Acta Chemica Scandinavica, 1996: 50: 609–622
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904-213X

Ether, Carbonate and Urethane Deoxynucleoside Derivatives as Prodrugs

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Hammer, K., Hatlelid, J., Grøtli, M., Arukwe, J., Klaveness, J., Rise, F. and Undheim, K., 1996. Ether, Carbonate and Urethane Deoxynucleoside Derivatives as Prodrugs. – Acta Chem. Scand. 50: 609–622. © Acta Chemica Scandinavica 1996.

3′-Deoxythymidine and its 3′-azido derivative, 2′,3′-dideoxycytidine, 2′,3′-dideoxyinosine and 2′,3′-dideoxyadenosine have been acylated to form carbonates and urethanes in chemoselective reactions. The nucleosides have been *N*- and/or *O*-alkylated by α-chloroethyl or chloromethyl alkyl carbonates to form α-alkyloxycarbonyloxyethyl or alkyloxycarbonyloxymethyl derivatives. The products are lipophilic in order to facilitate transport through biological membranes and are designed to be cleaved by esterases with liberation of the bioactive nucleoside. Initial esterase cleavage of the alkylated derivatives produces hemiacetals or -aminals which subsequently dissociate to the active nucleoside.

Anti-HIV nucleosides as a class penetrate the blood–brain barrier poorly. So far the only drugs approved for the treatment of AIDS are the deoxynucleosides 3′-azido-3′-deoxythymidine (AZT), 2′,3′-dideoxycytidine (ddC) and 2′,3′-dideoxyinosine (ddI) (Fig. 1) which, after phosporylation by cellular kinases to the 5′-triphosphate level, operate by simulating the natural nucleotide substrates that are incorporated into the growing DNA chain by the enzyme systems reverse transcriptase (RT). Since the effective nucleosides lack the 3′-hydroxy group for further synthesis, their incorporation as nucleotides into the DNA chain must result in chain termination.[1,2]

A variety of drug delivery techniques have been proposed to enhance the CNS delivery of the nucleoside.[3] These include prodrug approaches with simple esters,[4,5] ether lipid nucleosides,[6] a dihydropyridine carrier system for sustained delivery of 2′,3′-dideoxynucleosides involving intracellular redox formation of the pyridinium salt and gradual hydrolysis,[7] or as phosphoesters that are not readily hydrolyzable.[8] We have converted anti-HIV active nucleosides into lipophilic prodrugs that should cross the blood–brain barrier by passive diffusion more readily than the parent nucleoside. Ideally, the prodrugs should be relatively resistant towards systemic hydrolysis but sensitive to hydrolysis after passage of the biological membrane. Thus, after passage of the blood–brain barrier the lipophilic moiety will be cleaved off by enzymatic action, thereby liberating the parent nucleoside for subsequent phosphorylation to nucleotides (Fig. 2). Anti-HIV activity requires that the nucleoside or its prodrug is not an inhibitor of the phosphorylating enzymes. The simple and highly lipophilic esters of nucleosides suffer from extensive systemic ester cleavage. In the present approach we use lipophilic carbonate and urethane derivatives of nucleosides. This allows for a wide scope of variations in the alcohol, phenol or the amine in the carbonate or urethane derivatives which can be used to control the rates for enzymatic cleavages.[9] The target

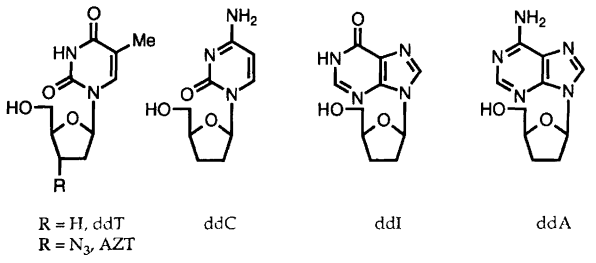

Fig. 1.

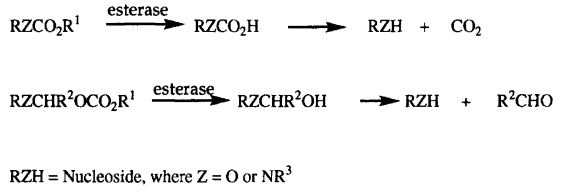

Fig. 2.

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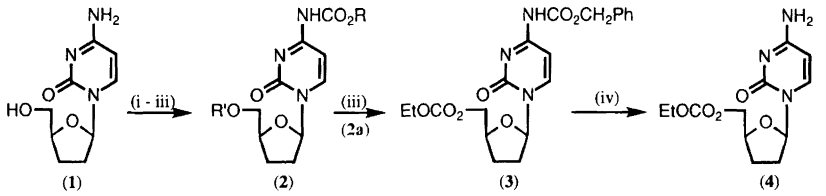


a R'= H, R = CH_2Ph
b R'= H R = Et
c R'= EtOCO R = Et

(i) $PhCH_2OCOCl$/DMAP/pyrid/DMF/RT (2a); (ii) $(EtOCO)_2O$/MeOH/Rfx (2b); (iii) $(EtOCO)_2O$/pyrid/DMAP/RT (2c); (iv) H_2/Pd(C)/EtOH

Scheme 1.

molecules should be relatively resistant towards hydrolysis during the distribution phase but made sensitive to hydrolysis after passage of the biological membrane. The urethanes are formed by acylation of a nitrogen in the nucleoside base with an alkyloxy- or aryloxycarbonyl chloride. Urethane formation in the nucleoside carbohydrate moiety is effected by reaction of a carbamoyl chloride with the nucleoside. Increase in lipophilicity can be effected by alkylation as in the preparation of 5′-*O*-ethers from anti-HIV nucleosides. Cleavage of the 5′-ethers to the active nucleosides, however, cannot be achieved.[6] In our approach the ether function is part of an acetal or aminal which is *O*-or *N*-acylated with the desired lipophilic carboxylic acid. An ester group allows for cleavage by esterases whereby chemically unstable hydroxymethyl derivatives are formed which subsequently will dissociate to furnish active nucleosides. We herein describe syntheses of prodrugs from both the carbonate/urethane and the ether classes of compounds, and some preliminary studies of stability, lipophilicity and *in vitro* anti-HIV activities.

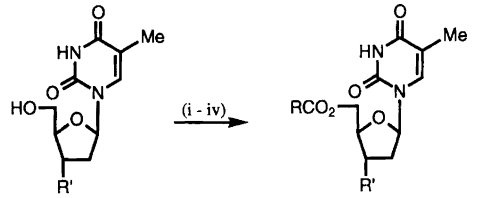
Acylation reactions. 2′,3′-Dideoxycytidine (**1**) is chemoselectively acylated on the 4-amino group with formation of the benzylurethane **2a** in pyridine solution using benzyl chloroformate with 4-dimethylaminopyridine (DMAP) as base. The 4-ethylurethane **2b** was prepared in high yield from diethyl pyrocarbonate and cytidine (**1**) by heating the reactants together in methanol. The reaction conditions are an adaption of those used for selective acetylation of the 4-amino group in cytidine.[10] Any 5′-OH acylated product formed in the reaction will subsequently be cleaved by methanol in a transesterification process leading to the observed selective *N*-acylation (**2b**). For 5′,N^4-bisacylation (**2c**) the reaction with diethyl pyrocarbonate was run with DMAP in pyridine.

The 5′-*O*-carbonate **4** is an isomer of the urethane **2b**. The former was prepared from the amino-protected benzylurethane **2a**, which was *O*-acylated using ethyl pyrocarbonate in pyridine to form the 5′-*O*-carbonate **3**. Subsequent removal of the protecting group by hydrogenolysis over palladium on charcoal gave the isomer **4**.

In the 3′-deoxythymidines **5** initial acylation is on the 5′-OH group (Scheme 2). The 5′-*O*-ethyl carbonates **6a** and **6b** were prepared with ethyl pyrocarbonate and DMAP in pyridine. In the preparation of the 5′-*O*-allyl carbonate **6c** the disodium salt of the azidopyrimidine **5b** was reacted with allyl chloroformate in excess of 1 mol equiv.; the alcoholate is the more reactive function. The urethane **6d** was prepared similarly in DMF, with *N*,*N*-diethylcarbamoyl chloride as acylating agent in high yield. The succinyl derivative **6e**, which is available from the reaction with succinic anhydride in pyridine, is an intermediate for the preparation of a simple acylated derivative of an *N*3-alkylated 3′-azidothymidine (**23d**) (Scheme 7; see later).

Acylation of 2′,3′-dideoxyinosine (**7**) is selective for the alcoholic hydroxyl group with formation of the carbonate **8** using the protocol with ethyl pyrocarbonate and DMAP in pyridine (Scheme 3).

In contrast to the selective *N*-acylation in 2′,3′-

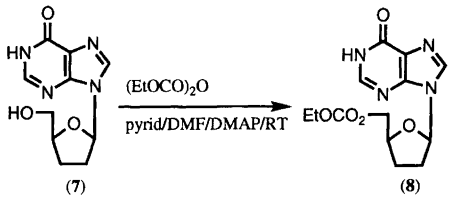


a R'= H
b R'= N_3

a R = OEt R'= H
b R = OEt R'= N_3
c R = $OCH_2CH{=}CH_2$ R'= N_3
d R = NEt_2 R'= N_3
e R = $CH_2CH_2CO_2H$ R'= N_3

(i) $(EtOCO)_2O$/pyrid/DMAP/RT (6a and 6b); (ii) $CH_2{=}CHCH_2O$-COCl/NaH/DMF/RT (6c); (iii) $(Et_2NCOCl$/NaH/DMF/RT (6d); (iv) Succinic anhydride/pyrid/RT (6e)

Scheme 2.



Scheme 3.

dideoxycytidine (**1**) the reaction of 2′,3′-dideoxyadenosine (**9**) is initially on the 5-hydroxyl group to form the 5′-*O*-carbonate **10** using ethyl pyrocarbonate and DMAP in pyridine (Scheme 4). With ethyl chloroformate and 1-methylimidazole as base the carbonate **10** is further acylated to the diacyl product **11**. Direct acylation of the adenosine **9** with palmitoyl chloride using DMAP in DMF/pyridine also gave primarily the 5′-*O*-acylated product **16** and some *N*,*O*-diacylated product; the products were readily isolated by flash chromatography. The palmitate **16** was also prepared by way of the N^6-benzyloxycarbonyl protected adenosine **14**, which was acylated essentially as above to form the protected palmitate **15**. The benzyloxycarbonyl protecting group was removed from **15** by hydrogenolysis over Pd(C) to yield the palmitate ester **16**. The protected adenosine **14** was primarily an intermediate for selective 5′-*O*-alkylation; compound **25** in Scheme 8. It was prepared by protection of the 5′-OH group as the silyl ether **12** by the reaction of **9** with dimethylhexylsilyl chloride (TDMS–Cl) using pyridine as base followed by N^6-acylation using benzyl chloroformate to furnish **13** and removal of the silyl group by tetrabutylammonium fluoride (TBAF) in dry THF (**14**).

