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THE SYNTHESIS AND HYDROLYSIS OF A SERIES OF DEOXY- AND DEOXYFLUORO-α-D-"GLUCOPYRANOSYL" PHOSPHATES

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ABSTRACT

The syntheses of three deoxy-α-D-"glucopyranosyl" phosphates and a series of dideoxymonofluoro- and dideoxydifluoro-α-D-glucopyranosyl phosphates are described. Rate constants for their acid-catalyzed hydrolysis were determined. Deoxygenation in the sugar ring was shown to increase the hydrolysis rate to the extent seen previously for acid-catalyzed hydrolysis of a series of phenyl deoxy-D-"glucopyranosides" [Mega and Matsushima, *J. Biochem. Tokyo*, 94 (1983) 1637]. This demonstrates that the transition states for these two reactions are essentially identical. By determining the rates of hydrolysis of a series of deoxy- and deoxyfluoro-substituted 6-deoxy-6-fluoro-α-D-glucopyranosyl phosphates, substituent effects on the sugar ring were demonstrated to be predictably additive and primarily electronic in nature, with no evidence of contributions from steric effects.

INTRODUCTION

A number of studies of acid-catalyzed hydrolysis of methyl and phenyl glycosides had previously been performed[1–3] and on the basis of such studies the following mechanism has been proposed. The first step is protonation of the glycosidic oxygen atom, followed by rate-determining heterolysis of the glycosidic bond, generating a glycosyloxonium ion intermediate that is rapidly trapped (hydrolyzed) by water. As evidence for such a mechanism, it has been shown[1,4,5] that deoxygenated glycosides are hydrolyzed more rapidly than is the parent compound. This is the expected consequence of the decreased inductive destabilization of the oxonium ion-like transition states, as a result of the replacement of electronegative hydroxyl groups by hydrogen atoms.

The acid-catalyzed hydrolysis of α-D-glucopyranosyl phosphate was, by a series of elegant studies[6,7] shown to proceed *via* a similar mechanism involving an oxonium ion intermediate, or at least a transition state having substantial oxonium-ion character. More recent studies[8] concerned the effects, on this reaction, of structural changes in the sugar, and the results obtained were quite consistent with those for the acid-catalyzed hydrolysis of equivalent methyl and aryl glycopyranosides[1,9]. Other recent work[10] examined the effects, on the rates of acid-

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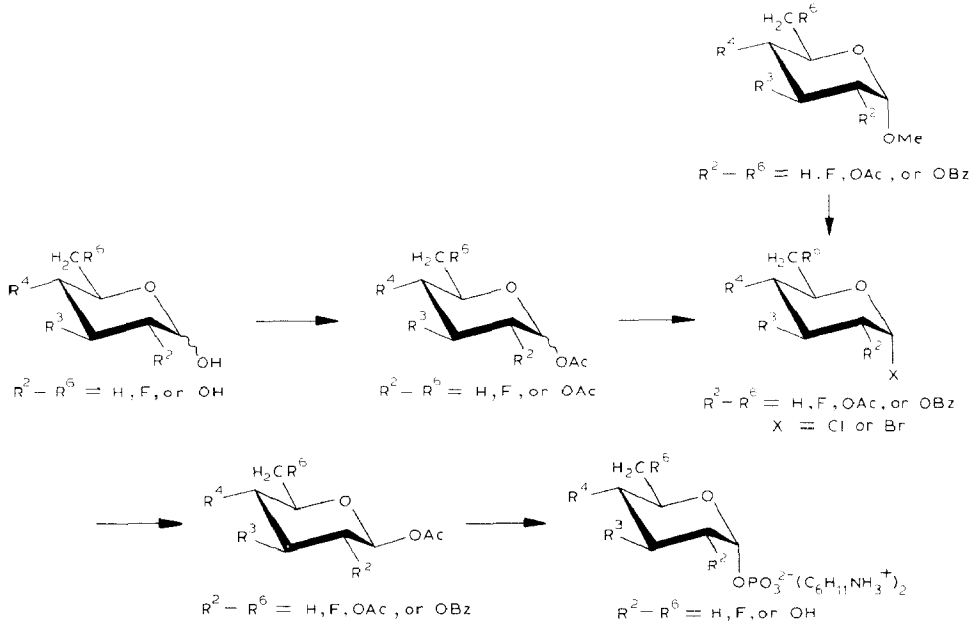
catalyzed hydrolysis, of the substitution of fluorine atoms for hydroxyl groups on the sugar ring. This substitution is of interest because it introduces minimal steric effects (as a fluorine atom is slightly smaller than a hydroxyl group) and maximal electronic effects, and indeed it led to considerable rate diminutions in all cases studied. No results have, however, been published on the effects of deoxygenation of the sugar ring on the rate of acid-catalyzed hydrolysis of glycopyranosyl phosphates. Nor has there been direct, experimental proof of the similarities of the structures of the transition states for the acid-catalyzed hydrolysis of glycosides and of glycopyranosyl phosphates. The present investigation, which stemmed from our interest in the use of deoxy and deoxyfluoro sugars to probe enzyme mechanisms, addresses these questions. The consequences of replacement of two hydroxyl groups on the sugar ring are also described.

RESULTS

Deoxygenation reactions were generally accomplished by the reduction, with tributyltin hydride, of the corresponding protected chlorodeoxy sugar, which in turn had been prepared by chlorination with sulfuryl chloride of the corresponding partially protected sugar. Fluorinations were generally performed by treating the appropriate partially protected sugar with diethylaminosulfur trifluoride (DAST). Doubly modified sugars were prepared by substitution of the 6-hydroxyl group of the appropriate partially protected deoxy- or deoxyfluoro-D-glucose derivatives with fluorine. The products were then converted into their β-per-*O*-acetyl



Scheme 1.

derivatives, generally by deprotection and acetylation, conversion into the α-glycosyl halide, and, finally, conversion of this into the β-acetate using mercuric acetate, as shown in Scheme 1. Alternatively, in several cases, the methyl glycoside was, by using dichloromethyl methyl ether[11], converted directly into the α-chloride, and thence into the β-acetate. The β-acetates were then phosphorylated by the MacDonald procedure[12]. Where possible, the phosphates were crystallized and recrystallized as their bis(cyclohexylammonium) salts. Successful synthesis was evidenced by satisfactory microanalyses and by the ^{1}H- and ^{19}F-n.m.r. data, presented in Tables I and II. In all cases, the magnitude of the H-1–H-2 coupling constant is from 3.5 to 4.0 Hz, indicating an equatorial proton at C-1, and thus the α-anomeric configuration of the sugar phosphate. The magnitude of most other, ring-associated, ^{1}H–^{1}H coupling constants (8.0 to 10.0 Hz) indicated a *trans*-diaxial arrangement of these protons, and thus a reasonably undistorted $^4C_1$(D) conformation.

First-order rate-constants for the hydrolysis, catalyzed by M $HClO_4$, of the modified glycopyranosyl phosphates are presented in Table III. Most of the rates were measured at 25°, but, for some slow-reacting phosphates, measurements were made at a series of higher temperatures, and values for 25° were then determined by extrapolation. The cyclohexylammonium counter-ion had previously been shown[10] to have no significant effect on hydrolysis rates under the conditions employed.

TABLE I

^{1}H AND ^{19}F-N.M.R. CHEMICAL SHIFTS FOR SUBSTITUTED α-D-GLUCOPYRANOSYL PHOSPHATES

Compound[a]	*Values of δ*								
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*F-6*	*F-X*
3-Deoxy	5.32	[b]	[b]	[b]	[b]	[b]	[b]		
4-Deoxy	5.48	3.38	3.85	[b]	4.18	3.59	3.59		
6-Deoxy	5.38	3.45	3.95	3.70	3.11	1.23	1.23		
2,6-Difluoro	5.60	4.35	[b]	3.55	[b]	4.74	4.68	235.88	200.96
3,6-Difluoro	5.45	[b]	[b]	[b]	4.00	[b]	[b]	235.18	202.05
4,6-Difluoro	5.44	3.52	4.02	4.42	4.16	4.63	4.63	236.07	200.19
3-Deoxy-6-fluoro	5.39	[b]	1.90[c] 2.18[d]	[b]	3.89	4.70	4.64	235.62	
4-Deoxy-6-fluoro	5.51	3.41	4.03	1.58[c] 2.02[d]	4.27	4.62	4.48	230.32	

[a]Compounds are named according to the hydroxyl group replaced in the parent compound; thus, 2,6-Difluoro means 2,6-dideoxy-2,6-difluoro. [b]Unassigned due to overlap. [c]Axial proton. [d]Equatorial proton.

TABLE II

^{1}H-N.M.R. COUPLING CONSTANTS FOR SUBSTITUTED α-D-GLUCOPYRANOSYL PHOSPHATES

Compound[a]	*Coupling constants (Hz)*												
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$^3J_{P,H-1}$	$^4J_{P,H-2}$	J_{gem}[b]	$^2J_{F,H}$	$^3J_{F,H}$	$J_{F,H}$
3-Deoxy	4.0	[c]	[c]	[c]	[c]	[c]	[c]	7.0	[c]	[c]			
4-Deoxy	3.3	9.1	9.2[d] 5.0[e]	[c]	3.0	6.5	12.1	7.2	1.5	12.9			
6-Deoxy	3.5	7.0	9.0	9.0	5.5	5.5		7.0	2.0				
2,6-Difluoro	3.6	9.0	9.5	9.5	2.9	1.5	10.0	7.8	2.2		48.0[f] 50.0[g]	[c] [c]	
3,6-Difluoro	3.5	[c]	[c]	10.8	[c]	[c]	[c]	7.2	2.0		48.7[f] 53.8[g]	30.6[f] [c]	3.5[h]
4,6-Difluoro	3.3	10.0	9.0	9.0	[c]	[c]	[c]	7.3	2.0		48.0[f] 51.0[g]	29.0[f] 16.0[g]	3.3[i]
3-Deoxy-6-fluoro	3.0	12.0 4.8	12.0 4.8	10.0	3.0	1.5	10.0	7.1	2.2	12.0	48.0	30.7	
4-Deoxy-6-fluoro	3.4	9.9	12.0 5.0	12.0 2.5	4.0	1.5	10.0	7.2	2.2	12.0	48.0	26.0	

[a]See footnote *a*, Table I. [b]Geminal coupling at the deoxy center. [c]Undetermined, due to signal overlap. [d]Coupling with axial proton at deoxy center. [e]Coupling with equatorial proton at deoxy center. [f]Coupling with F-6. [g]Coupling with ring fluorine atom. [h] $^4J_{F\text{-}3,H\text{-}1}$. [i] $^5J_{F\text{-}4,H\text{-}1}$.

