Tetrahedron Vol. 44, No. 2, pp. 625 to 636, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00
Pergamon Journals Ltd.

METHYL 5-O-TERT-BUTYLDIPHENYLSILYL-2-DEOXY-αß-D-THREO-PENTOFURANOSIDE AS A DIVERGENT INTERMEDIATE FOR THE SYNTHESIS OF 3'-SUBSTITUTED-2',3'-DIDEOXYNUCLEOSIDES: SYNTHESIS OF 3'-AZIDO-3'-DEOXYTHYMIDINE, 3'-DEOXY-3'-FLUOROTHYMIDINE AND 3'-CYANO-3'-DEOXYTHYMIDINE.

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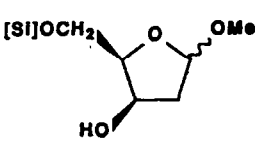
(*Received in UK* 12 *October* 1987)

The use of methyl 5-O-tert-butyldiphenylsilyl-2-deoxy-α,ß-D-threo-pentofuranoside, prepared from D-xylose, as a divergent intermediate for the synthesis of 3'-substituted-2',3'-dideoxynucleosides is illustrated by its conversion into 3'-azido-3'-deoxythymidine, 3'-deoxy-3'-fluorothymidine and 3'-cyano-3'-deoxythymidine.

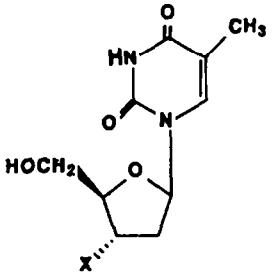
As a result of studies in connection with possible strategies for the chemotherapeutic treatment of AIDS, a number of 2',3'-dideoxynucleosides have been shown to be potent antiretroviral agents in vitro.[1,2] In particular, 3'-azido-3'-deoxythymidine (AZT) (2) is currently in clinical trial; also, the triphosphate of 3'-deoxy-3'-fluorothymidine (3) has been found to be a more potent inhibitor of HIV reverse transcriptase than the triphosphate of AZT.[3] Recently, Broder and co-workers[4] have indicated that 3'-cyano-3'-deoxythymidine (4) also shows promise in the protection of lymphocytes exposed to HIV.

Extensive studies on the synthesis and biological activity of 3'-azido[5,6] and 3'-amino[7] pyrimidine[8] and purine[9] 2',3'-dideoxyribonucleoside analogues have been reported; these analogues were almost invariably derived from the substitution of the 3'-OH function by an azide group in a 2'-deoxynucleoside, as in the case of the synthesis of AZT from thymidine.[10,11] The coupling of furanoside derivatives with silylated bases[12] in the presence of trialkylsilyl triflates allows the preparation of a very wide range of nucleoside analogues[13] in which the control[14] of the reaction conditions can lead to a high ratio of ß to α products.[15] An alternative approach[16] to the synthesis of AZT has been investigated in which a suitable derivative of thymine is coupled with a protected furanoside of 3-azido-2,3-dideoxy-D-erythro-pentose. Thus, methyl 3-azido-2,3-dideoxy-5-O-toluoyl-αß-D-erythro-pentofuranoside [17] was reacted with silylated thymine in the presence of tin (IV) chloride or trimethylsilyl triflate[18] to give a mixture of AZT (2) and the α-anomer (5). Although this approach yields both α and ß anomers, it has the advantage of the easy introduction of a number of nucleophiles at C-3 readily to provide intermediates suitable for efficient coupling to make nucleoside analogues, and this method may be particularly appropriate for the introduction of nucleophiles such as cyanide which are not easily introduced by double inversion procedures on thymidine.

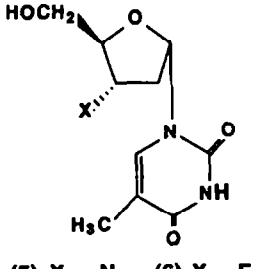


(1)

[SI] = $Ph_2{}^tBuSi$



(2) X = N_3 (3) X = F
(4) X = CN



(5) X = N_3 (6) X = F
(7) X = CN

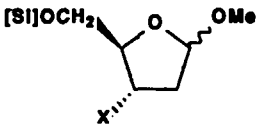
As described by Dyatkina and coworkers,[17,18] the key steps in this approach are (i) setting up an intermediate from xylose in which only the 2-OH group of xylose is free allowing deoxygenation, and (ii) the conversion of the resulting 2-deoxyxylose [methyl 2-deoxy-αß-D-threo-pentofuranoside] into a suitably protected intermediate (preferably easy to crystallise) which can be used for the introduction of a range of functional groups to give 3-substituted 2,3-dideoxyribose derivatives [methyl 3-substituted-2,3-deoxy-αß-D-erythro-pentofuranosides] such as the azido, fluoro,and cyano compounds. This paper describes a short synthesis from D-xylose of highly crystalline methyl 5-O-tert-butyldiphenylsilyl-2-deoxy-αß-D-threo-pentofuranoside (1), the conversions of (1) to the azido (8), fluoro (9) and cyano (10) sugars, and the subsequent coupling of these derivatives with silylated thymine in the presence of trialkylsilyl triflates to give the azido (2), fluoro (3) and cyano (4) thymidines, together with the corresponding α-epimers; a preliminary account of some of this work has been published.[19]

For the synthesis of methyl 5-O-tert-butyldiphenylsilyl-2-deoxy-α,ß-D-threo-pentofuranoside (1), D-xylose was converted as described by Baker[20] to methyl 3,5-O-isopropylidene-D-xylofuranoside (11), in which only the C-2 OH of xylose is unprotected, in a yield of 72%; although the anomers may readily be separated by flash chromatography, this mixture of anomers was treated with sodium hydride, carbon disulphide and methyl iodide to give the xanthates (12) (90% yield). Pure samples of the anomeric xanthates (12) were prepared from the individual anomers (11α) and (11ß).

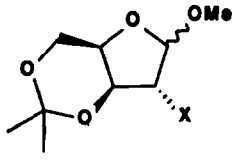
The mixture of xanthates (12) on heating with tributyltin hydride in xylene underwent the Barton deoxygenation[21] to give methyl 2-deoxy-3,5-O-isopropylidene-αß-D-threo-pentofuranoside (13). The efficiency of the deoxygenation of the xanthates (12) is sensitive to the concentration of the reactants, so that at higher concentrations lower yields of (13) were obtained; also, tin hydride reduction of the corresponding thionocarbonate[22] gave only low yields of (13). From experiments on the Barton deoxygenation of the individual anomers, it is clear that the ß-xanthate (12ß) undergoes a clean and highly efficient deoxygenation whereas the α-anomer (12α) gives a more complex reaction mixture. The volatility of the deoxygenated furanoside (13) makes efficient isolation from this reaction mixture by distillation difficult; moreover, since (13) is a fully protected sugar derivative, chromatographic separation of (13) from the tin residues was also troublesome. Thus the crude reaction mixture was methanolysed to the more polar diol (14)[17] which allows easy removal of the tin residues by partitioning between petrol and acetonitrile. During the methanolysis of the acetonide (13), equilibration of the methyl furanosides (14) occurred and the ratio (14α) to (14ß) of the anomers obtained was 4:1; methanolysis of the individual pure anomers (13α) and (13ß) under the same conditions gave an identical mixture of (14α) and (14ß). Selective reaction of the primary hydroxyl group in the diols (14) proceeded rapidly at 0°C with tert-butyldiphenylchlorosilane in the presence of imidazole to give (1) as a readily crystallised mass; there is no advantage in purifying any of the intermediates and the overall yield of the silyl ethers (1) from xanthates (12) is 55%. The ratio of the anomers (1α) to (1ß), which may easily be separated by flash chromatography, is approximately 4:1.

