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STEREO- AND REGIO-SELECTIVITY OF DIETHYLAMINOSULFUR TRIFLUORIDE AS A FLUORINATING REAGENT FOR METHYL GLYCOSIDES

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ABSTRACT

Methyl glycopyranosides reacted with diethylaminosulfur trifluoride (DAST) in the absence of solvent to yield methyl dideoxy-difluoro and deoxy-fluoro glycopyranosides. Methyl α-D-glycopyranosides produced 6-deoxy-6-fluoro- and 4,6-dideoxy-4,6-difluoro derivatives with Walden inversion at C-4. Methyl β-D-glucopyranoside also produced a 3,6-dideoxy-3,6-difluoro derivative, with Walden inversion at C-3. Methyl 6-*O*-trityl-α-D-glucopyranoside, reacted with DAST to yield the corresponding 4-deoxy-4-fluorogalactopyranoside derivative.

INTRODUCTION

Fluorinated carbohydrates have been reported to possess antitumor and other biological activities[1–4]. They have been used as inhibitors in examining the active sites of hexokinases[4], and may have value in studies of the biosynthesis and function of glycoproteins, and of lectin–carbohydrate interactions[5]. This study was initiated in order to determine whether the structure of oligosaccharides or glycopeptides can be clarified by ^{19}F-n.m.r. spectroscopy of their fluorinated derivatives.

Sharma and Korytnyk[6] successfully employed diethylaminosulfur trifluoride[7] (DAST) for synthesis of 6-deoxy-6-fluorohexoses. We have examined the utility of DAST as a fluorinating agent for oligosaccharides and methyl glycosides. Only methyl glycosides reacted with DAST, and yielded monofluoro- and difluoroglycosides. DAST replaced 6-hydroxyl groups and equatorial hydroxyl groups (except those on C-2) of methyl glycosides by fluorine. As will be seen, the position of the hydroxyl group that is fluorinated depends on the anomeric configuration of the glycoside. A major advantage of this reaction is that it decreases the number of stages involved in the synthesis of deoxyfluoro sugars. The stereo- and regio-selectivity of the reaction allows selection of the proper substrate for synthesis of a specific deoxyfluoro sugar.

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RESULTS AND DISCUSSION

All the compounds synthesized were characterized by their proton-coupled ^{19}F- and proton-decoupled ^{13}C-n.m.r. spectra. It was not possible to determine certain fluorine–carbon coupling constants because of the complexity of some ^{13}C-n.m.r. spectra. In certain cases, the proposed structures were confirmed by coupling patterns of the high-resolution ^1H-n.m.r. spectra.

Carbon-13 signals were assigned to individual atoms by comparing the spectra of products with those of the substrates and by considering the coupling patterns of the signals. Table I summarizes the ^{13}C chemical shifts of the substrates and products. Replacement of a hydroxyl group by fluorine causes a downfield shift of the fluorine-bearing carbon signal by (20.8 ±2.0) p.p.m. (average of 9 values). A fluorine atom shields the carbon atom adjacent to the fluorinated one. The signals of these carbon atoms are shifted upfield by (4.4 ±1.6) p.p.m. (average of 6 values).

As shown by Wary[8] the $^1J_{C,F}$ values increase with electronegativity of the geminal substituent. The $^1J_{C,F}$ value of C-6 is observed as 168.6 ±2.0 Hz and that at C-3 or C-4 is 179.8 ±1.8 Hz. These values agree with those observed by Wary[8]. The same author has shown that $^2J_{C,F}$ of monodeoxy monofluoro sugars has a constant value of 17.5 ±0.3 Hz when the coupled fluorine atom is *gauche* to the oxygen substituent of the coupled carbon atom. Most of the observed $^2J_{C,F}$ values are in good agreement with this value, but some of those from dideoxy difluoro sugars have larger coupling constants (see Table II). The magnitude of $^3J_{C,F}$ 5.5 ±0.8 Hz when the fluorine atom is *gauche* with respect to both the carbon atom concerned and the ring oxygen atom (average of four values). The value reported by Wary[8]

TABLE I

^{13}C CHEMICAL SHIFTS (P.P.M.)

