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SYNTHESIS OF 3-AMINO-2,3,6-TRIDEOXY-2-FLUORO-L-TALOSE AND -D-ALLOSE [(*R*)-2-FLUORO-L-DAUNOSAMINE AND (*R*)-2-FLUORO-D-RISTOSAMINE]

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ABSTRACT

The title compounds were synthesized (as methyl glycosides) starting from 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranose. Stereoselective methods of glycosylation gave, via the tri-*O*-acetylglycopyranosyl bromide, the methyl 2-deoxy-2-fluoro-α- and -β-D-glucopyranoside triacetates. Each anomer was *O*-deacetylated and further transformed into the corresponding, 4,6-*O*-benzylidenated 3-triflate, and the triflates were converted by azide displacement into the 3-azido-2,3-dideoxy-2-fluoroglycosides having the D-*allo* configuration. Hanesssian-Hullar reaction then furnished the corresponding 6-bromo-6-deoxy-4-benzoates, which were dehydrobrominated to give the methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy-2-fluoro-α- and -β-D-*ribo*-hex-5-enopyranosides. Debenzoylation of the α-anomer, followed by catalytic hydrogenation, led to methyl 3-amino-2,3,6-trideoxy-2-fluoro-β-L-talopyranoside [methyl (*R*)-2-fluoro-β-L-daunosaminide], whereas the same sequence applied to the β-anomer afforded methyl 3-amino-2,3,6-trideoxy-2-fluoro-β-D-allopyranoside [methyl (*R*)-2-fluoro-β-D-ristosaminide]. The overall yields for these 10-step sequences were 11–12 and 16%, respectively. The ^{1}H- and ^{13}C-n.m.r. data for the new fluoro sugar derivatives are discussed with respect to the dependence of $J_{F,H}$ and $J_{F,C}$ values on molecular geometry and substituent effects.

INTRODUCTION

For the continuation of our work[1,2] aimed at the synthesis of anthracycline analogs substituted by fluorine in the sugar moiety, 3-amino-2,3,6-trideoxy-2-fluoro-L-talose [**1**, (*R*)-2-fluoro-L-daunosamine] was required. Its condensation with daunomycinone should provide (2′*R*)-2′-fluorodaunorubicin, whose potential antitumor activity would be interesting to compare with that of the (2′*S*)-2′-fluoro epimer recently synthesized and tested[2,3]. It appears important to determine whether the orientation of the fluorine atom, axial or equatorial, influences the biological activity.

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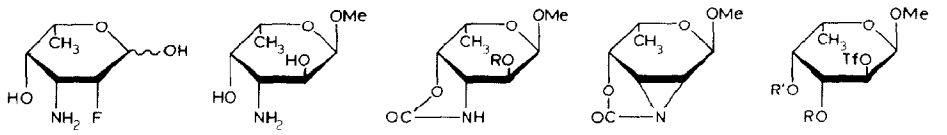
One approach to **1** started from methyl 3-amino-3,6-dideoxy-α-L-galactopyranoside (**2**), available[4] from L-rhamnose or L-fucose by nitromethane-cyclization methodology. The cyclic urethane **3** prepared from **2** gave a 2-trifluoromethanesulfonate (**4**), and it was hoped that **4** would be amenable to S_N2 displacement by fluoride ion at C-2, with the fused-ring structure preventing a possible 2,3-elimination, such as that reported[5] to occur on attempted displacement in an analogous 3-azido-2-triflate. However, treatment of **4** with tetrabutylammonium fluoride in acetonitrile solution did not lead to fluorination, but produced, with surprising ease (0.5 h, −20→+20°), the tricyclic compound **5***. In view of this result, 2-triflates of type **6**, bearing a nonparticipating oxygen function at C-3, were synthesized from L-fucose and subjected to fluoride displacement, with the intent of introducing the requisite amino group by subsequent manipulations. The approach failed completely, as displacement was accompanied by ring-oxygen migration, giving 2,5-anhydrosugar derivatives[6].

Following these experiences, we elaborated a successful approach to **1** and to its D-*allo* isomer [(*R*)-2-fluoro-D-ristosamine], as described herein.

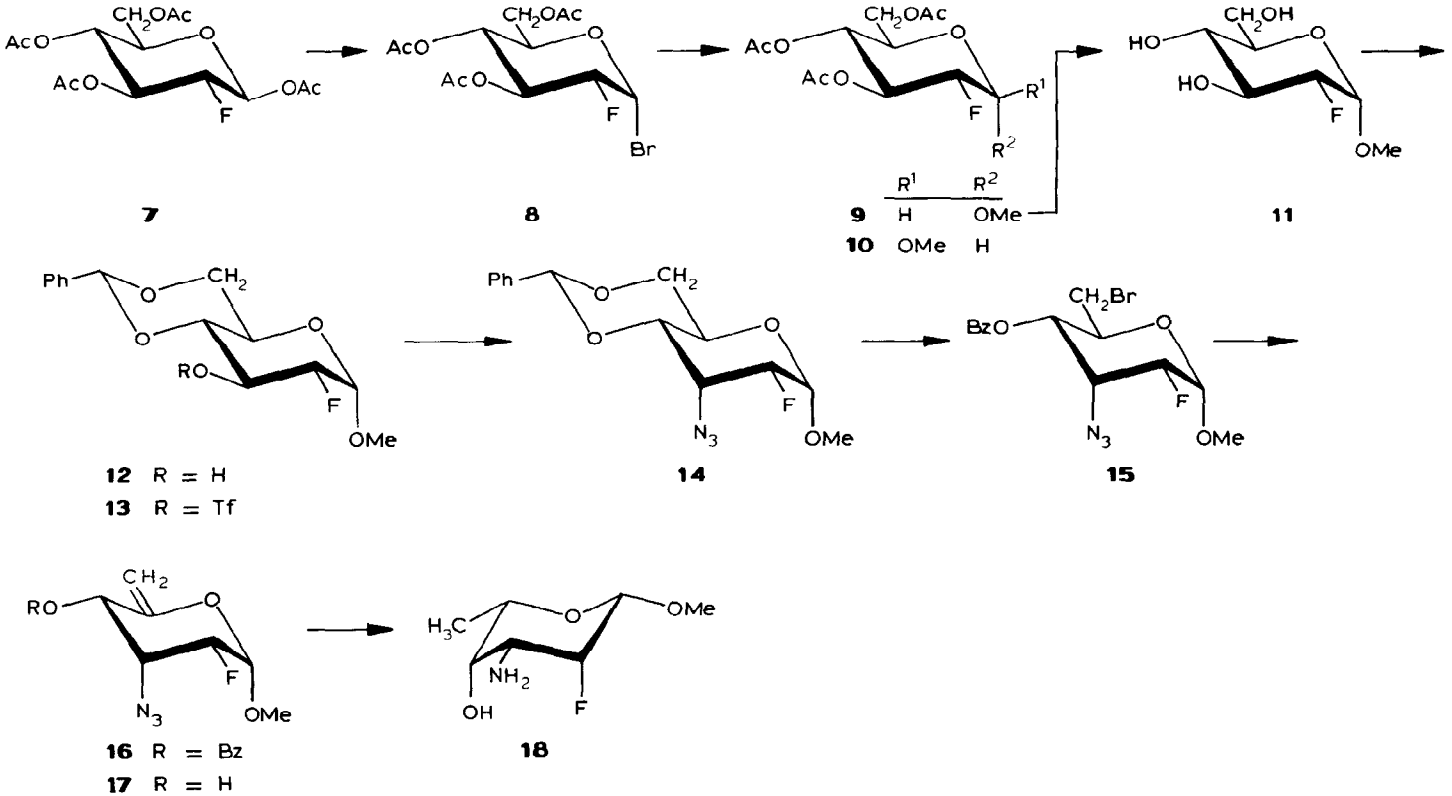
RESULTS AND DISCUSSION

The synthesis of methyl (*R*)-2-fluoro-β-L-daunosaminide (**18**) is illustrated in Scheme 1. It commenced with 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranose (**7**), which was prepared from D-mannose according to Kováč[7], and converted by the action of hydrogen bromide in acetic acid into the known[8,9] tri-*O*-acetylglycopyranosyl bromide **8**. Common ion-catalyzed methanolysis[10] of **8** in the presence of tetraethylammonium bromide and ethyldiisopropylamine gave the anomeric methyl glycosides in an α:β ratio of 6:1. Performed in refluxing dichloromethane–methanol at 50°, the glycosidation was slow (6 days), reflecting a low reactivity at the anomeric center owing to the inductive effect of the fluorine substituent, and considerable *O*-deacetylation occurred in the process. Nevertheless, after reacetylation of the crude product, and chromatographic separation, a 60% yield of pure, syrupy methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-gluco-



Bn = $C_6H_5CH_2$ Tf = F_3CSO_2

*These studies were performed by Mr. Youn Shu in this laboratory as part of his Ph.D. thesis research.


