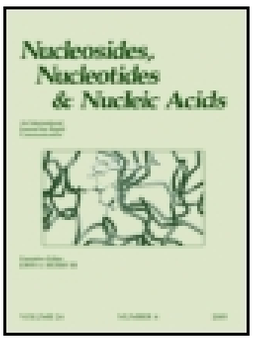

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SYNTHESIS OF 3'-N-SUBSTITUTED 3'-AMINO-3'-DEOXYTHYMIDINE DERIVATIVES

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ABSTRACT: A series of 3'-N-substituted 3'-amino-3'-deoxythymidine derivatives with alkyl, alkenyl and alkylaryl substituents was synthesized by two methods. The first method involved the reaction of 1-(2,3-dideoxy-3-O-mesyl-5-O-trityl-β-D-threo-pentofuranosyl)thymine with an appropriate amine. In the second method, 3'-amino-5'-O-trityl-3'-deoxythymidine served as a synthetic precursor which was reacted with an appropiate aldehyde or ketone followed by sodium borohydride reduction. An improved synthesis of 3'-amino-3'-deoxythymidine from 3'-azido-5'-O-trityl-3'-deoxythymidine using sodium borohydride was also described.

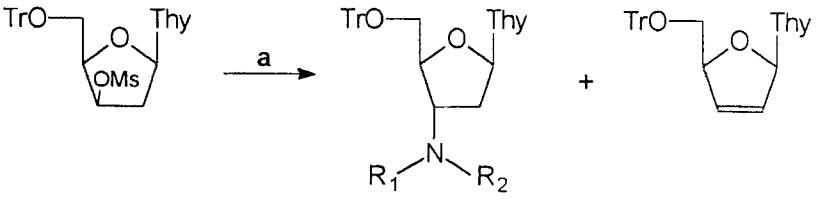
3'-Substituted 2',3'-dideoxynucleosides occupy a prominent position among inhibitors of human immunodeficiency virus-1 reverse transcriptase (HIV-1 RT).[1,2] The most important in this class of nucleoside analogues are 3'-azido-3'-deoxythymidine (AZT)[3] and 3'-fluoro-3'-deoxythymidine (FT).[4] These analogues are converted into their 5'-triphosphate forms by cellular enzymes, which are then recognized by HIV-1 RT as substrates and the corresponding nucleoside monophosphate moieties are incorporated into DNA chains. Since these analogues lack the 3'-hydroxyl group, their incorporation leads to DNA chain termination. It has been established that 5'-triphosphate of 3'-amino-3'-deoxythymidine strongly inhibits HIV-1 RT.[5] However, 3'-amino-3'-deoxythymidine shows high toxicity[6] and low activity as anti-HIV-1 agent[7,8] probably due to its poor intracellular phosphorylation.[9] On the other hand, 3'-amino-3'-deoxythymidine has been found to exhibit activity against Moloney murine leukemia which is caused by a mammalian T-lymphotropic retrovirus.[10]

Furthermore, 3'-amino- 3'-deoxythymidine inhibits the replication of L 1210 murine leukemia[11] and P815 mouse leukemia cells.[12]

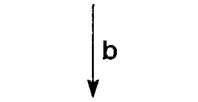
Some prior reports concerning the synthesis of 3'-N-substituted 2',3'-dideoxy nucleosides have appeared.[13-18] Recently Wengel et al. published the synthesis of 2',3'-dideoxy-3'-piperidino- and 2',3'-dideoxy-3'-pyrrolidino-D-ribohexofuranosyl nucleosides from tri-O-acetyl-D-glucal[19] and synthesis of 3'-N-acyl substituted 3'-amino-3'-deoxythymidine analogues with the acyl substituent derived from amino acids.[20] There are some reports on the synthesis of 3'-phthalimido-3'-deoxythymidine derivatives which are precursors for 3'-amino-3'-deoxythymidine.[21,22]

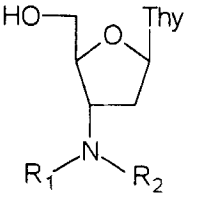
In this paper we present two methods of the synthesis of 3'-N-substituted analogues of 3'-amino-3'-deoxythymidine. In the first method, compounds **2a-h** were obtained by the reaction of 1-(2,3-dideoxy-3-O-mesyl-5-O-trityl-β-D-threo-pentofuranosyl)thymine **1** with the appriopriate amine in acetonitrile at 120°C in 40-46% isolated yield (Scheme I). This reaction, however, gave also β-elimination by-product 1-(2,3-dideoxy-5-O-trityl-β-D-glycero-pent-2-enofuranosyl)thymine **3** in about 40% yield. It should be mentioned that the desired products **2a-h** were easily separated from by-product **3** by silica gel flash chromatography. The identity of **3** was confirmed by spectroscopic means as well as by independent synthesis of **3** employing the literature method.[23] The attempts to increase the yield of substitution products **2a-h** by changing the leaving group for tosyl, the temperature of the reaction or solvent for dimethyl sulfoxide, dimethyl formamide and ethanol failed. Compounds **2a-h** were efficiently detritylated on cation-exchange resin (Dowex 50Wx2) to give **4a-h**.

