Synthetic Approaches towards Nucleocidin and Selected Analogues; anti-HIV Activity in 4'-Fluorinated Nucleoside Derivatives

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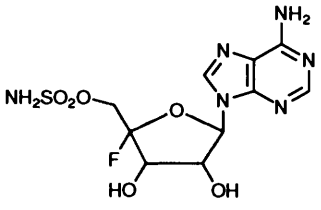
Nucleocidin **1** has been synthesised from the adenosine derivative **4** *via* the intermediacy of the dihalogeno compound **9**. The latter compound showed slight but significant activity against HIV-infected cells while the isomer **10** and the monohalogeno compound **60** were inactive. Synthetic approaches towards other 4'-fluorinated nucleoside derivatives are also described. The epimeric 4'-fluorinated nucleosides **26** and **27** displayed similar activity against HIV-infected cells to that observed for the dihalogenated compound **9**.

Nucleocidin **1**, one of the very few natural products containing a fluorine atom, has been isolated from *Streptomyces calvus* and its activity as an antitrypanosomal antibiotic has been described.[1-4]



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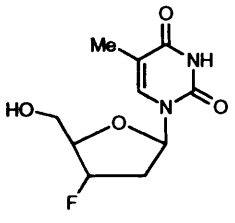

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The structural elucidation of this compound was reported in 1969,[5] and its synthesis was carried out by Moffatt and co-workers shortly thereafter.[6]

It is well established in various areas of medicinal chemistry that the introduction of fluorine into selected molecules has a profound effect on their biological activity. Of specific interest to this work were reports that fluorinated nucleosides showed activity against Human Immunodeficiency Virus (HIV). For example, 3'-fluoro-2',3,'-dideoxythymidine **2** was found to be a potent inhibitor of HIV-induced cytopathogenicity[7] and recently there has been considerable interest in the use of 2'-fluorinated nucleosides as agents against HIV.[8]

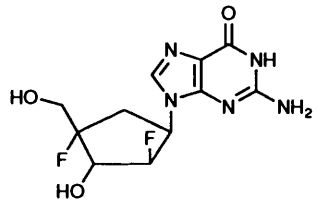
Furthermore, a recent publication[9a] by workers at Glaxo described the 4'-fluorinated carbocyclic nucleoside **3** which displays potent antiviral activity, in this case against Herpes simplex viruses.

While there has been considerable interest in modifications at the 2'- and 3'-positions of nucleosides much less is known about use of nucleosides which are modified at the 4'-position as HIV inhibitors. However recent reports[9b] of 4'-substituted nucleosides as inhibitors of HIV have demonstrated that these analogues are potentially very interesting.

It was decided to prepare nucleocidin **1** and analogues and to investigate the activity of selected members of the latter against HIV infected cells.

Results and Discussion

Repeated attempts following the reported procedure for isolation of nucleocidin from *Streptomyces calvus*[1] failed to yield any fluorine-containing metabolite. It was concluded that, probably due to repeated subculturing in a rich growth medium, the current stock strain of *S. calvus* ATCC 13382 has lost the potential to synthesize nucleocidin. Accordingly attention was focussed on the chemical synthesis of nucleocidin and other nucleosides containing 4'-fluorine substituents. The analogues selected for investigation, on the basis of the demonstrated interest in the use of 2'-deoxy-, 2',3'-dideoxy-, 3'-azido-, 2'-fluoro- and 3'-fluoro-nucleoside analogues against HIV, were the 4'-fluorinated derivatives of 2'-deoxyadenosine, 3'-fluoro-2',3'-dideoxyadenosine, and 2'-fluoro-2',3'-dideoxyadenosine, 3'-azido-2',3'-dideoxyuridine, 2',3'-dideoxyuridine, and 3'-azido-3'-deoxythymidine (AZT).



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Preparation of 4'-fluorinated nucleosides is complicated by the extreme lability of such compounds to acid-catalysed glycosidic cleavage as was observed by Moffatt and co-workers in their synthesis of nucleocidin[6] and also in some related research into the synthesis of 4'-fluorouridine derivatives.[10] The fact that the presence of a fluorine atom at the 4'-position makes the glycosidic linkage of a nucleoside unusually acid-labile was applied to the use of 5'-deoxy-4',5-difluorouridine as a prodrug of the anti-tumour agent 5-fluorouracil.[11]

Nucleocidin Preparation.—Following the synthetic sequence described for nucleocidin,[6] N^6,N^6-dibenzoyl-9-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)adenine **8** was prepared as outlined in Scheme 1. 2',3'-*O*-Isopropylideneadenosine **4** was *N*-benzoylated and then transformed into the 5'-*O*-methanesulphonate **6**. Treatment with potassium *tert*-butoxide resulted in the formation of the enol ether **7** which was transformed into the dibenzoylated enol ether **8** by benzoylation in pyridine.

Incorporation of a fluorine atom was achieved by treatment of **8** with iodine and silver fluoride in acetonitrile as illustrated in Scheme 2. The procedure employed was very similar to that described by Moffatt and co-workers,[6] except that the addition of iodine was carried out more slowly. Fortuitously, the ratio of **9**:**10** obtained was 3:1 whereas the optimum ratio reported in the earlier work[6] was 2:1. Thus, the proportion of the epimer **9** required for synthesis of nucleocidin had been considerably enhanced.

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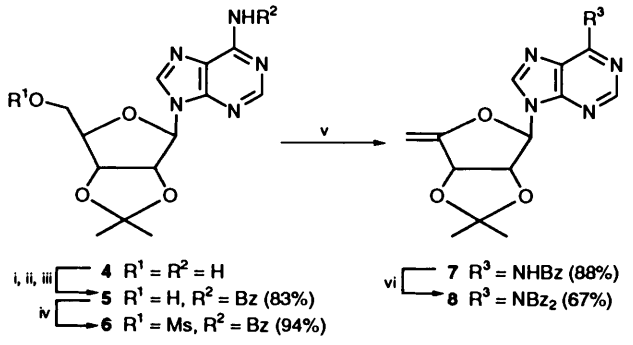
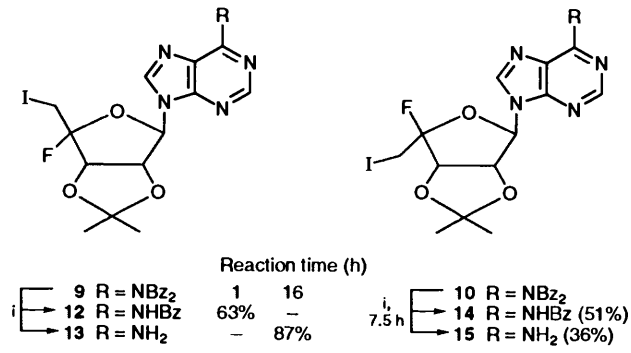


Scheme 1 *Reagents and conditions:* i, BzCl, pyridine, 0 °C; ii, KOH; iii, AcOH; iv, MsCl, pyridine; v, KOBu^t, THF; vi, BzCl, pyridine



Scheme 3 *Reagent:* i, NH_3–MeOH

An alternative method of iodofluorination was also investigated as outlined in Scheme 2. Bis(2,4,6-trimethylpyridine)iodine(I) tetrafluoroborate has been reported[12] as a useful reagent for iodofluorination of alkenes and enol ethers. It was hoped that by use of this reagent the ratio of **9**:**10** might be further improved. In fact, when the enol ether **8** was treated with the freshly prepared bis(2,4,6-trimethylpyridine)iodine(I) tetrafluoroborate complex the vinyl iodide **11** was formed. This compound was reported by Moffatt and co-workers[6] on treatment of a mixture of **9** and **10** with boron trifluoride–diethyl ether. Therefore, it may be assumed that subsequent to the iodofluorination of **8** by the bis(2,4,6-trimethylpyridine)-iodine(I) tetrafluoroborate, the presence of boron trifluoride effects elimination of hydrogen fluoride to form **11**. The vinyl iodide was assigned the *E* configuration (as illustrated in Scheme 2) by comparison of NMR data with those reported by Moffatt and co-workers;[6] however, there appears to be some confusion about this assignment of signals as mentioned by Moffatt in the report of subsequent studies.[13]

No identifiable product was isolated from treatment of the enol ether **8** with *m*-chloroperoxybenzoic acid in the presence of potassium fluoride.[14] It was thought that epoxidation under these conditions followed by ring opening with fluoride might lead to the required 4′-fluoronucleoside derivatives.

Partial separation of the epimeric fluoro iodides **9** and **10** was achieved by careful chromatography so that pure samples of each epimer could be obtained. Debenzoylation of these compounds was carried out as illustrated in Scheme 3.

Treatment of the α-fluoro epimer **9** with ammonia-saturated methanol gave a mixture of the monobenzoylated fluoroiodide **12** and the completely debenzoylated fluoroiodide **13**, from which **12** was isolated by chromatography (63%). By allowing a longer reaction time complete deprotection of the amino group was achieved and **13** was isolated in 87% yield.

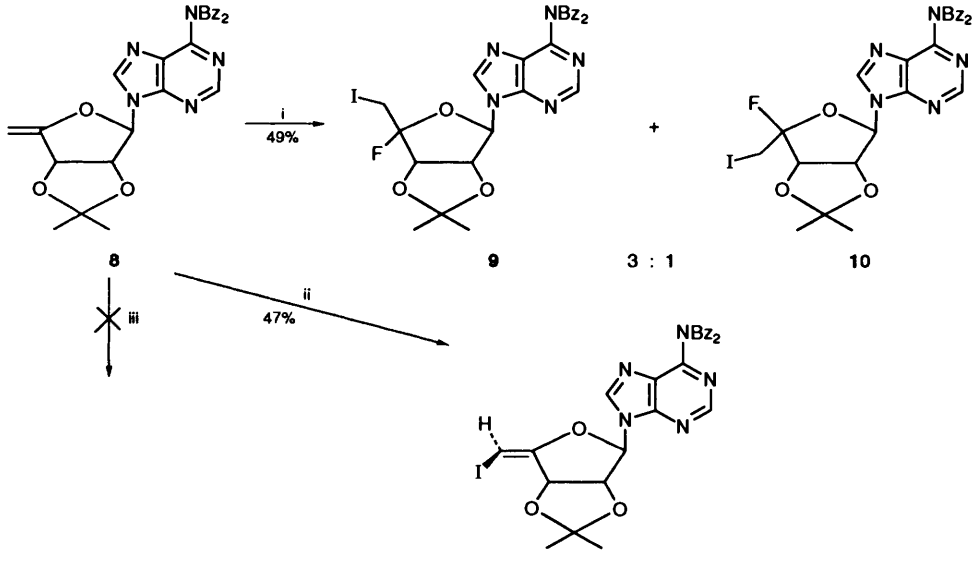
Similarly, the β-fluoro epimer **10** was deprotected to a mixture of the monobenzoylated **14** and completely debenzoylated **15** compounds. In this case, pure samples of each of **14** and **15** were isolated chromatographically.

An attempt was made to remove the isopropylidene protecting group from the fluoro iodides **9** and **10** but no identifiable product was isolated.

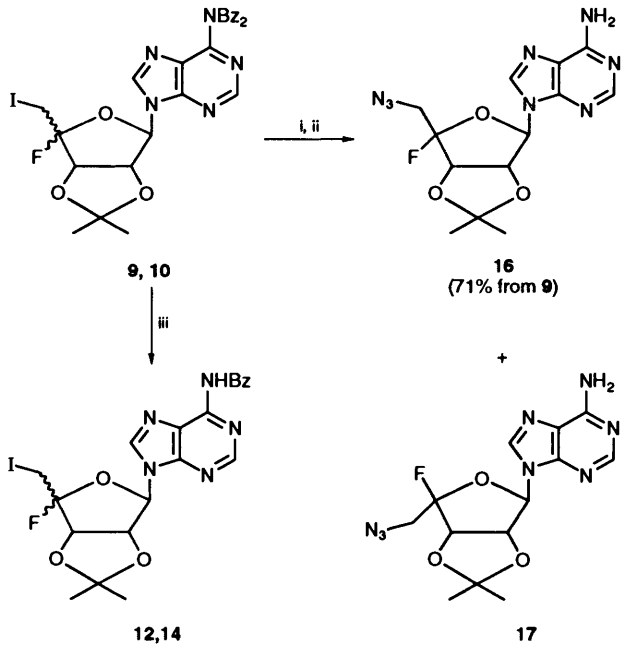
Substitution of the iodide moiety in compounds **9** and **10** proved very difficult as predicted by Moffatt[6] (Scheme 4). Treatment with potassium acetate and 18-crown-6 in tetrahydrofuran or potassium superoxide and 18-crown-6 in dimethylformamide gave no substitution of the iodide unit. The only isolable products were the monobenzoylated derivatives **12** and **14** indicating that attack at the N^6-benzyl group was favoured over displacement of iodide ion.

Nucleophilic substitution of iodide was achieved using sodium azide in *N*,*N*-dimethylformamide as described by Moffatt and co-workers.[6] Thus, the α-fluoro epimer **9** was transformed to the corresponding azide **16** while a mixture of the epimers **9** and **10** gave a mixture of azides **16** and **17**. As partial debenzoylation occurred during the course of the reaction, the crude product was completely debenzoylated using methanolic ammonia prior to purification.

The next step in the published synthesis of nucleocidin involved the photolytic conversion of the azide **16** into the



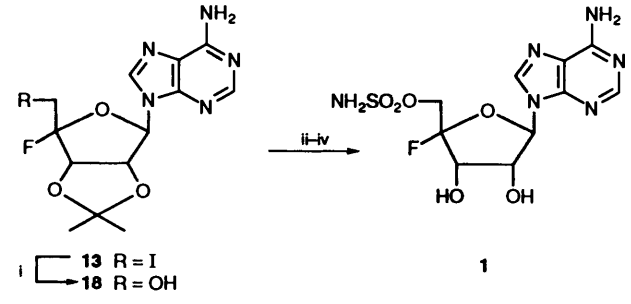
Scheme 2 *Reagents and conditions:* i, I_2, AgF, MeCN; ii, I (collidine)$_2BF_4$, CH_2Cl_2; iii, MCPBA, KF



Scheme 4 *Reagents and conditions:* i, NaN_3, DMF, heat; ii, NH_3–MeOH; iii, KOAc, 18-crown-6, THF *or* KO_2, 18-crown-6, DMF

corresponding primary alcohol. We found this step to be extremely capricious. Several attempts were made to effect this conversion; most of these attempts failed completely although on one occasion, in a small-scale experiment, a poor yield of the required alcohol was obtained.

The problem was solved (Scheme 5) by treating the iodide **13**



Scheme 5 *Reagents and conditions:* i, KO_2, 18-crown-6, DMSO, THF, (40%); ii, $(Bu_3Sn)_2O$, C_6H_6, heat; iii, NH_2SO_2Cl, Et_2O; iv, H_2O (29%)

with potassium superoxide (4 equiv.) and 18-crown-6 (4 equiv.) in dimethyl sulphoxide and tetrahydrofuran to give the required alcohol **18** directly (40% yield). This alcohol was converted into nucleocidin **1** in the prescribed manner.[6] Loss of the acetonide protecting group occurred during this procedure obviating the necessity for subsequent acid-catalysed hydrolysis, as described by Moffatt.[6] The identity of the target compound was established by comparison of the physical data with those reported in the literature. In particular, NMR spectra were entirely consistent with structure proposed for the fluorine-containing nucleoside (see Experimental section).

In fact, ^{19}F NMR studies proved very useful in the characterisation of most of the above-mentioned fluorinated nucleosides, particularly in assigning the stereochemistry at the 4′-position (Table 1). In general, where comparisons could be made, the signals from α-fluoro compounds appeared at higher field than that for the corresponding β-fluoro compounds. Also, the multiplicity of the signal was very different for the α- and β-fluoro epimers. Notably, the α-fluoro epimers exhibited a large coupling between 3′-H and F (J 9–17 Hz) and no coupling between 1′-H and F, while the β-fluoro epimers exhibited a

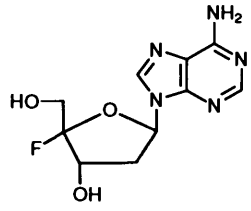
Table 1 Fluorine NMR signal of nucleosides **1**, **9**, **10**, **12**–**18**

Compd.	δ_F[a]/ppm	Multiplicity	$J_{1'F}$/Hz	$J_{3'F}$/Hz	$J_{5'F}$/Hz
1	43.26	dt	0	17.2	7.5
9	58.70	dt	0	11.5	18, 10
10	65.02	ddt	2.5	5.5	20, 15
12	59.10	dt	0	12	12
13	61.80	dt	0	14	15, 17
14	64.92	ddt	2	6	18
15	67.46	dddt	2	6	18
16	51.90	dt	0	13	13
17	56.60	ddt	2.5	7	16
18	47.95	dt	0	9	12.2

[a] δ_F quoted relative to hexafluorobenzene.

relatively small coupling between 3′-H and F (J 5.5–7 Hz) and a significant coupling between 1′-H and F (J 2–2.5 Hz).

