivative of **8**. The resulting synthon was converted, conventionally, to methyl 2-*O*-benzoyl-3-*O*-benzyl-6-*O*-trityl-(2-^{2}H)-β-D-glucopyranoside. Its conversion into the 6-*O*-trityl derivative of **17**, unsuccessful by treatment with dimethylaminosulfur trifluoride, was readily accomplished by the displacement of the triflyl group with fluoride ion contained in an ion-exchange resin.

INTRODUCTION

The flexibility of an antigen and its potential ability to adopt a particular conformation to fit a recognition site on an antibody is a matter of debate. NMR Spectroscopy offers ways to study the conformation of antibody-antigen complexes. Monoclonal immunoglobulins which we have studied in great detail (see papers cited in ref. 1 and 2) are specific for (1→6)-β-D-galactans (**1**). The antibody maximally binds the

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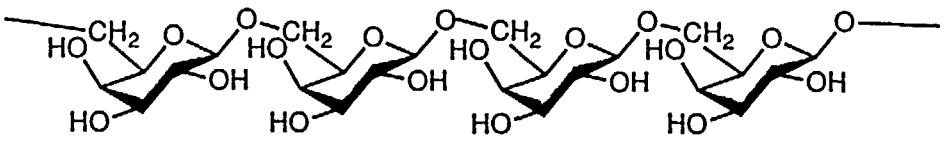
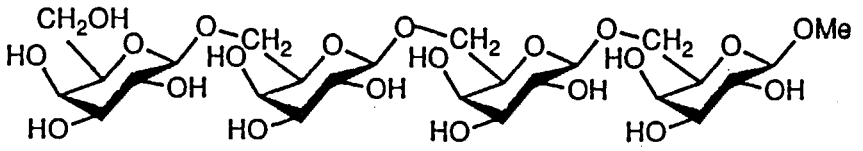
tetrasaccharide epitope, since the methyl β-glycoside **2** shows the same K_a as the corresponding penta- and the hexasaccharide.[1] Preliminary studies on the binding[2] of methyl 6-*O*-(β-D-galactopyranosyl)-β-D-galactopyranoside (**3**) by NMR spectroscopy had indicated that, in order to allow detailed analysis of the 2D NOE spectra, structural modifications in the ligand had to be made to effect ^1H chemical shift dispersion. This has been accomplished[2] by the use of the fluorinated analog of **3**, the disaccharide **4**, which was found to bind to the immunoglobulin studied with the same affinity as **3**. To remove a remaining ambiguity (the chemical shifts of H-2 and H-2' in the ^1H NMR spectra of **4** nearly coincide), we have investigated the conformational changes during binding using the 2-deutero analog of **4**, disaccharide **5**, the synthesis of which is reported here.