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*CH_3O*	*Unassigned signals*
1[a]	100.3	72.5	74.2	70.6	72.7	61.7	56.2	
4	102.5			92.8[b,c]		84.9[b,c]	57.9	69.9, 70.5, 71.5
5	102.0	73.7	75.5	71.0[d]	73.0[d]	84.8[b,d]	57.8	
6	99.3			89.5[b,d]		61.6[d]	55.5	68.2, 68.9, 69.6, 70.2 (Tri 87.0, 127.1, 127.8, 128.6, 143.7)
2[a]	101.9	71.2	71.8	68.0	73.7	62.1	55.9	
7	102.0	69.2	65.2[d]	89.4[b,c]	68.0	82.2[b,c]	54.5	
8[a]	104.3	74.2	76.9	70.8	76.9	61.9	58.3	
9	102.1[d]	70.7[d]	93.6[b,d]	66.3[c]	73.0	83.1[b,d]	56.8	
10	105.1			89.8[b,c]		82.6[b,c]	56.8	71.8, 72.0, 72.5, 72.6, 73.2
11	103.8	73.5	76.7	69.0[d]	74.7[d]	82.3[b,d]	55.9	

[a]Taken from ref. 10. [b]Fluorinated carbon atom. [c]Doublet of doublets. [d]Doublet.

TABLE II

CARBON–FLUORINE COUPLING CONSTANTS (Hz)

Compound	$^{1}J_{F\text{-}6,C\text{-}6}$	$^{2}J_{F\text{-}6,C\text{-}5}$	$^{3}J_{F\text{-}6,C\text{-}4}$	$^{1}J_{F\text{-}4,C\text{-}4}$	$^{2}J_{F\text{-}4,C\text{-}5}$	$^{3}J_{F\text{-}4,C\text{-}6}$	$^{2}J_{F\text{-}4,C\text{-}3}$	$^{1}J_{F\text{-}3,C\text{-}3}$	$^{2}J_{F\text{-}3,C\text{-}4}$	$^{3}J_{F\text{-}3,C\text{-}5}$	$^{2}J_{F\text{-}3,C\text{-}2}$	$^{3}J_{F\text{-}3,C\text{-}1}$
4	167.2		6.1	178.2		6.1						
5	168.4	17.1	6.1									
6				181.9	17.2	4.3						
7	166.1	17.1[a]	6.1	180.1	22.0[a]	5.5	17.1					
9	170.9	20.0	4.3					177.0	25.0	7.9	17.2	4.3
10	167.9		6.7	180.7		6.1						
11	170.9	18.3	7.3									

[a]Assignment is ambiguous.

TABLE III

^{19}F-CHEMICAL SHIFTS (P P M) AND FLUORINE–HYDROGEN COUPLING-CONSTANTS (Hz)

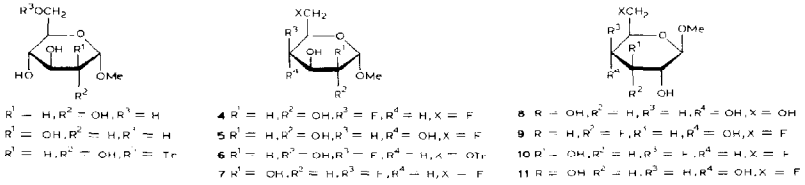
Compound	*F-6*	*F-4*	$J_{F\text{-}4,H\text{-}4}$	$J_{F\text{-}4,H\text{-}3/F\text{-}4,H\text{-}5}$	$J_{F\text{-}6,H\text{-}6}$	$J_{F\text{-}6,H\text{-}5}$	$J_{F\text{-}3,H\text{-}3}$	$J_{F\text{-}3,H\text{-}2/F\text{-}3,H\text{-}4}$
4	−229.9	−219.7	50.3	30.6	46.6	13.5		
5	−219.4				48.0	26.2		
6		−14.7	50.0	30.5				
7	−199.6	−196.7	51.3	31.7	46.7	14.6		
9	−196.3	−192.5			47.6	25.6	53.7	29.3
10	−206.2	−196.2	51.3	30.5	46.7	13.4		
11	−193.5				48.2	24.4		

for this system is 5.5 Hz. When the carbon atom concerned is *trans* to the fluorine atom and has two oxygen atoms and a hydrogen atom as its substituents, the magnitude of $^3J_{C,F}$ is[8] 11.7 Hz. The anomeric carbon atom of compound **9** has the same substituents, but is *gauche* with respect to the fluorine atom. The observed magnitude of $^3J_{C,F}$ for this system is 4.3 Hz. When the carbon atom concerned has as its substituents a hydroxyl group, a hydrogen atom, and a carbon atom and is *gauche* with respect to the fluorine atom, the reported[8] magnitude of $^3J_{C,F}$ is 1.6 Hz. Carbon atom 5 and F-3 of compound **9** have the same orientation and the same substituents at C-5, and the observed $^3J_{C,F}$ value is 7.9 Hz. This large difference could be related to the presence of the ring oxygen-atom and the CH_2F group as the substituents of C-5 of compound **9**, instead of a hydroxyl group and -CH(OH)(C or O) group, respectively, in the compounds of Wary[8].