Analogue Preparation.—Since 2′-deoxynucleosides have been demonstrated to possess anti-HIV activity, preparation of 2′-deoxynucleocidin **19** was attempted. In 2′-deoxynucleosides the



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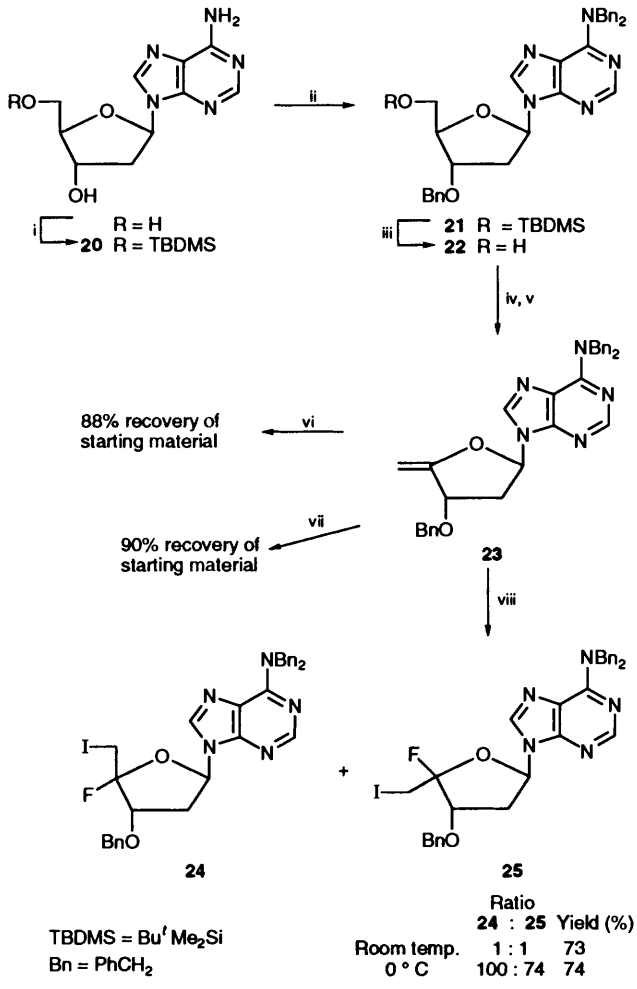
glycosidic link is more susceptible to hydrolysis than in the corresponding nucleoside.[15] As the 4′-fluoro substituent also appears to increase the lability of the glycosidic bond,[6,10,11] the 2′-deoxy analogue of nucleocidin could potentially undergo rapid hydrolysis. Notwithstanding this potential complication, the synthesis was undertaken following the route shown in Scheme 6.

2′-Deoxyadenosine was protected as the 5′-silylated derivative **20** followed by tribenzylation at the 3′-OH and primary amine groups to form the fully protected nucleoside **21**. Deprotection of the primary hydroxy group by treatment with TBAF produced the alcohol **22**, in 56% yield from 2′-deoxyadenosine, required for the introduction of the 4′-fluoro substituent using the methodology already described for the synthesis of nucleocidin.

The alcohol was transformed to the mesylate which was then treated, without purification, with potassium *tert*-butoxide to effect elimination to the enol ether **23** in an overall yield of 72% from the alcohol **22**. The enol ether proved unreactive towards pyridinium poly(hydrogen fluoride) with 90% recovery of starting material after 1 h at −70 °C. Similarly, when treated with silver fluoride and iodine in acetonitrile, the conditions employed in the nucleocidin synthesis, the enol ether was recovered unchanged (88%). However, when the enol ether was treated with silver fluoride and iodine in dichloromethane, incorporation of iodine and fluorine occurred to yield the epimeric products **24** and **25** in 74% combined yield. When the reaction was conducted at room temperature the epimeric ratio was 1:1, whereas lowering the reaction temperature to 0 °C favoured the formation of the α-fluoro epimer [ratio **24**:**25** 100:74] as evidenced by ^1H and ^{19}F NMR spectra. Thus, incorporation of a 4′-fluoro substituent into a 2′-deoxynucleoside had been successfully achieved.

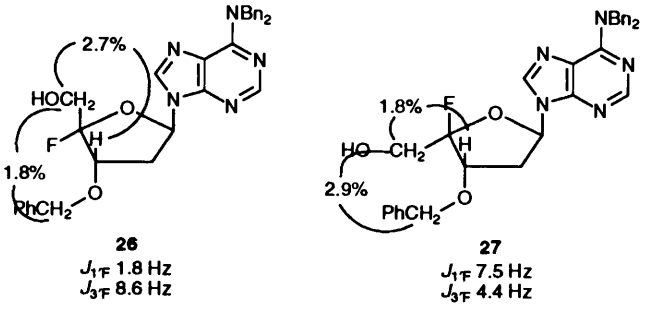
Separation of the epimeric dihalides **24** and **25** by chromatography was not possible. However, on treatment with potassium superoxide in the presence of 18-crown-6, displacement of the iodide was achieved, as shown in Scheme 7, and the



Scheme 6 *Reagents:* i, TBDMSCl, imidazole, DMF, room temp. (75%); ii, KOH, BnBr, Bu_4NBr, THF, room temp; iii, $Bu_4N^+F^-$, THF, room temp. (78%); iv, MsCl, Py, 0 °C; v, KOBu^t, THF, −78 °C (72%); vi, I_2, AgF, MeCN, −40 °C; vii $C_5H_6N^+(HF)_xF^-$, THF, −70 °C; viii, I_2, AgF, CH_2Cl_2.

epimeric fluoro alcohols **26** and **27** were isolated and proved readily separable chromatographically. Thus, the epimeric fluoro alcohols were obtained, albeit in low yields: 16% of the α-fluoro isomer and 8% of the β-fluoro isomer from an equimolar mixture of the epimeric iodides **24** and **25**.

Assignment of the stereochemistry of the fluoro alcohols **26** and **27** was based on coupling constants in their ^1H and ^{19}F NMR spectra and by NOE experiments. In the α-fluoro epimer **26**, the coupling constant between 1′-H and 4′-^{19}F was 1.8 Hz in comparison to 7.5 Hz for the β-fluoro epimer **27**. Furthermore, the coupling constant between 3′-H and 4′-^{19}F was larger, at 8.6 Hz, for the α-fluoro epimer **26** than for the β-fluoro epimer **27** at 4.4 Hz. The NOE results confirmed this assignment as illustrated in Scheme 8. Thus, 2.7% enhancement was observed

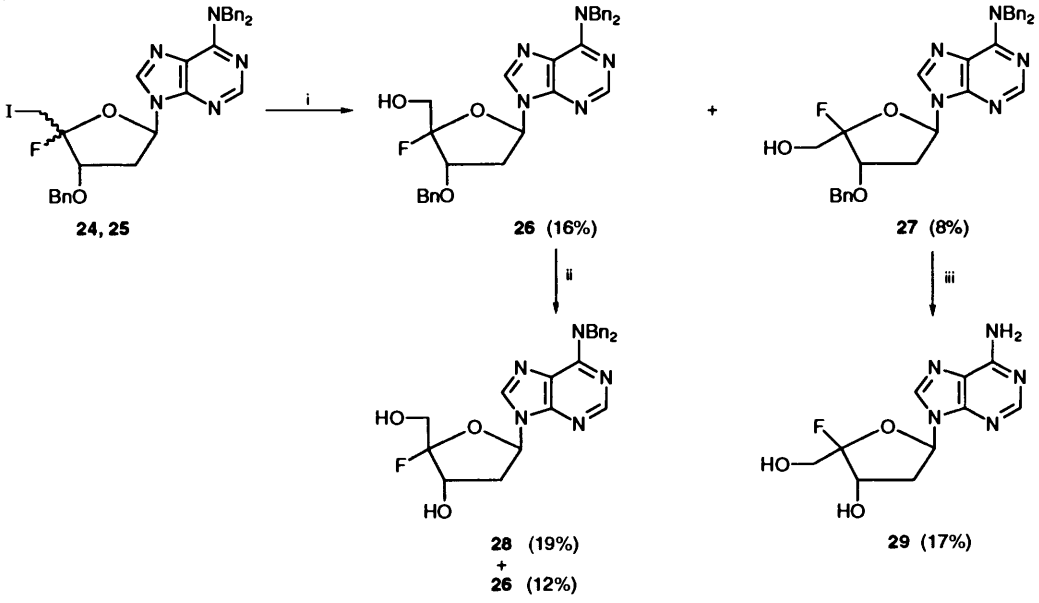


Scheme 8

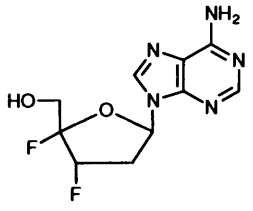
between the 3′-H and the 5′-H_2 in the α-fluoro epimer **26** compared to only 1.8% in the β-fluoro case. Similarly, the enhancement between 5′-H_2 and the benzylic CH_2 was larger for the β-fluoro epimer (2.9%) than the α-fluoro epimer (1.8%).

Complete deprotection of the β-fluoro epimer **27** to form 9-(2-deoxy-4-fluoro-α-L-lyxofuranosyl)adenine **29** was achieved using palladium hydroxide on carbon under an atmosphere of hydrogen, albeit in low yield (17%). However, in the α-fluoro epimer only the *O*-benzyl group was successfully removed despite use of a combination of palladium hydroxide on carbon and palladium on carbon. Thus, partial deprotection was achieved to form *N*,*N*-dibenzyl-2′-deoxy-4′-fluoroadenosine **28** in 19% yield, with 12% recovery of unchanged starting material, as illustrated in Scheme 7.

Since successful incorporation of a 4′-fluoro substituent into 2′-deoxyadenosine had been achieved as described above, synthesis of 2′,3′-dideoxy-3′,4′-difluoroadenosine **30** was attempted.



Scheme 7 *Reagents and conditions:* i, KO_2, 18-crown-6, DMSO, THF; ii, 20% $Pd(OH)_2/C$, 10% Pd/C, H_2, MeOH, room temp.; iii, 20% $Pd(OH)_2/C$, H_2, MeOH, room temp.



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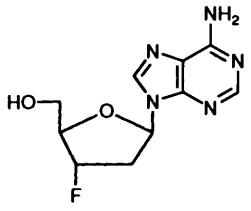

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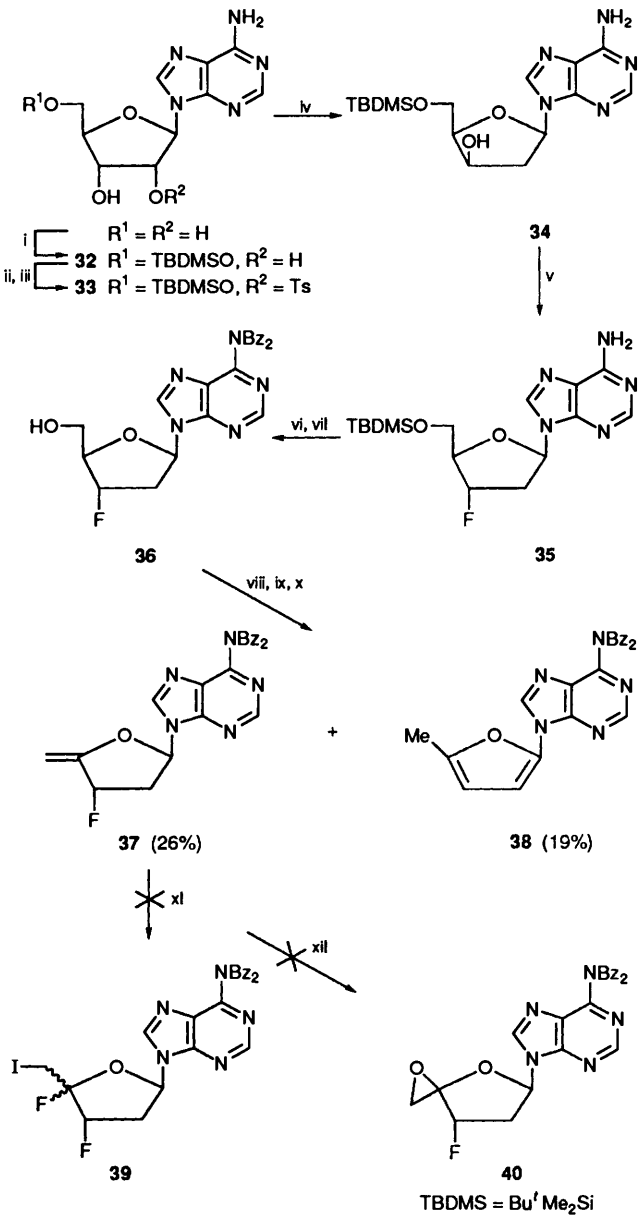
The strategy chosen for the synthesis of 2',3'-dideoxy-3',4'-difluoroadenosine **30** was to prepare, first, a suitably protected derivative of 3'-fluoro-2',3'-dideoxyadenosine **31** and then use the previously described method of iodofluorination to introduce the 4'-fluoro substituent, as shown in Scheme 9. The primary alcohol group of adenosine was selectively protected as a TBDMS derivative **32** (76%) after which treatment with dibutyltin oxide followed by toluene-*p*-sulfonyl chloride produced the 2'-tosylate derivative **33** in 81% yield. Reduction with lithium triethylborohydride furnished the 2'-deoxy derivative **34** in 56% yield. This alcohol reacted smoothly with DAST to give the 3'-α-fluoronucleoside **35** in 58% yield. The primary amino group on the adenine base was protected as its dibenzoyl derivative followed by desilylation of the primary hydroxy group to give the *N*-protected fluoronucleoside **36**. Without purification, this was transformed to the methanesulfonate derivative, which was treated with potassium *tert*-butoxide to effect elimination to form the enol ether **37** in 26% yield from the alcohol **36**. Since partial deprotection at nitrogen occurred during this sequence, further treatment with benzoyl chloride was carried out at the end of the sequence to ensure complete dibenzoylation at nitrogen. Formation of the enol ether was accompanied by the formation of a small amount (19%) of the furan derivative **38** also. The formation of similar furan derivatives has been reported.[16]

As observed earlier in the 2'-deoxy series, the enol ether **37** proved surprisingly unreactive—treatment with iodine and silver fluoride in acetonitrile resulted only in 67% recovery of the starting material **37**. Similarly, no reaction was observed on treatment with *m*CPBA in an attempt to form the epoxide **40**. Therefore, the reactivity of the enol ether derivatives of the 2'-deoxy nucleosides **23** and **37** is reduced considerably compared to that of enol ether **8** where an oxygenated functionality is present at the 2'-position.

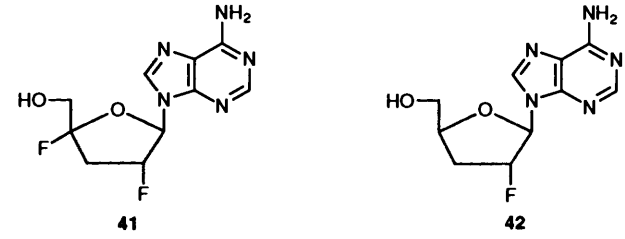
2'-Fluoro-2',3'-dideoxynucleocidin **41** was seen as an interesting target—the 2'-fluoro substituent should reduce the lability of the glycosidic bond to hydrolysis thereby stabilising the compound and synthetic intermediates considerably. Again the strategy employed involved preparation of a suitably protected form of 2'-fluoro-2',3'-dideoxyadenosine **42** and then iodofluorination of an enol ether derivative to introduce the 4'-fluoro substituent.

As shown in Scheme 10, adenosine was protected at its primary amino and hydroxy groups as its dityrityl derivative **43** (62%). Conversion into the dimethanesulfonate **44** followed, without purification, by treatment with potassium hydroxide and sodium borohydride in a benzene–methanol mixture produced the 3'-deoxynucleoside derivative **45** in 84% overall yield. Reaction with diethylaminosulfur trifluoride proceeded smoothly to give the required 2'-fluoronucleoside **46** in 65% yield. Partial deprotection to form the alcohol **47** was successful (42%). However, all attempts to form the enol ether **48** required for introduction of a 4'-fluoro substituent were unsuccessful. Reaction with methanesulfonyl chloride followed by potassium *tert*-butoxide furnished the furan **49** in 36% yield as the only isolable product.[16] Clearly elimination of the 5'-mesylate without concomitant elimination of HF is not possible.