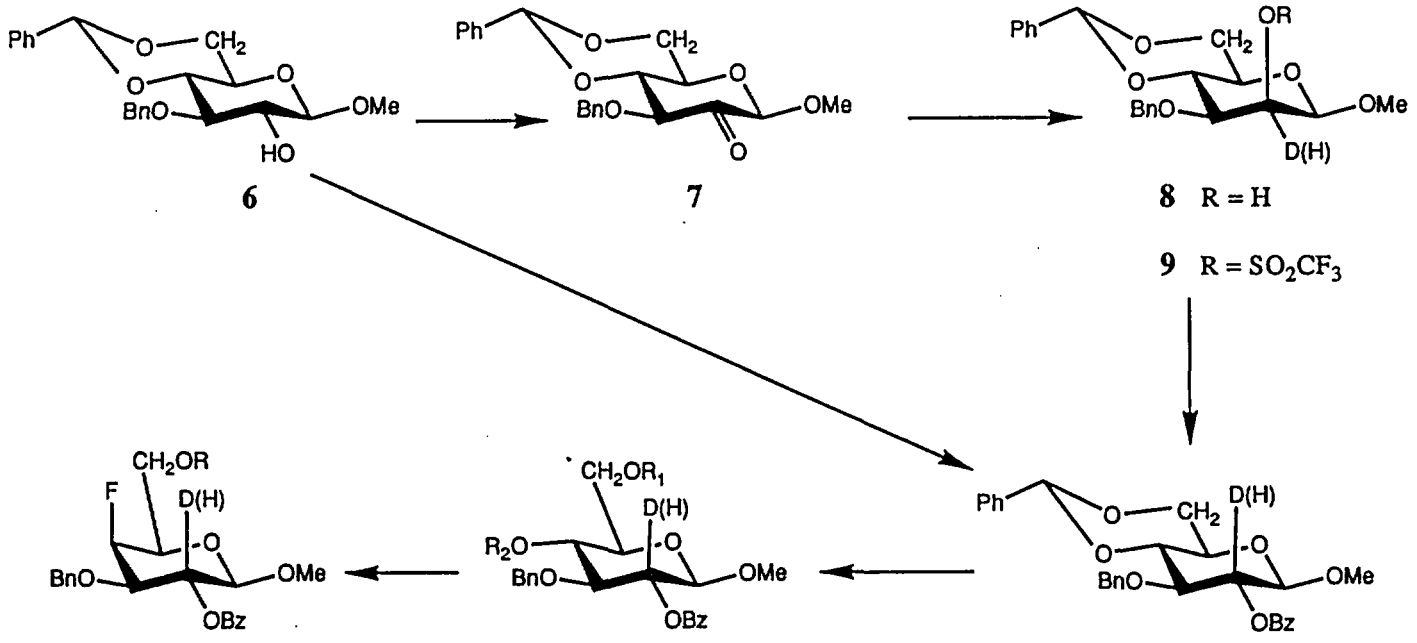
1



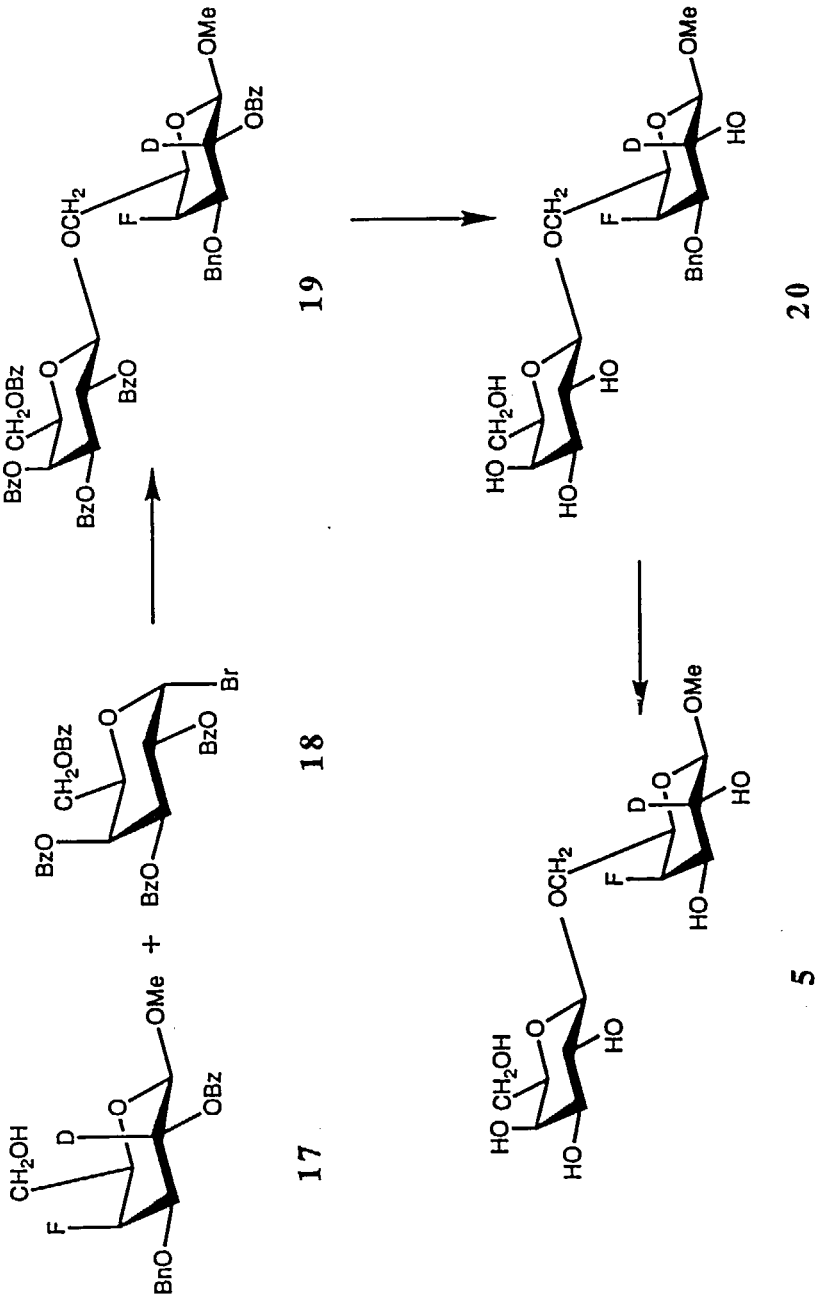
2

RESULTS AND DISCUSSION

We have previously described the syntheses of methyl 6-*O*-(β-D-galactopyranosyl)-β-D-galactopyranoside[3] (**3**) and methyl 4-deoxy-4-fluoro-6-*O*-(β-D-galactopyranosyl)-β-D-galactopyranoside[4] (**4**). The 2-deutero analog of **4**, disaccharide **5**, was synthesized by the reaction sequence shown in Schemes 1 and 2. The key intermediate in the synthesis of **5** was methyl 2-*O*-benzoyl-3-*O*-benzyl 4-deoxy-4-fluoro-(2-^2H)-β-D-galactopyranoside (**17**, 2D)[5] which bears both the deuterium and fluoro marker-atoms. The strategy

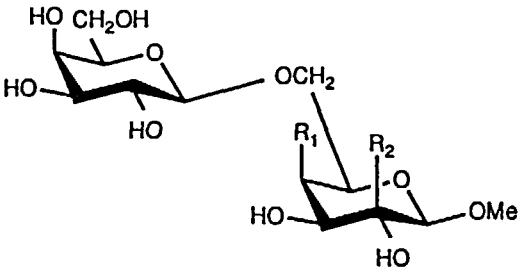


Scheme 1



Scheme 2

for its preparation involved stereo-controlled placement of deuterium at *C*-2, followed by introduction of the 4-fluoro substituent. Accordingly, ketone[6] **7**, prepared by ruthenium tetroxide oxidation[7] of **6** as described by Morris and Kiely[8], was reduced with sodium borodeuteride. The attack by the deuteride ion occurred largely from the α-face[6] (>10:1), to form the protected methyl (2-^{2}H)-β-D-mannopyranoside (**8**, 2D). Inversion at *C*-2 of alcohol **8** (2D), to produce the corresponding D-*gluco* derivative **10** (2D), was accomplished by subsequent displacement of triflate from intermediate **9** (2D)[9,10] with sodium benzoate.



3 $R_1 = OH, R_2 = H$

4 $R_1 = F, R_2 = H$

5 $R_1 = F, R_2 = D$