AcO
CH2OAc
AcO
OAc
F
7
Br
8
R1
R2
9 H OMe
10 OMe H
HO
CH2OH
OMe
11
Ph
CH2
RO
12 R = H
13 R = Tf
N3
14
CH2Br
BzO
15
16 R = Bz
17 R = H
H3C
NH2
OH
18

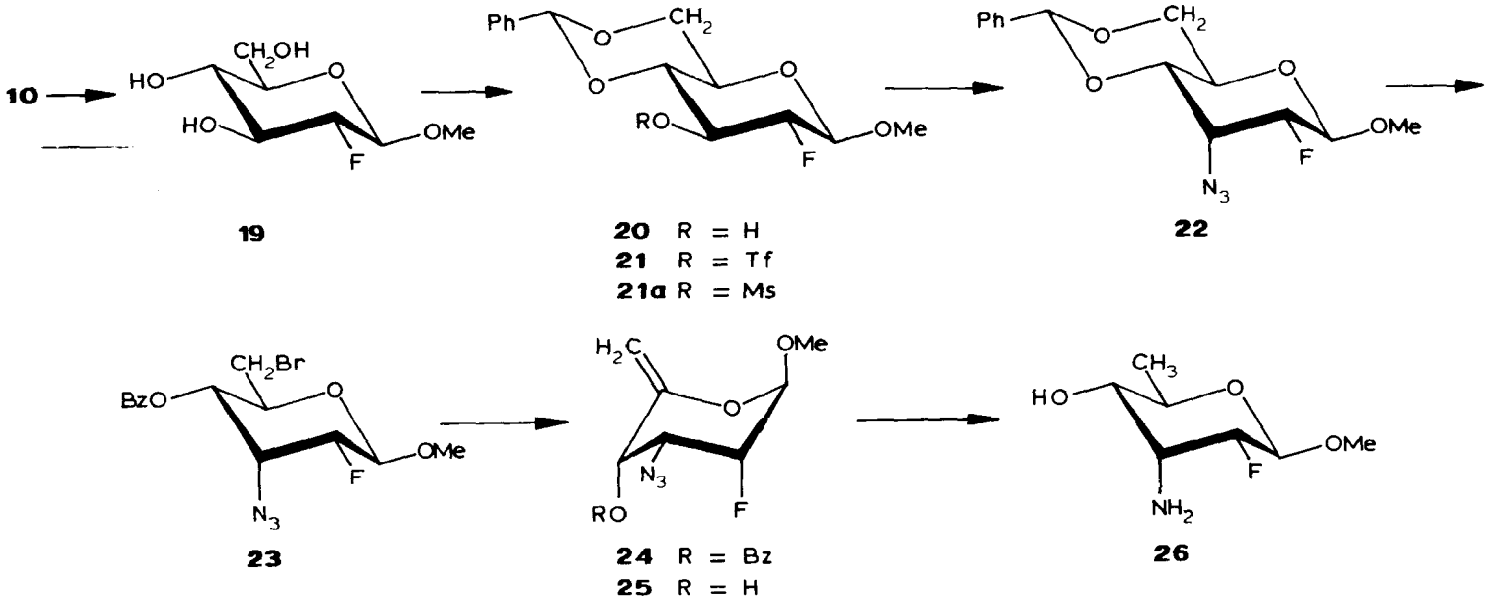
Scheme 1

pyranoside (**9**) and an 8.6% yield of its β-anomer **10** were isolated, together with 6% of unchanged **8**. The stereoselectivity of glycosidation was reversed when **8** was allowed to react with methanol in dichloromethane in the presence of silver triflate and 2,4,6-trimethylpyridine. This process was much faster (16 h, −40→+25°), and the α:β ratio of glycosides was 1:8. The known[11], crystalline **10** was isolated in 67% yield (based on **7**) without resort to chromatography.

The α-glycoside triacetate **9** was deacetylated (Zemplén), and the resulting triol **11** was benzylidenated to give the 4,6-acetal **12**. Trifluoromethylsulfonylation then afforded the 3-triflate **13**, which upon S_N2 displacement with lithium azide gave the 3-azido derivative **14**. Hanessian-Hullar reaction of **14** produced the 6-bromo-6-deoxyglycoside **15**. Dehydrobromination of **15** with silver fluoride in pyridine led to the 6-deoxy-5-enoside **16**, but only in poor yield (19%) after troublesome chromatographic separation from several unidentified side-products, although the same procedure was satisfactory in previous work[1] and with the β-anomer of **15** (see later on). Much superior results were obtained by treating **15** with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in refluxing benzene[12], which cleanly provided **16** in 90% yield. Following *O*-debenzoylation to **17** the product was hydrogenated over palladium oxyhydrate on barium sulfate (Kuhn catalyst)[13], which accomplished the simultaneous reduction of the azido group and the alkenic bond. Hydrogenation of the latter occurred predominantly on the unsubstituted face of the ring, furnishing crystalline methyl 3-amino-2,3,6-trideoxy-2-fluoro-β-L-talopyranoside (**18**) in 58% isolated yield. A minor by-product was obtained that appeared from spectroscopic evidence to be an isomer, probably the 5-epimer, although this was not rigorously established.

As concerns the last step in the sequence just described, we had previously cited[1] numerous references indicating that the hydrogenation of hex-5-enopyranosides takes place with good to excellent stereoselectivity at the face of the molecule opposite the anomeric group. The synthesis of methyl 3-amino-2,3,6-trideoxy-2-fluoro-β-D-allopyranoside [**26**, methyl (*R*)-2-fluoro-β-D-ristosaminide] confirmed this rule. In order to prepare the requisite β-anomeric 6-deoxy-5-enoside **25**, a sequence of transformations similar to that just outlined was applied to the β-glycoside **10** (see Scheme 2). All the reactions proceeded in full analogy to those of Scheme 1, except that the DBU method of dehydrobromination was not tried with **23**, since the silver fluoride method furnished **24** in good yield (74%). Additionally, the mesylate **21a** of **20** was prepared and also converted* into the azide **22**. Catalytic hydrogenation of **25**, performed as for **17**, indeed occurred preferentially from the predicted direction; only an insignificant proportion of stereoisomer appeared to be present in the crude hydrogenation product, according to the ^{1}H-n.m.r. spectrum, and chromatographically purified, crystalline **26** was obtained in 66% yield. Compound **25** was found to exist in the $^1C_4$ conformation favored by the anomeric effect, and it seems noteworthy that the axial C-2 and C-4 substituents did not markedly diminish the directional influence of the anomeric group in hydrogenation.

*The reaction of triflate **21** with azide ion in *N,N*-dimethylformamide (20 min at 40°), yielding 91% of **22**, was clearly superior to that of **21a**, which gave a 75% yield after reaction for 48 h at 100°.


10
CH2OH
HO
HO
O
OMe
F
19
Ph
O
CH2
O
RO
O
OMe
F
20 R = H
21 R = Tf
21a R = Ms
N3
22
CH2Br
BzO
O
OMe
F
N3
23
H2C
OMe
O
N3
RO
F
24 R = Bz
25 R = H
CH3
HO
O
OMe
F
NH2
26

Scheme 2

TABLE I

^{1}H-N.M.R. DATA AT 300 MHz FOR DEOXYFLUORO SUGARS IN CHLOROFORM-*d* SOLUTION

Compound	*Chemical shift*[a] *(δ)*									
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	OCH_3[b]	*PhCH*[b]	*Others*
8	6.51dd	4.52ddd	5.61dt	5.10d		4.4–4.1m				2.08, 2.07, 2.04[c]
9	4.95d	4.49ddd	5.53dt	5.00t	3.99ddd	4.25dd	4.08dd	3.46		2.07, 2.05, 2.02[c]
10	4.48dd	4.27ddd	5.30dt	5.02t	3.70ddd	4.27dd	4.12dd	3.58		2.07, 2.06, 2.02[c]
11[d]	4.84d	4.17ddd	[e]	3.13dt[f]	[e]	[e]	[e]	3.32		5.36d, 5.19d, 4.59t[g]
12	4.93d	4.43ddd	4.25m	3.48td	3.85sx	4.30dd	3.72t	3.46	5.52	2.58d[h]
13	5.03d	4.61ddd	5.29q	3.71td	3.90sx	4.35dd	3.77t	3.48	5.56	
14	4.89dd	4.60dt	4.48m	3.64ddd	4.18ddd	4.34dd	3.69t	3.50	5.53	
15	4.99dd	[i]	[i]	5.03ddd	4.39sp	3.59dd	3.48dd	3.56		
16	[j]	~4.9dt	4.35dt	5.63dt		[j]	4.91t	3.61		
17	4.98d	4.80dt	4.33sp	4.14dqn[k]		4.92~t	4.88d	3.56		2.49d[l]
18	4.31dd	4.57m	2.78dt	3.40nm	~3.55m	—— 1.37d ——		3.58		
19	4.40dd	3.84ddd	[m]	3.10dt[f]	3.16ddd	3.67ddd	[m]	3.41		5.45d, 5.20d, 4.59t[n]
20	4.51dd	4.24ddd	4.01dtd	3.53td	3.45ddd	4.37dd	3.77t	3.58	5.52	2.68[o]
21	4.57dd	4.42ddd	5.05ddd	3.78td	3.48ddd	4.42dd	3.81t	3.60	5.57	
21a	4.56dd	4.38ddd	4.92ddd	3.70td	3.49sx	4.40dd	3.79t	3.59	5.53	3.02s[p]
22	4.76dd	4.34ddd	4.47sp	3.65ddd	3.92ddd	4.37dd	3.71t	3.57	5.52	
23	4.83dd	4.46ddd	4.60qn	5.04ddd	4.17sp	3.57dd	3.44dd	3.61		
24	5.05dd	4.82dtd	3.76ddd	5.84dd		4.94d	4.92d	3.49		
25	4.95dd	4.68dsp	3.77dt	4.33dd		4.82d	4.76d	3.50		2.44dd[q]
26	4.63dd	4.26ddd	3.30ddd	—— 3.6–3.5m ——		—— 1.30d ——		3.53		