In the second method, compounds **2a-h** were prepared from 3'-amino-5'-O-trityl-3'-deoxythymidine **6**. Reaction of **6** with the appropriate aldehyde or ketone gave intermediate imine **7**, which after in situ reduction with sodium borohydride afforded compounds **2a-h** (Scheme II and III). This method gave in high yields (83-90%) compounds **2** (except **2a** and **2f**). In the case of compound **2a** the yield of the synthesis by the second method was low (25%) because **2a** underwent quickly further reaction to give **2b** (Scheme III). Also compound **2f** was obtained in low yield (40%) by this method, probably because the competitive Michael addition of **6** to acrolein took place. Thus in these two cases the first method of synthesis via nucleophilic substitution resulted in better



1 **2a-h** **3**





4a-h

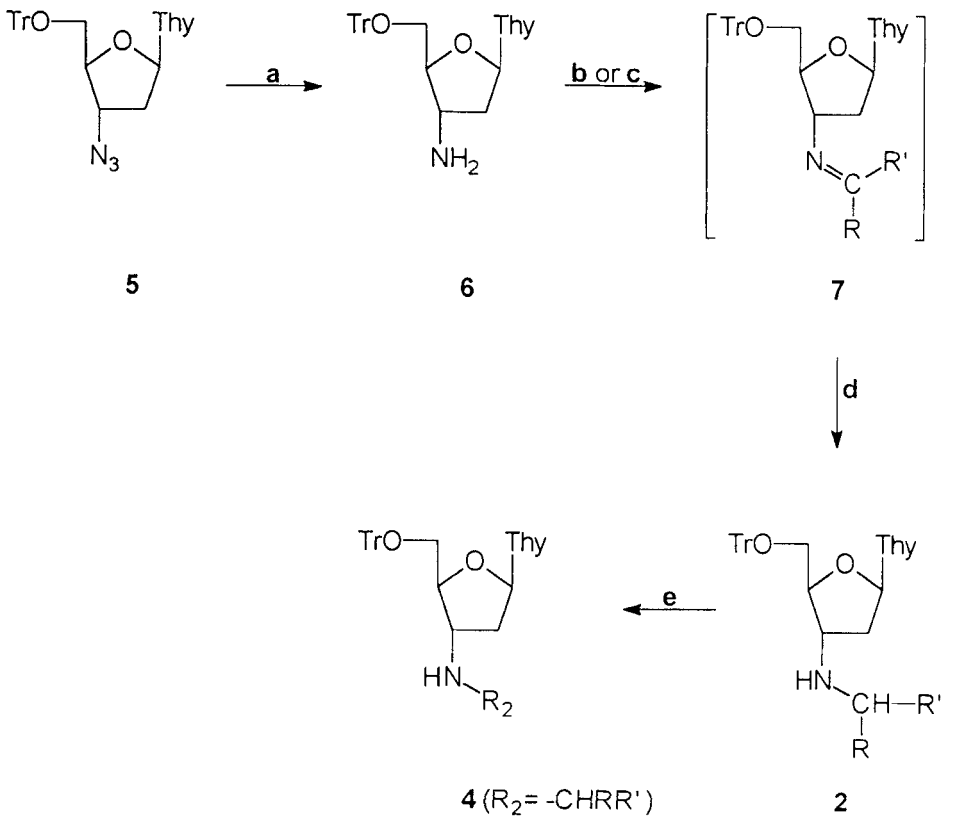
a: R_1-NH-R_2, CH_3CN, 120°C,18h; Dowex 50Wx2.

Tr = -CPh_3, Ms = -SO_2CH_3

Thy = thymin-1-yl

R_1 and R_2 see Table

Scheme I



a: $NaBH_4$, $CH_3CH(OH)CH_3$, 82°C, 14h; **b:** RCOR', R=H in each case, R' = -H, $-CH_3$, $-CH_2CH_3$, $-CH=CH_2$, -Ph or p-fluorophenyl; **c:** RCOR', R=R' $=CH_3$;

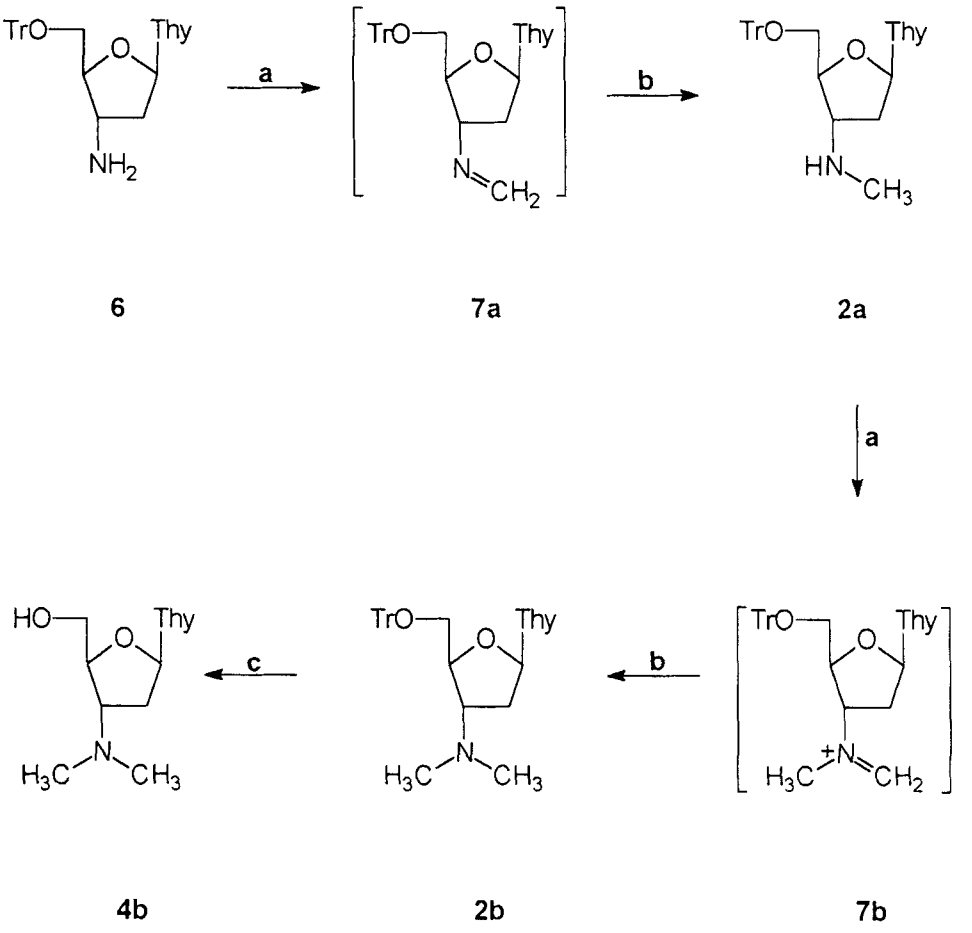
d: $NaBH_4$; **e:** Dowex 50Wx2.