TABLE III

OBSERVED FIRST-ORDER RATE-CONSTANTS FOR ACID-CATALYZED HYDROLYSIS OF SUBSTITUTED α-D-GLUCOPYRANOSYL PHOSPHATES[a]

Compound[b]	*Hydrolysis temperature (°C)*	$10^5 \times k_{obs}$ (k *in* s^{-1})
Not substituted	25	4.1
2-Deoxy[c]	0	700
	4	1020
	9	1950
	25	11,100[d]
3-Deoxy	25	31
4-Deoxy	25	111
6-Deoxy	25	21
2,6-Difluoro	64.5	2.8
	45	0.19
	25	0.0075[d]
3,6-Difluoro	81	93.7
	76	66.7
	64.5	19.4
	45	1.4
	25	0.080[d]
4,6-Difluoro	64.5	13.1
	45	0.79
	25	0.032
3-Deoxy-6-fluoro	25	6.1
4-Deoxy-6-fluoro	25	26

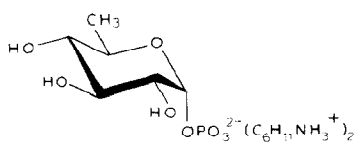
[a]Hydrolysis was performed in M $HClO_4$. Aliquots were removed at intervals, and assayed for release of phosphate. [b]For naming of compounds, see footnote *a*, Table I. [c]Assayed by a coupled enzyme method[14]. [d]These values were *not* measured, but were calculated from extrapolation of the rate constants obtained at other temperatures.

DISCUSSION

The synthesis of the deoxy-α-D-glucopyranosyl* phosphates proceeded readily, except in the case of the 2-deoxy compound. Despite a literature report to the contrary[13], all attempts to condense phosphoric acid and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranose gave mixtures (^{31}P-n.m.r.) that could not be resolved because of the extreme lability of the product. The desired product was eventually obtained by a three-step enzymic procedure, performed under neutral, buffered conditions as described elsewhere[14]. The 1-phosphoric esters of 6-deoxy-α-D-glucose [bis(cyclohexylammonium) salt, (**1**)] and 4-deoxy-α-D-*xylo*-hexose ("4-deoxy-α-D-glucose") were obtained by MacDonald phosphorylation of their β-per-*O*-acetate derivatives. The β-per-*O*-acetate of 6-deoxy-D-glucose was obtained

*Modified sugars are referred to throughout as modified D-glucose derivatives for ease of comparison, although this may lead to names that do not accord with the Rules.

by literature methods[15], and that of 4-deoxy-D-glucose by conversion of methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-α-D-*xylo*-hexopyranoside[16] (**2**) into the α-D-glycosyl chloride (**3**) by using 1,1-dichloromethyl methyl ether, and displacement of the chloride with use of mercuric acetate.



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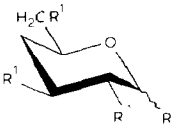
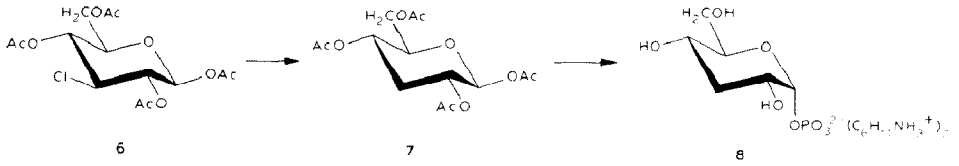


2 R = α-OMe, R' = OBz
3 R = α-Cl, R' = OBz
4 R = β-OAc, R' = OBz
5 R = α-$OPO_3^{2-}(C_6H_{11}NH_3^+)_2$, R' = OH

In the case of 3-deoxy-D-*ribo*-hexose ("3-deoxy-D-glucose"), unsatisfactory yields of the 1,2,4,6-tetraacetate were obtained by direct acetylation, because of the propensity of the free sugar to assume furanose forms in solution. Therefore, it was necessary first to convert the precursor 3-chloro-3-deoxy-D-glucose (which exists preferentially in the pyranose form) into its β-per-*O*-acetyl derivative (**6**), and then carry out the reduction to 1,2,4,6-tetra-*O*-acetyl-3-deoxy-β-D-"gluco-pyranose" (**7**) (see Scheme 2).

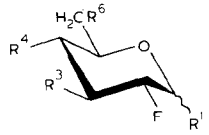


6 7 8

Scheme 2.

Syntheses of the doubly modified sugar phosphates were achieved by first preparing the partially protected deoxyfluoro or deoxy sugar having a free 6-hydroxyl group, replacing this with fluorine by using DAST, converting the product into its β-per-*O*-acetyl derivative, and phosphorylating this according to Mac-Donald[12]. Attempts to introduce fluorine directly at C-6 of unprotected deoxy- or deoxyfluoro-glycosides by using DAST as described[17] were generally unsuccessful. The major exception was 2,6-dideoxy-2,6-difluoro-D-glucose (**11**), which was prepared by treatment of trifluoromethyl 2-deoxy-2-fluoro-α-D-glucopyranoside[18] (**9**) with DAST, followed by acid-catalyzed hydrolysis of the trifluoromethyl glycoside.

The synthesis of 3,6-dideoxy-3,6-difluoro-α-D-glucose ("3,6-difluoro-D-glucose", **26**) was more complex. Controlled hydrolysis of the 5,6-*O*-isopropylidene group of 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[10] (**14**) gave good yields of the 1,2-*O*-isopropylidene derivative **16**, but direct fluoro-dehydroxylation of C-6 of this compound with DAST gave none of the desired product, but, instead, a pair of compounds each containing one fluorine atom, sub-



	R^1	R^3	R^4	R^6
9	α-OCF_3	OH	OH	OH
10	α-OCF_3	OH	OH	F
11	α/β-OH	OH	OH	F
12	β-OAc	OAc	OAc	F
13	α-$OPO_3^{2-}(C_6H_{11}NH_3^+)_2$	OH	OH	F

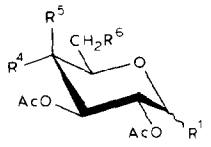
sequently shown to be the two diastereoisomers (Scheme 3) of the 5,6-cyclic sulfite derivative. Such by-products had been observed previously in reactions using DAST[19], but in this case it was somewhat surprising, in light of the previously reported successful fluorination of 1,2-*O*-isopropylidene-D-glucofuranose[17] (confirmed by us). Presumably the 3-hydroxyl group plays an important role in this reaction, reacting with DAST and providing a source for intramolecular delivery of fluoride to C-6 in a suitably efficient fashion to compete with the side reaction of cyclic sulfite formation. A derivative having a free 6-hydroxyl group and a protected 5-hydroxyl group was prepared by selective tritylation of the 6-hydroxyl group of 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (**16**) to give **18**, protection of the hydroxyl group as its methoxymethyl ether, giving **19**, and subsequent removal of the trityl group by using formic acid in diethyl ether[20]. Treatment of the protected derivative **20** with DAST gave good yields of the difluorinated product (**21**), which was deprotected by acid-catalyzed hydrolysis, to give 3,6-dideoxy-3,6-difluoro-D-glucopyranose (**26**); see Scheme 3.

1,2,3-Tri-*O*-acetyl-4,6-dideoxy-4,6-difluoro-D-glucose (**36**) was synthesized, with approximately equal efficiency, by two different routes. Treatment of methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside with DAST gave the 4-deoxy-4-fluoro-D-glucoside which was converted into methyl 4,6-dideoxy-4,6-difluoro-α-D-glucopyranoside as described previously[17]. Acetylation gave a derivative (**34**) that was converted into its α-glycosyl chloride (**35**), and **35** into the β-per-*O*-acetate (**36**). An alternative approach involved treatment of methyl 2,3-di-*O*-acetyl-α-D-galactopyranoside[21] (**33**) with DAST to give methyl 2,3-di-*O*-acetyl-4,6-dideoxy-4,6-difluoro-α-D-glucopyranoside (**34**), which was converted into the desired product as already described.

1,2,4-Tri-*O*-acetyl-3,6-dideoxy-6-fluoro-β-D-*ribo*-hexose (**31**) was prepared from 3-chloro-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[16] (**15**) as follows. Selective hydrolysis of the 5,6-*O*-isopropylidene gave the diol **17**; this was selectively pivaloylated at O-6, affording **22**, and **22** was treated with chloromethyl methyl ether to give the fully protected derivative (**23**) having a methoxymethyl

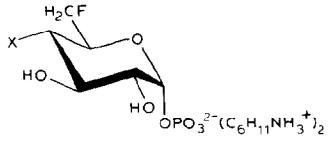
14 X = F
15 X = Cl
16 X = F
17 X = Cl
18 R5 = H, R6 = TrO, X = F
19 R5 = MeOCH2, R6 = TrO, X = F
20 R5 = MeOCH2, R6 = HO, X = F
21 R5 = MeOCH2, R6 = F, X = F
22 R5 = H, R6 = PivO, X = Cl
23 R5 = MeOCH2, R6 = PivO, X = Cl
24 R5 = MeOCH2, R6 = HO, X = Cl
25 R5 = MeOCH2, R6 = F, X = Cl
26 R = α/β-OH, R' = OH, X = F
27 R = β-OAc, R' = OAc, X = F
28 R = α-OPO3 2-(C6H11NH3+)2, R' = OH, X = F
29 R = α/β-OH, R' = OH, X = Cl
30 R = β-OAc, R' = OAc, X = Cl
31 R = β-OAc, R' = OAc, X = H
32 R = α-OPO3 2-(C6H11NH3+)2, R' = OH, X = H
Piv = Me3CCO
Tr = Ph3C
5,6-Cyclic sulfites

Scheme 3.



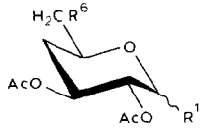
	R^1	R^4	R^5	R^6
33	α-OMe	H	OH	OH
34	α-OMe	F	H	F
35	α-Cl	F	H	F
36	β-OAc	F	H	F

ether protecting group at O-5. Treatment with sodium methoxide removed the pivaloyl group, yielding **24**, which was converted into the 3-chloro-3,6-dideoxy-6-fluoro derivative (**25**) upon treatment with DAST. Acid-catalyzed deprotection yielded the disubstituted sugar **29**, which was converted into its β-per-*O*-acetate (**30**), and **30** was reduced using tributyltin hydride, to give the desired 3,6-dideoxy-6-fluoro-β-per-*O*-acetate derivative **31**.



