Synthesis and Antiviral Activity of Some 3′-C-Difluoromethyl and 3′-Deoxy-3′-C-fluoromethyl Nucleosides

Mark J. Bamford, Paul L. Coe, and Richard T. Walker*

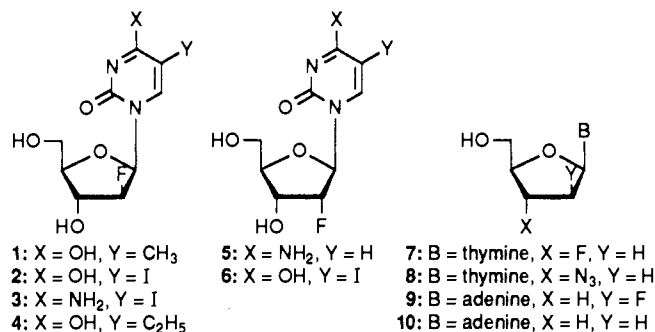*School of Chemistry, University of Birmingham, P.O. Box 363, Edgbaston, Birmingham, B15 2TT, England.*
Received January 9, 1990

The synthesis and antiviral activity of a number of 3′-C-difluoromethyl and 3′-deoxy-3′-C-fluoromethyl nucleosides are reported. The 3′-C-difluoromethyl nucleosides **26a** and **26b** were obtained by treatment of the corresponding 2′,5′-di-O-protected-3′-C-formyl nucleosides **25a** and **25b** with (diethylamino)sulfur trifluoride (DAST). Removal of the 2′-O-protecting group from **26a** and subsequent reaction with DAST furnished the 2′-deoxy-2′-fluoro-β-D-*ribo*-pentofuranosyl nucleoside **29**. Selective fluorination with DAST of the 5′-O-protected analogues 3′-deoxy-3′-C-hydroxymethyl derivatives **13a** and **13b** gave the 3′-deoxy-3′-C-fluoromethyl derivatives **30a** and **30b**, while nonselective fluorination afforded the 2′,3′-dideoxy-2′-fluoro-3′-C-fluoromethyl analogues **31a** and **31b**. The deprotected uracil analogue **17a** was iodinated to the 5-iodouracil derivative **18**. The fully deprotected fluorinated 3′-C-branched nucleosides **14–18** and **32** were evaluated for their antiviral activity. None were active against human immunodeficiency virus type-1 (HIV-1) at concentrations up to 100 μM. However, 5-iodouracil analogue **18** showed activity, comparable to that of acyclovir, against varicella zoster virus without observed cytotoxicity.
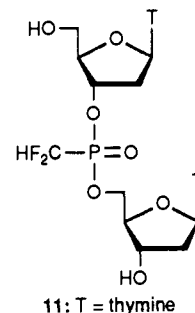
Introduction

A number of nucleosides substituted with fluorine in the sugar moiety show potent and selective antiviral activity. Perhaps the best known of these are the 1-(2-deoxy-2-fluoro-β-D-*arabino*-pentofuranosyl) nucleoside analogues of thymidine (FMAU) **1**, 5-iodouridine (FIAU) **2**, 5-iodo-cytidine (FIAC) **3**,[1] and 5-ethyluridine (FEAU) **4**.[2] These, and a number of other analogues, have a broad spectrum of antiherpes activity, as well as antitumor activity in some cases.[3] The *arabino*-pentofuranosyl sugar configuration is not a prerequisite for antiviral activity; however, 1-(2-deoxy-2-fluoro-β-D-*ribo*-pentofuranosyl)cytosine (**5**) possesses activity against a number of viruses including herpes simplex virus type-1 (HSV-1) and type-2 (HSV-2),[4] and the 5-iodouracil analogue **6** displays antiherpetic activity similar to that of **1**.[4] 1-(2,3-Dideoxy-3-fluoro-β-D-*erythro*-pentofuranosyl)thymine (FddT) (**7**)[5] is one of the most potent anti-human immunodeficiency virus type-1 (HIV-1) agents known (ID$_{50}$ = 0.05 μM in MT-4 cells) although it is more toxic than 3′-azidothymidine (AZT) (**8**).[6] Similarly, 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pento-furanosyl)adenine (2′-F*ara*ddA) (**9**)[7] was approximately as active as both **8** and 2′,3′-dideoxyadenosine (ddA) **10** in protecting ATH8 cells.

The CF$_2$ and CFH groups have been proposed[8–10] as reasonable isosteric and isopolar replacements for neutral oxygen, conferring phosphatase stability on nucleotide phosphate moieties.[8] In addition, the CF$_2$H and CH$_2$F groups have been employed[9,10] as preferable replacements for CH$_3$ in oligo(deoxyribonucleotide methyl phosphonate)

1: X = OH, Y = CH$_3$
2: X = OH, Y = I
3: X = NH$_2$, Y = I
4: X = OH, Y = C$_2$H$_5$

5: X = NH$_2$, Y = H
6: X = OH, Y = I

7: B = thymine, X = F, Y = H
8: B = thymine, X = N$_3$, Y = H
9: B = adenine, X = H, Y = F
10: B = adenine, X = H, Y = H

analogues such as **11**. The CF$_2$H is particularly favored
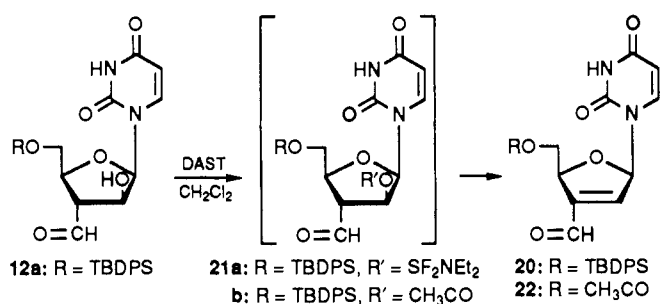

11: T = thymine

due to its ability to act as a hydrogen donor,[9,11] potentially allowing interaction with solvent and biological molecules. These reports stimulated our interest in the effect on biological activity of replacement of hydroxyl groups in the sugar moiety of nucleosides with the CF$_2$H and CH$_2$F groups. In particular, it appeared that the replacement of the 3′-hydroxyl may maintain recognition by key enzymes but that, due to the central role of this hydroxyl in the polymerization process, the processing of nucleosides in virally infected cells would be disrupted.

The CF$_2$H moiety has been obtained under mild conditions, including in nucleoside analogues,[12,13] by the reaction of an aldehyde with (diethylamino)sulfur trifluoride (DAST).[14,15] The CH$_2$F is similarly attainable by reaction of CH$_2$OH with DAST. Work in this laboratory[16] has
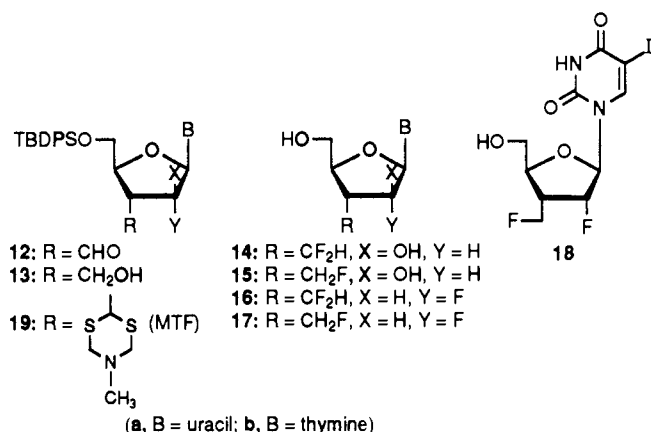
(1) Watanabe, K. A.; Reichman, U.; Hirota, K.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1979**, *22*, 21.

(2) Su, T.-L.; Watanabe, K. A.; Schinazi, R. F.; Fox, J. J. *J. Med. Chem.* **1986**, *29*, 151.

(3) Burchenal, J. H.; Chou, T.-C.; Lokys, L.; Smith, R. S.; Watanabe, K. A.; Su, T.-L.; Fox, J. J. *Cancer Res.* **1982**, *42*, 2598.

(4) Wohlrab, F.; Jamieson, A. T.; Hay, J.; Mengel, R.; Guschlbauer, W. *Biochim. Biophys. Acta* **1985**, *824*, 233.

(5) Matthes, E.; Lehmann, C.; Scholtz, D.; von Janta-Lipinski, M.; Gaertner, K.; Rosenthal, H. A.; Langen, P. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 78.

(6) Matthes, E.; Lehmann, C.; Scholtz, D.; Rosenthal, H. A.; Langen, P. *Biochem. Biophys. Res. Commun.* **1988**, *153*, 825.

(7) Marquez, V. E.; Tseng, C. K.-H.; Kelley, J. A.; Mitsuya, H.; Broder, S.; Roth, J. S.; Driscoll, J. S. *Biochem. Pharmacol.* **1987**, *36*, 2719.

(8) Blackburn, G. M.; Eckstein, F.; Kent, D. E.; Perree, D. *Nucleosides Nucleotides* **1985**, *4*, 165.

(9) Bergstrom, D. E.; Romo, E.; Shum, P. *Nucleosides Nucleotides* **1987**, *6*, 53.

(10) Bergstrom, D. E.; Shum, P. W. *J. Org. Chem.* **1988**, *53*, 3953.

(11) Nelson, D. D., Jr.; Fraser, G. T.; Klemperer, W. *Science* **1987**, *238*, 1670.