When an attempt was made to apply this methodology to the



Scheme 9 *Reagents:* i, TBDMSCl, Et_3N, DMAP, DMF, CH_2Cl_2, room temp. (76%); ii, $(Bu_2SnO)_2$, MeOH, reflux; iii, TsCl, Et_3N, room temp. (81%); iv, $LiEt_3BH$, THF, room temp. (56%); v, Et_2NSF_3, CH_2Cl_2, room temp. (58%); vi, PhCOCl, Py, 0 °C; vii, $Bu_4N^+F^-$, THF; viii, MsCl, Py, 0 °C; ix, KOBu', THF, −78 °C; x, PhCOCl, Py, 0 °C; xi, I_2, AgF, CH_3CN, −40 °C; xii, mCPBA, CH_2Cl_2, room temp.



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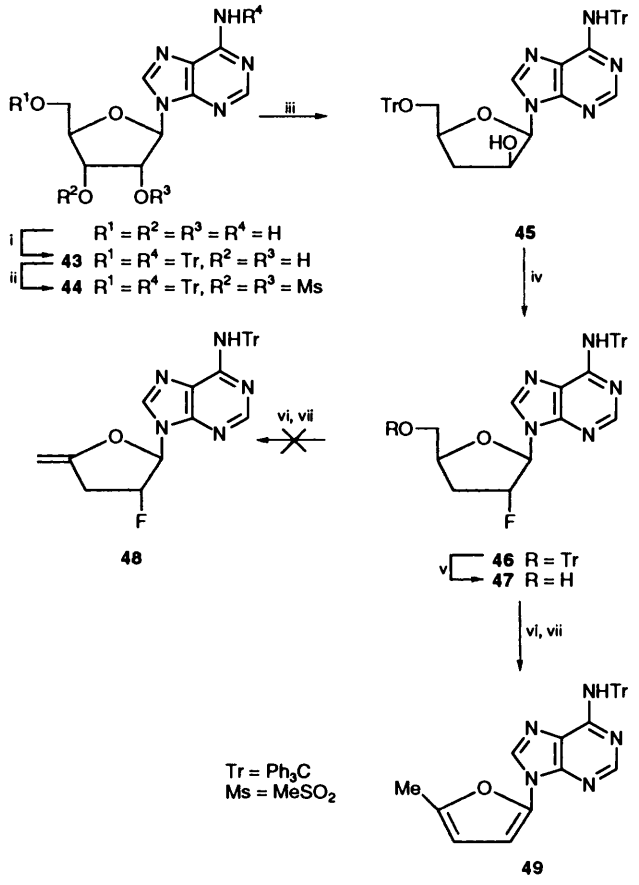
preparation of 4'-fluoro-2'3'-dideoxyuridine **50** and 4'-fluoro-3'-azido-2',3'-dideoxyuridine **51**, the elimination step to form the enol ether derivatives proved problematic. Treatment of the mesylates **52** and **53** with potassium *tert*-butoxide resulted in the formation of complex mixtures of products none of which could be identified as the enol ether required for the introduction of the 4'-fluoro substituent. The only product which was



Scheme 10 *Reagents:* i, TrCl, Py, 50 °C (62%); ii, MsCl, Py, room temp.; iii, KOH, $NaBH_4$, MeOH, C_6H_6 0–5 °C (84%); iv, Et_2NSF_3, CH_2Cl_2, room temp. (65%); v, TFA: $CHCl_3$ (1:9), room temp. (42%); vi, MsCl, Py, 0 °C; vii KOBu^t, THF, −78 °C (36%)

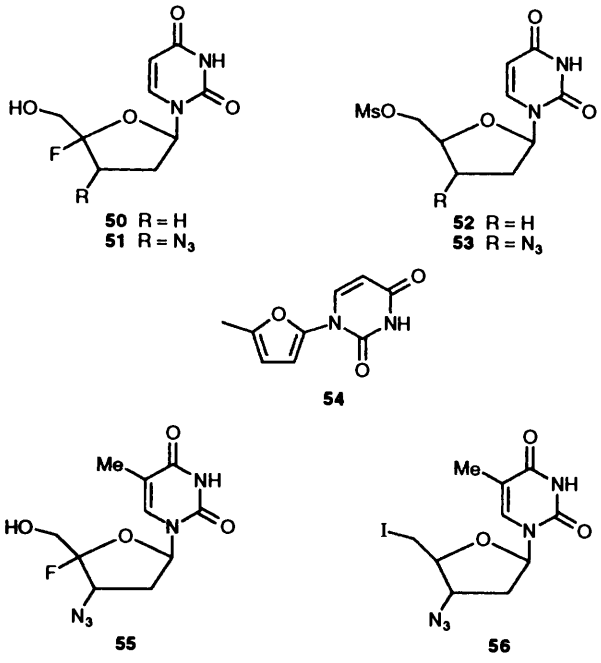
isolated and identified was a trace (< 5%) of the furan derivative **54** from the reaction with the mesylate **52**.

An attempt to use a modification of the above synthetic methodology, where diazabicyclononane (DBN)-catalysed elimination of HI is used to form the enol ether instead of potassium *tert*-butoxide effected elimination of mesylate, to prepare 4′-fluoro-AZT **55** was thwarted by the instability of 5′-iodo-5′-deoxyAZT **56**[17] towards bases such as DBN.

Biological Results.—Compounds **1**, **9**, **10**, **16**, **23**, **26** and **27** were tested for anti-HIV activity. Nucleocidin **1** was found to be extremely toxic to uninfected cells. The dihalogeno compound **9** showed slight anti-HIV activity (EC_{50} < 10 μmol dm^{-3}) but was toxic to the cells at doses >25 μmol dm^{-3}. The epimeric compound **10**, with the fluoro substituent on the β face, and also compound **16** were inactive. Interestingly, both the epimeric 4′-fluoro-2′-deoxynucleoside derivatives **26** and **27** possessed similar activity against HIV-infected cells to that observed for compound **9**, each with EC_{50} 4 μmol dm^{-3}, while the toxicity of the α-fluoro epimer **26** was lower (TC_{50} 250 μmol dm^3) than that of the β-fluoro epimer **27** (TC_{50} 10 μmol dm^{-3}) or the dihalogenated compound **9**. The enol ether **23** has similar activity (EC_{50} 4 μmol dm^{-3}, TC_{50} 50 μmol dm^{-3}). In comparison, AZT has EC_{50} 0.0032 μmol dm^{-3} and TC_{50} > 1000 μmol dm^{-3}.

In view of the small but reproducible response to the compound **9** the related non-fluorinated compounds **57**–**60** were prepared as summarised in Scheme 11.

2′,3′-*O*-Isopropylideneadenosine **4** was transformed to the corresponding 5′-iodo derivative **57**[18] using methyltriphenoxyphosphonium iodide as described by Moffatt and co-workers.[19] Removal of the isopropylidene group was accomplished by treatment with 90% formic acid to give 5′-iodoadenosine **58**.[19]



Treatment of N^6-benzoyl-2′-3′-*O*-isopropylideneadenosine **5** prepared from **4** as described above, with methyltriphenoxyphosphonium iodide furnished the iodide **59**.[19] Treatment of the iodide **59** with benzoyl chloride resulted in a mixture of two products—the required iodide **60** and the chloride **61** in a 3:2 ratio. Attempts to substitute chloride for iodide by treatment of the mixture with sodium iodide in acetone gave no change in the ratio of **60**:**61**. Instead a pure sample of the iodide **60**[20] was isolated by careful chromatography of the mixture. The chloride **61** was not isolated pure but identified by its spectral characteristics as a mixture with the iodide **60**.

Compounds **57**–**60** showed no activity against HIV. Most significantly the iodide **60** was inactive—therefore, the 4′-fluoro substituent is essential to the biological activity of the fluoro iodide **9**.

Summary and Conclusions.—We believe that nucleocidin **1** is no longer biosynthesized by *Streptomyces calvus* ATCC 13382. The compound was prepared (by modification of a literature procedure) in 12 steps from 2′,3′-*O*-isopropylideneadenosine **4**. One of the intermediates in the synthesis showed slight but significant activity against HIV-infected cells.

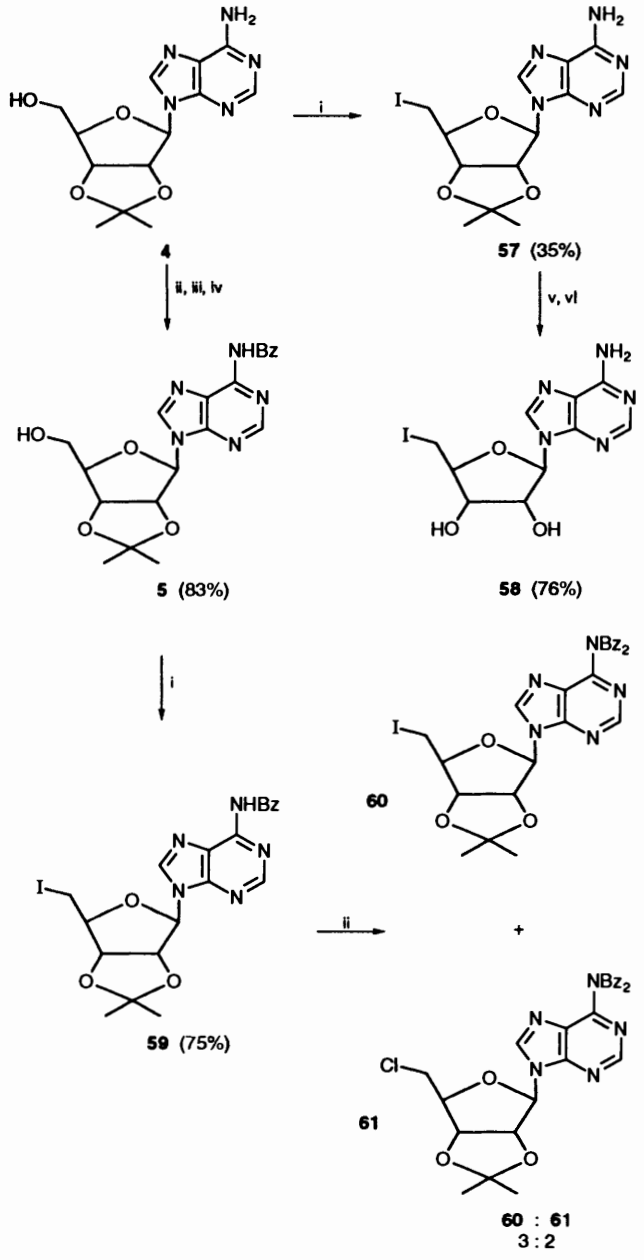
Activity against HIV has also been observed in the 4′-fluoro-2′-deoxynucleoside derivatives **26** and **27** and in an intermediate used for their synthesis **23**.

Experimental

All reactions were performed under nitrogen atmosphere except those indicated. Tetrahydrofuran and diethyl ether were dried and distilled from sodium metal and benzophenone prior to use. Dry dichloromethane, acetonitrile and pyridine were distilled from calcium hydride and stored over 4 Å molecular sieves. Dimethylformamide was dried by distillation from barium oxide and stored over 4 Å molecular sieves. Dimethyl sulfoxide was purchased from Aldrich Chemical Company.

Thin layer chromatography (TLC) was performed on precoated glass plates (Merck silica gel $60F_{254}$). Flash chromatography was performed using Merck silica 60 (40–63 μm).

IR spectra were recorded on a Perkin–Elmer 881 spectrophotometer. NMR spectra were obtained using a Bruker AM250 instrument; *J* values given in Hz. UV spectra were measured on a Philips PU8 700 spectrophotometer. Optical



Scheme 11 *Reagents and conditions:* i, $MeP(OPh)_3I$, CH_2Cl_2, −70 °C; ii, BzCl, pyridine, 0 °C; iii, KOH; iv, AcOH; v, HCO_2H (90%); vi, NH_3–MeOH

rotations were taken on an AA-1000 polarimeter and are recorded in units of 10^{-1} deg cm^2 g^{-1}.

N^6-*Benzoyl*-2′,3′-O-*isopropylideneadenosine* **5**.[6]—Benzoyl chloride (1.5 cm^3, 12.90 mmol) was added dropwise to a stirred solution of 2′,3′-*O*-isopropylideneadenosine (1.00 g, 3.25 mmol) in pyridine (10 cm^3) at 0 °C under argon and the mixture allowed to warm to room temperature over 1 h. The reaction mixture was quenched by addition of ice–water then evaporated. The residue was dissolved in chloroform and the solution washed with water, saturated aqueous sodium hydrogen carbonate and water and evaporated. The residue was dissolved in pyridine (9 cm^3) and the solution stirred vigorously for 20 min with a solution of potassium hydroxide (1.30 g) in water (9 cm^3). Acetic acid (1.2 cm^3) was then added to the mixture cooled in an ice-bath. Solvent evaporation from the mixture under reduced pressure left a residue which was partitioned between water and chloroform. The chloroform layer was separated, washed with water, twice with saturated aqueous sodium hydrogen carbonate and water and then dried and evaporated to give an orange solution. This was triturated with ethyl acetate and washed with ether to give the benzoylamine **5** as a white solid (1.11 g, 83%). This material was shown by NMR and TLC (9:1, $CHCl_3$–MeOH) to contain *ca.* 5% of 2′,3′-*O*-isopropylideneadenosine, but was sufficiently pure to use in subsequent transformations. A pure sample was obtained by chromatography over silica (eluent 5% methanol in dichloromethane) as a white crystalline solid, m.p. 146–148 °C; $[\alpha]_D^{20}$ −83 (*c* 2.4, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3352 (NH, OH), 1708 (adenine) and 1606 (CO amide); δ_H($CDCl_3$) 9.34 (1 H, br s, NH), 8.71, 8.20 (2 × 1 H, 2 × s, adenine-H), 7.37–8.02 (5 H, m, ArH), 5.97 (1 H, d, $J_{1'2'}$ 4, 1′-H), 5.60 (1 H, br d, *J* 8, OH), 5.19 (1 H, dd, $J_{1'2'}$ 4, $J_{2'3'}$ 6, 2′-H) 5.02 (1 H, dd, $J_{2'3'}$ 6, $J_{3'4'}$ 1, 3′-H) 4.45 (1 H, br d, $J_{3'4'}$ 1, 4′-H), 3.85–3.95 (1 H, br d, 5′a-H), 3.66–3.80 (1 H, m, 5′b-H), 1.61, 1.34 (6 H, 2 × s, 2 × CH_3); δ_C($CDCl_3$) 164.875 (CO), 152.294 (CH), 150.723 (C), 150.208 (C), 142.528 (CH), 133.541 (C), 132.761 (CH), 128.727 (CH), 127.994 (CH), 124.149 (C), 114.207 (CMe_2), 93.503, 86.561, 83.512, 81.514 (4 × CH), 63.016 (5′-CH_2) and 27.465 and 25.236 (2 × CH_3).

N^6-*Benzoyl* 2′,3′-O-*isopropylidene*-5′-O-*methylsulfonyl-adenosine* **6**.[6]—The alcohol **5** (29.0 g, 0.07 mol) was stirred in pyridine (300 cm^3) at 0 °C under argon while methanesulfonyl chloride (7.3 cm^3, 0.09 mol) was added to it dropwise. Stirring was continued at 0 °C for 3 h after which ice–water (100 cm^3) was added to the mixture; it was then evaporated under reduced pressure. A solution of the residue in dichloromethane was washed with water, saturated aqueous sodium hydrogen carbonate and water, dried and evaporated to give the mesylate **6** as a solid (32.0 g, 94%) which was sufficiently pure to use in subsequent transformations.

A white crystalline solid was obtained by chromatography on silica using 1% methanol in dichloromethane as eluent, m.p. 98–101 °C (decomp.); $[\alpha]_D^{20}$ −35 (*c* 0.9, EtOH); ν_{max}(KBr)/cm^{-1} 3267 (NH), 1698 (adenine), 1611 (CO amide) and 1581 (aromatic); δ_H($CDCl_3$) 8.74, 8.16 (2 × 1 H, 2 × s, adenine-H), 7.30–8.00 (5 H, m, ArH), 6.18 (1 H, d, $J_{1'2'}$ 2, 1′-H), 5.44 (1 H, dd, $J_{1'2'}$ 2, $J_{2'3'}$ 7, 2′-H), 5.11 (1 H, dd, $J_{2'3'}$ 7, $J_{3'4'}$ 3, 3′-H), 4.44–4.54 (1 H, m, 4′-H), 4.30–4.44 (2 H, m, 5′-H_2), 1.91 (3 H, s, CH_3SO_3) and 1.61 and 1.38 (2 × 3 H, 2 × s, 2 × CH_3); δ_C($CDCl_3$) 164.833 (CO), 152.652 (CH), 151.193 (C), 149.889 (C), 142.298 (CH), 133.517 (C), 132.810 (CH), 128.214 (CH), 127.946 (CH), 123.637 (C), 114.998 (CMe_2), 91.002, 84.694, 84.011, 81.243 (4 × CH), 68.307 (5′-CH_2), 37.623 (CH_3SO_2) and 27.091 and 25.303 (2 × CH_3).