Tr = $-CPh_3$

Thy = thymin-1-yl

R_2 see Table

Scheme II



a: formaldehyde; **b:** $NaBH_4$; **c:** Dowex 50Wx2.

Tr = $-CPh_3$

Thy = thymin-1-yl

Scheme III

TABLE. Yields of Compounds **2a-h**

Compound	Substituent		Isolated Yield (%)	
	R_1	R_2	Method 1	Method 2
2a	H	CH_3	45	25
2b	CH_3	CH_3	41	92
2c	H	CH_2CH_3	45	88
2d	H	$CH_2CH_2CH_3$	46	90
2e	H	$CH(CH_3)_2$	40	90
2f	H	$CH_2CH{=}CH_2$	45	40
2g	H	CH_2-Ph	43	83
2h	H	p-fluorobenzyl	41	85

yields (see Table). A similar method was employed by Morr and Ernst[24] for the synthesis of 3'-N-substituted derivatives of adenosine. In our approach 5'-O-trityl derivative of 3'-amino-3'-deoxythymidine **6** was used as a synthetic precursor which allowed easy purification of compounds **2a-h** by silica gel flash chromatography.

Furthermore, 3'-amino-5'-O-trityl-3'-deoxythymidine **6** was prepared from 3'-azido-5'-O-trityl-3'-deoxythymidine **5** by reduction with sodium borohydride in isopropanol in high yield (93%). Literature methods of synthesis of 3'-amino nucleosides from 3'-azido nucleosides involve catalytic hydrogenation,[25,26] reduction with triphenyl phosphine[27] and reduction with hydrogen sulfide.[28]

In summary, two complementary methods of the synthesis of 3'-N-substituted 3'-amino-3'-deoxythymidine derivatives are presented. The efficiency of each method depends on the nature of the introduced 3'-N-substituent. Although, in general the first method gives lower yields, the precursor **1** can be more easily obtained starting from thymidine than the precursor **6** used in the second method.

EXPERIMENTAL SECTION

Melting points were determined on a Boetius apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 243B polarimeter. Microanalyses were obtained on an elemental analyser Perkin-Elmer 240. UV spectra were recorded on a Shimadzu UV-160 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were determined on Varian-Gemini 300 MHz spectrometer. Mass spectra were made on a Jeol JMS-D-100 mass spectrometer. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} precoated (0.2 mm) plates and column chromatography was performed on Merck silica gel 60 H (5-40μm). Compound **1** was prepared according to the literature methods.[23,25,29]

Preparation of Compounds 2a-h from 1 (Method 1)

A mixture of **1** (0.5 g, 0.89 mmol) and appropriate amine (7.20 mmol) in acetonitrile (7 ml) was heated in a sealed glass tube at 120°C for 18h. After cooling, the tube was opened and the reaction mixture evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (chloroform-methanol 150:1 v/v) to give compound **2** (yield, see Table) and compound **3** (yield about 40%). Analytically pure samples of **2** were obtained by crystallization from ethanol (in the case of **2b** from methanol).

2a: m.p. 101-103°C. $[\alpha]^{23}_{D}$ +10° (c 1.03, CH_3OH). UV (CH_3OH) λ_{max} 266 nm, ε_{max} 9200. ^{1}H-NMR ($CDCl_3$) δ 1.52 (d, 3H, J=1.2 Hz, 5-CH_3), 2.29 (m, 2H, H-2', H-2"), 2.38 (s, 3H, 3'N-CH_3), 3.34 (dd, 1H, J=3.4 Hz, J=10.5 Hz, H-5"), 3.42 (m, 1H, H-4'), 3.50 (dd, 1H, J=3.3 Hz, J=10.5 Hz, H-5'), 3.94 (m, 1H, H-3'), 6.27 (t, 1H, J=6.2 Hz, H-1'), 7.25-7.34 (m, 9H, C-Ph_3), 7.41-7.45 (m, 6H, C-Ph_3), 7.58 (d, 1H, J=1.2 Hz, H-6). ^{13}C-NMR ($CDCl_3$) δ 12.12 (5-CH_3), 34.70 (C-2'), 38.80 (C-3'), 60.15 (3'N-CH_3), 63.99 (C-5'), 84.35 (C-1'), 84.89 (C-4'), 87.24 (C-Ph_3), 110.73 (C-5), 127.23 (Ph), 127.86 (Ph), 128.52 (Ph), 135.41 (C-6), 143.25 (Ph), 150.21 (C-2), 163.76 (C-4). MS, m/z (rel. int.) 497 (1), 496 (1), 495 (1), 372 (2), 371 (4), 370 (2), 255 (28), 254 (56), 243 (38), 130 (100), 129 (76), 126 (16), 125 (37). Anal. Calcd for $C_{30}H_{31}N_3O_4$: C, 72.42; H, 6.28; N, 8.44. Found: C, 72.63; H, 6.16; N, 8.52.

2b: m.p. 147-149°C. $[\alpha]^{23}_{D}$ +18° (c 0.65, $CHCl_3$). UV (CH_3OH) λ_{max} 267 nm, ε_{max} 9500. ^{1}H-NMR ($CDCl_3$) δ 1.46 (d, 3H, J=1.2 Hz, 5-CH_3), 2.05 (m, 1H,