37 X = H

38 X = F



	R^1	R^6
39	α-OMe	OH
40	α-OMe	F
41	α-Cl	F
42	β-OAc	F

Direct synthesis of methyl 4,6-dideoxy-6-fluoro-α-D-*xylo*-hexopyranoside ("methyl 4,6-dideoxy-6-fluoro-α-D-glucoside") from methyl 4-deoxy-α-D-glucopyranoside using DAST was attempted, but poor yields (<20%) were obtained and purification of the desired product was very difficult. It was therefore decided to protect the 2- and 3-hydroxyl groups prior to fluorination, as follows. Methyl 4-deoxy-α-D-"glucopyranoside"[16] was treated with chlorotriphenyl-

methane, the ether acetylated, and the acetate *O*-detritylated with formic acid in diethyl ether, yielding the desired methyl 2,3-di-*O*-acetyl-4-deoxy-α-D-glucopyranoside (**39**). Treatment with DAST proceeded well, yielding the fluorinated product (**40**). Reaction with 1,1-dichloromethyl methyl ether yielded the α-glycosyl chloride (**41**); this was converted into its β-peracetate (**42**) using mercuric acetate, and finally phosphorylated and deprotected to give **37**.

Hydrolyses

The mechanism of acid-catalyzed hydrolysis of α-D-glucopyranosyl phosphate has been fairly well established[6–8,10] and involves cleavage of the anomeric carbon–glycosidic oxygen bond. Thus, in M $HClO_4$, species undergoing hydrolysis are the neutral phosphoric ester and its conjugate acid, which are present in relative amounts reflecting the relevant ionization constant. Hydrolysis occurs *via* an oxocarbonium-ion intermediate, or at least *via* a transition state having substantial oxocarbonium-ion character. A true oxocarbonium-ion intermediate may not actually be involved in the light of recent evidence[3,22] that all glycoside solvolyses proceed through a pre-association mechanism. However, any species having substantial oxocarbonium-ion character will have to adopt a conformation in which C-5, O-5, C-1, and C-2 approach coplanarity; this is likely to be a half-chair or boat conformation.

Several factors relating to changes in sugar structure can be expected to affect the rates of such hydrolyses, as explained in more detail recently[10]. Probably, the major factor relating to the data presented herein is an electronic one. Inductive effects are particularly important, because nearby electronegative substituents will affect both the equilibrium constant for protonation (generating the conjugate acid) and the stability of the oxocarbonium ion-like transition state. Thus, substrates having a ring substituent more electronegative than the hydroxyl group should be hydrolyzed more slowly than the parent sugar, as was found for the deoxyfluoro-D-glucopyranosyl phosphates[10] and for methyl 2-chloro-2-deoxy-β-D-glucopyranoside[23]. Substrates having a less electronegative substituent, such as deoxy sugars, should be hydrolyzed more rapidly. This was seen for a series of alkyl[4] and phenyl[5] deoxyglycosides, and also here for the deoxy-D-glucopyranosyl phosphates. The similarity of these substituent effects for the two different reactions is best illustrated by Fig. 1, where the logarithm of the first-order rate-constants for acid-catalyzed hydrolysis of a series of phenyl deoxy-D-glucopyranosides, determined previously[5], is plotted against the same parameter for the series of deoxy-D-glucopyranosyl phosphates described in Table III. A good linear free-energy relationship ($\rho = 0.995$, slope = 0.94) is observed, indicating that the structure of the transition state is very similar in the two cases. The slope (0.94) indicates a slightly greater sensitivity of the phosphoric ester hydrolyses to substitution. This suggests that *either* the transition state for hydrolysis of the phosphoric esters has slightly more oxonium-ion character *or* that contributions from the acid-catalyzed (neutral species) and the conjugate acid reactions are somewhat different in the two cases.

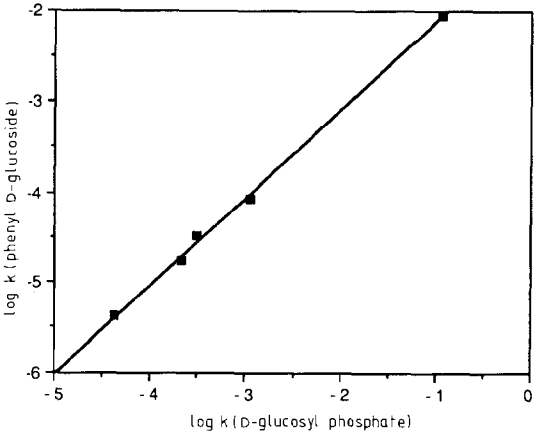


Fig. 1. Plot of the logarithm of the first-order rate-constants for hydrolysis at 37°, catalyzed with 3M HCl, of a series of phenyl deoxy-β-D-glucosides *versus* the logarithm of the rate constants for hydrolysis at 25°, catalyzed by M $HClO_4$, of the corresponding deoxy-α-D-glucopyranosyl phosphates; slope = 0.94. (Data from ref. 5 and the present work.)

However, it is quite likely that the conjugate-acid pathway contributes very little*, as the rate of the pH-independent hydrolysis (neutral pathway) of[24] 2,4-dinitrophenyl D-glucoside ($10^{-6}s^{-1}$) is quite consistent with the rate observed for α-D-glucopyranosyl phosphate, given the difference in leaving-group p*Ka* (4.1 *versus* 2.1) and assuming a β_{lg} of -1. It is therefore likely that the former is the correct explanation, although the differences are small in any case. The linearity of the plot provides convincing evidence for essentially identical transition-state structures in each case, and thus, very similar mechanisms. An equivalent plot was used[24] to demonstrate that methyl and 2,4-dinitrophenyl glycosides are hydrolyzed by identical mechanisms. Interestingly, as noted previously[10], the order of reactivity (2 deoxy > 4-deoxy > 3 deoxy > 6 deoxy) is exactly the converse of that observed for the deoxyfluoro substrates. Earlier workers[1,4,5] had suggested that this reactivity order (for the alkyl deoxy-D-glucosides) is a result of differing steric effects in each case. However, observation of the converse reactivity order with the deoxyfluoro substrates refutes this concept, because *both* the fluorine and hydrogen substituents are smaller than a hydroxyl group; this suggests that the effect is entirely electronic in origin.

Doubly modified substrates

Because it appeared that electronic effects are dominant in determining the relative reaction-rates for the variously substituted compounds, it was of interest to determine whether these effects are additive and therefore predictable for a disubstituted sugar. In addition, because the fluorination of C-6 is the simplest to

*We thank a referee for pointing this out.

achieve, and as a series of fluorinated and deoxygenated 6-deoxy-6-fluoro-α-D-glucopyranosyl phosphates was of interest in other studies on the enzyme phosphoglucomutase, this series of sugar phosphates was synthesized and their rates of acid-catalyzed hydrolysis determined. The simplest means for evaluating these data relative to those obtained previously for the monosubstituted sugars is to plot logarithms of the observed rate-constants for hydrolysis of each of the monosubstituted compounds against the equivalent value for the disubstituted derivative, as shown in Fig. 2. As is clearly seen, a good linear free-energy relationship is observed with a high correlation coefficient ($\rho = 0.998$), indicating that these effects are indeed essentially additive (in a logarithmic sense) and that there must be no sudden change in mechanism over this range (2600-fold rate differences). Thus, the rates are highly predictable, as would be expected for primarily electronic effects, while the slope (1.07) indicates that hydrolyses of the 6-deoxy-6-fluoro sugar phosphates are slightly more sensitive to further substitution in the ring than are the corresponding 6-hydroxy substrates. Again, this effect is small, and probably arises from some small synergistic electronic effect of the two fluorine atoms in decreasing the conjugate acid concentration or destabilizing the transition state.

Because several of these dideoxydifluoro sugar phosphates are hydrolyzed particularly slowly, resulting in very extended reaction-times, particularly at 25°, their hydrolysis rates were measured at several higher temperatures and extrapolated to 25° by means of an Arrhenius plot. Although this would allow estimates of activation enthalpies and entropies to be made, interpretation of these numbers is unwarranted, as these are "apparent" activation parameters that reflect the temperature dependence of some combination of two hydrolysis pathways, namely, that through the conjugate acid form and that through the neutral form. Observed temperature dependences may, therefore, reflect changing combinations of the

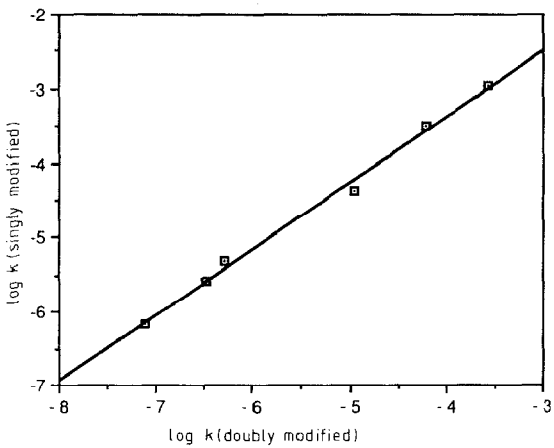


Fig. 2. Plot of the logarithm of the first-order rate-constants for hydrolysis at 25°, catalyzed with M $HClO_4$, of a series of monodeoxy- or monodeoxyfluoro-α-D-glucopyranosyl phosphates *versus* the equivalent parameters for the corresponding doubly-modified compounds containing a fluorine atom on C-6.

contributions from each pathway and not true activation parameters for a single pathway.

In conclusion, the primary consequence of replacing sugar hydroxyl groups by hydrogen, or by fluorine, upon rates of acid-catalyzed hydrolysis of glycosyl phosphates or glycosides appears to be electronic in origin. Rate effects are therefore predictable, and approximately additive. These results aid in the interpretation of recent studies on rates of glycosyl transfer, catalyzed by the enzyme glycogen phosphorylase, with these same analogs[25]. Because the deoxyfluoro substrates are consumed more slowly than the deoxysubstrates, this would suggest an oxocarbonium-ion mechanism for the enzyme also.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Thin-layer chromatography was performed on plates precoated with silica gel 60-F_{254} (E. Merck, Darmstadt), with detection by quenching of fluorescence, or by charring after spraying with 10% H_2SO_4 in ethanol. Column chromatography was performed on Merck silica gel 60 (180–230 mesh). Evaporations were conducted at temperatures below 50°. Reaction times required in the phosphorylations for optimal production of the α anomer in each case are presented. Shorter reaction times often led to significant production of the β anomer.

Nuclear magnetic resonance (n.m.r.) spectra were recorded either at 400 (^{1}H data) or 254 MHz (^{19}F data), unless noted otherwise. ^{1}H-Chemical shifts are given relative to external sodium 4,4-dimethyl-4-silapentane-1-sulfonate for samples in D_2O, and relative to Me_4Si for all other solvents. ^{19}F-N.m.r. chemical shifts (ϕ) were measured against external trifluoroacetic acid and are given in p.p.m. upfield from $CFCl_3$. ^{31}P-N.m.r. chemical shifts are given relative to a standard of orthophosphoric acid ($\delta = 0.0$).

