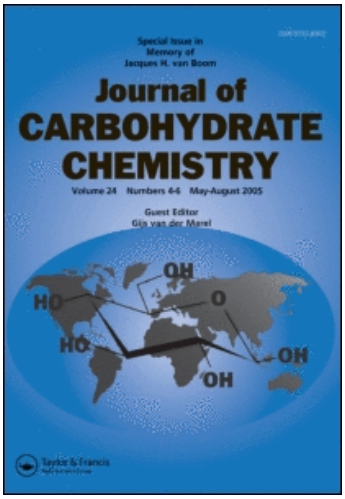

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^{13}C NMR SPECTRA OF METHYL DEOXYFLUORO-β-D-GALACTOPYRANOSIDES AND THEIR PER-O-ACETYL DERIVATIVES

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ABSTRACT

Methyl 6-deoxy-6-fluoro-β-D-galactopyranoside has been obtained by treatment of methyl β-D-galactopyranoside with diethylaminosulfur trifluoride (DAST). Improvements over the existing syntheses of methyl 2,3-di-O-benzyl-4-deoxy-4-fluoro-β-D-galactopyranoside from the corresponding 6-O-substituted 4-O-arylsulfonyl-D-gluco derivatives are described. ^{13}C NMR spectra of a series of methyl deoxyfluoro-β-D-galactopyranosides and their per-O-acetyl derivatives have been measured. The data obtained can be used as an aid for the interpretation of ^{13}C NMR spectra of deoxyfluoro-β-D-galactopyranose-containing oligosaccharides and related substances.

INTRODUCTION

Correct assignment of the lines in ^{13}C NMR spectra of oligosaccharides is often faciliated by comparison with the spectra of proper model compounds. It has been noted that the spectra of

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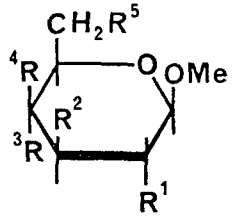
glycosyl units in oligosaccharides are similar to those of the corresponding monomeric methyl glycosides. Therefore, ^{13}C NMR spectra of methyl glycosides of monosaccharides that reflect the stereochemistry at the glycosidic center, as well as other structural peculiarities, are considered to be most suitable in aiding the interpretation of the spectra of related oligosaccharides.

In connection with studies of the modes of binding between immunoglobulins and (1→6)-β-D-galactoöligosaccharides we have in progress syntheses of methyl β-glycosides of (1→6)-β-D-galactobioses in which one hydroxyl group, either in the reducing or in the non-reducing moiety, is replaced by a fluorine atom. To aid in the interpretation of ^{13}C NMR spectra of such substances we have now measured spectra of the title compounds and calulated the fluorrine-induced substitution effects upon the individual ^{13}C chemical shifts.

RESULTS AND DISCUSSION

The 2- (2), 3- (3), and 4-fluoro (4) derivatives studied here have been previously synthesized in this laboratory.[1,2] Methyl 6-deoxy-6-fluoro-β-D-galactopyranoside (5) was prepared, by treatment of methyl β-D-galactopyranoside (1) with diethylaminosulfur trifluoride (DAST). Card[3] and others[4] have described selective, high-yielding monofluorination at the primary position of C-1 protected carbohydrates. However, with 1 as the starting material the reaction showed itself to be much less selective than in the previously reported cases and 5 was isolated in only ~15% yield.



	R^1	R^2	R^3	R^4	R^5
1	OH	OH	H	OH	OH
2	F	OH	H	OH	OH
3	OH	F	H	OH	OH
4	OH	OH	H	F	OH
5	OH	OH	H	OH	F
6	F	OAc	H	OAc	OAc
7	OAc	F	H	OAc	OAc
8	OAc	OAc	H	F	OAc
9	OAc	OAc	H	OAc	F
10	OBzl	OBzl	OH	H	OH
11	OBzl	OBzl	OH	H	OTr
12	OBzl	OBzl	OBrs	H	OTr
13	OBzl	OBzl	H	F	OTr
14	OBzl	OBzl	H	F	OH
15	OBzl	OBzl	OMs	H	OBz
16	OBzl	OBzl	H	F	OBz

To confirm the structure of 5 ^{13}C NMR spectroscopy was used. The proton-decoupled spectrum (Table 1) of 5 showed a total of 10 lines, 6 of which were parts of three doublets showing characteristic [3,5,6] $^{n}J_{CF}$ coupling constants. The position of the fluorine atom at C-6 was reflected by the absence of any signal at, or near to, δ 62.0, the region where the C-6 signal of methyl β-D-galactopyranoside normally appears. Instead, a doublet ($^{1}J_{CF}$ 164.8 Hz) was present at δ 83.1 showing, as expected, that due to the fluorine-substitution α-effect the C-6 signal was shifted much further downfield. The same could be concluded from the ^{13}C NMR data observed for the acetate 9, which were consistent with the assigned structure (Table 2).

