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SYNTHESIS OF (*S*)-2-FLUORO-L-DAUNOSAMINE AND (*S*)-2-FLUORO-D-RISTOSAMINE

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ABSTRACT

Derivatives of (*S*)-2-fluoro-L-daunosamine and (*S*)-2-fluoro-D-ristosamine were synthesized, starting ultimately from 2-amino-2-deoxy-D-glucose which was converted, according to the literature, into methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(methylsulfonyl)-α-D-glucopyranoside (**2**). Treatment of **2** with tetrabutylammonium fluoride gave a 63% yield of (known) methyl 3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-2-fluoro-α-D-altropyranoside (**4**), together with a 6% yield of its 2-benzamido-2,3-dideoxy-3-fluoro-α-D-*gluco* isomer. From **4**, the corresponding 6-bromo-2,3,6-trideoxyglycoside 4-benzoate (**6**) was obtained by Hanessian–Hullar reaction. Dehydrobromination of **6**, followed by catalytic hydrogenation of the resulting 5-enoside, and subsequent debenzoylation and *N*-trifluoroacetylation, afforded the fluorodaunosaminide, methyl 2,3,6-trideoxy-2-fluoro-3-trifluoroacetamido-β-L-galactopyranoside. Reductive debromination of **6**, followed by debenzoylation and *N*-trifluoroacetylation, gave the fluororistosaminide, methyl 2,3,6-trideoxy-2-fluoro-3-trifluoroacetamido-α-D-altropyranoside. The ^{1}H-n.m.r. spectra of the new aminofluoro sugars are discussed with respect to the effects of neighboring amino and acylamido substituents on geminal and vicinal ^{1}H–^{19}F coupling constants, in comparison with the reported effects of oxygen substituents.

INTRODUCTION

The clinical use of the important anticancer drugs adriamycin and daunorubicin is limited by their high cardiotoxicity, and worldwide efforts have been directed for many years toward improving the therapeutic value of these anthracyclines by chemical modification both in the aglycon and the glycon moiety. As far as alteration in the sugar component is concerned, promising leads have developed as a result of work involving the replacement of the natural daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose) by certain stereoisomers, structural variants, and other sugars[1–3]. It was originally believed that, for modified anthracyclines to show

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high antitumor activity, the 3′-amino group should be retained and C-2′ should remain unsubstituted. However, Horton and his coworkers have synthesized 3′-deamino-3′-hydroxy (and acetoxy) analogs of daunorubicin and adriamycin which displayed enhanced antitumor activity and(or) lowered toxicity[2], and recently[3], they reported that introduction of halogen (especially axial iodine) at C-2′ in such deamino analogs resulted in a further enhancement of efficacy *in vivo*. Fluorine substitution was not included in these studies, and analogs halogenated in the sugar moiety with retention of the 3′-amino function have not been recorded.

We therefore decided, in continuation of our own program on synthesis of aminopolydeoxy sugars[4,5] (some of which[5] may serve as daunosamine substitutes for modified anthracyclines), to prepare some related amino sugars bearing a fluorine atom at C-2, with a view to future coupling to anthracyclinone aglycons. A rationale for preparing such analogs is founded in the expectation that the strong, electron-withdrawing inductive effect of the fluorine substituent will increase their stability toward hydrolytic deactivation *in vivo*, whilst its small van der Waals radius should ensure minimal interference with the steric requirements of drug binding and transport. In the course of this project, it is planned to synthesize pairs of C-F epimers in order to test the influence of axial *vs.* equatorial halo substitution, which may well be expected to be less significant in fluoro analogs than in[3] iodo analogs. It is pertinent to note in this context that Tsuchiya *et al.*[6], having introduced fluorine to replace a methoxy group in the aminoglycoside antibiotic sporaricin A, observed lowered acute toxicity and, for the axial and equatorial fluoro epimers, antibacterial activities comparable to that of the parent compound. Furthermore, the availability of synthetic aminofluoro derivatives might benefit research into the involvement of the amino group as pertaining to the dual features of antitumor activity and cardiopathogenicity in natural anthracyclines.