*6-Deoxy-α-*D*-glucopyranosyl bis(cyclohexylammonium) phosphate* (**1**). — 1,2,3,4-Tetra-*O*-acetyl-6-deoxy-β-D-glucopyranose[24] (2 g, 6 mmol) was stirred with molten, anhydrous phosphoric acid (4.0 g) under vacuum for 2 h at 50°. Aqueous 2M lithium hydroxide (80 mL) was then added, and the mixture was kept overnight at room temperature. After filtration through Celite to remove the excess of lithium phosphate, the pH of the filtrate was adjusted to ~8 with Dowex 50W-X8 (H^+) cation-exchange resin. Lyophilization of this solution gave a powder which was dissolved in the minimal volume of water. The dilithium salt of the sugar phosphate was precipitated by addition of 1:4 methanol–acetone, and isolated by filtration. After drying, final purification was acomplished by conversion into the bis(cyclohexylammonium) salt by passage down a column of Dowex 50W-X8 (cyclohexylammonium) resin and repeated recrystallization from acetone–water (yield 0.824 g, 30%).

Anal. Calc. for $C_{18}H_{39}N_2O_8P$: C, 48.89; H, 8.88; N, 6.33. Found: C, 48.63; H, 8.50; N, 6.46.

*4-Deoxy-α-*D-xylo-*hexopyranosyl bis(cyclohexylammonium) phosphate* (**5**). — A solution of methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-α-D-*xylo*-hexopyranoside[19] (**2**; 1.0 g, 2.0 mmol) in 1,1-dichloromethyl methyl ether (3 mL) was stirred with a catalytic amount of freshly fused zinc chloride under nitrogen for 3 h at 65°, the solution evaporated, the resulting gum dissolved in dichloromethane and the solution washed three times with a saturated solution of sodium hydrogencarbonate, dried (sodium sulfate), and evaporated to a gum that crystallized from ether–pentane, to give 2,3,6-tri-*O*-benzoyl-4-deoxy-α-D-*xylo*-hexopyranosyl chloride (**3**; 0.798 g, 80%); m.p. 154–155°; ^{1}H-n.m.r. data ($CDCl_3$, 300 MHz): δ 8.10–7.33 (15 H, 3 C_6H_5CO), 6.52 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.87 (m, 1 H, H-3), 5.48 (dd, 1 H, $J_{2,1}$ 4.0, $J_{2,3}$ 10 Hz, H-2), 4.72 (m, 1 H, H-5), 4.50 (m, 2 H, H-6,6′), 2.58 (m, 1 H, H-4*a*), and 2.02 (m, 1 H, H-4*e*).

To a solution of glycosyl chloride **3** (7.5 g, 15 mmol) in glacial acetic acid (10 mL) was added mercuric acetate (9.5 g, 30 mmol). The mixture was stirred for 1 h at room temperature, processed (dichloromethane–water), dried (sodium sulfate), and evaporated to a gum that crystallized from ether–pentane. Recrystallization from methanol gave 1-*O*-acetyl-2,3,6-tri-*O*-benzoyl-4-deoxy-β-D-*xylo*-hexopyranose (**4**; 7.31 g, 100%); m.p. 115–116°; ^{1}H-n.m.r. data ($CDCl_3$, 300 MHz): δ 8.05–7.45 (15 H, 3 C_6H_5CO), 5.98 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.54 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 8.9 Hz, H-2), 5.49 (m, 1 H, H-3), 4.50 (m, 2 H, H-6,6′), 4.22 (m, 1 H, H-5), 2.53 (m, 1 H, H-4*e*), 2.08 (s, 3 H, OAc), and 1.92 (m, 1 H, H-4*a*).

The 1-acetate **4** (2.0 g, 4.1 mmol) and 4.05 g of anhydrous phosphoric acid were heated *in vacuo* for 1.5 h at 55°, as in the preparation of **1**. The mixture was then dissolved in 30 mL of dry tetrahydrofuran prior to addition of 2M lithium hydroxide (80 mL). The rest of the purification was performed exactly as for **1**, yielding **5** (0.4 g, 22%).

Anal. Calc. for $C_{18}H_{39}N_2O_8P \cdot 3\ H_2O$: C, 43.54; H, 9.13; N, 5.64. Found: C, 44.05; H, 9.00; N, 5.59.

*3-Deoxy-α-*D-ribo-*hexopyranosyl bis(cyclohexylammonium) phosphate* (**8**). — A solution of 3-chloro-3-deoxy-D-glucose[19] (3.4 g, 17 mmol) in 32 mL of dry pyridine was acetylated by addition of 18 mL of acetic anhydride (0° to room temperature). After 20 h, methanol was added to decompose the excess of anhydride, and the solution evaporated to a gum that was converted directly into the per-*O*-acetylated α-bromide by dissolution in 45% hydrogen bromide in acetic acid (25 mL). After 1 h at room temperature, dichloromethane was added, the mixture washed three times with ice water, dried (sodium sulfate), and evaporated, and the α-bromide converted into the β-per-*O*-acetate by reaction with 6 g of mercuric acetate in 70 mL of glacial acetic acid as for **3**. Recrystallization of the product from ether–pentane gave 1,2,4,6-tetra-*O*-acetyl-3-chloro-3-deoxy-β-D-glucopyranose (**6**; 4.6 g, 74%); m.p. 121–122°; ^{1}H-n.m.r. data ($CDCl_3$, 270 MHz): δ 5.66 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.23 (2 H, H-2,4), 4.20 (AB multiplet, 2 H, $J_{6,6'}$ 12.0, $J_{6,5}$ 2.5, $J_{6',5}$ 4.5 Hz, H-6,6′), 4.01 (t, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 10 Hz, H-3), 3.78 (m, 1 H, H-5), 2.15 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 2.08 (s, 3 H, OAc), and 2.01 (s, 3 H, OAc).

A solution of **6** (4.5 g, 1.22 mmol) in 30 mL of anhydrous toluene containing 20 mg of α,α'-azobisisobutyronitrile was reduced with 5.5 g of tributyltin hydride under dry nitrogen for 20 h at 80°, and evaporated; the product crystallized on trituration with pentane. Recrystallization from methanol gave pure 1,2,4,6-tetra-*O*-acetyl-3-deoxy-β-D-*ribo*-hexopyranoside (**7**; 3.42 g, 84%); m.p. 134–135°; ^{1}H-n.m.r. data ($CDCl_3$, 270 MHz): δ 5.70 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.93 (2 H, H-2,4), 4.18 (AB multiplet, $J_{6,6'}$ 12.1, $J_{6,5}$ 7.2, $J_{6',5}$ 3.8 Hz, H-6,6'), 3.83 (m, 1 H, H-5), 2.65 (dt, 1 H, $J_{3a,3e}$ 12.3, $J_{3e,4}$ 5.0, $J_{3e,2}$ 5.0 Hz, H-3*e*), 2.11 (s, 3 H, OAc), 2.09 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), and 1.57 (m, 1 H, $J_{3a,4}$ 10.9, $J_{3a,2}$ 10.9, $J_{3a,3e}$ 12.0 Hz, H-3*a*).

Reaction of **7** (2.0 g, 5.96 mmol) with 4.0 g of anhydrous phosphoric acid was performed exactly as for **1**, yielding **8** (0.84 g, 32%).

Anal. Calc. for $C_{18}H_{39}N_2O_8P \cdot 2\ H_2O$: C, 45.18; H, 9.06; N, 5.85. Found: C, 44.79; H, 8.76; N, 5.48.

1,3,4-Tri-O-acetyl-2,6-dideoxy-2,6-difluoro-β-D-glucopyranose (**12**). — Trifluoromethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranoside[18] (4.0 g, 10.6 mmol) was deacetylated by treatment with dry methanol (20 mL) containing 50mM sodium methoxide. After 15 min at room temperature, the base was neutralized by addition of Dowex 50W-X8 (H^+) resin. Filtration and evaporation yielded trifluoromethyl 2-deoxy-2-fluoro-α-D-glucopyranoside (**9**) as a yellowish gum (2.5 g, 10.0 mmol, 94%); ^{1}H-n.m.r. data (300 MHz, CD_3OD): δ 5.84 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.38 (ddd, 1 H, $J_{2,F}$ 50.0, $J_{2,3}$ 9.0, $J_{2,1}$ 4.0 Hz, H-2), 3.60–3.90 (m, 4 H, H-3,5,6,6'), and 3.46 (dd, 1 H, $J_{4,3}$ 10.0, $J_{4,5}$ 10.0 Hz, H-4).

Dry, ethanol-free dichloromethane (20 mL) was added to **9** (1.20 g, 4.80 mmol), and the suspension was cooled to −40°. DAST (3.73 mL, 28.8 mmol) was added with stirring, and the mixture allowed to warm to room temperature under anhydrous conditions. After 1 h, the solution was cooled to −40°, and the reaction quenched by addition of methanol (10 mL); the solution was evaporated, and the residue purified by flash chromatography (1:1 hexane–ethyl acetate), yielding trifluoromethyl 2,6-dideoxy-2,6-difluoro-α-D-glucopyranoside (**10**) as a colorless oil (0.67 g, 2.66 mmol, 56%); ^{1}H-n.m.r. data (400 MHz, $CDCl_3$): δ 5.76 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.71 (ddd, 1 H, $J_{6,F}$ 47.0, $J_{6,6'}$ 10.5, $J_{6,5}$ 3.0 Hz, H-6), 4.61 (ddd, 1 H, $J_{6',F}$ 48.0, $J_{6,6'}$ 10.5, $J_{6',5}$ 2.0 Hz, H-6'), 4.50 (ddd, 1 H, $J_{2,F}$ 48.0, $J_{2,3}$ 9.5, $J_{2,1}$ 3.8 Hz, H-2), 4.10 (ddd, 1 H, $J_{3,F}$ 12.0, $J_{3,2}$ 9.2, $J_{3,4}$ 9.2 Hz, H-3), 3.94 (dddd, 1 H, $J_{5,F}$ 27.0, $J_{5,4}$ 10.0, $J_{5,6}$ 3.0, $J_{5,6'}$ 2.0 Hz, H-5), and 3.75 (dd, 1 H, $J_{4,3} = J_{4,5} = 9.5$ Hz, H-4).