Conventional benzoylation of **6** produced the analog **10** (2H) which was used in defining reaction conditions for the introduction of the 4-fluoro substituent. Removal of the benzylidene group in **10** (2H) by hydrolysis with aqueous acetic acid gave **11** (2H), together with a small amount of the 6-*O*-acetyl derivative **12** (2H). Selective tritylation of the primary hydroxyl group in **11** (2H) yielded **13** (2H), along with some 4,6-di-*O*-trityl derivative **14** (2H). Direct displacement of the equatorial 4-hydroxyl group of **13** (2H) using dimethylaminosulfur trifluoride (DAST) was unsuccessful. In contrast, conversion of **13** (2H) to the corresponding 4-*O*-triflate derivative **15** (2H), followed by triflate displacement by fluoride ion, using an ion-exchange resin, occurred smoothly in 45 min, yielding **16** (2H). It is worth mentioning that the displacement[11] of the *p*-bromobenzenesulfonyloxy group in methyl 2,3-di-*O*-benzyl-4-*O*-brosyl-6-*O*-trityl-β-D-glucopyranoside required 3-4 days treatment by the same reagent. Detritylation of **16** (2D) with dilute acetic acid completed the synthesis of the nucleophile **17**.

Coupling of **17** (2D) with 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide[12] (**18**), promoted by silver triflate, gave the disaccharide **19** (2D) in a yield of 91%. Stepwise, conventional deprotection of **19** (2D) then yielded the title disaccharide **5**.