H-2"), 2.23 (s, 6H, 3'N-(CH_3)$_2$), 2.57 (m, 1H, H-2'), 3.29 (dd, 1H, J=3.5 Hz, J=10.6 Hz, H-5"), 3.44 (m, 1H, H-4'), 3.55 (dd, 1H, J=2.5 Hz, J=10.6 Hz, H-5'), 4.15 (m, 1H, H-3'), 6.21 (t, 1H, J=6.7 Hz, H-1'), 7.25-7.34 (m, 9H, C-Ph_3), 7.41-7.45 (m, 6H, C-Ph_3), 7.67 (d, 1H, J=1.2 Hz, H-6), 9.13 (br s, 1H, 3N-H). ^{13}C-NMR ($CDCl_3$) δ 11.98 (5-CH_3), 33.64 (C-2'), 42.10 (C-3'), 64.48 (3'N-(CH_3)$_2$), 64.90 (C-5'), 81.61 (C-1'), 85.25 (C-4'), 87.20 (C-Ph_3), 110.83 (C-5), 127.24 (Ph), 127.85 (Ph), 128.55 (Ph), 135.40 (C-6), 143.25 (Ph), 150.20 (C-2), 163.72 (C-4). MS, m/z (rel. int.) 511 (1), 510 (1), 509 (1), 386 (6), 385 (10), 384 (6), 369 (38), 268 (63), 243 (42), 143 (38), 142 (100), 127 (17), 126 (34). Anal. Calcd for $C_{31}H_{33}N_3O_4$: C, 72.78; H, 6.50; N, 8.21. Found: C, 72.65; H, 6.56; N, 8.33.

2c: m.p. 99-101°C. $[\alpha]^{23}_D$ +9° (c 1.04, CH_3OH). UV (CH_3OH) λ_{max} 266 nm, ε_{max} 9300. ^{1}H-NMR ($CDCl_3$) δ 1.08 (t, 3H, J=7.1 Hz, 3'N-C-CH_3), 1.52 (d, 3H, J=1.2 Hz, 5-CH_3), 2.29 (t, 2H, J=6.5 Hz, 3'N-CH_2), 2.56 (m, 1H, H-2"), 2.63 (m, 1H, H-2'), 3.36 (dd, 1H, J=3.3 Hz, J=10.5 Hz, H-5"), 3.48 (dd, 1H, J=3.2 Hz, J=10.5 Hz, H-5'), 3.53 (m, 1H, H-4'), 3.91 (m, 1H, H-3'), 6.25 (t, 1H, J=6.1 Hz, H-1'), 7.23-7.35 (m, 9H, C-Ph_3), 7.41-7.45 (m, 6H, C-Ph_3), 7.58 (d, 1H, J=1.2 Hz, H-6). ^{13}C-NMR ($CDCl_3$) δ 12.15 (5-CH_3), 15.47 (3'N-CH_2-CH_3), 39.46 (C-2'), 42.56 (C-3'), 58.21 (3'N-CH_2), 63.77 (C-5'), 84.60 (C- 1'), 84.93 (C-4'), 87.23 (C-Ph_3), 110.70 (C-5), 127.23 (Ph), 127.86 (Ph), 128.51 (Ph), 135.44 (C-6), 143.25 (Ph), 150.12 (C-2), 163.64 (C- 4). MS, m/z (rel. int.) 511 (1), 510 (1), 509 (1), 387 (4), 386 (6), 269 (6), 268 (45), 239 (10), 143 (18), 142 (100), 127 (10), 126 (35). Anal. Calcd for $C_{31}H_{33}N_3O_4$: C, 72.78; H, 6.50; N, 8.21. Found: C, 72.62; H, 6.58; N, 8.19.

2d: m.p. 161-162°C. $[\alpha]^{23}_D$ +11° (c 0.70, CH_3OH). UV (CH_3OH) λ_{max} 266 nm, ε_{max} 9400. ^{1}H-NMR ($CDCl_3$) δ 0.89 (t, 3H, J=7.3 Hz, 3'N-C-C-CH_3), 1.46 (sextet, 2H, J=7.3 Hz, 3'N-C- CH_2), 1.51 (s, 3H, 5-CH_3), 2.30 (t, 2H, J=6.9 Hz, 3'N-CH_2), 2.47 (m, 1H, H-2"), 2.54 (m, 1H, H-2'), 3.36 (dd, 1H, J=3.1 Hz, J=10.5 Hz, H-5"), 3.49 (dd, 1H, J=3.4 Hz, J=10.5 Hz, H-5'), 3.55 (m, 1H, H-4'), 3.91 (m, 1H, H-3'), 6.24 (t, 1H, J=6.1 Hz, H-1'), 7.24-7.34 (m, 9H, C-Ph_3), 7.42- 7.44 (m, 6H, C-Ph_3), 7.60 (s, 1H, H-6). ^{13}C-NMR ($CDCl_3$) δ 11.80 (3'N-CH_2-CH_2-CH_3), 12.12 (5-CH_3), 23.39 (3'N-CH_2-CH_2-CH_3), 39.56 (C-2'), 50.16 (C-3'), 58.19 (3'N-CH_2), 63.78 (C-5'), 84.64 (C-1'), 84.94 (C-4'), 87.24 (C-Ph_3), 110.67 (C-5), 127.21 (Ph), 127.85 (Ph), 128.54 (Ph), 135.42 (C-6), 143.30 (Ph), 150.18 (C-2),

163.68 (C-4). MS, m/z (rel. int.) 525 (1), 524 (1), 523 (1), 400 (2), 399 (2), 398 (2), 342 (2), 283 (11), 282 (45), 243 (26), 227 (49), 221 (38), 213 (32), 157 (70), 156 (100), 127 (17), 126 (36). Anal. Calcd for $C_{32}H_{35}N_3O_4$: C, 73.12; H, 6.71; N, 7.99. Found: C, 73.28; H, 6.78; N, 8.05.

