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SYNTHESIS OF 3'-SUBSTITUTED-2',3'-DIDEOXYNUCLEOSIDE ANALOGS AS POTENTIAL ANTI-AIDS DRUGS

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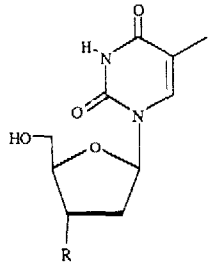
Abstract: *3'-Amino-3'-deoxythymidine 9 was prepared in six steps and in 67% overall yield from thymidine. Five derivatives of 9 and compound 17 were tested for their anti-HIV activity.*

In the fight against the human immunodeficiency virus (HIV), the etiological agent of AIDS, the enzyme reverse transcriptase (RT) stands out as a prime target for the development of chemotherapeutic agents. This enzyme catalyzes phosphodiester bond formation during the synthesis of a DNA copy of the viral RNA (reverse transcription), and is not found in the non-infected host cell[1]. To date, 2',3'-dideoxynucleoside analogs, and in particular 3'-azido-3'-deoxythymidine 1 (AZT) have proven to be effective as antiviral agents retarding the progression of attack on the immune system during the period in which they are administered. These compounds are incorporated through the action of RT into the nascent DNA chain where, because they lack the 3'-hydroxyl groups, they act as chain terminator[2]. However this is apparently not the sole mode of action of these molecules as compounds 2[3] and 3[4] which bear a close structural resemblance to AZT are almost devoid of activity. Intrigued by these observations, which may indicate that it is some aspect of the reactivity of the azide group in 1 which is also responsible for its action[5], we have prepared and have tested the anti-HIV activity of a series of 3'-amino-3'-deoxythymidine derivatives which can potentially interact chemically with the active site of RT (or one of the earlier enzymes).



