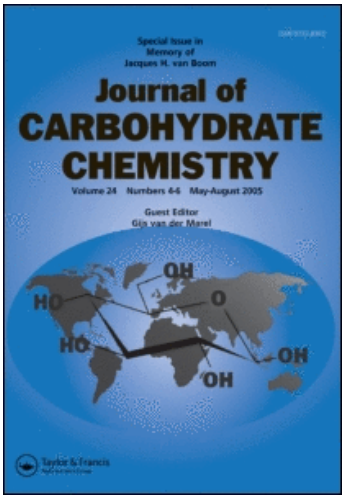

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SYNTHESIS OF SPECIFICALLY FLUORINATED METHYL β-GLYCOSIDES OF (1→6)-β-D-GALACTOOLIGOSACCHARIDES II. METHYL 4-DEOXY-4-FLUORO-6-O-(β-D-GALACTOPYRANOSYL)-β-D-GALACTOPYRANOSIDE

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ABSTRACT

Condensation of methyl 2,3-di-O-benzyl-4-deoxy-4-fluoro-β-D-galactopyranoside with 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide in the presence of mercuric cyanide in benzene afforded, in excellent yield, the β-linked product. Its deblocking, effected by hydrogenolytic cleavage of the benzyl groups followed by deacetylation or, alternatively, via a pathway where the sequence of the deblocking reactions was reversed, gave crystalline title disaccharide 10. The structures of the compounds involved in the synthesis were confirmed by ^{13}C NMR spectroscopy.

INTRODUCTION

The title compound was synthesized in connection with studies on the modes of binding of ligands to (1→6)-β-D-galactan-specific immunoglobulins. The importance of specifically fluorinated derivatives of methyl β-D-galactopyranoside in these studies has been rationalized.[1-5]

RESULTS AND DISCUSSION

The starting point in the synthesis of 10 was methyl 2,3-di-O-benzyl-4-deoxy-4-fluoro-D-galactopyranoside (2)[6] which, when

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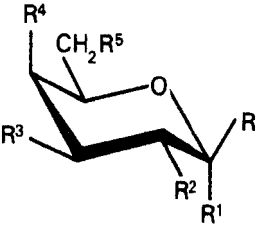
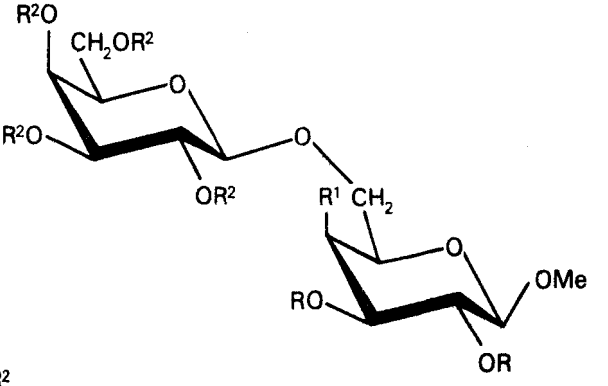
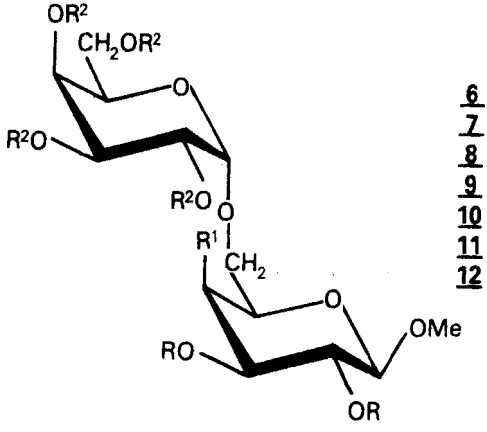


	R	R^1	R^2	R^3	R^4	R^5
1	H	Br	OAc	OAc	OAc	OAc
2	OMe	H	OBn	OBn	F	OH
3	OMe	H	OH	OH	F	OH