Sharma and Korytnyk[6] prepared a series of 6-deoxy-6-fluoroglycopyranose derivatives and observed $^2J_{H,F}$ to be 47.9 ±0.8 Hz. The average observed here is 47.3 ±0.7 Hz (see Table III). It was observed that the replacement of one geminal hydrogen atom by a carbon atom increases the magnitude of $^2J_{H,F}$. Consequently, this value at C-3 and C-4 is 51.3 ±1.3 Hz. It is evident that the magnitude of $^3J_{H\text{-}5,F\text{-}6}$ depends on the electronegativity of the axial substituent at C-4. Sharma and Korytnyk[6] observed that the magnitude of $^3J_{H\text{-}5,F\text{-}6}$ is 23.1 ±1.5 Hz when the axial substituent at C-4 is hydrogen. This value decreases[6] to 18.5 Hz when the axial substituent at C-4 is oxygen. We have observed that, when the axial substituent at C-4 is fluorine, the $^3J_{H\text{-}5,F\text{-}6}$ value decreases to 13.8 ±0.7 Hz. A similar trend with change of electronegativity of the second substituent at C-2 was observed by Hall and Manville[9] for the $^3J_{H\text{-}2,F\text{-}1}$ values of aldohexopyranosyl fluorides. It has been reported[10,11] that the magnitude of $^3J_{H,F}$ is 30.0 ±1.0 Hz when the two atoms are *trans*-diaxial, but this value decreases[12–21] to 23.0 Hz when the fluorine atom is at the anomeric carbon atom. The observed $^3J_{H,F}$ value is 30.5 ±0.8 Hz when both the fluorine and hydrogen atoms concerned are on ring carbon atoms. This observation confirms that the two atoms are *trans*-diaxial. The fluorine atoms are therefore in axial dispositions and the fluorination reactions at equatorial hydroxyl groups involve Walden inversion. This value is further evidence that the corresponding compounds have the $^4C_1$(D) conformation.

Methyl α-D-glucopyranoside (**1**) reacted with DAST to yield mainly methyl 4,6-dideoxy-4,6-difluoro-α-D-galactopyranoside[22] (**4**), plus methyl 6-deoxy-6-fluoro-α-D-glucopyranoside (**5**) as the minor product. Proton-coupled ^{19}F-n.m.r. spectra of compound **4** showed a triplet of doublets at δ −229.9. The coupling pattern and the $^2J_{H,F}$ value is evidence that this signal is given by F-6. The second signal was a doublet of triplets at δ −219.7. The magnitude of the vicinal coupling-constant is attributed to *trans*-diaxial coupling between fluorine and hydrogen. The C-2 atom does not bear the fluorine atom, as an axial fluorine atom at C-2 did not have two vicinal hydrogens in *trans*-diaxial arrangement to generate the coupling pattern observed. An axial fluorine atom at C-3 and C-4 would provide the observed coupling patterns. However, the ^{13}C-n.m.r. spectrum of compound **4** gives

evidence for the presence of fluorine at C-4. The ^{13}C-n.m.r. spectrum of compound **4** consists of two doublets of doublets with one-bond and three-bond carbon–fluorine coupling. The absence of fluorine coupling at the anomeric carbon atom is further evidence that C-3 is not fluorinated. The anomeric-proton signal is a doublet at δ 4.77 having a coupling constant of 3.97 Hz, proving evidence for the absence of long-range coupling between fluorine and H-1. The proton at C-4 gives a doublet of doublets at δ 4.82 ($J_{F,H}$ 50.50, $^3J_{H,H}$ 2.59 Hz). The smaller coupling is that with H-3. This observation reveals that the coupling between H-4 and H-5 is near zero. It has been observed[23] that the $^3J_{H\text{-}4,H\text{-}3}$ and $^3J_{H\text{-}4,H\text{-}5}$ values of galactopyranoside derivatives are 3.5 and 1.0 Hz, respectively. Brimacombe[24] has reported these values for 3-deoxy-3-fluoro-D-galactose to be 3.8 and 0.5 Hz, respectively. The ^{19}F-n.m.r. spectrum of product **5** showed a triplet of doublets at δ −219.4. This coupling pattern is evidence that the fluorine atom is at C-6. Furthermore, the downfield shift of the ^{13}C-n.m.r. signal of C-6 to δ 84.9 and its coupling with the fluorine atom ($J_{C,F}$ 168.4 Hz) confirms the proposed location of the fluorine atom.