RESULTS

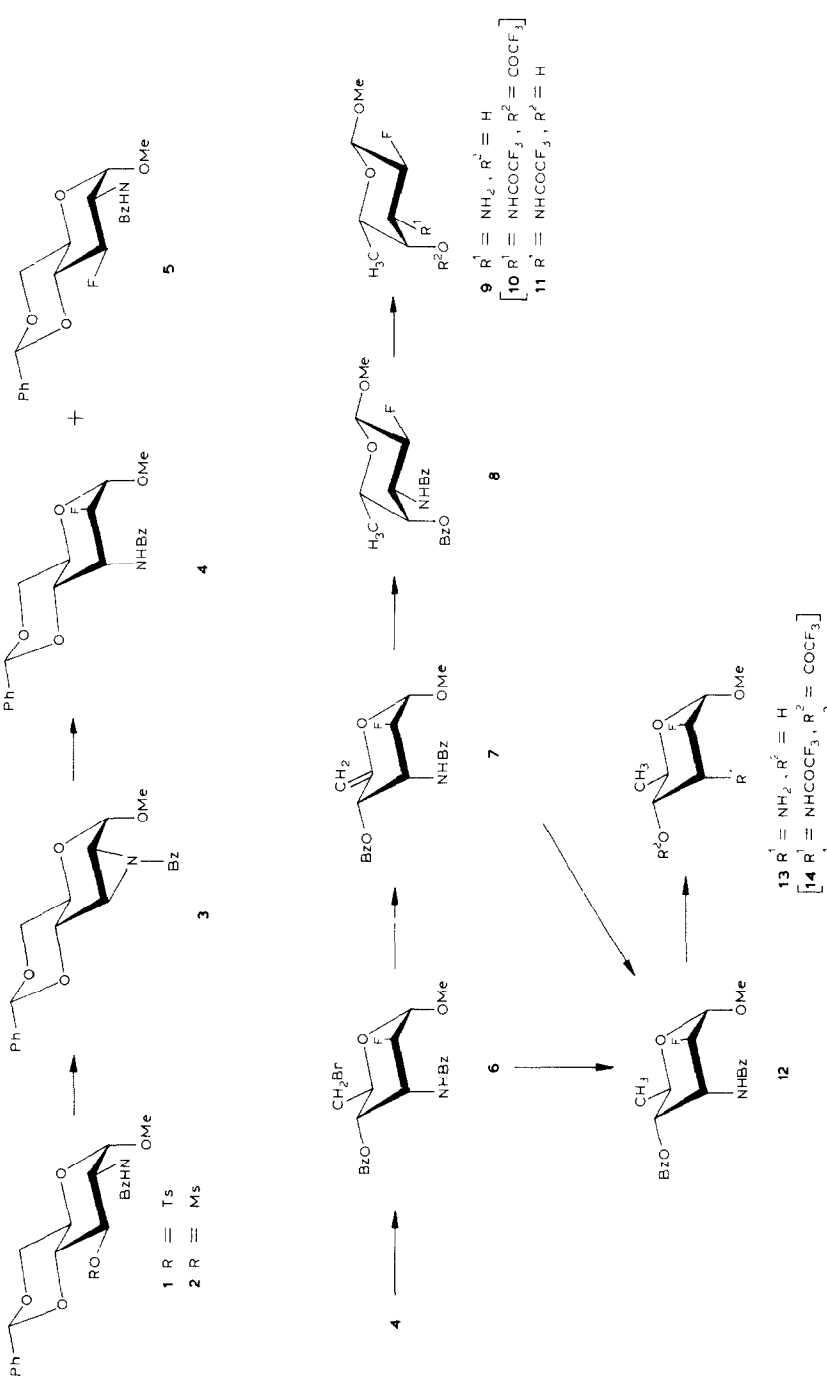
We describe here the synthesis of 3-amino-2,3,6-trideoxy-2-fluoro-L-galactose [(*S*)-2-fluoro-L-daunosamine] and its D-*altro* isomer [(*S*)-2-fluoro-D-ristosamine], which were prepared as the *N*-trifluoroacetylated methyl glycosides **11** and **15**, respectively. The starting point was the known methyl 3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-2-fluoro-α-D-altropyranoside (**4**). This compound had been obtained, in 35% yield, by Hough *et al.*[7] who had treated methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-tosyl-α-D-glucopyranoside (**1**) with tetrabutylammonium fluoride in hexamethylphosphoric triamide or acetonitrile solution. We performed the same reaction with the corresponding 3-mesylate **2** in acetonitrile and isolated **4** in 63% yield, together with 6% of a crystalline isomer which proved to be the 2-benzamido-3-fluoro analog having the D-*gluco* configuration (**5**). Although Hough and his coworkers, who have demonstrated[7] the transformation of **1** to proceed through the *N*-benzoylepimine **3**, had on other occasions[8] encountered similar ring-openings of *N*-acylepimines (including that of **3** with ammonium chloride)

which additionally gave minor proportions of 2,3-diequatorially substituted products, they[7] did not observe the formation of **5** from **1**. We noticed that **5** was difficult to distinguish from intermediary **3** by t.l.c., so that it may have escaped detection. The combined yield of isolated fluoro glycosides (**4** and **5**) being only 75%, the fate of a considerable proportion of the starting sulfonate **2** remained unknown; the presence of chromatographically slow-moving, unidentified but fluorine-free by-products[7] was confirmed in our hands. Nevertheless, it remains a valid conclusion that introduction of fluoride (as that of other nucleophiles[8]) *via* the epimine **3** occurs predominantly by the diaxial mode*.

The three crucial steps that followed emulated the pioneering daunosamine synthesis of Horton and Weckerle[9]. Thus, the benzylidene acetal **4** was converted, by Hanessian–Hullar reaction with *N*-bromosuccinimide in carbon tetrachloride, into methyl 3-benzamido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-2-fluoro-α-D-altropyranoside (**6**), isolated crystalline in 82% yield. Dehydrobromination of **6** was performed with silver fluoride in pyridine by the established, general procedure[10], to afford a 93% yield of the crystalline, 5,6-unsaturated derivative **7**. Catalytic hydrogenation of **7** in the presence of palladium-on-barium sulfate furnished stereoselectively the 2-fluorodaunosamine derivative **8**, isolated crystalline in 62% yield. The mother liquor contained a mixture of **8** and the 5-epimer **12**, according to the ^{1}H-n.m.r. spectrum, indicating that the hydrogenation was not fully stereospecific under the conditions employed. Catalytic addition of hydrogen to hex-5-enopyranosides generally takes place at the face of the molecule opposite to the anomeric group, with good to excellent stereoselectivity[9,11–17]. Catalysts that have been used were platinum oxide[11], palladium black[12], palladium-on-barium sulfate[9,13], palladium-on-carbon[14–16], and Raney nickel[15,17]; and in at least one instance[15], selectivity was influenced by the choice of catalyst. Substrates successfully employed were 4-benzoates[13a,15,16] (such as **7**) and 4-acetoxy[11,12,17a] as well as 4-hydroxy[9,13b,c,17b] analogs but, in some cases, difficulties were encountered with 4-benzoates and were overcome by prior *O*-debenzoylation[14,17c]. The survey suggests that improvements in the present synthesis might be achievable by such variations in procedure.