2e: m.p. 103-105°C. $[\alpha]^{23}_D$ +14° (c 0.74, CH_3OH). UV (CH_3OH) λ_{max} 267 nm, ε_{max} 9200. ^{1}H-NMR ($CDCl_3$) δ 1.02 (dd, 6H, J=6.2 Hz, J=8.9 Hz, 3'N-C-$(CH_3)_2$), 1.52 (d, 3H, J=1.1 Hz, 5-CH_3), 2.24 (m, 1H, H-2"), 2.33 (septet, 1H, J=5.2 Hz, 3'N-CH), 2.79 (m, 1H, H-2'), 3.36 (dd, 1H, J=3.2 Hz, J=10.6 Hz, H-5"), 3.48 (dd, 1H, J=3.1 Hz, J=10.6 Hz, H-5'), 3.84 (m, 1H, H-3'), 6.22 (dd, 1H, J=5.2 Hz, J=6.6 Hz, H-1'), 7.23-7.34 (m, 9H, C-Ph_3), 7.42-7.46 (m, 6H, C-Ph_3), 7.64 (d, 1H, J=1.1 Hz, H-6). ^{13}C-NMR ($CDCl_3$) δ 12.17 (5-CH_3), 23.03 (3'N-CH-$(CH_3)_2$), 23.73 (3'N-CH-$(CH_3)_2$), 40.37 (C-2'), 47.12 (C-3'), 55.04 (3'N-CH), 63.22 (C-5'), 84.95 (C-1'), 84.99 (C-4'), 87.17 (C-Ph_3), 110.65 (C-5), 127.23 (Ph), 127.87 (Ph), 128.52 (Ph), 135.43 (C-6), 143.27 (Ph), 150.09 (C-2), 163.62 (C-4). MS, m/z (rel. int.) 525 (1), 524 (1), 511 (2), 510 (2), 283 (12), 282 (38), 243 (23), 240 (56), 239 (38), 224 (12), 157 (70), 156 (100), 127 (17), 126 (34). Anal. Calcd for $C_{32}H_{35}N_3O_4$: C, 73.12; H, 6.71; N, 7.99. Found: C, 73.01; H, 6.68; N, 7.92.

2f: m.p. 92-94°C. $[\alpha]^{23}_D$ +19° (c 0.70, CH_3OH). UV (CH_3OH), λ_{max} 267 nm, ε_{max} 9400. ^{1}H-NMR δ 1.51 (d, 3H, J=1.1 Hz, 5-CH_3), 2.29 (m, 2H, H-2', H-2"), 3.21 (m, 2H, 3'N-CH_2), 3.37 (dd, 1H, J=3.3 Hz, J=10.5 Hz, H-5"), 3.49 (dd, 1H, J=3.2 Hz, J=10.5 Hz, H-5'), 3.60 (m, 1H, H-4'), 3.92 (m, 1H, H-3'), 5.09-5.18 (m, 2H, =CH_2), 5.79-5.88 (m, 1H, -CH=), 6.27 (t, 1H, J=6.1 Hz, H-1'), 7.27-7.35 (m, 9H, C-Ph_3), 7.42-7.45 (m, 6H, C-Ph_3), 7.60 (d, 1H, J=1.1 Hz, H-6), 8.79 (br s, 1H, 3N-H). ^{13}C-NMR ($CDCl_3$) δ 12.11 (5-CH_3), 39.48 (C-2'), 50.63 (C-3'), 57.44 (3'N-CH_2-), 63.67 (C-5'), 84.57 (C-1'), 84.90 (C- 4'), 87.24 (C-Ph_3), 110.74 (C-5), 116.38 (=CH_2), 127.25 (Ph), 127.87 (Ph), 128.52 (Ph), 135.41 (C-6), 135.96 (-CH=), 143.22 (Ph), 150.15 (C- 2), 163.66 (C-4). MS, m/z (rel. int.) 523 (1), 522 (1), 521 (1), 398 (2), 397 (2), 396 (2), 281 (21), 280 (38), 155 (100), 154 (48), 128 (14), 127 (23), 126 (38). Anal. Calcd for $C_{32}H_{33}N_3O_4$: C, 73.40; H, 6.35; N, 8.03. Found: C, 73.31; H, 6.31; N, 8.12.

2g: m.p. 90-92°C. $[\alpha]^{23}_D$ +28° (c 1.00, CH_3OH). UV (CH_3OH) λ_{max} 266 nm, ε_{max} 9300. ^{1}H-NMR ($CDCl_3$) δ 1.47 (d, 3H, J=1.2 Hz, 5-CH_3), 2.30 (m, 2H,

H-2', H-2"), 3.36 (dd, 1H, J=3.3 Hz, J=10.5 Hz, H-5"), 3.46 (dd, 1H, J=3.3 Hz, J=10.5 Hz, H-5'), 3.60 (m, 1H, H-4'), 3.75 (dd, 2H, J=13.2 Hz, J=26.6 Hz, 3'N-CH_2), 3.94 (m, 1H, H-3'), 6.28 (t, 1H, J=6.0 Hz, H-1'), 7.21-7.32 (m, 14H, C-Ph_3, CH_2-Ph), 7.36-7.40 (m, 6H, C-Ph_3), 7.55 (d, 1H, J=1.2 Hz, H-6), 8.25 (br s, 1H, 3N-H). ^{13}C-NMR ($CDCl_3$) δ 12.04 (5-CH_3), 39.48 (C-2'), 52.15 (C- 3'), 57.45 (3'N-CH_2), 63.70 (C-5'), 84.49 (C-1'), 84.93 (C-4'), 87.27 (C-Ph_3), 110.72 (C-5), 127.11 (Ph), 127.22 (Ph), 127.85 (Ph), 128.42 (Ph), 128.55 (Ph), 135.35 (C-6), 139.37 (Ph), 143.25 (Ph), 150.13 (Ph), 163.58 (C-4). MS, m/z (rel. int.) 573 (1), 572 (1), 571 (1), 448 (5), 447 (7), 446 (5), 357 (9), 331 (21), 330 (28), 243 (44), 205 (100), 206 (77), 127 (11), 126 (18). Anal. Calcd for $C_{36}H_{35}N_3O_4$: C, 75.37; H, 6.15; N, 7.32. Found: C, 75.28; H, 6.11; N, 7.26.