	Coupling constants, $J_{H,H}$ values (Hz)							$J_{F,H}$ *values (Hz)*			
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{F,1}$	$J_{F,2}$	$J_{F,3}$	$J_{F,4}$
8	4.3	9.4	9.8	9.8				1.3	49.3	11.0	~1
9	3.9	9.6	9.5	9.5	4.6	2.4	12.4	<0.5	49.2	12.1	<0.5
10	7.7	9.1	9.3	10.0	4.7	2.4	12.4	2.9	50.5	14.6	<0.5
11[d]	3.8	9.4	9.5	9.5	2	~5	12	<0.5	49.2	~13	[r]
12	3.9	9.0	~9	9.5	4.6	10.1	10.1	<0.5	48.4	~11.5	~1
13	3.9	9.1	9.5	9.5	4.6	10.2	10.2	<0.5	48.8	10.2	1
14	4.1	4.1	3.2	9.5	5.1	10.4	10.4	~0.5	43.6	6.5	1.5
15	~4	4.2	3.4	10	2.5	6.3	11.3	<0.5	43.6	[r]	1.6
16	3.7	3.7	3.8	(1.5)[s]				[r]	[r]	10.8	1.5
17	3.8	3.6	4.2	(1.8)[s]				<0.5	44.6	8.3	
18	<1	~3	~3	<1	6.5 ($J_{5,Me}$)			20.5	50.5	33.6	
19[d]	7.8	8.9	9.5	9.5	1.9	~6	11.8	2.2	51	[r]	
20	7.6	8.5	9	9.5	4.7	9.5	10.7	3.8	50.0	15	0.5
21	7.4	8.6	9.8	~9.5	5	~9.5	10.7	4.2	49.2	13.2	0.9
21a	7.5	8.6	9.7	~9.6	5.1	~9.6	10.5	3.9	49.5	14.0	1.0
22	7.7	3.8	2.8	9.2	5	10.3	10.3	2.0	46.3	6.6	1.3
23	7.7	3.8	3.2	9.5	2.7	6.6	11.3	1.4	46.8	7.4	1.5
24	2.7	2.8	3.8				1.3	7.1	48.7	30.1	
25	3.7	2.9	~3.5				1.4	6.4	48.4	25.8	
26	7.6	4.4	~1		6.3 ($J_{5,Me}$)			2.0	48.1	9.2	

[a]P.p.m. from Me_4Si, measured from the $CHCl_3$ lock signal at δ 7.24. Multiplicities are indicated as d, doublet; m, multiplet; nm, narrow multiplet; q, quartet; qn, quintet; sp, septet; sx, sextet; s, singlet; and t, triplet. [b]Singlets. [c]Three s (9 H) for $OCOCH_3$. [d]In dimethyl sulfoxide-d_6, with Me_4Si as reference. [e]H-3,5,6,6' gave partially overlapping multiplets, simplified on D_2O exchange, in the δ 3.7–3.35 region. [f]Reduced to t on D_2O exchange. [g]Three O*H* signals, exchangeable; $J_{H,OH}$ 5.5, 6.0, and 5.9 Hz, respectively. [h]Exchangeable, OH-3; $J_{3,OH}$ 2.4 Hz. [i]H-2 resonated as a doublet ($J_{F,2}$ 43.6 Hz) of triplets. The downfield t (0.5 H) was at δ 4.81, and the upfield t coincided with the H-3 signal to give a multiplet at δ 4.67–4.63. [j]The H-1 and H-6 signals coincided with part of the H-2 signal to give a narrow multiplet (2.5 H) at δ 4.99–4.94. [k]Collapsing to nm on D_2O exchange. [l]Exchangeable, OH-4; $J_{4,OH}$ 11.2 Hz. [m]H-1 and H-6' gave coinciding multiplets in the δ 3.5–3.35 region, simplified on D_2O exchange but not resolvable. [n]Three O*H* signals, exchangeable; $J_{H,OH}$ 5.6, 5.4, and 5.9 Hz, respectively. [o]Exchangeable, OH-3; $J_{3,OH}$ 2.7 Hz. [p]CH_3SO_3 signal (3 H). [q]Exchangeable, OH-4; $J_{F,OH}$ 4.8, $J_{4,OH}$ 9.8 Hz. [r]Not determinable. [s]$J_{4,6}$ (allylic coupling).

Nuclear magnetic resonance spectra. — The ^{1}H-n.m.r. data for the new compounds (Table I) are in full accord with the structures depicted. The ^{1}H–^{1}H vicinal coupling constants require no comment, except for those of **18, 24,** and **25**. Thus, the *gauche* 1,2 protons in **18** display a coupling (<0.5 Hz) that is exceptionally small for an *ax–eq* disposition; the diminution is attributed to the antiperiplanar relationships between H-1 and F-2, and between H-2 and the ring oxygen atom. The 5-enosides of the β-series, **24** and **25**, exhibit small $J_{H\text{-}1,H\text{-}2}$ values (2.7 and 3.8 Hz), setting them apart from their precursors and from the reduction product **26**, all of which have couplings in the range of 7.4–7.7 Hz, as expected for an H-1*ax*-H-2*ax* relation. Clearly, **24** and **25** prefer the inverted, $^1C_4$ conformation having an axially oriented anomeric group; inversion is favored by the anomeric effect and, because of the 5,6-ene structure, not countervailed by a bulky axial substituent at C-5.

The ^{19}F–^{1}H couplings (Table I) corroborate the structural assignments. Those compounds possessing vicinal *trans*-diaxial F–H arrangement (**18, 24,** and **25**) show large $^3J_{F,H}$ values (20.5–33.6 Hz), of the magnitude reported[14,15] for numerous similar examples. It may be noted that the smallest of these values (20.5 Hz) is for $J_{H\text{-}1,F\text{-}2}$ in **18**, where the coupling fragment bears two oxygen substituents, and the largest value (33.6 Hz) is that for $J_{F\text{-}2,H\text{-}3}$ in the same molecule, referring to a coupling fragment that bears only one, less electronegative, substituent (NH_2). The intermediate $J_{F\text{-}2,H\text{-}3}$ values for **24** and **25** may reflect the greater electronegativity of the azido substituent, as compared to an amino group*, or small, conformationally determined angular differences†.

The remainder of the fluoroglycosides considered here possess *gauche* vicinal F–H relationships, and the corresponding ^{19}F–^{1}H couplings should therefore fall in the range of 0–16 Hz. Phillips and Wray[15] have evaluated the dependency of the magnitude of J_{gauche} on effects of oxygen substituents and bond geometries; they assigned empirical parameters to the factors involved and assumed these to be additively contributory. Applying these authors' procedure of calculation, we have assessed[1] the observed $^3J_{H\text{-}1,F\text{-}2}$ and $^3J_{F\text{-}2,H\text{-}3}$ values for a series of 2-deoxy-2-fluoroglycosides bearing an amino or acylamino substituent instead of oxygen at C-3, and have noted appreciable influences of such replacement in certain geometric situations. For the present series of compounds, observed and calculated $J_{H\text{-}1,F\text{-}2}$ values compare well if one bears in mind that possible deviations of ~1–2 Hz are inherent in the procedure[1,15]. Thus, a coupling of 2 Hz is calculated for both the α-glycosides **9** and **11–13** and the β-glycosides **10** and **19–21a**, but it appears from Table I that

*The inductive electron-withdrawing effect of the azido group is quantitatively comparable to that of a fluorine atom[16].

†Replacement of the C-5 methyl by an *exo*-methylene substituent increases the conformational mobility of the chair conformation and should facilitate a slight outward movement of O-4, which would lessen both the O-4–F-2 diaxial interaction and the eclipsing of the H-4 and methylene bonds. The resultant small changes in dihedral angles involving the C-2,3,4 region of the molecule might manifest themselves in the ^{19}F–^{1}H coupling, which is apt to be more sensitive to such changes than the corresponding ^{1}H–^{1}H couplings[14].

the *trans* H-1–F-2 coupling in the former group is consistently near zero*, whereas the *cis* H-1–F-2 coupling in the latter group is ~2–4 Hz. In both series, the number and kinds of electronegative substituents on the coupling fragment are the same, and only one (and the same) antiparallel relationship between a coupled nucleus and oxygen is present in each[17]. Thus, the most plausible explanation for the observed divergences appears to be minor distortions of the pyranose chairs conditioned by the fluorine substituent. The same trend is apparent in the derivatives in which the equatorial O-3 is replaced by an axial azido or amino substituent. These should show somewhat larger $J_{H\text{-}1,F\text{-}2}$ values because the diminishing effect of an oxygen atom vicinal to one of the coupled nuclei (F) and *anti* to the C-1,2 bond[15] is absent; the calculated $J_{H\text{-}1,F\text{-}2}$ value is 4 Hz both for the α-glycosides (**14, 15,** and **17**) and for the β-glycosides (**22, 23,** and **26**). Actually, coupling is still near zero in the former group, and marginally larger (1.4–2.0 Hz) in the latter. That these couplings are equal to (α-series) or slightly *smaller* than (β-series) those in the aforementioned 3-oxygenated analogs, instead of being moderately larger, may be due to a hitherto unrecognized effect of an axial nitrogenous substituent vicinal to the equatorial fluorine atom but outside the coupling pathway. It is to be recalled in this connection that axial nitrogen substituents (NH_2, NHBz, and $NHCOCF_3$) at C-3, flanking an *axial* fluorine atom at C-2, have the opposite effect of *increasing* $J_{H\text{-}1,F\text{-}2}$ by 4–6 Hz over the calculated value (see compounds **6, 7, 12, 13,** and **15** in ref. 1). Finally the effect of an equatorial azido group at C-3 adjacent to axial F-2 (compounds **24** and **25**) appears to be no different from that expected for an equatorial oxygen substituent in the same situation; and indeed the H-1–F-2 couplings found for **24** and **25** were very close to the value of 6 Hz calculated[15] for a 3-oxygenated analog.