Washed Dowex 50W-X8 (H^+) resin was added to a solution of **10** (0.67 g, 2.66 mmol) in water (30 mL), and the mixture was refluxed for 60 min, cooled, filtered, and the filtrate evaporated; the resulting oil was passed through silica gel (ethyl acetate), yielding 2,6-dideoxy-2,6-difluoro-D-glucopyranose (**11**) as a clear gum (0.37 g, 2.0 mmol, 76%); ^{19}F-n.m.r. data (254 MHz, D_2O): φ 200.47 (ddd, $J_{F,2}$ 51.3, $J_{F,3}$ 15.0, $J_{F,1}$ 2.4 Hz, F-2), 200.59 (dd, $J_{F,2}$ 49.3, $J_{F,3}$ 13.4 Hz, F-2), 235.94 (dt, $J_{F,5}$ 25.7, $J_{F,6+6'}$ 47.5 Hz, F-6), and 236.50 (dt, $J_{F,5}$ 28.6, $J_{F,6+6'}$ 47.5 Hz, F-6).

A solution of **11** (0.37 g, 2.0 mmol) was treated, appropriately scaled, exactly as in the synthesis of **5**. The bromination required 8 h for completion. The product, 1,3,4-tri-*O*-acetyl-2,6-dideoxy-2,6-difluoro-β-D-glucopyranose (**12**), crystallized from ethyl acetate–pentane (yield 0.44 g, 1.41 mmol, 71%); m.p. 135–135.5°; ^{1}H-n.m.r. data (400 MHz, $CDCl_3$): δ 5.75 (dd, 1 H, $J_{1,2}$ 8.1, $J_{1,F}$ 3.3 Hz, H-1), 5.35 (ddd, 1 H, $J_{3,F}$ 14.3, $J_{3,4}$ 9.1 Hz, H-3), 5.06 (dd, 1 H, $J_{4,3} = J_{4,5} = 9.6$ Hz, H-4), 4.50 (ddd, 1 H, $J_{6,F}$ 47.0, $J_{6,6'}$ 10.0, $J_{6,5}$ 2.3 Hz, H-6), 4.45 (ddd, 1 H, $J_{6',F}$ 47.0, $J_{6',6}$ 10.0, $J_{6',5}$ 1.0 Hz, H-6'), 4.43 (ddd, 1 H, $J_{2,F}$ 50.0, $J_{2,1}$ 9.0, $J_{2,3}$ 9.0 Hz, H-2), 4.07 (dddd, 1 H, $J_{5,F}$ 23.0, $J_{5,4}$ 10.2, $J_{5,6}$ 3.5, $J_{5,6'}$ 2.0 Hz, H-5), and 2.18, 2.07, and 2.04 (3 s, 9 H, 3 AcO); ^{19}F-n.m.r. data (254 MHz, $CDCl_3$): φ 201.46 (dd, $J_{F,2}$ 51.6, $J_{F,3}$ 13.3 Hz, F-2) and 234.35 (dt, $J_{F,5}$ 22.8, $J_{F,6+6'}$ 47.2 Hz, F-6).

Anal. Calc. for $C_{12}H_6F_2O_7$: C, 46.46; H, 5.20. Found: C, 46.65; H, 5.20.

2,6-Dideoxy-2,6-difluoro-α-D-glucopyranosyl bis(cyclohexylammonium) phosphate (**13**). — The triacetate **12** (0.40 g, 1.29 mmol) was treated with anhydrous phosphoric acid (0.89 g, 9.0 mmol) for 9 h, as described in the synthesis of **1**. The lithium salt was not isolated, the lithium being removed by passage down a column of cold Dowex 50W-X8 (H^+) resin into an excess of cyclohexylamine in water. The product could not be crystallized, and was isolated as a freeze-dried powder (**13**; 0.363 g, 0.71 mmol, 61%); ^{31}P-n.m.r. data (121 MHz, D_2O): δ −4.63 (dd, $J_{P,1}$ 7.7, $J_{P,2}$ 2.2 Hz).

Anal. Calc. for $C_{18}H_{37}F_2N_2O_7P \cdot H_2O$: C, 45.00; H, 8.18; N, 5.83. Found: C, 45.15; H, 8.19; N, 5.74.

1,2,4-Tri-O-acetyl-3,6-dideoxy-3,6-difluoro-β-D-glucopyranose (**27**). — Methanol (12.5 mL) and dilute sulfuric acid (0.8% v/v, 12.5 mL) were added to 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[16] (**14**; 2.35 g, 8.97 mmol), and the mixture was stirred for 8 h at room temperature. Solid barium carbonate was added to neutrality, and after boiling, cooling, and filtering through Celite, the filtrate was evaporated, to give colorless, oily 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (**16**; 1.86 g, 8.38 mmol, 93%); ^{1}H-n.m.r. data (270 MHz, $CDCl_3$): δ 5.85 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.00 (dd, 1 H, $J_{3,F}$ 49.5, $J_{3,4}$ 2.5 Hz, H-3), 4.60 (dd, 1 H, $J_{2,F}$ 10.5, $J_{2,1}$ 4.0 Hz, H-2), 4.06 (ddd, 1 H, $J_{4,F}$ 34.5, $J_{4,5}$ 9.5, $J_{4,3}$ 2.5 Hz, H-4), 3.58–3.91 (m, 3 H, H-5,6,6'), 2.95 (s, 2 H, OH-5,6), 1.43, and 1.26 (2 s, 6 H, 2 Me).

To a solution of **16** (1.41 g, 6.36 mmol) in dry pyridine (12 mL) was added chlorotriphenylmethane (1.95 g, 7.0 mmol), and the solution was heated for 16 h at 40°. Ice (0.1 g) was added, and after 2 h the pyridine was co-evaporated with toluene to an oil that was dissolved in chloroform and the solution washed with 10% sodium hydrogencarbonate solution, dried (magnesium sulfate), filtered, and the filtrate evaporated to an oil that was purified by flash chromatography (4:1 hexane–ethyl acetate), to yield 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-6-*O*-(triphenylmethyl)-α-D-glucofuranose (**18**) as a clear gum (2.21 g, 4.76 mmol, 75%); ^{1}H-n.m.r. data (300 MHz, $CDCl_3$): δ 7.50–7.20 (m, 15 H, 3 Ph), 5.94 (d, $J_{1,2}$ 4.0 Hz, H-1), 5.12 (dd, 1 H, $J_{3,F}$ 50.1, $J_{3,4}$ 1.3 Hz, H-3), 4.70 (dd, 1 H, $J_{2,F}$ 10.4, $J_{2,1}$ 3.8

Hz, H-2), 4.27 (ddd, 1 H, $J_{4,F}$ 29.4, $J_{4,5}$ 9.2, $J_{4,3}$ 1.3 Hz, H-4), 4.02 (m, 1 H, H-5), 3.41 (dd, 1 H, $J_{6,6'}$ 10.0, $J_{6,5}$ 3.3 Hz, H-6), 3.37 (dd, 1 H, $J_{6',6}$ 10.0, $J_{6',5}$ 5.0 Hz, H-6'), 2.46 (d, 1 H, $J_{OH,5}$ 6.0 Hz, OH-5), 1.49, and 1.33 (2 s, 6 H, 2 Me).

Monochloromethyl methyl ether (1.08 mL, 14.3 mmol) was added to a mixture of **18** (2.21 g, 4.76 mmol) and dry ethyldiisopropylamine (3.32 mL, 18 mmol) in dry dichloromethane (60 mL). After 10 d at room temperature, the solution was evaporated, the residue dissolved in chloroform, and the solution washed successively with ice-cold M hydrochloric acid and saturated sodium hydrogencarbonate solution, dried (magnesium sulfate), and evaporated to an oil that was dissolved in diethyl ether (20 mL) and an equal volume of 70% formic added. After 20 min, more ether (100 mL) was added, and the solution was washed successively with 10% aqueous sodium chloride and saturated sodium hydrogencarbonate solution, and dried (magnesium sulfate); concentration followed by flash chromatography (1:1 hexane–ethyl acetate) yielded 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-5-*O*-(methoxymethyl)-α-D-glucofuranose (**20**) as a clear oil (0.79 g, 2.96 mmol, 62%); ^{1}H-n.m.r. data (300 MHz, $CDCl_3$): δ 5.97 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.04 (dd, 1 H, $J_{3,F}$ 50.8, $J_{3,4}$ 2.3 Hz, H-3), 4.73 (m, 3 H, H-2), 4.21 (ddd, 1 H, $J_{4,F}$ 29.3, $J_{4,5}$ 9.5, $J_{4,3}$ 2.3 Hz, H-4), 3.88 (m, 2 H, H-6,6'), 3.70 (dd, 1 H, $J_{5,4}$ 11.0, $J_{5,6}$ 5.4 Hz, H-5), 3.44 (s, 3 H, OMe), 1.49, and 1.32 (2 s, 6 H, 2 Me).

A solution of **20** (0.78 g, 2.93 mmol) and dry 2,4,6-trimethylpyridine (1.16 mL, 8.8 mmol) in dry, ethanol-free dichloromethane (8 mL) was treated with DAST (1.16 mL, 8.8 mmol) at −20° under anhydrous conditions. The solution was allowed to warm to room temperature, and stirred for 48 h. Dichloromethane (30 mL) was added, and the solution washed successively with cold M hydrochloric acid and saturated sodium hydrogencarbonate solution, dried (magnesium sulfate), and evaporated; the residue was purified by flash chromatography (2:1 hexane–ethyl acetate), to yield yellowish, oily 3,6-dideoxy-3,6-difluoro-1,2-*O*-isopropylidene-5-*O*-(methoxymethyl)-α-D-glucofuranose (**21**; 0.50 g, 1.85 mmol, 63%); ^{1}H-n.m.r. data (300 MHz, $CDCl_3$): δ 5.98 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 5.07 (dd, 1 H, $J_{3,F}$ 50.4, $J_{3,4}$ 2.1 Hz, H-3), 4.52–4.86 (m, 5 H, CH_2, H-2,6,6'), 4.32 (ddd, 1 H, $J_{4,F}$ 29.1, $J_{4,5}$ 9.4, $J_{4,3}$ 2.2 Hz, H-4), 3.98 (dddd, 1 H, $J_{5,F}$ 25.9, $J_{5,4}$ 9.4, $J_{5,6}$ 3.8, $J_{5,6'}$ 1.9 Hz, H-5), 3.47 (s, 3 H, MeO), 1.53, and 1.36 (2 s, 6 H, 2 Me); ^{19}F-n.m.r. data (254 MHz, $CDCl_3$): φ 202.51 (ddd, $J_{F,3}$ 50.0, $J_{F,4}$ 28.9, $J_{F,2}$ 10.5 Hz, F-3) and 232.62 (dt, $J_{F,5}$ 25.2, $J_{F,6+6'}$ 47.3 Hz, F-6).