1 R^1 = H, R^2 = OH, R^3 = H
2 R^1 = OH, R^2 = H, R^3 = H
3 R^1 = H, R^2 = OH, R^3 = Tr
4 R^1 = H, R^2 = OH, R^3 = F, R^4 = H, X = F
5 R^1 = H, R^2 = OH, R^3 = H, R^4 = OH, X = F
6 R^1 = H, R^2 = OH, R^3 = F, R^4 = H, X = OTr
7 R^1 = OH, R^2 = H, R^3 = F, R^4 = H, X = F
8 R = OH, R^2 = H, R^3 = H, R^4 = OH, X = OH
9 R = H, R^2 = F, R^1 = H, R^4 = OH, X = F
10 R^1 = OH, R^2 = H, R^3 = F, R^4 = H, X = F
11 R = OH R^2 = H, R^3 = H, R^4 = OH, X = F

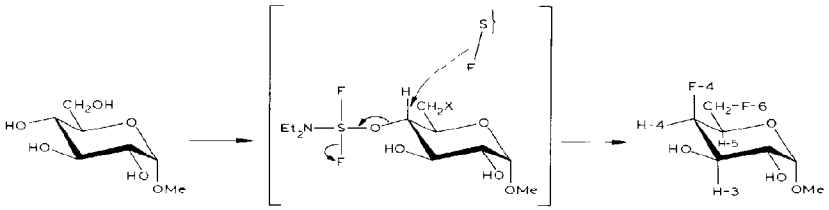
Methyl α-D-mannopyranoside (**2**) reacted with DAST to yield methyl 4,6-dideoxy-4,6-difluoro-α-D-talopyranoside (**7**). The triplets of doublets at δ −199.6 in the ^{19}F-n.m.r. spectrum of compound **7** indicate the fluorine atom to be at C-6. The doublet of triplets at δ −196.7 represents an axial fluorine atom on a ring-carbon atom having two, vicinal *trans*-diaxial hydrogen atoms. Only axial fluorine substitution at C-4 can achieve this arrangement, and so the second fluorine atom must be at C-4. The ^{13}C-n.m.r. spectrum of this compound provides further evidence for the assignment. The ^{13}C-n.m.r. spectrum showed three doublets of doublets at δ 89.4, 82.2, and 68.0. The coupling constants of 6.1 and 5.5 Hz are attributed to three-bond carbon–fluorine coupling to C-4 and C-6, respectively. The $J_{C,F}$ values of 17.1 and 22.0 Hz are attributed to the two-bond carbon–fluorine coupling to C-5 by both fluorine atoms. The anomeric carbon atom resonates at δ 102.0 without being coupled with the fluorine atom, providing further evidence that the fluorine atom is not at C-2 or C-3.

Methyl β-D-glucopyranoside (**8**) reacted with DAST to yield methyl 3,6-dideoxy-3,6-difluoro-β-D-allopyranoside (**9**), methyl 4,6-dideoxy-4,6-difluoro-β-D-galactopyranoside (**10**), and methyl-6-deoxy-6-fluoro-β-D-glucopyranoside (**11**). The proton-coupled ^{19}F-n.m.r. spectrum of compound **9** showed a triplet of doub-