As concerns *gauche* F-2–H-3 coupling, $J_{F\text{-}2,H\text{-}3}$ = 14.5 Hz has been reported for both 2-deoxy-2-fluoro-α-D-glucopyranose and its β-anomer, a value closely bracketed by the calculated figures (15.5 and 13.5, respectively)[15]. The same calculated constants should apply to corresponding methyl glycosides, and in fact the β-D-glucopyranosides **10, 20, 21,** and **21a** conformed to expectations ($J_{F\text{-}2,H\text{-}3}$ 13.2–15 Hz), while the α-anomers **9, 12,** and **13** (and the bromide **8**) showed considerably smaller values (10.2–12.1 Hz; see also the disaccharides[9] mentioned in the footnote*). These results seem to point up a limitation in the predictive power of the calculations. For the 3-azido α-glycosides **14–17** and β-glycosides **22** and **23**, calculation of $J_{F\text{-}2,H\text{-}3}$ gives 11.5 and 9.5 Hz, respectively, *i.e.*, a decrease of 4 Hz under the assumption that an azido group positioned directly on the coupling fragment is equivalent to an oxygen substituent in terms of diminution of coupling. The observed values for **14, 16,** and **17** are 6.5–10.8 Hz, and for **22** and **23**, ~7 Hz, again appreciably smaller than calculated but showing the predicted trend.

*Shelling and coworkers[9] reported $J_{H\text{-}1',F\text{-}2'}$ = 0.0 Hz for five different disaccharides containing a 2′-deoxy-2′-fluoro-α-D-glucopyranosyl or -galactopyranosyl unit; $J_{F\text{-}2',H\text{-}3'}$ was 11.5–11.8 Hz for four per-*O*-acetylated derivatives in $CDCl_3$, and 13.2 Hz for free 2′-deoxy-2′-fluoromaltose in Me_2SO-d_6.

The magnitude of *geminal* ^{19}F–^{1}H coupling constants in fluoropyranose systems similarly depends on the presence and orientation of electronegative substituents on adjacent carbon atoms. To predict such ^{2}J data, positive or negative empirical increments may be added to a basic value of 50 Hz derived from measurements in unperturbed model systems[18], and we have found[1] that increments applicable to oxygen substituents can be used for certain nitrogen substituents without causing serious deviations. Basically, an electronegative substituent situated antiparallel to one of the coupled nuclei, ^{1}H (factor *A*) or ^{19}F (factor *B*), decreases ^{2}J by 2 Hz, and a *gauche* arrangement between such a substituent and the fluorine atom (factor *C*) entails an increase by 1 Hz. So calculated, the compounds in Table I fall in four categories, embodying the factors as follows: *a*, $A + 3C$ (**18**); *b*, $B + 2C$ (**10, 19–21a**); *c*, $A + B + 2C$ (**8, 9, 11–13, 22–26**); and *d*, $2A + B + 2C$ (**14–17**), corresponding to calculated ^{2}J values of 51 (*a*), 50 (*b*), 48 (*c*), and 46 Hz (*d*). The observed values (Table I) were 50.5 (*a*), 50.1 ±0.9 (*b*), 47.8 ±1.5 (*c*), and 44.1 ±0.5 Hz (*d*), in qualitative agreement. We have previously recorded[1] $J_{F\text{-}2,H\text{-}2} = 45.5 \pm 0.5$ Hz for five 2-deoxy-2-fluoro-α-D-altropyranoside derivatives whose structural features $A + 2B + C$ correspond to a calculated value of 45 Hz*.

The ^{13}C-n.m.r. data recorded in Table II show the following regularities. For most of the pairs of anomers listed, the $^{1}J_{F,C}$ value decreases by 3–5 Hz from the α-anomer (*cis* MeO-1–F-2; range, 188–199 Hz) to the β-anomer (*trans*-diequatorial MeO-1–F-2; range, 183–194.5 Hz). The decrease is ~12 Hz in the special case of the 5-enoside pairs **16, 24** and **17, 25**, where the β-anomers adopt a *trans*-diaxial MeO-1–F-2 orientation owing to chair inversion. In both anomeric series, $^{1}J_{F,C}$ increases, in a parallel fashion,with increasing electronegativity of the C-3 substituent: OH < OAc < OTf≈N_3. The effect of an NH_2 group (in **18** and **26**) is similar to that of an OH group.

The geminal ^{19}F–^{13}C couplings ($^{2}J_{F,C}$) were found to fall into the expected[19] ranges. Thus, $J_{C\text{-}1,F\text{-}2}$ was 15.1 Hz for **18**, the only representative having *gauche* relationships between F-2 and both oxygen atoms attached to C-1. The coupling was 28–29 Hz for **24** and **25**, the only two molecules having F-2 and MeO-1 *trans*-diaxially arranged, and it was 22 ±2.3 Hz for all the other compounds, in which F-2 is oriented *anti* to the ring oxygen atom. (The bromide **8** provided an exception.) The $J_{F\text{-}2,C\text{-}3}$ values lay in the range of 17.7 ±2.5 Hz for all compounds listed, as was expected for structures wherein the coupled C-atom does not bear an electronegative substituent in *anti* orientation with respect to the F-atom.

The vicinal coupling constants ($^{3}J_{F\text{-}2,C\text{-}4}$) were zero for the three compounds (**18, 24,** and **25**) which contain a *gauche* F-2–C-4 arrangement, and ranged from 4.2 to 10.4 Hz for the remaining derivatives, all of which embody an *anti* F-2–C-4 arrangement.

*The calculated value given earlier[1], 47 Hz, had been computed as directed[18], *i.e.*, without taking the factor *A* into account. The present set of new data clearly indicates that this factor should not be neglected.

TABLE II

^{13}C-N.M.R. DATA AT 75.43 MHz FOR DEOXYFLUORO SUGARS IN CHLOROFORM-*d* SOLUTION

Compound	*Chemical shifts*[a] *(p.p.m.)*									*Coupling constants (Hz)*				
	C-1[b]	*C-2*[b]	*C-3*[b]	*C-4*[b]	*C-5*[c]	*C-6*[c]	OCH_3	*PhCH*[c]	*Others*	$J_{F,1}$	$J_{F,2}$	$J_{F,3}$	$J_{F,3}$	$J_{F,OMe}$
8	86.3	85.2	71.7	66.6	72.1	60.9			*d*	36.1	188.6	18.9	7.1	
9	96.9	87.3	70.6	68.1	67.2	61.3	59.7d		*d*	20.4	194.5	19.5	7.2	2.2
10	101.3	89.4	72.8	68.2	71.8	61.8	57.4s		*d*	22.6	190.3	19.9	7.3	
11[e]	96.4	90.5	71.3	69.8	72.5	60.5	54.2d			20.7	188.2	16.5	7.7	2.7
12	97.8	90.3	69.4	80.6	62.1	68.9	55.6d	102.0d[f]	*g*	20.2	191.3	19.5	8.6	~1
13	97.9	86.9	83.0	77.7	62.3	68.5	55.9s	101.5	*g,h*	19.7	198.9	19.7	6.4	
14	97.4	85.2	59.1	76.9	58.1	69.0	56.4s	102.0d[i]	*g*	21.7	198.2	17.0	~8	
15	97.0	85.2	59.2	69.5	64.6	31.8	56.6d		*j*	21.6	197.6	16.7	5.0	2.7
16	98.8	85.2	59.3	67.6	148.2	100.4	57.0s		*j*	20.8	197.3	16.6	4.9	
17	98.2	86.3	61.6	66.4	152.7	99.1	56.7d			21.0	195.5	15.6	5.3	1.9
18	100.6	91.5	52.9	73.0s	72.1	16.6	57.2d			15.1	182.2	16.4	0	2.3
19[k]	101.4	92.7	74.9	70.1	76.8	61.4	57.9s			22.6	183.5	17.1	8.0	
20	101.9	92.6	72.3	79.9	66.1	68.5	57.5s	101.9	*g*	23.6	185.9	19.4	9.0	
21	101.7	89.3	84.4	77.2	65.7	68.2	57.9s	101.3	*g,h*	23.2	193.8	20.2	10.4	
21a	101.9	90.1	80.0	77.7	65.9	68.4	57.7s	101.6	*g,l*	23.3	191.8	20.1	7.5	
22	99.7	88.0	61.0	77.2	63.9	68.9	57.5s	102.0	*g*	24.3	194.1	17.0	5.7	
23	99.0	87.6	61.1	70.0	71.1	31.4	57.3d		*j*	23.3	194.5	16.7	4.4	3
24	99.3	87.0	55.9	69.2s	149.8	103.7	55.9s		*j*	29.3	186.0	16.4	0	
25	99.4	88.4	58.9	68.9s	154.0	100.2	56.2s			28.3	183.0	15.1	0	
26	98.5	89.7	52.0	71.9	70.2	17.7	56.8d			23.5	186.0	18.2	4.2	3.3

[a]With reference to the tetramethylsilane signal. [b]Doublet unless indicated otherwise. [c]Singlet unless indicated otherwise. [d]Three resonances at 170.4–169.3 (*CO*) and three at 20.7–20.4 (CH_3) p.p.m. for acetyl groups. [e]In dimethylsulfoxide-d_6. [f]$J_{F,C}$ 2.2 Hz. [g]Four resonances at 136 ±0.35, 129.2 ±0.1, 128.3 ±0.1, and 126 ±0.2 p.p.m. for the phenyl group-. [h]Doublet at 118.4 p.p.m. for CF_3; $J_{F,C}$ 319 Hz. [i]$J_{F,C}$ 2.8 Hz, [j]A signal at 165.0 ±0.3 (*CO*) and four signals at 133.7 ±0.3, 129.95 ±0.05, and in the range of 129.2–128.3 p.p.m. for the benzoyl group. [k]In D_2O, with 1,4-dioxane as internal standard. [l]Signal at 39.1 p.p.m. for CH_3SO_3.