2h: m.p. 88-89°C. $[\alpha]^{23}_D$ +30° (c 1.00, CH_3OH). UV (CH_3OH) λ_{max} 265 nm, ε_{max} 9400. ^{1}H-NMR ($CDCl_3$) δ 1.48 (d, 3H, J=0.9 Hz, 5-CH_3), 2.30 (m, 2H, H-2', H-2"), 3.35 (dd, 1H, J=3.3 Hz, J=10.4 Hz, H-5"), 3.47 (dd, 1H, J=3.3 Hz, J=10.4 Hz, H-5'), 3.56 (m, 1H, H-4'), 3.72 (dd, 2H, J=13.3 Hz, J=28.7 Hz, 3'N-CH_2), 3.93 (m, 1H, H-3'), 6.28 (t, 1H, J=6.1 Hz, H-1'), 6.97 (m, 2H, FPh), 7.17-7.33 (m, 11H, C-Ph_3, FPh), 7.36-7.40 (m, 6H, C-Ph_3), 7.56 (d, 1H, J=0.9 Hz, H-6), 8.42 (br s, 1H, 3N-H). ^{19}F-NMR ($CDCl_3$) Φ 114.93 (m, 1F, FPh). ^{13}C-NMR ($CDCl_3$) δ 12.06 (5-CH_3), 39.46 (C-2'), 51.43 (C-3'), 57.53 (3'N-CH_2), 63.70 (C-5'), 84.46 (C-1'), 84.96 (C-4'), 87.33 (C-Ph_3), 110.80 (C-5), 115.12 (FPh), 115.41 (FPh), 127.30 (Ph), 127.90 (Ph), 128.56 (Ph), 129.39 (FPh), 129.49 (FPh), 135.36 (C-6), 143.22 (C-Ph_3), 149.96 (C-2), 163.52 (C-4). MS, m/z (rel. int.) 591 (1), 590 (1), 589 (2), 466 (5), 465 (8), 464 (5), 349 (12), 348 (31), 243 (53), 224 (14), 223 (63), 164 (100), 163 (67), 127 (14), 126 (35). Anal. Calcd for $C_{36}H_{34}FN_3O_4$: C, 73.08; H, 5.79; N, 7.10. Found: C, 73.23; H, 5.83; N, 7.07.

Detritylation of Compounds 2a-h on Dowex 50Wx2

A solution of **2** (0.3 g) in methanol (25 ml) and water (5 ml) was applied to a column (4 x 6 cm) of Dowex 50Wx2 (H^+) (50-100 mesh). The column was eluted with methanol (100 ml) in order to remove triphenylmethanol and than with 1M ammonium hydroxide. The fractions containing **4** were combined and evaporated under reduced pressure. The residue as

white solid foam was dried in vacuo over phosphorus pentoxide to afford product **4** in pure form, yield about 80%.

4a: m.p. 164-166°C (CH_3OH). $[\alpha]^{23}_D$ +34° (c 0.75, CH_3OH). UV (H_2O) λ_{max} 265 nm, ε_{max} 8300. ^{1}H-NMR (DMSO-d_6) δ 1.74 (s, 3H, 5-CH_3), 2.01 (m, 2H, H-2',H-2"), 2.25 (s, 3H, 3'N-CH_3), 3.11 (m, 1H, H-4'), 3.42-3.66 (m, 3H, H-3', H-5', H-5"), 6.13 (t, 1H, J=6.6 Hz, H-1'), 7.57 (s, 1H, H-6). ^{13}C-NMR (DMSO-d_6) δ 12.98 (5-CH_3), 34.30 (C-2'), 37.19 (C-3'), 59.83 (3'N-CH_3), 61.93 (C-5'), 83.96 (C-1'), 84.84 (C-4'), 109.05 (C-5), 135.36 (C-6), 153.06 (C-2), 167.36 (C-4). MS, m/z (rel.int.) 255 (8), 198 (7), 195 (7), 194 (7), 153 (16), 145 (7), 144 (16), 143 (10), 131 (14), 130 (96), 129 (100), 128 (15), 127 (21), 126 (79). Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.61; H, 6.65; N, 16.34.

4b: m.p. 182-183°C (CH_3OH). $[\alpha]^{23}_D$ +49.5° (c 0.75, CH_3OH). UV (H_2O) λ_{max} 266 nm, ε_{max} 8400. ^{1}H-NMR (DMSO-d_6) δ 1.77 (d, 3H, J=1.2 Hz, 5-CH_3), 1.92 (m, 1H, H-2"), 2.18 (s, 6H, 3'N-$(CH_3)_2$), 2.32 (m, 1H, H-2'), 3.15 (m, 1H, H-4'), 3.53 (dd, 1H, J=3.9 Hz, J=12.0 Hz, H-5"), 3.64 (dd, 1H, J=3.0 Hz, J=12.0 Hz, H-5'), 3.91 (m, 1H, H-3'), 6.04 (t, 1H, J=6.5 Hz, H-1'), 7.76 (d, 1H, J=1.2 Hz, H-6). ^{13}C-NMR (DMSO-d_6) δ 12.85 (5-CH_3), 31.85 (C-2'), 41.96 (C-3'), 62.32 (3'N-$(CH_3)_2$), 64.33 (C-5'), 81.81 (C-1'), 84.09 (C-4'), 108.90 (C-5), 135.14 (C-6), 152.70 (C-2), 166.86 (C-4). MS, m/z (rel. int.) 269 (41), 200 (10), 198 (10), 144 (42), 143 (100), 127 (11), 126 (29). Anal. Calcd for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.31; H, 7.22; N, 15.54.

4c: m.p. 151-153°C (CH_3OH). $[\alpha]^{23}_D$ +45° (c 0.76, CH_3OH). UV (H_2O) λ_{max} 265 nm, ε_{max} 8300. ^{1}H-NMR (DMSO-d_6) δ 1.01 (t, 3H, J=7.0 Hz, 3'N-C-CH_3), 1.77 (d, 3H, J=1.1 Hz, 5-CH_3), 2.06 (q, 2H, J=6.1 Hz, 3'N-CH_2), 3.25 (m, 1H, H-4'), 3.54 (dd, 1H, J=3.3 Hz, J=11.3 Hz, H-5"), 3.60 (m, 2H, H-3', H-5'), 6.10 (t, 1H, J=6.5 Hz, H-1'), 7.75 (d, 1H, J=1.1 Hz, H-6), 11.24 (br s, 1H, 3N-H). ^{13}C-NMR (DMSO-d_6) δ 12.24 (5-CH_3), 15.30 (3'N-CH_2-CH_3), 37.70 (C-2'), 41.70 (C-3'), 57.62 (3'N-CH_2), 61.61 (C-5'), 83.82 (C-1'), 85.36 (C-4'), 108.92 (C-5), 136.02 (C-6), 150.16 (C-2), 163.48 (C-4). MS, m/z (rel. int.) 269 (12), 254 (5), 226 (5), 209 (7), 198 (11), 180 (9), 153 (11), 145 (11), 144 (97), 143 (100), 137 (9), 127 (19), 126 (32). Anal. Calcd for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.63; H, 7.21; N, 15.52.