lets at δ −196.3 and a doublet of triplets at δ −192.5. The triplet of doublets is caused by the fluorine atom at C-6, and the doublet of triplets by an axial fluorine atom located at either C-2, C-3, or C-4. The ^{13}C-n.m.r. spectrum of compound **9** provides valuable information confirming that the fluorine atom is at C-3. The anomeric carbon atom gives a doublet at δ 102.1 ($J_{C,F}$ 4.3 Hz). The magnitude of this coupling is in the range of three-bond carbon–fluorine couplings ruling out the possibility that fluorine is at C-2. The two doublets at δ 93.6 and 83.1 correspond to the carbon atoms bearing fluorine atoms. The absence of long-range coupling of fluorine in these two signals is evidence that the second fluorine atom is not located at C-4. The existence of two doublets of doublets at δ 73.0 and 66.3 confirms that the fluorine atom is at C-3, because both C-4 and C-5 should give rise to doublets of doublets with two-bond and three-bond fluorine–carbon coupling-constants. The doublet at δ 70.7 corresponds to C-2, showing a two-bond carbon–fluorine coupling constant. The anomeric proton gives a doublet of doublets (J 8.02 and 1.26 Hz) at δ 4.50. Holland *et al.*[25] have reported the value of $^3J_{H\text{-}1,H\text{-}2}$ of β-glucopyranoside derivatives to be 10.0 Hz, and thus the observed coupling constant of 8.02 Hz may be attributed to vicinal proton–proton coupling. A number of authors[12,14–16,26] have reported $^4J_{F,H}$ to be 1.5 ±0.5 Hz, and thus the smaller coupling, (1.26 Hz) arises from four-bond coupling of fluorine with the anomeric proton, confirming the presence of fluorine at C-3. The proton at C-3 gives two broad lines having J 53.44 Hz. Each line is composed of four unresolved lines. The proton at C-3 is *gauche* to H-2 and H-4. The weak coupling of these two protons with H-3 broadens the doublet through geminal fluorine coupling for H-3. The ^{19}F-n.m.r. spectrum of compound **10** consists of a triplet of doublets at δ −206.2 and a doublet of triplets at δ −196.2. The former signal is given by F-6. The latter signal arises from an axial fluorine atom attached to a ring carbon atom. The ^{13}C-n.m.r. spectrum of compound **10** provides evidence that the fluorine atom is at C-4. The anomeric carbon atom gives a singlet at δ 105.1, proving that fluorine is not located at C-2 or C-3. The fluorinated carbon atoms give doublets of doublets with one- and three-bond carbon–fluorine couplings. These observations confirm the existence of a fluorine atom at C-4. The ^{19}F-n.m.r. spectrum of product **11** shows a triplet of doublets at δ −193.5. The C-6 signal in its ^{13}C-n.m.r. spectrum is a doublet ($J_{C,F}$ 170.9 Hz) and is shifted downfield to δ 82.3. These observations provide evidence that the fluorine atom is at C-6.

Sharma and Korytnyk[6] have shown that DAST reacts with a hydroxyl group at C-6 to produce 6-deoxy-6-fluoro sugars in high yields when the other hydroxyl groups are protected. We investigated the reactivity of DAST with methyl α-D-glucopyranoside protected at O-6. Methyl 6-*O*-trityl-α-D-glucopyranoside (**3**) reacted with DAST to yield methyl 4-deoxy-4-fluoro-6-*O*-trityl-α-D-galactopyranoside (**6**). The ^{19}F-n.m.r. spectrum of **6** shows a doublet of triplets at δ −14.7. The ^{13}C-n.m.r. spectrum of **6** shows a singlet at δ 99.3 for the anomeric carbon atom. The lack of long-range fluorine coupling to this atom provides evidence that fluorine is not located at C-2 or C-3. The doublet at δ 61.6 corresponds to C-6.

The magnitude of the coupling constant of the C-6 signal confirms the presence of fluorine at C-4. The high-resolution ^{1}H-n.m.r. spectrum of compound **6** shows a doublet at δ 4.7 (J 5.34 Hz anomeric proton), which is not affected by the fluorine atom. The proton at C-4 gives a doublet of doublets ($^1J_{H,F}$ 50.90 and $^3J_{H,H}$ 2.53 Hz). The smaller value is attributed to the vicinal coupling of H-3. There is no observable coupling between H-4 and H-5 of compound **6**.