Alkylation reactions. In the alkylation reactions chloromethyl esters and chloromethyl or α-chloroethyl carbonate esters were used for selective 5′-*O*-alkylation in cytidine. The 4-amino group was protected by acylation (Scheme 5) as a benzyl (**2a**) or ethyl (**2b**) urethane. For the alkylation with chloromethyl pivalate 2 mol equiv. of NaH were used as base to yield the *O*-alkylated products **17a** and **17b**. The products **17** are both prodrug target compounds which are 5′-*O*-alkylated and N^4-acylated as a urethane. Removal of the benzyloxycarbonyl group in **17a** was by hydrogenolysis over Pd(C), which provided another target compound, viz. the 5′-*O*-alkylated 2′,3′-dideoxycytidine **18**.

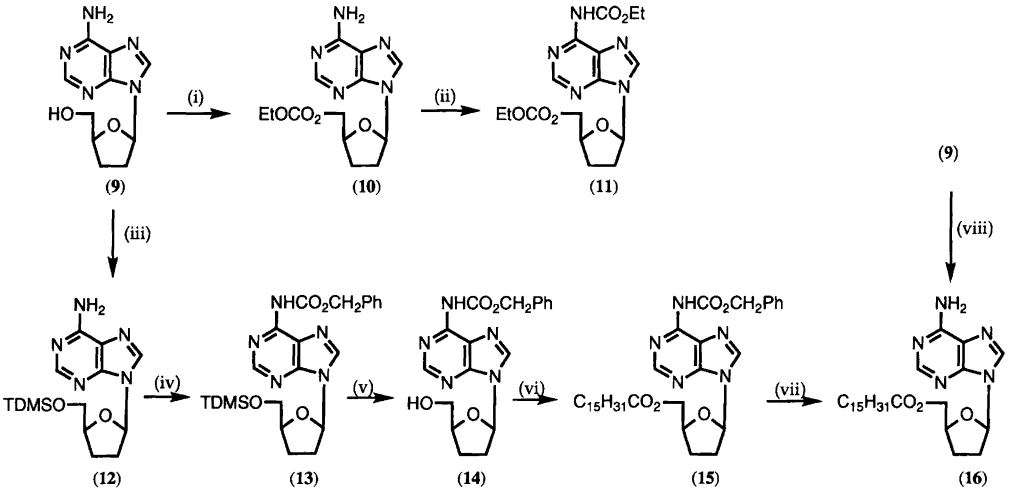
In the 3′-deoxythymidine series **5** clean *N*3-alkylation involves initial 5′-*O*-silylation by TDMS-Cl and imidazolole as base. The products **19** were alkylated either by chloromethyl pivalate or by α-chloroethyl ethyl carbonate using potassium carbonate as base to furnish the *N*3-alkylated products **20**. Desilylation by TBAF in dry THF gave the target compounds, the *N*3-alkylated esters **21a** and **21b** and the carbonates **21c** and **21d**.

The 5′-*O*-alkylated product **22a** is an isomer of the *N*3-alkylated product **21a** (Scheme 6). The former was prepared by direct alkylation of the thymidine **5a** with 1 mol equiv. of chloromethyl pivalate and NaH as base; the 5′-OH group is selectively alkylated. With excess alkylating agent the *N*3,5′-*O*-dialkylated product **22b** was obtained.

The final group of target compounds in the thymidine series were the 5′-*O*-acylated and *N*3-alkylated derivatives **23**. The 5′-oxygen is part of a carbonate **23a** and **23b**, a urethane (**23c**) or a simple ester (**23d**). The alkylation of the 5′-*O*-acylated thymidine (**6**) was effected with α-chloroethyl ethyl carbonate and potassium carbonate as base.

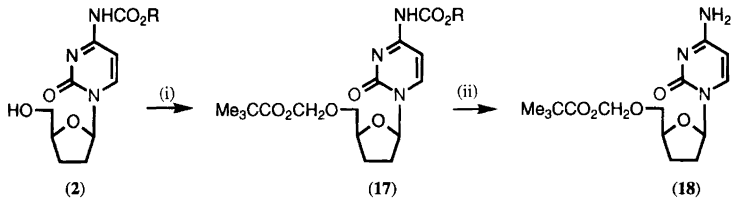
In the adenosine series clean 5′-*O*-alkylation was effected using the N^6-benzyloxycarbonyl derivative **14** as the substrate for the reaction with chloromethyl pivalate and NaH as base. The product **24** is a 5′-*O*-alkylated-6-adenosylurethane. The 5′-*O*-alkylated 2′,3′-dideoxyadenosine **25** was available from **24** by hydrogenolysis over Pd(C).

The principle for esterase cleavage of carbonates and urethanes is indicated in Fig. 2. The carbonic or carbamic acid, after enzymatic cleavage, is chemically unstable,



(i) $(EtOCO)_2O$/DMAP/pyrid/DMF/RT; (ii) EtOCOCl/1-methylimidazole/CH_2Cl_2/RT; (iii) TDMS–Cl/imidazole/pyrid /RT; (iv) $PhCH_2OCOCl$/1-methylimidazole/CH_2Cl_2/RT; (v) TBAF/THF/RT; (vi) $C_{15}H_{31}COCl$/DMAP/pyrid/RT; (vii) H_2/Pd(C)EtOH; (viii) $C_{15}H_{31}COCl$/DMAP/pyrid/DMF/RT

Scheme 4.

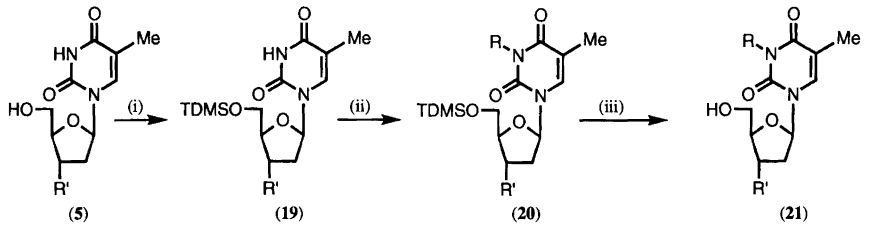


(2) (17) (18)

a R = CH_2Ph
b R = Et

(i) $Me_3CCO_2CH_2Cl$/NaH/DMF/RT
(ii) H_2/Pd(C)/EtOH

Scheme 5.



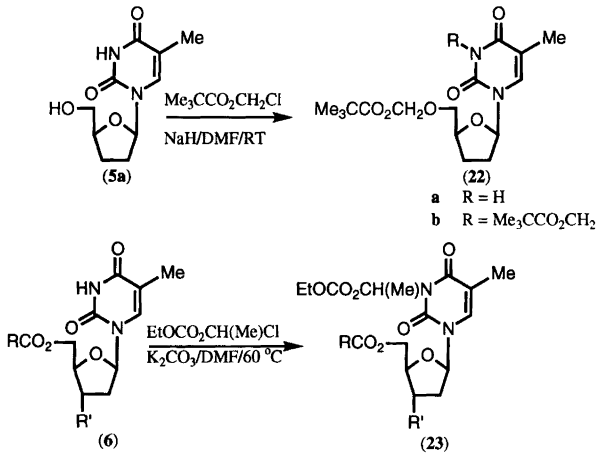
(5) (19) (20) (21)

a R'= H
b R'= N_3

a R = $Me_3CCO_2CH_2$ R'= H
b R = $Me_3CCO_2CH_2$ R'= N_3
c R = $EtOCO_2(CH)Me$ R'= H
d R = $EtOCO_2(CH)Me$ R'= N_3

(i) TDMS-Cl/imidazole/DMF/RT
(ii) RCl/K_2CO_3/DMF/20 - 50 °C
(iii) TBAF/THF/RT

Scheme 6.



(5a) (22) (6) (23)

a R = H
b R = $Me_3CCO_2CH_2$

a R = OEt R'= H
b R = OEt R'= N_3
d R = NEt_2 R'= N_3
e R= $HO_2CCH_2CH_2$ R'= N_3

a R = OEt R'= H
b R = OEt R'= N_3
c R = NEt_2 R'= N_3
d R= $HO_2CCH_2CH_2$ R'= N_3

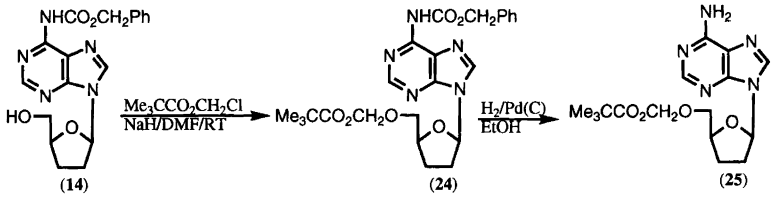
Scheme 7.

which leads to gradual liberation of the hydroxy or amino function. In the alkyl series the enzymatic product is a chemically unstable hemiacetal or -aminal which dissociates to the hydroxy or amino derivative.

Stabilities, partition coefficients and biological activities. Chemical stability of the nucleoside derivatives was investigated in gastrointestinal fluids, simulated by 0.1 M HCl and phosphate buffer at pH 7.4. There was little degradation at pH 7.4 after 24 h. In 0.1 M HCl the half life of ddC, ddA, ddI and their derivatives was less than 30 min, with the exception of slower degradation of long-chain fatty acid derivatives. The degradation was to the parent nucleoside or its degradation products. A gradient HPLC system was used for analyses.

The derivatives of ddC, ddA, ddT, AZT and ddI showed an increased lipophilia compared to their parent drugs in the system 1-octanol/phosphate buffer pH 7.4. The partition coefficients (*P*) are given in Table 1.

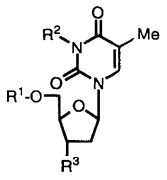
The compounds were submitted to National Cancer



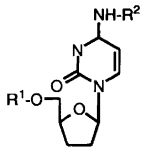
(14) (24) (25)

Scheme 8.

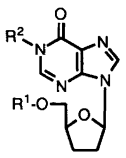
Table 1. Partition coefficients (*P*) in 1-octanol/aqueous buffer pH 7.4 system, and *in vitro* anti-HIV data. ddN = dideoxynucleosides as listed below.