The potential of (1) as an intermediate for the synthesis of a range of 3-substituted-2,3-dideoxy-D-erythro-pentofuranosides is illustrated by the preparation of azide (8), fluoride (9) and cyanide (10). Esterification of the free hydroxyl group in the anomeric mixture (1) with trifluoromethanesulphonic anhydride in the presence of pyridine gave the anomeric triflates (15); reaction of the triflates (15) with sodium azide in dimethylformamide was complete in 1 h at room temperature to give the protected azides (8) in 82% overall yield from (1). The silyl protecting

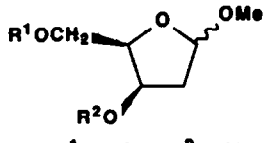
group could be removed from (8) on treatment with tetra-butylammonium fluoride to give (16), allowing a choice of protecting groups for the primary alcohol functionality to be introduced. When (15α) was treated with excess tetra-butylammonium fluoride in THF at room temperature, the triflate underwent displacement and the silyl protecting was removed to give methyl 2,3-dideoxy-3-fluoro-α-D-erythro-pentofuranoside (17α) in 46% yield. It was possible to displace the triflate without concurrent desilylation; thus treatment of the β-triflate (15β) with tetra-butylammonium fluoride at -30°C gave (9β) in 38% yield. Attempts to prepare the cyanides (10) by reaction of the triflates (15) with potassium cyanide under a variety of conditions were unsuccessful. However, reaction of (15α) with tetra-butylammonium cyanide in MeCN at room temperature gave the protected cyanofuranoside (10α) in 67% yield; much lower yields of the corresponding cyanide (10β) were obtained when the β-triflate (15β) was treated under the same conditions.



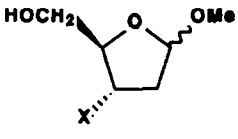
(8) X = N_3 (9) X = F
(10) X = CN



(11) X = OH
(12) X = O.CS.SMe
(13) X = H



(1) R^1 = [Si] R^2 = H
(14) R^1 = R^2 = H
(15) R^1 = [Si] R^2 = SO_2CF_3



(16) X = N_3
(17) X = F

(18)

The three 3-substituted-2,3-dideoxy-D-erythro-pentofuranosides (8) (9) and (10) all underwent efficient coupling with 5-methyl-2,4-bis(trimethyl-siloxy)pyrimidine (18)[23] in the presence of trialkylsilyltriflates to give the corresponding silylated deoxynucleosides which were subsequently deprotected. Thus, the azides (8) gave AZT (2), identical to an authentic sample,[24] in an overall yield of 33%, together with the corresponding α-anomer (5) in 29% yield. The fluorosugar (9α) under similar conditions gave 3'-deoxy-3'-fluorothymidine (3)[25] in 44% yield, together with the corresponding α-anomer (6) in 20% yield; the structure of (6) was determined principally by NMR experiments. The cyanide (10α) was converted to a mixture of 3'-cyano-3'-deoxythymidine (4) [35% yield] and the α-anomer (7) [35% yield]; the physical properties of (4) and (7) have not been previously reported and the stereochemistry of these compounds is ascribed mainly on the basis of nOe experiments.

The assignments of the proton spectra of compound (4) and (7), and (3) and (6), were made on the basis of chemical shifts and coupling patterns. The relative stereochemistry was then determined by equilibrium nOe measurements. Particularly clear evidence for the stereochemistry was provided by the observations of nOe's between substituents in a 1,3 relationship. Thus for the α-anomer of the cyanonucleoside (7) nOe's were observed between H-1' and H-3' [irradiation of H-1' generated a 3.5% enhancement of H-3', and irradiation of H-3' enhanced H-1' by 9%],

and H-6 and H-4' [irradiation of H-6 generated a 5% enhancement of H-4', and irradiation of H-4' enhanced H-6 by 7%]; in contrast, for the ß-anomer 3'-cyano-3'-deoxythymidine (4), H-6 and H-3' showed mutual nOe's [irradiation of H-6 generated a 6% enhancement of H-3', and irradiation of H-3' enhanced H-6 by 8%], as did H-1' and H-4' [irradiation of H-1' generated a 5% enhancement of H-4', and irradiation of H-4' enhanced H-1' by 4%]. Other nOe's observed in the cyano compounds (4) and (7) were also consistent with the assigned stereochemistry; analogous results were also obtained for the fluoro compounds (3)[25] and (6).

This work indicates that the crystalline intermediate (1) may be a useful intermediate for the preparation of a range of nucleoside analogues; work is currently in progress to optimise the ß:α ratio of products formed in the coupling of other derivatives of the azido sugars (8) with heterocyclic bases.

Experimental

M.p.s were recorded on a Kofler block. Infra red spectra were recorded on a Perkin-Elmer 297 spectrophotometer. Ultra violet spectra were recorded on a Perkin-Elmer 555 spectrophotometer. ^{1}H NMR spectra were run at 300 MHz on a Bruker WH 300 spectrometer (500 MHz on a Bruker AM 500 spectrometer); ^{13}C NMR spectra were recorded on a Bruker AM 250 (62.9 MHz) or a Bruker AM 500 (125.0 MHz) spectrometer. Mass spectra were recorded on VG Micromass ZAB 1F or MM 30F spectrometers. Microanalyses were performed by the microanalytical services of the Dyson Perrins Laboratory. TLC was performed on glass plates coated with silica gel Blend 41, and compounds were visualised with a spray of 5% v/v sulphuric acid in methanol or a solution of 5% dodecamolybdophosphoric acid in ethanol. Flash chromatography was carried out using Merck Kieselgel 60, 230-400 mesh. Tetrahydrofuran was distilled from a solution dried with sodium in the presence of benzophenone under dry nitrogen. 5-Methyl-2,4-bis(trimethylsiloxy)pyrimidine (18) was prepared as previously described.[23]

Methyl 3,5-O-Isopropylidene-αß-D-xylofuranoside (11) was prepared from D-xylose in 72% yield by the method described by Baker;[20] the larger scale reactions were carried out on this mixture of anomers in which the ratio of (11α):(11ß) was approximately 3:2. For the purpose of preparing unambiguous samples of pure anomers of later intermediates, the anomers (11α) and (11ß) were separated by flash chromatography.

Methyl 3,5-O-Isopropylidene-2-O-[(methylthio)-thiocarbonyl]-αß-D-xylofuranoside(12). Sodium hydride (50% dispersion, 5.0 g, 104 mmol) was added in portions to a stirred solution of methyl 3,5-O-isopropylidene-αß-D-xylofuranoside (11) (12.0 g, 58.8 mmol) in tetrahydrofuran (250 ml) at room temperature; after 30 min, carbon disulphide (12.0 ml, 199 mmol) was added in one portion and the reaction mixture was stirred for a further 30 min. Iodomethane (8 ml, 129 mmol) was then added and the stirring continued for another 15 min; excess sodium hydride was then destroyed by dropwise addition of acetic acid (2 ml). The reaction mixture was then diluted with ether (250 ml), filtered and the solvents removed in vacuo to give the crude product as a brown-yellow oil, which was purified by distillation (Kugelrohr: bath temperature 170°-185°C, 0.02-0.2 mm Hg) after passing through a silica gel pad (6 cm x 15 cm) with gradient elution by hexane-ether to give the xanthates (12), oil, (15.6 g, 90%) (Found C, 45.06; H, 6.32. $C_{11}H_{18}O_5S_2$ requires C, 44.88; H, 6.16%.) in α:ß ratio of approximately 7:3 . This material was used directly in the next step. It was not possible to separate the anomers of the xanthate (12) at this stage; accordingly, the individual anomers of the alcohol (11) were converted to the corresponding anomerically pure xanthates in order to obtain spectrosopic data on each anomer:

Methyl 3,5-O-isopropylidene-2-O-[(methylthio)-thiocarbonyl]-α-D-xylofuranoside(12α), yellow oil, $[\alpha]_D^{20}$ +147° (c, 0.92 in $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.40 (3H, s, Me), 1.43 (3H, s, Me), 2.60 (3H, s, Me), 3.40 (3H, s, OMe), 3.90 (1H, dd, H-5, $J_{4,5}$ 4.3 Hz, $J_{5',5}$ 12.4 Hz), 4.07 (1H, dd, H-5', $J_{4,5'}$ 4.3 Hz), 4.17 (1H, m, H-4), 4.54 (1H, dd, H-3, $J_{2,3}$ 2.0 Hz, $J_{3,4}$ 4.0 Hz), 5.36 (1H, d, H-1, $J_{1,2}$ 4.5 Hz), 5.71 (1H, dd, H-2). ^{13}C NMR ($CDCl_3$) δ 19.42 (q, Me), 20.81 (q, Me), 27.45 (q, Me), 56.18 (q, OMe), 60.12 (t, CH_2O), 70.89 (d, CHO), 73.49 (d, CHO), 86.02 (d, C-2), 98.76 (s, $Me_2\underline{C}$), 101.26 (d, C-1) and 215.45 (s, C=S). m/z (ACE, NH_3): 295 ($M+H^+$, 100%), 263 (20%), 101 (27%) and 85 (22%).

Methyl 3,5-O-isopropylidene-2-O-[(methylthio)-thiocarbonyl]-β-D-xylofuranoside(12β), yellow oil, $[\alpha]_D^{20}$ -29° (c, 0.90 in $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.40 (3H, s, Me), 1.41 (3H, s, Me), 2.59 (3H, s, Me), 3.45 (3H, s, OMe), 3.86 (1H, dd, H-5, $J_{4,5}$ 5.6 Hz, $J_{5',5}$ 12.0 Hz), 4.00 (1H, dd, H-5', $J_{4,5'}$ 4.9 Hz), 4.29 (1H, m, H-4), 4.40 (1H, d, H-3, $J_{3,4}$ 3.4 Hz), 5.09 (1H, s, H-1), 5.77 (1H, s, H-2). ^{13}C NMR ($CDCl_3$) δ 19.46 (q, Me), 21.13 (q, Me), 26.82 (q, Me), 55.40 (q, OMe), 60.67 (t, CH_2O), 72.76 (d, CHO), 75.62 (d, CHO), 88.93 (d, C-2), 98.76 (s, $Me_2\underline{C}$), 107.56 (d, C-1) and 214.29 (s, C=S). m/z (ACE, NH_3): 295 ($M+H^+$, 95%), 263 (100%), 111 (50%), 101 (47%) and 85 (36%).

Methyl 5-O-tert-Butyldiphenylsilyl-2-deoxy-αβ-D-threo-pentofuranoside (1). Dry nitrogen was bubbled through a solution of the xanthates (12) (6.0 g, 20.41 mmol) in xylene (200 ml) for 20 min at room temperature; the solution was then heated to 135°C and tri-n-butyltin hydride (9.0 ml, 9.74 g, 33.46 mmol) was added. The reaction mixture was maintained at 135-150°C for 12 h and subsequently cooled to room temperature. Methanol (200 ml) and p-toluenesulphonic acid (6.63 g, 34.85 mmol) were then added and the mixture stirred at room temperature; after one hour the reaction was quenched with aqueous ammonium hydroxide (SG 0.88, 30 ml) and stirred for a further 30 min. The solvent was removed in vacuo and the residue extracted with ethyl acetate (150 ml); after removal of the ethyl acetate, the remaining oil was dissolved in acetonitrile (100 ml). The acetonitrile solution was then washed with petroleum ether (b.p. 40-60, 3 x 100 ml) to remove most of the tin residues. The acetonitrile was then removed and the residue of the crude diol (14) (3.81 g) was dissolved in dimethyl formamide (30 ml) together with imidazole (3.06 g, 45 mmol); the solution was cooled to 0°C and tert-butyldiphenylchlorosilane (4.0 ml, 4.23 g, 15.38 mmol) was added dropwise. After stirring at 0°C for 20 min, the solvent was removed and the residue purified by flash chromatography (ether:hexane, 1:1.5) to give the product (1), (4.31 g, 55% for the three steps) as a white crystalline mass, (Found C, 68.30; H, 8.16. $C_{22}H_{30}O_4Si$ requires C, 68.36; H, 7.82%). The anomers, which were formed in a ratio of (1α):(1β) of 4:1, are readily separated by flash chromatography.

Methyl 5-O-tert-butyldiphenylsilyl-2-deoxy-α-D-threo-pentofuranoside (1α): m.p. 84°-85°C, $[\alpha]_D^{20}$ +56° (c, 1.16 in $CHCl_3$), ^1H NMR ($CDCl_3$) δ 1.58 (9H, s, Me_3C), 2.19 (2H, m, H-2 and H-2'), 2.99 (1H, d, OH, J 5.3 Hz), 3.35 (3H, s, OMe), 3.94-4.09 (3H, m, H-3, H-5 and H-5'), 4.61 (1H m, H-4), 5.17 (1H, t, H-1, J 4.2Hz) and 7.38-7.75 (10H. m, Ar). ^{13}C NMR ($CDCl_3$) δ 19.36 (s), 27.00 (s), 42.82 (t), 55.38 (q), 63.17 (t), 72.82 (d), 79.44 (d), 104.72 (d), 128.03 (d), 130.14 (d), 132.82 (s), 133.09 (s), 135.72 (d) and 135.84 (d). m/z (DCI,NH_3): 404 (22%, $M+NH_4^+$), 372 (100%, $M+H-Me^+$).

Methyl 5-O-tert-butyldiphenylsilyl-2-deoxy-β-D-threo-pentofuranoside (1β): m.p. 66°-67°C, $[\alpha]_D^{20}$ -54° (c, 0.31 in $CHCl_3$), ^1H NMR ($CDCl_3$) δ 1.57 (9H, s, Me_3C), 2.13 (2H, m, H-2 and H-2'), 2.96 (1H, d, OH, J 9.7 Hz), 3.31 (3H, s, OMe), 3.87 (1H, dd, H-5, $J_{5,5'}$ 10.2 Hz, $J_{4,5}$ 5.7 Hz), 4.03-4.14 (2H, m, H-3 and H-5'), 4.35 (1H, m, H-4), 5.06 (1H, dd, H-1, $J_{1,2'}$ 1.8 Hz, $J_{1,2}$ 3.5 Hz) and 7.36-7.75 (10H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 19.39 (s), 27.03 (s), 41.62 (t), 55.12 (q), 63.88 (t), 71.68 (d), 84.79

(d), 105.25 (d), 127.87 (d), 129.86 (d), 133.65 (s) and 135.82 (d). m/z (DCI,NH_3): 404 (33%, $M+NH_4^+$), 372 (100%, $M+H-Me^+$).

Methyl 2-Deoxy-3,5-O-isopropylidene-αß-D-threo-pentofuranoside (13). Tributyltin hydride (3.0 ml, 3.25 g, 11.15 mmol) was added to a solution of the xanthates (12) in xylene (60 ml) through which dry nitrogen was bubbled. The temperature of the stirred reaction mixture was then raised to reflux within 30 min; the mixture was refluxed for a further 5 h and then cooled to room temperature and the xylene removed *in vacuo*. The resulting residue was purified by flash chromatography by gradient elution (ether-hexane), allowing easy separation of the two anomers (13); the α-anomer (13α) is less polar than the ß-anomer (13ß). The deoxygenated material (13) is volatile and considerable loss of product is caused by purification at this stage.