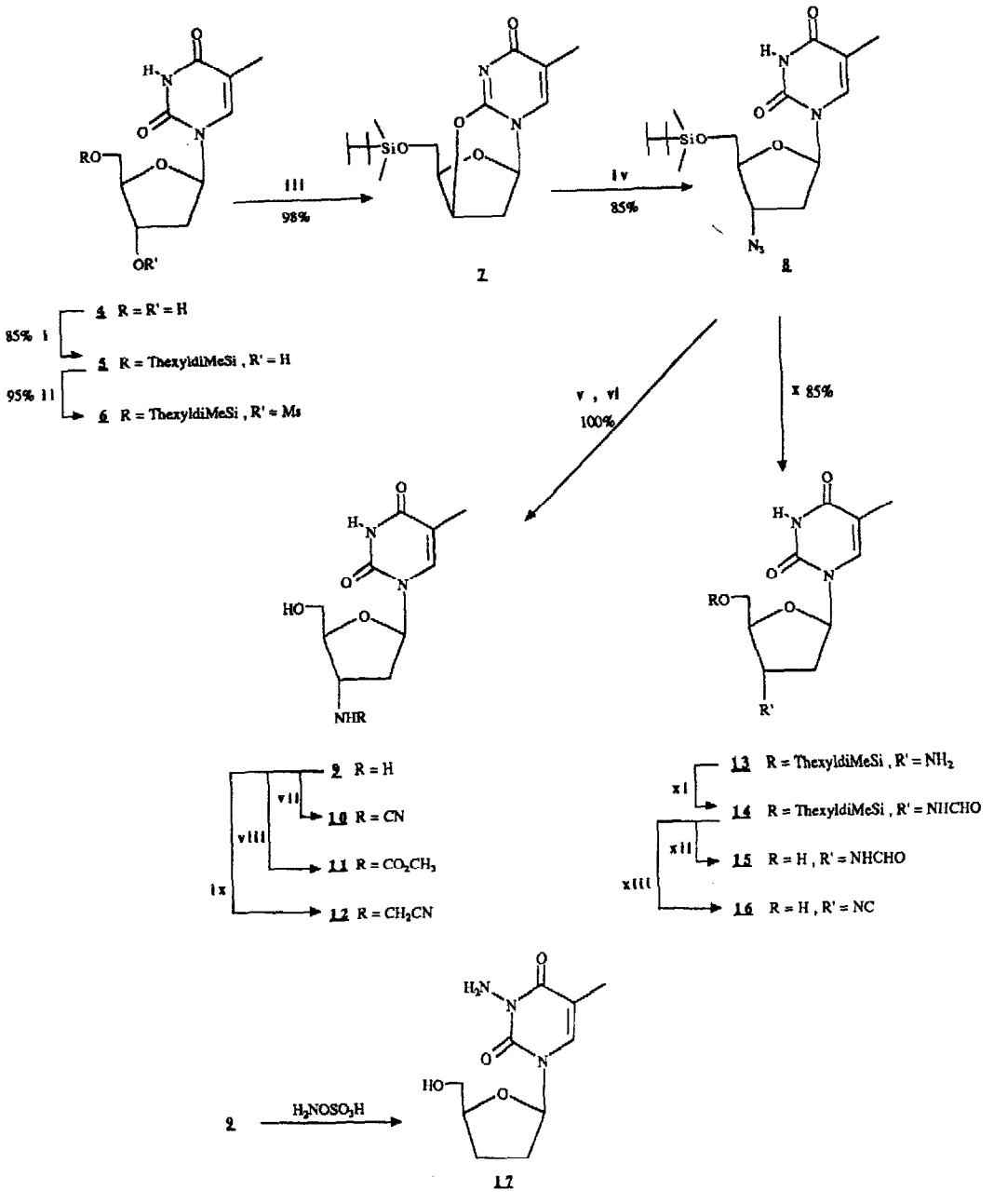
1 R = N_3
2 R = CN
3 R = SCN

3'-Amino-3'-deoxythymidine 9 was prepared in six steps and in 67% overall yield from thymidine 4 by substantial amelioration of an established sequence[6] (scheme 1). This entails displacement, via a 2,3'-anhydrothymidine intermediate, of the mesylate group in a 3'-O-mesylthymidine derivative by azide ion[6] followed by reduction of the 3'-azido group in the derived product[7]. The obtention of the 2,3'-anhydronucleoside as a discrete intermediate in this scheme is important as direct displacement of the mesyl group in 6 (when R = trityl) leads to formation of a mixture of 3'-epimeric azide products.[8] Although 2,3'-anhydrothymidine itself can be prepared from 4 in a single step (Y = 50%)[6,9] we found it easier to work with intermediates substituted at the 5' position by a O-thexyldimethylsilyl group. This alcohol protecting group is more readily removed than the conventionally employed O-trityl group.[10]

5'-O-Thexyldimethylsilylthymidine 5 (mp 178-180°C (acetone); $[\alpha]_D$ + 8° (acetone)) was obtained in 85% yield from the reaction of 4 with thexyldimethylsilyl chloride after flash chromatographic separation (silica; CH_2Cl_2: MeOH, 8:2) from minor amounts (<5%) of the 3',5'-bis-silylated product. Mesylate 6 (mp 96-98°C (acetone); $[\alpha]_D$ + 11° (acetone)) was then prepared by reaction of 5 with methanesulfonyl chloride in pyridine at 0°C (Y = 95%). Subsequent treatment of a THF solution of 6 with DBU (reflux 2h) followed by normal work-up and silica flash chromatography (hexane-EtOAc, 1:1) gave the 2,3'-anhydrothymidine derivative 7 (colorless crystals mp 162-164°C, $[\alpha]_D$ - 60° (acetone), 10g scale) in 98% yield[11]. Comparable yields are obtained for this step using sodium hydride in THF. Introduction of the azide function at C-3' was achieved by reaction of 7 with NaN_3 in hot DMF[6]. 5'-O-thexyldimethylsilyl AZT 8 (mp 80-82°C (EtOH); $[\alpha]_D$ + 39° ($CHCl_3$)) was isolated in 85% yield after purification by silica flash chromatography (hexane-EtOAc, 1:2). The 5'-deprotection and azide reduction steps were then carried out without isolation of the intermediate AZT. This involved treatment of compound 8 with DOWEX-50 (H^+) in methanol, filtration to remove the resin, addition of Pd/C (0.1 equiv.) and reaction of AZT under 1 atm. of hydrogen overnight. 3'-Amino-3'-deoxythymidine 9 was thus obtained pure and in almost quantitative yield as a colorless solid (mp 159-160°C (EtOH); lit[12] 160-161°C).