(12) McCarthy, J. R.; Jarvi, E. T.; Matthews, D. P.; Edwards, M. L.; Prakash, N. J.; Bowlin, T. L.; Mehdi, S.; Sunkara, P. S.; Bey, P. *J. Am. Chem. Soc.* **1989**, *111*, 1127.

(13) Matulic-Adamic, J.; Takahashi, K.; Chou, T.-C.; Gadler, H.; Price, R. W.; Reddy, A. R. V.; Kalman, T. I.; Watanabe, K. A. *J. Med. Chem.* **1988**, *31*, 1642.

(14) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

(15) Hudlicky, M. *Org. React. (N.Y.)* **1988**, *35*, 513.

Scheme I

12a: R = TBDPS   **21a:** R = TBDPS, R' = SF$_2$NEt$_2$ **20:** R = TBDPS
                      b: R = TBDPS, R' = CH$_3$CO   **22:** R = CH$_3$CO

established an efficient and high yielding route to both 3'-deoxy-3'-*C*-formyl- and 3'-deoxy-3'-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl nucleoside derivatives **12a** and **12b**, and **13a** and **13b**, respectively. This paper describes the conversion of **12a** and **12b** into the 3'-*C*-difluoromethyl derivatives **14a** and **14b**, and of **13a** and **13b** into the 3'-*C*-fluoromethyl derivatives **15a** and **15b**, respectively. Their conversion into the 2',3'-dideoxy-2'-fluoro-*ribo*-pentofuranosyl analogues **16a**, **16b**, **17a**, and **17b** is also described, as is the formation of 5-iodouracil derivative **18**, an analogue of the antiviral **6**. The antiviral effects of all the new fluorinated nucleoside analogues are reported.
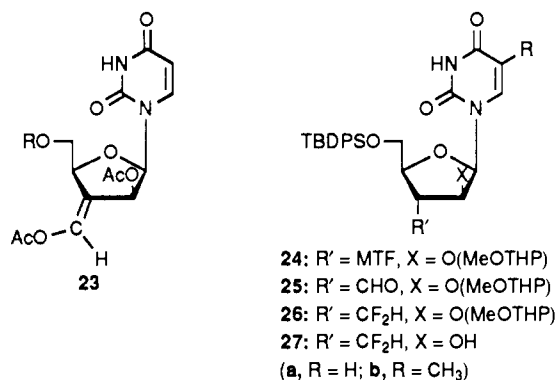

12: R = CHO
13: R = CH$_2$OH

19: R = S⌒S (MTF)
        N
        |
        CH$_3$

14: R = CF$_2$H, X = OH, Y = H
15: R = CH$_2$F, X = OH, Y = H
16: R = CF$_2$H, X = H, Y = F
17: R = CH$_2$F, X = H, Y = F

18

(**a**, B = uracil; **b**, B = thymine)

Chemistry

The key intermediate 1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-*C*-formyl-β-D-*arabino*-pentofuranosyl] nucleosides **12** were obtained from the 3'-*C*-(4,5-dihydro-5-methyl-1,3,5-dithiazin-2-yl) analogues **19** as previously described.[16] Attempted direct fluorination of **12a** with DAST (Scheme I) resulted in 2',3'-elimination to give 2',3'-didehydro-3'-*C*-formyl-β-D-*glycero*-pent-2'-enofuranosyl derivative **20** (30%), presumably as a result of selective formation of the 2'-*O*-derivatized intermediate **21a**. Spectral data for **20** agreed with that previously obtained[16] for the 5'-*O*-acetyl derivative **22**. Such elimination products in reactions of DAST are well documented.[18-24] The identity of **20** was confirmed by syn-

thesis of an authentic sample; reaction of **12a** with 1.1 equiv of acetic anhydride in pyridine gave **20** (62%), but it also gave a nucleoside consistent with structure **23** (17%). Only one geometric isomer of **23**, possessing the more stable *E* configuration, was observed by ^{1}H NMR, suggesting thermodynamic control. Also, only one configuration at C2' was observed, while Michael-type addition of acetate anion at C2' of **20** might be expected to occur not only from below but also to some extent from above the plane of the sugar ring. This suggests that **23** is formed either by direct trapping of the enol form of **21b** or by 1,2-addition of acetic anhydride to **21b** with subsequent elimination of acetic acid.[17] Attempted desilylation of **20** and **23** gave decomposition to a number of unisolated products.

Reaction of compounds **19a** and **19b** with 9 equiv of 4-methoxy-5,6-dihydro-2*H*-pyran[21] afforded the fully derivatized **24a** (87%) and **24b** (79%), respectively. Mercuric salt catalyzed hydrolysis[16] gave particularly efficient conversion into the 3'-*C*-formyl nucleosides **25a** (98%) and **25b** (93%), respectively. The subsequent fluorination of **25a** and **25b** with DAST allowed isolation in high yield (82-88%) of the 3'-*C*-difluoromethyl nucleosides **26a** and **26b**, respectively. Attempted removal of the 2'-*O*-4-methoxytetrahydropyran-4-yl (MeOTHP) group from **26a** in a 1:1 mixture of 0.01 M HCl[21] and 1,4-dioxane was unsuccessful. Use of trifluoroacetic acid (TFA) in *n*-butyl alcohol (*n*-BuOH),[22] however, allowed conversion of compounds **26a** and **26b** into the desired 2'-*O*-deprotected nucleosides **27a** and **27b**, respectively, but in only 50%

23

24: R' = MTF, X = O(MeOTHP)
25: R' = CHO, X = O(MeOTHP)
26: R' = CF$_2$H, X = O(MeOTHP)
27: R' = CF$_2$H, X = OH

(**a**, R = H; **b**, R = CH$_3$)

yield. The previous report[20] that a 5'-*O*-MeOTHP group was more readily removed than a 2'-*O*-MeOTHP group suggests that steric effects are important in this specific acid catalyzed reaction; the combination of the arabino configuration and the bulky 5'-*O*-protecting group is likely to make the 2'-*O*-MeOTHP group in **26a** and **26b** especially hindered. Desilylation[23] of **27a** gave the fully deprotected **14a** (93%). A lower yield was obtained in desilylation of the fully derivatized **26b** to give **28** (57%), again suggesting steric hindrance of the 5'-*O*-protecting group. Removal of the remaining 2'-*O*-MeOTHP group from **28** to give **14b** was readily effected with 0.01 M HCl in 83% yield, confirming the steric effect of the 5'-*O*-protecting group on hydrolysis at the 2'-position; that the reaction time was 9 h suggests that such effects were still considerable in **28**, however.

Fluorination of uridine derivative **27a** with DAST to give **29** (72%), followed by desilylation (93%), gave 1-[2,3-dideoxy-3-*C*-(difluoromethyl)-2-fluoro-β-D-*ribo*-pentofuranosyl]uracil (**16a**).

(16) Bamford, M. J.; Coe, P. L.; Walker, R. T. *J. Med. Chem.*, following paper in this issue.
(17) Allen, C. F. H.; Normington, J. B.; Wilson, C. V. *Can. J. Res.* **1934**, *11*, 382.
(18) Tewson, T. J.; Welch, M. J. *J. Org. Chem.* **1978**, *43*, 1090.
(19) Somekh, L.; Shanzer, A. *J. Org. Chem.* **1983**, *48*, 907.
(20) Green, M. J.; Shue, H.-J.; Tanabe, M.; Yasuda, D. M.; McPhail, A. T.; Onan, K. D. *J. Chem. Soc., Chem. Commun.* **1977**, 611.
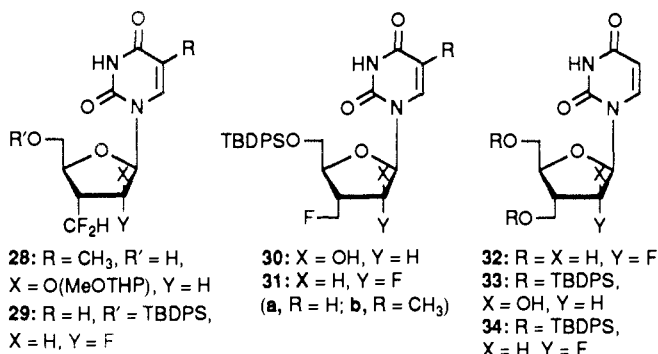(21) Reese, C. B.; Saffhill, R.; Sulston, J. E. *Tetrahedron* **1970**, *26*, 1023.
(22) MacCoss, M.; Cameron, D. J. *Carbohydr. Res.* **1978**, *60*, 206.
(23) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

(24) Michelson, A. M. In *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. J., Eds.; Interscience: New York, 1968; p 491.

Selective fluorination of the primary hydroxyl group of compounds 13a and 13b with 1.1 equiv. DAST at –60 °C gave 30a (65%) and 30b (32%), respectively. Desilylation afforded the fully deprotected 3'-deoxy-3'-*C*-(fluoromethyl) derivatives 15 (34–52%). Reaction of 13a and 13b with 2.2 equiv of DAST at 18 °C produced the difluoro derivatives 31a (50%) and 31b (45%), which were desilylated to 17a and 17b (80–83%), respectively. Uracil derivative 17a was converted[24] to the 5-iodouracil analogue 18 in 70% yield. 1-[2,3-Dideoxy-2-fluoro-3-(hydroxymethyl)-β-D-*ribo*-pentofuranosyl]uracil (32) was obtained by selective silylation of 13a with 1.1 equiv of *tert*-butylchlorodiphenylsilane to give 33 (96%), followed by reaction with 2 equiv of DAST to give 34 (64%) and desilylation (64%).

