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METHYL 5-O-TERT-BUTYLDIPHENYLSILYL-2-DEOXY-D-THREO-PENTOFURANOSIDE; AN APPROACH TO THE SYNTHESIS OF 3'-SUBSTITUTED-2',3'-DIDEOXYNUCLEOSIDES INCLUDING 3'-AZIDO-3'-DEOXYTHYMIDINE AND OF 3'-SUBSTITUTED-2',3'-DIDEOXY-C-NUCLEOSIDES

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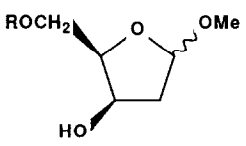
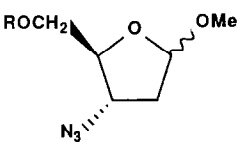
The Barton deoxygenation of methyl 3,5-O-isopropylidene-αß-D-xylofuranoside is the key step in a short synthesis of methyl 5-O-tert-butyldiphenylsilyl-2-deoxy-αß-D-threo-pentofuranoside (1) from D-xylose. The syntheses of methyl 2,3-dideoxy-3-fluoro-αß-D-erythro-pentofuranoside and of a protected 3-azido-2,3-dideoxy-D-erythro-pentofuranose, a possible intermediate for the synthesis of 3'-azido-3'-deoxythymidine (AZT), are reported and the potential of (1) as a divergent intermediate for the preparation of 3'-substituted-2',3'-dideoxynucleosides and C-nucleoside analogues is discussed.

One possible chemotherapeutic strategy for the treatment of AIDS is the development of compounds capable of blocking one or more steps of the replicative cycle of the virus, HTLV-III/LAV.[1,2] 3'-Azido-3'-deoxythymidine (AZT) has been found to be active against the AIDS virus[3] and is in clinical trial.[4] 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 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] Recently an alternative approach[12] 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 (5)[13] was reacted with silylated thymine in the presence of tin (IV) chloride or trimethylsilyl triflate;[14] however, the yield of AZT in this coupling reaction was only modest and the α/ß ratio of azidodeoxynucleosides was unfavorable.[15] This paper describes a short synthesis from D-xylose of highly crystalline methyl 5-O-tert-butyldiphenylsilyl-2-deoxy-αß-D-threo-pentofuranoside (1) in which only the



(1) R= [Si]

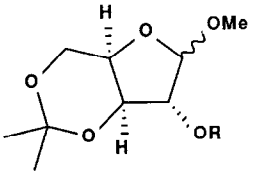
(2) R= H



(3) R= [Si]

(4) R= H

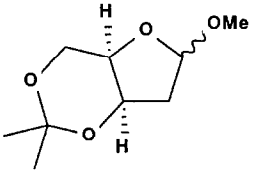
(5) R= p-Me-C_6H_4CO



(6) R= H

(7) R= CSSMe

(8) R= CSOPh



(9)

[Si]= t-$BuPh_2Si$

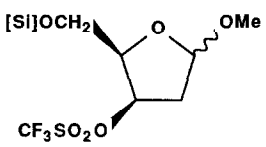
final product is purified by column chromatography; the efficient conversions of (1) to methyl 3-azido-5-O-tert-butyldiphenylsilyl-2,3-dideoxy-αß-D-erythro-pentofuranoside (3) and to methyl 2,3-dideoxy-3-fluoro-αß-D-erythro-pentofuranoside (11) are reported.

D-Xylose was treated with methanolic hydrogen chloride under kinetic conditions and subsequently with acetone and anhydrous copper (II) sulphate to give, as previously reported,[16] methyl 3,5-O-isopropylidene-D-xylofuranoside (6), in which only the C-2 OH of xylose is unprotected, in a yield of 72%.[17] The mixture of anomers with sodium hydride, carbon disulphide and methyl iodide gave the xanthates (7)[18] (90% yield) which can be purified by distillation. The xanthates (7) on heating with tributyltin hydride in xylene underwent the Barton deoxygenation[19] to give methyl 2-deoxy-3,5-O-isopropylidene-αß-D-threo-pentofuranoside (9).[20] The efficiency of the deoxygenation of the xanthates is sensitive to the concentration of the reactants so that at higher concentrations, lower yields of (9) were obtained; also, tin hydride reduction of the corresponding thionocarbonate (8)[21] gave only low yields of (9). Addition of p-toluenesulphonic acid and methanol to the xylene solution at the end of the deoxygenation reaction caused selective hydrolysis of the isopropylidene group to give methyl 2-deoxy-αß-D-threo-pentofuranoside (2). During the methanolysis of the acetonide (9), equilibration of the methyl furanosides occurred and the α:ß ratio of the anomers (2) was 4:1. After removal of the solvent, the tin residues from the deoxygenation were readily separated from the polar diols (2) by partitioning between petrol and acetonitrile. Selective reaction of the primary hydroxyl group in the diols (2) proceeded rapidly at 0°C with tert-butyldiphenylchlorosilane in the presence of imidazole to give (1) from xanthates (7) without needing to purify the intermediates.[22] The procedure for the conversion of the xanthates (7) to (1) in an overall yield of 55% on a 6 g scale is given below.