	R	R^1	R^2
6	Bn	F	Ac
7	H	F	Ac
8	Bn	F	H
9	Ac	F	Ac
10	H	F	H
11	Ac	OAc	Ac
12	H	OH	H



	R	R^1	R^2
4	Bn	F	Ac
5	Ac	OAc	Ac

condensed in benzene with 1.5 molar excess of 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide[7] in the presence of mercuric cyanide and mercuric bromide, gave an excellent yield of methyl 2,3-di-O-benzyl-4-deoxy-4-fluoro-6-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (6). A minor by-product (~2%) isolated by chromatography of the crude condensation product, was shown by ^{13}C NMR spectroscopy to be the α-linked disaccharide 4. Its spectrum was interpreted with the aid of the assigned spectrum[6] of 2 and the corresponding nonfluorinated disaccharide[8] 5. Fig. 1 shows the development of the assignment of the lines in the spectrum of 4. Here, compound 2 is a model for the reducing end-unit and the 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl residue in 5 is the model for the nonreducing end-unit in the oligosaccharide 4. As can be seen, the spectrum of 4 shows lines with practically the same chemical shifts as those assigned in the spectrum of 5 to the carbon atoms of the nonreducing D-galactose moiety. Also, the differences in the position of the lines assigned in the spectrum of 4 to the reducing end-unit, reflecting the glycosylation-induced shifts due to substitution at HO-6 in 2, are in agreement with the general rules of ^{13}C NMR spectroscopy of carbohydrates (c.f. e.g. ref. 9 and 10). The spectrum of 6 was interpreted (Fig. 2) in a similar manner using as an aid the assigned spectra of 2 and 11[8].

The conversion 6→10 was done in two different ways and comprised simple hydrogenolytic cleavage of the benzyl groups, followed by catalytic deacetylation (Zemplen) or, alternatively, through the pathway where the sequence of these reactions was reversed. Both ways were straightforward, high yielding, and gave readily crystallizable 10 in high yield. The lines in the ^{13}C NMR spectrum of 10 were assigned (Fig. 3) using spectral data of methyl 4-deoxy-4-fluoro-β-D-galactopyranoside[6] and the corresponding nonfluorinated disaccharide derivative[8] 12. Noteworthy is the fluorine-induced upfield shift of lines for C-3, C-5 and C-6 in the spectrum of 10, compared to the shift of analogous lines in the spectrum of 12.