N^6-*Benzoyl*-9-(5-*deoxy*-2,3-*O*-*isopropylidene*-β-D-erythro-*pent*-4-*enofuranosyl*)*adenine* **7**.[6]—Potassium *tert*-butoxide (3.44 g, 0.031 mol) was stirred in dry tetrahydrofuran (80 cm^3) at −78 °C under argon while the mesylate **6** (5.00 g, 10 mmol) in dry tetrahydrofuran (60 cm^3) was added dropwise over 20 min. Stirring was continued for 3 h while the mixture slowly returned to room temperature. The mixture was then poured onto ice (400 g) containing sodium acetate (10 g) and acetic acid (1.5 cm^3), diluted with dichloromethane (200 cm^3) and stirred for 20 min. The layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined extracts were dried and concentrated to give **7** as a brown solid (3.53 g, 88%). Recrystallisation from benzene–hexane gave a white crystalline solid, m.p. 148–149 °C (lit.,[6] 151–153 °C); $[\alpha]_D^{20}$ +47.5 (*c* 1.0, MeOH); λ_{max}(MeOH)/nm 230 (ε 14 960) and 277 (ε 16 400); ν_{max}(KBr)/cm^{-1} 3412, 3265 (NH), 1695 (adenine), 1609 (CO amide) and 1581 (aromatic); δ_H($CDCl_3$) 9.30 (1 H, br s, NH), 8.77, 8.05 (2 × 1 H, 2 × s, adenine-H), 7.30–8.10 (5 H, m, ArH), 6.31 (1 H, s, 1′-H), 5.32 (1 H, d, $J_{2'3'}$ 6, 2′-H), 5.55 (1

H, dd, $J_{2'3'}$ 6, $J_{3'5'b}$ 1, 3'-H), 4.67 (1 H, dd, $J_{5'a5'b}$ 2, $J_{3'5'b}$ 1, 5'b-H), 4.53 (1 H, d, $J_{5'a5'b}$ 2, 5'a-H) and 1.57 and 1.42 (2 × 3H, 2 × s, 2 × CH_3); $\delta_C(CDCl_3)$ 164.760 (CO), 161.487 (C), 152.874 (CH), 151.228 (C), 149.840 (C), 141.648 (CH), 133.554 (C), 132.762 (CH), 128.789 (CH), 127.934 (CH), 123.669 (C), 114.344 (CMe_2), 90.729 (CH), 88.943 (CH_2-5'), 82.661 (CH), 79.558 (CH) and 26.783 and 25.675 (2 × CH_3).

N^6,N^6-*Dibenzoyl*-9-(5-*deoxy*-2,3-O-*isopropylidene*-β-D-erythro-*pent*-4-*enofuranosyl*)*adenine* **8**.[6]—The monobenzoylated amine **7** (0.20 g, 0.51 mmol) in pyridine (2 cm^3) was stirred at 0 °C under argon while benzoyl chloride (0.12 cm^3, 1.00 mmol) was added dropwise to it. Stirring was continued for 3 h while the mixture slowly warmed to room temperature. It was then poured onto ice (5 g) and extracted with dichloromethane (3 × 10 cm^3). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate and water, dried and evaporated under reduced pressure to give an orange oil. This was purified by chromatography on silica using 5% acetone in dichloromethane as eluent to give the dibenzoylated product **8** as a white solid (0.17 g, 67%). Recrystallisation of the latter from ethanol gave white crystals, m.p. 94–97 °C (decomp.); $[\alpha]_D^{20}$ +137 (*c* 0.44, MeOH); λ_{max}(MeOH)/nm 253.1 (ε 21 900) 275sh (ε 18 000) [lit.,[6] 250 nm (ε 21 000) and 272 nm (ε 16 500)]; ν_{max}(KBr)/cm^{-1} 2990, 1703 (Ad and CO), 1599, 1579 (Ar, C=C) and 1493 (Ar); $\delta_H(CDCl_3)$ 8.62, 8.05 (2 × 1 H, 2 × s, Ad-H), 7.20–7.90 (10 H, m, ArH), 6.27 (1 H, br s, $J_{1'2'}$ < 1, 1'-H), 5.49 (1 H, br d, $J_{2'3'}$ 6, $J_{3'5'b}$ < 1, 3'-H), 5.26 (1 H, dd, $J_{2'3'}$ 6 Hz, $J_{1'2'}$ < 1, 2'-H), 4.63 (1 H, dd, $J_{5'a5'b}$ 3, $J_{3'5'b}$ < 1, 5'b-H), 4.49 (1 H, d, $J_{5'a5'b}$ 3,5'a-H) and 1.42 and 1.56 (2 × 3 H, 2 × s, 2 × CH_3); $\delta_C(CDCl_3)$ 172.192 (CO), 161.396 (C), 152.504 (CH), 152.192 (C), 143.276 (CH) (Ad), 134.134 (C), 133.005 (CH), 129.464 (CH), 128.729 (CH) (Ar), 114.445 (C, CMe_2), 90.770 (CH), 89.144 (CH_2-5'), 82.665 (CH), 79.442 (CH), 26.790 and 25.654 (2 × CH_3).

N^6,N^6-*Dibenzoyl*-5'-*deoxy*-4'-*fluoro*-5'-*iodo*-2',3'-*O*-*isopropylideneadenosine* **9**[6] *and* N^6,N^6-*Dibenzoyl*-9-(5-*deoxy*-4-*fluoro*-5-*iodo*-2,3-O-*isopropylidene*-α-L-*lyxofuranosyl*)*adenine* **10**.[6]—The enol ether **8** (0.50 g, 1.0 mmol) was stirred vigorously in dry acetonitrile (60 cm^3) with silver fluoride (1.00 g, 7.9 mmol) at −40 °C while a solution of iodine (1.02 g, 4.0 mmol) in acetonitrile (28 cm^3) was added dropwise over 1.5 h. The mixture was allowed to return slowly to room temperature at which point it was evaporated to dryness. The residue was partitioned between dichloromethane and aqueous sodium hydrogen carbonate, sodium chloride, and sodium thiosulfate. The organic phase was separated and washed with water, dried and evaporated. Chromatography of the residue on silica with 2% acetone in dichloromethane gave a mixture of the fluoro iodides **9** and **10** as a foam (0.32 g, 49%). ^1H and ^{19}F NMR spectroscopy showed this to be a 3:1 mixture of **9**:**10**. Careful chromatography gave pure samples of each epimer as foams, the more polar component being **9**.

F-β-epimer **10**: $[\alpha]_D^{20}$ −178 (*c* 0.15, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 1699 (Ad, CO), 1593, 1574, 1491 (Ar) and 1233; $\delta_H(CDCl_3)$ 8.70, 8.24 (2 × 1 H, 2 × s, Ad-H), 7.30–8.00 (10 H, m, ArH), 6.48 (1 H, dd, $J_{1'2'}$ 0.5, $J_{1'F}$ 2.5, 1'-H), 5.58 (1 H, dd, $J_{2'3'}$ 5.5, $J_{1'2'}$ 0.5, 2'-H), 5.08 (1 H, dd appears at t, $J_{2'3'}$ 5.5, $J_{3'F}$ 5.5, 3'-H), 3.40–3.70 (2 H, m, H_2-5') and 1.58 and 1.40 (2 × 3 H, 2 × s, 2 × CH_3); $\delta_F(CDCl_3)$ 65.02 ppm (ddt, $J_{3'F}$ 5.5, $J_{5'aF}$ 15, $J_{5'bF}$ 20, $J_{1'F}$ 2.5).

F-α-epimer **9**: $[\alpha]_D^{20}$ +24 (*c* 0.42, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 1698 (Ad, CO), 1595, 1577, 1493 (Ar) and 1234; $\delta_H(CDCl_3)$ 8.67 and 8.18 (2 × 1 H, 2 × s, Ad-H), 7.30–7.90 (10 H, m, ArH), 6.36 (1 H, br s, $J_{1'2'}$ 1, 1'-H), 5.41 (1 H, dd, $J_{2'3'}$ 6.5, $J_{3'F}$ 11.5, 3'-H), 5.27 (1 H, dd, $J_{1'2'}$ 1, $J_{2'3'}$ 6.5, 2'-H), 3.50–3.60 (2 H, m, H_2-5') and 1.63 and 1.38 (2 × 3 H, 2 × s, 2 × CH_3); $\delta_F(CDCl_3)$ 58.7 (dt, $J_{3'F}$ 11.5, $J_{5'aF}$ 18, $J_{5'bF}$ 10); $\delta_C(CDCl_3)$ 172.21 (CO), 152.51 (CH), 152.39 (C), 152.17 (C), 144.11 (CH) (Ad), 134.05 (C), 133.14 (CH), 132.98 (CH), 129.47 (CH) (Ar), 117.05 (CMe_2), 114.46 (C-4', $J_{4'F}$ 239), 88.73 (CH-1'), 83.44 (CH-2'), 81.77 (CH-3', $J_{3'F}$ 21), 25.99, 25.87 (2 × CH_3) and 3.25 (CH_2-5', $J_{5'F}$ 35).

N^6,N^6-*Dibenzoyl*-9-(5-*deoxy*-5-*iodo*-2,3-O-*isopropylidene*-β-D-erythro-*pent*-4-*enofuranosyl*)*adenine* **11**.[6,12] Collidine (0.07 cm^3, 0.50 mmol) was stirred in dry dichloromethane (1 cm^3) under nitrogen while silver tetrafluoroborate (0.05 g, 0.25 mmol) was added to it. Stirring was continued for 10 min after which iodine (0.06 g, 0.25 mmol) was added to the mixture. After being stirred for a further 10 min, the mixture was filtered through glass wool; this solution of the reagent in dichloromethane was used directly. Thus, a solution of the enol ether **8** (0.10 g, 0.20 mmol) in dichloromethane (1 cm^3) was added to the reagent solution to form a green solution which faded to yellow over 15 min. Stirring was continued for 2 h after which the mixture was filtered, washed with water, aqueous sodium thiosulfate and water, dried and evaporated. Purification of the residue by chromatography on silica using 2% acetone in dichloromethane as eluent followed by recrystallisation from ethanol gave the vinyl iodide **11** as white crystals (0.06 g, 47%), m.p. 176–177 °C (lit.,[6] 176–177 °C); ν_{max}(KBr)/cm^{-1} 1704 (Ad), 1597, 1576 (Ar, C=C) and 1234; $\delta_H(CDCl_3)$ 8.60 and 8.10 (2 × 1 H, 2 × s, Ad-H), 7.30–8.00 (10 H, m, ArH), 6.40 (1 H, s, 1'-H), 5.61 (1 H, d, $J_{2'3'}$ 6, 3'-H), 5.49 (1 H, s, 5'-H), 5.40 (1 H, d, $J_{2'3'}$ 6, 2'-H) and 1.55 and 1.42 (2 × 3 H, 2 × 5, 2 × CH_3).

N^6-*Benzoyl*-5'-*deoxy*-4'-*fluoro*-5'-*iodo*-2',3'-O-*isopropylideneadenosine* **12** *and* 5'-*Deoxy*-4'-*fluoro*-5'-*iodo*-2',3'-O-*isopropylideneadenosine* **13**.—The fluoro iodide **9** (0.17 g, 0.26 mmol) was stirred for 1 h at room temperature in ammonia-saturated methanol (10 cm^3). The mixture was then concentrated under reduced pressure and purified by chromatography on silica using 25% ethyl acetate 75% dichloromethane as eluent. The less polar fraction obtained was the monobenzoylated fluoro iodide **12** as a white foam (0.09 g, 63%), $[\alpha]_D^{20}$ +10 (*c* 0.12, CH_2Cl_2); $\lambda_{max}(CH_2Cl_2)$/nm 279.8 (ε_{max} 21400) and 235.1 (ε_{max} 13600); ν_{max}(KBr)/cm^{-1} 3435 (NH), 1696 (Ad), 1606 (CO), 1579 (Ar), 1243, 1086; $\delta_H(CDCl_3)$ 9.30 (1 H, br s, NH), 8.68 and 8.16 (2 × 1 H, 2 × s, Ad-H), 8.10–7.40 (5 H, m, ArH), 6.37 (1 H, br s, 1'-H), 5.44 (1 H, dd, $J_{2'3'}$ 6.5, $J_{3'F}$ 12, 3'-H), 5.27 (1 H, dd, $J_{2'3'}$ 6.5, $J_{1'2'}$ 1, 2'-H), 3.61–3.39 (2 H, m, 5'-H_2), 1.66, 1.39 (2 × 3 H, 2 × s, 2 × CH_3); $\delta_F(CDCl_3)$ 59.10 (dt, $J_{3'F}$ 12, $J_{5'F}$ 12 Hz). Minor impurity at 65.10 is the epimer **14** (2%); $\delta_C(CDCl_3)$ 164.788 (CO), 152.887 (CH), 151.159 (C), 150.108 (C), 142.266 (CH), 133.510 (C) (Ad), 132.807 (CH), 128.797 (CH), 127.967 (CH), 123.929 (C), (Ar), 116.965 (CMe_2), 114.473 (C-4', $J_{C\text{-}4'\text{-}F}$ 239), 88.779 (CH), 83.494 (CH), (C-1', C-2'), 81.230 (C-3', $J_{C\text{-}3'F}$ 20), 25.978, 25.804 (2 × CH_3), 3.191 (CH_2-5', $J_{C\text{-}5'\text{-}F}$ 35) (Found: $[M + H]^+$ 540.0544. $C_{20}H_{20}FIN_5O_4$ requires M^+, 540.05443). The more polar fraction was predominantly the debenzoylated fluoro iodide **13** but contained 15% of the epimeric fluoro iodide **15** and also ammonium benzoate.

5'-*Deoxy*-4'-*fluoro*-5'-*iodo*-2',3'-O-*isopropylideneadenosine* **13**.—A solution of the fluoro iodo compound **9** (236 mg, 0.37 mmol) in ammonia-saturated methanol (10 cm^3) was stirred at room temperature for 16 h after which the solvents were removed. The residue was purified on a silica column by elution with 30% acetone in dichloromethane to give the title compound **13** as a pale yellow oil (144 mg, 87%); ν_{max}(KBr)/cm^{-1} 3408, 2928, 1638, 1609 and 1579; $\delta_H(CDCl_3)$ 8.34 (1 H, s, 8-H), 7.89 (1 H, s, 2-H), 6.30 (1 H, d, $J_{1'2'}$ 1.0, 1'-H), 5.89 (2 H, br s, NH_2), 5.49 (1 H, dd, $J_{3'F}$ 12.2, $J_{3'2'}$ 6.4, 3'-H), 5.29 (1 H, dd, $J_{2'3'}$ 6.4, $J_{2'1'}$ 1.0, 2'-H), 3.65–3.46 (2 H, m, 5'-H), 1.65 (3 H, s, Me) and 1.41 (3 H, s, Me); $\delta_F(CDCl_3)$ 59.25–59.05 (dt, $J_{F3'}$

12.2, $J_{F5'}$ 16.5, 13.5) (Found: $[M + H]^+$ 436.0282, $C_{13}H_{16}FIN_5O_3$ requires 436.0282).