28: R = CH₃, R' = H,
X = O(MeOTHP), Y = H
29: R = H, R' = TBDPS,
X = H, Y = F

30: X = OH, Y = H
31: X = H, Y = F
(a, R = H; b, R = CH₃)

32: R = X = H, Y = F
33: R = TBDPS,
X = OH, Y = H
34: R = TBDPS,
X = H, Y = F

The assignment of structure of all compounds was based on ¹⁹F and ¹H NMR data. The ¹H NMR resonances of H₁', δ = 6 ppm (d, J = 5 Hz) and H₂', δ = 4.3 ppm (q (t on D₂O-shake)) were characteristic[16,25] of the *arabino*-pentofuranosyl nucleosides. The 2'-deoxy-2'-fluoro-β-D-*ribo*-pentofuranosyl nucleosides displayed a ¹⁹F resonance (an ill-resolved ddd due to coupling with H₁', H₂', and H₃') at a chemical shift (δ – 194) characteristic of a secondary fluorine; additionally the ¹H NMR spectrum displayed a large heteronuclear coupling ($^2J_{HF}$ = 52 Hz) and downfield shift (δ 5.50) for H₂' and a large *vicinal* coupling ($^3J_{HF}$ = 20 Hz) for H₁' (δ 5.95). The ribo-configuration was confirmed by the very large coupling between F₂' and H₃' ($^3J_{HF}$ = 35 Hz) suggesting an exceptionally high contribution to the conformer equilibrium of that sugar conformation (C₃'-endo) for which F₂' and H₃' are trans-diaxial. Also, the coupling between H₁' and H₂' was negligible due to a 90° dihedral angle, and $^3J_{H3'-H4'}$ was particularly large (10.5 Hz) resulting from a further trans-diaxial arrangement. This strong preference for the C₃'-endo conformation is in agreement with previous observations with 2'-deoxy-2'-fluoro-β-D-*ribo*-pentofuranosyl nucleosides,[26,27] but is perhaps more pronounced in this case due to the steric preference of the more bulky 3'-C-substituent for an equatorial orientation.

The 3'-*C*-fluoromethyl derivatives displayed a characteristic doublet and triplet in the ¹H and ¹⁹F NMR spectra, respectively, due to coupling ($^2J_{HF}$ = 47 Hz) of the primary fluorine and H₃''. The relative populations of the possible rotamers about the C₃'-C₃'' bond were deduced from $^3J_{H3'-F3''}$. $^3J_{HF}$ for a trans arrangement of the coupled nuclei is generally around 30 Hz,[28] while for a gauche arrangement $^3J_{HF}$ is reported[28] to be smaller at around 6.5–13.5 Hz. For

the *arabino*-pentofuranosyl nucleosides $^3J_{HF}$ = 22–25 Hz, suggesting a preference for the conformation in which F₃'' and H₃' are trans, thus relieving interactions of F₃'' with both OH₂' and ROCH₂₄'. The smaller $^3J_{H3'F3''}$ = 14–15 Hz for the 2'-deoxy-2'-fluoro-β-D-*ribo*-pentofuranosyl derivatives may be due to a favored gauche arrangement[29] in order to relieve interactions between F₃'' and F₂', but this may also be due to a fully time-averaged coupling constant with little conformational preference.[28]

The 3'-*C*-difluoromethyl derivatives displayed a characteristic triplet ($^2J_{HF}$ = 55 Hz) for the CF₂H group in the ¹H NMR spectrum. The coupling pattern of the ¹⁹F NMR signal for the CF₂H fluorines was highly dependent on the nature of the rest of the molecule. For the fully deprotected 3'-deoxy-3'-*C*-(difluoromethyl)-β-D-*arabino*-pentofuranosyl nucleosides 14a and 14b a simple doublet ($^2J_{HF}$ = 55 Hz) of doublets ($^3J_{HF}$ = 15.3 Hz) was observed, due to either the electronic environments of the two fluorine positions being insufficiently different or to rapid rotation on the NMR timescale about the C₃'-C₃'' bond so that the potential anisochronicity of the prochiral fluorines was not observed. This may be resolved by variable-temperature NMR, but such experiments have yet to be conducted. For the 2',3'-dideoxy-2'-fluoro-β-D-*ribo*-pentofuranosyl nucleoside 16a a highly resolved AB system was apparent with a difference in δ for the two fluorines (Δδ) of 6.2 ppm. This may be due either to increased interaction between F₃'' and F₂' resulting in some conformational preference about the C₃'-C₃'' bond or to a greater difference in the electronic environments of the two fluorines. It is also possible that hydrogen bonding between H₃'' and F₂' can contribute to the non-equivalency of both F₃''s. The 2',5'-di-O-protected-*arabino*-pentofuranosyl analogues 26a and 26b displayed an intermediary Δδ for the geminal fluorines. The result is a very strongly coupled AB spin system for which J_{FF} ≫ the difference in the chemical shifts of the two nuclides. Hence, the AB character, and so J_{FF} have become so pronounced that the intensity of the outer lines of the four in the spectrum arising for these two spins have radically diminished in intensity.

The compounds synthesized in this report represent a new class of fluorinated- and 3'-C-branched-sugar nucleosides. Studies towards the synthesis of the 2'-deoxy analogues of 14b and 15b, both potentially chain-terminating antiviral agents, are continuing in this laboratory, as is the synthesis of other 5-substituted derivatives of these compounds.

Antiviral Testing

Antiviral and cytotoxicity testing was carried out on compounds 14a, 14b, 15a, 15b, 16a, 17a, 17b, 18a, 18b, and 32 against HIV-1 in MT-4 cells, HSV-1 and -2 in Vero cells, human cytomegalovirus (CMV) in MRC-5 cells, varicella zoster virus (VZV) in MRC-5 and/or CV-1 cells, and influenza-A in MDCK cells, all up to 100 µM. (*E*)-5-(2-Bromovinyl)-2'-deoxyuridine (BVDU) was assayed as reference.

None of the compounds showed activity against HIV-1. Inactivity of the *arabino*-pentofuranosyl analogue of 8 has been previously noted[30] and so the inactivity of 14 and 15 is not surprising. Similarly, we have established in this report that the 3'-*C*-branched-2',3'-dideoxy-2'-fluoro-β-D-*ribo*-pentofuranosyl nucleosides show a strong preference for a C3'-endo sugar conformation, while it has recently been proposed[31] that a C3'-exo conformation may be a

(25) Hollenberg, D. H.; Watanabe, K. A.; Fox, J. J. *J. Med. Chem.* 1977, 20, 113.
(26) Cushley, R. J.; Codington, J. F.; Fox, J. J. *Can. J. Chem.* 1968, 46, 1131.
(27) Blandin, M.; Son, T.-D.; Catlin, J. C.; Guschlbauer, W. *Biochim. Biophys. Acta* 1974, 361, 249.
(28) Phillips, L.; Wray, V. *J. Chem. Soc. B* 1971, 1618.

(29) Hall, L. D.; Evelyn, L. *Chem. Ind.* 1968, 183.
(30) Webb, T. R.; Mitsuya, H.; Broder, S. *J. Med. Chem.* 1988, 31, 1475.

prerequisite for anti-HIV activity.

Of the compounds tested only 5-iodouracil derivative **18** showed significant antiviral activity; **18** inhibited VZV with an IC_{50} of 5.3 μg/mL in CV-1 cells. It was inactive against the other viruses but none of the compounds exhibited toxic effects in uninfected Vero cells up to 100 μM. Thus, the activity of **18** is reduced compared to that of **6**, suggesting that the 3'-C-fluoromethyl substituent is detrimental. The effect of this, and the difluoromethyl substituent, in a molecule with no other modifications to the sugar moiety remains to be elucidated, however. That some activity was observed is encouragement for future studies in this area.

Experimental Section

General Procedures. Melting points were obtained on a Gallenkamp apparatus. ¹H NMR spectra were recorded with a JEOL FX90Q (90 MHz) or a JEOL GX270 (270 MHz) spectrometer in DMSO solution relative to an internal tetramethylsilane reference. ¹⁹F NMR spectra were recorded in the same solvent with the 90-MHz machine with trichlorofluoromethane as internal standard. FAB mass spectra were obtained on a Kratos MS80 spectrometer from samples dissolved in DMSO with 3-nitrobenzyl alcohol as matrix; sodium ion doping to give enhanced peaks was used as necessary. Samples for UV spectrophotometry were dissolved in spectroscopic grade ethanol and spectra were recorded on a Perkin-Elmer 552 spectrophotometer. Precoated, aluminum-backed, silica gel TLC plates (silica gel F₂₅₄, 0.2-mm thickness) were supplied by E. Merck, A.G. Detection was achieved under UV light (254 nm) or by spraying with 30% H₂SO₄ in ethanol and heating. Column chromatography was performed on silica gel 60, 230–400 mesh (Merck).