Syntheses of certain selectively fluorinated methyl β-D-glycosides of (1→6)-β-D-galactoöligosaccharides require a protected methyl 4-deoxy-4-fluoro-β-D-galactopyranoside as the inital nucleophile in the condensation reaction. A compound of this type, namely methyl 2,3-di-O-benzyl-4-deoxy-4-fluoro-β-D-galactopyranoside (14) has previously been synthesized by two independent routes. In the earlier work[7] methyl 2,3-di-O-benzyl-4-(p-bromobenzenesulfonyl)-6-O-trityl-β-D-glucopyranoside (12), when treated with tetrabutylammonium fluoride, gave the corresponding 4-deoxy-4-fluoro-D-galacto derivative (13) in ~30% yield. Recently, Ittah et al.[1] treated methyl 2,3-di-O-benzyl-6-O-benzoyl-4-O-mesyl-β-D-glucopyranoside (15) with the F^--form of an anion exchange resin[8] and the yield of the resulting 16 was ~50%. It is possible to combine the advantages of the two approaches, namely the use of the better leaving brosyl group, as well as the use of the easier to handle, stable anion-exchange resin[1] in place of the extremely moisture-sensitive fluorine

TABLE 1

^{13}C NMR Chemical Shift of Methyl Deoxyfluoro-β-D-galactopyranosides (2-5)

Compound	Carbon Atom						
	C-1	C-2	C-3	C-4	C-5	C-6	Me
2	101.2	91.6	71.3	69.3	75.4	60.9	57.1
3	103.2	69.5	93.2	67.0	74.0	60.7	57.4
4	103.6	70.9	71.6	89.5	73.7	59.9	57.4
5	104.0	70.6	72.6	68.4	73.4	83.1	57.4

TABLE 2

^{13}C NMR Chemical Shifts of Per-O-Acetates (6 - 9) of Methyl Deoxyfluoro-β-D-galactopyranosides

Compound	Carbon Atom						
	C-1	C-2	C-3	C-4	C-5	C-6	Me
6	101.6	88.0	71.0	67.7	70.6	61.1	57.3
7	101.3	69.7	88.8	66.9	69.8	61.2	56.9
8	101.7	68.6	70.8[a]	85.9	71.8[a]	61.4	56.7
9	101.8	68.6	70.1	66.9	71.3	80.7	56.8

[a]The assignments may be reversed

donor.[7] Thus we have treated 12 with Amberlyst A-26 (F^--form) and the resulting fluoro derivative 13 was isolated in a yield of 75%. It is worth mentioning that we have experienced difficulties in the preparation of 12 when following the described procedure.[7] Tritylation of methyl 2,3-di-O-benzyl-β-D-glucopyranoside (10) went smoothly, but the HO-4 in 11 was found to be rather resistant to brosylation. Under the conditions described,[7] only ~40% conver-

sion of 11 into 12 was observed by TLC. Our use of a much larger excess of the brosylation reagent and the addition to the reaction mixture of a stronger base, N,N-dimethylaminopyridine (DMAP), drove the reaction to completion and the desired compound 12 was obtained in 88% yield, following purification of the crude product by column chromatography.

Compounds under investigation produced ^{13}C NMR spectra showing separate signals for each carbon atom. The carbon-signal assignments for methyl deoxyfluoro-β-D-galactopyranosides (2 - 5, Table 1) and their acetates (6 - 9, Table 2) were done by comparison with data for methyl β-D-galactopyranoside[9] and its per-O-acetate,[10] respectively. Carbon bound to fluorine was easily distinguished by the large geminal coupling and its characteristic low-field chemical shift. Carbons β to, and further removed from the fluorine-bearing carbon were distinguished by the characteristic magnitude of their couplings.[6] Wray[6] in his detailed study of the ^{13}C NMR spectra of some deoxyfluoroaldoses emphasized the importance of taking spectra at two field strengths for the identification of fluorine-coupled nuclei with similar chemical shifts. Therefore, spectra of those compounds where assignments were less straightforward, were taken with both 100 and 60 MHz instruments. In this way, for example, it was possible to choose the right peaks for the fluorine coupled carbons C-2 and C-5 in the spectra of 8 and, based on the resulting $^{n}J_{CF}$, to determine unambiguously the chemical shifts for the respective carbon atoms.