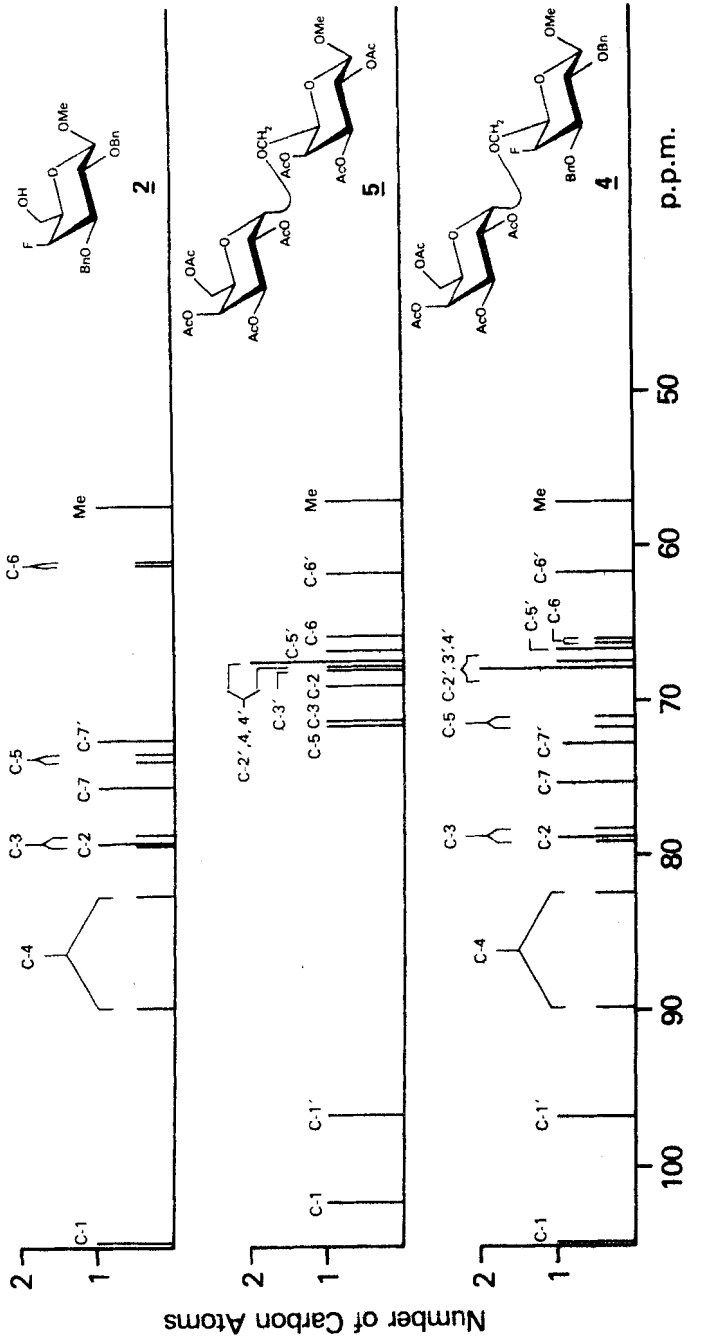


Fig. 1 Development of the assignment of lines in the ^{13}C NMR spectrum of 4, based on the spectra of 2 and 5 (C-7,C-7′ denotes benzylic carbon atoms)