X = OSF_2NEt_2

Scheme 1

The mechanism of the reaction of DAST with alcohols have been discussed in detail by Middleton[27]. By consideration of the products, the mechanism shown (Scheme 1) may be proposed. The oxygen atom of a hydroxyl group replaces a fluorine atom of DAST, with loss of hydrogen fluoride, as described by Middleton[27] and Tewson and Welch[28]. This intermediate (not isolated) is not be formed at axial hydroxyl groups because of 1,3-interactions, nor at the equatorial 2-hydroxyl group because of non-bonded interactions with the methoxyl group at the anomeric carbon atom. The sulfoxo derivative formed is replaced by a fluorine by the SN2 route. This fluorine ion may be derived from a molecule of DAST or of hydrogen fluoride. This concept is confirmed by the observed products. The fluoride ion or its precursor has to approach C-3 through the α-plane to replace the sulfoxo group at C-3, but for C-4, the fluoride ion has to approach from the β-plane. The α-plane of α-glycosides is sterically hindered by the axial methoxyl group, preventing the fluorination of α-glycosides at C-3. However the α-plane of β-glycosides is not hindered, and replacement of the sulfoxo group at C-3 by fluorine is possible. The β-plane of both α- and β-glycosides is not sterically hindered, and consequently replacement of the sulfoxo group at C-4 by fluoride ions is possible for both α- and β-glycosides. No traces of fluoro products retaining the configuration at C-3 or C-4 were found. This result provided additional confirmation for the SN2 displacement-mechanism.

EXPERIMENTAL

Materials and general methods. — All ^{13}C- and ^{19}F-n.m.r. spectra were re-

corded with a JEOL-JNM-FX100 spectrometer. Proton-decoupled ^{13}C-n.m.r. spectra were recorded in acetone-d_6 and chemical shifts (δ) are given in p.p.m. from tetramethylsilane. The spectral width was 5000 Hz with 8192 data points. ^{19}F-N.m.r. spectra were recorded in a mixture of 10:1 (v/v) acetone-d_6–$CFCl_3$ and the chemical shifts (δ) are given in p.p.m. from the fluorine signal of trichlorofluoromethane. The spectral width was 5000 Hz with 8192 data points. ^{1}H-N.m.r. spectra were recorded with a Bruker WH-400 spectrometer in acetone-d_6 and chemical shifts (δ) are given with respect to the internal tetramethylsilane signal. The spectral width was 2500 Hz with 8192 data points. Solutions used were 0.5M for all n.m.r. spectra. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Specific rotations were recorded with an Autopol III-Automatic Polarimeter at 589 nm, with abs. ethanol as solvent. Melting points (uncorrected) were determined with a Thomas–Hoover Uni-Melt capillary melting-point apparatus.

Sulfur tetrafluoride gas was purchased from Matheson Gas Company. Diethylaminotrimethylsilane was obtained from PCR Chemicals, Inc., Gainesville, Florida, and methyl glycopyranosides from Sigma Chemical Co., St. Louis, and all were used without further purification. Organic solvents (Fisher Scientific Co., St. Louis) were distilled prior to use. Silica gel (100–200 mesh) for column chromatography was purchased from Sigma Chemical Co., St. Louis. Analytical t.l.c. was performed on Silica gel-G, Analtech Uniplats of thickness 250 μm.

Diethylaminosulfur trifluoride was synthesized by the procedure described by Markovskii *et al.*[7]. Methyl 6-*O*-trityl-α-D-glucopyranoside (**3**) was prepared according to the method described[29].

Except for methyl α-D-glucopyranoside (**1**) the carbohydrates were dried over phosphorus pentaoxide under vacuum for 2 days at the temperature of boiling benzene before reaction with DAST. Compound **1** was dried under the same conditions, but at 100°. The dried substrate was added to a 2.3-molar excess of diethylaminosulfur trifluoride kept under nitrogen at −10° unless otherwise mentioned. The temperature was maintained for 2 h at −10° and then the mixture was allowed to warm to room temperature and stirred overnight. Methanol (10 mL) was added to the resulting, clear red or yellow solution at −20°. The solution was evaporated in a rotary evaporator and the resulting syrup chromatographed on a column of silica gel. The fractions eluted were monitored on plates of silica gel-G, and the eluted materials were made visible by charring with 5% concentrated sulfuric acid in ethanol.

Methyl 4,6-dideoxy-4,6-difluoro-α-D-galactopyranoside (**4**). Methyl α-D-glucopyranoside (**1**, 1 g, 5 mmol), was added to diethylaminosulfur trifluoride at room temperature. The standard isolation procedure gave a syrup that was chromatographed on a column of silica gel with 5:1 (v/v) chloroform–methanol as eluant. T.l.c. plates developed with 5:1 (v/v) chloroform–methanol showed two spots (R_F 0.57 and 0.43). The product having R_F 0.57 (0.61 g, 60%) was recrystal-

lized from ethanol; m.p. 135–136°, $[\alpha]_D$ +282.9° (*c* 0.0022); ^{1}H-n.m.r.: δ 4.77 (d, 1 H, $J_{H\text{-}3,H\text{-}4}$ 2.59 Hz).