The $^{1-3}J_{CF}$ coupling constants (Table 3) found throughout the present study differ by as much as one order of magnitude. The

TABLE 3

J_{CF} Values for Methyl Deoxyfluoro-β-D-galactopyransides and (in Parentheses) their Acetates

Compound	Carbon Atom					
	C-1	C-2	C-3	C-4	C-5	C-6
2 (6)	23.2 (22.0)	179.4 (186.8)	17.1 (20.8)	8.5 (8.5)	0 (0)	0 (0)
3 (7)	11.0 (11.0)	19.5 (19.5)	183.1 (192.9)	17.1 (17.1)	7.3 (6.1)	3.6 (0)
4 (8)	0 (0)	0 (0)	18.3 (18.3[a])	177.0 (185.6)	17.1 (17.1[a])	4.9 (4.9)
5 (9)	0 (0)	0 (0)	0 (0)	7.3 (6.1)	20.8 (23.2)	164.8 (171.5)

[a]The assignments may be reversed

sharp decrease of the intensity of the CF interaction, when going from geminal- through vicinal- to three bond interactions makes routine assignment of the interacting carbon atoms to the respective doublets easy. In only one instance (compound 4, Table 3) a $^{4}J_{CF}$ was observed, but even in this case the differences between $^{3}J_{CF}$ and $^{4}J_{CF}$ was sufficient, taking into account also the ^{13}C chemical shifts, to distinguish between C-5 and C-6.

Chemical shift-effects due to fluorination, calculated as the difference between the shift of a particular carbon in a methyl deoxyfluoro-β-D-galactopyranoside and the shift of the same carbon in the parent compound, methyl β-D-galactopyranoside, are given in Table 4. The observed strong downfield fluorination shift (positive α-effect) of ~20 ppm is consistent with values found in similar systems.[3,6] All other fluorination shift effects were found to be negative and, particularly the β-effects, similar to those observed on acetylation of a hydroxyl group in a carbohydrate.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns melting point apparatus. Optical rotations were measured at 25 °C with a Perkin-Elmer automatic polarimeter, Model 241 MC. Thin-layer chromatography (TLC) on precoated plates of silica gel GF (250 μm, Analtech, Inc.) was performed with A, dichloromethane-methanol 8:1; B, dichloromethane-acetone 1:1; C, carbon tetrachloride acetone 4:1; D, toluene-acetone 8:1; E, toluene-acetone 4:1; F, toluene-ethyl acetate 10:1; G, toluene-acetone 25:1; and H, petroleum ether-diethyl ether 4:1. Compounds were detected by charring with 5% sul-

TABLE 4

^{13}C NMR Chemical Shift Effects of Monofluorination in Methyl Deoxyfluoro-β-D-galactopyranosides[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	Me
2	-3.7	+19.8	-2.6	-0.5	-0.8	-1.2	-1.2
3	-1.7	-2.3	+19.3	-2.8	-2.2	-1.4	-0.9
4	-1.3	-0.9	-2.3	+19.7	-2.5	-2.2	-0.9
5	-0.9	-1.2	-1.3	-1.4	-2.8	+21.0	-0.9

[a]Data for the parent compound, methyl β-D-galactopyranoside taken from ref. 9.

furic acid in ethanol or by UV light. Gradient elution column chromatography was performed on silica gel (Merck, Cat. No 9385). Amberlyst A-26 (F^--form) was a product of Fluka A.G. DAST was purchased from Aldrich Chemical Co., and was used as supplied. Methyl β-D-galactopyranoside, obtained from Sigma Chemical Co., was dried at 40°/133 Pa for 16h.