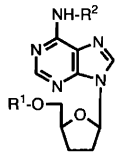
R^3 = H, ddT
R^3 = N_3, AZT



ddC



ddI



ddA

No.	ddN	R^1	R^2	P	IC50 (M)	EC50 (M)
1	ddC	H	H	0.034	$>1.00\times10^{-5}$	6.58×10^{-8}
2a	ddC	H	$PhCH_2OCO$	41.0	$>3.63\times10^{-4}$	3.15×10^{-7}
2b	ddC	H	EtOCO	1.66	$>8.83\times10^{-4}$	2.96×10^{-7}
2c	ddC	EtOCO	EtOCO	19.7	$>1.67\times10^{-4}$	5.68×10^{-5}
3	ddC	EtOCO	$PhCH_2OCO$	—	5.58×10^{-5}	8.61×10^{-6}
4	ddC	EtOCO	H	0.72	1.03×10^{-4}	2.96×10^{-7}
5a	ddT	H	H	0.23	—	—
5b	AZT	H	H	1.21	$>1.00\times10^{-6}$	3.14×10^{-9}
6a	ddT	EtOCO	H	—	$>8.40\times10^{-4}$	5.68×10^{-6}
6b	AZT	EtOCO	H	12.8	4.22×10^{-4}	$<1.70\times10^{-7}$
6c	AZT	$CH_2=CHCH_2OCO$	H	1.21	$>5.00\times10^{-6}$	1.21×10^{-8}
6d	AZT	Et_2NCO	H	26.2	$>4.90\times10^{-4}$	1.95×10^{-4}
6e	AZT	$HO_2CH_2CH_2CO$	H	0.04	$>6.80\times10^{-4}$	1.20×10^{-6}
7	ddI	H	H	0.060	$>2.00\times10^{-5}$	5.73×10^{-6}
8	ddI	EtOCO	H	—	$>5.86\times10^{-4}$	1.56×10^{-5}
9	ddA	H	H	0.52	—	—
10	ddA	EtOCO	H	—	6.93×10^{-4}	3.38×10^{-6}
11	ddA	EtOCO	EtOCO	—	$>6.59\times10^{-4}$	2.77×10^{-4}
16	ddA	$C_{15}H_{31}CO$	H	>1000	$>1.50\times10^{-5}$	6.25×10^{-6}
17a	ddC	$Me_3CCO_2CH_2$	$PhCH_2OCO$	—	1.40×10^{-4}	6.25×10^{-7}
17b	ddC	$Me_3CCO_2CH_2$	EtOCO	—	4.10×10^{-4}	2.95×10^{-9}
18	ddC	$Me_3CCO_2CH_2$	H	8.08	$>7.70\times10^{-6}$	4.00×10^{-8}
21a	ddT	H	$Me_3CCO_2CH_2$	—	$>5.60\times10^{-5}$	—
21b	AZT	H	$Me_3CCO_2CH_2$	—	$>3.40\times10^{-6}$	1.20×10^{-8}
21c	ddT	H	$EtOCO_2(CH)Me$	—	$>7.30\times10^{-4}$	9.30×10^{-6}
21d	AZT	H	$EtOCO_2(CH)Me$	11.0	$>4.70\times10^{-6}$	1.80×10^{-8}
22a	ddT	$Me_3CCO_2CH_2$	H	—	4.93×10^{-4}	2.18×10^{-5}
22b	ddT	$Me_3CCO_2CH_2$	$Me_3CCO_2CH_2$	—	7.35×10^{-5}	—
23a	ddT	EtOCO	$EtOCO_2(CH)Me$	—	$>8.69\times10^{-5}$	7.03×10^{-6}
23b	AZT	EtOCO	$EtOCO_2(CH)Me$	89.9	$>1.50\times10^{-4}$	2.00×10^{-8}
23c	AZT	Et_2NCO	$EtOCO_2(CH)Me$	158.3	$>2.70\times10^{-4}$	2.95×10^{-5}
23d	AZT	$HO_2C(CH_2)_2CO$	$EtOCO_2(CH)Me$	20.6	$>3.70\times10^{-4}$	5.25×10^{-6}
24	ddA	$Me_3CCO_2CH_2$	$PhCH_2OCO$	—	1.40×10^{-4}	6.37×10^{-7}

Institute, NIH, USA, for *in vitro* anti-HIV drug testing. The test system used detects agents acting at any stage of the virus reproductive cycle.[11] The essay basically involves the killing of T4 lymphocytes by HIV. Small amounts of HIV are added to the cells, and a complete cycle of virus reproduction is necessary to obtain the required cell killing. Agents that interact with virions, cells or virus gene-products will protect cells from cytolysis. AZT-treated cells serve as reference in the screens. The data given are approximate values for 50% effective concentration [EC50(M)], 50% inhibitory concentration [IC50(M)] which can be transformed into therapeutic index (TI = IC50/EC50).

Most compounds show high activity in the anti-HIV test system and are somewhat less potent than the parent nucleosides, but the EC50 values indicate a high prodrug-to-drug conversion. The therapeutic index TI > 2120 for 4-cytidinyl ethyl urethane (**2b**) is to be compared with the value > 1500 for the parent nucleoside **1**, the partition coefficients (*P*) being 1.66 and 0.034, respectively. The highest activities are found in the AZT series, which also contains the most active parent nucleoside **5b**. The value TI > 2484 for the 5-ethyl carbonate **6b** is to be compared with TI > 300 for the parent **5b**, with *P*-values 12.8 and 1.21, respectively. TI drops to > 3 in the corresponding *N,N*-dietylurethane **6d**, whereas *P* is increased to 26.2. This may indicate a slower cleavage of the carbamoyl group. A similar effect of the carbamoyl group is seen by comparison of the analogous structures, the carbonate **23b** and the urethane **23c**, which are both *N*3-alkylated. TI drops from > 7500 **23b** to **23c**, while *P* is increased from 89.9 to 158.3. The carbonate **23b** has by far the

highest TI value in the series of compounds which have been tested. A comparison of the effective concentration and the inhibitory concentration for AZT shows EC50 3.14×10^{-9} and IC50 $> 1.00 \times 10^{-6}$ for AZT, and EC50 2.00×10^{-8} and IC50 $> 1.50 \times 10^{-4}$ for the carbonate **23b**, whereas the *P*-values, taken in the same order, are 1.21 and 89.9. However, for a more meaningful prodrug/drug comparison of biological activities, studies need to be carried out using *in vivo* AIDS models. As expected, there is no strict relationship between the *P*-values and the therapeutic index (TI50).

Interpretation of the data is also complicated by the possibility that the target compounds or their metabolites with an unsubstituted 5′-OH group can be converted into phosphate esters by cellular kinases and thus may act as antiviral compounds by themselves.

Experimental

The ^{1}H NMR spectra were recorded at 300 MHz with either a Varian Unity Plus 300, a Varian XL-300 (manual), a Varian XL-300 (automatic) or at 200 MHz with a Varian Gemini 200 instrument. The ^{13}C NMR spectra were recorded at 75 or 50 MHz. Chemical shifts are reported in ppm using $CDCl_3$ (77.00 ppm) or TMS (0.00 ppm) as references in ^{13}C spectra, and residual $CHCl_3$ (7.24 ppm) as reference in ^{1}H spectra. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential, and ammonia, isobutane or methane was used for chemical ionization (CI); the spectra are presented as *m/z* (% rel. int.). Desorption chemical ionization mass spectra are reported as DCI-MS. High-resolution mass spectra are reported as HR-MS. Fast atom bombardment spectra (FAB-MS) were obtained from M-Scan Ltd., Ascot, UK. Dry THF was distilled from sodium and benzophenone. All melting points (m.p.) are uncorrected.

Partition coefficient measurements. 1-Octanol/aqueous phase partition coefficients were determined at ambient temperature using the shake flask procedure. An aliquot (12.5 µl) of a 10^{-2} M solution of the compound in phosphate buffer pH 7.4 was diluted to 2.5 ml with the phosphate buffer, previously saturated with 1-octanol. An equal volume of 1-octanol, previously saturated with the phosphate buffer, was added to give a total volume of 5 ml. The mixture was shaken vigorously for 30 min, and the contents were allowed to stand for 15 min. The two phases were separated and centrifuged at 1000*g* for 5 min. The UV absorbance of both phases were measured at 350 and 271 nm for the side-chain derivative or parent drug, respectively. The partition coefficients were calculated from the ratio of the absorbance between the 1-octanol and the aqueous phases. All *P* values in Table 1 are mean values of three determinations.

Chemical stability tests. The nucleoside (30 γg/ml) was dissolved in 0.1 M HCl and in phosphate buffer at pH 7.4, and the samples were incubated at 37 °C. Samples were withdrawn after 3, 6 and 24 h. Gradient HPLC was used for analysis using a HP 1090 system with a diode-array detector on a column (250 × 4 mm) of Lichrosper 60 RP8 Select B (5 µm). The mobile phase was 0.05 M aq. NaH2PO4 (A) and MeCN (B). Gradients: 3% (B) (0–5 min); linear increase to 60% (B) (5–30 min); linear increase to 75% (B) (35–59 min). The flow rate was 1.2 ml min^{-1}, temp. 45 °C. UV detection was at 220 nm.

Anti-HIV activity. The compounds were submitted to National Cancer Institute, NIH for *in vitro* and anti-HIV drug testing according to the protocol described.[10] The test system used detects agents acting at any stage of the virus reproductive cycle. The activity data are given in Table 1.

N^4-*Benzyloxycarbonyl-2′,3′-dideoxycytidine* (**2a**). 2′,3′-Dideoxycytidine (1.44 g, 6.84 mmol) and DMAP (1.00 g, 8.21 mmol) were dissolved in dry DMF (40 ml) and pyridine (20 ml). Benzyl chloroformate (1.20 ml, 8.46 mmol) was added at 0 °C. The mixture was left at ambient temperature for 18 h under an atmosphere of dry nitrogen. The solvents were removed at reduced pressure and the residue was dissolved in chloroform (50 ml), and water (30 ml) was added. The aqueous layer was extracted with chloroform (2 × 50 ml). The combined chloroform layers were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography using chloroform/diethyl ether/ethanol (5:4:1) as eluent. Yield 1.76 g (74%); glassy material. Anal. $C_{17}H_{19}N_3O_5$: C, H. ^{1}H NMR (300 MHz): δ 1.82–1.98 (m, 2H), 2.10–2.22 (m, 1H), 2.42–2.59 (m, 1H), 3.05 (b, 1H, OH), 3.76 and 3.80 (ABX, 2H, H-5′), 4.24 (m, 1H, H-4′), 5.17 (s, 2H, CH2), 6.06 (dd, 1H, H-1′), 7.24 (d, *J* 7.6 Hz) 1H, H-5), 7.32 (5H, Ph), 7.93 (b, 1H, NH), 8.50 (d, *J* 7.6 Hz, 1H, H-6). ^{13}C NMR (75 MHz): δ 24.10, 33.37, 62.93, 67.85, 82.72, 88.19, 94.26, 128.33, 128.44, 128.64, 134.94, 145.01, 152.28, 155.23, 162.11. MS(CI, isobutane): 108 (19), 107 (21), 101 (47), 93 (10), 92 (100), 83 (13).