A mixture of tetrahydrofuran, water, and trifluoroacetic acid (1:1:4 v/v, 20 mL) was added to **21** (0.50 g, 1.85 mmol), the solution was kept for 8 h at room temperature, evaporated, and the product passed through silica gel (ethyl acetate), yielding, after evaporation, 3,6-dideoxy-3,6-difluoro-D-glucopyranose (**26**) as a colorless gum (0.29 g, 1.58 mmol); ^{19}F-n.m.r. data (254 MHz, D_2O): φ 187.22 (ddd, $J_{F,3}$ 52.7, $J_{F,4} = J_{F,2}$ = 13.6 Hz, F-3), 192.18 (ddd, $J_{F,3}$ 54.0, $J_{F,4} = J_{F,2}$ = 13.3 Hz, F-3), 227.15 (dt, $J_{F,5}$ 26.3, $J_{F,6+6'}$ 47.3, F-6), and 227.67 (dt, $J_{F,5}$ 28.5, $J_{F,6+6'}$ 47.3 Hz, F-6).

A solution of **26** (0.28 g, 1.52 mmol) in dry pyridine was treated,

appropriately scaled, exactly as in the synthesis of **6**. Reaction times for bromination and conversion into the β-acetate were both 1 h. Crystallization from ethyl acetate–pentane yielded colorless crystals of **27** (0.37 g, 1.19 mmol, 79%); m.p. 127–127.5°; ^{1}H-n.m.r. data (300 MHz, $CDCl_3$): δ 5.68 (d, 1 H, $J_{1,2}$ 8.5 Hz, H-1), 5.26 (m, 2 H, H-2,4), 4.63 (ddd, 1 H, $J_{3,F}$ 48.8, $J_{3,4} = J_{3,2} = 9.0$ Hz, H-3), 4.55 (ddd, 1 H, $J_{6,F}$ 48.0, $J_{6,6'}$ 10.2, $J_{6,5}$ 3.6 Hz, H-6), 4.45 (ddd, 1 H, $J_{6',F}$ 48.0, $J_{6',6}$ 10.2, $J_{6',5}$ 5.4 Hz, H-6'), 3.76 (dddd, 1 H, $J_{5,F}$ 21.2, $J_{5,4}$ 13.1, $J_{5,6'}$ 5.4, $J_{5,6}$ 3.6 Hz, H-5), 2.11, 2.12, and 2.13 (3 s, 9 H, 3 AcO); ^{19}F-n.m.r. data (254 MHz, $CDCl_3$): φ 196.53 (ddd, $J_{F,3}$ 51.8, $J_{F,4} = J_{F,2}$ = 12.6 Hz, F-3), and 232.95 (dt, $J_{F,5}$ 21.3, $J_{F,6,6'}$ 47.0 Hz, F-6).

Anal. Calc. for $C_{12}H_{16}F_2O_7$: C, 46.46; H, 5.20. Found: C, 46.67; H, 5.39.

3-Deoxy-3-fluoro-1,2-O-isopropylidene-α-D-glucofuranose 5,6-sulfite. — Reaction of **16** (0.15 g, 0.68 mmol) with DAST (0.36 mL, 2.72 mmol) in dry, ethanol-free dichloromethane (1.5 mL), performed exactly as in the preparation of **10**, gave two major products in equal proportions. The two compounds were separated by flash chromatography (2:1 hexane–ethyl acetate, R_F 0.36, 0.30), which was repeated twice.

Isomer 1: ^{1}H-n.m.r. data (400 MHz, $CDCl_3$): δ 5.98 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.10 (dd, 1 H, $J_{3,F}$ 50.0, $J_{3,4}$ 2.0 Hz, H-3), 4.60–4.78 (m, 4 H, H-2,5,6,6'), 4.50 (ddd, 1 H, $J_{4,F}$ 27.2, $J_{4,5}$ 8.6, $J_{4,3}$ 2.0 Hz, H-4), 1.50, and 1.33 (2 s, 6 H, 2 Me); ^{19}F-n.m.r. data (254 MHz, $CDCl_3$): φ 210.91 ($J_{F,3}$ 49.9, $J_{F,4}$ 27.1, $J_{F,2}$ 10.4 Hz); f.a.b.-mass spectrum: (M + 1) = 269.

Anal. Calc. for $C_9H_{13}FO_6S$: C, 40.30; H, 4.88. Found: C, 40.60; H, 5.02.

Isomer 2: ^{1}H-n.m.r. data (400 MHz, $CDCl_3$): δ 5.98 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.10 (ddd, $J_{5,4}$ 7.6, $J_{5,6}$ 6.5, $J_{5,6'}$ 4.0 Hz, H-5), 5.04 (dd, 1 H, $J_{3,F}$ 50.0, $J_{3,4}$ 2.0 Hz, H-3), 4.79 (dd, 1 H, $J_{6,6'}$ 9.0, $J_{6,5}$ 6.5 Hz, H-6), 4.73 (dd, 1 H, $J_{2,F}$ 10.3, $J_{2,1}$ 3.6 Hz, H-2), 4.58 (dd, 1 H, $J_{6',6}$ 9.0, $J_{6',5}$ 4.0 Hz, H-6'), 4.18 (ddd, 1 H, $J_{4,F}$ 28.3, $J_{4,5}$ 7.6, $J_{4,3}$ 2.0 Hz, H-4), 1.50, and 1.33 (2 s, 6 H, 2 Me); ^{19}F-n.m.r. data (254 MHz, $CDCl_3$): φ 210.66 ($J_{F,3}$ 50.0, $J_{F,4}$ 28.3, $J_{F,2}$ 10.4 Hz); f.a.b.-mass spectrum: (M + 1) = 269.

Anal. Calc. for $C_9H_{13}FO_6S$: C, 40.30; H, 4.88; S, 11.95. Found: C, 40.99; H, 5.05; S, 11.58.

3,6-Dideoxy-3,6-difluoro-α-D-glucopyranosyl bis(cyclohexylammonium) phosphate (**28**). — The triacetate **27** (0.25 g, 0.81 mmol) was treated with anhydrous phosphoric acid (0.56 g, 5.7 mmol) exactly as in the synthesis of **13**. Crystallization and repeated recrystallization yielded the colorless bis(cyclohexylammonium) salt **28** (0.33 g, 0.72 mmol, 88%); ^{31}P-n.m.r. data (121 MHz, D_2O): δ −4.67 (dd, $J_{P,1}$ 7.2, $J_{P,2}$ 2.0 Hz).

Anal. Calc. for $C_{18}H_{37}F_2N_2O_7P \cdot H_2O$: C, 45.00; H, 8.20; N, 5.86. Found: C, 45.00; H, 8.18; N, 5.83.

1,2,4-Tri-O-acetyl-3,6-dideoxy-6-fluoro-β-D-ribo-hexopyranose (**31**). — 3-Chloro-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**15**; 2.9 g, 10.4 mmol) was treated with dilute sulfuric acid and methanol exactly as described in the synthesis of **16**, yielding 3-chloro-3-deoxy-1,2-*O*-isopropylidene-α-D-gluco-

furanose (**17**) as an oil (2.2 g, 9.2 mmol, 89%); ^{1}H-n.m.r. data (270 MHz, $CDCl_3$): δ 5.92 (d, 1 H, $J_{1,2}$ 3.1 Hz, H-1), 4.71 (d, 1 H, $J_{2,1}$ 3.7 Hz, H-2), 4.50 (d, 1 H, $J_{3,4}$ 3.1 Hz, H-3), 4.26 (dd, 1 H, $J_{4,5}$ 8.9, $J_{4,3}$ 3.1 Hz, H-4), 3.95 (m, 1 H, H-5), 3.87 (d, 1 H, $J_{6,6'}$ 10.0 Hz, H-6), 3.72 (d, 1 H, $J_{6',6}$ 10.0 Hz, H-6'), 3.39, 3.13 (2 s, 6 H, OH-5,6), 1.50, and 1.32 (2 s, 6 H, 2 Me).

To a solution of **17** (2.0 g, 8.8 mmol) in dry pyridine (40 mL) at −40° was added pivaloyl chloride (1.23 mL, 10.0 mmol) with stirring. The solution was allowed to warm to room temperature, and, after 15 min, the reaction was quenched with methanol (5 mL). The pyridine was evaporated with the aid of toluene, the residue dissolved in dichloromethane and the solution successively washed with cold 0.5M hydrochloric acid and saturated sodium hydrogencarbonate solution, dried (magnesium sulfate), the suspension filtered, the filtrate evaporated, and the residue purified by flash chromatography (2:1 hexane–ethyl acetate), to yield 3-chloro-3-deoxy-1,2-*O*-isopropylidene-6-*O*-pivaloyl-α-D-glucofuranose (**22**) as a colorless oil (2.2 g, 6.8 mmol, 77%); ^{1}H-n.m.r. data (400 MHz, $CDCl_3$): δ 5.95 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.73 (d, 1 H, $J_{2,1}$ 3.5 Hz, H-2), 4.46 (m, 2 H, H-6,6'), 4.27 (dd, 1 H, J 9.2, 2.8 Hz), 4.22 (dd, 1 H, J 12.0, 5.5 Hz), 5.12 (m, 1 H, H-5), 3.52 (d, 1 H, $J_{OH,5}$ 5.0 Hz, OH-5), 1.50, 1.31 (2 s, 6 H, 2 Me), and 1.22 (s, 9 H, Me_3C).

Dry ethyldiisopropylamine (9.3 mL, 54 mmol) and **22** (2.16 g, 6.7 mmol) were dissolved in dry dichloromethane (50 mL). After flushing with nitrogen and cooling to −20°, monochloromethyl methyl ether (3.05 mL, 40.2 mmol) was added dropwise. After 3 d at room temperature, the solution was evaporated, the residue dissolved in dichloromethane, and the solution successively washed with cold 0.5M hydrochloric acid and saturated sodium hydrogencarbonate solution, dried (magnesium sulfate), evaporated, and the residue was purified by flash chromatography (4:1 hexane–ethyl acetate), and crystallized from hexane–ethyl acetate, yielding 3-chloro-3-deoxy-1,2-*O*-isopropylidene-5-*O*-(methoxymethyl)-6-*O*-pivaloyl-α-D-glucofuranose (**23**) (2.18 g, 5.9 mmol, 89%); m.p. 92–93°; ^{1}H-n.m.r. data (400 MHz, $CDCl_3$): δ 5.95 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.75 (dd, 1 H, J 10.10 Hz), 4.74 (d, 2 H, J 6.1 Hz, OCH_2O), 4.62 (dd, 1 H, J 12.3, 1.9 Hz), 4.46 (m, 2 H, H-6,6'), 4.13 (dd, J 12.2, 1.9 Hz), 4.05 (dm, 1 H, $J_{5,4}$ 9.5 Hz, H-5), 3.40 (s, 3 H, OMe), 1.50, 1.32 (2 s, 6 H, 2 Me), and 1.23 (s, 9 H, Me_3C).