N^6-Benzoyl-9-(5-deoxy-4-fluoro-5-iodo-2,3-O-isopropylidene-α-L-lyxofuranosyl)adenine **14** *and 9-(5-Deoxy-4-fluoro-5-iodo-2,3-O-isopropylidene-α-L-lyxofuranosyl)adenine* **15**.—The fluoro iodide **10** (0.087 g, 0.14 mmol) was stirred in ammonia-saturated methanol (4 cm^3) at room temperature for 7.5 h after which the mixture was concentrated under reduced pressure and purified by chromatography on silica using 2% methanol in dichloromethane to give the monobenzoylated fluoro iodide **14** (0.037 g, 51%) and the debenzoylated fluoro iodide **15** (0.021 g, 36%). The fluoro iodide **14** was repurified by chromatography on silica with 40% ethyl acetate in dichloromethane as eluent to give a white foam which was shown by ^{19}F NMR spectroscopy to be 96% pure; ν_{max}(KBr)/cm $^{-1}$ 3444 (NH), 1694 (Ad), 1606 (CO), 1585 (Ar), 1248 and 1073; δ_H($CDCl_3$) 9.10 (1 H, br s, NH), 8.84, 8.18 (2 × 1 H, 2 × s, Ad-H), 8.10–7.40 (5 H, m, ArH), 6.49 (1 H, dd, $J_{1'2'}$ 1, $J_{1'F}$ 2, 1'-H), 5.64 (1 H, dd, $J_{2'3'}$ 6, $J_{1'2'}$ 1, 2'-H), 5.11 (1 H, dd appears as t, $J_{2'3'} = J_{3'F}$ 6, 3'-H), 3.70–3.49 (2 H, m, 5'-H_2) and 1.63 and 1.45 (2 × 3 H, 2 × s, 2 × CH_3); δ_F($CDCl_3$) 64.92 (ddt, $J_{1'F}$ 2, $J_{3'F}$ 6, $J_{5'F}$ 18) [Minor impurity (4%) at 58.6 ppm] (Found: $[M^+]$ 539.0466. $C_{20}H_{19}FIN_5O_4$ requires M^+, 539.0466.) The fluoro iodide **15** was repurified by chromatography on silica using ethyl acetate as eluent to give a white foam which was shown to be 98% pure by ^{19}F NMR spectroscopy, ν_{max}(KBr)/cm^{-1} 3430, 3324, 3166 (NH), 1662, 1598 (Ad), 1202 and 1096; δ_H ([$^2H_6$]acetone) 8.23 (1 H, s, 2-H), 8.11 (1 H, br s, 8-H), 6.56 (2 H, br s, NH_2), 6.50 (1 H, dd, $J_{1'2'}$ 1, $J_{1'F}$ 2, 1'-H), 5.89 (1 H, dd, $J_{1'2'}$ 1, $J_{2'3'}$ 6, 2'-H), 5.34 (1 H, t, $J_{2'3'}$ 6, $J_{3'F}$ 6, 3'-H), 3.69–3.54 (2 H, m, 5'-H) and 1.60 and 1.45 (2 × 3 H, 2 × s, 2 × CH_3); δ_F([$^2H_6$]acetone) 67.46 (ddt, $J_{5'F}$ 18, $J_{3'F}$ 6, $J_{1'F}$ 2) (Found: $[M + H]^+$ 436.0282. $C_{13}H_{16}FIN_5O_3$ requires 436.0282).

5'-Azido-5'-deoxy-4'-fluoro-2',3'-O-isopropylideneadenosine **16**.[6]—A solution of the iodide **9** (0.13 g, 0.20 mmol) and sodium azide (0.07 g, 1.01 mmol) in dry *N*,*N*-dimethylformamide (3 cm^3) was heated at 95 °C while being stirred under argon for 17 h in a foil-wrapped flask. The solvent was removed under reduced pressure and the residue was stirred in methanol saturated with ammonia (10 cm^3) for 16 h. The mixture was evaporated and the residue purified by chromatography on silica to give the azide **16** as a white foam (0.05 g, 71%); ν_{max}(film)/cm $^{-1}$ 3337, 3186 (NH), 2112 (N_3) and 1656; δ_H($CDCl_3$) 8.41, 7.93 (2 × 1 H, 2 × s, Ad-H), 6.38 (1 H, br s, 1'-H), 6.24 (2 H, br s, NH_2), 5.55 (1 H, dd, $J_{2'3'}$ 6, $J_{3'F}$ 13, 3'-H), 5.34 (1 H, dd, $J_{2'3'}$ 6, $J_{1'2'}$ 1, 2'-H), 3.61 (2 H, d, $J_{5'F}$ 13, 5'-H_2) and 1.65 and 1.41 (2 × 3 H, 2 × s, 2 × CH_3); δ_F($CDCl_3$) 51.9 (dt appears as q, $J_{3'F}$ 13, $J_{5'F}$ 13).

Treatment of the Fluoro Iodides **9** *and* **10** *with Potassium Superoxide* (3:1 *Epimer Ratio*).—Potassium superoxide (0.033 g, 4.65 × 10^{-4} mol) in DMF was stirred under argon at room temperature while a solution of the fluoro iodide mixture **9** and **10** (0.100 g, 1.55 × 10^{-4} mol) and 18-crown-6 (0.026 g, 1.00 × 10^{-4} mol) in DMF (2 cm^3) was added. Stirring was continued for 16 h after which methanol (1 cm^3) was added to the reaction mixture whilst it was cooled in an ice-bath. Water (2 cm^3) was added to the mixture which was then extracted with dichloromethane (× 3). The combined organic extracts were washed with water, dried and evaporated. Chromatography of the residue on silica using 1% methanol in dichloromethane gave the monobenzoylated fluoro iodides **12** and **14** (0.049 g, 59%). Spectral characteristics were as described earlier for these compounds.

Treatment of the Fluoro Iodides **9** *and* **10** *with Potassium Acetate* (3:1 *Epimer Ratio*).—The fluoro iodides **9** and **10** (0.050 g, 7.77 × 10^{-5} mol), potassium acetate (0.076 g, 7.77 × 10^{-5} mol) and 18-crown-6 (0.050 g, 1.89 × 10^{-4} mol) were stirred in tetrahydrofuran (4 cm^3) at room temperature under argon for 17 h and then refluxed for 22 h. The reaction mixture was diluted with dichloromethane, washed with water (× 2), dried and evaporated at reduced pressure. Chromatography of the residue on silica using 10% acetone in dichloromethane gave the monobenzoylated fluoro iodides **12** and **14** as a white foam (0.022 g, 53%). Spectral characteristics were as described earlier for these compounds.

4'-Fluoro-2',3'-O-isopropylideneadenosine **18**.—*Method A*. A solution of the fluoro iodide **13** (60 mg, 0.14 mmol) in THF (7 cm^3) was added dropwise to a suspension of KO_2 (55 mg, 0.77 mol) and 18-crown-6 (230 mg, 0.87 mmol) in anhydrous DMSO (5 cm^3) under argon. The yellow reaction mixture was stirred at room temperature for 2 days after which brine (2 cm^3) was added to it and stirring continued for 30 min. After removal of THF under reduced pressure, the residue was partitioned between chloroform and water. The aqueous phase was extracted with chloroform (× 3) and the combined organic extracts were dried and evaporated under reduced pressure. The residue was purified by chromatography on silica by elution with 5% methanol in dichloromethane to give the fluoro alcohol **18** as a white gum (20 mg, 40%); $[\alpha]_D^{20}$ −15 (*c* 0.96, MeOH); ν_{max}(Nujol)/cm^{-1} 3147 (NH), 1685, 1609 and 1101 cm^{-1}; δ_H($CDCl_3$) 8.3, 7.9 (2 × 1 H, 2 × s, Ad-H), 6.75 (2 H, s, NH_2), 6.26 (1 H, d, $J_{1'2'}$ 2.5, 1'-H), 5.5 (1 H, dd, $J_{3'F}$ 9, $J_{3'2'}$ 7, 3'-H), 5.16 (1 H, dd, $J_{2'3'}$ 7, $J_{2'1'}$ 2.5, 2'-H), 4.8 (1 H, br s, OH), 3.90 (2 H, m, 2 × 5'-H) and 1.29 and 1.45 (2 × 3 H, 2 × s, 2 × CH_3); δ_F([$^2H_4$]methanol) 47.95 (dt, $J_{3'F}$ 9, $J_{5'F}$ 12.2) (Found: $[M + H]^+$ 326.1265, $C_{13}H_{17}FN_5O_4$ requires 326.1263).

Method B[6]. A solution of the 5'-azide **16** (90 mg, 0.26 mmol) in THF (5 cm^3) and benzene (100 cm^3) was degassed with nitrogen and irradiated with a 125 W mercury lamp for 6 h. The completion of the reaction was indicated by TLC (5% acetone in dichloromethane). After removal of the solvents, the residue was treated with dioxane (9 cm^3) and 0.5 mol dm^{-3} hydrochloric acid (0.9 cm^3) at room temperature for 5 min. The solution was neutralised with solid sodium hydrogen carbonate and sodium borohydride (135 mg, 0.35 mmol) was added portionwise over 20 min. Excess of borohydride was destroyed by acidification with acetic acid and the mixture was then neutralised with sodium hydrogen carbonate and evaporated to dryness. The residue was partitioned between chloroform and water. The organic phase was dried ($MgSO_4$), filtered and evaporated. The residue was purified by preparative TLC using dichloromethane–methanol (9:1) as eluent. The most polar band was eluted to give the title compound **18** as a colourless gum (9 mg, 11%), spectral characteristics of which were described as above.

4'-Fluoro-5'-O-sulfamoyladenosine **1** (*Nucleocidin*).[6,22]—A suspension of the fluoro alcohol **18** (50 mg, 0.15 mmol) and hexabutyldistannoxane (0.2 g, 0.55 mmol) in benzene (6 cm^3) was heated under reflux for 2 h. The resulting clear solution was cooled to 5 °C under nitrogen and a solution of freshly prepared[21] sulfamoyl chloride (83 mg, 0.7 mmol) in dry diethyl ether (5 cm^3) was added dropwise to it. The reaction mixture was stirred for 10 min after which the solvent was removed. The residue was extracted with hot hexane (× 3) and the insoluble residue was quickly treated with dilute methanolic ammonia and evaporated. The residue was dissolved in a minimum amount of hot water. White crystals which slowly formed were filtered off; they were the monohydrate of nucleocidin **1** (17 mg, 29%), m.p. 144–148 °C. (lit.,[6] 145–147 °C); $[\alpha]_D^{20}$ −37 (*c* 0.5, MeOH) [lit.,[22] $[\alpha]_D^{24.5}$ −33.3 (*c* 1.05, EtOH/HCl)]; λ_{max}(MeOH)/nm 258.6 (ε 15000) [lit.,[6] 259 (ε 15100)];

ν_{max}(Nujol)/cm^{-1} 3200, 1658, 1608, 1461 and 1377; δ_H([$^2H_4$]-methanol) 8.21, 8.23 (2 × 1 H, 2 × s, Ad-H), 6.33 (1 H, d, $J_{1',2'}$ 2.4, 1'-H), 4.9 (1 H, dd, $J_{3',F}$ 17.2, $J_{3',2'}$ 6.4, 3'-H), 4.69 (1 H, dd, $J_{2',1'}$ 2.4, $J_{2',3'}$ 6.4, 2'-H), 4.34 (2 H, d, $J_{5',F}$ 7.5, 2 × 5'-H); δ_F 43.11 (dt, $J_{3',F}$ 17.2, $J_{5',F}$ 7.5) (Found: M$^+$, 382.0729. $C_{10}H_{13}FN_6O_6S{\cdot}H_2O$ requires 382.0706).

5'-O-tert-*Butyldimethylsilyl*-2'-*deoxyadenosine* **20**.—A mixture of 2'-deoxyadenosine (co-evaporated with pyridine) (1.5 g, 5.6 mmol), imidazole (0.38 g, 5.6 mmol) and *tert*-butyldimethylsilyl chloride (927 mg, 6 mmol) in DMF (40 cm^3) was stirred at room temperature overnight. Methanol (2 cm^3) was added to the mixture and the solvent was removed under reduced pressure. The residue was then purified on a silica column by elution with 5% methanol in dichloromethane to give compound **20** as a white solid (1.53 g, 75%), m.p. 169–170 °C; ν_{max}(KBr)/cm^{-1} 3431, 3129, 1649, 1599 and 1109; δ_H([$^2H_6$]DMSO) 8.26 (1 H, s, 8-H), 8.12 (1 H, s, 2-H), 7.22 (2 H, br s, NH_2), 6.4–6.3 (1 H, t, $J_{1',2'}$ 6.5, 1'-H), 5.33 (1 H, d, $J_{3'\text{-OH}}$ 4.5, 3'-OH), 4.44–4.38 (1 H, m, 3'-H), 3.90–3.80 (2 H, m, 4'-H, 5'-H), 3.74–3.66 (1 H, m, 5'-H), 2.68–2.38 (2 H, m, 2'-CH_2), 0.85 (9 H, s, Bu^t) and 0.02 (6 H, s, Me_2Si); *m/z* 365 (M$^+$).

2'-*Deoxy*-N^6,N^6,3'-O-*tribenzyladenosine* **22**.—Benzyl bromide (11 cm^3, 92 mmol) was added to a stirred suspension of compound **20** (806 mg, 2.2 mmol), powdered potassium hydroxide (730 mg, 13 mmol) and tetrabutylammonium bromide (265 mg, 0.8 mmol) in THF (60 cm^3) at 0 °C. The reaction mixture was stirred at room temperature for 3 h and then filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was filtered through silica. It was washed first with light petroleum (b.p. 40–60 °C) to remove the excess of benzyl bromide and then with a mixture of light petroleum and ethyl acetate (85:15) to give a pale yellow oil. This oil was dissolved in THF (60 cm^3) and tetrabutylammonium fluoride (1.0 mol dm^{-3} solution in THF; 6.6 cm^3) was added. The reaction mixture was stirred at room temperature for 2 h and then quenched with water (4 cm^3). After removal of the solvent, the residue was purified on silica by elution with 1% methanol in dichloromethane to give compound **22** as a pale yellow foam (0.9 g, 78%); $[\alpha]_D^{20}$ + 14 (*c* 1.07, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3235, 3031, 2922, 1584, 1476 and 1097; δ_H($CDCl_3$) 8.32 (1 H, s, 8-H), 7.76 (1 H, s, 2-H), 7.47–7.21 (15 H, m, Ph), 6.27 (1 H, dd, $J_{1',2'}$ 9.8, 5.5, 1'-H), 5.6–5.0 [4 H, br s, N(CH_2Ph)$_2$], 4.62 (2 H, br s, OCH_2Ph), 4.52 (1 H, d, $J_{3',2'}$ 5.4, 3'-H), 4.40 (1 H, br s, 4'-H), 4.04 (1 H, dd, $J_{5',5'}$ 12.8, $J_{5',4'}$ 1.5, 5'-H), 3.76 (1 H, dd, $J_{5',5'}$ 12.8, $J_{5',4'}$ 1.2, 5'-H), 3.18–3.08 (1 H, ddd, $J_{2',1'}$ 9.8, $J_{2',2'}$ 13.3, $J_{2',3'}$ 5.4, 2'-H), 2.44 (1 H, dd, $J_{2',2'}$ 13.3, $J_{2',1'}$ 5.5, 2'-H) (Found: [M + H]$^+$, 522.2505. $C_{31}H_{32}N_5O_3$ requires 522.2505).

N^6,N^6-*Dibenzyl*-9-(3-O-*benzyl*-2,5-*dideoxy*-β-D-erythro-*pent*-4-*enofuranosyl*)*adenine* **23**.—Methanesulfonyl chloride (0.2 cm^3) was added dropwise to a stirred solution of compound **22** (330 mg, 0.6 mmol) in pyridine (3 cm^3) at 0 °C. The reaction mixture was stirred for 1 h and then ice was added to it. After this, the solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. The solution was washed with aqueous sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and evaporated to give a pale yellow foam. This foam was dissolved in THF (6 cm^3) and the solution cooled to −78 °C. A solution of KOBu^t (0.2 g, 1.8 mmol) in THF (4 cm^3) was then slowly added to it. The reaction mixture was allowed to warm to room temperature over 1 h after which a solution prepared with acetic acid (0.5 cm^3) and sodium acetate (3.3 g) in water (133 cm^3) was added to it; the mixture was then stirred for a further 5 min and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried ($MgSO_4$) and evaporated. The residue was purified on a silica column by elution with 30% ethyl acetate in light petroleum (b.p. 40–60 °C) to give compound **23** as an oil (228 mg, 72%); ν_{max}(film)/cm^{-1} 3032, 1660, 1577, 1225 and 953; δ_H($CDCl_3$) 8.41 (1 H, s, 8-H), 7.82 (1 H, s, 2-H), 7.38–7.26 (15 H, m, Ph), 6.72 (1 H, dd, $J_{1',2'}$ 7.6, 6.0, 1'-H), 5.30 [4 H, br s, N(CH_2Ph)$_2$], 4.76 (1 H, d, J_{ab} 11.5, 3'-OH_aCH$_b$Ph), 4.67 (1 H, dd, $J_{3',2'}$ 5.7, 2.3, 3'-H), 4.63 (1 H, d, $J_{5',5'}$ 2, 5'-H), 4.55 (1 H, d, J_{ba} 11.5, 3'-OH_bCH$_a$Ph), 4.34 (1 H, d, $J_{5',5'}$ 2, 5'-H), 3.0–2.90 (1 H, ddd, $J_{2',2'}$ 13.5, $J_{2',1'}$ 7.6, $J_{2',3'}$ 5.7, 2'-H) and 2.74–2.66 (1 H, ddd, $J_{2',2'}$ 13.5, $J_{2',1'}$ 6.0, $J_{2',3'}$ 2.3, 2'-H) (Found: [M + H]$^+$ 504.2400. $C_{31}H_{30}N_5O_2$ requires 504.2399).