2′,3′-Dideoxy-N^4-*ethyloxycarbonylcytidine* (**2b**). 2′,3′-Dideoxycytidine (774 mg, 3.37 mmol) was dissolved in methanol (250 ml), and the mixture was heated to reflux. Diethyl pyrocarbonate was added portionwise every hour for 4 h [4 × (1.00 ml, 6.91 mmol)]. The solvent was removed at reduced pressure, and the product was purified by flash chromatography using chloroform/diethyl ether/ethanol (5:4:1) as eluent. Yield 875 mg (92%); white solid. M.p. 90–92 °C. Anal. $C_{12}H_{17}N_3O_5$: C, H. ^{1}H NMR (200 MHz): δ 1.29 (t, *J* 7 Hz, 3H, CH3), 1.85–2.55 (m, 4H, H-3′, H-2′), 3.72–4.02 (ABX, 2H, H-5′), 4.20 (q, *J* 7 Hz, 2H, CH_2), 4.22 (m, 1H, H-4′), 6.04, 6.06 (dd, *J* 2 Hz, 4 Hz, 1H, H-1′), 7.19 (d, *J* 6 Hz, 1H, H-5), 7.79 (bs, 1H, NH), 8.36 (d, *J* 6 Hz, 1H, H-6). ^{13}C NMR (50 MHz): δ 14.22, 24.16, 33.39, 62.27, 62.86, 82.81, 88.14, 94.29, 144.92, 152.43, 162.23, 170.72. MS(EI):

283 (2.3, M^+), 138 (31), 137 (51), 111 (36), 109 (39), 101 (27), 100 (33), 95 (16), 83 (14), 81 (12). HR-MS: mol. wt. obs.: 283.1163. Calc. for $C_{12}H_{17}N_3O_5$: 283.1168.

5'-O, N^4-Bis(ethoxycarbonyl)-2',3'-dideoxycytidine (**2c**). 2',3'-Dideoxycytidine (105 mg, 0.50 mmol) and DMAP (360 mg, 2.95 mmol) were dissolved in pyridine (20 ml). Diethyl pyrocarbonate (2.00 ml, 13.8 mmol) was added dropwise to the solution at 0 °C. The mixture was left at ambient temperature, under dry nitrogen for 18 h. Pyridine was removed at reduced pressure, and the product was purified by flash chromatography using chloroform/diethyl ether/ethanol (5:4:1) as eluent. Yield 136 mg (77%); colourless crystals. M.p. 121–123 °C. Anal. found: $C_{15}H_{21}N_3O_7$: C, H. ^{1}H NMR (200 MHz): δ 1.29 (t, *J* 7 Hz, 3H, CH3), 1.31 (t, *J* 7 Hz, 3H, CH3), 1.68–2.62 (m, 4H, H-3', H-2'), 4.16–4.48 (m, 7H, 2 × CH_2, H-4', H-5'), 6.04 (dd, *J* 3.8 Hz, 1H, H-1'), 7.19 (d, *J* 8 Hz, 1H, H-5), 8.14 (d, *J* 8 Hz, 1H, H-6). ^{13}C NMR (50 MHz): δ 14.36, 25.01, 33.29, 62.43, 62.52, 64.59, 67.52, 79.59, 88.14, 94.22, 144.04, 155.05, 162.28. FAB-MS: 378 (M^+ + Na), 356 (M + H).

N^4-Benzyloxycarbonyl-2',3'-dideoxy-5'-O-ethoxycarbonylcytidine (**3**). N^4-Benzyloxycarbonyl-2',3'-dideoxycytidine (1.33 g, 3.86 mmol) and DMAP (737 mg, 6.04 mmol) were dissolved in pyridine (50 ml). Diethyl pyrocarbonate (1.00 ml, 6.91 mmol) was added dropwise at 0 °C. The solvent was evaporated after stirring for 2 h at ambient temperature under dry nitrogen, and the product was purified by flash chromatography using chloroform/diethyl ether/ethanol (5:4:1) as eluent. Yield 1.51 g (94%); colourless oil. Anal. $C_{20}H_{23}N_3O_7$: C, H. ^{1}H NMR (200 MHz): δ 1.29 (t, *J* 7 Hz, 3H, CH_3), 1.77–2.54 (m, 4H, H-2', H-3'), 4.20–4.41 (m, 3H, H-4', H-5'), 4.17 (q, *J* 7 Hz, 2H, CH_2), 5.13 (s, 2H, CH_2), 6.00 (dd, *J* 2.5, 3.9, 1H, H-1'), 7.17–7.33 (m, 6H, Ph, H-5), 8.11 (d, *J* 7 Hz, 1H, H-6), 8.20 (bs, 1H, NH). ^{13}C NMR (50 MHz): δ 13.89, 25.53, 32.87, 64.28, 67.27, 67.55, 79.39, 85.88, 94.19, 128.23, 128.52, 128.59, 135.13, 144.06, 155.03, 162.43.

2',3'-Dideoxy-5'-O-ethoxycarbonylcytidine (**4**). N^4-Benzyloxycarbonyl-2', 3'-dideoxy-5'-*O*-ethoxycarbonylcytidine (1.51 g, 3.62 mmol) was dissolved in dry ethanol (150 ml) and palladium on charcoal (190 mg, 10%) was added. Hydrogen gas was bubbled slowly through the solution for 1 h, the ethanol was evaporated and the product was purified by flash chromatography using chloroform/ethanol (99:1) and (9:1) as eluents. Yield 660 mg (65%); glassy material. Anal. $C_{12}H_{17}N_3O_5$: C, H. ^{1}H NMR (300 MHz): δ 1.33 (t, *J* 7 Hz, 3H, CH_3), 1.65–1.85 (m, 1H), 1.90–2.18 (m, 1H), 2.40–2.55 (m, 1H), 4.23 (q, *J* 7 Hz, 2H, CH_2), 4.28–4.43 (m, 3H, H4', H5'), 5.74 (d, *J* 7.4 Hz, 1H, H-5), 6.07 (dd, 1H, H-1'), 7.78 (d, *J* 7.4 Hz, 1H, H-6). ^{13}C NMR (75 MHz): δ 14.24, 25.31, 32.99, 64.39, 67.90, 78.68, 87.36, 93.54, 140.90, 154.99, 155.87, 165.63.

3'-Deoxy-5'-O-ethoxycarbonylthymidine (**6a**). 3'-Deoxythymidine (70 mg, 0.31 mmol) and DMAP (43 mg, 0.35 mmol) were dissolved in pyridine (4 ml) under dry nitrogen. The solution was cooled to 0 °C, and diethyl pyrocarbonate (0.20 ml, 1.38 mmol) was added. The solvent was evaporated after being stirred for 3 h at ambient temperature. Toluene (2 × 10 ml) was added and distilled off. The product was purified by chromatotron chromatography using chloroform/diethyl ether/ethanol (5:4:1) as eluent. Yield 84 mg (91%); off-white solid. M.p. 90–92 °C. ^{1}H NMR (200 MHz): δ 1.33 (t, *J* 7.0 Hz, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.89–2.47 (m, 4H, H-2', H-3'), 4.19–4.49 (m, 5H, CH_2, H-4', H-5'), 6.13 (m, 1H, H-1'), 7.57 (d, *J* 1.2 Hz, 1H, H-6), 8.43 (s, 1H, NH). ^{13}C NMR (50 MHz): δ 12.19, 13.99, 25.09, 32.29, 64.41, 67.50, 78.24, 85.88, 110.61, 135.81, 150.70, 155.08, 164.35. FAB-MS: 299 (M+H).

3'-Azido-3'-deoxy-5'-O-ethoxycarbonylthymidine (**6b**). 3'-Azido-3'-deoxythymidine (321 mg, 1.20 mmol) and DMAP (217 mg, 1.78 mmol) were dissolved in pyridine (10 ml). Diethyl pyrocarbonate (1.00 ml, 6.91 mmol) was added at 0 °C, and the mixture was left at ambient temperature under dry nitrogen for 1 h. The pyridine was removed at reduced pressure, and the product was purified by flash chromatography using chloroform/ethanol (9:1) as eluent. Yield 400 mg (98%); white foamy product. Anal. $C_{13}H_{17}N_5O_6$: C, H. ^{1}H NMR (200 MHz): δ 1.32 (t, *J* 7 Hz, 3H, CH_3), 1.93 (s, 3H, CH_3), 2.41 (m, 2H, H-2'), 4.07 (m, 1H, H3'), 4.24 (q, *J* 7 Hz, 2H, CH_2), 4.19–4.42 (m, 3H, H-5', H-4'), 6.24 (t, *J* 6 Hz, 1H, H-1'), 7.40 (d, *J* 1 Hz, 1H, H-6), 9.15 (s, 1H, NH). ^{13}C NMR (50 MHz): δ 12.48, 14.25, 37.78, 60.02, 64.80, 66.12, 81.59, 84.94, 111.43, 135.26, 150.32, 154.62, 163.78.

5'-O-Allyloxycarbonyl-3'-azido-3'-deoxythymidine (**6c**). 3'-Azido-3'-deoxythymidine (973 mg, 3.64 mmol) was dissolved in DMF (20 ml). The solution was cooled to 0 °C and sodium hydride [324 mg, 8.10 mmol (60–65% in oil)] was added under dry nitrogen. The suspension was stirred vigorously for 30 min while allyl chloroformate (0.42 ml, 4.00 mmol) was added dropwise. After 2 h at ambient temperature, the reaction was stopped by adding a saturated solution of ammonium chloride (20 ml). The solvents were evaporated at reduced pressure, and the residue was purified by flash chromatography using chloroform/diethyl ether (1:1) as eluent. Yield 890 mg (69%); yellowish oil. ^{1}H NMR (200 MHz): δ 1.92 (s, 3H, CH_3), 2.37–2.48 (m, 2H, H-2'), 4.05–4.10 (m, 1H, H-3'), 4.24–4.51 (m, 3H, H-4' and H-5'), 4.66 (d, *J* 5.9 Hz, 2H, CH_2), 5.29–5.43 (m, 2H, CH_2), 5.85–6.02 (m, 1H, CH), 6.24 (t, *J* 6.3 Hz, 1H, H-1'), 7.38 (d, *J* 1.2 Hz, 1H, H-6), 9.27 (s, 1H, N-H). ^{13}C NMR (50 MHz): δ 12.26, 37.47, 59.87, 66.22, 69.06, 81.51, 84.84, 111.46, 119.87, 131.03, 136.36, 150.55, 154.57, 164.15. MS(EI): 351 (4, M^+), 226 (9), 127 (17), 126 (100), 95 (65).