General Procedure for the Fluorination of 3'-C-Formyl Nucleosides. Dry 3'-formyl nucleoside[16] (0.302 mmol) was dissolved in dry dichloromethane (1.5 mL). Under dry nitrogen with stirring at room temperature (diethylamino)sulfur trifluoride (DAST) (0.1 mL, 0.79 mmol) was then added. After 90 min the reaction mixture was partitioned between dichloromethane and aqueous sodium bicarbonate. The organic layer was evaporated to a foaming gum and purified by flash silica column chromatography with chloroform–ethanol 15:1 as solvent.

Reaction of 1-[5-O-(tert-Butyldiphenylsilyl)-3-deoxy-3-C-formyl-β-D-arabino-pentofuranosyl]uracil (12a) with DAST. Reaction of **12a**[16] (98 mg, 0.198 mmol) by the general procedure led to the isolation of starting material (18 mg, 18%) and the less polar 1-[5-O-(tert-butyldiphenylsilyl)-2,3-dideydro-2,3-dideoxy-3-C-formyl-β-D-glycero-pent-2-enofuranosyl]uracil (**20**) (30 mg, 30%): UV λ_{max} 259 (ϵ 7950); λ_{min} 237 nm (ϵ 4475); ¹H NMR δ 11.45 (1 H, s, NH), 10.00 (1 H, s, CHO), 7.65–7.40 (11 H, m, H6, Ph₂), 7.25 (1 H, s, H1'), 7.00 (1 H, s, H2'), 5.10 (1 H, s, H4'), 4.60 (1 H, d, H5), 4.00 (2 H, m H5'), 1.00 (9 H, s, tBu); MS m/z 477 (M + H)⁺, 495 (M + Na)⁺.

Reaction of 12a with Acetic Anhydride. **12a** (200 mg, 0.404 mmol) was dissolved in dry pyridine (5 mL), and acetic anhydride (0.042 mL, 0.44 mmol) was added. This was stirred overnight at room temperature with exclusion of moisture. Solvent was removed in vacuo and the residue coevaporated with toluene and then acetone. The resultant foam was chromatographed on a silica gel column with chloroform–ethanol 20:1 to give **20** (120 mg, 62%) and 1-[2-O-acetyl-3-C-(acetyloxymethylene)-5-O-(tert-butyldiphenylsilyl)-3-deoxy-β-D-arabino-pentofuranosyl]uracil (**23**) (40 mg, 17%). First eluted nucleoside (**23**): UV λ_{max} 260 nm (ϵ 9640); λ_{min} 235 nm (ϵ 2360); ¹H NMR δ 11.40 (1 H, bd, NH), 7.70–7.40 (12 H, m, H6, H3'', Ph₂), 6.15 (1 H, d,, H1'), 5.70 (1 H, d, H2'), 5.50 (1 H, d, H5), 4.90 (1 H, m, H4'), 4.00 (2 H, m, H5'), 2.00 (3 H, s, acetyl-3''), 1.80 (3 H, s, acetyl-2'), 1.05 (9 H, s, tBu); MS m/z 579 (M + H)⁺, 601 (M + Na)⁺. Anal. (C₃₀H₃₄N₂O₈Si) C, H, N. Second eluted nucleoside (**20**): UV λ_{max} 260 nm (ϵ 8980); ¹H NMR δ 11.45 (1 H, bd, NH), 10.00 (1 H, s, CHO), 7.70–7.40 (11 H, m, H6, Ph₂), 7.25 (1 H, s, H1'), 7.00 (1 H, s, H2'), 5.10 (1 H, m, H4'), 4.65 (1 H, d, H5), 4.15–3.95 (2 H, m, H5'), 1.00 (9 H,

(31) Van Roey, P.; Salerno, J. M.; Chu, C.-K.; Schinazi, R. F. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 3929.

s, tBu); MS m/z 477 (M + H)⁺, 499 (M + Na)⁺. Anal. (C₂₆-H₂₈N₂O₅Si·0.1H₂O) C, H, N.

General Procedure for Reaction with 5,6-Dihydro-4-methoxy-2H-pyran. Nucleoside (0.167 mmol) was combined with p-toluenesulphonic acid monohydrate (2.5 mg, 0.013 mmol) in dry 1,4-dioxane (1 mL). To this was added 5,6-dihydro-4-methoxy-2H-pyran (0.168 mL, 1.498 mmol), and the mixture was stirred with exclusion of moisture at room temperature overnight. The solution was neutralized with sodium methoxide in methanol (1 M) and then solvent removed, initially at the water-pump and then under high vacuum. The yellow gum was chromatographed on a silica gel column with chloroform–ethanol 20:1 to give the product as a white foam.

1-[5-O-(tert-Butyldiphenylsilyl)-3-deoxy-3-C-(4,5-dihydro-5-methyl-1,3,5-dithiazin-2-yl)-2-O-(4-methoxytetrahydropyran-4-yl)-β-D-arabino-pentofuranosyl]uracil (24a). Reaction of 1-[5-O-(tert-butyldiphenylsilyl)-3-deoxy-3-C-(4,5-dihydro-5-methyl-1,3,5-dithiazin-2-yl)-β-D-arabino-pentofuranosyl]uracil (**19a**)[16] (100 mg, 0.167 mmol) with 5,6-dihydro-4-methoxy-2H-pyran was effected by the general procedure to give **24a** (94 mg, 87%): UV λ_{max} 261 nm (ϵ 8525); ¹H NMR δ 11.45 (1 H, bd, NH), 7.70–7.40 (11 H, m, H6, Ph₂), 6.10 (1 H, d, H1'), 5.45 (1 H, d, H5), 4.90 (3 H, m, SCHS, SCH₂N), 4.60 (1 H, m, H2'), 4.35 (1 H, m, H4'), 4.20 (2 H, m, SCH₂N), 3.90 (2 H, m, H5'), 3.70–3.30 (4 H, m, CH₂OCH₂), 3.00 (3 H, s, OCH₃), 2.70 (1 H, m, H3'), 2.45 (3 H, s, NCH₃), 1.90–1.50 (4 H, m, CH₂CCH₂), 1.05 (9 H, s, tBu); MS m/z 714 (M + H)⁺, 682 (M – MeO)⁺.

1-[5-O-(tert-Butyldiphenylsilyl)-3-deoxy-3-C-(4,5-dihydro-5-methyl-1,3,5-dithiazin-2-yl)-2-O-(4-methoxytetrahydropyran-4-yl)-β-D-arabino-pentofuranosyl]thymine (24b). 1-[5-O-(tert-Butyldiphenylsilyl)-3-deoxy-3-(4,5-dihydro-5-methyl-1,3,5-dithiazin-2-yl)-β-D-arabino-pentofuranosyl]thymine (**19b**)[16] (0.50 g, 0.85 mmol) was reacted with 4-methoxy-5,6-dihydro-2H-pyran according to the general procedure to give **24b** as a white foam (0.49 g, 79%): UV λ_{max} 265 nm (ϵ 9470); λ_{min} 235 nm; ¹H NMR δ 11.47 (1 H, s, NH), 7.70–7.40 (11 H, m, H6, Ph₂), 6.06 (1 H, d, H1'), 4.90 (3 H, m, SCHS, SCH₂N), 4.47 (1 H, m, H2'), 4.29 (1 H, m, H4'), 4.20 (2 H, m, SCH₂N), 3.90 (2 H, m, H5'), 3.63–3.50 (4 H, m, CH₂OCH₂), 3.04 (3 H, s, OCH₃), 2.81 (1 H, m, H3'), 2.45 (3 H, s, NCH₃), 1.90–1.30 (4 H, m, CH₂CCH₂), 1.58 (3 H, s, CH₃), 1.05 (9 H, s, tBu); MS m/z 728 (M + H)⁺, 750 (M + Na)⁺, 696 (M – MeO)⁺.

1-[5-O-(tert-Butyldiphenylsilyl)-3-deoxy-3-C-(difluoromethyl)-2-O-(4-methoxytetrahydropyran-4-yl)-β-D-arabino-pentofuranosyl]uracil (26a). 24a (0.36 g, 0.504 mmol) was hydrolyzed with mercuric salts for 5 min at 0 °C by the procedure previously reported.[16] Chromatography of the crude product (0.28 g, 98%) on a silica gel column with chloroform–ethanol 9:1 gave 1-[5-O-(tert-butyldiphenylsilyl)-3-deoxy-3-C-formyl-2-O-(4-methoxytetrahydropyran-4-yl)-β-D-arabino-pentofuranosyl]uracil (**25a**) as a white foam (0.22 g, 72%): UV λ_{max} 261 nm (ϵ 10135); λ_{min} 235 nm (ϵ 3140); ¹H NMR δ 11.45 (1 H, bd, NH), 9.70 (1 H, d, CHO), 7.70–7.40 (11 H, m, H6, Ph₂), 6.25 (1 H, d, H1'), 5.35 (1 H, d, H5), 5.10 (1 H, t, H2'), 4.25 (1 H, m, H4'), 3.95–3.80 (2 H, m, H5'), 3.50–3.35 (4 H, m, CH₂OCH₂), 3.25 (1 H, m, H3'), 3.00 (3 H, s, OCH₃), 1.80–1.40 (4 H, m, CH₂CCH₂), 1.00 (9 H, s, tBu); MS m/z 609 (M + H)⁺, 577 (M – MeO)⁺. **25a** (0.87 g, 1.431 mmol) was fluorinated with DAST according to the general procedure to give **26a** as a white foam (0.79 g, 88%): ¹H NMR δ 11.40 (1 H, s, NH), 7.70–7.40 (11 H, m, H6, Ph₂), 6.03 (1 H, t, H1'), 6.03, 5.79 and 5.74 (1 H, t, (J = 66 Hz) of m, CF₂H), 5.46 (1 H, d, H5), 4.44 (1 H, d of m, H2'), 4.08 (1 H, m, H4'), 3.95–3.80 (2 H, m, H5'), 3.73–3.51 (4 H, m, CH₂OCH₂), 2.97 (4 H, s + m, H3', OCH₃), 1.76–1.50 (4 H, m, CH₂CCH₂), 1.03 (9 H, s, tBu); ¹⁹F NMR (84.3 MHz), δ –127 (part of AB system, J = 56 Hz).