Attempted Reactions of N^6,N^6-*Dibenzyl*-9-(3-O-*benzyl*-2,5-*dideoxy*-β-D-erythro-*pent*-4-*enofuranosyl*)*adenine* **23**.—

(a) *With silver fluoride and iodine in acetonitrile*.— A solution of iodine (920 mg, 3.6 mmol) in acetonitrile (10 cm^3) was added dropwise to a stirred suspension of the enol ether **23** (228 mg, 0.45 mmol), silver fluoride (457 mg, 3.6 mmol) in acetonitrile (20 cm^3) at −40 °C. The reaction mixture was allowed to warm to room temperature over 1 h after which an aqueous solution of sodium hydrogen carbonate, sodium thiosulfate and sodium chloride was added to it. The mixture was extracted with dichloromethane and the extract was dried ($MgSO_4$) and evaporated. The residue was purified on silica by elution with 5% acetone in dichloromethane to give a pale yellow foam, which was confirmed to be the enol ether **23** (0.2 g, 88% recovery).

(b) *With hydrogen fluoride–pyridine*. A solution of the enol ether **23** (252 mg, 0.5 mmol) in THF (2 cm^3) was added to a precooled solution of hydrogen fluoride–pyridine (0.85 cm^3) in THF (2 cm^3) at −70 °C in a plastic bottle. The reaction mixture was stirred for 1 h and then quenched with ice–water. Dichloromethane was added to the mixture which was then poured into cooled aqueous sodium hydrogen carbonate. The combined dichloromethane extracts were dried ($MgSO_4$) and evaporated and the enol ether **23** was recovered after purification by chromatography (227 mg, 90% recovery).

(c) *With silver fluoride and iodine in dichloromethane*. A solution of iodine (194 mg, 0.76 mmol) in dichloromethane (5 cm^3) was added dropwise to a stirred mixture of the enol ether **23** (172 mg, 0.34 mmol) and silver fluoride (242 mg, 1.9 mmol) in dichloromethane (10 cm^3) at room temperature over 1 h. Stirring of the mixture was continued for 30 min after which 5% aqueous sodium hydrogen carbonate (10 cm^3) and 5% aqueous sodium thiosulfate (10 cm^3) were added to it. The mixture was then shaken thoroughly and filtered. The filtrate was extracted with dichloromethane and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified on silica by elution with ethyl acetate–light petroleum (b.p. 40–60 °C) (1:1) to give a colourless foam. The ^{1}H and ^{19}F NMR spectra showed this to be a 1:1 mixture of **24**:**25** (166 mg, 75%); δ_H($CDCl_3$) 8.42, 8.31 (1 H, 2 s, 8-H), 8.0 and 7.79 (1 H, 2 s, 2-H), 7.50–7.18 (15 H, m, Ph), 6.93–6.86 (0.5 H, m, 1'-H), 6.46–6.42 (0.5 H, m, 1'-H), 5.55–5.10 [4 H, br, N(CH_2Ph)$_2$], 4.80–4.50 (3 H, m, 3'-OCH_2Ph, 3'-H), 3.66–3.40 (2 H, m, 5'-H) and 3.0–2.60 (2 H, m, 2'-CH_2); δ_F($CDCl_3$) 66.0–65.78 (m) and 52.90–52.70 (dt, *J* 16.5, 6.5).

2'-*Deoxy*-4'-*fluoro*-N^6,N^6, 3'-O-*tribenzyladenosine* **26** *and* N^6,N^6-*Dibenzyl*-9-(3-O-*benzyl*-2-*deoxy*-4-*fluoro*-α-L-*lyxofuranosyl*)*adenine* **27**.—Potassium superoxide (95 mg, 1.3 mmol) and 18-crown-6 (345 mg, 1.3 mmol) were added to stirred solution of a 1:1 mixture of **24**:**25** (215 mg, 0.33 mmol) in THF (18 cm^3) and DMSO (13 cm^3) at room temperature. The mixture was stirred for 1 d, after which additional potassium superoxide (95 mg) and 18-crown-6 (345 mg) were added to it and stirring was continued for a further day. Brine (2 cm^3) was added to the mixture which was stirred for a further 30 min and then partitioned between CH_2Cl_2 and water. The organic phase was

separated, dried ($MgSO_4$) and evaporated and the residue was purified on silica by elution with 15% ethyl acetate in light petroleum (b.p. 40–60 °C). The less polar fraction was confirmed to be the α-F-isomer **26** (28 mg, 16%), $[\alpha]_D^{20}$ −20 (*c* 0.16, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3400, 2929, 2858, 1593, 1455 and 1071; δ_H($CDCl_3$) 8.34 (1 H, s, 8-H), 7.72 (1 H, s, 2-H), 7.50–7.18 (15 H, m, Ph), 6.54–6.46 (1 H, ddd, $J_{1'F}$ 1.8, $J_{1'2'}$ 6.2, 6.8, 1'-H), 5.6–5.0 [4 H, br, N(CH_2Ph)$_2$], 4.96–4.84 (1 H, ddd, $J_{3'F}$ 8.6, $J_{3'2'}$ 5.1, 7.1, 3'-H), 4.83 (1 H, d, J_{ab} 12.0, 3'-O$H_a$$CH_b$Ph), 4.66 (1 H, d, J_{ba} 12.0 Hz, 3'-O$H_b$$CH_a$Ph), 4.02 (1 H, dd, $J_{5'5'}$ 11.9, $J_{5'F}$ 1.6, 5'-H), 3.87 (1 H, dd, $J_{5'5'}$ 11.9, $J_{5'F}$ 1.5, 5'-H), 3.03–2.9 (1 H, ddd, $J_{2'2'}$ 13.2, $J_{2'1'}$ 6.2, $J_{2'3'}$ 7.1, 2'-H) and 2.68–2.57 (1 H, ddd, $J_{2'2'}$ 13.2, $J_{2'1'}$ 6.8, $J_{2'3'}$ 5.1, 2'-H); δ_F($CDCl_3$) 38.40 (dd, *J* 8.6, ~1.5) (Found: M^+, 539.2333, $C_{31}H_{30}FN_5O_3$ requires 539.2333). The more polar fraction was the β-F isomer **27** obtained as a white powder (14 mg, 8%), $[\alpha]_D^{20}$ +37.5 (*c* 0.1, $CHCl_3$); ν_{max}(KBr) cm^{-1} 3425, 3030, 1595, 1479 and 1069; δ_H($CDCl_3$) 8.42 (1 H, s, 8-H), 7.99 (1 H, s, 2-H), 7.38–7.26 (15 H, m, Ph), 6.92–6.86 (1 H, ddd, $J_{1'F}$ 7.5, $J_{1'2'}$ 6.5, 7.5, 1'-H), 5.5–5.0 [4 H, br, N(CH_2Ph)$_2$], 4.76 (1 H, d, J_{ab} 12.0, 3'-O$H_a$$CH_b$Ph), 4.66 (1 H, d, J_{ba} 12.0, 3'-O$H_b$$CH_a$Ph), 4.47 (1 H, t, $J_{3'F}$, $J_{3'2'}$ 4.4, 3'-H), 4.06–3.96 (2 H, m, 5'-CH_2), 2.9–2.8 (1 H, dd, $J_{1'2'}$ 6.5, $J_{2'2'}$ 14.2, 2'-H), 2.70–2.59 (1 H, m, 2'-H) of 2.05 (1 H, br s, OH); δ_F($CDCl_3$) 55.55–55.35 (m); *m*/*z* 540 (MH^+); (Found: $[M + H]^+$, 540.2388. $C_{31}H_{31}FN_5O_3$ requires 540.2411).

9-(2-*Deoxy*-4-*fluoro*-α-L-*lyxofuranosyl*)*adenine* **29**.—The benzyl-protected compound **27** (24 mg, 0.04 mmol) and 20% $Pd(OH)_2$ on carbon (40 mg) were stirred in methanol (3 cm^3) under a hydrogen atmosphere at room temperature. After 5 d, the reaction mixture was filtered through Celite which was washed thoroughly with methanol. The filtrate was evaporated and the residue was purified on a silica column by elution with 5% methanol in dichloromethane. Compound **29** was obtained (2 mg, 17%), ν_{max}($CHCl_3$)/cm^{-1} 3433, 3033, 1620 and 1066; δ_H($CDCl_3$) 8.42 (1 H, s, 8-H), 8.03 (1 H, s, 2-H), 6.94–6.86 (1 H, m, 1'-H), 4.80–4.76 (1 H, m, 3'-H), 4.06 (2 H, dd, $J_{5'5'}$ 14.0, $J_{5'F}$ 1, 5'-H) and 2.76–2.70 (2 H, m, 2'-CH_2); δ_F($CDCl_3$) 54.9–54.7 (m) (Found: M^+, 269.0911. $C_{10}H_{12}FN_5O_3$ requires 269.0924).

Debenzylation of 2'-*Deoxy*-4'-*fluoro*-N^6,N^6, 3'-O-*tribenzyladenosine* **26**.—A mixture of compound **26** (65 mg, 0.12 mmol), 20% $Pd(OH)_2$ on carbon (100 mg) and 10% Pd on carbon (50 mg) in methanol was stirred at room temperature under a hydrogen atmosphere for 3 d. The reaction mixture was filtered through Celite which was washed thoroughly with methanol. After evaporation of the filtrate, the residue was purified by chromatography on silica by elution with 5% methanol in dichloromethane. The less polar fraction was compound **26** (8 mg, 12%). The more polar fraction was confirmed to be N^6,N^6-*dibenzyl*-2'-*deoxy*-4'-*fluoroadenosine* **28** (10 mg, 19%), $[\alpha]_D^{20}$ +4.8 (*c* 0.66, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3200, 3018, 1592 and 1072; δ_H($CDCl_3$) 8.34 (1 H, s, 8-H), 7.76 (1 H, s, 2-H), 7.39–7.21 [10 H, m, N(CH_2*Ph*)$_2$], 6.54–6.50 (1 H, dt, $J_{1'F}$ 1.8, $J_{1'2'}$ 7.0, 6.0, 1'-H), 5.5–5.1 [4 H, br s, N(CH_2Ph)$_2$], 5.08–5.01 (1 H, dq, $J_{3'F}$ 8.6, $J_{3'2'}$ 6.5, 7.0, $J_{3'OH}$ 4.5, 3'-H), 4.01 (1 H, dd, $J_{5'5'}$ 12.0, $J_{5'F}$ 2.0, 5'-H), 3.89 (1 H, dd, $J_{5'5'}$ 12.0, $J_{5'F}$ 1.5, 5'-H), 3.15–3.05 (1 H, dt, $J_{1'2'}$ 7.0, $J_{2'3'}$ 6.5, $J_{2'2'}$ 13.5, 2'-H), 2.62–2.51 (1 H, dt, $J_{2'1'}$ 6.0, $J_{2'3'}$ 7.0, $J_{2'2'}$ 13.5, 2'-H); δ_F($CDCl_3$) 37.50–37.40 (br d) (Found: $[M + H]^+$, 450.1938. $C_{24}H_{25}FN_5O_3$ requires 450.1941).

5'-O-tert-*Butyldimethylsilyladenosine* **32**.—A mixture of adenosine (1.068 g, 4 mmol), *tert*-butyldimethylsilyl chloride (0.66 g, 4.4 mmol), triethylamine (0.56 ml, 4 mmol) and 4-dimethylaminopyridine (73 mg, 0.6 mmol) in dichloromethane (10 cm^3) and DMF (20 cm^3) was stirred at room temperature overnight. Methanol (2 cm^3) was added to the mixture and the solvent was removed under reduced pressure. The residue was then purified on a silica column by elution with 5% methanol in dichloromethane to give the title compound **32** as a white solid (1.15 g, 76%), m.p. 176–178 ° (recryst. from EtOH); δ_H([$^2H_6$]-DMSO) 8.28 (1 H, s, 8-H), 8.15 (1 H, s, 2-H), 7.25 (2 H, br s, NH_2), 5.91 (1 H, d, $J_{1'2'}$ 5.0, 1'-H), 5.51 (1 H, d, $J_{2'\text{-}OH}$ 5.5, 2'-OH), 5.17 (1 H, d, $J_{3'\text{-}OH}$ 5.0, 3'-OH), 4.55 (1 H, q, $J_{2'1'}$, $J_{2'3'}$ 5.0, $J_{2'OH}$ 5.5, 2'-H), 4.19 (1 H, q, $J_{3'\text{-}OH}$, $J_{3'2'}$, $J_{3'4'}$ 5.0, 3'-H), 3.96 (1 H, q, $J_{4'5'}$ 4.0, $J_{4'3'}$ 5.0, 4'-H), 3.88 (1 H, dd, $J_{5'5'}$ 12.0, $J_{5'4'}$, 4.0, 5'-H), 3.75 (1 H, dd, $J_{5'5'}$ 12.0 , $J_{5'4'}$ 4.0, 5'-H), 0.88 (9 H, s, Bu^t) and 0.05 (6 H, s, Me_2).

5'-O-tert-*Butyldimethylsilyl*-2'-O-p-*tolylsulfonyladenosine* **33**.—A mixture of 5'-*O*-*tert*-butyldimethylsilyladenosine **32** (476 mg, 1.24 mmol), dibutyltin oxide (313 mg, 1.25 mmol) and methanol (25 cm^3) was heated under reflux for 30 min and then cooled to room temperature. Triethylamine (2.6 cm^3, 18.6 mmol) and toluene-*p*-sulfonyl chloride (3.55 g, 18.6 mmol) were added to the reaction mixture which was then stirred for 5 min. After removal of the solvent, the residue was partitioned between ethyl acetate and water. The organic phase was dried ($MgSO_4$) and evaporated and the residue was purified on silica by elution with 5% methanol in dichloromethane to give compound **33** as a colourless foam (540 mg, 81%); ν_{max}(KBr)/cm^{-1} 3382, 2929, 1596, 1471, 1364, 1176 and 833; δ_H($CDCl_3$) 8.2 (1 H, s, 8-H), 7.96 (1 H, s, 2-H), 7.48 (2 H, d, *J* 8.0, Ar), 7.01 (2 H, d, *J* 8.0, Ar), 6.20 (1 H, d, $J_{1'2'}$ 6.5, 1'-H), 5.76 (2 H, br s, NH_2), 5.42 (1 H, dd, $J_{2'3'}$ 5.0, $J_{2'1'}$ 6.5, 2'-H), 4.62 (1 H, dd, $J_{3'2'}$ 5.0, $J_{3'4'}$ 4.5, 3'-H), 4.29–4.26 (1 H, m, 4'-H), 3.95 (1 H, dd, $J_{5'5'}$ 11.5, $J_{5'4'}$ 3.0, 5'-H), 3.84 (1 H, dd, $J_{5'5'}$ 11.5, $J_{5'4'}$ 2.5, 5'-H), 2.34 (3 H, s, Me), 0.96 (9H, s, Bu^t), 0.144 (3 H, s, MeSi) and 0.139 (3 H, s, MeSi) (Found: $[M + H]^+$, 536.2000. $C_{23}H_{34}N_5O_6$ SSi requires 536.1999).

9-(5-O-tert-*Butyldimethylsilyl*-2-*deoxy*-β-D-threo-*pentofuranosyl*)*adenine* **34**.—Lithium triethylborohydride (1.0 mol dm^{-3} solution in THF; 10 cm^3) was added to a stirred solution of compound **33** (535 mg, 1 mmol) in THF (10 cm^3) at room temperature. The reaction mixture was stirred for 3 h and then quenched carefully with ice. After removal of the solvent at reduced pressure, the residue was partitioned between ethyl acetate and water and the organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (5% methanol in dichloromethane) to give compound **34** as a colourless foam (204 mg, 56%); ν_{max}(KBr)/cm^{-1} 3178, 2933, 1653, 1474, 1095 and 836; δ_H($CDCl_3$) 8.32 (1 H, s, 8-H), 7.99 (1 H, s, 2-H), 6.18–6.10 (1 H, m, 1'-H), 5.78 (2 H, br s, NH_2), 4.50–4.40 (1 H, m, 3'-H), 4.15–4.06 (1 H, m, 4'-H), 4.01–3.91 (2 H, m, 5'-H), 2.92–2.80 (1 H, m, 2'-H), 2.60–2.50 (1 H, m, 2'-H), 0.89 (9 H, s, Bu^t) and 0.06 (6 H, s, Me_2Si) (Found: $[M + H]^+$, 366.1961. $C_{16}H_{28}N_5O_3Si$ requires 366.1961).

9-(5-O-tert-*Butyldimethylsilyl*-2,3-*dideoxy*-3-*fluoro*-β-D-erythro-*pentofuranosyl*)*adenine* **35**.—Diethylaminosulfur trifluoride (0.4 cm^3) was added to a stirred solution of compound **34** (190 mg, 0.52 mmol) in dichloromethane (15 cm^3) at room temperature. The reaction mixture was stirred for 30 min after which aqueous sodium hydrogen carbonate was added to it. The mixture was then extracted with CH_2Cl_2. The extract was washed with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (5% methanol in dichloromethane) to give the fluoro compound **35** as a white foam (110 mg, 58%); ν_{max}(KBr)/cm^{-1} 3356, 3175, 2959, 2861, 1657, 1601, 1576, 1094 and 836; δ_H($CDCl_3$) 8.35 (1 H, s, 8-H), 8.11 (1 H, s, 2-H), 6.52

(1 H, dd, $J_{1'2'}$ 7.0, 6.5, 1'-H), 5.71 (2 H, br s, NH_2), 5.45–5.20 (1 H, ddt, $J_{3'F}$ 54, $J_{3'2'}$ 2.5, $J_{3'4'}$ 4.0, 3'-H), 4.40 (1 H, dd, $J_{4'F}$ 26, $J_{4'3'}$ 4.0, 4'-H), 3.94–3.82 (2H, m, 5'-H), 2.88–2.69 (2 H, m, 2'-CH_2), 0.92 (9 H, s, Bu^t) and 0.10 (6 H, s, Me_2Si) (Found: $[M + H]^+$, 368.1918. $C_{16}H_{27}FN_5O_2Si$ requires 368.1918).