Some of the compounds exhibited a small long-range coupling (2–3 Hz) of fluorine with the glycosidic methoxyl carbon-atom (through four bonds), or with a benzylidene acetal carbon-atom (through five bonds).

EXPERIMENTAL

General methods. — The following solvent combinations (v/v) and others specifically mentioned were used for chromatography: ethyl acetate–hexane, (*A*) 2:1, (*B*) 1:1, (*C*) 1:2, (*D*) 1:4, and (*E*) 1:6; ether–hexane, (*F*) 4:1, (*G*) 2:1, (*H*) 1:1, (*I*) 1:2, (*J*) 1:3, (*K*) 1:4, (*L*) 1:5; methanol–ethyl acetate, (*M*) 1:2, (*N*) 1:5; and methanol–chloroform (*O*) 3:8. Column chromatography was performed on Silica Gel Merck 7734 (100–200 mesh). Optical rotations were determined at ~25° with a Perkin–Elmer 241 polarimeter and refer to chloroform solutions, $c = 1$, unless otherwise specified. Infrared data (ν_{max}) were recorded using Nujol mulls for solids, and thin films for syrups; the i.r. spectra of all compounds were consistent with the assigned structures, and only a few especially significant bands are listed. Mass spectral data (*m/z*) were obtained in the chemical ionization mode, using ether as the ionizing gas unless otherwise noted.

3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl bromide (**8**). — To a chilled (0°) solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucose[7] (**7**, 8.16 g) in $CHCl_3$ (15 mL) was added 80 mL of 45% HBr in acetic acid, dropwise and under continued cooling. After completion, the mixture was kept at 25° for 3 h, when t.l.c. (solvent *B*) showed a single spot for **8** (R_F 0.68); **7** (R_F 0.57) was absent. The mixture was poured into, and stirred briefly with, ice water (450 mL) which was then extracted with $CHCl_3$ (500 mL, in 7 portions). The yellow extract was washed with several portions of ice-cold, saturated $NaHCO_3$ solution until first the CO_2 evolution ceased, and subsequently the organic layer became colorless. The layer was then washed once with water, dried (Na_2SO_4), and evaporated with added ether and hexane. The resulting syrup, which crystallized immediately upon scratching, was triturated with a small volume of ether–hexane. The fine, white needles were kept overnight at 0° under the mother liquor, recovered by decantation, washed with cold hexane containing a little ether, and dried (7.96 g, 90%); m.p. 86–87° (87.5° after recrystallization), $[\alpha]_D$ +215° (lit.[8] m.p. 79–80°, $[\alpha]_D$ +229° and[9] m.p. 75–76°, $[\alpha]_D$ +209°); m.s.: *m/z* 373, 371 ($M^+ + 1$), 313, 311 ($M^+ + 1 -$ AcOH), 291 ($M^+ + 1 -$ HBr), 231 ($M^+ + 1 -$ AcOH − HBr).

Anal. Calc. for $C_{12}H_{16}BrFO_7$ (371.4): C, 38.81; H, 4.34; Br, 21.52. Found: C, 38.58; H, 4.41; Br, 21.66.

Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranoside (**9**) *and its β-anomer* **10**. — *Method A*. Glassware used was flame-dried, the solvent CH_2Cl_2 was dried by distillation from P_2O_5, and absolute methanol was distilled from $Mg(OCH_3)_2$. To crystalline **8** (7.90 g) in CH_2Cl_2 (200 mL) was added crushed molecular sieve 4A (8.5 g, oven-dried), followed by Bu_4NBr (4.5 g, dried *in vacuo* for 8 h at 110°), ethyldiisopropylamine (3.7 mL), and absolute methanol (34 mL).

The mixture was stirred at 25°, protected from light and moisture. Monitoring by t.l.c. (double irrigation with solvent *H*) revealed the slow consumption of **8** (R_F 0.63) and formation of **9** (R_F 0.52) as the main product, accompanied by marginally more-slow moving **10** (R_F 0.50) and some immobile material. When the reaction was essentially complete (7–10 days; several experiments) the mixture was filtered with suction through sintered glass, the filter cake washed well with CH_2Cl_2 followed by methanol, and the filtrate concentrated to give a syrup, which was dissolved in CH_2Cl_2 (250 mL). The solution was sequentially washed with water, 5% aqueous HCl, and water, dried (Na_2SO_4), and evaporated to give a syrup. Crystallization from ether–hexane gave a first crop of solids (2.17 g) having m.p. 76–78° and consisting chiefly of stout prisms (**9**), with a small admixture of fine needles (**10**).

It was found that a substantial proportion of glycosidic products were contained in the aqueous extracts. The combined aqueous phases were therefore neutralized with solid $NaHCO_3$ and evaporated to dryness. The salt mass was extracted twice with boiling ethyl acetate (200 mL), which was filtered while hot. Evaporation of the extracts gave a syrup of partially deacetylated material (slow-moving in t.l.c.), which was treated overnight at room temperature with acetic anhydride (10 mL) and pyridine (10 mL) in the presence of a catalytic amount of 4-dimethylaminopyridine. The product obtained after conventional processing showed a t.l.c. pattern (R_F 0.5–0.6) identical with that of the aforementioned syrup from the CH_2Cl_2 phase, and on crystallization from ether–hexane it likewise deposited a crop (1.73 g) of glycosides, m.p. 76–78°. The mother liquor was combined with that from the first crystalline crop, and processed by column chromatography (45 g of SiO_2, solvent *J*). This afforded fractions of pure **9** (380 mg) and mixtures of **9** and **10** (230 mg), for a total yield of 4.51 g (66%) of glycosides. In a separate experiment, a 70% yield with an $\alpha:\beta$ ratio of 61:9 was obtained.

Chromatographically pure **9** had m.p. 80–81°, $[\alpha]_D$ +183°; m.s.: *m/z* 323 (M^+ +1), 291 (M^+ + 1 − MeOH), 231 (M^+ + 1 − MeOH − AcOH), 263, 231 (M^+ + 1 − MeOH − 2 AcOH), and 203.

Anal. Calc. for $C_{13}H_{19}FO_8$ (322.3): C, 48.45; H, 5.94; F, 5.89. Found: C, 48.26; H, 6.12; F, 5.79.

The main fractions of **9** (obtained by direct crystallization, m.p. 76–78°) contained an estimated 10% of **10**. It was possible (but laborious) to reduce this content somewhat by fractional crystallization from ethyl acetate (or ether)–hexane, to obtain products melting at 79–80° and showing $[\alpha]_D$ +176 ±0.5°. However, attainment of complete anomeric purity without resort to chromatography was not practical, nor was it necessary for performing the next step.

The fractions of crystalline β-anomer **10** isolated chromatographically or by fractional crystallization had m.p. 130–132° to 133–134° and $[\alpha]_D$ +33.4 ±0.3° (*c* 2); lit.[11] m.p. 130–132°, $[\alpha]_D$ +33°.

When glycosidations were performed at 55° they were finished after 2 days and similar yields of glycosides were obtained, but the $\alpha:\beta$ ratio appeared somewhat smaller (~4:1).

Method B. Glycosyl bromide (**8**) was prepared from **7** (3.52 g) as described. The crude, syrupy **8** was used without purification; after thorough drying *in vacuo* it was dissolved in dry dichloromethane (25 mL) and added at −40° to a mixture of absolute methanol (70 mL), dichloromethane (70 mL), silver triflate (4.85 g), 2,4,6-trimethylpyridine (2.25 mL), and powdered, freshly dried molecular sieve 4A (17.5 g). The reaction mixture was stirred overnight, with the temperature being allowed to rise gradually to +25°. T.l.c. (solvent *H*) indicated the complete consumption of **8** and formation of **9** and **10**. The solution was filtered through a bed of Celite, concentrated to a small volume, diluted with chloroform (150 mL), washed with aqueous $NaHCO_3$ then water, dried over $MgSO_4$, and evaporated. The yellow, solid residue was extracted with boiling ether (200 mL) which was filtered from the remaining, insoluble material while still warm. Concentration of the filtrate to a volume of ~70 mL, and cooling, caused crystallization of colorless **10** (2.16 g, 67%), m.p. 131–132°, identical in every respect (i.r., ^{1}H-n.m.r., t.l.c.) with **10** obtained by method A.

Column chromatography of the ethereal mother liquor (solvent *I*) gave a mixture (520 mg, 16%) of **9** and **10** in a ratio of ~4:3 (by n.m.r.).