1-[5-O-(tert-Butyldiphenylsilyl)-3-deoxy-3-C-(difluoromethyl)-2-O-(4-methoxytetrahydropyran-4-yl)-β-D-arabino-pentofuranosyl]thymine (26b). 24b (0.49 g, 0.673 mmol) was hydrolyzed[16] for 7 min at 0 °C as before to give 1-[5-O-(tert-butyldiphenylsilyl)-3-deoxy-3-C-formyl-2-O-(4-methoxytetrahydropyran-4-yl)-β-D-arabino-pentofuranosyl]thymine (**25b**) as a white foam (0.39 g, 93%). This was used directly: UV λ_{max} 266 nm (ϵ 8380); λ_{min} 236 nm (ϵ 630); ¹H NMR δ 11.45 (1 H, s, NH), 9.70 (1 H, s, CHO), 7.70–7.35 (11 H, m, H6, Ph₂), 6.20 (1 H, d, H1'), 5.20 (1 H, t, H2'), 4.25 (1 H,

m, H4′), 4.00–3.80 (2 H, m, H5′), 3.65–3.40 (4 H, m, CH₂OCH₂), 3.25 (1 H, m, H3′), 3.00 (3 H, s, OCH₃), 1.80–1.20 (4 H, m, CH₂CCH₂), 1.60 (3 H, s, CH₃), 1.05 (9 H, s, *t*Bu); MS *m/z* 623 (M + H)⁺, 645 (M + Na)⁺. **25b** (0.188 g, 0.302 mmol) was fluorinated according to the general procedure to give **26b** as a white foam (0.16 g, 82%): UV λ_max 265 nm (ε 7630); λ_min 236 nm (ε 800); ¹H NMR δ 11.50 (1 H, s, NH), 7.70–7.45 (10 H, m, Ph₂), 6.88 (1 H, s, H6), 6.61, 6.41 and 6.19 (1 H, t, (*J* = 55.3 Hz) of d (*J* = 3.7 Hz), CF₂H), 6.04 (1 H, d, H1′), 4.55 (1 H, m, H2′), 4.10 (1 H, m, H4′), 4.00–3.80 (2 H, m, H5′), 3.65–3.35 (4 H, m, CH₂OCH₂), 3.05 (3 H, s, OMe), 2.90 (1 H, m, H3′), 1.80–1.20 (4 H, m, CH₂CCH₂), 1.35 (3 H, s, CH₃), 1.05 (9 H, s, *t*Bu); ¹⁹F NMR (84.3 MHz), δ −120 (1 F, possibly d (*J* = 53.9 Hz) of d (*J* = 15.3 Hz) of d (*J* = 22.1 Hz), but to which pairs of nuclei these couplings refer is not clear, CF₂H); MS *m/z* 667 (M + Na)⁺.

General Procedure for Desilylation with Tetrabutylammonium Fluoride (TBAF). *tert*-Butyldiphenylsilyl nucleoside (0.40 mmol) was dissolved in dry THF (20 mL), and TBAF (dried under high vacuum) (0.140 g, 0.535 mmol) was added. Stirring was continued with exclusion of moisture until TLC indicated complete reaction. Solvent was then removed in vacuo and the residue purified by column chromatography.

1-[3-Deoxy-3-*C*-(difluoromethyl)-β-D-*arabino*-pentofuranosyl]uracil (14a). **26a** (0.22 g, 0.349 mmol) was dissolved in a mixture of *n*-butyl alcohol (8.7 mL) and trifluoroacetic acid (2.9 mL) (to give a 0.03 M solution), and the mixture was stirred at room temperature for 10 min. TLC then indicated reaction to a more polar nucleoside to be complete. The reaction mixture was quenched with *n*-butyl alcohol (18 mL) and evaporated under high vacuum at, or below, 40 °C. The gummy residue was chromatographed on a silica gel column with chloroform–ethanol 20:1 to furnish 1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-*C*-(difluoromethyl)-β-D-*arabino*-pentofuranosyl]uracil (27a) as a white foam (0.09 g, 50%): ¹H NMR δ 11.34 (1 H, s, NH), 7.63–7.44 (11 H, m, H6, Ph₂), 6.54, 6.33 and 6.13 (1 H, t, (*J* = 55.8 Hz) of d (*J* = 4.5 Hz), CF₂H), 5.97 (1 H, d, H1′), 5.84 (1 H, d, OH-2′), 5.28 (1 H, d, H5), 4.43 (1 H, q (t on D₂O-shake), H2′), 3.95–3.82 (2 H, m, H5′), 4.10 (1 H, m, H4′), 2.75 (1 H, m, H3′), 1.02 (9 H, s, *t*Bu); MS *m/z* 517 (M + H)⁺, 539 (M + Na)⁺. **27a** (0.18 g, 0.348 mmol) was desilylated according to the general procedure. Flash column chromatography on silica with chloroform–ethanol 6:1 as eluent furnished **14a** as a white solid (0.09 g, 93%). A sample was recrystallized from ethyl acetate: UV λ_max 262 nm (ε 10 450); λ_min 230 nm (ε 1990); ¹H NMR δ 11.30 (1 H, bd, NH), 7.75 (1 H, d, H6), 6.50, 6.30 and 6.10 (1 H, t (*J* = 55.7 Hz) of d, CF₂H), 5.90 (1 H, d, H1′), 5.75 (1 H, m, OH2′), 5.60 (1 H, d, H5), 5.20 (1 H, m, OH5′), 4.40 (1 H, m (t on D₂O-shake), H2′), 3.95 (1 H, m, H4′), 3.70–3.50 (2 H, m, H5′), 2.57 (1 H, m, H3′); ¹⁹F NMR (84.3 MHz) δ −120 (2 F, d (*J* = 55 Hz) of d (*J* = 15.4 Hz), CF₂H); MS *m/z* 279 (M + H)⁺, 301 (M + Na)⁺. Anal. (C₁₀H₁₂F₂N₂O₅) C, H, N.

1-[3-Deoxy-3-*C*-(difluoromethyl)-β-D-*arabino*-pentofuranosyl]thymine (14b). Removal of the silyl protecting group from **26b** (0.14 g, 0.217 mmol) was carried out by the general procedure with a reaction period of 3 h. The crude product was chromatographed on a silica gel column with chloroform–ethanol 9:1 to furnish 1-[3-deoxy-3-*C*-(difluoromethyl)-2-*O*-(4-methoxytetrahydropyran-4-yl)-β-D-*arabino*-pentofuranosyl]thymine (28) as a white foam (50 mg, 57%): UV λ_max 266 nm (ε 6000); λ_min 232 nm; ¹H NMR δ 11.42 (1 H, s, NH), 7.56 (1 H, s, H6), 6.56, 6.35 and 6.15 (1 H, t (*J* = 55.4 Hz) of d (*J* = 3.50 Hz), CF₂H), 6.00 (1 H, d, H1′), 5.15 (1 H, t, OH5′), 4.50 (1 H, t, H2′), 3.96 (1 H, m, H4′), 3.75–3.35 (6 H, m, H5′, CH₂OCH₂), 2.80 (1 H, m, H3′), 1.79 (3 H, s, CH₃), 1.75–1.25 (4 H, m, CH₂CCH₂); MS *m/z* 407 (M + H)⁺, 429 (M + Na)⁺. Compound **28** (50 mg, 0.123 mmol) was dissolved in a mixture of HCl (0.01 M, 4.4 mL) and 1,4-dioxane (1 mL) and stirred at room temperature for 9 h. The solution was neutralized with sodium hydroxide (0.1 M) and evaporated in vacuo. Coevaporation with acetone and then ether gave a white solid which was chromatographed on a silica gel column with chloroform–ethanol 9:1. Evaporation of solvent yielded **14b** (0.03 g, 83%): mp 183–185 °C; UV λ_max 267 nm (ε 10 310); λ_min 234 nm (ε 1970); ¹H NMR δ 11.28 (1 H, s, NH), 7.62 (1 H, s, H6), 6.50, 6.29 and 6.08 (1 H, t (*J* = 55.7 Hz) of d (*J* = 4.40 Hz), CF₂H), 5.90 (1 H, d, H1′), 5.71 (1 H, d, OH2′), 5.20 (1 H, t, OH5′), 4.38 (1 H, q (t on D₂O-shake), H2′), 3.93 (1 H, m,

H4′), 3.70–3.55 (2 H, m, H5′), 2.60 (1 H, m, H3′), 1.77 (3 H, s, CH₃); ¹⁹F NMR (84.3 MHz) δ −119.5 (2 F, d (*J* = 54.9 Hz) of d (*J* = 15.3 Hz), CF₂H); MS *m/z* 293 (M + H)⁺, 315 (M + Na)⁺, 585 (2M + H)⁺. Anal. (C₁₁H₁₄F₂N₂O₅) C, H, N.