EXPERIMENTAL

General Methods.– Melting points were determined on a Kofler hot stage. Optical rotations were measured at 25°C with a Perkin Elmer automatic polarimeter, Model 241 MC. All reactions were monitored by thin-layer chromatography (TLC) on precoated slides of Silica Gel G F254 (Analtech). Detection was effected by charring with 5% sulfuric acid in ethanol and, when applicable, with UV light. Preparative chromatography was performed by gradient elution from columns of Silica Gel 60 (Merck, No. 9385, or No. 15111). ^{1}H- and ^{13}C-NMR spectra were measured at ambient temperature using Varian FX 300 or Bruker AM 500 spectrometers. Solvents for compounds used in measurements are reported as required. Chemical shifts found in the spectra recorded for solutions in $CDCl_3$ and D_2O are reported, respectively, using Me_4Si and methanol as internal standards (δ_{MeOH} *vs.* δ_{Me_4Si} 49.0). Proton-signal assignments were made by first-order analysis of the spectra, and were supported by homonuclear decoupling experiments. Of the two magnetically non-equivalent geminal protons, the one resonating at a higher field is denoted Ha and the one resonating at a lower field is denoted Hb. Carbon-signal assignments were made by mutual comparison of the spectra, and by comparison with spectra of related substances. Amberlyst A-26 (F^--form) was purchased from Fluka Chemical company. Solutions in organic solvents were dried with anhydrous sodium sulfate, and concentrated at 40°/2 kPa.

***Methyl 2-O-Benzoyl-3-O-benzyl-4,6-O-benzylidene-β-D-glucopyranoside* (10, 2H).**– A mixture of **6** (186 mg, 0.5 mmol), prepared as described,[7] and benzoyl chloride (100 mg, 0.7 mmol) in pyridine (2 mL) was kept at room temperature for 1 h. The mixture was processed conventionally and, after purification by chromatography, crystallized from ethanol, to give 165 mg (69%) of **10** (2H), mp 118-119°C, $[\alpha]_D$ +34° (c 0.6, chloroform). ^{1}H-n.m.r. ($CDCl_3$): δ 3.47 (s, 3 H, OMe), 3.52 (m, 1 H, H-5), 3.84 (dd, 1 H, $J_{5,6a}$ 4 Hz, $J_{6a,6b}$ 10.5 Hz, H-6a), 3.87 (t, 1 H, $J_{2,3}$ 7.5 Hz, H-3), 3.88 (t, 1 H, $J_{4,5}$ 9 Hz, H-4), 4.40 (dd, 1 H, $J_{5,6b}$ 5 Hz, H-6b), 4.55 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1), 4.70, 4.83 (AB, 2H, J 12 Hz, benzylic protons), 5.30 (dd, 1 H, H-2), 5.61 (s, 1 H, benzylidene proton); ^{13}C-n.m.r. ($CDCl_3$): δ 57.0 (OMe), 66.3 (C-5), 68.7 (C-6), 73.2 (C-2), 74.0 (CH_2-benzylic), 78.0 (C-4), 81.7 (C-3), 101.3 (CH-benzylidene), 102.6 (C-1).

Anal. Calcd for $C_{28}H_{28}O_7$: C, 70.6; H, 5.92. Found: C, 70.5; H, 5.93.

***Methyl 2-O-Benzoyl-3-O-benzyl-4,6-O-benzylidene-(2-^{2}H)-β-D-glucopyranoside* (10, 2D).**– To a solution of 3.72 g (10 mmol) of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside[7] (**6**) in ethanol-free chloroform (35 mL) was added a solution of

sodium metaperiodate (2.5 g, 11.7 mmol) in water (35 mL), followed by potassium carbonate (150 mg), benzyl trimethylammonium chloride (50 mg) and activated[13] ruthenium dioxide (25 mg). The mixture was stirred vigorously and, after 1 h, TLC showed that approximately 50% of the starting material was still unchanged. A fresh portion of sodium metaperiodate (1.5 g) was added, followed by two more portions (0.7 g each) at hourly intervals, while stirring was continued. When the reaction was almost complete (TLC), the excess of the oxidation reagent was destroyed by addition of isopropyl alcohol (4 mL) and, after 10 min, the mixture was partitioned between dichloromethane and water. The dark organic phase was dried and concentrated, to give crude **7** (3 g) which was sufficiently pure for the next step.