3'-Azido-3'-deoxy-5'-O-*diethylcarbamoylthymidine* (**6d**). 3'-Azido-3'-deoxythymidine (1.00 g, 3.75 mmol) was dissolved in DMF (7 ml) under dry nitrogen. The solution was cooled to 0 °C and sodium hydride (327 mg, 7.50 mmol (55% in oil) added. Diethylcarbamoyl chloride (0.50 ml, 3.75 mmol) was added to the reaction mixture after 10 min and a saturated solution of ammonium chloride (20 ml) after 36 h at ambient temperature. The solvents were removed at reduced pressure, and the product was purified by chromatotron chromatography using chloroform/diethyl ether (1:1) as eluent. Yield 1.32 g (95%); pale yellow oil. Anal. $C_{15}H_{22}N_6O_5$: C, H. ^{1}H NMR (300 MHz): δ 1.14 (t, *J* 7 Hz, 6H, $2\times CH_3$), 1.92 (d, *J* 1 Hz, 3H, CH_3), 2.21–2.50 (m, 2H, H-2'), 3.30 (m, 4H, $2\times CH_2$), 4.12–4.37 (m, 4H, H-3', H-4', H-5'), 6.14 (t, *J* 7 Hz, 1H, H-1'), 7.24 (d, *J* 1 Hz, 1H, H-6), 9.18 (s, 1H, NH). ^{13}C NMR (75 MHz): δ 12.57, 13.40, 14.15, 37.58, 41.33, 42.15, 61.02, 64.22, 82.28, 85.29, 111.30, 134.96, 150.13, 155.14, 163.68. MS(EI): 366 (0.8, M^+), 198 (41), 126 (60), 102 (12), 100 (37), 96 (25), 95 (39), 81 (100).

3'-Azido-3'-deoxy-5'-O-*hemisuccinylthymidine* (**6e**). 3'-Azido-3'-deoxythymidine (757 mg, 2.84 mmol) and succinic anhydride (677 mg, 6.77 mmol) were dissolved in pyridine (15 ml). The solution was stirred under dry nitrogen for 30 h at ambient temperature. Then the solvent was evaporated. The residue was purified by flash chromatography using chloroform/diethyl diethyl ether/ethanol (5:4:1) as eluent. Yield 716 mg (69%); off-white crystals. Anal. $C_{14}H_{17}N_5O_7$: C, H.^{1}H NMR (200 MHz: δ 1.95 (s, 3H, CH_3), 2.35–2.90 (m, 6H, $2\times CH_2$, H-2'), 4.09–4.85 (m, 4H, H-3', H-4', H-5'), 5.90 (m, 1H, H-1'), 7.43 (d, *J* 1Hz, 1H, H-6), 10.62 (s, 1H, NH). ^{13}C NMR (50 MHz): δ 12.38, 28.67, 28.91, 37.97, 60.13, 63.03, 82.80, 85.72, 109.52, 137.44, 149.05, 166.30, 172.60, 177.66. MS(EI): 367 (32, M^+), 310 (9), 268 (12), 267 (55), 243 (19), 242 (100), 239 (11), 158 (69).

2',3'-Dideoxy-5'-O-*ethoxycarbonylinosine* (**8**). A solution of 2',3'-dideoxyinosine (255 mg, 1.08 mmol) and DMAP (315 mg, 2.58 mmol) in pyridine (5 ml) and DMF (2 ml) was cooled to 0 °C, and diethyl pyrocarbonate (0.60 ml, 4.15 mmol) was added dropwise. Solvents were evaporated at reduced pressure after 18 h at ambient temperature under dry nitrogen. The residue was purified by flash chromatography using chloroform/ethanol (9:1) as eluent. Yield 253 mg (76%); colourless oil. ^{1}H NMR (200 MHz): δ 1.24 (t, *J* 7 Hz, 3H, CH_3), 2.14 (m, 2H, H-3'), 2.50 (m, 2H, H-2'), 4.14 (q, *J* 7 Hz, 2H, CH_2), 4.15–4.40 (m, 3H, H-4', H-5'), 6.26 (m, 1H, H-1'), 8.07 (s, 1H, H-2 or H-8), 8.28 (s, 1H, H-2 or H-8). ^{13}C NMR (50 MHz): δ 13.92, 25.88, 32.49, 64.30, 68.01, 78.93, 85.57, 125.05, 138.44, 145.46, 148.43, 155.09, 159.25. MS(EI): 308 (12, M^+), 205 (14), 173 (42), 137 (93), 136 (91), 83 (100). HR-MS: mol. wt. obs.: 308.1117. Calc. for $C_{13}H_{16}N_4O_5$: 308.1121.

2',3'-Dideoxy-5'-O-*ethoxycarbonyladenosine* (**10**). A mixture of 2',3'-dideoxyadenosine (300 mg, 1.28 mmol) and DMAP (160 mg, 1.28 mmol) in dry pyridine (5 ml) and dry DMF (5 ml) was cooled to 0 °C, and diethyl pyrocarbonate (0.28 ml, 1.92 mmol) was added dropwise. The resulting mixture was stirred for 21 h at ambient temperature. The solvents were removed at reduced pressure, and the crude product purified by flash chromatography using chloroform/ethanol (6:1) as eluent. Yield 160 mg (49%); white solid. M.p. 121 °C. ^{1}H NMR (200 MHz): δ 1.29 (t, *J* 7 Hz, 3H, CH_3), 2.16 (m, 2H, H-3'), 2.56 (m, 2H, H-2'), 4.19 (q, *J* 7 Hz, 2H, CH_2), 4.39 (m, 3H, H-5', H-4'), 6.31 (m, 3H, H-1', NH_2), 8.13 (s, 1H, H-2 or H-8), 8.32 (s, 1H, H-2 or H-8). ^{13}C NMR (50 MHz): δ 14.20, 26.01, 32.57, 64.36, 68.15, 78.84, 85.57, 120.00, 138.90, 149.15, 152.32, 154.94, 155.32. MS(EI): 307 (8, M^+), 218 (14), 217 (25), 136 (75), 135 (100), 108 (26), 83 (64), 82 (54). HR-MS: mol. wt. obs.: 307.1277. Calc. for $C_{13}H_{17}N_5O_4$: 307.1281.

N^6-*5*-O-*Bis(ethoxycarbonyl)-2',3'-dideoxyadenosine* (**11**). Ethyl chloroformate (0.14 ml, 1.50 mmol) in dichloromethane (3 ml) was cooled to 0 °C and 1-methylimidazole (0.12 ml, 1.50 mmol) was added. The mixture was kept at ambient temperature for 45 min and then cooled to 0 °C. 2',3'-dideoxy-5'-*O*-ethoxycarbonyladenosine (233 mg, 0.76 mmol) in dichloromethane (5 ml) was added dropwise. The solvents were removed at reduced pressure and the residue purified by flash chromatography using chloroform/ethanol (9:1) as eluent. Yield 193 mg (68%); colourless oil. ^{1}H NMR (200 MHz): δ 1.29 (t, *J* 7 Hz, 3H, CH_3), 1.34 (t, *J* 7 Hz, 3H, CH_3), 2.18 (m, 2H, H-3'), 2.58 (m, 2H, H-2'), 4.14–4.46 (m, 7H, H-5', H-4', $2\times CH_2$), 6.37 (m, 1H, H-1'), 8.32 (s, 1H, H-2 or H-8), 8.74 (s, 1H, H-2 or H-8). ^{13}C NMR (50 MHz): δ 14.19, 14.33, 25.91, 32.63, 62.11, 64.41, 68.01, 79.10, 85.84, 122.18, 141.00, 149.42, 150.50, 151.13, 152.63, 154.92. MS(EI): 379 (15, M^+), 334 (21), 333 (100), 307 (10), 306 (22), 290 (22), 289 (34), 279 (48). HR-MS: mol. wt. obs.: 379.1493. Calc. for $C_{16}H_{21}N_5O_6$, 379.1492.

2',3'-Dideoxy-5'-O-thexyldimethylsilyladenosine (**12**). 2',3'-Dideoxyadenosine (2.67 g, 11.37 mmol) and imidazole (2.36 g, 34.71 mmol) in pyridine (50 ml) were cooled to 0 °C and thexyldimethylsilyl chloride (2.50 ml, 12.75 mmol) was added dropwise. After 6 h at ambient temperature, the solvent was evaporated, and the silylated product isolated by flash chromatography using chloroform/diethyl ether/ethanol (5:4:1) as eluent. Yield 4.29 g (100%); white solid.

N^6-*Benzyloxycarbonyl-2',3'-dideoxy-5'*-O-*thexyldimethylsilyladenosine* (**13**). 1-Methylimidazole (1.20 ml, 15.06 mmol) and benzyl chloroformate (2.00 ml, 14.19 mmol) were added to a solution of 2',3'-dideoxy-5'-*O*-thexyldimethylsilyladenosine (1.67 g, 4.42 mmol) in dry dichloromethane (100 ml) at 0 °C. The mixture was

stirred overnight at ambient temperature, the solvent removed and the crude acylated product purified by flash chromatography using chloroform/diethyl ether (1:1) and chloroform/diethyl ether/ethanol (5:4:1) as eluents. Yield 1.40 g (62%); slightly yellow oil.

N^6-*Benzyloxycarbonyl-2',3'-dideoxyadenosine* (**14**). N^6-Benzyloxycarbonyl-2',3'-dideoxy-5'-*O*-thexyldimethylsilyladenosine (1.57 g, 3.15 mmol) in dry THF (50 ml) was cooled to 0 °C, and a solution of tetrabutylammonium fluoride in THF (15.00 ml, 3.75 mmol) was added dropwise. Saturated ammonium chloride solution (20 ml) was added after 30 min at ambient temperature. The aqueous phase was washed with chloroform (2 × 50 ml). The combined organic phases were dried ($MgSO_4$) and concentrated, and the product was purified by chromatotron chromatography using chloroform and chloroform/diethyl ether/ethanol (5:4:1) as eluents. Yield 0.61 g (52%); colourless foamy oil. ^{1}H NMR (200 MHz): δ: 2.05–2.55 (m, 4H, H-3', H-2'), 3.81 (ABX, 2H, H-5'), 4.26 (m, 1H, H-4'), 5.24 (s, 2H, CH2), 6.10 (t, *J* 6 Hz, 1H, H-1'), 8.16 (s, 1H, H-8 or H-2), 8.67 (s, 1H, H-8 or H-2). ^{13}C NMR (50 MHz): δ 26.02, 32.99, 63.94, 67.61, 81.91, 86.62, 121.99, 127.67, 127.71, 127.76, 134.70, 141.03, 148.79, 149.33, 150.23, 151.34.