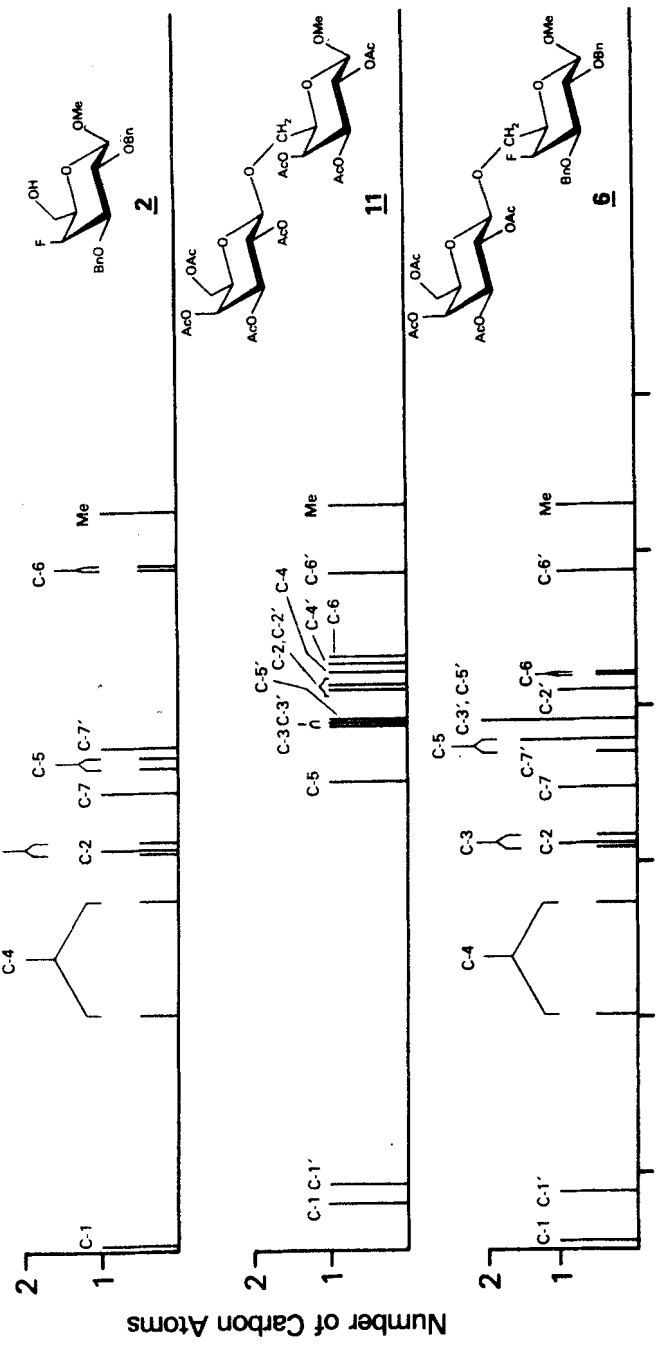


Fig. 2 Development of the assignment of lines in the ^{13}C NMR spectrum of 6, based on interpreted spectra of 2 and 11 (C-7,C-7′ denotes benzylic carbon atoms)

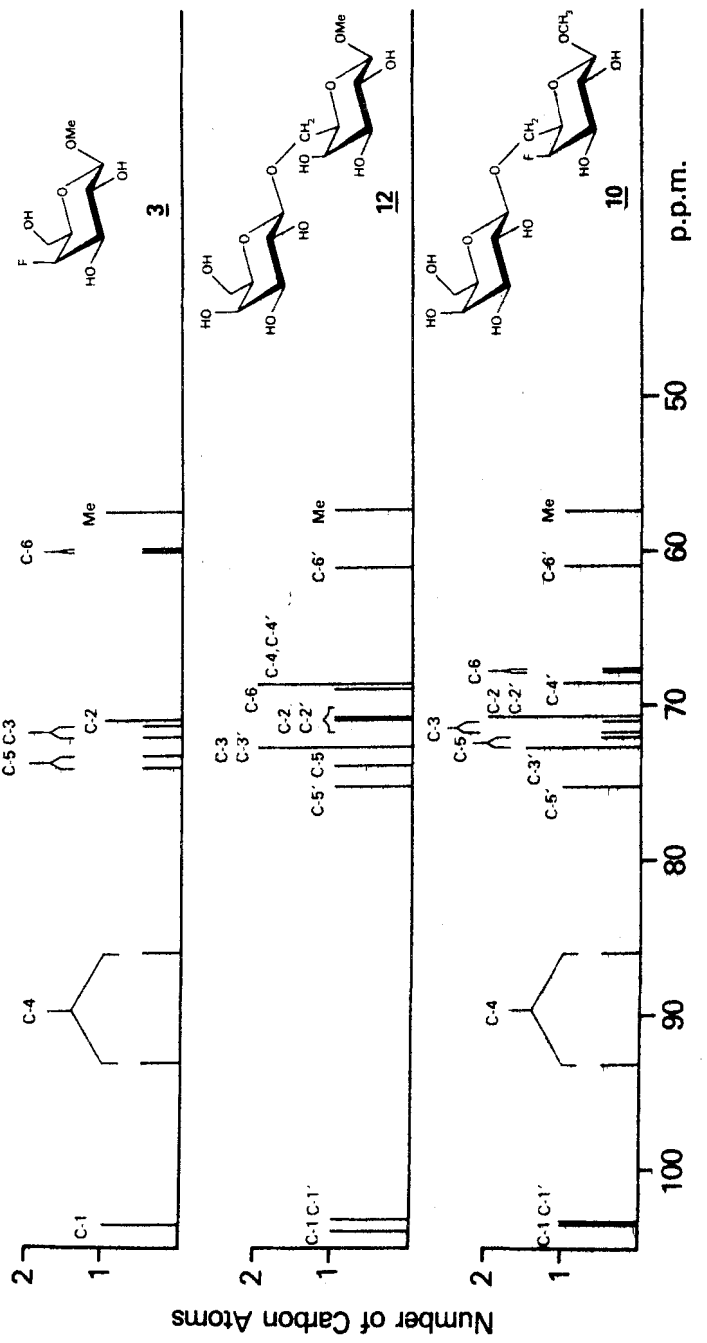


Fig. 3 Development of the assignment of lines in the spectrum of 10 based on interpreted spectra of 3 and 12