Compound **8** was then saponified with sodium hydroxide in 2-methoxyethanol–water, which effected simultaneous *O*- and[8,18] *N*-debenzoylation, to provide crystalline methyl 3-amino-2,3,6-trideoxy-2-fluoro-β-L-galactopyranoside [**9**, methyl (*s*)-2-fluoro-β-daunosaminide] in 85% yield. Pertrifluoroacetylation of **9** should furnish the *N,O*-protected glycoside **10** which, on the basis of precedents recorded in the literature[1], should be convertible into a glycosyl halide for the purpose of eventual coupling with anthracyclinone aglycons. The acylation was per-

*An alternative pathway from a 3-sulfonate (**1** or **2**) to **5**, involving *O*-participation of the *N*-benzoyl group to form an intermediary oxazoline which, on nucleophilic opening at C-3, would generate the 2-benzamido-3-fluoro structure, can probably be discounted because the oxazoline in question, independently prepared, has been found to be very resistant toward nucleophilic attack even by azide ion in boiling *N,N*-dimethylformamide[8].


1 R = Ts
2 R = Ms
3
4
5
6
7
8
9 R¹ = NH₂, R² = H
10 R¹ = NHCOCF₃, R² = COCF₃
11 R¹ = NHCOCF₃, R² = H
12
13 R¹ = NH₂, R² = H
14 R¹ = NHCOCF₃, R² = COCF₃
15 R¹ = NHCOCF₃, R² = H

formed, but the crude *N,O*-di(trifluoroacetyl) derivative (**10**) was immediately *O*-deacetylated by methanolysis at room temperature[19], in order to produce the more-stable *N*-trifluoroacetyl compound **11** that can be stored conveniently, and re-esterified as and when required. The yield of crystalline **11** from **9** was 83%.

To obtain the D-*altro* isomer **15**, the key intermediate **6** was first reductively debrominated with tributyltin hydride (which does not affect the fluoro substituent)[20], to yield quantitatively the crystalline 2-fluoro-D-ristosamine derivative **12**. The latter underwent saponification with sodium hydroxide in aqueous 2-methoxyethanol, affording a quantitative yield of syrupy methyl 3-amino-2,3,6-trideoxy-2-fluoro-α-D-altropyranoside [**13**, methyl (*S*)-2-fluoro-α-D-ristosaminide], fully characterized by spectroscopy. It crystallized (62% recovery) on storage and, by the procedure described for the isomer **9**, was converted *via* **14** (characterized only by t.l.c.) into the crystalline target trifloroacetamide **15**, isolated pure in 60% yield.

The structures of all the new compounds described were ascertained by elemental microanalyses, mass-spectral and i.r. data, and n.m.r. spectroscopy; see Table I for the ^{1}H-n.m.r. data, and Table II for the ^{13}C-n.m.r. data. Although the structures could be deduced readily and unambiguously from the spectra by routine interpretation, a few details of the ^{1}H-n.m.r. data (Table I) will be discussed, especially because of some interesting observations that were made in regard to ^{19}F–^{1}H coupling interactions.

Thus, the α-D-*gluco* configuration of the minor product **5** (obtained besides the known[7] isomer **4**) was clearly indicated by the size of the ring-proton, ^{1}H–^{1}H coupling constants ($^3J_{1,2}$ 3.7, $^3J_{2,3}$, $^3J_{4,5}$ 9–10 Hz), and the position of the fluorine substituent at C-3 was confirmed by the ^{19}F–^{1}H couplings that were present in the H-3 signal ($^2J_{F\text{-}3,H\text{-}3}$ 53.6 Hz) and the vicinal-proton signals ($^3J_{F\text{-}3,H\text{-}2}$ and $^3J_{F\text{-}3,H\text{-}4}$ ~12 Hz, in harmony with *gauche* H–C–C–H arrangements). Additionally, **5** showed small, long-range couplings $^4J_{F\text{-}3,H\text{-}1}$ and $^5J_{F\text{-}3,H\text{-}6e}$ due to W and extended W orientations of the nuclei involved. By contrast, all of the α-D-*altro* compounds, namely **6, 12, 13,** and **15**, showed a very small (1.5 Hz) vicinal proton–proton coupling for H-1,2, small couplings for H-2,3 (3–3.5 Hz) as well as H-3,4 (4–4.5 Hz), and a large vicinal coupling for H-4,5 (9–10 Hz), indicative of the assigned configuration in the normal, $^4C_1$(D) conformation. (Compound **6**, of course, could *a priori* be assumed to have that configuration by virtue of its stereochemically unambiguous derivation from known **4**.) The 5-enoside **7** displayed $^3J_{H,H}$ values closely similar to those of the foregoing altrosides, as required for the α-D-*arabino* configuration depicted. The compounds **8, 9,** and **11**, on the other hand, exhibited $^3J_{H\text{-}1,2}$ 7.5, $^3J_{H\text{-}2,3}$ 10, $^3J_{H\text{-}3,4}$ 3.5, and $^3J_{H\text{-}4,5}$ 1 Hz, revealing clearly the β-L-*galacto* configuration in the normal, $^1C_4$(L) conformation. The position of the fluorine substituent on C-2 in either series was readily apparent from a splitting of each H-2 signal into two equal parts, each integrating to 0.5 proton, with $^2J_{F,H}$ values to be found in the narrow ranges of 45–46 Hz for the D-*altro* compounds (and **7**), and 51–53 Hz for the L-*galacto* compounds. Inspection of Table I also reveals a striking, groupwise corre-