*Methyl 2-deoxy-2-fluoro-α-*D*-glucopyranoside* (**11**). — Treatment of pure **9** with 0.025M $NaOCH_3$ solution (15 mL/g) for 1 h at 25°, followed by deionization with Amberlite IR-120 (H^+) resin and evaporation of the solution, quantitatively gave syrupy **11** which readily crystallized on the addition and evaporation of ethyl acetate. Recrystallized from boiling ethyl acetate the rectangular prisms had m.p. 143–143.5°, $[\alpha]_D$ +162° (*c* 1, water); m.s.: *m/z* 197 ($M^+ + 1$), 177 ($M^+ + 1 - HF$), and 165 ($M^+ + 1 - MeOH$).

Routinely, samples of **9** containing 7–15% of anomer **10** were used. Thus, a sample (4.28 g) in methanol (45 mL) and 0.1M $NaOCH_3$ solution (15 mL) furnished a crystalline, crude product from which were elaborated, by recrystallization from ethyl acetate, fractions of **11** melting at 140–12° and showing $[\alpha]_D$ +159–162°, totalling 2.29 g (88%).

Anal. Calc. for $C_7H_{13}FO_5$ (196.2): C, 42.86; H, 6.68; F, 9.69. Found: C, 43.08; H, 6.78; F, 9.79.

*Methyl 4,6-O-benzylidene-2-deoxy-2-fluoro-α-*D*-glucopyranoside* (**12**). — To a stirred suspension of **11** (7.43 g) in dry acetonitrile (200 mL, distilled from P_2O_5) was added α,α-dimethoxytoluene (9 mL) and *p*-toluenesulfonic acid (TsOH; 100 mg). A clear solution resulted, and the acetalation was nearly complete after 1 h (t.l.c. with ethyl acetate; R_F 0.95 for **12**, 0.2 for traces of **11**). The solution was concentrated to one-half its volume at 35°, whereby **11** disappeared completely. However, t.l.c. with solvent *B* now showed a minor by-product (R_F 0.8) accompanying the major product (R_F 0.6), as well as some immobile material. Crystallization of **12** commenced during the concentrating and was allowed to continue at −18°. The crop was isolated and washed with cold ether containing 2 drops of triethylamine (5.58 g, m.p. 162–163°). To the combined mother liquor and washings methanol (10 mL) was then added, causing the by-product (R_F 0.8) to disappear in

the course of 0.5 h; presumably it was a derivative of **12** having OH-3 involved in formation of a mixed, acyclic acetal which was readily methanolyzed. Following careful neutralization with Et_3N of the TsOH present, the mother liquor was concentrated partially, to give a second crop of **12** (2.11 g, m.p. 162–164°), and then evaporated to dryness. The residue was extracted with boiling ethyl acetate, and the cooled and filtered extract was washed with water, which removed the aforementioned immobile impurity (t.l.c.). Drying and evaporation of the solvent gave a solid from which further crops of **12** (1.70 and 0.25 g, m.p. 163–164 and 159–161°, $[\alpha]_D$ +111 ±5°) were obtained by recrystallization. The final mother liquor was revealed by t.l.c. (solvent *B*) to contain **12** accompanied by marginally faster-moving anomer **20** that originated from the **19** present as a minor contaminant in the **11** used. Column chromatography (solvent *J*) produced another 180 mg of pure **12**, m.p. 163–164°, $[\alpha]_D$ +116.3°, for a total yield of 9.82 g (91%); m.s.: *m/z* 285 ($M^+ + 1$), 253 ($M^+ + 1 - MeOH$), and 207 ($M^+ + 1 - Ph$). A similar run gave a 93% yield.

Anal. Calc. for $C_{14}H_{17}FO_5$ (284.3): C, 59.15; H, 6.03; F, 6.68. Found: C, 59.38; H, 6.29; F, 6.49.

Methyl 4,6-O-benzylidene-2-deoxy-2-fluoro-3-O-(trifluoromethylsulfonyl)-α-D-glucopyranoside (**13**). — Triflic anhydride (4.15 mL) in dry CH_2Cl_2 (20 mL) was added dropwise to a mixture of pyridine (4.0 mL) and CH_2Cl_2 (20 mL), at −10°. After 10 min a solution of **12** (3.50 g) in CH_2Cl_2 (30 mL) was added dropwise, and after a further 15 min the formation of **13** (R_F 0.75, solvent *B*) was complete. The mixture was shaken sequentially with 5% HCl, saturated aqueous $NaHCO_3$, and water. After drying (Na_2SO_4) and treatment with activated carbon, the organic phase was evaporated with eventual additions of toluene and hexane, to give chromatographically homogeneous **13** (4.85 g, 94%) as a faintly yellowish solid. Recrystallized from ether–hexane, an analytical sample had m.p. 96–97°, $[\alpha]_D$ +79.9°; m.s.: *m/z* 417 ($M^+ + 1$), 385 ($M^+ + 1 - MeOH$), 339 ($M^+ - Ph$), 267 ($M + 1 - TfOH$), and 247 ($M^+ + 1 - TfOH - HF$).

Anal. Calc. for $C_{15}H_{16}F_4O_7S$ (416.3): C, 43.27; H, 3.87; S, 7.70. Found: C, 43.08; H, 3.96; S, 7.46.

Methyl 3-azido-4,6-O-benzylidene-2,3-dideoxy-2-fluoro-α-D-allopyranoside (**14**). — A mixture of **13** (13.4 g) and LiN_3 (6.2 g) in dry *N,N*-dimethylformamide (60 mL) was heated for 13 h at 75°. Conversion of **13** (R_F 0.5) into **14** (R_F 0.4) was monitored by t.l.c. (solvent *C*), which also showed a minor by-product (R_F 0.7) and traces of slow-moving decomposition products. The mixture was diluted with CH_2Cl_2 (400 mL), washed exhaustively with water and brine, dried (Na_2SO_4), and evaporated. Three successive portions of toluene were evaporated from the reddish-brown residue, which was then passed by means of solvent *C* through a bed of SiO_2 (230–400 mesh, 60 g) contained in a sintered-glass funnel. The colored impurities were retained by the gel, and forefractions containing the by-product (R_F 0.7) together with some **14** were set aside. Evaporation of the main eluate gave a colorless crystal mass that was recrystallized from ether–hexane to yield pure **14**

(5.90 g), m.p. 140°. Column chromatography (70 g of SiO_2) of the forefractions with 1:8 followed by 1:6 ethyl acetate–hexane as eluents gave homogeneous by-product (218 mg, 2.5%) and additional **14** (755 mg) for a total yield of 6.66 g (67%) of the latter; $[\alpha]_D$ +76.8°, ν_{max} 2140 and 2160 cm^{-1} (doublet, N_3); m.s.: *m/z* 310 ($M^+ + 1$), 282 ($M^+ + 1 - N_2$), 278 ($M^+ + 1 -$ MeOH), and 250 ($M^+ + 1 - N_2 -$ MeOH).

Anal. Calc. for $C_{14}H_{16}FN_3O_4$ (309.3): C, 54.37; H, 5.21; N, 13.58. Found: C, 54.41; H, 5.41; N, 13.59.

The crystalline by-product (R_F 0.7) proved to be *methyl 4,6-O-benzylidene-2,3-dideoxy-2-fluoro-α-*D-erythro-*hex-2-enopyranoside*, m.p. 149–150° (with sublimation); $[\alpha]_D$ +133°, ν_{max} 1690 cm^{-1} (doublet, medium strong, C=C); m.s.: *m/z* 267 ($M^+ + 1$) and 235 ($M^+ + 1 -$ MeOH); ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 7.5–7.35 (m, 5 H, Ph-H), 5.64 (ddd, $J_{1,3}$ 1.2, $J_{3,4}$ 1.8, $J_{3,F}$ 13.5 Hz, H-3), 5.54 (s, PhC*H*), 4.86 (dd, $J_{1,F}$ 0.5, $J_{1,3}$ 1.2 Hz, H-1), 4.32–4.25 (complex m, 2 H, H-6*eq*,4, analyzed by resolution enhancement as ddd and tdd, with $J_{5,6eq}$ 4.5, $J_{6ax,6eq}$ 10, $J_{3,4}$ 1.8, $J_{4,F}$ 6.5, $J_{4,5}$ 8.7 Hz, and unassigned 1-Hz long-range coupling), 3.93 (ddd, *J* 4.5, 8.5, and 10 Hz, H-5), 3.81 (t, $J_{5,6ax} = J_{6ax,6eq} = 10$ Hz, H-6*ax*), 3.50 (s, 3 H, OMe); ^{13}C-n.m.r. (50.29 MHz, $CDCl_3$): δ 156.5 (d, $J_{2,F}$ 272 Hz, C-2), 137.8, 130.1, 129.2, and 127.1 (C_6H_5), 107.3 (d, $J_{3,F}$ 12.9 Hz, C-3), 102.8 (PhCH), 95.5 (d, $J_{1,F}$ 34.2 Hz, C-1), 75.6 (d, $J_{4,F}$ 7.7 Hz, H-4), 69.5 (C-6), 65.4 (C-5), and 57.0 (OCH_3).

Anal. Calc. for $C_{14}H_{15}FO_4$ (266.3): C, 63.15; H, 5.68; F, 7.14. Found: C, 63.34; H, 5.85; F, 7.35.