^{13}C NMR spectra of 2 - 5 were obtained for solutions in D_2O (internal standard MeOH, δ MeOH vs. Me_4Si, 49.0). Spectra of other compounds were obtained for solutions in $CDCl_3$ (internal standard Me_4Si). Chemical shifts given in Tables 1 and 2 are given in ppm downfield from Me_4Si. The NMR instruments used were Jeol FX 100 and Jeol FX 60 models operating for ^{13}C NMR at 25.16 and 15.03 MHz, respectively. Unless otherwise stated, solutions were concentrated at 40°/2 kPa. Molecular sieves were activated by heating for 16 h at 160°/133 Pa. Compounds 2, 3, 4, 7, and 8 were prepared as described.[1,2,7]

Methyl 6-deoxy-6-fluoro-β-D-galactopyranoside (5). – DAST (3.75 mL) was added slowly and with the exclusion of atmospheric moisture to a suspension of finely powdered 1 (1 g) in dry dichloromethane which was kept at -40 °C. Cooling was removed and stirring was continued, while the mixture was allowed to attain room temperature. A clear yellow solution formed after ~20 min and after a total of 45 min the reaction was terminated by rapid cooling (-20 °C) and the addition of methanol (10 mL). Solid sodium bicarbonate (3 g) was added, and the mixture was stirred until effervescence ceased. TLC (solvent A) then showed that the mix-

ture was complex and still contained some starting material (R_f 0.1). After filtration and concentration of the filtrate at 50°/133 Pa, the residue was chromatographed and the slowest moving product (R_f 0.3, solvent B) was isolated to give 5 (156 mg, 15.4%), which solidified on concentration. Crystallization from ethyl acetate gave snow-white material, mp 122-123 °C, lit.[11] mp 117-118 °C.

Anal. Calcd for $C_7H_{13}FO_5$: C, 42.85; H, 6.33. Found: C, 42,73; H, 6.78.

Methyl 2,3,4,-tri-O-acetyl-6-deoxy-6-fluoro-β-D-galactopyranoside (9).– A solution of 5 (50 mg) in pyridine (0.5 mL) was treated with acetic anhydride (1 mL) for 16h. TLC (solvent C) showed that the reaction was complete and that a single product (R_f 0.5) was formed. After conventional processing the product 9 was isolated in a virtually theoretical yield. Crystallization from ethanol gave material melting at 110-111 °C, lit.[11] mp 108 °C.

Anal. Calcd. for $C_{13}H_{19}FO_8$: C, 48.45; H, 5.94. Found: C, 48.10; H, 6.13.

Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-galactopyranoside (6). – Compound 2 was treated as described for the preparation of 9 and after isolation of the product in the usual manner, and crystallization from ethanol-isopropyl ether, 6 showed mp 113-114 °C and $[\alpha]_D$ + 27.8° (c 1.04, chloroform).

Anal. Calcd for $C_{13}H_{19}FO_8$: C, 48.45; H, 5.94. Found C, 48.29; H, 6.20.

Methyl 2,3-di-O-benzyl-β-D-glucopyranoside(10). – Sodium hydride (9 g, 50% in mineral oil, washed three times with petroleum ether) was added to a solution of methyl 4,6-O-benzylidene-

β-D-glucopyranoside[12] in dry 1,2-dimethoxyethane (800 mL), contained in a 2 L round bottom flask. Benzyl bromide (100 g) was added after 10 min, and the mixture was stirred at 60-70 °C with the exclusion of atmospheric moisture for 24h. TLC (solvent D) showed that the reaction was complete. The mixture was cooled (0 °C), and methanol was added until effervescence ceased, to destroy the excess of the benzylation reagent. Organic solvents were removed by evaporation with periodical addition of water, and the product crystallized. The solid material was filtered off, washed with water (twice) and hexane (twice). The solution of the crude product in dichloromethane was washed with water (twice), dried and concentrated, to give a chromatographically pure solid residue (38 g, 92%), which was used for the next step. A portion (1 g,) when recrystallized from dichloromethane-hexane melted at 118-120 °C, lit.[13] mp 118-119 °C.

The foregoing product (37 g) was dissolved in a boiling acetic acid-ethanol mixture (4:1, 250 mL), and water (50 mL) was added slowly. The solution was heated at 90 °C for two hours, and then concentrated to dryness; co-distillation with water and toluene removed acetic acid. Methyl 6-O-acetyl-2,3-di-O-benzyl-β-D-glucopyranoside, formed[1] on concentration of a solution of 10 in dilute acetic acid was reconverted to 10 by deacetylation (Zemplen), and 10 was crystallized from methanol. Further crops (total yield 28 g, 94.6%) were obtained from the concentrated mother liquor by crystallization from isopropyl ether containing a little ethanol. A portion, when recrystallized from methanol melted at 122 °C, lit.[14] mp 122-

123 °C. ^{13}C NMR data (δ): 104.9 (C-1), 83.9 (C-3), 81.9 (C-2), 75.2 (double intensity, C-5, CH_2- benzylic), 74.6 (CH_2- benzylic, 70.1 (C-4), 62.0 (C-6), 57.2 (Me).