TABLE I

^{1}H-N M R -SPECTRAL DATA AT 300 MHz

Compound[a]	*Chemical shifts (δ)*[b]									
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*NH*	*C-Me*	*O-Me*
5[c]	4.89~t	4.43cm	4.97dt	4.05dt	3.72dt	4.28ddd[d]	3.87t	8.79d		3.34
6	5.01dnd	4.70ddd	5.30tt	5.40ddd	4.25ddd	3.61dd	3.51dd	7 31d		3.65
7	5.03dnq	4.86ddd	5.24cm	5.98ddd		4.97t	4.83[e]	7.03d		3.62
8	~4.62m[e]	4.55ddd	4.80m	5.65ddd	4.05dq			6.32d	1.27d	3.66
9[f]	4.36dd	4.17ddd	3.02ddd	3.62dt	3.68dq				1.35d	3.56
11[g]	4.55dnd[e]	4 46ddd	4.30cm	3.81td	3.90dq			8.65b	1.26d	3.48
12	4.92dnt	4.67ddd	5.23cm	5.28ddd	4.16dq			7.33d	1.32d	3.58
13[h]	4.75dnt	4.57ddd	3.45m	3.26m	3.60dq				1.34d	3.40
15[i]	4.84dnt	4.60ddd	4.73qn	3.83m	3.76dq			7.56b	1.36d	3.52

	First-order coupling (Hz), $J_{H,H}$ values									*$J_{F,H}$ values*				
	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6(6')}$	$J_{5,Me}$	$J_{6,6'}$	$^3J_{H,NH}$	$J_{F,1}$	$J_{F,2}$	$J_{F,3}$	$J_{F,4}$	*Other*
5	3.7		9.8	9.4	9.0	4.8, 10.3		10.0	8.1	~3	12.1	53.6	12.4	0.7[j], 1.9[k]
6	1.5		3.5	4.0	10	2.4, 8.2		10.9	~9	8	45	~9	2	
7	2.0	~1.5	4	4 8		(1.5)[l]		1.5	10	8	46	8	3.3	
8	7.4		10.7	3.7	1.0		6.4		8	3.0[m]	52.9[m]	12.5	~2	
9	7.6		9.5	3	~1		6.5			3.3	51.0	13	3	
11	7.4		10.4	3.1	1.1		6.4			<0.5	50.7[m]	13.5	3.1	
12	1.5	~1.5	3.2	4	9.8		6.3		9	8	45.3	8–9[n]	2	
13	1.6	~1.5	3.2	[o]	10		6.2			10.2	45.5	[o]		
15	1.5	~1.5	3.5	4 5	9		6.6			7.8	45.0	9		

[a]In chloroform-*d* unless indicated otherwise. All aryl-substituted compounds showed the appropriate signals in the δ 7.3–8.0 region; the *Ph*-CH singlet of **5** was at δ 5.74. [b]Signal characteristics: b, broad; cm, complex multiplet; d, doublet; m, multiplet; n, narrow; q, quartet; qn, quintet; t, triplet. [c]In dimethyl sulfoxide-d_6. [d]H-6eq. [e]Signal overlapped by downfield part (dd) of the H-2 signal (ddd). [f]Singlets due to OH and NH_2 occurred at δ 2.17 and 2.29 [g]In acetone-d_6. [h]Broad signals at δ 1.9–2.3 due to OH and NH_2. [i]Broad singlet at δ 2.16 (OH). [j]$^4J_{F\text{-}3,H\text{-}5}$ value. [k]$^5J_{F\text{-}3,H\text{-}6}$ value. [l]Refers to allylic coupling $J_{4,6}$. [m]Measured splitting, not necessarily the true *J* value because of second-order effects. [n]Approximated from the pattern of the complex, H-3 multiplet. [o]Not determined because of ill-resolved signal.

TABLE II

^{13}C-N M R SPECTRAL DATA

Compound[a]	*Chemical shifts*[b] (*^{13}C-^{19}F couplings, Hz, in parentheses*)						
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*OMe*
6[c]	98.5 (30.7)	86.6 (179.8)	47.0 (28.3)	67.7	67.0	31.9	56.2
7[d]	100.1 (31.5)	86.9 (180.1)	48.5 (27.3)	66.7	149.8	99.5	56.4
8[c]	102.3 (21.5)	88.9 (187.5)	52.7 (17.5)	73.2 (7.8)	70.9	16.4	57.2
9[c]	101.6 (23.0)	92.7 (180.4)	55.6 (18.1)	72.2 (8.3)	71.9	16.3	56.7
11[d,e]	102.6 (22.4)	89.1 (184.0)	55.5 (16.1)	71.2 (7.8)	72.1	16.4	56.4
12[c]	98.4 (30.8)	86.9 (179.2)	46.9 (18.1)	70.1 (8.3)	62.7	17.5	56.0
13[d]	98.5 (32.0)	89.1 (~176)	50.6 (24.0)	67.8	64.5	17.6	55.4
15[d]	97.7 (30.2)	86.1 (178.0)	49.9 (28.1)	68.7	64.4	17.4	55.8

[a]In chloroform-d_6, unless indicated otherwise. [b]With reference to the tetramethylsilane signal (p.p.m.). [c]At 75.43 MHz. [d]At 20.00 MHz. [e]In acetone-d_6.

spondence of vicinal F-2,H-1 couplings, which amounted to 8–10 Hz in the α-D-*altro* series (and in **7**), but to only ~0–3 Hz in the β-L-*galacto* series, even though the angular relation of the coupled nuclei is similar *(gauche)* in both series. For the nuclei F-2,H-3 (*gauche* likewise), the values observed were 8–9 Hz for altrosides*, and ~13 Hz for the galactosides.