Preparation of the analogs 10-12 from 9 was achieved as follows. Reaction of 9 with cyanogen bromide in methanol containing sodium acetate gave the cyanamide 10 (mp 92°C ($CHCl_3$); $[\alpha]_D$ + 9° (MeOH)) isolated in 85% yield after purification (silica; CH_2Cl_2:MeOH, 95:5). Carbamate 11 (mp 105-106°C (EtOH)) was prepared by reaction of 9 with methyl chloroformate in pyridine-CH_2Cl_2 (Y = 48%), and the relatively sensitive aminonitrile 12 was obtained in 35% yield after purification (silica) by reaction of 9 with aqueous formaldehyde and $NaHSO_3$ followed by KCN. For the preparation of analogs 15 and 16, the azide group in 8 was first reduced ($SnCl_2$, MeOH, 85%)[7b], and intermediate 13 (mp 150°C; $[\alpha]_D$ + 12° ($CHCl_3$)) was reacted with 2,4,5-trichlorophenyl formate[13] in DMF containing ethyldiisopropylamine to give 14 (mp 176-178°C (MeOH); $[\alpha]_D$ - 8° ($CHCl_3$), 90%). Deprotection of 14 (Bu_4NF, THF) gave 15 (mp 194°C ($CHCl_3$-hexane); $[\alpha]_D$ + 28° (MeOH), 90%) whereas treatment of 14 with CCl_4, triethylamine, and triphenylphosphine in CH_2Cl_2 followed by liberation of the 5'-hydroxyl group gave the isonitrile 16 (mp 150°C (hexane-acetone); $[\alpha]_D$ + 9.5° ($CHCl_3$) (Y = 72% for the last two steps[14]).

The reaction of 9 with hydroxylamine-O-sulfonic acid gave 3-amino-3'-deoxythymidine 17 rather than the 3'-hydrazino derivative as the hydrazino group in the initially formed product is oxidized to the corresponding imide followed by loss of nitrogen.[15]



Reagents : i) ThexyldiMeSiCl, imidazole, DMF, 0° ; ii) MsCl, pyridine, 0 °; iii) DBU, THF, reflux; iv) NaN_3, DMF, 120°; v) DOWEX 50 (H^+), CH_3OH; vi) H_2, Pd/C, CH_3OH; vii) BrCN, NaOAc, CH_3OH, 20°; viii) $ClCO_2CH_3$, O°, pyridine- CH_2Cl_2; ix) $NaHSO_3$, H_2CO, KCN, 60° - 20°; x) $SnCl_2$, CH_3OH; xi) 2,4,5-trichlorophenyl formate, DIEA, DMF, 0-20°; xii) $(C_4H_9)_4NF$, THF, 20°; xiii) CCl_4, Et_3N, $(Ph)_3P$, CH_2Cl_2, 60°.

Nucleoside analogs 10-12 and 15-17 were tested for activity against the strain LAV of HIV-1 in CEM cells. The products were compared for their cytotoxicity and inhibitory effects on HIV induced cytopathogenicity. Assays were performed in the range of 0.05 to 100 μM but all compounds were found to be completely inactive compared to AZT (2 μM) used as reference.

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