4d: $[\alpha]^{23}_D$ +46° (c 0.82, CH_3OH). UV (H_2O) λ_{max} 266 nm, ε_{max} 8500. ^{1}H-NMR (CD_3OD) δ 0.95 (t, 3H, J=7.4 Hz, 3'N-C-C-CH_3), 1.54 (sextet, 2H, J=7.4 Hz, 3'N-C-CH_2), 1.88 (s, 3H, 5-CH_3), 2.25 (t, 2H, J=6.6 Hz, 3'N-CH_2), 2.56 (m, 2H, H-2', H-2"), 3.42 (m, 1H, H-4'), 3.77 (dd, 1H, J=4.6 Hz, J=12.9 Hz, H-5"), 3.85 (m, 2H, H-3', H-5'), 6.23 (t, 1H, J=6.3 Hz, H-1'), 7.85 (s, 1H, H-6). ^{13}C-NMR (CD_3OD) δ 12.11 (3'N-CH_2-CH_2-CH_3), 12.50 (5-CH_3), 23.88 (3'N-CH_2-CH_2), 39.34 (C-2'), 51.07 (C-3'), 58.85 (3'N-CH_2), 63.15 (C-5'), 86.30 (C-1'), 86.89 (C-4'), 111.20 (C-5), 138.05 (C-6), 152.27 (C-2), 166.40 (C-4). MS, m/z (rel. int.) 283 (11), 255 (7), 254 (32), 198 (9), 180 (9), 158 (61), 157 (100), 140 (14), 128 (39), 127 (21), 126 (36). Anal. Calcd for $C_{13}H_{21}N_3O_4$: C, 55.11; H, 7.47; N, 14.83. Found: C, 55.23; H, 7.50; N, 14.94.

4e: $[\alpha]^{23}_D$ +48° (c 0.78, CH_3OH). UV (H_2O) λ_{max} 266 nm, ε_{max} 8400. ^{1}H-NMR ($CDCl_3$) δ 1.09 (t, 6H, J=6.0 Hz, 3'N-C-$(CH_3)_2$), 1.93 (d, 3H, J=1.2 Hz, 5-CH_3), 2.17 (m, 1H, H-2"), 2.39 (septet, 1H, J=5.0 Hz, 3'N-CH), 2.89 (m, 1H, H-2'), 3.55 (m, 1H, H-4'), 3.78 (m, 1H, H-3'), 3.85 (dd, 1H, J=3.4 Hz, J=11.7 Hz, H-5"), 3.96 (dd, 1H, J=3.5 Hz, J=11.7 Hz, H-5'), 6.16 (dd, 1H, J=5.0 Hz, J=7.0 Hz, H-1'), 7.43 (d, 1H, J=1.2 Hz, H-6). ^{13}C-NMR ($CDCl_3$) δ 12.68 (5-CH_3), 22.73 (3'N-CH-$(CH_3)_2$), 23.73 (3'N-CH-$(CH_3)_2$), 39.54 (C-2'), 47.32 (C-3'), 55.02 (3'N-CH), 62.48 (C-5'), 85.36 (C-1'), 85.66 (C-4'), 110.80 (C-5), 136.23 (C-6), 150.27 (C-2), 163.78 (C-4). MS, m/z (rel.int.) 283 (21), 269 (14), 268 (78), 223 (14), 198 (10), 180 (59), 159 (11), 158 (89), 157 (100), 142 (33), 140 (20), 137 (16), 128 (23), 127 (28), 126 (38). Anal. Calcd for $C_{13}H_{21}N_3O_4$: C, 55.11; H, 7.47; N, 14.83. Found: C, 55.26; H, 7.43; N, 14.71.

4f: $[\alpha]^{23}_D$ +50° (c 0.86, CH_3OH). UV (H_2O) λ_{max} 266 nm, ε_{max} 8500. ^{1}H-NMR (DMSO-d_6) δ 1.72 (s, 3H, 5-CH_3), 1.99 (m, 2H, H-2', H-2"), 3.15 (m, 2H, 3'N-CH_2), 3.24 (m, 1H, H-4'), 3.52 (dd, 1H, J=3.8 Hz, J=11.4 Hz, H-5"), 3.60 (dd, 1H, J=3.3 Hz, J=11.4 Hz, H-5'), 3.65 (m, 1H, H-3'), 5.02-5.19 (m, 2H, =CH_2), 5.78- 5.91 (m, 1H, -CH=), 6.17 (t, 1H, J=6.6 Hz, H-1'), 7.45 (s, 1H, H-6). ^{13}C-NMR (DMSO-d_6) δ 13.30 (5-CH_3), 37.65 (C-2'), 49.95 (C-3'), 57.49 (3'N-CH_2), 61.90 (C-5'), 83.88 (C-1'), 84.79 (C-4'), 108.93 (C-5), 115.04 (=CH_2), 134.76 (-CH=), 137.45 (C-6), 154.96 (C-2), 169.88 (C-4), MS, m/z (rel. int.) 281 (19), 226 (12), 198 (12), 180 (48), 156 (100), 155 (81), 140 (14), 138 (45), 137 (31), 128 (17), 127 (48), 126 (57). Anal. Calcd for $C_{13}H_{19}N_3O_4$: C, 55.51; H, 6.81; N, 14.94. Found: C, 55.39; H, 6.80; N, 14.98.