The anomeric xanthates (12) were deoxygenated separately; by inspection of the reaction mixtures using t.l.c. it is apparent that the deoxygenation of (13ß) occurs very cleanly, whereas the reaction mixture in the deoxygenation of (13α) is more complicated.

Methyl 2-deoxy-3,5-O-isopropylidene-α-D-threo-pentofuranoside (13α), less polar anomer, oil, $[\alpha]_D^{20}$ $+114^0$ (*c*, 0.80 in $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.39 (3H, s, Me), 1.45 (3H, s, Me), 2.06 (1H, m, H-2, $J_{2,2'}$ 14.4 Hz, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 5.5 Hz), 2.43 (1H, dd, H-2', $J_{1,2'}$ 5.8 Hz, $J_{2',3}$ 0 Hz), 3.41 (3H, s, OMe), 3.87 (1H, m), 4.01 (1H, dd, H-5, $J_{4,5}$ 2.4 Hz, $J_{5',5}$ 13.1 Hz), 4.12 (1H, dd, H-5', $J_{4,5'}$ 3.3 Hz), 4.43 (1H, m, H-4), 5.27 (1H, dd, H-1). ^{13}C NMR ($CDCl_3$) δ 19.42 (q, Me), 28.42 (q, Me), 41.09 (t, CH_2), 55.51 (q, OMe), 60.26 (t, CH_2O), 70.01 (d, CHO), 72.27 (d, CHO), 97.55 (s, Me_2C), and 104.97 (d, C-1). *m/z* (CI, NH_3): 189 ($M+H^+$, 21%), 173 ($M-Me^+$, 83%), 157 (72%), 100 (44%) and 87 (100%). (Found C, 56.98; H, 8.47. $C_9H_{16}O_4$ requires C, 57.47; H, 8.57%).

Methyl 2-deoxy-3,5-O-isopropylidene-ß-D-threo-pentofuranoside (13ß), more polar anomer, oil, $[\alpha]_D^{20}$ -124^0 (*c*, 1.18 in $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.39 (3H, s, Me), 1.40 (3H, s, Me), 2.13 (1H, m, H-2), 2.21 (1H, m, H-2'), 3.40 (3H, s, OMe), 3.77 (1H, dd, H-5, $J_{4,5}$ 6.8 Hz, $J_{5',5}$ 11.5 Hz), 3.95 (1H, dd, H-5', $J_{4,5'}$ 5.8Hz), 4.11 (1H, m), 4.38 (1H, m), 5.09 (1H, dd, H-1, $J_{1,2}$ 5.3 Hz, $J_{1,2'}$ 1.2 Hz). ^{13}C NMR ($CDCl_3$) δ 21.58 (q, Me), 26.34 (q, Me), 39.40 (t, CH_2), 54.80 (q, OMe), 60.98(t, CH_2O), 69.30 (d, CHO), 76.39 (d, CHO), 98.38 (s, Me_2C), and 105.32 (d, C-1). *m/z* (CI, NH_3): 206 ($M+NH_4^+$, 6%), 189 ($M+H^+$, 25%), 174 ($M+H-Me^+$, 100%),and 157 (32%). (Found C, 56.70; H, 8.28. $C_9H_{16}O_4$ requires C, 57.47; H, 8.57%).

Methyl 2-Deoxy-αß-D-threo-pentofuranoside (14). The acetonide (13) (70 mg, 0.37 mmol) was stirred with p-toluenesulphonic acid (5 mg) in toluene (7 ml) and methanol (3 ml) at room temperature. After 8 h, the reaction was quenched with aqueous ammonium hydroxide (SG 0.88) and the mixture was evaporated to leave a residue which was purified by flash chromatography (ethyl acetate) to give methyl 2-deoxy-αß-D-threo-pentofuranoside (14) (48 mg, 87%), colourless oil, as an equilibrium mixture of the two anomers (ratio of (14α):(14ß) was aprroximately 4:1). The data for (14α) and (14ß) was consistent that previously reported.[17] Note: excess p-toluene sulphonic acid is necessary when the reaction was hydrolysed directly in the presence of tin material from the tin hydride reduction.

Both anomerically pure (13α) and (13ß) were hydrolysed separately under these conditions to give the same equilibrium mixture of anomers. The mixture of the epimeric furanosides (14) was treated with tert-butyldiphenylchlorosilane to give protected derivatives (1α) and (1ß), identical to the material described above.

Methyl 3-Azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-αβ-D-erythro-pentofuranoside (8). A solution of the alcohol (1) (2.08 g, 5.38 mmol, α:β ratio approx. 4:1) in dichloromethane (20 ml), cooled to -50°C under nitrogen, was treated with pyridine (1.3 ml, 1.27 g, 16.13 mmol) and subsequently with trifluoromethane sulphonic anhydride (1.4 ml, 2.28 g, 8.06 mmol). The reaction mixture was stirred for 2 h (-50°C to 0°C), diluted with chloroform (50 ml), washed with aqueous hydrochloric acid (2N, 50 ml) and water (2 x 50 ml) and then dried (magnesium sulphate). The solvent was then removed to give the crude triflate (15) which was used without further purification. A suspension of sodium azide (1.05 g, 16.13 mmol) was stirred in a solution of the triflate in dimethyl formamide (15 ml) at room temperature for 1 h, after which time the displacement of trifluoromethanesulphonate by azide was complete. The solvent was removed *in vacuo* and the residue purified by flash chromatography to give methyl 3-azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-αβ-D-erythro-pentofuranoside (8), as a light yellow oil, (1.81 g, 82%; α:β ratio approx. 4:1) (Found C, 64.04; H, 7.14; N, 9.93. $C_{22}H_{29}N_3O_3Si$ requires C, 64.20; H, 7.10; N, 10.21%).

Each of the anomeric alcohols (1) was taken through this procedure to provide samples of the anomers (8).

Methyl 3-azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-α-D-erythro-pentofuranoside (8α), light yellow oil, $[\alpha]_D^{20}$ +84° (c, 0.68 in $CHCl_3$); ν_{max} (neat): 2100 (azide) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.08 (9H, s, tert-butyl), 2.04 (1H, m, H-2), 2.36 (1H, m, H-2'), 3.39 (3H, s, OMe), 3.75 (2H, m, H-5 and H-5', $J_{4,5}$ 4.3 Hz, $J_{5,5'}$ 11.0 Hz), 4.08 (2H, m, H-3 amd H-4), 5.08 (1H, dd, H-1, $J_{1,2}$ 5.2 Hz, $J_{1,2'}$ 0.9 Hz), 7.3-7.7 (10H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 19.45 (s, $Me_3\underline{C}$), 27.01 (q, $\underline{Me}_3C$), 38.95 (t, C-2), 55.14 (q, OMe), 60.96 (d, C-3), 64.20 (t, CH_2O), 83.49 (d, C-4), 104.96 (d, C-1), 127.93 (d), 127.98 (d), 129.99 (d), 133.37 (s), 135.78 (d) and 135.83 (d). m/z (CI, NH_3): 429 ($M+NH_4^+$, 55%), 397 ($M+H-Me^+$, 100%).

Methyl 3-azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-β-D-erythro-pentofuranoside (8β), light yellow oil, $[\alpha]_D^{20}$ -48° (c, 0.15 in $CHCl_3$); ν_{max} (neat): 2100 (azide) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.09 (9H, s, tert-butyl), 2.08 (1H, m, H-2), 2.23 (1H, m, H-2'), 3.27 (3H, s, OMe), 3.72 (2H, m, H-5 and H-5'), 4.01 (1H, m), 4.19 (1H, m), 5.04 (1H, dd, H-1, $J_{1,2}$ 5.2 Hz, $J_{1,2'}$ 2.0 Hz), 7.3-7.7 (10H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 19.44 (s, $Me_3\underline{C}$), 27.00 (q, $\underline{Me}_3C$), 38.92 (t, C-2), 55.24 (q, OMe), 61.70 (d, C-3), 64.83 (t, CH_2O), 84.28 (d, C-4), 104.93 (d, C-1), 127.95 (d), 129.97 (d), 133.39 (s), and 135.78 (d). m/z (CI, NH_3): 429 ($M+NH_4^+$, 55%), 397 ($M+H-Me^+$, 52%), 386 ($M+NH_4-Me-N_2^+$, 100%).