Anal. Calc. for $C_7H_{12}O_4F_2$: C, 42.42; H, 6.06; F, 19.19. Found: C, 42.41; H, 6.22; F, 18.95.

The crude product having R_F 0.43 (0.90 g, 9.4%) was identified as methyl 6-deoxy-6-fluoro-α-D-glucopyranoside (**5**) by its n.m.r. data and was not further characterized.

Methyl 4-deoxy-4-fluoro-6-O-trityl-α-D-galactopyranoside (**6**). — Methyl 6-*O*-trityl-α-D-glucopyranoside (**3**, 1.5 g, 3.44 mmol) was added to diethylaminosulfur trifluoride (1.5 mL, 11.5 mmol). The standard isolation gave a syrup that was eluted from a column of silica gel with 1:1:19 (v/v/v) methanol–ethyl acetate–chloroform. The t.l.c. plates were developed with the same solvent. Compound **6** (0.63 g, 42%), R_F 0.51, was recrystallized from abs. ethanol; m.p. 162–163°, $[\alpha]_D$ +50.4° (*c* 0.0014); ^{1}H-n.m.r.: δ 4.71 (d, 1 H, $J_{H\text{-}1,H\text{-}2}$ 5.34 Hz), and 4.82 (dd, 1 H, $J_{H\text{-}4,F\text{-}4}$ 50.90 Hz, $J_{H\text{-}4,H\text{-}3}$ 2.53 Hz).

Anal. Calc. for $C_{26}H_{27}O_5F$: C, 71.23; H, 6.16; F, 4.34. Found: C, 71.22; F, 6.39; F, 4.33.

Methyl 4,6-dideoxy-4,6-difluoro-α-D-talopyranoside (**7**). — Methyl α-D-mannopyranoside (**2**, 1 g, 5 mmol) was added to diethylaminosulfur trifluoride. The standard isolation gave a syrup that was chromatographed on a column of silica gel with 6:1 (v/v) chloroform–methanol, with monitoring by t.l.c. (same solvent). The major product (**7**) had R_F 0.81. The minor component (0.01 g) having R_F 0.62 was obtained in <1% yield and was not further characterized. Compound **7** (0.73 g, 72%) crystallized from ethanol; m.p. 88–89°, $[\alpha]_D$ +105.1° (*c* 0.008).

Anal. Calc. for $C_7H_{12}O_4F_2$: C, 42.42; H, 6.06; F, 19.19. Found: C, 42.61; H, 6.15; F, 19.21.

Methyl 3,6-dideoxy-3,6-difluoro-β-D-allopyranoside (**9**). — Methyl β-D-glucopyranoside (2 g, 10 mmol) was added to diethylaminosulfur trifluoride. The syrup obtained by the standard procedure, was chromatographed on a column of silica gel with 1:6:10 (v/v/v) methanol–chloroform–ethyl acetate. The t.l.c. plates were developed with the same mixture. Three products were observed, having R_F values 0.63, 0.52, and 0.30. That having R_F 0.63 corresponded to compound **9**. It (0.66 g, 32%) was recrystallized from abs. ethanol; m.p. 122–124°, $[\alpha]_D$ −37.1° (*c* 0.0087); ^{1}H-n.m.r.: δ 4.50 (dd, 1 H, $J_{H\text{-}1,H\text{-}2}$ 8.02, $J_{H\text{-}1,F\text{-}3}$ 1.26 Hz), and 4.91 (broad doublet, 1 H, $J_{H\text{-}3,F\text{-}3}$ 53.44 Hz).

Anal. Calc. for $C_7H_{12}O_4F_2$: C, 42.42; H, 6.06; F, 19.19. Found: C, 42.25; H, 6.12; F, 18.97.

Methyl 4,6-dideoxy-4,6-difluoro-α-D-galactopyranoside (**10**). — Compound **10** (0.17 g, 8.1%) had R_F 0.52 and was recrystallized from abs. ethanol; m.p. 114–116°, $[\alpha]_D$ −26.1°.

Anal. Calc. $C_7H_{12}O_4F_2$: C, 42.42; H, 6.06; F, 19.19. Found: C, 42.58; H, 6.24; F, 18.97.

The crude product having R_F 0.30 was identified as methyl 6-deoxy-6-fluoro-β-D-glucopyranoside (**11**) by its n.m.r. data; it was not further characterized.

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