EXPERIMENTAL

Melting points were determined with a Buchi melting point apparatus. Optical rotations (c~1) were measured at 23° in chloroform except for 10 which was taken in water, using a Perkin-Elmer automatic polarimeter, Model 241 MC. Gradient elution preparative chromatography was performed on columns of slurry-packed Silica Gel 60 (Merck, Cat. No. 9385). Thin-layer chromatography (TLC) on pre-coated plates of silica gel (250 μm, Analtech, Inc.) was performed with A, carbon tetrachloride-acetone 4:1; B, dichloromethane-acetone 10:1; and C, dichloromethane-methanol 10:1. The solvent ratios are based on volumes. Detection was effected by charring with 5% (v/v) sulfuric acid in ethanol. ^{13}C NMR spectra were recorded at 25.16 MHz with a Jeol FX 100 spectrometer. Spectra of 4, 6, 7 and 9 were taken in chloroform-d (internal standard, Me_4Si) and those of 8 and 10 in methanol-d_4-chloroform-d (1:4, internal standard, Me_4Si) and D_2O (internal standard, MeOH, MeOH vs. Me_4Si, 49.0 p.p.m.), respectively. Solutions in organic solvents were dried with anhydrous sodium sulfate, and concentrated at 42°/2 kPa.

Methyl 2,3-di-O-benzyl-4-deoxy-4-fluoro-6-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (6). - The bromide 1 (3.26 g, 7.92 mmol) was added to a stirred suspension of the nucleophile 2 (2 g, 5.3 mmol), Drierite (5 g), mercuric cyanide (1 g, ~4 mmol) and mercuric bromide (0.8 g) in dry benzene (20 mL), which had been stirred for 1 h. After a reaction period of 2 h, TLC (solvent A) showed that only traces of unconverted nucleophile were present (R_F 0.25). The mixture was filtered, and the filtrate was partitioned between dichloromethane and 1M aqueous potassium bromide solution. The dichloromethane solution was dried, concentrated, and the residue was chromatographed to give first the α-linked disaccharide 4 (R_F 0.5) which was obtained as a hygroscopic glassy solid (100 mg, 2.6%). ^{13}C NMR data (δ): 104.6 (C-1); 96.7 (C-1'); 86.1 (C-4, $^1J_{CF}$ 183.1 Hz); 78.9 (C-2); 78.8 (C-3, $^2J_{CF}$ 17.1 Hz); 75.2 (CH_2, benzylic); 72.8 (CH_2, benzylic); 71.4 (C-5, $^2J_{CF}$ 17.1 Hz); 67.9, 67.5 (2C + 1C, C-2',

C-3', C-4'); 66.6 (C-5'); 66.2 (C-6, $^{3}J_{CF}$ 6.1 Hz); 61.7 (C-6'); 57.1 (Me).

Subsequently eluted was the desired disaccharide derivative 6 (3.5 g, 93%, glassy solid) which, when dried at 80°/133 Pa, showed $[\alpha]_D$-14°. ^{13}C NMR data (δ): 104.5 (C-1); 101.3 (C-1'); 86.2 (C-4, $^{1}J_{CF}$ 183.1 Hz); 78.8 (C-2); 78.7 (C-3, $^{2}J_{CF}$ 17.1 Hz); 75.2 (CH_2, benzylic); 72.6 (C-5, $^{2}J_{CF}$ 18.3 Hz); 72.3 (CH_2, benzylic); 70.8 (2C, C-3', C-5'); 68.9 (C-2'); 68.1 (C-6, $^{3}J_{CF}$ 3.7 Hz); 67.1 (C-4'); 61.3 (C-6'); 57.0 (Me).

Anal. Calcd for $C_{35}H_{43}FO_{14}$: C, 59.48; H, 6.13; F, 2.68. Found: C, 59.49; H, 5.42; F, 2.92.