The regularities in the ^{19}F–^{1}H coupling interactions just mentioned deserve comment. Phillips and Wray[21] have evaluated a large body of such data, pertaining to fluorinated carbohydrates[22], as have the groups of Hall and Foster (partly in joint research)[23]. In these studies, empirical rules were advanced for some dependencies of coupling constants on molecular geometry and on the nature of substituents present. Thus, geminal ^{19}F–^{1}H coupling in fluoropyranose systems varies in a consistent manner within a range of ~5 Hz, depending on the electronegativity of vicinal substituents (with oxygen and halogen substituents only having been considered), and it varies similarly, and again consistently, with the spatial orientation of those substituents. Individual contributions of such substituent effects behave additively, and have been tabulated, so that $^{2}J_{F,H}$ can be calculated for any given fluoropyranose structure, by adding (positive or negative) increments to a basic value of 50 Hz, derived from measurements in unperturbed model-systems[21b]. If

*Our data (Table I) agreed completely with the geminal and vicinal $J_{F,H}$ values (44–46 and 8–9 Hz, respectively) reported (ref. 7) for the α-D-*altro* compound **4** and the 4,6-dibenzoate and -diacetate prepared from it following debenzylidenation.

one uses this procedure[21b] for the present series of aminofluoro sugars, tentatively allowing the parameters proposed for oxygen substituents to apply, unchanged, to the various nitrogen substituents (*i.e.*, without initially attempting to differentiate any effects of electronegativity), then one obtains $^2J_{F,H}$ values of 47 Hz for the α-D-*altro* compounds, 50 Hz, for the β-L-*galacto* compounds, and 52 Hz for the α-D-*gluco* compound **5**. It is satisfying to note that the trend in these empirically calculated figures accords well with the trend actually observed (45.0 ±1, 51.8 ±1.1, and 53.6); evidently, the approximations made in using parameters originally elaborated for oxygen rather than nitrogen substituents caused no deviations larger than those to be expected (1–2 Hz)[21b] from this method in any event. In fact, the use of modified increments reflecting the lower electronegativity of nitrogen, which might seem appropriate, would lead to a convergence of the calculated values toward the base value of 50 Hz, and thus to an *increased* discrepancy with the experimental data. Moreover, it is noteworthy that each pair of configurationally identical amino- and trifluoroacetamido-glycosides (**9/11** and **13/15**) showed no significant difference in $^2J_{F,H}$. The observations tend to suggest that an additional factor operates in amino-nitrogen substituents, compensating for differential electronegativities.

Let us now turn to the vicinal ^{19}F–^1H interactions, where the situation appears to be more complex. Similar calculation procedures have been proposed[21a], permitting the prediction of variations, in *gauche* couplings, from the unperturbed value (16.0 Hz) observed in fluoroethane. The standard deviations from experimental data for a large variety of fluorinated pyranoses was less than 1 Hz, independently of the nature of oxygen substituent (OH, OMe, OBz, or OAc)[21a]. Three additively contributory factors were used (numerical increments in parentheses): *a*, the number of substituent oxygen atoms on the carbon atoms of the coupling fragment (−2.5 Hz each); *b*, the presence of an oxygen atom antiperiplanar to the fluorine atom *via* the coupling pathway (−7 Hz); and *c*, the presence of an oxygen group vicinal and antiperiplanar to the C–C bond of the coupling pathway (−2 Hz when the coupled nucleus, either F or H, that is situated on the central carbon atom of the system is equatorial, or +2 Hz when it is axial). So calculated, $^3J_{F\text{-}2,H\text{-}1}$ = 2 Hz is predicted for 2-deoxy-2-fluoro-β-L-galactopyranose-$^1C_4$. The values found for the 3-aminated derivatives **8, 9,** and **11** were quite close (<0.5–3.3 Hz), indicating that factor *c*, which is the only one having experienced structural changes, is not particularly sensitive to replacing the oxygen by an amino or acylamino group. By contrast, the $^3J_{F\text{-}2,H\text{-}1}$ values of 8–10 Hz found for the 3-aminated altrosides **6, 12, 13,** and **15** (and also for the related enoside **7**) differed substantially from the value of 4 Hz calculated for 2-deoxy-2-fluoro-α-D-altropyranose-$^4C_1$. In this case, factor *c* does not enter into the computation, as the (axial) 3-substituent is not antiperiplanar with the C-1,2 bond. Evidently, an axial amino or acylamino group, *trans*-vicinal to an axial fluorine atom but situated *outside* the coupling pathway (as opposed to the situation in factor *b*, above), makes an appreciable, *positive* contribution (4–6 Hz) to the amount of *gauche* F,H coupling.