Sodium borodeuteride (4.4 g) was added in small portions to a solution of the foregoing material in a mixture of tetrahydrofuran-methanol (1:1, 200 mL). After 1 h, when TLC showed that the conversion was complete, the mixture was concentrated, and the residue was partitioned between dichloromethane and water. The organic extract was dried, concentrated, and the residue was chromatographed, to give methyl 3-*O*-benzyl-4,6-*O*-benzylidene-(2-^{2}H)-β-D-mannopyranoside (**8**, 2D),[5,14] the NMR characteristics of which fully supported the anticipated structure.[15]

A mixture of **8** (2D) (1 g, 2.7 mmol) and pyridine (2 mL) in dichloromethane (15 mL) was cooled to -10°C, and triflic anhydride (1 mL, 6 mmol) was added with stirring. The yellow mixture was allowed to warm to room temperature and, after 1.5 h, partitioned between ice-water and dichloromethane. The dichloromethane solution was dried, concentrated, and chromatographed, to give 1.2 g (89%) of **9** (2D) which was used for the next step.

A stirred mixture of **9** (2D) (7.8 g) and sodium benzoate (6.5 g, 3 equiv) in DMF (150 mL) was heated under gentle reflux. The reaction mixture remained heterogeneous and a copious floculent solid formed. When the reaction was complete (TLC, ~3 h), the mixture was cooled and diluted with dichloromethane (150 mL). The insoluble material was filtered off and washed with additional dichloromethane. The combined filtrates were concentrated with azeotropic co-distillation of xylene. Crystallization from ethanol, and chromatography of the material that remained in the mother liquor gave 6.4 g (86%) of **10** (2D) which exhibited properties corresponding to the 2-protio analog.[15]

***Methyl 2-O-Benzoyl-3-O-benzyl-β-D-glucopyranoside* (11, 2H).**– A solution of **10** (2H) (1.48 g) in a mixture of acetic acid (15 mL), water (3 mL) and ethanol (2 mL) was stirred at 80°C until TLC showed that the reaction was complete (~1 h). The mixture was concentrated, and the residue was crystallized from toluene, to yield **11**(2H) (0.86 g, 71 %), mp 135-136°C, $[\alpha]_D$ +12° (c 0.6, chloroform). ^{1}H-n.m.r. ($CDCl_3$): δ 3.45 (m, 1 H,

H-5), 3.46 (s, 3 H, OMe), 3.70 (t, 1 H, $J_{3,4}$ 9 Hz, H-3), 3.81 (t, 1 H, $J_{4,5}$ 9 Hz, H-4), 3.87 (dd, 1 H, $J_{5,6a}$ 5 Hz, $J_{6a,6b}$ 10 Hz, H-6a), 3.94 (dd, 1 H, $J_{5,6b}$ 3 Hz, H-6b), 4.49 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.73, 4.67 (AB, 2 H, J 11 Hz, benzylic protons), 5.23 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2); ^{13}C-n.m.r. ($CDCl_3$): δ 57.0 (OMe), 62.2 (C-6), 70.4 (C-4), 73.5 (C-2), 74.5 (CH_2-benzylic), 75.3 (C-5), 82.3 (C-3), 102.1 (C-1).

Anal. Calcd for $C_{21}H_{24}O_7$: C, 65.0; H, 6.19. Found: C, 64.8; H, 6.23.

Methyl 2-O-Benzoyl-3-O-benzyl-(2-^{2}H)-β-D-glucopyranoside **(11, 2D)** ***and methyl 6-O-acetyl-2-O-benzoyl-3-O-benzyl-(2-^{2}H)-β-D-glucopyranoside*** **(12, 2D).**– A solution of 7.3 g of **10** (2D) in a mixture of acetic acid:water: ethanol 6:1:0.8 (78 mL) was heated at 70°C for 1.5 h. TLC showed then the reaction to be complete. The solution was concentrated with co-evaporation of water, ethanol and toluene, to remove acetic acid. Crystallization from toluene yielded 5.2 g of **11** (2D). Chromatography of the material in the mother liquor gave first the amorphous **12** (2D) (200 mg, 3%), $[\alpha]_D$ +6° (c 0.6, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 2.11 (s, 3 H, COMe), 3.46 (s, 3 H, OMe), 3.54 (m, 1 H, H-5), 3.6-3.7 (m, 2 H, H-3,4), 4.35 (dd, 1 H, $J_{5,6a}$ 2 Hz, $J_{6a,6b}$ 12 Hz, H-6a), 4.46 (dd, 1 H, $J_{5,6b}$ 5 Hz, H-6b), 4.47 (s, 1 H, H-1), 4.71 (s, 2 H, benzylic protons); ^{13}C-n.m.r. ($CDCl_3$): δ 20.9 (COMe), 56.8 (OMe), 63.1 (C-6), 70.1 (C-4), 73.1 (C-2), 74.0 (C-5), 74.7 (CH_2-benzylic), 82.0 (C-3), 102.0 (C-1).