Methyl 4-deoxy-4-fluoro-6-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (7). - A solution of 6 (3.1 g) in ethanol (150 mL) was hydrogenated in the presence of 5% palladium-on-charcoal catalyst until TLC (solvent B) showed that either the starting material (R_F 0.9) or the intermediate mono-O-benzyl derivatives (R_F 0.5 and 0.6) were no longer present in the reaction mixture. The product 7 (R_F 0.1) was isolated conventionally, and the glassy solid obtained showed $[\alpha]_D$-27. ^{13}C NMR data (δ): 103.7 (C-1); 101.3 (C-1'); 88.8 (C-4, $^{1}J_{CF}$ 180.7 Hz); 72.9 (C-5, $^{2}J_{CF}$ 17.1 Hz); 72.2 (C-3, $^{2}J_{CF}$ 17.1 Hz); 71.4 (C-2); 70.8 (2C, C-3', C-5'); 68.9 (C-2'); 67.8 (C-6, $^{3}J_{CF}$ ~3Hz); 67.1 (C-4'); 61.3 (C-6'); 57.1 (Me).

Anal. Calcd for $C_{21}H_{31}FO_{14}$: C, 47.90; H, 5.93; F, 3.60. Found: C, 47.68; H, 6.23; F, 3.61.

Methyl 2,3-di-O-benzyl-4-deoxy-4-fluoro-6-O-(β-D-galactopyranosyl)-β-D-galactopyranoside (8). - A solution of compound 6 (100 mg) in methanol (20 mL) was treated with methanolic 1M sodium methoxide (1 mL). After 2 h at room temperature TLC (solvent C) showed that all starting material (R_F 0.95) had disappeared and that a single product was formed (R_F 0.3). The solution was neutralized with Amberlite IR 120 (H^+-form) resin and concentrated, to give a solid residue (75 mg, ~100%). Two crystallizations from ethanol gave material melting at 175-175.5° and having $[\alpha]_D$-13°. ^{13}C NMR data (δ): 104.7 (C-1); 103.9

(C-1'); 86.2 (C-4, $^{1}J_{CF}$ 181.9 Hz); 79.2 (C-3, $^{2}J_{CF}$ 18.3 Hz); 79.1 (C-2); 75.5 (C-5'); 75.1 (CH_2, benzylic); 73.8 (C-3'); 72.5 (CH_2, benzylic); 72.4 (C-5, $^{2}J_{CF}$ 18.3 Hz); 71.4 (C-2'); 69.0 (C-4'); 67.5 (C-6, $^{3}J_{CF}$ 4.9 Hz); 61.5 (C-6'); 57.4 (Me).

Anal. Calcd for $C_{27}H_{35}FO_{10}$: C, 60.21; H, 6.55; F, 3.52. Found: C, 60.18; H, 6.85; F, 3.21.

Methyl 4-deoxy-4-fluoro-6-O-(β-D-galactopyranosyl)-β-D-galactopyranoside (10). - a) A solution of 7 (200 mg) in methanol (20 mL) was treated overnight as described for the preparation of 8. After neutralization with Amberlite IR 120 (H^+-form) resin, the solution was concentrated to a small volume and the desired compound 10 crystallized in a virtually theoretical yield. Recrystallization of a portion from ethanol gave material melting at 214-215° and having $[\alpha]_D$-20°. ^{13}C NMR data (δ): 103.5 (C-1); 103.4 (C-1'); 89.6 (C-4, $^{1}J_{CF}$ 178.2 Hz); 75.2 (C-5'); 72.7 (C-3'); 72.4 (C-5, $^{2}J_{CF}$ 17.1 Hz); 71.4 (C-3, $^{2}J_{CF}$ 18.3 Hz); 70.8 (2C, C-2, C-2'); 68.6 (C-4'); 67.8 (C-6, $^{3}J_{CF}$ 3.6 Hz); 61.0 (C-6'), 57.4 (Me).

Anal. Calcd for $C_{13}H_{23}FO_{10}$: C, 43.57; H, 6.47; F, 5.30. Found: C, 43.56; H, 6.35; F, 5.04.

b) A solution of 8, when treated as described for the preparation of 7, afforded, after conventional processing, material melting at 213-215°, which was in all respects identical with the above described substance.

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