N^6-*Benzyloxycarbonyl-2',3'-dideoxy-5'*-O-*palmitoyladenosine* (**15**). Palmitoyl chloride (0.75 ml, 2.40 mmol) was added to a solution of N^6-benzyloxycarbonyl-2',3'-dideoxyadenosine (247 mg, 0.67 mmol) and DMAP (296 mg, 2.43 mmol) in dry pyridine (50 ml) at 0 °C. The solvent was evaporated after 4 h at ambient temperature, and the N^6-protected nucleoside purified by flash chromatography using chloroform/diethyl ether (1:1) as eluent. Yield 287 mg (70%); colourless oil.

2',3'-Dideoxy-5'-O-*palmitoyladenosine* (**16**). *(A) By hydrogenolysis of* (**15**). N^6-Benzyloxycarbonyl-2',3'-dideoxy-5'-*O*-palmitoyladenosine (287 mg, 0.47 mmol) and palladium on charcoal (30 mg, 10%) in dry ethanol (50 ml) were kept under an atmosphere of hydrogen (1 atm) for 48 h. The solvent was removed and the crude, deprotected product was purified by flash chromatography using chloroform/ethanol (4:1) as eluent. Yield 94 mg (42%), white waxy material. ^{1}H NMR (200 MHz): δ 0.87 (t, *J* 7 Hz, 3H, CH_3), 1.23 (m, 26H, 13 × CH_2), 2.14 (m, 2H, H-3'), 2.33 (t, *J* 7 Hz, 2H, $CH_2C{=}O$), 2.59 (m, 2H, H-2'), 4.31–4.44 (m, 3H, H-4', H-5'), 6.24 (s, 2H, NH_2), 6.30 (m, 1H, H-1'), 8.13 (s, 1H, H-2 or H-8), 8.34 (s, 1H, H-2 or H-8). ^{13}C NMR (50 MHz): δ 14.09, 22.66, 24.83, 26.03, 29.08, 29.22, 29.22, 29.32, 29.42, 29.56, 29.62, 29.65, 31.89, 32.65, 34.06, 64.84, 79.38, 85.81, 120.09, 139.00, 149.05, 151.96, 155.07, 173.53.

(B). By direct acylation. 2',3'-Dideoxyadenosine (100 mg, 0.43 mmol) and DMAP (52 mg, 0.43 mmol) were dissolved in dry pyridine (5 ml) and dry DMF (5 ml). Palmitoyl chloride (130 µl, 0.43 mmol) was added dropwise at ambient temperature under nitrogen and the mixture was stirred at ambient temperature for 18 h. The solvents were removed at reduced pressure and the product isolated from the residue by flash chromatography using chloroform/diethyl ether/ethanol (5:4:1) as eluent. 2',3'-Dideoxy-5'-*O*,N^6-bis(palmitoyl)adenosine was first eluated. Yield 30 mg (10%); colourless oil. ^{1}H NMR (300 MHz): δ 0.85 (t, *J* 7 Hz, 6H, 2 × CH_3), 1.23 (bs, 52H, 26 × CH_2), 2.14 (m, 2H, H-3'), 2.29 (t, *J* 7 Hz, 2H, $CH_2C{=}O$), 2.59 (m, 2H, H-2'), 2.83 (t, *J* 7 Hz, 2H, $CH_2C{=}O$), 4.29–4.42 (m, 3H, H-5', H-4'), 6.32 (m, 1H, H-1'), 8.23 (s, 1H, H-2 or H-8), 8.66 (s, 1H, H-2 or H-8), 8.70 (s, 1H, NH). ^{13}C NMR (75 MHz): δ 14.09, 22.67, 24.84, 24.92, 25.98, 29.09, 29.25, 29.34, 29.41, 29.43, 29.48, 29.58, 29.63, 29.67, 31.90, 32.64, 34.06, 37.90, 64.73, 79.59, 86.04, 122.26, 140.98, 149.21, 150.48, 152.34, 172.85, 173.49.

The second component eluated from the column was 2',3'-dideoxy-5'-*O*-palmitoyladenosine. Yield 123 mg (61%); white waxy material.

N^4-*Benzyloxycarbonyl-2',3'-dideoxy-5'*-O-*pivaloyloxymethylcytidine* (**17a**). N^4-Benzyl-oxycarbonyl-2',3'-dideoxycytidine (500 mg, 1.50 mmol) was dissolved in DMF (30 ml). The solution was cooled to −40 °C and sodium hydride (150 mg, 3.75 mmol [60–65% in oil)] was added under dry nitrogen. The suspension was stirred vigorously at ambient temperature and cooled to −20 °C before addition of chloromethyl pivalate (0.24 ml, 1.67 mmol). The resulting mixture was left at ambient temperature for 18 h under an atmosphere of dry nitrogen. A saturated solution of ammonium chloride (20 ml) was added, and the mixture was extracted with chloroform (3 × 50 ml) and the organic layers dried ($MgSO_4$). After evaporation of the solvents, the residue was purified using flash chromatography with chloroform/diethyl ether/ethanol (10:9:1) as eluent. Yield 241 mg (36%); pale yellow oil. Anal. $C_{23}H_{29}N_3O_7$: C, H. ^{1}H NMR (200 MHz): δ 1.19 (s, 9H, 3 × CH_3), 1.82–2.50 (m, 4H, H-3', H-2'), 3.67–4.07 (ABX, 2H, H-5'), 4.19–4.38 (m, 1H, H-4'), 5.16 (s, 2H, CH_2), 5.24 and 5.36 (AB, 2H, CH_2), 6.00–6.04 (dd, *J* 2 Hz, *J* 4 Hz, 1H, H-1'), 7.16 (d, *J* 8 Hz, 1H, H-5), 7.24–7.35 (m, 5H, Ph), 7.94 (bs, 1H, NH), 8.23 (d, *J* 8 Hz, 1H, H-6). ^{13}C NMR (50 MHz): δ 24.83, 27.40, 33.73, 39.16, 67.65, 69.60, 80.39, 87.53, 88.25, 93.82, 126.12, 126.48, 127.48, 127.72, 127.83, 134.40, 143.56, 161.14, 176.49. MS(CI, NH3): 185 (13), 124 (10), 121 (14), 108 (14), 107 (12), 106 (100), 105 (19), 101 (17), 94 (11).

2',3'-Dideoxy-N^4-*ethoxycarbonyl-5'*-O-*pivaloyloxymethylcytidine* (**17b**). 2',3'-Dideoxy-N^4-ethoxycarbonylcytidine (776 mg, 2.71 mmol) was dissolved in DMF (20 ml). The solution was cooled to −50 °C and sodium hydride [280 mg, 7.58 mmol (60−65% in oil)] was added under dry nitrogen. Chloromethyl pivalate (0.45 ml, 3.14 mmol) was added after 30 min of vigorous stirring at 0 °C. The reaction mixture was left at ambient temperature for another 30 min. A saturated solution of ammo-

nium chloride (100 ml) was added. The mixture was extracted with chloroform (3 × 150 ml), and the combined chloroform layers were dried ($MgSO_4$). The solvents were evaporated and the product was purified by flash chromatography using chloroform/diethyl ether/ethanol (5:4:1) as eluent. Yield 629 mg (58%); yellow oil. ^{1}H NMR (200 MHz): δ 1.22 (s, 9H, 3 × CH_3), 1.31 (t, *J* 7 Hz, 3H, CH_3), 1.82–2.52 (m, 4H, H-3′, H-2′), 3.69–4.11 (ABX, 2H, H-5′), 4.23 (AB, 2H, CH_2), 4.18–4.37 (m, 1H, H-4′), 5.32 and 5.40 (AB, 2H, CH_2), 6.04–6.08 (dd, *J* 2 Hz, 4Hz, 1H, H-1′), 7.20 (d, *J* 7 Hz, 1H, H-5), 7.65 (b, NH), 8.26 (d, *J* 7 Hz, 1H, H-6). ^{13}C NMR (75 MHz): δ 14.20, 24.24, 26.95, 33.43, 38.87, 62.23, 69.51, 80.60, 87.80, 88.42, 94.08, 144.50, 152.34, 155.10, 162.16, 177.82. MS(EI): 397 (0.2, M^+), 215 (3), 185 (28), 184 (15), 138 (25), 137 (19), 134 (24), 113 (26), 112 (21), 85 (18). HR-MS: mol. wt. obs.: 397.1841. Calc. for $C_{18}H_{27}N_3O_7$: 397.1849.

*2′,3′-Dideoxy-5′-*O*-pivaloyloxymethylcytidine* (**18**). N^4-Benzyloxycarbonyl-2′,3′-dideoxy-5′-*O*-pivaloyloxymethylcytidine (525 mg, 1.14 mmol) was dissolved in dry ethanol (50 ml). Palladium on charcoal (162 mg, 10%) was added and the hydrogenolysis was carried out at ambient temperature at 1 atm for 10 min. The product was purified by flash chromatography, using chloroform/ethanol (9:1) as eluent. Yield 313 mg (84%); white solid. M.p. 172 °C. Anal. $C_{15}H_{23}N_3O_5$: C, H. ^{1}H NMR (200 MHz): δ 1.23 (s, 9H, 3 × CH_3), 1.90–2.60 (m, 4H, H-3′, H-2′), 3.68–4.10 (ABX, 2H, H-5′), 4.10–4.35 (m, 1H, H-4′), 5.20, 5.45 (dd, *J* 6Hz, 43 Hz, 2H, CH_2), 5.72 (d, *J* 7 Hz, 1H, H-5), 6.08 (m, 1H, H-1′), 7.91 (d, *J* 7 Hz, 1H, H-6). ^{13}C NMR (50 MHz): δ 24.92, 26.80, 32.89, 38.69, 70.16, 79.37, 86.66, 88.43, 94.27, 140.44, 155.98, 165.94, 177.69. MS(CI, NH_3): 232 (5.3, $M^+ + 1$), 136 (3.8), 130 (4), 119 (20), 118 (14), 112 (17), 102 (25), 101 (65), 100 (47).

*3′-Deoxy-5′-*O*-thexyldimethylsilylthymidine* (**19a**). 3′-Deoxythymidine (818 mg, 3.62 mmol) and imidazole (598 mg, 8.79 mmol) were dissolved in DMF (30 ml). The solution was cooled to 0 °C, the xyldimethylsilyl chloride (0.72 g, 3.67 mmol) was added dropwise, and the reaction mixture was stirred for 4 h at ambient temperature. DMF was removed at redced pressure. The product was purified by flash chromatography using chloroform/diethyl ether/ethanol (5:4:1) as eluent. Yield 1.17 g (88%); white solid. M.p. 109–110 °C. ^{1}H NMR (200 MHz): δ 0.14 (s, 6H, 2 × CH_3Si), 0.87 (s, 12H, 4 × CH_3), 1.65 (hept, 1H, CH), 1.92 (d, *J* 1.0 Hz, 3H, CH_3), 1.92–2.41 (m, 4H, H-2′, H-3′), 3.86 (ABX, 2H, H-5′), 4.14 (m, 1H, H-4′), 6.06 (m, 1H, H-1′), 7.52 (d, 1.2 Hz, 1H, H-6), 8.85 (s, 1H, NH). ^{13}C-NMR (75 MHz): δ −3.44, −3.36, 12.53, 18.37, 18.48, 20.18, 20.38, 25.38, 25.44, 32.37, 33.97, 64.30, 80.83, 85.74, 110.21, 135.59, 150.28, 163.80.