N^6,N^6-*Dibenzoyl*-9-(3-*fluoro*-2,3,5-*trideoxy*-β-D-erythro-*pent*-4-*enofuranosyl*)*adenine* **37**.—Benzoyl chloride (0.2 cm^3, 1.56 mmol) was added dropwise to a stirred solution of the fluoro compound **35** (190 mg, 0.52 mmol) in pyridine (4 cm^3) at 0 °C. The reaction mixture was stirred for 1 h and then ice was added to it. After removal of the solvent at reduced pressure, the residue was dissolved in dichloromethane and the solution washed with aqueous sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and evaporated. The resulting compound was dissolved in THF (4 cm^3) and tetrabutylammonium fluoride (1.0 mol dm^{-3} solution in THF; 2 cm^3) was added to the solution. The mixture was stirred at room temperature for 2 h after which the reaction was quenched with water and the mixture extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated to give a white foam which was dissolved in pyridine (3 cm^3) and treated with methanesulfonyl chloride (0.2 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature over 1 h whereupon ice was added to it and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane and the solution washed with aqueous sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and evaporated. The resulting residue was thoroughly dried and dissolved in THF (5 cm^3) and the solution cooled to −78 °C. A solution of KOBu^t (174 mg, 1.5 mmol) in THF (5 cm^3) was then added to it dropwise. After this the reaction mixture was allowed to warm to room temperature over 2 h when it was quenched with water and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), filtered and evaporated and the residue was dissolved in pyridine (2 cm^3). Benzoyl chloride (0.2 cm^3) was added at 0 °C to the solution which was then stirred at room temperature for 3 h and, subsequently, quenched with ice. Solvent was removed from the mixture and the residue was dissolved in dichloromethane and the solution washed with aqueous sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and evaporated. The residue was purified on silica by elution with 5% acetone in dichloromethane. The less polar fraction was confirmed to be 5-(N^6,N^6-*dibenzoyladenin*-9-*yl*)-2-*methylfuran* **38** (41 mg, 19%); ν_{max}(film)/cm^{-1} 3414, 3024, 1709, 1624 and 1595; δ_H($CDCl_3$) 9.00 (1 H, s, 8'-H), 8.60 (1 H, s, 2'-H), 8.3–7.5 (10 H, m, Bz), 6.85 (1 H, d, *J* 4.0, 4-H), 6.40 (1 H, d, *J* 4.0, 3-H) and 2.5 (3 H, s, 2-Me) (Found: M^+, 423.132. $C_{24}H_{17}N_5O_3$ requires 423.133). The more polar fraction was the enol ether **37** (60 mg, 26%); ν_{max}(KBr)/cm^{-1} 3418, 1703, 1599, 1578 and 1237; δ_H($CDCl_3$) 8.66 (1 H, s, 8-H), 8.14 (1 H, s, 2-H), 7.87–7.26 (10 H, m, Bz), 6.70–6.64 (1 H, t, $J_{1'2'}$ 6.5, 1'-H), 5.82–5.56 (1 H, ddd, $J_{3'F}$ 56, $J_{3'2'}$ 6.0, 2.0, 3'-H), 4.74 (1 H, dd, $J_{5'5'}$ 2.5, $J_{5'F}$ 6.0, 5'-H), 4.59 (1 H, dd, $J_{5'5'}$ 2.5, $J_{5'F}$ 6.5, 5'-H) and 3.32–2.82 (2 H, m, 2'-CH_2) (Found: $[M + H]^+$ 444.1470. $C_{24}H_{19}FN_5O_3$ requires 444.1472).

Attempted Iodofluorination of N^6,N^6-*Dibenzoyl*-9-(3-*fluoro*-2,3,5-*trideoxy*-β-D-erythro-*pent*-4-*enofuranosyl*)*adenine* **37**.—A solution of iodine (143 mg, 0.56 mmol) in acetonitrile (2 cm^3) was added dropwise to a stirred suspension of the enol ether **37** (60 mg, 0.14 mmol) and silver fluoride (142 mg, 1.1 mmol) acetonitrile (4 cm^3) at −40 °C. The reaction mixture was allowed to warm to room temperature over 1 h and was then partitioned between dichloromethane and aqueous sodium hydrogen carbonate. The organic phase was washed with aqueous sodium thiosulfate and brine, dried ($MgSO_4$) and evaporated. Purification of the residue on silica by elution with 5% acetone in dichloromethane gave the enol ether **37** as the only compound isolated (40 mg, 67% recovery).

N^6,5'-O-*Bis*(*triphenylmethyl*)*adenosine* **43**.—A mixture of adenosine (1.34 g, 5 mmol) and triphenylmethyl chloride (4.2 g, 15 mmol) in pyridine (15 cm^3) was heated at 50 °C overnight. The reaction was quenched with ethanol (5 cm^3) and the mixture was concentrated under reduced pressure and co-evaporated with toluene. The residue suspended in toluene (100 cm^3) was shaken well and filtered. The filtrate was concentrated and the residue was dissolved in a mixture of toluene and ethyl acetate (85:15; 20 cm^3) at room temperature. The resulting precipitate was filtered off and recrystallised from ethanol to give compound **43** as colourless crystals (2.34 g, 62%), m.p. 219–221 °C [lit.,[23] 215–216 °C]; ν_{max}(KBr)/cm^{-1} 3283, 1605, 1467 and 1290; δ_H([$^2H_6$]DMSO) 8.31 (1 H, s, 8-H), 7.81 (1 H, s, 2-H), 7.42 (1 H, s, NH), 7.26–7.17 (30 H, m, Ph_3C), 5.92 (1 H, d, $J_{1'2'}$ 5.0, 1'-H), 5.48 (1 H, d, $J_{2'\text{-OH}}$ 5.5, 2'-OH), 5.18 (1 H, d, $J_{3'\text{-OH}}$ 6.0, 3'-OH), 4.74 (1 H, m, 2'-H), 4.30 (1 H, m, 3'-H), 4.06 (1 H, q, $J_{4'5'}$ 4.5, $J_{4'3'}$ 5, 4'-H) and 3.22 (2 H, d, $J_{5'4'}$ 4.5, 5'-H); *m*/*z* 752 (MH^+).

N^6-*Triphenylmethyl*-9-(3-*deoxy*-5-O-*triphenylmethyl*-β-D-threo-*pentofuranosyl*)*adenine* **45**.—Methanesulfonyl chloride (1.66 cm^3, 21.4 mmol) was added dropwise to a solution of the bistrityl compound **43** (1.92 g, 2.56 mmol) in pyridine (25 cm^3) at room temperature and the mixture was stirred for 3 h. Ice was then added to it and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane and the solution washed with aqueous sodium hydrogen carbonate, water and brine, dried ($MgSO_4$) and evaporated to give a pale yellow foam. This foam was thoroughly dried and dissolved in a mixture of benzene (13 cm^3) and methanol (31 cm^3) and the solution cooled to 0 °C. A solution of potassium hydroxide (1.4 g) in methanol (10 cm^3) was added to the mixture and this was followed by addition of sodium borohydride (292 mg, 7.7 mmol). The reaction mixture was then stirred at room temperature overnight. Acetone (6 cm^3) was added to the mixture while it was being cooled after which the solvents were removed under reduced pressure and the residue partitioned between dichloromethane and water. The organic phase was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was purified on a silica column by elution with 5% acetone in dichloromethane to give compound **45** as a colourless foam (1.57 g, 84%); ν_{max}(KBr)/cm^{-1} 3420, 1599, 1445 and 1292; δ_H([$^2H_6$]DMSO) 8.18 (1 H, s, 8-H), 7.84 (1 H, s, 2-H), 7.34–7.10 (31 H, m, NH, Ph_3C), 6.19 (1 H, d, $J_{1'2'}$ 5.3, 1'-H), 5.43 (1 H, d, $J_{2'\text{-OH}}$ 4.9, 2'-OH), 4.54–4.46 (1 H, m, 2'-H), 4.30–4.26 (1 H, m, 4'-H), 3.42–3.36 (1 H, m, 5'-H), 3.14–3.08 (1 H, m, 5'-H), 2.44–2.30 (1 H, m, 3'-H) and 2.05–1.94 (1 H, m, 3'-H) (Found: M^+, 735.3210. $C_{48}H_{41}N_5O_3$ requires 735.3209).

N^6-*Triphenylmethyl*-9-(2,3-*dideoxy*-2-*fluoro*-5-O-*triphenylmethyl*-β-D-erythro-*pentofuranosyl*)*adenine* **46**.—Diethylaminosulfur trifluoride (1.2 cm^3) was added to a stirred solution of compound **45** (1.57 g, 2.1 mmol) in dichloromethane (50 cm^3) at room temperature. The reaction mixture was stirred overnight and then quenched with aqueous sodium hydrogen carbonate. The mixture was extracted with dichloromethane and the combined extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was then purified on a silica column by elution with 2% acetone in dichloromethane to give compound **46** as a colourless foam (1.04 g, 66%); ν_{max}(KBr)/cm^{-1} 3419, 3060, 1599, 1445, 1287 and 1076; δ_H($CDCl_3$) 8.0 (1 H, s, 8-H), 7.90 (1 H, s, 2-H), 7.5–7.17 (30 H, m, Ph_3C), 6.96 (1 H, s, NH), 6.22 (1 H, d, $J_{1'F}$ 18.2, 1'-H), 5.67 (1 H, dd, $J_{2'F}$ 51.9, $J_{2'3'}$ 4.3, 2'-H), 4.7–4.6 (1 H, m, 4'-H),

3.48–3.36 (2 H, m, 5'-H), 2.64–2.20 (2 H, m, 3'-CH_2); δ_F-($CDCl_3$) – 18.6 to –18.0 (m, $J_{F1'}$ 18.2, $J_{F2'}$ 51.9, $J_{F3'}$ 40.5, 20.5) (Found: M^+, 731.3170. $C_{48}H_{40}FN_5O_2$ requires 737.3166).

*N⁶-Triphenylmethyl-9-(2,3-dideoxy-2-fluoro-β-*D-erythro-*pentofuranosyl)adenine* **47**.—The dityl fluoro compound **46** (592 mg, 0.8 mmol) was stirred in a mixture of chloroform and trifluoroacetic acid (9:1, 10 cm^3) at room temperature. The course of the reaction was followed by TLC (10% methanol in dichloromethane). The reaction mixture was neutralised with 2 mol dm^{-3} aqueous sodium hydroxide. After removal of the solvent under reduced pressure, the residue was purified on a silica column by elution with 5% methanol in dichloromethane to give compound **47** as a colourless foam (170 mg, 42%); ν_{max}(Nujol)/cm^{-1} 3305, 2946, 2860, 1606, 1469 and 1061; δ_H-($CDCl_3$) 8.00 (1 H, s, 8-H), 7.90 (1 H, s, 2-H), 7.35–7.25 (15 H, m, Ph_3C), 7.1 (1 H, s, NH), 6.02 (1 H, dd, $J_{1'F}$ 16.5, $J_{1'2'}$ 3.5, 1'-H), 5.64 (1 H, dm, $J_{2'F}$ 54, $J_{2'1'}$ 3.5, $J_{2'3'}$ 6.6, 5.0, 2'-H), 4.64–4.56 (1 H, m, $J_{4'3'}$ 7.6, 6.6, $J_{4'5'}$ 2.1, 1.7, 4'-H), 4.04 (1 H, dt, $J_{5'5''}$ 12.7, $J_{5'4'}$ 1.7, $J_{5'F}$ 2.0, 5'-H), 3.60 (1 H, dd, $J_{5''5'}$ 12.7, $J_{5''4'}$ 2.1, 5'-H), 2.96–2.78 (1 H, m, 3'-H) and 2.50–2.30 (1 H, m, 3'-H); δ_F-($CDCl_3$) – 22.65 to –23.15 (m, $J_{F1'}$ 16.5, $J_{F2'}$ 54, $J_{F5'}$ 2.0, $J_{F3'}$ 14.5, 23) (Found: M^+, 495.2071. $C_{29}H_{26}FN_5O_2$ requires 495.20709).

*Attempted Elimination in N⁶-Triphenylmethyl-9-(2,3-dideoxy-2-fluoro-β-*D-erythro-*pentofuranosyl)adenine* **47**.—Methanesulfonyl chloride (0.2 cm^3) was added to a stirred solution of compound **47** (150 mg, 0.3 mmol) in pyridine (5 cm^3) at 0 °C. After the mixture had been stirred for 1 h, ice was added to it and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane and the solution washed with water, aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and evaporated to give a brown foam. This foam was then dissolved in THF (10 cm^3) and the solution cooled to –78 °C. A solution of potassium *tert*-butoxide (120 mg, 1 mmol) in THF (5 cm^3) was then added dropwise to it. After the reaction mixture had been allowed to warm to room temperature over 3 h ice–water was added to it and then extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and evaporated and the residue was purified on silica by elution with 5% acetone in dichloromethane to give a pale yellow oil which was *2-methyl-5-(N⁶-triphenylmethyladenin-9-yl)furan* **49** (50 mg, 36%), ν_{max}(film)/cm^{-1} 3419, 3060, 1606 and 1492; δ_H($CDCl_3$) 8.20 (1 H, s, 8'-H), 8.10 (1 H, s, 2'-H), 7.60–7.20 (15 H, m, Ph_3C), 7.10 (1 H, s, NH), 6.60 (1 H, d, *J* 3.0, 4-H), 6.20 (1 H, d, *J* 3.0, 3-H) and 2.30 (3 H, s, Me) (Found: M^+, 457.1900. $C_{29}H_{23}N_5O$ requires 457.1902).

2',3'-Dideoxy-5'-O-methylsulfonyluridine **52**.—2',3'-Dideoxyuridine (0.22 g, 1 mmol) was stirred in pyridine (3 cm^3) at 0 °C under argon while methanesulfonyl chloride (0.10 ml, 1.3 mmol) was added dropwise to it. The reaction mixture was stirred at 0 °C for 2 h and then poured onto ice (10 g) and extracted with dichloromethane (3 × 8 cm^3). The combined organic extracts were washed with water and brine, dried and evaporated. The residue was purified by chromatography on silica using 2% methanol in dichloromethane as eluent to give the mesylate **52** as a white crystalline solid (0.209 g, 72%), m.p. 142–143 °C; $[\alpha]_D^{20}$ +43.5 (*c* 0.4, CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3181, 3118 (NH), 1683 (uracil), 1459, 1338, 1170 (mesylate) and 997; δ_H($CDCl_3$) 9.00 (1 H, br s, NH), 7.55 (1 H, d, J_{56} 8, 6-H), 6.09 (1H,dd,$J_{1'2'a}$4.5,$J_{1'2'b}$7.5,1'-H),5.75(1H,d,J_{56}8,5-H),4.54–4.30 (3 H, m, 4'-H, 5'-H_2), 3.08 (3 H, s, CH_3SO_3), 2.52–2.38 (1 H, m), 2.22–1.92 (3 H, m, 2'-H_2, 3'-H_2); δ_C($CDCl_3$) 162.946 (C-4), 150.254 (C-2), 139.551 (6-CH), 102-462 (5-CH), 86.527 (1'-CH), 77.877 (4'-CH), 69.636 (5'-CH_2), 37.836 (CH_3), 31.781 (2'-CH_2) and 25.676 (3'-CH_2).