For $^3J_{F\text{-}2,H\text{-}3}$ in 2-deoxy-2-fluoro-β-L-galactopyranose-$^1C_4$ the calculated value is 11.5 Hz, and the analogs **8, 9,** and **11** showed 12.5–13.5 Hz, indicating that the factor *a* also is not very sensitive to exchanging oxygen for nitrogen as an (equatorial) substituent atom. The marginal, if at all significant, effect of this exchange appears to parallel that observed for factor *c*, and in both cases the power to decrease vicinal coupling was, in nitrogen, nearly the same as, or at most slightly smaller than, that in oxygen (In terms of factor *c*, the $NHCOCF_3$ group appeared slightly more effective; see the exceptionally small F-2,H-2 coupling in **11**.) Convincing support for this general notion was provided by the two vicinal F,H couplings present in the 2-benzamido-3-fluoroglucoside **5**, which possesses for either coupling pathway the structural features defining factors *a* and *c*: for the F-3,H-2 interaction, *a* is due to the 2-benzamido group and *c*, to the O-4 atom; and for the F-3,H-4 interaction, these same features apply in reverse order. The calculated $J_{F,H}$ values (implying OH instead of NHBz) are identical (11.5 Hz), and the values found were 12.1 and 12.4. However, as far as factor *a* is concerned, the foregoing congruity holds only for *equatorial* nitrogen substituents on the coupling fragment. Thus, the altrosides **6, 12,** and **15**, as well as those referred to in a preceding footnote, and also the enoside **7** (all of which possess an *axial* nitrogen substituent, constituting factor *a* for the F-2,H-3 coupling) displayed $J_{F\text{-}2,H\text{-}3}$ 8–10 Hz, whereas the value calculated for 2-deoxy-2-fluoro-α-D-altropyranose is 4.5 Hz. In the latter molecule, the OH-3 group, simultaneously embodying factors *a* and *b*, contributes −9.5 Hz to the calculation, and it is seen that a nitrogen substituent in the same place is only about half as active in diminishing the vicinal coupling, with a contribution of −4 to −6 Hz. In summary, then, the foregoing comparison of substituent effects on ^{19}F–^1H coupling in fluoropyranosides indicates that the effects of oxygen and (amino) nitrogen substituents may be near-equivalent in some cases, but markedly different in others, depending upon the substitution pattern. Good correlations in $J_{F,H}$ values among structurally comparable sets of aminofluoroglycosides were noted.

After this work had been completed, a new approach to L-daunosamine was described[16], similar in concept to the present synthesis of **8**; it employed the known reaction[8] of **1** to give the 2-chloro analog of **4**, with the chlorine atom to be removed reductively at a subsequent stage. Several further, 2,3-vicinal aminofluoroglycosides were recently synthesized[24] by fluorination of 2,3-(*N,N*-diallylaziridinium)pento- and hexo-pyranosides, followed by *N*-deallylation.

EXPERIMENTAL

General methods. — The following solvent combination (v/v) were employed for chromatography: *A*, 3:7 ethyl acetate–cyclohexane; *B*, the same solvents, but 1:4; *C* the same, but 1:9; *D*, ethyl acetate–hexane, 3:2; *E*, the same solvents, but 3:7; *F* the same, but 1:4; *G*, 1:4 ether–benzene; *H*, the same, but 1:9; *I*, 3:2 acetone–benzene; and *J*, the same, but 1:9. In t.l.c., spots were made visible by

spraying the plates with 5% sulfuric acid in ethanol, and heating them briefly on a hot-plate. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at ~25°, and refer to chloroform solutions unless indicated otherwise.

Methyl 3-benzamido-4,6-O-benzylidene-2,3-dideoxy-2-fluoro-α-D-altropyranoside (**4**) *and methyl 2-benzamido-4,6-O-benzylidene-2,3-dideoxy-3-fluoro-α-D-glucopyranoside* (**5**). — Methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(methylsulfonyl)-α-D-glucopyranoside (**2**) was prepared as described[25]; m.p. 196°, $[\alpha]_D$ +76.8°; lit.[25] m.p. 195–195.5°, $[\alpha]_D$ +77.5°. In the operations that follow, scrupulous exclusion of moisture was mandatory; oven-dried apparatus and a dry nitrogen atmosphere were provided for the reaction, and solutions were transferred by syringe in a drybox. Tetrabutylammonium fluoride trihydrate (31.5 g, 0.1 mol) was dehydrated by heating it for 3 days at 55°, in an oil-pump vacuum over a large quantity of phosphorus pentaoxide, and then dissolved in acetonitrile (36 mL, previously distilled from P_2O_5), and the solution stored over 4Å molecular sieve. One-third of the volume of this reagent (containing 0.033 mol of the anhydrous fluoride) was used for the reaction with **2** (2.0 g, 4.32 mmol). The crystalline sugar was mixed with part of the reagent (~11 mmol), the mixture was stirred and gently heated (oil bath, 80°), the remainder of the reagent (22 mmol) was added dropwise in the course of 5 h, and heating was then continued for 18–20 h. Monitoring by t.l.c. (solvent *A*) indicated rapid consumption of **2** and gradual formation of two, slightly faster-moving products, together with slow-moving by-products. The faster-moving spot that appeared first was judged to be due to the *N*-benzoylepimine **3** (by comparison with an authentic sample[26]), and the second spot, which appeared more slowly (and migrated faster than the first), was due to the fluoroaltroside **4**. The spot corresponding to **3** gradually decreased in intensity but did not disappear completely because, as was subsequently ascertained, the minor reaction product **5** has almost the same R_F value in the system employed. The slow-moving material seen additionally consisted of at least two by-products, as was revealed by t.l.c. with solvent *D* (which did not differentiate **3**, **4**, and **5**).