4g: $[\alpha]^{23}_D$ +38.5° (c 0.95, CH_3OH). UV (H_2O) λ_{max} 266 nm, ε_{max} 9200. ^{1}H-NMR ($CDCl_3$) δ 1.91 (d, 3H, J=1.2 Hz, 5-CH_3), 2.21 (m, 1H, H-2"), 2.35 (m, 1H, H-2'), 3.52 (m, 1H, H-4'), 3.77-3.83 (m, 3H, 3'N-CH_2, H-5"), 3.87 (m, 1H, H-3'), 3.91 (dd, 1H, J=3.1 Hz, J=11.4 Hz, H-5'), 6.18 (t, 1H, J=6.2 Hz, H-1'), 7.29-7.34 (m, 5H, Ph), 7.39 (d, 1H, J=1.2 Hz, H-6), ^{13}C-NMR ($CDCl_3$) δ 12.59 (5-CH_3), 38.78 (C-2'), 52.29 (C-3'), 57.53 (3'N-CH_2), 62.73 (C-5'), 85.36 (C-1'), 85.80 (C-4'), 110.79 (C-5), 127.21 (Ph), 127.95 (Ph), 128.45 (Ph), 136.27 (Ph), 139.39 (C-6), 150.35 (C-2), 163.83 (C-4). MS, m/z (rel. int.) 331 (7), 207 (13), 206 (74), 205 (100), 188 (15), 180 (61), 176 (28), 174 (22), 162 (37), 148 (15), 147 (26), 144 (15), 132 (22), 127 (17), 126 (43). Anal. Calcd for $C_{17}H_{21}N_3O_4$: C, 61.62; H, 6.39; N, 12.68. Found: C, 61.75; H, 6.28; N, 12.63.

4h: $[\alpha]^{23}_D$ +40° (c 0.77, CH_3OH). UV (H_2O) λ_{max} 267 nm, ε_{max} 9200. ^{1}H-NMR ($CDCl_3$) δ 1.88 (d, 3H, J=1.0 Hz, 5-CH_3), 2.20 (m, 1H, H-2"), 2.31 (m, 1H, H-2'), 3.49 (m, 1H, H-4'), 3.72-3.95 (m, 4H, 3'N-CH_2, H-3', H-5"), 3.93 (dd, 1H, J=3.1 Hz, J=11.4 Hz, H-5'), 6.19 (t, 1H, J=6.3 Hz, H-1'), 7.00 (m, 2H, FPh), 7.26-7.31 (m, 2H, FPh), 7.37 (d, 1H, J=1.0 Hz, C-6). ^{19}F-NMR ($CDCl_3$) Φ 115.10 (m, 1F, FPh). ^{13}C-NMR ($CDCl_3$) δ 12.67 (5-CH_3), 38.64 (C-2'), 51.56 (C-3'), 57.56 (3'N-CH_2), 62.76 (C-5'), 85.34 (C-1'), 85.83 (C-4'), 110.88 (C-5), 115.12 (FPh), 115.40 (FPh), 129.44 (FPh), 135.18 (C-6), 136.14 (FPh), 150.75 (C-2), 163.51 (C-4). MS, m/z (rel. int.) 349 (5), 226 (8), 225 (39), 224 (50), 206 (11), 205 (8), 184 (18), 182 (26), 170 (63), 165 (14), 164 (100), 162 (14), 150 (14), 127 (16), 126 (55). Anal. Calcd for $C_{17}H_{20}FN_3O_4$: C, 58.45; H, 5.77; N, 12.03. Found: C, 58.57; H, 5.79; N, 12.14.

Preparation of 3'-Azido-5'-O-trityl-3'-deoxythymidine 5 from 1

A mixture of **1** (5 g, 8.89 mmol) and sodium azide (1 g, 15.38 mmol) in dry ethylene glycol (30 ml) was stirred at 120°C for 45 min. The cooled reaction mixture was poured into ice-water (200 ml) and the resulting precipitate was collected by filtration, washed with water and dried in vacuo over phosphorus pentoxide to afford product **5** (4.40 g, yield 87%).

Preparation of 3'-Amino-5'-O-trityl-3'-deoxythymidine 6 from 5

To a solution of **5** (1.0 g, 1.96 mmol) in isopropanol (30 ml) was added sodium borohydride (0.30 g, 7.93 mmol). The reaction mixture was

refluxed with stirring for 14 h and evaporated under reduced pressure. To the residue was added methanol (25 ml) and concentrated ammonium hydroxide (4 ml). The mixture was stirred at room temperature for 1h, concentrated under reduced pressure to a small volume (about 7ml), diluted with water (30 ml) and extracted with chloroform (3x20 ml). The combined organic extracts were dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was crystallized from ethanol to give **6** (0.88 g, yield 93%). The compound **6** was detritylated on Dowex 50Wx2 (H^+) to afford 3'-amino-3'-deoxythymidine as described above for compounds **2a-h**.

Preparation of Compounds 2a-h from 6 (Method 2)

To a solution of **6** (0.40 g, 0.83 mmol) in ethanol (60 ml) and water (7 ml) was added acetate buffer (1.7 ml), which was prepared from sodium acetate trihydrate (2.5 g), glacial acetic acid (8.4 ml) and water (25 ml). Then to the mixture was added an appropriate aldehyde or ketone (1.24 mmol). The reaction mixture was stirred at 0-5°C for 5 min and sodium borohydride (0.18 g, 4.76 mmol) was added in portions (0.03 g) during 30 min. When TLC showed a complete reaction the mixture was evaporated under reduced pressure. To the residue was added water (25 ml) and the mixture was extracted with chloroform (3x20 ml). The combined organic extracts were washed with water (20 ml), dried over magnesium sulphate, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (chloroform-methanol 150:1 v/v) to give compound **2** (yield, see Table). Analytically pure samples of **2** were obtained by crystallization from ethanol (in the case of **2b** from methanol). Compounds **2a-h** were detritylated on Dowex 50Wx2 (H^+), as described above, to afford **4a-h**.

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