Methyl 3-Azido-2,3-dideoxy-αβ-D-erythro-pentofuranoside (16). The silyl ether (8) [α:β anomeric ratio 4:1] (223 mg, 0.54 mmol) in tetrahydrofuran (1 ml) was stirred with tetra-butylammonium fluoride (1.0 M solution in tetrahydrofuran, 1 ml) at room temperature. After 1 h, the solvent was removed and the residue purified by flash chromatography to give methyl 3-azido-2,3-dideoxy-αβ-D-erythro-pentofuranoside (16), [α:β anomeric ratio 4:1] (82 mg, 87%), an oil, the anomers of (16) being separated during the flash chromatography:

Methyl 3-azido-2,3-dideoxy-α-D-erythro-pentofuranoside (16α), oil, $[\alpha]_D^{20}$ +235° (c, 0.91 in $CHCl_3$); ν_{max} (neat): 3600-3200 (br, OH), 2100 (azide) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.79 (1H, dd, OH), 2.05 (1H, m, H-2, $J_{1,2}$ 1.4 Hz, $J_{2,2'}$ 14.1 Hz, $J_{2,3}$ 3.6 Hz), 2.41 (1H, m, H-2', $J_{1,2'}$ 5.2 Hz, $J_{2',3}$ 8.9 Hz), 3.40 (3H, s, OMe), 3.69 (1H, m), 3.93 (3H, m), 5.09 (1H, dd, H-1,). ^{13}C NMR ($CDCl_3$) δ 39.23 (t, C-2), 55.18 (q, OMe), 59.97 (d, C-3), 62.41 (t, CH_2O), 82.49 (d, C-4) and 104.80 (d, C-1). m/z (CI, NH_3): 191 ($M+NH_4^+$, 32%), 159 ($M+H-Me^+$, 100%). (Found: C, 41.36; H, 6.51. $C_6H_{11}N_3O_3$ requires C, 41.62; H, 6.40%).

Methyl 3-azido-2,3-dideoxy-β-D-erythro-pentofuranoside (16β), oil, $[\alpha]_D^{20}$ -67° (c, 0.18 in $CHCl_3$); ν_{max} (neat): 3600-3200 (br, OH), 2100 (azide) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.17 (1H, m, H-2, $J_{1,2}$ 5.5 Hz, $J_{2,2'}$ 13.8 Hz, $J_{2,3}$ 6.8 Hz), 2.36 (1H, m, H-2', $J_{1,2'}$ 1.7 Hz, $J_{2',3}$ 7.4 Hz), 2.53 (1H, dd, OH), 3.41 (3H, s, OMe), 3.64 (1H, m), 3.78 (1H, m), 4.09-4.78 (2H, m), 5.11 (1H, dd, H-1,). ^{13}C NMR ($CDCl_3$) δ 39.46 (t, C-2), 55.50 (q, OMe), 60.57 (d, C-3), 63.51 (t, CH_2O), 85.19 (d, C-4) and 105.14 (d, C-1). m/z (CI, NH_3): 191 ($M+NH_4^+$, 38%), 159 ($M+H-Me^+$, 100%).

Methyl 2,3-Dideoxy-3-fluoro-α-D-erythro-pentofuranoside (17α). A solution of the pure alcohol (1α) (1.16 g, 3.0 mmol, pure α anomer) in dichloromethane (15 ml), cooled to -50°C under nitrogen, was treated with pyridine (0.78 ml, 9.66 mmol) and subsequently with trifluoromethane sulphonic anhydride (0.78 ml, 4.64 mmol). The reaction mixture was stirred for 40 min (-50°C to 0°C), diluted with chloroform (15 ml), washed with aqueous hydrochloric acid (2N, 20 ml) and water (20 ml) and then dried (magnesium sulphate). The solvent was then removed to give the crude triflate (15α) which was used without further purification. A solution of the crude triflate (15α) in tetrahydrofuran (6.6 ml) was treated with tetra-n-butylammonium fluoride in tetrahydrofuran (1M, 6.6 ml, 6.6 mmol) at room temperature. After 1.5 h, the solvent was removed and the residue purified by flash chromatography (ethyl acetate/hexane, 3:2) to give methyl 2,3-dideoxy-3-fluoro-α-D-erythro-pentofuranoside (17α), (206 mg, 46%) oil, $[\alpha]_D^{20}$ +153° (c, 0.12 in $CHCl_3$); ν_{max} (neat): 3600-3200 (br, OH) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.25 (2H, m, H-2 and H-2'), 3.43 (3H, s, OMe), 3.80 (2H, m, H-5 and H-5'), 4.36 (1H, m, H-4, $J_{H-4,F}$ 26.2 Hz), 5.03 (½H, m, ½H-3, $J_{H-3,F}$ 56.4 Hz), 5.16 (1H, d, H-1, J 4.2 Hz), 5.22 (½H, m, ½H-3). ^{13}C NMR ($CDCl_3$) δ 40.34 (C-2, $J_{C-2,F}$ 20.8 Hz), 55.30 (q, OMe), 62.51 (C-5, $J_{C-5,F}$ 6.8 Hz), 84.26 (C-4, $J_{C-4,F}$ 25.8 Hz), 93.74 (C-3, $J_{C-3,F}$ 179.3 Hz) and 105.48 (d, C-1). m/z (CI, NH_3): 168 ($M+NH_4^+$, 35%), 136 ($M+H-Me^+$, 100%). (Found: C, 47.64; H, 7.99. $C_6H_{11}FO_3$ requires C, 48.00; H, 7.38%).

Methyl 5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-3-fluoro-α-D-erythro-pentofuranoside (9α). tert-Butyldiphenylchlorosilane (0.52 ml, 2.0 mmol) was added to a solution of the fluoroalcohol (17α) (200 mg, 1.3 mmol) in dimethylformamide (5 ml) in the presence of imidazole (272 mg, 4.0 mmol) at room temperature. After 40 min, the solvent was removed and the residue purified by flash chromatography (ether/hexane, 1:4) to give methyl 5-O-tert-butyldiphenylsilyl-2,3-dideoxy-3-fluoro-α-D-erythro-pentofuranoside (9α), oil, (398 mg, 77%), $[\alpha]_D^{20}$ +64° (c, 0.59 in $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.05 (9H, s, tert-butyl), 2.22 (1H, m, H-2), 2.33 (1H, m, H-2'), 3.42 (3H, s, OMe), 3.68 (1H, dd, H-5, $J_{4,5}$ 4.3 Hz, $J_{5,5'}$ 11.0 Hz), 3.80 (1H, dd, H-5', $J_{4,5'}$ 3.3 Hz), 4.39 (1H, m, H-4), 5.23 (2H, m, H-1 and H-3), 7.3-7.7 (10H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 19.24 (s, $Me_3\underline{C}$), 26.81 (q, $\underline{Me_3}C$), 39.90 (C-2, $J_{F,C-2}$ 20.8 Hz), 55.13 (q, OMe), 63.84 (C-5, $J_{F,C-5}$ 9.4 Hz), 84.72 (C-4, $J_{F,C-4}$ 24.5 Hz), 94.14 (C-3, $J_{F,C-3}$ 177.4 Hz), 105.46 (d, C-1), 127.76 (d), 127.81 (d), 129.82 (d), 129.87 (d), 133.16 (s), 135.55 (d) and 135.63 (d). m/z (DCI, NH_3): 406 ($M+NH_4^+$, 53%), 374 ($M+H-Me^+$, 100%). (Found C, 67.79; H, 7.78. $C_{22}H_{29}FO_3Si$ requires C, 68.01; H, 7.52%).