The mixture was poured into ice–water, and the precipitate was collected, washed with water, dissolved in ethyl acetate, and combined with an ethyl acetate extract of the aqueous filtrate. The organic solution was washed with water, dried ($MgSO_4$), concentrated, and chromatographed on a dry-packed column of silica gel (80 g, 60–200 mesh) with solvent *C* followed by solvent *B* as eluants, to give **4** (1.05 g, 63%) as an amorphous, and **5** (100 mg, 6%) as a crystalline solid.

The 2-fluoroaltroside **4** showed $[\alpha]_D$ +107.5° (*c* 1.2), and its ^{1}H-n.m.r. data agreed with those reported[7].

The 3-fluoroglucoside **5** showed, after recrystallization from ethyl acetate–hexane, m.p. 274–275°, $[\alpha]_D$ +77° (*c* 0.1); mass spectrum (c.i., ether): *m/z* 388; see Table I for the ^{1}H-n.m.r. data.

Anal. Calc. for $C_{21}H_{22}FNO_5$ (387.4): C, 65.10; H, 5.72; N, 3.62. Found: C, 64.92; H, 5.80; N, 3.46.

Methyl 3-benzamido-4-O-benzoyl-6-bromo-2,3,6-trideoxy-2-fluoro-α-D-altro-

pyranoside (**6**). — To a solution of **4** (1.14 g, 2.9 mmol) in dry carbon tetrachloride (40 mL, previously passed through a layer of neutral aluminum oxide) was added *N*-bromosuccinimide (540 mg, 3 mmol) and barium carbonate (0.3 g). The mixture was boiled under reflux for 3 h and then filtered, and the filter residue was washed several times with hot carbon tetrachloride. The combined filtrate was evaporated, and the resulting solid dissolved in ether. Washing with water, drying ($MgSO_4$), and evaporation of the solution led to a foam that crystallized from ether–hexane to give **6** (1.123 g, 82.4%), m.p. 112–114°, $[\alpha]_D$ +101° (*c* 1.3); mass spectrum (c.i., ether), *m/z* 466 and 468.

Anal. Calc. for $C_{21}H_{21}BrFNO_5$ (466.3): C, 54.09; H, 4.54; N, 3.00. Found: C, 54.03; H, 4.67; N, 2.90.

*Methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-2-fluoro-α-*D-arabino-*hex-5-enopyranoside* (**7**). — A solution of **6** (322 mg, 0.69 mmol) in dry pyridine (5 mL) containing a few crystals of 4-(dimethylamino)pyridine was stirred with silver fluoride (160 mg, 1.26 mmol) for 6 h at room temperature, in the dark. Several solvent systems that were tried failed to separate **6** and the product **7** satisfactorily in t.l.c.; with solvent *E*, the R_F values were quite similar, but the spots had distinguishable colors (violet and brownish, respectively). The mixture was diluted with ether (30 mL) and filtered, and the filter residue was washed exhaustively with ether. Evaporation of the filtrate gave a syrup from which several portions of added toluene were evaporated. A solution of the syrup in ether was then passed through a short column of silica gel, and evaporated, to give **7** that crystallized from hexane–ether; yield, 253 mg (93%); m.p. 120–122°; $[\alpha]_D$ +131.5° (*c* 0.45); mass spectrum (e.i.): *m/z* 385.

Anal. Calc. for $C_{21}H_{20}FNO_5$ (385.4): C, 65.45; H, 5.23; F, 4.93; N, 3.63. Found: C, 65.37; H, 5.11; F, 4.78; N, 3.47.

*Methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-2-fluoro-β-*L-galactopyranoside* (**8**). — Brown palladium oxyhydrate on barium sulfate (Kuhn catalyst[27], 0.66 g) suspended in methanol (15 mL) was prehydrogenated, compound **7** (544 mg) in methanol (15 mL) was then added, and hydrogenation was performed at ordinary temperature and pressure for 2 h. The conversion of **7** into more slowly migrating **8** (major product) and its 5-epimer **12** (minor product) was monitored by t.l.c. (solvent *H*). Filtration, exhaustive washing of the catalyst with methanol, and evaporation of the filtrate gave a material that was chromatographed on a dry-packed column of silica gel (25 g, 60–200 mesh), by use of solvent *H* (30 mL) followed by solvent *G*. Early fractions contained mixtures of **12, 8,** and traces of **7**. Later fractions yielded pure **8** which crystallized on trituration with ether and hexane as white needles (338 mg, 62%), m.p. 194–196°, $[\alpha]_D$ −154.4° (*c* 0.8); mass spectrum (c.i., ether): *m/z* 388.

Anal. Calc. for $C_{21}H_{22}FNO_5$ (387.4): C, 65.10; H, 5.72; N, 3.61. Found: C, 64.97; H, 5.71; N, 3.63.