1-(2,3-Dideoxy-3-*C*-(difluoromethyl)-2-fluoro-β-D-*ribo*-pentofuranosyl)uracil (16a). **27a** (0.11 g, 0.213 mmol) was dissolved in dry dichloromethane (1.05 mL). (Diethylamino)sulfur trifluoride (0.04 mL, 0.329 mmol) was then added dropwise with stirring at room temperature under dry nitrogen. After 1 h the mixture was worked up as before and the crude product purified by silica column chromatography with chloroform–ethanol 20:1 as eluent. Evaporation of solvent furnished 1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-3-*C*-(difluoromethyl)-2-fluoro-β-D-*ribo*-pentofuranosyl]uracil (29) as a white foam (80 mg, 72%): ¹H NMR δ 11.35 (1 H, bd, NH), 7.75 (1 H, d, H6), 7.70–7.40 (10 H, m, Ph₂), 6.55, 6.35 and 6.15 (1 H, t (*J* = 56.7 Hz) of d (*J* = 6.2 Hz), CF₂H), 6.00 and 5.90 (1 H, d (*J* = 21.3 Hz), H1′), 5.75 and 5.55 (1 H, d (*J* = 52.1 Hz) of d (*J* = 4.6 Hz), H2′), 5.20 (1 H, d, H5), 4.55 (1 H, d (*J* = 10.1 Hz), H4′), 4.05–3.80 (2 H, m, H5′), 3.05 (1 H, m, H3′), 1.00 (9 H, s, *t*Bu); MS *m/z* 519 (M + H)⁺, 541 (M + Na)⁺, 461 (M − *t*Bu)⁺. Compound **29** (0.08 g, 0.154 mmol) was deprotected in a reaction time of 2 h by the general procedure. The resultant gum was flash chromatographed on a silica gel column with chloroform–ethanol 9:1 to give **16a** as a white solid (0.04 g, 93%). This was recrystallized from chloroform: UV λ_max 259 nm (ε 9595); λ_min 228 nm (ε 1500); ¹H NMR δ 11.39 (1 H, s, NH), 7.97 (1 H, d, H6), 6.53, 6.32 and 6.12 (1 H, t (*J* = 55 Hz) of d (*J* = 6.0 Hz), CFH), 5.90 (1 H, d (*J* = 20.0 Hz), H1′), 5.60 (1 H, d, H5), 5.60 and 5.40 (1 H, d (*J* = 52 Hz) of d (*J* = 4.9 Hz), H2′), 5.37 (1 H, bd, OH5′), 4.43 (1 H, d (*J* = 10.4 Hz), H4′), 3.85–3.54 (2 H, m, H5′), 3.00 (1 H, m, H3′); ¹⁹F NMR (84.3 MHz) δ −118 (2 F, AB system (δ_Fa −114.9; δ_Fb −121.0) (*J* = 295 Hz) of d (*J* = 55 Hz) of m, CF₂H), −194 (1 F, m, F2′); ¹⁹F NMR (¹H decoupled, 84.3 MHz) δ −118 (2 F, AB system of d (⁴*J*_FFa = 2.9 Hz; ⁴*J*_FFb = 6.9 Hz), F3′), −194 [1 F, d (*J* = 6.7 Hz) of d (*J* = 3.3 Hz), F2′]; MS *m/z* 281 (M + H)⁺. Anal. (C₁₀H₁₁F₃N₂O₄) C, H, N.

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-3-*C*-(fluoromethyl)-β-D-*arabino*-pentofuranosyl]uracil (30a). DAST (0.07 mL, 0.53 mmol) was dissolved in dichloromethane (0.75 mL) and the reaction vessel flushed with dry nitrogen. The mixture was cooled to −60 °C, and then a solution of 1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]uracil (13a) (0.20 g, 0.403 mmol) in dry dichloromethane (2.0 mL) was added dropwise with stirring. The mixture was allowed to warm slowly to room temperature over 1 h and stirring was continued for a further 45 min. The mixture was diluted with dichloromethane (25 mL) and washed with aqueous sodium bicarbonate (25 mL). The organic layer was evaporated, and residues of water were removed by coevaporation with acetone to give a solid. This was chromatographed on a silica gel column with chloroform–ethanol 9:1 to give **30a** as a white foam (130 mg, 65%). A sample was recrystallized from diethyl ether: UV λ_max 264 nm (ε 7760); λ_min 235 nm (ε 360); ¹H NMR δ 11.20 (1 H, bd, NH), 7.70–7.40 (11 H, m, H6, Ph₂), 5.99 (1 H, d, H1′), 5.72 (1 H, d, OH2′), 5.19 (1 H, d, H5), 4.67 and 4.50 (2 H, d (*J* = 47.4 Hz) of d (*J* = 5.3 Hz), CH₂F), 4.27 (1 H, q (t on D₂O-shake), H2′), 3.99–3.83 (3 H, m, H4′, H5′), 3.15 (1 H, m, H3′), 1.02 (9 H, s, *t*Bu); ¹⁹F NMR (84.6 MHz) δ −224 (d (*J* = 22.4 Hz) of t (*J* = 47.3 Hz), CH₂F); MS *m/z* 499 (M + H)⁺, 521 (M + Na)⁺. Anal. (C₂₆H₃₁FN₂O₅Si) C, H, N.

1-[3-Deoxy-3-*C*-(fluoromethyl)-β-D-*arabino*-pentofuranosyl]uracil (15a). Desilylation of **30a** (0.17 g, 0.341 mmol) was effected in 5 min by the general procedure. Chromatography of the crude product on a silica gel column with chloroform–ethanol 4:1 gave **15a** as a white solid (30 mg, 34%). This was crystallized from ethyl acetate: UV λ_max 262 (ε 10 650); λ_min (ε 2280); λ_max 208 nm (ε 9020); ¹H NMR δ 11.25 (1 H, bd, NH), 7.80 (1 H, d, H6), 5.95 (1 H, d, H1′), 5.70 (1 H, d, OH2′), 5.60 (1 H, d, H5), 5.15 (1 H, bd, OH5′), 4.70 and 4.50 (2 H, d (*J* = 47.4 Hz) of d (*J* = 5.1 Hz), CH₂F), 4.25 (1 H, q (t on D₂O-shake), H2′), 3.80 (1 H, m, H4′), 3.75–3.55 (2 H, m, H5′), 2.40–2.25 (1 H, m, H3′); ¹⁹F NMR (84.26 MHz) δ −224.7 (d (*J* = 24.4 Hz) of t (*J* = 47.3 Hz), CH₂F). Anal. (C₁₀H₁₃FN₂O₅) C, H, N.

1-[3-Deoxy-3-*C*-(fluoromethyl)-β-D-*arabino*-pentofuranosyl]thymine (15b). 1-[5-*O*-(*tert*-Butyldiphenylsilyl)-3-

deoxy-3-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]thymine (13b)[16] (100 mg, 0.196 mmol) was treated with DAST as for its uracil analogue above; workup as before was followed by silica column chromatography with chloroform–ethanol 20:1 to give **1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-3-(fluoromethyl)-β-D-*arabino*-pentofuranosyl]thymine (30b)** as a white foam (30 mg, 32%). This was reprecipitated from ether with hexane: ¹H NMR δ 11.31 (1 H, s, NH), 7.67–7.35 (11 H, m, H6, Ph₂), 5.98 (1 H, d, H1'), 5.64 (1 H, d, OH2'), 4.68 and 4.51 (2 H, d (*J* = 47.2 Hz) of d (*J* = 5.2 Hz), CH₂F), 4.23 (1 H, q (t on D₂O-shake), H2'), 3.99–3.89 (3 H, m, H4', H5'), 2.50 (1 H, m, H3'), 1.53 (3 H, s, CH₃), 1.02 (9 H, s, *t*Bu); MS *m/z* 513 (M + H)⁺, 535 (M + Na)⁺. Compound 30b (70 mg, 0.140 mmol) was treated with fluoride ion under the conditions of the general procedure, and the crude product was flash chromatographed on a silica gel column with chloroform–ethanol 9:1 to give 15b as a white solid (20 mg, 52%). This was crystallized from chloroform–acetone, mp 207–209 °C: UV λ_max 268 nm (ε 10 820); λ_min 235 nm (ε 2340); ¹H NMR δ 11.23 (1 H, s, NH), 7.72 (1 H, s, H6), 5.93 (1 H, d, H1'), 5.61 (1 H, d, OH2'), 5.17 (1 H, t, OH5'), 4.67 and 4.50 (2 H, d (*J* = 47.5 Hz) of d (*J* = 4.95 Hz), CH₂F), 4.24 (1 H, q (t on D₂O-shake), H2'), 3.80–3.58 (3 H, m, H4', H5'), 2.35 (1 H, m, H3'), 1.76 (3 H, s, CH₃); ¹⁹F NMR (84.3 MHz) δ -225 (d (*J* = 24.4 Hz) of t (*J* = 47.3 Hz), CH₂F); MS *m/z* 275 (M + H)⁺, 297 (M + Na)⁺, 549 (2M + H)⁺. Anal. (C₁₁H₁₅FN₂O₅) C, H, N.