Methyl 2,3-di-O-benzyl-4-O-brosyl-6-O-trityl-β-D-glucopyranoside (12). – Trityl choride (4.1 g, 14.7 mmol) was added to a solution of 10 (5 g, 13.3 mmol) in pyridine (25 mL) and the mixture was kept at 50 °C for 24h. TLC (solvent F) showed only traces of the starting material (R_f 0.05) to be present. One fifth of the mixture was withdrawn and the trityl derivative 11 was isolated in the usual manner as a hygroscopic amorphous solid. ^{13}C NMR data (δ): 104.5 (C-1), 84.1 (C-3), 81.8 (C-2), 75.1 (CH_2- benzylic), 74.5 (CH_2- benzylic), 74.1 (C-5), 71.3 (C-4), 63.8 (C-6), 56.6 (Me).

To the remaining mixture brosyl chloride (13.6 g, 53.4 mmol) and DMAP (6.5 g, 53.4 mmol) were periodically added in equimolar amount over a period of 36 h. After 48 h only traces of 11 (R_f 04) were present, as shown by TLC (solvent G). The mixture was worked up conventionally and the crude product was eluted from a column of silica gel to give 12 as a white solid foam, $[\alpha]_D$-9.7° (c 1.5, chloroform), lit.[7] $[\alpha]_D$-7.1° (c 3.3, chloroform) for 12 of questionable purity. ^{13}C NMR data (δ): 104.3 (C-1), 82.4 (C-3), 81.2 (C-3), 78.4 (C-4), 74.9 (CH_2- benzylic), 74.4 (CH_2- benzylic), 73.3 (C-5), 63.0 (C-6), 56.8 (Me).

Anal. Calcd. for $C_{46}H_{43}BrO_8S$: Br, 9.55; S, 3.83. Found: Br, 9.33, S, 3.88.

Methyl 2,3-di-O-benzyl-4-deoxy-4-fluoro-6-O-trityl-β-D-galactopyranoside (13). – Amberlyst A-26 (F^-–form, 15 g) was dehydrated

by stirring in benzene (110 mL) under reflux for 8h in a Soxhlet extractor containing activated molecular sieves 3A. The brosyl derivative 12 (2.8 g) was introduced and the mixture was refluxed with stirring and exclusion of atmospheric moisture until TLC (solvent H) showed that only traces of the starting material were present (~3-4 days). The mixture was filtered, the resin washed with several portions of dichloromethane, and the filtrate and washings were concentrated. The residue was chromatographed to give 13 (1.6 g, 77%), which crystallized on concentration, mp 136-138 °C, lit.[7] mp 137-138 °C. ^{13}C NMR data (δ): 104.4 (C-1), 86.2 (d, $^{1}J_{CF}$ 184.3 Hz, C-4), 79.0 (d, $^{2}J_{CF}$ 17.1 Hz, C-3), 78.9 (C-2), 75.1 (CH_2- benzylic), 72.4 (CH_2- benzylic), 72.1 (d, $^{2}J_{CF}$ 17.1 Hz, C-5), 61.6 (d, $^{3}J_{CF}$ 2.4 Hz, C-6), 56.6 (Me).

Methyl 2,3-di-O-benzyl-4-deoxy-4-fluoro-β-D-galactopyranoside (14). – Water was added to a solution of 13 (2 g) in hot acetic acid (10 mL), a small amount of turbidity was clarified by addition of a little ethanol, and the solution was kept at 90° until TLC (solvent G) showed complete disappearance of the starting material. The solution was concentrated and the residue was processed as described for the preparation of 10. The crude product was chromatographed to give 14 (1.1 g, 90.4%), mp 107-108 °C, lit.[1] mp 90-96 °C, lit.[7] mp 105-106 °C. ^{13}C NMR data (δ): 104.6 (C-1), 86.0 (d, $^{1}J_{CF}$ 181.9 Hz, C-4), 79.0 (C-2), 78.8 (d, $^{2}J_{CF}$ 18.3 Hz, C-3), 75.3 (CH_2- benzylic), 73.4 (d, $^{2}J_{CF}$ 18.1 Hz, C-5), 72.4 (CH_2- benzylic), 60.8 (d, $^{3}J_{CF}$ 4.9 Hz, C-6), 57.2 (Me).

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