Methyl 5-O-tert-Butyldiphenylsilyl-2,3-dideoxy-3-fluoro-β-D-erythro-pentofuranoside (9β). A solution of the pure β anomer (1β) (120 mg, 0.31 mmol) in dichloromethane (5 ml), cooled to -50°C under nitrogen, was treated with pyridine (73 mg, 0.93 mmol) and subsequently with trifluoromethanesulphonic anhydride (132 mg, 0.47 mmol). The reaction mixture was stirred for 40 min (-50°C to 0°C), diluted with chloroform (10 ml), washed with aqueous hydrochloric acid (2N, 10 ml) and water (10 ml) and then dried (magnesium sulphate). The solvent was then removed to give the crude triflate

(15β) which was used without further purification. A solution of the crude triflate (15β) in tetrahydrofuran (2 ml) was treated with tetra-n-butylammonium fluoride in tetrahydrofuran (1M, 0.4 ml, 0.4 mmol) at -30°C. The reaction mixture was allowed to warm up to room temperature and then stirred overnight; the solvent was removed and the residue purified by flash chromatography (ethyl acetate/hexane, 1:10) to give methyl 5-O-tert-butyldiphenylsilyl-2,3-dideoxy-3-fluoro-β-D-erythro-pentofuranoside (9β), oil, (46 mg, 38%), $[\alpha]_D^{20}$ -45° (c, 0.25 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.08 (9H, s, tert-butyl), 2.18 (1H, m, H-2), 2.40 (1H, m, H-2'), 3.31 (3H, s, OMe), 3.57-3.77 (2H, m, H-5 and H-5'), 4.30 (1H, m, H-4), 5.18 (½H, m, H-1 and ½H-3), 5.38 (½H, m, ½H-3), 7.3-7.7 (10H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 19.19 (s, $Me_3\underline{C}$), 26.78 (q, $\underline{Me_3}C$), 39.42 (C-2, $J_{F,C-2}$ 22.0 Hz), 55.51 (q, OMe), 63.81 (C-5, $J_{F,C-5}$ 9.4 Hz), 84.62 (C-4, $J_{F,C-4}$ 21.4 Hz), 94.58 (C-3, $J_{F,C-3}$ 177.4 Hz), 105.66 (d, C-1), 127.75 (d), 129.80 (d), 133.23 (s) and 135.57 (d). m/z (DCI, NH_3): 406 ($M+NH_4^+$, 33%), 374 ($M+H-Me^+$, 35%) and 337 (100%). (Found C, 67.79; H, 7.78. $C_{22}H_{29}FO_3Si$ requires C, 68.01; H, 7.52%).

Methyl 5-O-tert-Butyldiphenylsilyl-3-cyano-2,3-dideoxy-α-D-erythro-pentofuranoside (10α). A solution of the pure alcohol (1α) (739 mg, 1.91 mmol, pure α anomer) in dichloromethane (15 ml), cooled to -50°C under nitrogen, was treated with pyridine (454 mg, 5.74 mmol) and subsequently with trifluoromethanesulphonic anhydride (810 mg, 2.87 mmol). The reaction mixture was stirred for 40 min (-50°C to 0°C), diluted with chloroform (15 ml), washed with aqueous hydrochloric acid (2N, 30 ml) and water (2 x 50 ml) and then dried (magnesium sulphate). The solvent was then removed to give the crude triflate (15α) which was used without further purification. The crude triflate (15α) was stirred with a solution of tetra-n-butylammonium cyanide (1.03 g, 3.83 mmol) in acetonitrile (15 ml) at room temperature for 30 min; the solvent was then removed and the residue partitioned between water (50 ml) and ether (50 ml). The ether layer was then dried (magnesium sulphate) and the solvent removed to give a residue which was purified by flash chromatography (ether:hexane, 1:3) to afford methyl 5-O-tert-butyldiphenylsilyl-3-cyano-2,3-dideoxy-α-D-erythro-pentofuranoside (10α), pale yellow oil, (507 mg, 67%), $[\alpha]_D^{20}$ +83° (c, 0.25 in $CHCl_3$); ν_{max} (neat): 2240 (nitrile, weak) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.07 (9H, s, tert-butyl), 2.23 (1H, m, H-2), 2.37 (1H, m, H-2'), 3.16 (1H, m, H-3), 3.37 (3H, s, OMe), 3.81 (2H, d, H-5 and H-5', $J_{4,5}$ 3.8 Hz), 4.35 (1H, m, H-4), 5.12 (1H, dd, H-1, $J_{1,2}$ 4.9 Hz, $J_{1,2'}$ 1.4 Hz), 7.3-7.7 (10H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 19.21 (s, $Me_3\underline{C}$), 26.73 (q, $\underline{Me_3}C$), 28.10 (d, C-3), 37.18 (t, C-2), 54.84 (q, OMe), 63.54 (t, C-5), 80.82 (d, C-4), 104.69 (d, C-1), 120.45 (s), 127.74 (d), 127.80 (d), 129.84 (d), 129.90 (d), 132.79 (s), 132.85 (s), 135.48 (d) and 135.57 (d). m/z (CI, NH_3): 413 ($M+NH_4^+$, 100%). (Found C, 69.77; H, 7.57; N, 3.97. $C_{23}H_{29}NO_3Si$ requires C, 69.84; H, 7.39; N, 3.54%).

Methyl 5-O-tert-Butyldiphenylsilyl-3-cyano-2,3-dideoxy-β-D-erythro-pentofuranoside (10β). The procedure described above for the preparation of (10α) was used for the conversion of the alcohol (1β) into (10β); in this case much lower yields were acheived for the displacement reaction, and methyl 5-O-tert-butyldiphenylsilyl-3-cyano-2,3-dideoxy-β-D-erythro-pentofuranoside (10β), was obtained in only 27% yield as a yellow oil, $[\alpha]_D^{20}$ -18° (c, 0.22 in $CHCl_3$); ν_{max} (neat): 2240 (nitrile, weak) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.10 (9H, s, tert-butyl), 2.25 (1H, m, H-2), 2.34 (1H, m, H-2'), 3.25 (3H, s, OMe), 3.31 (1H, m, H-3), 3.70 (1H, dd, H-5, $J_{4,5}$ 6.3 Hz, $J_{5,5'}$ 10.7 Hz), 3.83 (1H, dd, H-5', $J_{4,5'}$ 4.4 Hz), 4.32 (1H, m, H-4), 5.05 (1H, d, H-1, J 4.6Hz), 7.3-7.7 (10H, m, Ar). ^{13}C NMR ($CDCl_3$) δ 13.30 (s, $Me_3\underline{C}$), 26.83 (q, $\underline{Me_3}C$), 29.21 (d, C-3), 37.95 (t, C-2), 54.80 (q, OMe), 65.17 (t, C-5), 82.82 (d, C-4), 104.44 (d, C-1), 119.88 (s), 127.91 (d), 129.94 (d), 129.99 (d), 133.21 (s), and

135.66 (d). m/z (CI, NH_3): 413 ($M+NH_4^+$, 100%). (Found C, 69.79; H, 7.57. $C_{23}H_{29}NO_3Si$ requires C, 69.84; H, 7.39%).