Treatment of 2',3'-Dideoxy-5'-O-methylsulfonyluridine **52** *with Potassium* tert*-Butoxide*.—Potassium *tert*-butoxide (0.116 g, 1.03 mmol) was stirred in THF (3 cm^3) at –78 °C under argon while a solution of the mesylate **52** (0.100 g, 0.34 mmol) in THF (3 cm^3) was added dropwise to it. The reaction mixture was stirred for 2.5 h while slowly returning to room temperature and then stirred at this temperature for a further 20 h. The suspension was poured onto water (30 cm^3) containing sodium acetate (1 g) and acetic acid (0.1 cm^3) whilst being stirred in an ice-bath. The solution was extracted with dichloromethane (× 3) and the combined extracts were washed with water, dried and concentrated under reduced pressure. The residue was chromatographed on silica using 2% methanol in dichloromethane as eluent. The only identifiable product isolated was the furan derivative **54**, a pale yellow foam (2 mg). 1-[2-(5-Methylfuryl)]uracil: δ_H($CDCl_3$) 8.20 (1 H, br s, NH), 7.43 (1 H, d, $J_{5'6'}$ 7, 6'-H), 6.34 (1 H, d, J_{34} 3, 3-H), 6.08 (1 H, dd, J_{34} 3, $J_{4\text{-Me}}$ 1, 4-H), 5.81 (1 H, dd, $J_{5'6'7}$, $J_{5'\text{-NH}}$ 2, 5'-H) and 2.33 (3 H, d, $J_{4\text{-Me}}$ 1, CH_3) (Found: M^+, 192.0535. $C_9H_8N_2O_3$ requires 192.05348).

3'-Azido-2',3'-dideoxy-5'-O-methylsulfonyluridine **53**.—3'-Azido-2',3'-dideoxyuridine (0.050 g, 1.97 × 10^{-4} mol) in dichloromethane (4 cm^3) was stirred at 0 °C under argon whilst pyridine (0.5 cm^3) was added to it followed by methanesulfonyl chloride (0.1 cm^3, 1.3 × 10^{-3} mol). The reaction mixture was stirred for 2 h and then stored at 5 °C for 3 d. The mixture was concentrated under reduced pressure and purified by chromatography on silica using 2% methanol in dichloromethane as eluent to give the mesylate **53** as a white foam (0.045 g, 69%); δ_H($CDCl_3$) 9.30 (1 H, br s, NH), 7.45 (1 H, d, J_{56} 8, 6-H), 6.11 (1 H, t, $J_{1'2'}$ 6.5, 1'-H), 5.78 (1 H, d, J_{56} 8, 5-H), 4.54–4.30 (3 H, m, 4'-H, 5'-H_2), 4.12–4.04 (1 H, m, 3'-H), 3.12 (3 H, s, CH_3SO_3) and 2.56–2.38 (2 H, m, 2'-H).

5'-Deoxy-5'-iodo-2'3'-O-isopropylideneadenosine **57**.[18,19]—A suspension of *2',3'-O*-isopropylideneadenosine **4** (0.307 g, 1.0 mmol) in dry dichloromethane (20 cm^3) was stirred under nitrogen at –70 °C while methyltriphenoxyphosphonium iodide (0.685 g, 1.5 mmol) was added to it. The reaction mixture was allowed to return to room temperature and then stirred for 2 h. After this it was diluted with dichloromethane (50 cm^3), washed with aqueous sodium thiosulfate and water, dried and concentrated. The residue was purified by chromatography on silica using 2% methanol in dichloromethane as eluent to give the iodide **57** as a gum which formed a white crystalline solid on trituration with dichloromethane (0.144 g, 35%), m.p. 220–225 °C [lit.,[18] 103–104 °C (decomp.)]; $[\alpha]_D^{20}$ –85 (*c* 0.19, MeOH); λ_{max}(MeOH)/nm 259.6 (ε 15 600) [lit.[18] λ_{max} 259 nm (ε 14 000)]; ν_{max}(KBr)/cm^{-1} 3321, 3162 (NH), 1670, 1603 (Ad) and 1086; δ_H([$^2H_4$]methanol) 8.26, 8.22 (2 × 1 H, 2 × s, Ad-H), 6.23 (1 H, d, $J_{1'2'}$ 2.5, 1'-H), 5.54 (1 H, dd, $J_{2'3'}$ 6, $J_{1'2'}$ 2.5, 2'-H), 5.08 (1 H, dd, $J_{2'3'}$ 6, $J_{3'4'}$ 3, 3'-H), 4.37 (1 H, ddd, $J_{3'4'}$ 3, $J_{4'5'a}$ 6, $J_{4'5'b}$ 7.5, 4'-H), 3.47 (1 H, dd, $J_{5'a5'b}$ 11, $J_{4'5'b}$ 7.5, $5'_b$-H), 3.32 (1 H, dd, $J_{5'a5'b}$ 11, $J_{4'5'a}$ 6, $5'_a$-H) and 1.59 and 1.39 (2 × 3 H, 2 × s, 2 × CH_3) (Found: $[M + H]^+$, 418.0376. $C_{13}H_{17}IN_5O_3$ requires 418.0376).

5'-Deoxy-5'-iodoadenosine **58**.[19]—The iodide **57** (0.079 g, 0.19 mmol) was stirred in 90% formic acid (5 cm^3) at room temperature for 19 h after which the solvent was removed under reduced pressure. The residue was purified by preparative TLC (85% CH_2Cl_2, 15% MeOH, 0.1% HCO_2H) the compound being washed from the silica with acetone–methanol (1:1). The solid obtained was passed through a column of Sephadex LH20 using methanol as eluent. The residue was dissolved twice in methanol

saturated with ammonia and evaporated to neutralise any residual formic acid. Trituration with ether gave **58** as a white crystalline solid (0.054 g, 76%), m.p. decomp. > 200 °C (lit.,[19] 171–172 °C); $[\alpha]_D^{20}$ −12 (*c* 0.16, methanol); λ_{max}(MeOH)/nm 259.5 (ε 11 200); ν_{max}(KBr)/cm^{-1} 3338 (NH, OH), 1641 (Ad), 1354; δ_H(CD_3OD) 8.55 (2 H, s, NH_2), 8.29 and 8.21 (2 × 1 H, 2 × s, Ad-H), 6.02 (1 H, d, $J_{1'2'}$ 6, 1'-H), 4.85 (1 H, dd, $J_{1'2'}$ 6, $J_{2'3'}$ 5, 2'-H), 4.30 (1 H, dd, $J_{2'3'}$ 5, $J_{3'4'}$ 4, 3'-H), 4.06 (1 H, dt, $J_{3'4'}$ 4, $J_{3'5'}$ 6, 4'-H) and 3.66–3.46 (2 H, dAB, $J_{5'a5'b}$ 11, $J_{4'5'}$ 6, 5'-H_2).

N^6-*Benzoyl-5'-deoxy-5'-iodo-2',3'-O-isopropylideneadenosine* **59**.[19]—*N*^{6}-Benzoyl-2',3'-*O*-isopropylideneadenosine **5** (1.00 g, 2.43 mmol) was stirred in dichloromethane (40 cm^3) at −78 °C under nitrogen while methyltriphenoxyphosphonium iodide (1.65 g, 3.65 mmol) was added to it. The mixture was allowed to return to room temperature and stirring was continued for 2 h. Methanol (0.5 cm^3) was added to quench the reaction after which the mixture was diluted with dichloromethane (80 cm^3), washed with aqueous sodium thiosulfate (× 3) and then water, dried and evaporated under reduced pressure. Purification by chromatography on silica using 2% methanol in dichloromethane as eluent gave the iodide **59** as a white foam (0.95 g, 75%); $[\alpha]_D^{20}$ −64° (*c* 0.43, ethanol); ν_{max}(KBr)/cm^{-1} 1691, 1608, 1582 (CO, Ad) and 1079; δ_H($CDCl_3$) 9.20 (1 H, br s, NH), 8.76 (1 H, s), 8.17 (1 H, s) (Ad-H), 8.04–7.45 (5H, m, Ar-H), 6.19 (1 H, d, $J_{1'2'}$ 2.5, 1'-H), 5.48 (1 H, dd, $J_{1'2'}$ 2.5, $J_{2'3'}$ 6, 2'-H), 5.06 (1 H, dd, $J_{2'3'}$ 6, $J_{3'4'}$ 3, 3'-H), 4.46–4.36 (1 H, m, 4'-H), 3.43 (1 H, dd, J_{gem} 10.5, $J_{4'5'a}$ 8, 5'$_a$-H), 3.25 (1 H, dd, J_{gem} 10.5, $J_{4'5'b}$ 5.5, 5'$_b$-H) and 1.41 and 1.62 (2 × 3 H, 2 × s, 2 × CH_3); δ_C($CDCl_3$) 152.719 (CH), 151.102 (C), 149.955 (C), 142.496 (CH) (Ad), 133.607 (C), 132.785 (CH), 128.821 (CH), 127.930 (CH) (Ar), 123.750 (C, Ad), 114.841 (CMe_2), 91.181 (CH), 86.778 (CH), 84.363 (CH), 84.267 (CH), (C-1'–4'), 27.070 (CH_3), 25.339 (CH_3) and 5.052 (CH_2-5') (Found: $[M + H]^+$ 522.0640. $C_{20}H_{21}IN_5O_4$ requires 522.0638).

N^6,N^6-*Dibenzoyl-5'-deoxy-5'-iodo-2',3'-O-isopropylidene-adenosine* **60**.[20]—The iodide **59** (0.43 g, 0.82 mmol) was stirred in pyridine (4 cm^3) at 0 °C under argon while benzoyl chloride (0.12 cm^3, 1.00 mmol) was added dropwise to it. Stirring was continued for 3 h while the mixture slowly returned to room temperature. The mixture was then again chilled to 0 °C and further benzoyl chloride (0.12 cm^3, 1.00 mmol) was added. Stirring was continued at room temperature for 16 h after which the mixture was poured onto ice and extracted with dichloromethane (× 3). The combined extracts were washed with water, dried and concentrated under reduced pressure to give a yellow oil which was purified by chromatography on silica using 2% acetone in dichloromethane as eluent to give a mixture of the iodide **60** and a compound which was tentatively assigned as the chloride **61** as a white foam (0.42 g). ^{1}H NMR shows that the ratio of iodide to chloride is 60:40. Treatment of the mixture with an excess of sodium iodide in refluxing acetone did not change the ratio of the compounds. A pure sample of the iodide **60** was obtained by careful chromatography using 1% acetone in dichloromethane as eluent. The pure iodide **60** was obtained in this way, as a white foam, m.p. 100 °C (decomp.); $[\alpha]_D^{20}$ −58 (*c* 0.2, MeOH); ν_{max}(KBr)/cm^{-1} 1702 (Ad, CO), 1599, 1578, 1449 (Ar), 1237 and 1086 cm^{-1}; δ_H($CDCl_3$) 8.70 (1 H, s), 8.27 (1 H, s) (Ad-H), 7.30–8.00 (10 H, m, ArH), 6.20 (1 H, d, $J_{1'2'}$ 2.5, 1'-H), 5.44(1H,dd,$J_{1'2'}$2.5,$J_{2'3'}$6.5,2'-H),5.03(1H,dd,$J_{2'3'}$6.5,$J_{3'4'}$3.5, 3'-H), 4.37–4.46 (1 H, m, 4'-H), 3.44 (1H, dd, $J_{5'a5'b}$ 11, $J_{4'5'a}$ 7.5, 5'$_a$-H), 3.31 (1 H, dd, $J_{5'a5'b}$ 11, $J_{4'5'b}$ 5.5, 5'$_b$-H) and 1.64 and 1.43 (2 × 3 H, 2 × s, 2 × CH_3); λ_{max}(EtOH)/nm 252 (ε 26 500) and 275 (ε 21 400) [lit.,[20] λ_{max}/nm 250 (ε 27 600) and 270 (ε 21 700)]; δ_C($CDCl_3$) 172.185 (CO), 152.353 (CH), 152.286 (C), 152.220 (C), 144.117 (CH) (Ad), 134.139 (C), 133.004 (CH), 129.471 (CH), 128.734 (CH) (Ph), 115.056 (CMe_2), 91.037, 86.290, 84.303, 84.244 (4 × CH, C-1'–C-4'), 27.095 (CH_3), 25.335 (CH_3) and 5.084 (5'-CH_2).

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References

1 S. O. Thomas, V. L. R. Singleton, J. A. Lowery, R. W. Sharpe, L. M. Pruess, J. N. Porter, J. H. Mowat and N. Bohonos, *Antibiotics Annual*, 1956–1957, 716.
2 R. I. Hewitt, A. R. Gumble, L. H. Taylor and W. S. Wallace, *Antibiotics Annual*, 1956–1957, 722.
3 E. J. Backus, H. D. Tresner and T. H. Campbell, *Antibiotics and Chemotherapy*, 1957, VII, 532.
4 S. O. Thomas, J. A. Lowery and V. L. R. Singleton, US P. 2,914,525, Nov. 24, 1959.
5 G. O. Morton, J. E. Lancaster, G. E. Van Lear, W. Fulmor and W. E. Meyer, *J. Am. Chem. Soc.*, 1969, **91**, 1535; C. W. Waller, J. B. Patrick, W. Fulmer and W. E. Meyer, *J. Am. Chem. Soc.*, 1957, **79**, 1011.
6 I. D. Jenkins, J. P. H. Verheyden and J. G. Moffatt, *J. Am. Chem. Soc.*, 1971, **93**, 4323; I. D. Jenkins, J. P. H. Verheyden and J. G. Moffatt, *J. Am. Chem. Soc.*, 1976, **98**, 3346.
7 P. Herdewijn, J. Balzarini, E. De Clercq, R. Pauwels, M. Baba, S. Broder and H. Vanderhaeghe, *J. Med. Chem.*, 1987, **30**, 1270.
8 V. E. Marquez, C. K.-H. Tseng, H. Mitsuya, S. Aoki, J. A. Kelley, H. Ford, Jr., J. S. Roth, S. Broder, D. G. Johns and J. S. Driscoll, *J. Med. Chem.*, 1990, **33**, 978; J. A. Martin, D. J. Bushnell, I. B. Duncan, S. J. Dunsdon, M. J. Hall, P. J. Machin, J. H. Merrett, K. E. P. Parkes, N. A. Roberts, G. J. Thomas, S. A. Galpin and D. Kinchington, *J. Med. Chem.*, 1990, **33**, 2137; K. A. Watanabe, K. Harada, J. Zeidler, J. Matulic-Adamic, K. Takahashi, W.-Y. Ren, L.-C. Cheng, J. J. Fox, T.-C. Chou, Q.-Y. Zhu, B. Polsky, J. W. M. Gold and D. Armstrong, *J. Med. Chem.*, 1990, **33**, 2145; R. Z. Sterzycki, I. Ghazzouli, V. Brankovan, J. C. Martin and M. M. Mansuri, *J. Med. Chem.*, 1990, **33**, 2150.
9 (*a*) K. Biggadike and A. D. Borthwick, *J. Chem. Soc., Chem. Commun.*, 1990, 1380; (*b*) C. O.-Yang, H. Y. Wu, E. B. Fraser-Smith and K. A. M. Walker, *Tetrahedron Lett.*, 1992, **33**, 37; C. O.-Yang, W. Kurz, E. M. Eugui, M. J. McRoberts, J. P. H. Verheyden, L. J. Kurz and K. A. M. Walker, *Tetrahedron Lett.*, 1992, **33**, 41.
10 G. R. Owen, J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, 1976, **41**, 3010.
11 S. Ajmera, A. R. Bapat, E. Stephenian and P. V. Danenberg, *J. Med. Chem.*, 1988, **31**, 1094.
12 R. D. Evans and J. H. Schauble, *Synthesis*, 1987, 551.
13 G. W. Craig, E. D. Sternberg, G. H. Jones and J. G. Moffatt, *J. Org. Chem.*, 1986, **51**, 1258.
14 F. Camps, J. Coll, A. Messeguer and M. A. Pericàs, *Tetrahedron Lett.*, 1981, **22**, 3895; F. Camps, J. Coll, A. Messeguer and F. Pujol, *J. Org. Chem.*, 1982, **47**, 5402.
15 E. Zielonacka-Lis, *Nucleosides Nucleotides*, 1989, **8**, 383.
16 (*a*) B. V. Joshi and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 1992, 441; (*b*) J. P. Horwitz, J. Chua, M. A. Da Rooge, M. Noel and I. L. Klundt, *J. Org. Chem.*, 1966, **31**, 205.
17 T.-S. Lin, Z.-Y. Shen, E. M. August, V. Brankovan, H. Yang, I. Ghazzouli and W. H. Prusoff, *J. Med. Chem.*, 1989, **32**, 1891.
18 M. MacCoss, E. K. Ryu, R. S. White and R. L. Last, *J. Org. Chem.*, 1980, **45**, 788.
19 S. D. Dimitrijevich, J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, 1979, **44**, 400; J. P. H. Verheyden and J. G. Moffat, *J. Org. Chem.*, 1970, **35**, 2319.
20 J. Zylber, R. Pontikis, A. Merrien, C. Merienne, M. Baran-Marszak, and A. Gaudemer, *Tetrahedron*, 1980, **36**, 1579.
21 R. Graf, *Chem. Ber.*, 1959, **92**, 509.
22 *Dictionary of Organic Compounds*, 5th edn, vol. 4, N-01703.
23 H.-U. Blank, D. Frahna, A. Myles and W. Pfleiderer, *Liebigs Ann. Chem.*, 1970, **742**, 34.

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