Dry methanol (10 mL) containing 0.2M sodium methoxide was added to **23** (2.18 g, 5.9 mmol) and the solution kept for 2 d at room temperature. After neutralization as described in the preparation of **9**, the residue was purified by flash chromatography (1:1 hexane–ethyl acetate) to give 3-chloro-3-deoxy-1,2-*O*-isopropylidene-5-*O*-(methoxymethyl)-α-D-glucofuranose (**24**) as an oil (1.53 g, 5.4 mmol, 93%); ^{1}H-n.m.r. data (270 MHz, $CDCl_3$): δ 5.96 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.75 (d, 2 H, $J_{CH2,5}$ 4.0 Hz, OCH_2O), 4.71 (d, 1 H, J 3.5 Hz), 4.42 (d, 1 H, J 3.5 Hz), 4.31 (dd, 1 H, J 9.0, 3.5 Hz), 3.88 (m, 2 H, H-6,6'), 3.70 (m, 1 H, H-5), 3.44 (s, 3 H, OMe), 3.02 (t, 1 H, $J_{OH,6} = J_{OH,6'} = 4.0$ Hz, OH-6), 1.50, and 1.32 (2 s, 6 H, 2 Me).

A solution of **24** (1.53 g, 5.4 mmol) and 2,4,6-trimethylpyridine (2.16 mL, 16.2 mmol) was treated with DAST (2.16 mL, 16.2 mmol) exactly as for the preparation of **21**, with a reaction time of 21 h. Flash chromatography yielded 3-chloro-3,6-dideoxy-6-fluoro-1,2-*O*-isopropylidene-5-*O*-(methoxymethyl)-α-D-glucofuranose (**25**) as a colorless gum (0.75 g, 2.6 mmol, 49%); ^{1}H-n.m.r. data (400 MHz, $CDCl_3$): δ 5.95 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.78 (ddd, 1 H, $J_{6,F}$ 47.6, $J_{6,6'}$ 10.2, $J_{6,5}$ 1.9 Hz, H-6), 4.62 (ddd, 1 H, $J_{6',F}$ 46.5, $J_{6',6}$ 10.2, $J_{6',5}$ 3.5 Hz, H-6'), 4.80 (d, 2 H, $J_{CH2,5}$ 4.8 Hz, CH_2), 4.75 (d, 1 H, $J_{2,1}$ 3.4 Hz, H-2), 4.46 (m, 2 H, H-3,4), 3.96 (ddm, 1 H, $J_{5,F}$ 26.0, $J_{5,4}$ 9.0 Hz, H-5), 3.44 (s, 3 H, OMe), 1.55, and 1.33 (2 s, 3 H, 2 Me).

Deprotection of **25** (0.53 g, 1.87 mmol) was achieved exactly as described for the synthesis of **26**. After 5 h at room temperature, the solution was evaporated, to give crystalline material. Recrystallization from ethyl acetate–hexane yielded 3-chloro-3,6-dideoxy-6-fluoro-D-glucopyranose (**29**) (0.325 g, 1.63 mmol, 87%); m.p. 159–161°; ^{19}F-n.m.r. data (254 MHz, D_2O): φ 236.05 (dt, $J_{F,5}$ 26.2, $J_{F,6+6'}$ 47.3 Hz), and 236.66 (dt, $J_{F,5}$ 28.6, $J_{F,6,6'}$ 47.4 Hz).

A solution of **29** (0.31 g, 1.55 mmol) in dry pyridine was treated as in the synthesis of **6**, appropriately scaled. Crystallization from ethyl acetate–hexane yielded 1,2,4-tri-*O*-acetyl-3-chloro-3,6-dideoxy-6-fluoro-β-D-glucopyranose (**30**) (0.405 g, 1.24 mmol, 80%); m.p. 145–146°; ^{1}H-n.m.r. data (300 MHz, $CDCl_3$): δ 5.68 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 5.22 (dd, 1 H, $J_{2,1} = J_{2,3}$ = 8.4 Hz, H-2), 5.19 (dd, 1 H, $J_{4,3} = J_{4,5}$ = 9.0 Hz, H-4), 4.53 (ddd, 1 H, $J_{6,F}$ 46.6, $J_{6,6'}$ 10.0, $J_{6,5}$ 2.7 Hz, H-6), 4.39 (ddd, 1 H, $J_{6',F}$ 46.6, $J_{6',6}$ 10.0, $J_{6',5}$ 4.4 Hz, H-6'), 4.03 (dd, 1 H, $J_{3,4} = J_{3,2}$ = 10.0 Hz, H-3), 3.78 (dddd, 1 H, $J_{5,F}$ 21.1, $J_{5,4}$ 10.0, $J_{5,6'}$ 4.6, $J_{5,6}$ 2.7 Hz, H-5), 2.17, and 2.12 (2 s, 9 H, 3 OAc); ^{19}F-n.m.r. data (254 MHz, $CDCl_3$): φ 232.49 (dt, $J_{F,5}$ 20.7, $J_{F,6+6'}$ 47.0 Hz).

The chlorodeoxy per-*O*-acetate **30** (0.20 g, 0.61 mmol) was reduced as in the preparation of **7**, suitably scaled. The product was purified by flash chromatography (1:1 hexane–ethyl acetate) and crystallized from ethyl acetate–hexane, to yield **31** (0.15 g, 0.49 mmol, 81%); m.p. 130.5–131°; ^{1}H-n.m.r. data (270 MHz, $CDCl_3$): δ 5.72 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.90 (m, 2 H, H-2,4), 4.54 (ddd, 1 H, $J_{6,F}$ 47.8, $J_{6,6'}$ 10.0, $J_{6,5}$ 2.7 Hz, H-6), 4.44 (ddd, 1 H, $J_{6',F}$ 47.4, $J_{6',6}$ 10.0, $J_{6',5}$ 4.0 Hz, H-6'), 3.82 (dddd, 1 H, $J_{5,F}$ 23.0, $J_{5,4}$ 9.5, $J_{5,6'}$ 4.0, $J_{5,6}$ 2.7 Hz, H-5), 2.68 (ddd, 1 H, $J_{3e,3a}$ 12.5, $J_{3e,4}$ 5.0, $J_{3e,2}$ 5.0, H-3*e*), 2.11, 2.06, 2.04 (3 s, 9 H, 3 OAc), and 1.69 (ddd, 1 H, $J_{3a,3e}$ 12.0, $J_{3a,4}$ 12.0, $J_{3a,2}$ 12.0 H-3*a*).

Anal. Calc. for $C_{12}H_{17}FO_7$: C, 49.32; H, 5.86. Found: C, 49.54; H, 5.91.

3,6-Dideoxy-6-fluoro-α-D-ribo-hexopyranosyl bis(cyclohexylammonium) phosphate (**32**). — The per-*O*-acetate **31** (0.15 g, 0.51 mmol) was treated with anhydrous phosphoric acid (0.35 g, 3.6 mmol) exactly as for the preparation of **28**, with a reaction time of 2.5 h. Three recrystallizations yielded the product **32** (0.15 g, 0.34 mmol, 67%); ^{31}P-n.m.r. data (121 MHz, D_2O): δ −4.58 (dd, $J_{P,1}$ 7.1, $J_{P,2}$ 2.2 Hz).

Anal. Calc. for $C_{18}H_{38}FN_2O_7P$: C, 48.64; H, 8.62; N, 6.30. Found: C, 48.28; H, 8.46; N, 6.00.

4,6-Dideoxy-4,6-difluoro-α-D-glucopyranosyl bis(cyclohexylammonium) phosphate (**37**). — Methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-galactopyranoside (5.36 g, 14.6 mmol) was treated with 80% aqueous acetic acid (70 mL), the mixture heated for 2 h at 60°, cooled, and evaporated, and the product crystallized from ethyl acetate–hexane, to yield colorless crystals of methyl 2,3-di-*O*-acetyl-α-D-galactopyranoside (**33**; 3.52 g, 12.6 mmol, 86%); m.p. 94–95°; ^{1}H-n.m.r. data (300 MHz, $CDCl_3$): δ 5.27 (m, 2 H, H-2,3), 5.02 (d, $J_{1,2}$ 2.5 Hz, H-1), 4.28 (bs, 1 H, H-5), 4.00–3.85 (m, 3 H, H-4,6,6′), 3.40 (s, 3 H, OMe), 2.17 (s, 2 H, OH-4,6), 2.12, and 2.09 (2 s, 6 H, 2 AcO).

A solution of **33** (1.50 g, 5.4 mmol) and 2,4,6-trimethylpyridine (4.3 mL, 32.6 mmol) in dry, ethanol-free dichloromethane (20 mL) was treated with DAST (4.31 mL, 32.6 mmol) as described in the synthesis of **21**. After 20 h, the reaction was worked up, and the product purified by flash chromatography (50:1 dichloromethane–ethyl acetate), to give methyl 2,3-di-*O*-acetyl-4,6-dideoxy-4,6-difluoro-α-D-glucopyranoside (**34**) as a gum (0.47 g, 1.69 mmol, 31%); ^{1}H-n.m.r. data (270 MHz, $CDCl_3$): δ 5.65 (dt, 1 H, $J_{3,F}$ 14.0, $J_{3,4} = J_{3,2}$ = 9.4 Hz, H-3), 4.97 (t, 1 H, $J_{1,F} = J_{1,2}$ = 2.9 Hz, H-1), 4.84 (dd, 1 H, $J_{2,3}$ 9.7, $J_{2,1}$ 3.0 Hz, H-2), 4.68 (d, 2 H, $J_{6+6',F}$ 46.8, H-6,6′), 4.57 (ddd, 1 H, $J_{4,F}$ 50.0, $J_{4,5} = J_{4,3}$ = 9.5 Hz, H-4), 4.00 (dm, 1 H, $J_{5,F}$ 25.5 Hz, H-5), 3.46 (s, 3 H, OMe), 2.15, and 2.12 (2 s, 6 H, 2 AcO); ^{19}F-n.m.r. data (254 MHz, $CDCl_3$): φ 198.69 (dd, $J_{F,4}$ 50.5, $J_{F,3}$ 14.0 Hz, F-4) and 236.24 (dt, $J_{F,5}$ 25.8, $J_{F,6} = J_{F,6'}$ = 47.1 Hz, F-6).