*Methyl 3-azido-4-O-benzoyl-6-bromo-2,3,6-trideoxy-2-fluoro-α-*D-*allopyranoside* (**15**). — Carbon tetrachloride was dried by distillation from CaH_2, followed by passage through freshly activated, neutral, chromatography-grade Al_2O_3. *N*-Bromosuccinimide (NBS) and $BaCO_3$ were dried *in vacuo* for 4 h at 110°. A mixture of **14** (6.65 g), $BaCO_3$ (4.2 g), and NBS (4.23 g) in CCl_4 (350 mL) was magnetically stirred and boiled under reflux for 1 h, after which time all of the **14** (R_F 0.4) was consumed and a strong spot for **15** (R_F 0.6) was visible on t.l.c. (solvent *H*), together with traces of slow-moving material (R_F 0.2). The mixture was filtered through Celite, the filter cake washed repeatedly with hot CCl_4, and the filtrate evaporated, with the addition of some ether towards the end. A solution of the resulting yellow syrup in ether (50 mL) was washed twice with aqueous $NaHCO_3$ solution followed by brine and water, dried (Na_2SO_4), and evaporated. The dried syrup crystallized readily when rubbed with a small volume of 95% ethanol. The mass was triturated carefully with the ethanol, stored overnight at 0°, isolated, and washed with cold ethanol to give a main crop of **15** (6.35 g), m.p. 86.5–87°. Processing of the ethanolic mother liquor, first by crystallization and then by column chromatography (solvent *H*) of the noncrystallizable remainder, provided additional **15** (0.45 g, m.p. 85.5–86.5°), for a total yield of 81.5%; $[\alpha]_D$ +73.2°; ν_{max} 2140 with shoulder at 2160 (N_3), and 1740 cm^{-1} (ester CO); m.s.: *m/z* 390, 388 ($M^+ + 1$), 362, 360 ($M^+ + 1 - N_2$), 358, 356 ($M^+ + 1 -$ MeOH), and 287, 285.

Anal. Calc. for $C_{14}H_{15}BrFN_3O_4$ (388.2): C, 43.32; H, 3.90; Br, 20.58; N, 10.82. Found: C, 43.57; H, 4.05; Br, 20.79; N, 10.48.

Continued elution of the column gave unidentified by-products (160 mg) followed by a homogeneous syrup (R_F 0.2; 260 mg), $[\alpha]_D$ +128.5° (*c* 1.5), which was shown by spectroscopy to be *methyl 3-azido-6-*O*-benzoyl-2,3-dideoxy-2-fluoro-α-*D*-allopyranoside:* ν_{max} 3470, 2120, and 1720 cm^{-1}; m.s. (Me_4Si): *m/z* 398 (M^+ + 73); ^{13}C-n.m.r. (50.29 MHz, $CDCl_3$): δ 133.5, 129.7, 129.5, 128.5 (C_6H_5), 96.5 (d, *J* 21.5 Hz, C-1), 86.0 (d, *J* 197 Hz, C-2), 66.2 (C-5), 66.0 (d, *J* 5 Hz, C-4), 63.5 (C-6), 61.3 (d, *J* 15.5 Hz, C-3), and 56.0 (CH_3). The ^{1}H-n.m.r. data ($CDCl_3$) agreed with the assigned structure. In particular, H-4 gave a multiplet at δ 3.60, which after acetylation of the substance was shifted to δ 4.92 (ddd, $J_{4,F}$ 1.6, $J_{3,4}$ 3.5, $J_{4,5}$ 10.1 Hz; coinciding with d, $J_{1,2}$ 4.3, $J_{1,F} < 0.7$ Hz, for H-1); H-2 of the acetate resonated at δ 4.65 (dt, $J_{2,F}$ 43.8, $J_{1,2} = J_{2,3} = 4.3$ Hz).

*Methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy-2-fluoro-α-*D*-ribo-hex-5-enopyranoside* (**16**). — A solution of **15** (6.65 g) and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU; 4.7 mL) in dry benzene (235 mL) was gently boiled under reflux (oil bath, 90°), with magnetic stirring. Care must be taken to avoid local overheating of the flask. A gradual replacement of **15** (R_F 0.55) by **16** (R_F 0.45) was observed in t.l.c. (solvent *C*). After 3 h, more DBU (2.35 mL) was added, and refluxing was continued for a further 4 h to complete the reaction. The mixture was allowed to cool, diluted with some benzene, and filtered to remove the crystalline DBU hydrobromide (4.0 g, quantitative) that had deposited slowly during the course of the reaction. The brownish-yellow filtrate was washed with 5% HCl (5 x 40 mL), whereby it turned almost colorless, and then with aqueous $NaHCO_3$ (2 × 50 mL) followed by water. It was then dried (Na_2SO_4), treated with some activated carbon, and evaporated to give **16** as a faintly yellow syrup (4.73 g, dried *in vacuo*; 90%), $[\alpha]_D$ +90.5°; ν_{max} 2110 (N_3), 1730 (ester CO), 1670 (enol ether), 1600, and 1585 (arom.) cm^{-1}; m.s.: *m/z* 308 (M^+ + 1), 280 (M^+ + 1 − N_2), 265 (M^+ − N_3), 233 (M^+ − N_3 − MeOH).

Anal. Calc. for $C_{14}H_{14}FN_3O_4$ (307.3): C, 54.72; H, 4.59; N, 13.67. Found: C, 54.61; H, 4.80; N, 13.76.

*Methyl 3-azido-2,3,6-trideoxy-2-fluoro-α-*D*-ribo-hex-5-enopyranoside* (**17**). — To a solution of **16** (4.72 g) in absolute methanol (100 mL) at room temperature was added $NaOCH_3$ (from 155 mg of Na in 13 mL of methanol). The conversion of **16** (R_F 0.45) into **17** (R_F 0.3) was complete after 10 min (t.l.c., solvent *C*). The solution was carefully made neutral with dilute methanolic acetic acid (**17** does not tolerate acidic conditions), and evaporated, to give a syrup that was passed through a column of SiO_2 (4 × 15 cm) by means of solvent *J*. After the elution of methyl benzoate, **17** (2.84 g, 91%) was collected and crystallized from ether; m.p. 79–80°, raised to 82.5–83.5° by recrystallization from ethyl acetate–hexane; $[\alpha]_D$ +250°; ν_{max} 3490 (sharp, OH), 2110 (N_3), and 1665 (enol ether) cm^{-1}; m.s.: *m/z* 204 (M^+ + 1), 176 (M^+ + 1 − N_2), 172 (M^+ + 1 − MeOH), 149, and 143.

Anal. Calc. for $C_7H_{10}FN_3O_3$ (203.2): C, 41.38; H, 4.96; N, 20.68. Found: C, 41.74; H, 5.15; N, 21.00.

*Methyl 3-amino-2,3,6-trideoxy-2-fluoro-β-*L*-talopyranoside* (**18**). — Brown

palladium oxyhydrate on barium sulfate[13] (7.0 g) was prehydrogenated in methanol (110 mL). A solution of **17** (2.00 g) in methanol (50 mL) was added, and the suspension was vigorously shaken for 4 h under H_2 at ordinary pressure, after which time H_2 uptake had ceased and t.l.c. (solvent *O*) indicated replacement of **17** (R_F 0.9) by **18** (R_F 0.25, ninhydrin-positive) accompanied by traces of by-products (R_F 0.1, 0.3–0.4). The catalyst was filtered off over Celite and washed exhaustively with methanol. The slightly brownish filtrate was evaporated to give an off-white solid that dissolved incompletely in chloroform (40 mL). Hexane was added dropwise to incipient cloudiness of the supernatant chloroform solution, and after overnight cooling (0°) of the mixture the white, insoluble deposit (140 mg) was isolated. Recrystallized by dissolution in moist, boiling methanol followed by the addition of excess ethanol, the by-product had no distinct melting point but decomposed gradually between 160 and 200°, with partial sublimation of needles; it gave a molecular-ion peak at *m/z* 180 like **18** but differed from the latter in its i.r. and ^{1}H-n.m.r. spectra and $[\alpha]_D$ value of +46°, *c* 0.8 in moist methanol. The solution containing the main product was concentrated and mixed with a small quantity of SiO_2, which was layered on a column of SiO_2 (60 g, 70–230 mesh) for chromatography using 1:10 methanol–chloroform. Forefractions containing fast-moving impurities were discarded, and homogeneous **18** was then collected (1.00 g, 58%), m.p. 147–149° with decomposition, raised to 149–150° (with sublimation) in a sealed capillary; $[\alpha]_D$ +59.2° (*c* 0.75); ν_{max} 3375, 3315 (sharp), 3150 (broad), 1590 cm^{-1}; m.s.: *m/z* 180 ($M^+ + 1$), 160 ($M^+ + 1 - HF$), 148 ($M^+ + 1 - MeOH$).

Anal. Calc. for $C_7H_{14}FNO_3$ (179.2): C, 46.92; H, 7.87; N, 7.81; F, 10.60. Found: C, 46.71; H, 7.84; N, 7.62; F, 10.41.

Further elution of the column with 5% acetic acid in methanol produced unidentified, ninhydrin-positive material (230 mg).

*Methyl 2-deoxy-2-fluoro-β-*D*-glucopyranoside* (**19**). — Compound **10** (1.282 g) was deacetylated as described for **9**. The crude product was passed through a short column of SiO_2 with solvent *M*, yielding **19** (763 mg, 98%) as colorless crystals, m.p. 149–150° and $[\alpha]_D$ −29° (*c* 0.6, water); lit.[11] m.p. 148–150°, $[\alpha]_D$ −29°.

*Methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-β-*D*-glucopyranoside* (**20**). — Compound **19** (2.07 g) was benzylidenated as described for **11**. Conversion of **19** (R_F 0.0) into **20** (R_F 0.66) was monitored by t.l.c. (solvent *A*). Processing gave solid **20** (2.65 g, 88%), m.p. 189–191° (recrystallized from ether), $[\alpha]_D$ −53.7°; m.s.: *m/z* 285 ($M^+ + 1$) and 253 ($M^+ + 1 - MeOH$).