*3′-Azido-3′-deoxy-5′-*O*-thexyldimethylsilylthymidine* (**19b**). 3′-Azido-3′-deoxythymidine (1.02 g, 3.80 mmol) and imidazole (0.71 g, 10.49 mmol) were dissolved in DMF (10 ml). The solution was cooled to 0 °C and thexyldimethylsilyl chloride (0.82 ml, 4.18 mmol) added. The solvent was removed at reduced pressure after 2 h under nitrogen at ambient temperature. The residue was purified by flash chromatography using chloroform/ethanol (9:1) as eluent. Yield 1.49 g (96%); white solid. ^{1}H NMR (300 MHz): δ 0.17 (2 × s, 6H, 2 × CH_3Si), 0.88 (m, 12H, 4 × CH_3), 1.65 (hept, *J* 7 Hz, 1H, CH), 1.94 (d, *J* 1 Hz, 3H, CH_3), 2.14–2.44 (m, 2H, H-2′), 3.71–4.21 (m, 4H, H-3′, H-4′, H-5′), 6.21 (t, *J* 7 Hz, 1H, H-1′), 7.39 (d, *J* 1 Hz, 1H, H-6), 8.99 (s, 1H, NH). ^{13}C NMR (75 MHz): δ −3.50, −3.29, 12.55, 18.46, 18.53, 20.27, 20.40, 25.15, 34.03, 37.87, 60.44, 62.64, 84.38, 84.45, 111.09, 134.93, 150.20, 163.80.

*3′-Deoxy-3-pivaloyloxymetyl-5′-*O*-thexyldimethylsilylthymidine* (**20a**). 3′-Deoxy-5′-*O*-thexyldimethylsilylthymidine (196 mg, 0.54 mmol) was dissolved in DMF (5 ml). Dry potassium carbonate (123 mg, 0.89 mmol) was added, and the suspension was stirred at ambient temperature under dry nitrogen for 45 min. The mixture was cooled to 0 °C and chloromethyl pivalate (0.10 ml, 0.70 mmol) was added dropwise. The solvent was evaporated at reduced pressure after 16 h at ambient temperature, and the product was purified on chromatotron chromatography using hexane/ethyl acetate (2:1) as an eluent. Yield 213 mg (83%); colourless oil. ^{1}H NMR (200 MHz): δ 0.12 (s, 6H, CH_3-Si), 0.88 (s, 12H, 4 × CH_3), 1.18 (s, 9H, 3 × CH_3), 1.65 (m, 1H, $(CH_3)2CH$), 1.95 (s, 3H, CH_3), 1.97–2.40 (m, 4H, H-2′, H-3′), 3.85 (ABX, 2H, H-5′), 4.13 (m, 1H, H-4′), 5.95 (d, *J* 1.6 Hz, 2H, CH_2), 6.07 (m, 1H, H-1′), 7.63 (d, *J* 1.2 Hz, 1H, H-6). ^{13}C NMR (50 MHz): δ −3.41, −3.34, 13.20, 18.39, 18.50, 20.19, 20.42, 25.40, 27.00, 32.47, 33.98, 38.79, 64.29, 64.97, 81.01, 86.42, 109.43, 134.60, 150.30, 162.66, 177.52.

*3′-Azido-3′-deoxy-3-pivaloyloxymethyl-5′-*O*-thexyldimethylsilylthymidine* (**20b**). 3′-Azido-3′-deoxy-5′-*O*-thexyldimethylsilylthymidine (1.50 g, 3.70 mmol) was dissolved in DMF (10 ml). Dry potassium carbonate (0.61 g, 4.40 mmol) was added and the suspension was stirred at ambient temperature under dry nitrogen for 1 h. The suspension was cooled to 0 °C and chloromethyl pivalate (0.55 ml, 3.80 mmol) added. The solvent was evaporated at reduced pressure after 15 h at ambient temperature. The product was purified by chromatotron chromatography using hexane/ethyl acetate (2:1) as eluent. Yield 1.67 g (86%); yellow oil. ^{1}H NMR (300 MHz): δ 0.17 (2 × s, 6H, 2 × CH_3-Si), 0.90 (m, 12H, 4 × CH_3), 1.18 (s, 9H, 3 × CH_3), 1.66 (m, 1H, CH), 1.96 (d, *J* 1 Hz, 3H, CH_3), 2.35 (m, 2H, H-2′), 3.79–4.25 (m, 4H, H-3′, H-4′, H-5′), 5.96 (d, *J* 2 Hz, 2H, CH_2), 6.22 (t, *J* 7 Hz, 1H, H-1′), 7.42 (d, *J* 1 Hz, 1H, H-6). ^{13}C NMR (75 MHz): δ −3.50, −3.30, 13.18, 18.45, 18.53, 20.24, 20.40, 25.39,

27.03, 34.00, 39.00, 60.37, 62.63, 65.02, 84.47, 85.12, 110.27, 133.02, 150.19, 162.42, 177.50.

3'-Deoxy-3-[1-(ethoxycarbonyloxy)ethyl]-5'-O-thexyldimethylsilylthymidine (**20c**). 3'-Deoxy-5'-*O*-thexyldimethylsilylthymidine (314 mg, 0.85 mmol) was dissolved in DMF (15 ml). Dry potassium carbonate (285 mg, 2.06 mmol) was added, and the solution was stirred at ambient temperature for 1.5 h under dry nitrogen. 1-Chloroethyl ethyl carbonate (0.18 ml, 1.35 mmol) was added, and the temperature was increased to 65 °C. The solvent was removed at reduced pressure after 17 h. Chloroform (50 ml) and water (20 ml) were added. The aqueous phase was washed with chloroform (2 × 30 ml). The combined chloroform layers were dried ($MgSO_4$), and the product was purified by flash chromatography using chloroform and chloroform/diethyl ether (9:1) as eluents. Yield 188 mg (45%); colourless oil. ^{1}H NMR (300 MHz): δ 0.13 (s, 6H, 2 × CH_3Si), 0.88 (m, 12H, CH_3), 1.28 (t, *J* 7 Hz, 3H, CH_3), 1.63 (m, 1H, CH), 1.85 (dd, 3H, CH_3), 1.91 (d, *J* 1.2 Hz, 3H, CH_3), 1.88–2.42 (m, 4H, H-3', H-2'), 3.82 (ABX, 2H, H-5'), 4.11–4.19 (m, 3H, CH_2, H-4'), 6.06 (m, 1H, H-1'), 7.24 (m, 1H, CH), 6.48 (dd, 1H, H-6).

3'-Azido-3'-deoxy-3-[1-(ethoxycarbonyloxy)ethyl]-5'-O-thexyldimethylsilylthymidine (**20d**). Dry potassium carbonate (0.50 g, 3.58 mmol) was added to a solution of 3'-azido-3'-deoxy-5'-*O*-thexyldimethylsilylthymidine (1.46 g, 3.58 mmol) in DMF (10 ml). The suspension was stirred at ambient temperaure for 3 h under dry nitrogen. 1-Chloroethyl ethyl carbonate (0.50 ml, 3.77 mmol) was added and the temperature was increased to 40 °C. The temperature was increased to 55 °C after 18 h and the mixture stirred for another 5 h. The solvent was evaporated at reduced pressure, and the residue purified by chromatotron chromatography using hexane/ethyl acetate (2:1) as eluent. Yield 1.36 g (72%); yellow oil. ^{1}H NMR (300 MHz): δ 0.17 (2 × s, 6H, 2 × CH_3Si), 0.90 (m, 12H, 4 × CH_3), 1.28 (t, *J* 7 Hz, 3H, CH_3), 1.65 (m, 1H, CH), 1.85 (d, *J* 7 Hz, 3H, CH_3), 1.92 (d, *J* 1 Hz, 3H, CH_3), 2.12–2.55 (m, 2H, H-2'), 3.68–4.35 (m, 6H, CH_2, H-3', H-4', H-5'), 6.21 (m, 1H, H-1'), 7.22 (m, 1H, CH), 7.36 (d, *J* 1 Hz, 1H, H-6). ^{13}C NMR (75 MHz): δ −3.50, −3.30, 13.21, 14.15, 17.91, 18.47, 18.53, 20.26, 20.40, 25.40, 34.03, 37.90, 37.99, 60.32, 62.60, 64.36, 77.48, 84.35, 84.42, 84.87, 84.95, 110.38, 133.63, 149.74, 153.82, 153.85, 162.48.

3'-Deoxy-3-pivaloyloxymethylthymidine (**21a**). 3'-Deoxy-3-pivaloyloxymethyl-5'-*O*-thexyldimethylsilylthymidine (468 mg, 0.97 mmol) was dissolved in THF (40 ml) and the solution cooled to 0 °C. A solution of 0.25 M tetrabutylammonium fluoride in THF (4.5 ml, 1.13 mmol) was added dropwise. Saturated ammonium chloride solution (10 ml) was added after 10 min at ambient temperature. More water (20 ml) was added, and the organic layer was separated. The aqueous phase was washed with chloroform (2 × 50 ml). The combined organic phases were dried ($MgSO_4$) and the solvents were evaporated. The product was purified by flash chromatography using chloroform and chloroform/ethanol (9:1) as eluents. Yield 327 mg (99%); yellowish oil. Anal. found: $C_{16}H_{24}N_2O_6$: C, H. ^{1}H NMR (200 MHz): δ 1.18 (s, 9H, 3 × CH_3), 1.93 (s, 3H, CH_3), 1.95–2.41 (m, 4H, H-2', H-3'), 3.85 (ABX, 2H, H-5'), 4.17 (m, 1H, H-4'), 5.92 (s, 2H, CH_2), 6.11 (m, 1H, H-1'), 7.63 (d, *J* 1.2 Hz, 1H, H-6). ^{13}C NMR (50 MHz) δ: 13.21, 24.99, 26.99, 32.34, 38.80, 63.44, 64.98, 81.25, 86.80, 109.64, 135.18, 150.33, 162.61, 177.56.