Anal. Calcd for $C_{23}H_{25}DO_8$: C, 64.0; H, 6.26. Found: C, 64.1; H, 6.27.

Eluted next was a further amount of **11** (2D) (195 mg, total yield 91%), which exhibited properties corresponding to those of the 2-protio analog described above.[15]

Methyl 2-O-Benzoyl-3-O-benzyl-6-O-triphenylmethyl-β-D-glucopyranoside **(13, 2H).**–A solution of **11** (2 H) (750 mg) and trityl chloride (810 mg, 1.5 equiv) in pyridine (10 mL) was stirred at 80°C. After 4 h, when TLC showed that a considerable amount of unchanged starting material was still present, more trityl chloride (270 mg, 0.5 equiv) was added, and stirring was continued overnight. The mixture was processed conventionally, and chromatography[16] of the crude product gave amorphous **13** (2H) in a practically theoretical yield, $[\alpha]_D$ +7° (c 0.7, chloroform). ^{1}H-n.m.r. ($CDCl_3$): δ 3.42-3.48 (m, 3 H, H-5,6a,6b), 3.49 (s, 3 H, OMe), 3.66 (t, 1 H, $J_{2,3}$ 9 Hz, H-3), 3.87 (t, 1 H, $J_{3,4}$ 9 Hz, H-4), 4.49 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.70 (s, 2 H, benzylic protons), 5.28 (t, 1 H, $J_{2,3}$ 8.5 Hz, H-2); ^{13}C-n.m.r. ($CDCl_3$): δ 56.4 (OMe), 63.9 (C-6), 72.1 (CH_2-benzylic), 73.4 (C-2), 74.2, 74.5 (C-4,5), 82.3 (C-3), 87.0 (Ph_3C), 101.9 (C-1).

Anal. Calcd for $C_{40}H_{38}O_7$: C, 76.2; H, 6.03. Found: C, 76.0; H, 6.11.

Methyl 2-O-Benzoyl-3-O-benzyl-6-O-triphenylmethyl-(2-^{2}H)-β-D-glucopyranoside **(13, 2D)** ***and Methyl 2-O-Benzoyl-3-O-benzyl-4,6-di-O-triphenylmethyl-(2-^{2}H)-β-D-glucopyranoside*** **(14, 2D).**— Compound **11** (2D) (3.26 g) was treated essentially as described above for the protio analog. The crude product was chromatographed, to give **13** (2D) (5 g, 94%), which showed characteristics corresponding to those of the 2-protio analog.[15]

Early fractions were rechromatographed, to yield the di-*O*-trityl derivative **14** (2D) (0.4 g, 5%), mp 184-186°C (from dichloromethane-ethanol), $[\alpha]_D$ +2° (c 0.7, chloroform). ^{1}H-n.m.r. ($CDCl_3$): δ 2.85 (d, 1 H, $J_{3,4}$ 5 Hz, H-3), 3.12 (d, 2 H, $J_{6a,6b}$ 6 Hz, H-6a,6b), 3.57 (t, 1 H, $J_{4,5}$ 4.5 Hz, H-5), 3.61 (s, 3 H, OMe), 3.78, 4.34 (AB, 2 H, *J* 11.7 Hz, benzylic protons), 4.54 (m, 1 H, H-4), 5.04 (s, 1 H, H-1). ^{13}C-n.m.r. ($CDCl_3$): δ 56.5 (OMe), 65.6 (C-6), 71.2, 72.1 (C-5, CH_2-benzylic), 74.9 (C-2), 78.9, 79.6 (C-3,4), 88.6, 86.5 (2 x Ph_3C), 101.0 (C-1).

Anal. Calcd. for $C_{59}H_{51}DO_7$: C, 81.1; H, 6.07. Found: C, 81.2; H, 6.19.