1-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-fluoro-3-*C*-(fluoromethyl)-β-D-*ribo*-pentofuranosyl]uracil (31a). 13a (0.20 g, 0.403 mmol) was dissolved in dry dichloromethane (2 mL) and added dropwise to a solution of DAST (0.14 mL, 0.866 mmol) in dry dichloromethane (1.5 mL) with stirring under an atmosphere of dry nitrogen at -60 °C. The mixture was then allowed to warm to room temperature and stirring continued for 6.5 h. The solution was partitioned between dichloromethane and water, and the organic layer was evaporated to an off-white solid which was column chromatographed on silica with chloroform–ethanol 9:1. Further column chromatography with diethyl ether–hexane 4:1 as solvent gave 31a as a white foam (0.10 g, 50%): UV λ_max 260 nm (ε 8990); λ_min 234 nm (ε 1440); ¹H NMR δ 11.45 (1 H, s, NH), 7.80 (1 H, d, H6), 7.70–7.40 (10 H, m, Ph₂), 5.96 and 5.89 (1 H, d (*J* = 20.3 Hz), H1'), 5.57 and 5.37 (1 H, d (*J* = 52.3 Hz) of m, H2'), 5.17 (1 H, d, H5), 4.80–4.45 (2 H, AB (*J* = 46 Hz), CH₂F), 4.25 (1 H, d (*J* = 10.9 Hz), H4'), 4.10–3.80 (2 H, m, H5'), 2.95 (1 H, m, H3'), 1.05 (9 H, s, *t*Bu); ¹⁹F NMR (84.3 MHz), δ -193.7 (1 F, ddd, F2'), -224 (1 F, d (*J* = 15.3 Hz) of t (*J* = 47.3 Hz), CH₂F); MS *m/z* 501 (M + H)⁺, 523 (M + Na)⁺. Anal. (C₂₆H₃₀F₂N₂O₄Si) C, H, N.

1-[2,3-Dideoxy-2-fluoro-3-*C*-(fluoromethyl)-β-D-*ribo*-pentofuranosyl]uracil (17a). Deprotection of 31a (0.23 g, 0.459 mmol) was achieved by the general procedure with a reaction time of 80 min. The crude product was purified by silica column chromatography with chloroform–ethanol 9:1 to give 17a as a white solid (0.1 g, 83%), which was crystallized from ethyl acetate: UV λ_max 260 nm (ε 9000); λ_min 229 nm (ε 430); ¹H NMR δ 11.39 (1 H, s, NH), 8.00 (1 H, d, H6), 5.90 (1 H, d (*J* = 19 Hz), H1'), 5.60 (1 H, d, H5), 5.50 and 5.30 (1 H, d (*J* = 52.3 Hz) of d (*J* = 4 Hz), H2'), 5.30 (1 H, t, OH5'), 4.80–4.50 (2 H, m, CH₂F), 4.15 (1 H, d (*J* = 10.1 Hz), H4'), 3.85–3.60 (2 H, m, H5'), 2.80 (1 H, m, H3'); ¹⁹F NMR (84.3 MHz) δ -195 (1 F, m, F2'), -224.4 (1 F, (*J* = 15.3 Hz) of t (*J* = 45.8 Hz), CH₂F); *m/z* 263 (M + H)⁺, 285 (M + Na)⁺, 525 (2M + H)⁺, 547 (2M + Na)⁺. Anal. (C₁₀H₁₂F₂N₂O₄) C, H, N.

1-[2,3-Dideoxy-2-fluoro-3-*C*-(fluoromethyl)-β-D-*ribo*-pentofuranosyl]thymine (17b). 13a (0.20 g, 0.392 mmol) was treated with DAST by the method for compound 31a above. The crude product was flash chromatographed on a silica gel column with chloroform–ethanol 15:1 to give **1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-fluoro-3-*C*-(fluoromethyl)-β-D-*ribo*-pentofuranosyl]thymine (31b)** as a white foam (90 mg, 45%): UV λ_max 265 nm (ε 8150); ¹H NMR δ 11.35 (1 H, bd, NH), 7.75–7.35 (11 H, m, H6, Ph₂), 5.97 and 5.89 (1 H, d (*J* = 22 Hz), H1'), 5.58 and 5.39 (1 H, d (*J* = 52.7 Hz) of d (*J* = 5.44 Hz), H2'), 4.80–4.50 (2 H, AB, CH₂F), 4.25 (1 H, m, H4'), 4.05–3.85 (2 H, m, H5'), 3.00 (1 H, m, H3'), 1.48 (3 H, s, CH₃), 1.02 (9 H, s, *t*Bu); ¹⁹F NMR (84.3 MHz) δ -193 (1 F, ddd, F2'), -224 (1 F, d (*J* = 15.3 Hz) of t (*J* = 45.8 Hz), CH₂F); MS *m/z* 515 (M + H)⁺, 495 (M – F)⁺, 457 (M – *t*Bu)⁺, 437 (M – *t*Bu – HF)⁺. Deprotection

of 31b (80 mg, 0.155 mmol) according to the general procedure followed by silica column chromatography with chloroform–ethanol 9:1 gave 17b as a white powder (34 mg, 80%). This was crystallized from ether–chloroform 1:1 by addition of hexane, mp 156–160 °C: UV λ_max 266 nm (ε 8300); λ_min 232 nm (ε 455); ¹H NMR δ 11.35 (1 H, s, NH), 7.89 (1 H, s, H6), 5.90 (1 H, d (*J* = 19.3 Hz), H1'), 5.44 and 5.25 (1 H, d (*J* = 52.3 Hz) of d (*J* = 4.3 Hz), H2'), 5.35 (1 H, t, OH-5'), 4.80–4.50 (2 H, m, CH₂F), 4.10 (1 H, d (*J* = 10.4 Hz), H4'), 3.85–3.60 (2 H, m, H5'), 2.95–2.70 (1 H, m, H3'), 1.75 (3 H, s, CH₃); ¹⁹F NMR (84.3 MHz) δ -194.5 (1 F, d (*J* = 51.9 Hz) of d (*J* = 32.1 Hz) of d (*J* = 19.9 Hz), F2'), -224.2 (1 F, d (*J* = 14.3 Hz) of t (*J* = 46.6 Hz), CH₂F); MS *m/z* 277 (M + H)⁺, 299 (M + Na)⁺. Anal. (C₁₁H₁₄F₂N₂O₄) C, H, N.

1-[2,3-Dideoxy-2-fluoro-3-*C*-(fluoromethyl)-β-D-*ribo*-pentofuranosyl]-5-iodouracil (18). Uracil derivative 17a (41 mg, 0.156 mmol) was dissolved in a mixture of 1,4-dioxane (1.26 mL) and M/2 nitric acid (0.31 mL). Iodine (80 mg, 0.312 mmol) was added and the dark red-brown solution refluxed for 3 h. The mixture was then allowed to cool and evaporated in vacuo to a brown solid. This was repeatedly coevaporated with ethanol to give a light orange-pink solid, which was washed with diethyl ether (3 × 1 mL) and dried in vacuo. The crude product was purified by chromatography on a silica column with chloroform–ethanol 15:1 as solvent to give 18 as a white powder (42 mg, 70%). This was precipitated from chloroform with hexane: ¹H NMR δ 11.72 (1 H, s, NH), 8.63 (1 H, s, H6), 5.86 (1 H, d (*J* = 17.8 Hz), H1'), 5.48 (1 H, m, OH5'), 5.48 and 5.26 (1 H, d (*J* = 52.4 Hz) of d, H2'), 4.77–4.51 (2 H, m, CH₂F), 4.15 (1 H, d (*J* = 10.4 Hz), H4'), 3.86–3.57 (2 H, m, H5'), 2.80 (1 H, m, H3'); ¹⁹F NMR (84.3 MHz) δ -195.3 (1 F, d (*J* = 51.1 Hz) of d (*J* = 34.3 Hz) of d (*J* = 16.1 Hz), F2'), -224.8 (1 F, d (*J* = 14.3 Hz) of t (*J* = 47.3 Hz), CH₂F); MS *m/z* 389 (M + H)⁺, 411 (M + Na)⁺. Anal. (C₁₀H₁₁F₂IN₂O₄) C, H, N.