3'-Azido-3'-deoxythymidine (2) and 1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)-thymine (5). A mixture of the anomeric azides (8) (2.36 g, 5.74 mmol) and 5-methyl-2,4-bis(trimethylsiloxy)pyrimidine (18) (1.71 g, 6.33 mmol) in acetonitrile (20 ml) was treated with tert-butyldimethylsilyl triflate (1.45 ml, 1.67g, 6.32 mmol) and stirred at room temperature. After 1 h, no starting material remained and the solution had turned dark brown; the reaction was quenched by addition of excess sodium bicarbonate and the resulting mixture stirred for 0.5 h at room temperature. The solvent was then removed and the residue partitioned between chloroform (100 ml) and brine (50 ml); the organic layer was washed with water (50 ml), dried (magnesium sulphate) and the solvent removed to give a brown oil from which the silyl protecting group was removed by stirring with 50% aqueous trifluoroacetic acid (40 ml) for 20 h at room temperature. The solvent was removed and the residue co-distilled with toluene (30 ml) to give the crude product as a syrup which was purifed by flash chromatography (ethyl acetate-hexane, 10:1) to give (2) and (5) in a combined yield of 62 %.

3'-Azido-3'-deoxythymidine (2), (498 mg, 33%), less polar isomer (R_f 0.50 in ethyl acetate), m.p. 122^0-123^0C (lit.[26] m.p. 118^0-120^0C); $[\alpha]_D^{20}$ $+47^0$ (c, 0.5 in H_2O) [authentic material[24] $[\alpha]_D^{20}$ $+50^0$ (c, 0.5 in H_2O)]; $[\alpha]_D^{20}$ $+59^0$ (c, 0..79 in MeOH). ν_{max}(KBr) 2100 (N_3) 1750-1600 cm^{-1}. λ_{max} (MeOH) 263 nm. ^{1}H NMR (CD_3OD) δ 1.87 (3H, d, Me, J 1.1 Hz), 2.39 (2H, m, H-2a' and H-2b'), 3.73 (1H, dd, H-5a', $J_{5a',5b'}$ 12.1 Hz, $J_{4',5a'}$ 3.3 Hz), 3.83 (1H, dd, H-5b', $J_{4',5b'}$ 3.2 Hz), 3.91 (1H, m, H-3'), 4.36 (1H, m, H-4'), 6.17 (1H, t, H-1' J 6.4 Hz), 7.79 (1H, q, H-6, J 1.1 Hz). [^{1}H NMR of the authentic material[24] was identical to the ^{1}H NMR of this synthetic material]. ^{13}C NMR (CD_3OD) δ 12.39 (q, Me), 38.23 (t, C-2'), 61.64 (d, C-3'), 62.41 (t, C-5'), 86.05 (two d, C-1' and C-4'), 111.59 (s, C-5), 138.01 (d, C-6), 152.25 and 166.31 (two s, C-2 and C-4). m/z (DCI, NH_3): 285 ($M+NH_4^+$, 3%), 268 ($M+H^+$, 51%), 242 ($M+NH_4-N_2-Me^+$, 20%) and 96 (100%). (Found C, 44.96; H, 4.83; N, 26.40. $C_{10}H_{13}N_5O_4$ requires C, 44.94; H, 4.90; N, 26.21%).

1-(3-Azido-2,3-dideoxy-α-D-erythro-pentofuranosyl)thymine (5), (437 mg, 29%), more polar isomer (R_f 0.40 in ethyl acetate), m.p. 72^0-73^0C (lit.[9] hygroscopic powder) $[\alpha]_D^{20}$ $+41^0$ (c, 0.58 in H_2O), $[\alpha]_D^{20}$ $+37^0$ (c, 1.02 in MeOH). ν_{max}(KBr) 2100 (N_3) 1750-1600 cm^{-1}. λ_{max} (H_2O) 267 nm (lit.[9] λ_{max} (H_2O) 268 nm). ^{1}H NMR (CD_3OD) δ 1.90 (3H, d, Me, J 1.2 Hz), 2.23 (1H, m, H-2a'), 2.79 (1H, m, H-2b'), 3.64 (2H, m, H-5a' and H-5b'), 4.30 (2H, m, H-3' amd H-4'), 6.13 (1H, dd, H-1', J 3.8 and 7.8 Hz), 7.54 (1H, q, H-6, J 1.2 Hz). ^{13}C NMR (CD_3OD) δ 12.48 (q, Me), 38.72 (t, C-2'), 62.35 (d, C-3'). 63.17 (t, C-5'), 87.72 and 87.88 (two d, C-1' and C-4'), 111.11 (s, C-5), 137.69 (d, C-6), 152.25 and 166.46 (two s, C-2 and C-4). m/z (DCI, NH_3): 285 ($M+NH_4^+$, 3%), 268 ($M+H^+$, 73%), 242 ($M+NH_4-N_2-Me^+$, 39%) and 96 (100%). (Found C, 45.10; H, 4.83; N, 26.40. $C_{10}H_{13}N_5O_4$ requires C, 44.94; H, 4.90; N, 26.21%).

3'-Deoxy-3'-fluorothymidine (3) and 1-(2,3-Dideoxy-3-fluoro-α-D-erythro-pentofuranosyl)thymine (6). Trimethylsilyl triflate (214 mg, 0.97 mmol) was added to a stirred solution of the fluoride (9α) (312 mg, 0.80 mmol) and 5-methyl-2,4-bis(trimethylsiloxy)pyrimidine (18) (326 mg, 1.21 mmol) in acetonitrile (6 ml) at room temperature. After 40 min, the reaction was quenched with excess sodium bicarbonate and the solvent removed; the residue was partitioned between chloroform (50 ml) and brine (50 ml). The organic layer was then dried (magnesium sulphate) and evaporated to give an oil from which the silyl protecting group was removed by addition of tetra-n-butylammonium fluoride (1M in tetrahydrofuran, 1.0 ml, 1.0 mmol) to a solution of the crude products in tetrahydrofuran (5 ml). After 30 min at room

temperature, the solvent was removed to give a yellow oil which was purified by flash chromatography (ethyl acetate/hexane, 10:1) to give the anomers (3) and (6) in a combined yield of 64%.

3'-Deoxy-3'-fluorothymidine (3), (87 mg, 44%), less polar isomer (R_f 0.44 in ethyl acetate), m.p. 178°-179°C (ethyl acetate/hexane) [lit.[25] 176°-177°C]; $[\alpha]_{365}^{20}$ +50.9 $[\alpha]_{436}^{20}$ +12.9° $[\alpha]_{546}^{20}$ +1.99° $[\alpha]_{578}^{20}$ +1.00° $[\alpha]_{D}^{20}$+0.80° (c, 1.0 in MeOH) [lit.[25] $[\alpha]_{D}^{20}$ -6.3° (MeOH)] ν_{max}(KBr) 1750-1600 cm^{-1}. λ_{max} (MeOH) 263 nm. ^1H NMR (CD_3OD) δ 1.88 (3H, d, Me, J 1.1 Hz), 2.37 (2H, m, H-2a' and H-2b'), 3.78 (2H, m, H-5a'and H-5b'), 4.24 (1H, m, H-4', $J_{4',5'}$ 3.2 Hz, $J_{4',F}$ 27.6 Hz), 5.27 (1H, m, H-3', $J_{3',F}$ 53.9 Hz), 6.32 (1H, dd, H-1', J 5.6 Hz, 9.2 Hz), 7.82 (1H, q, H-6, J 1.1 Hz). ^{13}C NMR (CD_3OD) δ 12.42 (q, Me), 39.08 (dt, C-2', $J_{C-2',F}$ 20.8 Hz), 62.71 (dt, C-5', $J_{C-5',F}$ 10.7 Hz), 86.32 (d, C-1'), 86.89 (dd, C-4', $J_{C-4',F}$ 23.9 Hz), 95.89 (dd, C-3', $J_{C-3',F}$ 176.1 Hz) 111.87 (s, C-5), 137.86 (d, C-6), 152.39 and 166.30 (two s, C-2 and C-4). m/z (DCI, NH_3): 262 ($M+NH_4^+$, 5%), 245 ($M+H^+$, 100%) and 127 (57%). (Found C, 49.16; H, 5.28; N, 11.25. $C_{10}H_{13}FN_2O_4$ requires C, 49.18; H, 5.36; N, 11.47%).