*Methyl 3-amino-2,3,6-trideoxy-2-fluoro-β-*L-*galactopyranoside* (**9**). — Compound **8** (426 mg) was saponified by boiling it under reflux in a solution of sodium

hydroxide (1 g) in 3:1 (v/v) 2-methoxyethanol–water (25 mL) for 18 h, followed by further boiling (3 h) with additional sodium hydroxide (0.2 g) in 2:3 (v/v) 2-methoxyethanol–water (10 mL). Formation of a single, slow-moving, ninhydrin-positive product was indicated by t.l.c. (solvent *I*). The cooled mixture was diluted with water, extracted with chloroform (5 ×), concentrated to a conveniently small volume, and subjected to an overnight, continuous extraction with chloroform. The combined extracts were dried ($MgSO_4$), and evaporated, to give crystalline material. Recrystallization from ethyl acetate–ether–hexane furnished pure **9** (168 mg, 85.3%), m.p. 177–178°, $[\alpha]_D$ +9.4° (*c* 1.2); mass spectrum (c.i., ether): *m/z* 180.

Anal. Calc. for $C_7H_{14}FNO_3$ (179.2): C, 46.92; H, 7.88; N, 7.82. Found: C, 46.85; H, 7.70; N, 7.60.

*Methyl 2,3,6-trideoxy-2-fluoro-3-trifluoroacetamido-β-*L*-galactopyranoside* (**11**). — A chilled solution of **9** (44 mg) and trifluoroacetic anhydride (0.6 mL) in anhydrous ether (1.8 mL) was stirred for 3 h at 0°. T.l.c. with solvent *I* then revealed a single, fast-moving product (the *N,O*-diacyl derivative **10**). The solvent was evaporated, with repeated additions of fresh ether, and the residue was dissolved in methanol (2.5 mL) and allowed to stand for 16 h at room temperature. Complete conversion of **10** (R_F 0.5) into **11** (R_F 0.15) was indicated by t.l.c. (solvent *F*). Following evaporation of the methanol, the product was crystallized from ethyl acetate–hexane; yield, 56 mg (83%), m.p. 238–240° with sublimation, $[\alpha]_D$ −67.7° (*c* 0.3, methanol); mass spectrum (c.i., ether): *m/z* 276.

Anal. Calc. for $C_9H_{13}F_4NO_4$ (275.2): C, 39.28; H, 4.76; N, 5.09. Found: C, 39.42; H, 5.00; N, 4.99.

*Methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-2-fluoro-α-*D*-altropyranoside* (**12**). — The 6-bromoglycoside **6** (569 mg, 1.22 mmol), tributyltin hydride (0.80 mL, 3 mmol), and azobis(isobutyronitrile) (26 mg) were heated, under nitrogen, in dry benzene (10 mL, distilled over sodium) at the reflux temperature for 6.5 h. The conversion of **6** into slightly slower-moving **12** was monitored by t.l.c. (solvent *G*). A faster-moving spot was due to non-carbohydrate material. After cooling, a small amount of silica gel was added to the mixture, and the solvent was evaporated. The impregnated gel was placed onto a dry-packed column (20 g of SiO_2), which was eluted with solvent *F*. The fractions containing only **12** gave the product in almost quantitative yield (466 mg, 98.5%), crystallized from ether–hexane; m.p. 119–120°, $[\alpha]_D$ +159.4° (*c* 0.5); mass spectrum (c.i., ether): *m/z* 388.

Anal. Calc. for $C_{21}H_{22}FNO_5$ (387.4): C, 65.10; H, 5.72; N, 3.61. Found: C, 65.27; H, 5.81; N, 3.53.

*Methyl 3-amino-2,3,6-trideoxy-2-fluoro-α-*D*-altropyranoside* (**13**). — Compound **12** (470 mg) was saponified by boiling it for 29 h in a solution of sodium hydroxide (1.4 g) in 2-methoxyethanol (26 mL) and water (9 mL). T.l.c. with solvent *J* revealed the complete conversion of **12** into a single, slow-moving, ninhydrin-positive product. The cooled mixture was diluted with some water and extracted with chloroform (6 times). The dried extract was concentrated to give a yellow syrup which was passed through a bed of silica gel with chloroform followed

by ethanol. Evaporation of the effluent gave **13** (216 mg, 99%), still syrupy and not entirely pure but securely characterized by its ^{1}H- and ^{13}C-n.m.r. spectra. On storage in a refrigerator, slow crystallization occurred, and recrystallization from ether–hexane then gave 131 mg (62%) of **13** showing m.p. 79–81° and $[\alpha]_D$ +146° (*c* 0.2).

Anal. Calc. for $C_7H_{14}FNO_3$ (179.2): C, 46.92; H, 7.87; N, 7.82. Found: C, 47.06; H, 7.75; N, 7.91.

*Methyl 2,3,6-trideoxy-2-fluoro-3-trifluoroacetamido-α-*D*-altropyranoside* (**15**). — The trifluoroacetylation of **13** (94 mg) to give the *N,O*-diacyl derivative **14** (R_F 0.48, solvent *F*; characterized by t.l.c. only), and the subsequent methanolysis to give **15** (R_F 0.25), were performed in full analogy to the operations described for **11**, except that the reaction times were 9 and 12 h, respectively. The product was purified by passage through a small column of silica gel by means of solvent *F*, and it crystallized on storage at 0°. Recrystallization from ether–hexane gave **15** (87 mg, 60%), m.p. 95–96.5°, $[\alpha]_D$ +28.4° (*c* 0.32); mass spectrum (c.i., ether): *m/z* 276.

Anal. Calc. for $C_9H_{13}F_4NO_4$ (275.2): C, 39.28; H, 4.76; N, 5.09. Found: C, 39.55; H, 4.83; N, 5.10.

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