Methyl 2-O-Benzoyl-3-O-benzyl-4-deoxy-4-fluoro-β-D-galactopyranoside **(17, 2H).**— Trifluoromethansulfonic anhydride (0.3 mL, 1.8 mmol) was added slowly, at -10°C, to a stirred solution of 300 mg (0.48 mmol) of **13** (2H) in a mixture of dichloromethane (5 mL) and pyridine (0.5 mL). The mixture was allowed to warm slowly and, after 1.5 h, TLC indicated complete conversion of the starting material. Ice-water was added, the phases were separated, and the dried organic phase was concentrated with co-evaporation of toluene. The solution of the product **15** (2H), obtained after chromatography of the crude product, in dry benzene (3 mL) was added to a stirred suspension of Amberlyst A-26 (F^--form) (10 g) in benzene (25 mL). Before use, the resin and benzene were dried by overnight reflux in a Soxhlet apparatus containing 3Å molecular sieves. The heterogeneous reaction was stirred at 80°C under these conditions until TLC showed that the reaction was complete (~45 min). The mixture was filtered, the solvent was evaporated, the crude product was chromatographed, and the thus obtained **16** (2H) was subjected to hydrolysis (at 80°C for 1 h), using a water-ethanol-acetic acid (1:1:5, 7 mL) mixture. After conventional processing, chromatography yielded amorphous **17** (2H) (70 mg, 38% over 3 steps from **13**), $[\alpha]_D$ +31° (c 0.6, chloroform).^{1}H-n.m.r. ($CDCl_3$): δ 3.48 (s, 3 H, OMe), 3.65 (ddd, 1 H, $J_{F,5}$ 23.1 Hz, H-5), 3.71 (ddd, 1 H, $J_{F,3}$ 27.8 Hz, $J_{2,3}$ 10 Hz, $J_{3,4}$ 2 Hz, H-3), 3.84 (dd, 1 H, $J_{5,6a}$ 5.5 Hz, $J_{6a,6b}$ 11 Hz, H-6a), 3.96 (dd, 1 H, $J_{5,6b}$ 7.5 Hz, H-6b), 4.49 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.56, 4.72 (AB, 2 H, *J* 12.5 Hz, benzylic protons), 4.92 (dd, 1 H, $J_{F,4}$ 50 Hz, H-4), 5.51 (dd, 1 H, H-2); ^{13}C-n.m.r. ($CDCl_3$): δ 56.7 (OMe), 60.9 ($J_{F,C}$ 5 Hz, C-6), 70.9 (C-2), 71.3

(CH_2-benzylic), 73.9 ($J_{F,C}$ 18.3 Hz, C-5), 76.9 ($J_{F,C}$ 18.4, C-3), 85.2 ($J_{F,C}$ 185.3, C-4), 102.1 (C-1).

Anal. Calcd for $C_{21}H_{23}FO_6$: C, 64.6; H, 5.90; F, 4.87. Found: C, 64.2; H, 5.89; F, 4.84.

Methyl 2-O-Benzoyl-3-O-benzyl-4-deoxy-4-fluoro-(2-^{2}H)-β-D-galactopyranoside **(17, 2D).**– Repetition of the above procedure, starting with 7.4 g of **13** (2D), produced 1.1 g, 23%) of **17** (2D). The obtained material exhibited chromatographic and spectroscopic characteristics corresponding with those of **17** (2H).[15]

Methyl 2-O-Benzoyl-3-O-benzyl-4-deoxy-4-fluoro-6-O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-(2-^{2}H)-β-D-galactopyranoside **(19).**– A solution of 1.03 g, (2.6 mmol) of **17** (2D), **18** (2.06 g, 3.1 mmol) and 2,4,6-trimethylpyridine (275 µL, 0.8 equiv) in dichloromethane (10 mL) was added slowly to a suspension of 0.935 g (1.4 equiv) of silver triflate in dichloromethane (10 mL), stirred under nitrogen at -20°C. After 5 min, TLC showed the reaction to be complete. After neutralization with 2,4,6-trimethylpyridine, the mixture was filtered through a bed of Celite, the filtrate was washed successively with aqueous sodium thiosulfate solution and water, dried, and concentrated. The crude product was chromatographed, to give amorphous **19** (2.33 g, 91%) which exhibited $[\alpha]_D$ +68° (c 0.7, chloroform). ^{1}H-n.m.r. ($CDCl_3$): δ 3.16 (s, 3 H, OMe), 3.55 (dd, 1 H, $J_{F,3}$ 30.2 Hz, $J_{3,4}$ 2.4 Hz, H-3), 3.64 (dt, 1 H, $J_{F,5}$ 27.9 Hz, H-5), 3.95 (dd, 1 H, $J_{5,6a}$ 7 Hz, $J_{6a,6b}$ 10 Hz, H-6a), 4.12 (dd, 1 H, $J_{5,6b}$ 5 Hz, H-6b), 4.30 (s, 1 H, H-1), 4.37 (1 H, t, $J_{5',6'a} = J_{5',6'b}$ 6.5 Hz, H-5'), 4.46, 4.64 (AB, 2 H, J 12 Hz, benzylic protons), 4.46 (dd, 1 H, $J_{6'a,6'b}$ 11 Hz, H-6'a), 4.68 (dd, 1 H, H-6'b), 4.83 (dd, 1 H, $J_{F,C}$ 49.9 Hz, $J_{4,5}$ <1 Hz, H-4), 4.95 (d, 1 H, $J_{1',2'}$ 8 Hz, H-1'), 5.64 (dd, 1 H, $J_{3',4'}$ 3.5 Hz, $J_{2',3'}$ 10.5 Hz, H-3'), 5.81 (dd, 1 H, H-2'), 6.01 (bd, 1 H, $J_{4',5'}$ <1 Hz, $J_{3',4'}$ 3 Hz, H-4'); ^{13}C-n.m.r. ($CDCl_3$): δ 56.3 (OMe), 62.0 (H-6'), 68.1 (2 C, C-6,4'), 69.8 (C-2'), 70.5 (C-2), 71.2 (CH_2-benzylic), 71.5 (2 C, C-3'5'), 72.6 ($J_{F,C}$ 17.9 Hz, C-5), 76.4 ($J_{F,C}$ 18.2 Hz, C-3), 85.3 ($J_{F,C}$ 186.2 Hz, C-4), 101.7 (2 C, C-1,1').