1-(2,3-Dideoxy-3-fluoro-α-D-erythro-pentofuranosyl)thymine (6), (39 mg, 20%), more polar isomer (R_f 0.32 in ethyl acetate), m.p. 161°-163°C (ethyl acetate/hexane); $[\alpha]_{365}^{20}$ -136.5 $[\alpha]_{436}^{20}$ -39.7° $[\alpha]_{546}^{20}$ -8.62° $[\alpha]_{578}^{20}$ -5.86° $[\alpha]_{D}^{20}$-5.5° (c, 0.3 in MeOH) ν_{max}(KBr) 1750-1600 cm^{-1}. λ_{max} (MeOH) 264 nm. ^1H NMR (CD_3OD) δ 1.88 (3H, d, Me, J 1.2 Hz), 2.37 (1H, dd, H-2a', $J_{2a',F}$ 24.2 Hz, $J_{2a',2b'}$ 15.8 Hz), 2.76 (1H, m, H-2b'), 3.64 (2H, m, H-5a'and H-5b'), 4.66 (1H, two t, H-4', $J_{3',4'}$ 4.0 Hz, $J_{4',5'}$ 4.0 Hz, $J_{4',F}$ 24.0 Hz), 5.28 (1H, dd, H-3', $J_{3',F}$ 54.2 Hz, $J_{2b',3'}$ 5.2 Hz), 6.27 (1H, dd, H-1', J 7.5 Hz, 1.6 Hz), 7.48 (1H, q, H-6, J 1.2 Hz). ^{13}C NMR (CD_3OD) δ 12.51 (q, Me), 40.42 (dt, C-2', $J_{C-2',F}$ 20.1 Hz), 62.85 (dt, C-5', $J_{C-5',F}$ 11.3 Hz), 88.24 (d, C-1'), 89.32 (dd, C-4', $J_{C-4',F}$ 22.6 Hz), 95.73 (dd, C-3', $J_{C-3',F}$ 174.2 Hz), 111.00 (s, C-5), 137.48 (d, C-6), [signals for C-2 and C-4 were too weak]. m/z (ACE, NH_3): 262 ($M+NH_4^+$, 5%), 245 ($M+H^+$, 100%) and 127 (40%). (Found C, 49.45; H, 5.12; N, 11.04. $C_{10}H_{13}FN_2O_4$ requires C, 49.18; H, 5.36; N, 11.47%).

3'-Cyano-3'-deoxythymidine (4) and 1-(3-Cyano-2,3-dideoxy-α-D-erythro-pentofuranosyl)thymine (7). Trimethylsilyl triflate (280 mg, 1.26 mmol) was added to a stirred solution of the cyanide (10α) (416 mg, 1.05 mmol) and 5-methyl-2,4-bis(trimethyl-siloxy)pyrimidine (18) (341 mg, 1.26 mmol) in acetonitrile (10 ml) at room temperature. After 2.5 h, the reaction was quenched with excess sodium bicarbonate and the solvent removed; the residue was partitioned between chloroform (30 ml) and brine (30 ml). The organic layer was then dried (magnesium sulphate) and evaporated to give an oil from which the silyl protecting group was removed by addition of tetra-n-butylammonium fluoride (1M in tetrahydrofuran, 1.5 ml, 1.5 mmol) to a solution of the crude products in tetrahydrofuran (5 ml). After 1 h at room temperature, the solvent was removed to give a light brown oil which was purified by flash chromatography (ethyl acetate/hexane, 10:1) to give the anomers (4) and (7) in a combined yield of 70%.

3'-Cyano-3'-deoxythymidine (4), (93 mg, 35%), less polar isomer (R_f 0.44 in ethyl acetate), m.p. 133°-134°C (ethyl acetate/hexane), $[\alpha]_{365}^{20}$ +184° $[\alpha]_{436}^{20}$ +84.4° $[\alpha]_{546}^{20}$ +40.4° $[\alpha]_{578}^{20}$ +34.0° $[\alpha]_{D}^{20}$+32.4° (c, 0.25 in MeOH) ν_{max}(KBr) 2240 (weak,CN) 1750-1600 cm^{-1}. λ_{max} (MeOH) 264 nm. ^1H NMR (CD_3OD) δ 1.71 (3H, d, Me, J 1.2 Hz), 2.50 (1H, m, H-2a') 2.69 (1H, m, H-2b'), 3.36 (1H, q, H-3', J 9.2 Hz), 3.68 (1H, dd, H-5a', $J_{5a',5b'}$ 12.8 Hz, $J_{4',5a'}$ 4.0 Hz), 3.80 (1H, dd, H-5b', $J_{4',5b'}$ 3.2 Hz), 4.21 (1H, m, H-4'), 6.04 (1H, dd, H-1' J 4.0 Hz, 7.6 Hz), 7.43 (1H, q, H-6, J 1.2 Hz). ^{13}C NMR (CD_3OD) δ 12.36 (q, Me), 28.74 (d, C-3'), 37.21 (t, C-2'), 61.39 (t, C-5'), 84.73 and 86.81 (two d, C-1' and C-4'), 111.43 (s, C-5), 119.99 (s, CN), 138.23 (d, C-6), 152.14 and 166.30 (two s, C-2 and C-4). m/z (DCI, NH_3): 252 ($M+H^+$, 48%) and

127 (100%). (Found C, 52.57; H, 5.16; N, 16.52. $C_{11}H_{13}N_3O_4$ requires C, 52.58; H, 5.18; N, 16.73%).

1-(3-Cyano-2,3-dideoxy-α-D-erythro-pentofuranosyl)thymine (7), (92 mg, 35%), more polar isomer (R_f 0.33 in ethyl acetate), m.p. 177°-181°C (ethyl acetate) $[\alpha]_{365}^{20}$ -27.6 $[\alpha]_{436}^{20}$ +26.4° $[\alpha]_{546}^{20}$ +29.2° $[\alpha]_{578}^{20}$ +27.6° $[\alpha]_D^{20}$ +27.2° (c, 0.25 in MeOH) ν_{max}(KBr) 2240 (weak, CN) 1750-1600 cm^{-1}. λ_{max} (MeOH) 264 nm. ^1H NMR (CD_3OD) δ 1.90 (3H, d, Me, J 1.0 Hz), 2.54 (1H, m, H-2a') 2.87 (1H, m, H-2b'), 3.43 (1H, m, H-3'), 3.63 (1H, dd, H-5a', $J_{5a',5b'}$ 12.4 Hz, $J_{4',5a'}$ 3.7 Hz), 3.77 (1H, dd, H-5b', $J_{4',5b'}$ 3.4 Hz), 4.64 (1H, m, H-4'), 6.10 (1H, t, H-1' J 6.2 Hz), 7.55 (1H, q, H-6, J 1.0 Hz). ^{13}C NMR (CD_3OD) δ 12.35 (q, Me), 30.05 (d, C-3'), 37.06 (t, C-2'), 62.76 (t, C-5'), 85.09 and 88.70 (two d, C-1' and C-4'), 111.69 (s, C-5), 120.34 (s, CN), 138.05 (d, C-6), [signals for C-2 and C-4 were too weak]. m/z (DCI, NH_3): 269 ($M+NH_4^+$, 44%), 252 ($M+H^+$, 100%) and 127 (52%). (Found C, 52.40; H, 5.15; N, 16.46. $C_{11}H_{13}N_3O_4$ requires C, 52.58; H, 5.18; N, 16.73%).[27]

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27. A SERC post-doctoral fellowship (to JCS) is gratefully acknowledged.