1-[2,3-Dideoxy-2-fluoro-3-*C*-(hydroxymethyl)-β-D-*ribo*-pentofuranosyl]uracil (32). 13a (0.148 g, 0.298 mmol) was dissolved in dry DMF (1.30 mL), and dry triethylamine (0.051 mL, 0.365 mmol) and DMAP (9 mg, 0.07 mmol) were added, followed by dropwise addition of *tert*-butyldichlorodiphenylsilane (0.084 mL, 0.324 mmol). This was stirred at room temperature with exclusion of moisture overnight, producing copious white crystalline deposit. Water (0.15 mL) was added and the clear solution stirred for 30 min. Solvent was removed under high vacuum, and the orange partitioned between water and ethyl acetate. The organic layer was dried (MgSO₄), filtered, and evaporated. The product was chromatographed on a silica gel column with chloroform–ethanol 20:1, and evaporation of solvent in vacuo gave 1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-*C*-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-deoxy-β-D-*arabino*-pentofuranosyl]uracil (33) as a white foam (0.21 g, 96%): ¹H NMR δ 11.28 (1 H, s, NH), 7.62–7.37 (21 H, H6, (Ph₂)₂), 6.02 (1 H, d, H1'), 5.56 (1 H, d, OH2'), 5.20 (1 H, d, H5), 4.29 (1 H, q (t on D₂O-shake), H2'), 3.99 (1 H, d, H4'), 3.99–3.65 (4 H, m, H5', H3''), 2.30 (1 H, m, H3'), 0.98 and 0.97 (18 H, 2s, (*t*Bu)₂). 33 (0.25 g, 0.340 mmol) was dissolved in dry dichloromethane (2 mL) under dry nitrogen. DAST (0.091 mL, 0.69 mmol) was then added at room temperature and stirred for 2 h. The mixture was worked up in the usual way, and the resultant colorless gum was chromatographed on a silica column with chloroform–ethanol 30:1. Removal of solvent in vacuo gave **1-[5-*O*-(*tert*-butyldiphenylsilyl)-3-*C*-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-2,3-dideoxy-2-fluoro-β-D-*ribo*-pentofuranosyl]uracil (34)** as a white foam (0.16 g, 64%): ¹H NMR δ 11.40 (1 H, s, NH), 7.80–7.30 (21 H, m, H6, (Ph₂)₂), 5.95 (1 H, d (*J* = 20 Hz), H1'), 5.55 and 5.40 (1 H, d (*J* = 52.2 Hz) of d (*J* = 4.2 Hz), H2'), 5.20 (1 H, d, H5), 4.15–4.05 (2 H, m, H5'), 3.85–3.70 (3 H, m, H4', H3''), 2.90 (1 H, m, H3'), 1.00 (18 H, 2s, (*t*Bu)₂); ¹⁹F NMR (84.3 MHz) δ -194 (m, F2'); MS *m/z* 759 (M + Na)⁺. Compound 34 (0.22 g, 0.299 mmol) was desilylated by the general procedure with a reaction period of 3 h. The crude product was purified by flash silica column chromatography with chloroform–ethanol 4:1 as eluent. Evaporation of solvent gave 32 as a white powder (50 mg, 64%), which was crystallized from ethyl acetate: UV λ_max 261 nm (ε 8370); λ_min 228 nm; ¹H NMR δ 11.31 (1 H, s, NH), 8.08 (1 H, d, H6), 5.86 (1 H, d (*J* = 17.6 Hz), H1'), 5.59 (1 H, d, H5), 5.33 and 5.14 (1 H, d (*J* = 51.8 Hz) of d (*J* = 4.30 Hz), H2'), 5.27 (1 H, t, OH5'), 4.82 (1 H, t, OH3''), 3.98 (1 H, d (*J* = 10.6 Hz), H4'),

3.86–3.30 (4 H, m, H5′, H3″), 2.40 (1 H, m, H3′); MS *m/z* 261 (M + H)⁺, 283 (M + Na)⁺. Anal. (C₁₀H₁₃FN₂O₅) C, H, N.

Antiviral Assay Procedures. Determination of antiviral activity and cytotoxicity was carried out as previously described.[16]

Synthesis and Antiviral Activity of 3'-Deoxy-3'-*C*-hydroxymethyl Nucleosides

Mark J. Bamford, Paul L. Coe, and Richard T. Walker*

*School of Chemistry, University of Birmingham, P.O. Box 363, Edgbaston, Birmingham, B15 2TT, England.
Received January 9, 1990*

A series of 3′-branched-chain sugar nucleosides, in particular 3′-deoxy-3′-*C*-hydroxymethyl nucleosides, have been synthesized and evaluated as antiviral agents. Reaction of 1-(2,3-epoxy-5-*O*-trityl-β-D-*lyxo*-pentofuranosyl) derivatives **12** and **13**, of uracil and thymine, respectively, with 5,6-dihydro-2-lithio-5-methyl-1,3,5-dithiazine **14** afforded the corresponding 3′-functionalized nucleosides **15** and **16**, respectively. Replacement of the trityl group with *tert*-butyldiphenylsilyl allowed high yielding hydrolysis of the 3′-function to give the 3′-deoxy-3′-*C*-formyl-β-D-*arabino*-pentofuranosyl nucleosides **21** and **22**. Desilylation afforded the 1-(3-deoxy-3-*C*-formyl-β-D-*lyxo*-pentofuranosyl) 3′,5′-*O*-hemiacetal nucleosides **33** and **34**, respectively. Reduction of the formyl group of **21** and **22**, followed by desilylation, yielded the 3′-deoxy-3′-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl) analogues **7** and **8**, respectively. The uracil base moiety of **7** was converted to 5-iodouracil and then to (*E*)-5-(2-bromovinyl)uracil to furnish an analogue **10** of BV*ara*U. The 1-(3-deoxy-3-*C*-(hydroxymethyl)-β-D-*lyxo*-pentofuranosyl) and 1-(2,3-dideoxy-3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl) derivatives of uracil (**31** and **6**, respectively) and 5-iodouracil (**32** and **9**, respectively) were also obtained. All novel, fully deprotected nucleoside analogues were evaluated for antiviral activity against human immunodeficiency virus type-1, herpes simplex virus types-1 and -2, varicella zoster virus, human cytomegalovirus and influenza A. Of the compounds tested only (*E*)-5-(2-bromovinyl)-1-[3-deoxy-3-*C*-(hydroxymethyl)-β-D-*arabino*-pentofuranosyl]uracil (**10**) inhibited VZV (alone), but did so at concentrations well below the cytotoxicity threshold.

Introduction

Nucleosides and nucleoside analogues have achieved considerable success in the fight against viral infection.[1] The first nucleoside antiviral, and the first antiviral chemotherapeutic agent to be licensed for use in humans, was 5-iodo-2′-deoxyuridine (**1**, IDU). This was successful in the topical treatment of herpes simplex keratitis in rabbits and man.[2] However, its selectivity was poor. The search for improved activity led to compounds such as (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (**2**, BVDU) which has been shown to be active against a number of viruses. In particular, it is one of the most potent and selective agents known against herpes simplex virus type-1 (HSV-1) (MIC = 0.007–0.01 µg/mL⁻¹)[3] and varicella zoster virus (VZV) (MIC = 0.0002–0.003 µg mL⁻¹).[4] Its selectivity stems from its 5′-phosphorylation by virus-induced thymidine kinase[5] initially to the monophosphate and then probably also to the diphosphate.[6] The 5′-triphosphate (BVDUTP), obtained through further phosphorylation by cellular kinases,

then inhibits viral polymerase (selectively[7]) and can also be incorporated by this polymerase into viral DNA.[8]

For a number of years now it has been recognized that branched-chain sugar nucleosides show biological activity.[9] For example, 2′,3′-dideoxy-3′-*C*-(hydroxymethyl)thioguanosine (**3**), a simple 3′-homologue of 2′-deoxythioguanosine, was found[10] to be inhibitory to the growth of WI-L2 cells. It was proposed[10] that acceptance by kinase and polymerase enzymes was improved if two primary hydroxyls were provided. More recently, the naturally occurring purine nucleosides analogue oxetanocin **4** and its derivatives were shown to be effective anti-human immunodeficiency virus type-1 (HIV-1)[11] and antiherpes virus[12] agents. Such reports prompted us to investigate the effect on biological activity of an hydroxymethyl substituent at the 3′-position of pyrimidine nucleoside analogues, with a view to maintaining or improving acceptance by viral enzymes and improving selectivity. It is known that modifications at the 3′-position of, for example, BVDU can be tolerated by processing enzymes; 3′-amino-(*E*)-5-(2-bromovinyl)-2′,3′-dideoxyuridine (**5**,

(1) Robins, R. K.; Revankar, G. R. In *Antiviral Drug Development: A Multi-Disciplinary Approach*; De Clercq, E., Walker, R. T., Eds.; Plenum Press: New York, 1988; p 11.
(2) Kaufman, H. E. *Proc. Soc. Exptl. Biol. Med.* **1962**, *109*, 251.
(3) De Clercq, E.; Descamps, J.; De Somer, J.; Barr, P. J.; Jones, A. S.; Walker, R. T. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2947.
(4) De Clercq, E.; Walker, R. T. *Pharmacol. Ther.* **1984**, *26*, 1.
(5) Cheng, Y.-C.; Dutschman, G.; De Clercq, E.; Jones, A. S.; Rahim, S. G.; Verhelst, G.; Walker, R. T. *Mol. Pharmacol.* **1981**, *20*, 230.
(6) Fyfe, J. A. *Mol. Pharmacol.* **1982**, *21*, 432.

(7) Allaudeen, H. S.; Kozarich, J. W.; Bertino, J. R.; De Clercq, E. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 2698.
(8) Allaudeen, H. S.; Chen, M. S.; Lee, J. J.; De Clercq, E.; Prusoff, W. H. *J. Biol. Chem.* **1982**, *257*, 603.
(9) Yoshimura, J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69.
(10) Acton, E. M.; Goerner, R. N.; Uh, H. S.; Ryan, K. J.; Henry, D. W. *J. Med. Chem.* **1979**, *22*, 518.
(11) Seki, J.-I.; Shimada, N.; Takahashi, K.; Takita, T.; Takeuchi, T.; Hoshino, H. *Antimicrob. Agents Chemother.* **1989**, *33*, 773.
(12) Nishiyama, Y.; Yamamoto, N.; Takahash, K.; Shimada, N. *Antimicrob. Agents Chemother.* **1988**, *32*, 1053.