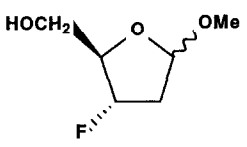
Esterification of the free hydroxyl group in (1) with trifluoromethanesulphonic anhydride in the presence of pyridine gave the triflates (10); reaction of the triflates (10) with sodium azide in dimethylformamide was complete in 1 h at room temperature to give the protected azides (3) in 82% overall yield from (1). The ease and rapidity of this displacement indicates that treatment of the triflates (10) will allow the efficient introduction of other functional groups at C-3 of the sugar to provide access to other C-3' functionalised-2',3'-dideoxynucleoside analogues. For example, reaction of the triflate (10) with tetrabutylammonium fluoride in tetrahydrofuran proceeds with displacement of fluoride and simultaneous removal of the silyl protecting group to give methyl 2,3-dideoxy-3-fluoro-αß-D-erythro-pentofuranoside (11)[23] in 51% yield; 3'-fluoro-3'-deoxythymidine triphosphate has been found to be a more potent inhibitor of HIV reverse transcriptase than the triphosphate of AZT.[24]

The silyl protecting group in (1) was easily removed by treatment with tetrabutyl ammonium fluoride in tetrahydrofuran at room temperature to give methyl 3-azido-2,3-dideoxy-αß-D-erythro-pentofuranoside (4) in 87% yield. Subsequent protection of the primary hydroxyl group by groups such as benzoyl, chlorobenzoyl and 9-fluorenylmethoxycarbonyl[25] will allow studies to optimise the α/ß ratio in coupling of the protected sugar with silylated thymine.

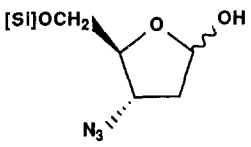
Mild hydrolysis of the anomeric methoxyl group in (3) by aqueous acetic acid gave the 5-silylated 3-azido-2,3-dideoxy-D-erythro-pentose (12) in 60% yield.



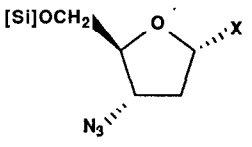
(10)



(11)



(12)



(13)

The free anomeric OH group in (12) should allow the preparation under mild conditions of a series of α anomers of structure (13) in which different leaving groups X could be evaluated in S_N2 displacements both by derivatives of heterocyclic bases to optimise the yields of the required ß-azidodeoxynucleoside[26] and by suitable carbon nucleophiles to allow the synthesis of C-deoxynucleoside analogues of AZT. The lactol (12) would allow direct preparation of C-deoxynucleoside analogues of AZT by the use of the Wittig reaction.[27] In summary this paper reports the efficient synthesis of intermediates suitable for elaboration to 3'-substituted-2',3'-dideoxynucleosides and to 3'-substituted-2',3'-dideoxy-C-nucleosides.

Methyl 5-O-tert-Butyldiphenylsilyl-2-deoxy-αß-D-erythro-pentofuranoside (1). Dry nitrogen was bubbled through a solution of the xanthates (7) (6.0 g, 20.41 mmol) in xylene (200 ml) for 20 min at room temperature under nitrogen; the solution was then heated to 135° 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) were then added and the mixture stirred at room temperature; after one hour the reaction was quenched with aqueous 0.88 ammonium hydroxide (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 (2) (3.81 g) was dissolved in dimethyl formamide (30 ml) together with imidazole (3.06 g, 45 mmol); the solution was cooled to 0° and tert-butyldiphenylchlorosilane (4.0 ml, 4.23 g, 15.38 mmol) was added dropwise. After stirring at 0° 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 as a mixture of anomers which are readily separated by flash chromatography. Data for α-anomer of (1): 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), 2.18-2.20 (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'), 4.59-4.63 (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^+) (Found C, 68.30; H, 8.16. $C_{22}H_{30}O_4Si$ requires C, 68.36; H, 7.82%).

Data for ß-anomer of (1): 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), 2.12-2.14 (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'), 4.32-4.38 (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%, $M+H-Me^+$).[27,28]

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17. The α:ß ratio of the anomers of (6) was about 1.5:1.
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22. All the reactions were performed both on anomeric mixtures as well as on the individual pure anomers. Each anomer of all the intermediates has been characterised.
23. Data for α-anomer of (11): $[\alpha]_D^{20}$ +148° (c, 0.47 in $CHCl_3$), ^{13}C NMR ($CDCl_3$) δ 40.32 (C2, $J_{C2,F}$ 20.8 Hz), 55.30 (OMe), 62.51 (C5, $J_{C5,F}$ 8.8 Hz), 84.26 (C4, $J_{C4,F}$ 25.8 Hz), 93.74 (C3, $J_{C3,F}$ 179.3 Hz) and 105.48 (C1, $J_{C1,F}$ 0 Hz).
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