Anal. Calc. for $C_{14}H_{17}FO_5$ (284.3): C, 59.15; H, 6.03; F, 6.68. Found: C, 59.08; H, 6.08; F, 6.83.

*Methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-3-*O*-(trifluoromethylsulfonyl)-β-*D*-glucopyranoside* (**21**). — Compound **20** (2.65 g) was triflated as described for **13**. Conversion of **20** (R_F 0.2) into **21** (R_F 0.4) was monitored by t.l.c. (solvent *H*). Processing gave solid **21** (3.51 g, 90%). Recrystallized from ether–hexane, an analytical sample was obtained as long needles, m.p. 117° (dec., with sintering from

109°), $[\alpha]_D$ −32.6°; m.s.: *m/z* 417 ($M^+ + 1$), 385 ($M^+ + 1 - MeOH$), 339 ($M^+ - C_6H_5$), 267 ($M^+ + 1 - TfOH$), and 247 ($M^+ + 1 - TfOH - HF$).

Anal. Calc. for $C_{15}H_{16}F_4O_7S$ (416.3): C, 43.27; H, 3.87; S, 7.70. Found: C, 43.40; H, 4.07; S, 7.63.

Methyl 4,6-O-benzylidene-2-deoxy-2-fluoro-3-O-(methylsulfonyl)-β-D-glucopyranoside (**21a**). — To a cold (0°) solution of **20** (100 mg) in pyridine (3 mL) was added methanesulfonyl chloride (0.05 mL), and the mixture was stored overnight at room temperature. Conversion of **20** (R_F 0.5) into **21a** (R_F 0.4) appeared complete (t.l.c., double irrigation with solvent *H*). Several portions of methanol were sequentially added to and evaporated from the reaction mixture, which was then diluted with chloroform (20 mL) and washed with 5% HCl, water, $NaHCO_3$ solution, and water (15 mL of each). Dried ($MgSO_4$) and evaporated, the solution gave a syrup that was chromatographed with solvent *J* on a silica gel column, to furnish crystalline **21a** (108 mg, 85%), m.p. 174–175°, $[\alpha]_D$ −42.5°; m.s.: *m/z* 363 ($M^+ + 1$), 331 ($M^+ + 1 - MeOH$), and 285 ($M^+ - C_6H_5$).

Anal. Calc. for $C_{15}H_{19}FO_7S$ (362.4): C, 49.72; H, 5.28; S, 8.49. Found: C, 49.82; H, 5.19; S, 8.66.

Methyl 3-azido-4,6-O-benzylidene-2,3-dideoxy-2-fluoro-β-D-allopyranoside (**22**). — *A. From triflate* **21**. Freshly prepared **21** (3.41 g, not recrystallized) in dry *N,N*-dimethylformamide (15 mL) was treated with NaN_3 (1.82 g) for 20 min at 40°. (Note that the analogous reaction of **13** was much slower and required LiN_3; NaN_3 had proved unsatisfactory.) The resulting **22** was difficult to distinguish on t.l.c. from **21**, although the latter was seen to migrate marginally more slowly (R_F ~0.50 *vs.* 0.52, double irrigation with solvent *G*). The reaction mixture was poured into dichloromethane (60 mL), and the solution was washed with water (5 × 40 mL), dried ($MgSO_4$), and evaporated, to give a yellow syrup from which colorless, crystalline **22** (2.31 g, 91%) was obtained after chromatographic purification (solvent *D*); m.p. 102–104°, $[\alpha]_D$ −76.0°; ν_{max}^{KBr} 2136 and 2104 (doublet, N_3) cm^{-1}; m.s.: *m/z* 310 ($M^+ + 1$), 282 ($M^+ + 1 - N_2$), 278 ($M^+ + 1 - MeOH$), 250 ($M^+ + 1 - N_2 - MeOH$), and 232 ($M^+ - C_6H_5$).

Anal. Calc. for $C_{14}H_{16}FN_3O_4$ (309.3): C, 54.37; H, 5.21; N, 13.58. Found: C, 54.48; H, 5.12; N, 13.56.

B. From mesylate **21a**. A mixture of **21a** (60 mg) and NaN_3 (32 mg) in *N,N*-dimethylformamide (4 mL) was heated for 48 h at 100°, after which the reaction appeared complete (t.l.c.). The solvent was coevaporated with added toluene, and the residue purified by column chromatography (solvent *D*). The crystalline product (41 mg, 75%) was identical with **22** from method A.

Methyl 3-azido-4-O-benzoyl-6-bromo-2,3,6-trideoxy-2-fluoro-β-D-allopyranoside (**23**). — Compound **22** (714 mg) was allowed to react with *N*-bromosuccinimide (451 mg) in the presence of $BaCO_3$ (500 mg) in boiling carbon tetrachloride (40 mL) as described for **14**. After 1 h, the conversion of **22** (R_F 0.4) into **23** (R_F 0.55) appeared complete (t.l.c., double irrigation with solvent *I*). Processing as for **15** gave **23** (677 mg, 77%) as a syrup which failed to crystallize; $[\alpha]_D$ −66.3°; ν_{max}

2140 and 2100 (doublet, N_3), 1740 (ester CO) cm^{-1}; m.s.: *m/z* 390 and 388 ($M^+ + 1$), 362 and 360 ($M^+ + 1 - N_2$), 358 and 356 ($M^+ + 1$ − MeOH), 286 and 284.

Anal. Calc. for $C_{14}H_{15}BrFN_3O_4$ (388.2): C, 43.32; H, 3.90; N, 10.82. Found: C, 43.33; H, 4.00; N, 10.74.

*Methyl 3-azido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-β-*D-ribo*-hex-5-enopyranoside* (**24**). — A mixture of **23** (0.60 g), AgF (0.40 g), and a few crystals of 4-dimethylaminopyridine in dry pyridine (7 mL) was stirred for 24 h at room temperature, protected from light. Mobilities in t.l.c. for **23** and the product, **24**, were nearly the same (R_F 0.53 and 0.55 after quadruple irrigation with solvent *L*). The reaction mixture was diluted with ether and filtered, and the residue was washed exhaustively with warm ether followed by warm ethyl acetate. The combined filtrates were concentrated to a syrup, which was subjected to several additions and evaporations of toluene before it was purified by column chromatography (solvent *K*). This gave a syrupy **24** (0.35 g, 74%), which failed to crystallize; $[\alpha]_D$ −112°; ν_{max} 2110 (N_3), 1725 (ester CO), 1670 (enol ether), 1600, and 1585 (arom.) cm^{-1}; m.s.: *m/z* 308 ($M^+ + 1$), 265 ($M^+ - N_3$), and 233 ($M^+ - N_3$ − MeOH).

Anal. Calc. for $C_{14}H_{14}FN_3O_4$ (307.3): C, 54.72; H, 4.59; N, 13.67. Found: C, 54.91; H, 4.53; N, 13.93.

*Methyl 3-azido-2,3,6-trideoxy-2-fluoro-β-*D-ribo*-hex-5-enopyranoside* (**25**). — Compound **24** (323 mg) was debenzoylated in methanol (7 mL) by the addition of 0.1M sodium methoxide (1 mL) at room temperature. Complete conversion of **24** (R_F 0.5) into **25** (R_F 0.3) within 2 h was indicated by t.l.c. (solvent *H*). After neutralization with acetic acid, the solution was evaporated and the product passed through a silica gel column (solvent *J*), to give pure **25** (185 mg, 90%) as a syrup, $[\alpha]_D$ +4°, $[\alpha]_{436}$ +16.5°; ν_{max} 3450 (broad, OH), 2105 (N_3), and 1665 (enol ether) cm^{-1}; m.s.: *m/z* 204 ($M^+ + 1$), 176 ($M^+ + 1 - N_2$), 172 ($M^+ + 1$ − MeOH), 149, and 143.

Anal. Calc. for $C_7H_{10}FN_3O_3$ (203.2): C, 41.38; H, 4.96; N, 20.68. Found: C, 41.63; H, 5.17; N, 20.47.

*Methyl 3-amino-2,3,6-trideoxy-2-fluoro-β-*D-*allopyranoside* (**26**). — A suspension of brown palladium oxyhydrate on barium sulfate[13] (0.2 g) in methanol (10 mL) was prehydrogenated, and **25** (86 mg) in methanol (5 mL) was then added. The mixture was shaken vigorously for 2 h under H_2 at ordinary pressure, after which time the spot for **25** (R_F 0.5) was completely replaced by that for **26** (R_F 0.15; t.l.c. with ether), and the solution gave a positive ninhydrin test. The catalyst was filtered off and washed *exhaustively* with warm methanol (it tends to adsorb the product stubbornly). Removal of the solvent and column chromatography (solvent *F*) of the residue furnished crystalline **26** (50 mg, 66%), m.p. 121–123°, $[\alpha]_D$ −45.5°; ν_{max}^{KBr} 3370, 3310 (sharp), 3150 (broad), and 1580 cm^{-1}; m.s.: *m/z* 180 ($M^+ + 1$), 160 ($M^+ + 1$ − HF), 148 ($M^+ + 1$ − MeOH), 128 ($M^+ + 1$ − MeOH − HF).

Anal. Calc. for $C_7H_{14}FNO_3$ (179.2): C, 46.92; H, 7.87; F, 10.60; N, 7.81. Found: C, 47.18; H, 7.72; F, 10.37; N, 7.52.

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