Anal. Calcd for $C_{55}H_{48}DFO_{15}$: C, 68.1, H, 5.16; F, 1.96. Found: C, 68.2; H, 5.11; F, 1.99.

Methyl 3-O-Benzyl-4-deoxy-4-fluoro-6-O-(β-D-galactopyranosyl)-(2-^{2}H)-β-D-galactopyranoside **(20).**– To a solution of **19** (2.13 g) in toluene (20 mL) was added at 50°C hot methanol (100 mL), followed by methanolic sodium methoxide, until the solution was strongly alkaline to litmus. The solution was kept at 50°C for 2 h, cooled to room temperature, and neutralized with Amberlite IR 120 (H^+-form) resin. After

concentration and evaporation of solvents with co-evaporation with water to remove methyl benzoate, the product was crystallized from ethanol-acetone and recrystallized from ethyl acetate-acetone to yield **20** (860 mg, 87%). Final recrystallization from the same solvent gave material, mp 160-161°, $[\alpha]_D$ -8.4 (c 0.8, chloroform).^{1}H-n.m.r. (D_2O): δ 3.55 (s, 3 H, OMe), 4.39 (s, 1 H, H-1), 4.42 (d, 1 H, $J_{1',2'}$ 8 Hz, H-1'), 4.70, 4.78 (AB, 2 H, J 11.8 Hz, benzylic protons), 5.03 (dd, 1 H, $J_{F,4}$ 49.9 Hz, $J_{3,4}$ 2.5 Hz, H-4); ^{13}C-n.m.r. (D_2O): δ 58.4 (OMe), 61.9 (C-6'), 68.7 ($J_{F,C}$ 4.9 Hz, C-6), 69.6 (C-4'), 71.6 (CH_2-benzylic), 73.1 (C-2'), 73.3 ($J_{F,C}$ 17.0 Hz, C-5), 73.6 (C-3'), 76.1 (C-5'), 79.5 ($J_{F,C}$ 17.3, C-3), 87.4 ($J_{F,C}$ 179.2 Hz, C-4), 104.3 (C-1,1').

Anal. Calcd for $C_{20}H_{28}DFO_{10}$: C, 53.5; H, 6.68; F, 4.23. Found: C, 53.2; H, 6.31; F, 4.44.

***Methyl 4-Deoxy-4-fluoro-6-O-(β-D-galactopyranosyl)-(2-^{2}H)-β-D-galactopyranoside* (5).**— A solution of compound **20** (700 mg) in methanol was stirred for 3 h in an atmosphere of hydrogen, at atmospheric pressure and at room temperature in the presence of 5% palladium-on-charcoal catalyst (400 mg). After conventional processing, crystallization from ethanol yielded **5** (482 mg, 86%), which exhibited properties consistent with those of the 2-protio analog.[4,15]

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16. Column chromatography of tritylated compounds was performed with addition of 0.1% (v/v) of pyridine to the eluant.