A solution of **34** (0.53 g, 1.88 mmol) in dichloromethyl methyl ether (10 mL) was treated exactly as described in the preparation of **3**. After a reaction time of 8 h, the mixture was worked up, the product purified by flash chromatography (dichloromethane), and 2,3-di-*O*-acetyl-4,6-dideoxy-4,6-difluoro-α-D-glucopyranosyl chloride (**35**) crystallized from ethyl acetate–hexane (yield 0.24 g, 0.84 mmol, 45%); m.p. 109–110°; ^{1}H-n.m.r. data (400 MHz, $CDCl_3$): δ 6.20 (t, 1 H, $J_{1,F} = J_{1,2}$ = 3.5 Hz, H-1), 5.70 (dt, 1 H, $J_{3,F}$ 13.6, $J_{3,2} = J_{3,4}$ = 8.5 Hz, H-3), 4.87 (ddd, 1 H, $J_{2,3}$ 10.0, $J_{2,1}$ 4.0, $J_{2,4}$ 1.0 Hz, H-2), 4.62 (ddt, 1 H, $J_{4,F}$ 46.0, $J_{4,3} = J_{4,5}$ = 8.5, $J_{4,2}$ 1.0 Hz, H-4), 4.46–4.71 (m, 2 H, H-6,6′), 4.21 (dm, 1 H, $J_{5,F}$ 27.0 Hz, H-5), 2.05, and 2.03 (2 s, 6 H, 2 AcO).

A solution of **35** (0.24 g, 0.84 mmol) and mercuric acetate (0.53 g, 1.69 mmol) in glacial acetic acid was treated exactly as in the preparation of **4**. The product, 1,2,3-tri-*O*-acetyl-4,6-dideoxy-4,6-difluoro-β-D-glucopyranose (**36**), crystallized from diethyl ether–pentane (yield 0.18 g, 0.60 mmol, 73%); m.p. 116–119°; ^{1}H-n.m.r. data (270 MHz, $CDCl_3$): δ 5.74 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.39 (dt, 1 H, $J_{3,F}$ 14.8, $J_{3,4} = J_{3,2}$ = 9.2 Hz, H-3), 5.08 (t, 1 H, $J_{2,3} = J_{2,4}$ = 8.8 Hz, H-2), 4.50–4.80 (m, 3 H, H-4,6,6′), 4.81 (dm, 1 H, $J_{5,F}$ 26.0 Hz, H-5), 2.11, 2.10, and 2.04 (3 s, 9 H, 3 AcO).

The per-*O*-acetate **36** (0.18 g, 0.60 mmol) and anhydrous phosphoric acid (0.41 g, 4.2 mmol) were treated for 3 h exactly as described in the synthesis of **13**.

Three recrystallizations yielded the product **37** (0.16 g, 0.34 mmol, 58%); ^{31}P-n.m.r. data (121 MHz, D_2O): δ −4.76 (dd, $J_{P,1}$ 7.3, $J_{P,2}$ 2.0 Hz).

Anal. Calc. for $C_{18}H_{37}F_2N_2O_7P$: C, 46.75; H, 8.00; N, 6.06. Found: C, 46.47; H, 8.04; N, 6.10.

*4,6-Dideoxy-6-fluoro-α-*D-xylo-*hexopyranosyl bis(cyclohexylammonium) phosphate* (**38**). — To a solution of methyl 4-deoxy-α-D-*xylo*-hexopyranoside (0.20 g, 1.12 mmol) in dry pyridine (2 mL) was added chlorotriphenylmethane (0.51 g, 1.84 mmol), and the solution was heated under anhydrous conditions for 24 h at 40°. More pyridine (3 mL) was added, the solution was cooled to 0°, and acetic anhydride (3 mL) was added. After 2 d, the solution was poured into saturated aqueous sodium hydrogencarbonate, and the mixture stirred for 2 h, extracted with chloroform, the extract dried (magnesium sulfate), evaporated with the aid of toluene, and the residue dissolved in diethyl ether (3 mL). Formic acid (3 mL, 70%) was added, and after 20 min, more ether (20 mL) was added. The mixture was successively washed with water and saturated sodium hydrogencarbonate solution, dried (magnesium sulfate), and evaporated. The residue was purified by flash chromatography (4:1 hexane–ethyl acetate), yielding methyl 2,3-di-*O*-acetyl-4-deoxy-α-D-*xylo*-hexopyranoside (**39**) as a gum (0.10 g, 0.38 mmol, 34%); ^{1}H-n.m.r. data (300 MHz, $CDCl_3$): δ 5.31 (ddd, 1 H, $J_{3,4a} = J_{3,2} = 10.4$, $J_{3,4e}$ 5.2 Hz, H-3), 4.94 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.84 (dd, 1 H, $J_{2,3}$ 10.4, $J_{2,1}$ 3.5 Hz, H-2), 3.95 (m, 1 H, H-5), 3.69 (d, 1 H, $J_{6,6'}$ 12.0 Hz, H-6), 3.56 (d, 1 H, $J_{6',6}$ 12.0 Hz, H-6'), 3.39 (s, 3 H, OMe), 2.02–2.18 (m, 7 H, 2 AcO, H4*e*), and 1.63 (ddd, 1 H, $J_{4a,3} = J_{4a,4e} = J_{4a,5} = 11.0$ Hz, H-4*a*).

Compound **39** (0.46 g, 1.75 mmol) and 2,4,6-trimethylpyridine (0.46 mL, 3.51 mmol) were dissolved in dry, ethanol-free dichloromethane (10 mL). The mixture was treated with DAST (0.46 mL, 3.51 mmol) as described in the synthesis of **21**, worked up after 28 h, and purified by flash chromatography (3:2 hexane–ethyl acetate), to yield methyl 2,3-di-*O*-acetyl-4,6-dideoxy-6-fluoro-α-D-*xylo*-hexopyranoside (**40**) as a gum (0.31 g, 1.17 mmol, 66%); ^{1}H-n.m.r. data (270 MHz, $CDCl_3$): δ 5.31 (ddd, 1 H, $J_{3,4a} = J_{3,2} = 10.5$, $J_{3,4e}$ 5.0 Hz, H-3), 4.95 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.87 (dd, 1 H, $J_{2,3}$ 10.5, $J_{2,1}$ 4.0 Hz, H-2), 4.42 (dm, 2 H, $J_{6+6',F}$ 48.0 Hz, H-6,6'), 4.08 (m, 1 H, H-5), 3.40 (s, 3 H, MeO), 2.18 (dm, 1 H, $J_{4e,4a}$ 12.0 Hz, H-4*e*), 2.02, 2.08 (2 s, 6 H, 2 AcO), and 1.64 (ddd, 1 H, $J_{4a,3} = J_{4a,5} = J_{4a,4e} = 12.0$ Hz, H-4*a*).

A solution of **40** (0.30 g, 1.14 mmol) in dichloromethyl methyl ether (6 mL) was treated exactly as in the preparation of **3**. Purification was achieved by flash chromatography (2:1 hexane–ethyl acetate), to yield 2,3-di-*O*-acetyl-4,6-dideoxy-6-fluoro-α-D-*xylo*-hexopyranosyl chloride (**41**) as a gum (0.22 g, 0.82 mmol, 72%); ^{1}H-n.m.r. data (270 MHz, $CDCl_3$): δ 6.35 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.40 (ddd, 1 H, $J_{3,4a} = J_{3,2} = 10.5$, $J_{3,4e}$ 5.0 Hz, H-3), 4.96 (dd, 1 H, $J_{2,3}$ 10.5, $J_{2,1}$ 4.0 Hz, H-2), 4.33–4.61 (m, 3 H, H-5,6,6'), 2.28 (ddd, 1 H, $J_{4e,4a}$ 12.0, $J_{4e,3}$ 4.8, $J_{4e,5}$ 2.1 Hz, H-4*e*), 2.12, 2.07 (2 s, 6 H, 2 AcO), and 1.80 (ddd, 1 H, $J_{4a,3} = J_{4a,5} = J_{4a,4e} = 12.0$ Hz, H-4*a*).

A solution of chloride **41** (0.30 g, 1.13 mmol) and mercuric acetate (0.54 g, 1.7 mmol) in glacial acetic acid was treated exactly as described for the preparation of **4**. The product, 1,2,3-tri-*O*-acetyl-4,6-dideoxy-6-fluoro-β-D-*xylo*-hexopyranose (**42**), crystallized from diethyl ether–pentane (yield 0.25 g, 0.85 mmol, 76%); m.p. 102.5–103°; ^{1}H-n.m.r. data (270 MHz, $CDCl_3$): δ 5.68 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.02–5.08 (m, 2 H, H-2,3), 4.45 (dm, 2 H, $J_{6+6',F}$ 47.0 Hz, H-6,6'), 3.91 (m, 1 H, H-5), 2.04–2.18 (m, 7 H, H-4*e*, 2 AcO), and 1.74 (ddd, 1 H, $J_{4a,3} = J_{4a,5} = J_{4a,4e}$ = 12.0 Hz, H-4*a*).

The per-*O*-acetate **42** (0.15 g, 0.51 mmol) and anhydrous phosphoric acid (0.35 g, 3.6 mmol) were treated for 2.5 h exactly as described in the synthesis of **13**. The brown bis(cyclohexylammonium) salt was recrystallized three times, to yield **38** as an off-white powder (0.056 g, 0.13 mmol, 25%); ^{31}P-n.m.r. data (121 MHz, D_2O): δ −4.61 (dd, $J_{P,1}$ 7.2, $J_{P,2}$ 2.2 Hz).

Anal. Calc. for $C_{18}H_{38}FN_2O_7P$: C, 48.64; H, 8.62; N, 6.30. Found: C, 48.71; H, 8.58; N, 6.37.

Hydrolysis studies. — Hydrolysis conditions employed were essentially identical to those described previously[10]. Acid-catalyzed hydrolysis was monitored by incubating a solution of the sugar phosphate (~1.5 mM) in 1.0M perchloric acid at the desired temperature (±0.02°), removing 0.1-mL aliquots at appropriate intervals, and analyzing for phosphate released (by using the assay of Baginski *et al.*[26]). Total-hydrolysis data were obtained by heating samples (in triplicate) for 30 min in a boiling-water bath, and data obtained in this way agreed closely with calculated values in all cases. The assay employed is more sensitive than the standard Fiske–Subbarow assay, allowing use of smaller aliquots. It is also more useful for acid-sensitive phosphoric esters, because any hydrolysis of the phosphoric ester after addition of the reducing agent results in no further color development. Rates of hydrolysis of 2-deoxy-α-D-*arabino*-hexopyranosyl phosphate could not be determined by this method, as the acidic conditions of the assay prior to addition of the reducing agent resulted in substantial hydrolysis of the phosphoric ester. Thus, an enzymic assay which operates at neutral pH values was developed[14]. In this case, due to the high rate of reaction, hydrolysis rates were determined at lower temperatures, and extrapolated to 25°.

Rate constants were determined from plots of $\log[(A_T - A_t)/A_T]$ *versus* time, where A_t is the absorbance value at time t, and A_T is the absorbance value for the totally hydrolyzed sample. Plots were linear to at least two half-lives for each compound studied, with correlation coefficients greater than 0.981 and comprising from 5 to 15 data points in each case.

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