3'-Azido-3'-deoxy-3-pivaloyloxymethylthymidine (**21b**). 3'-Azido-3'-deoxy-3-pivaloyloxymethyl-5'-*O*-thexyldimethylsilylthymidine (1.61 g, 3.10 mmol) was dissolved in dry THF (10 ml), the solution was cooled to 0 °C, and a solution of tetrabutylammonium fluoride 0.25 M in THF (20 ml, 5.00 mmol) was added dropwise under dry nitrogen. A saturated solution of ammonium chloride (50 ml) was added after 25 min. The THF layer was removed, and the aqueous layer was washed with chloroform (2 × 50 ml). The combined organic layers were dried (Na_2SO_4) and the solvents were removed at reduced pressure. The residue was purified by chromatotron chromatography using chloroform/diethyl ether (1:1) as eluent. Yield 0.77 g (65%); pale yellow oil. Anal. $C_{16}H_{23}N_5O_6$: C, H. ^{1}H NMR (300 MHz): δ 1.19 (s, 9H, 3 × CH_3), 1.94 (d, *J* 1 Hz, 3H, CH_3), 2.52 (m, 2H, H-2'), 3.84–4.40 (m, 4H, H-3', H-4', H-5'), 5.94 (d, *J* 1 Hz, 2H, CH_2), 6.13 (t, *J* 7 Hz, 1H, H-1'), 7.50 (d, *J* 7 Hz, 1H, H-6). ^{13}C NMR (75 MHz): δ 13.21, 27.02, 37.51, 39.00, 59.89, 61.95, 64.99, 84.51, 86.90, 110.45, 135.49, 150.28, 162.42, 177.60. MS(CI, CH_4): 382 (100, $M^+ + 1$), 339 (13), 281 (17), 280 (83), 241 (79), 139 (65).

3'-Deoxy-3-[1-(ethoxycarbonyloxy)ethyl]thymidine (**21c**). 3'-Deoxy-3-[1-(ethoxycarbonyloxy)ethyl]-5'-*O*-thexyldimethylsilylthymidine (542 mg, 1.12 mmol) was dissolved in THF (20 ml) and the solution cooled to 0 °C. A solution of tetrabutylammonium fluoride in THF (5.0 ml, 1.25 mmol) was added under dry nitrogen. Saturated ammonium chloride solution (50 ml) was added after 20 min at ambient temperature, the organic layer was separated and the aqueous phase was washed with chloroform (2 × 50 ml). The combined organic layers were dried ($MgSO_4$) and evaporated. The product was purified on chromatotron chromatography using chloroform and chloroform/diethyl ether (1:1) as eluents. Yield 307 mg (80%); pale yellow oil. Anal. $C_{15}H_{22}N_2O_7$: C, H ^{1}H NMR (200 MHz): δ 1.18 (t, *J* 7 Hz, 3H, CH_3), 1.75 (d, *J* 7 Hz, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.84–2.35 (m, 4H, H-2', H-3'), 3.80 (ABX, 2H, H-5'), 4.01–4.15 (m, 3H, CH_2, H-4'), 5.98 (m, 1H, H-1'), 7.12 (d, *J* 7 Hz, 1H, CH), 7.67 (s, 1H, H-6). ^{13}C NMR (50 MHz): δ 12.68, 13.65, 17.38, 24.44, 32.16, 62.69, 63.86, 76.89, 81.08, 86.08, 108.86, 134.86, 149.31, 153.23, 162.33. MS(CI, CH_4): 343 (42), 287 (16), 255 (18), 254 (28), 253 (100),

153 (70). HR-MS: mol. wt. obs., 342.1425. Calc. for $C_{15}H_{22}N_2O_7$, 342.1427.

3'-Azido-3'-deoxy-3-[1-(ethoxycarbonyloxy)ethyl]thymidine (**21d**). 3'-Azido-3'-deoxy-3-[1-(ethoxycarbonyloxy)ethyl]-5'-*O*-thexyldimethylsilylthymidine (1.28 g, 2.40 mmol) was dissolved in dry THF (20 ml). The solution was cooled to 0 °C, and a solution of 0.25 M tetrabutylammonium fluoride (12 ml, 3.00 mmol) was added dropwise under an atmosphere of dry nitrogen. A saturated solution of ammonium chloride (20 ml) was added after 50 min. The THF layer was removed, and the aqueous layer was washed with chloroform (3 × 50 ml). The combined organic layers were dried (Na_2SO_4) and evaporated at reduced pressure. The residue was purified by chromatotron chromatography using chloroform/diethyl ether (1:1) as eluent. Yield 643 mg (70%); colourless oil. Anal. $C_{15}H_{21}N_5O_7$: C, H. ^{1}H NMR (300 MHz): δ 1.29 (t, *J* 7 Hz, 3H, CH_3), 1.85 (d, *J* 6 Hz, 3H, CH_3), 1.91 (d, *J* 1 Hz, 3H, CH_3), 2.42 (m, 2H, H-2'), 3.84–4.40 (m, 6H, H-3', H-4', H-5', CH_2), 6.14 (dd, *J* 6 Hz, 5 Hz, 1H, H-1'), 7.22 (q, *J* 6 Hz, 1H, CH), 7.44 (d, *J* 1 Hz, 1H, H-6). ^{13}C NMR (75 MHz): δ 13.22, 14.14, 17.88, 37.51, 37.57, 59.76, 59.83, 61.85, 61.90, 64.44, 77.48, 84.37, 84.40, 86.44, 86.55, 110.54, 135.05, 135.11, 149.82, 153.83, 162.49. FAB-MS: 384 (*M*+H).

3'-Deoxy-5'-O-pivaloyloxymethylthymidine (**22a**). 3'-Deoxythymidine (412 mg, 1.82 mmol) was dissolved in DMF (15 ml) under dry nitrogen. The solution was cooled to 0 °C and sodium hydride [185 mg, 4.62 mmol (60–65% in oil)] was added. The suspension was stirred at ambient temperature for 1.5 h. Chloromethyl pivalate (0.28 ml, 1.95 mmol) was added, and the mixture was stirred for 6 h at ambient temperature. Saturated ammonium chloride solution (50 ml) was added, and the solvents were removed under reduced pressure. The product was purified by chromatotron chromatography using chloroform/diethyl ether/ethanol (5:4:1) as eluent. Yield 260 mg (42%); yellowish crystals. M.p. 96–100 °C (diethyl ether). ^{1}H NMR (200 MHz): δ 1.23 (s, 9H, 3 × CH_3), 1.93 (s, 3H, CH_3), 1.81–2.41 (m, 4H, H-2', H-3'), 3.70–4.08 (ABX, 2H, H-5'), 4.20–4.37 (m, 1H, H-4'), 5.35 (d, *J* 3.0 Hz, 2H, CH_2), 6.06 (m, 1H, H-1'), 7.61 (d, *J* 1.2 Hz, 1H, H-6), 9.28 (s, 1H, NH). ^{13}C NMR (50 MHz): δ 13.39, 26.81, 27.99, 32.69, 33.29, 65.72, 77.00, 78.61, 86.57, 111.23, 136.40, 135.33, 150.80, 164.20. MS(CI, NH_3): 341 (41), 311 (15), 241 (14), 239 (100), 232 (11), 127 (27), 113 (25). HR-MS: mol. wt. obs.: 340.1627. Calc. for $C_{16}H_{24}N_2O_6$: 340.1634.

3'-Deoxy-5'-O, N3-bis(pivaloyloxymethyl)thymidine (**22b**). 3'-Deoxythymidine (502 mg, 2.22 mmol) was dissolved in DMF (25 ml), the solution was cooled to 0 °C and sodium hydride [227 mg, 5.68 mmol (60–65% in oil)] was added. The suspension was stirred for 1.5 h under dry nitrogen at 0 °C, then chloromethyl pivalate (2.00 ml, 13.95 mmol) was added. The mixture was stirred at ambient temperature for 17 h. Saturated ammonium chloride solution (50 ml) and chloroform (50 ml) were added. The aqueous phase was washed with chloroform (2 × 50 ml). The combined organic layers were dried ($MgSO_4$), and the solvents were evaporated. The product was purified by flash chromatography using chloroform and chloroform/diethyl ether (4:1) as eluents. Yield 230 mg (23%); yellowish oil. Anal. $C_{22}H_{34}N_2O_8$: C, H. ^{1}H NMR (200 MHz): δ 1.11 (s, 9H, 3 × CH_3), 1.16 (s, 9H, 3 × CH_3), 1.90 (s, 3H, CH_3), 1.95–2.34 (m, 4H, H-3', H-2'), 3.67–4.22 (m, 3H, H-5', H-4'), 5.31 (d, *J* 2.5 Hz, 2H, CH_2), 5.88 (s, 2H, CH_2), 6.06 (m, 1H, H-1'), 7.61 (d, *J* 1.0 Hz, 1H, H-6). ^{13}C NMR (50 MHz): δ 14.21, 26.26, 28.03, 33.57, 39.72, 65.71, 70.98, 80.22, 87.13, 89.18, 109.92, 135.30, 150.50, 162.70, 177.41, 177.75. MS(EI): 454 (9.5, M^+), 352 (37), 322 (17), 251 (33), 241 (25), 214 (21), 186 (11), 185 (100), 112 (81).

3'-Deoxy-5'-O-ethoxycarbonyl-3-[1-(ethoxycarbonyloxy)-ethyl]thymidine (**23a**). 3'-Deoxy-5'-*O*-ethoxycarbonylthymidine (71 mg, 0.24 mmol) was dissolved in DMF (5 ml), dry potassium carbonate (56 mg, 0.41 mmol) added and the suspension was stirred at ambient temperature, under dry nitrogen for 1.5 h. 1-Chloroethyl ethyl carbonate (0.04 ml, 0.30 mmol) was added at 0 °C and mixture was stirred at 60 °C for 18 h. The solvent was removed at reduced pressure, and the product was purified on chromatotron chromatography using chloroform/diethyl ether (1:1) as eluent. Yield 79 mg (81%); yellowish oil. Found: C 52.72; H 6.61. Calc. for $C_{18}H_{26}N_2O_9$: C 52.17; H 6.32. ^{1}H NMR (200 MHz): δ 1.19–1.30 (m, 6H, 2 × CH_3), 1.80 (d, *J* 6.5 Hz, 3H, CH_3), 1.88 (s, 3H, CH_3), 1.92–2.07 (m, 2H, H-3'), 2.32–2.38 (m, 2H, H-2'), 4.06–4.41 (m, 7H, 2 × CH_2, H-5', H-4'), 6.07 (m, 1H, H-1'), 7.18 (m, 1H, CH), 7.49 (d, *J* 1.0 Hz, 1H, H-6). ^{13}C NMR (50 MHz): δ 13.18, 14.16, 14.32, 18.05, 25.46, 32.52, 64.15, 64.33, 67.46, 77.27, 78.22, 86.20, 109.44, 133.90, 149.31, 153.20, 154.32, 161.99. MS(EI): 414 (1.6, M^+), 173 (35), 155 (10), 153 (24), 83 (100).

3'-Azido-3'-deoxy-5'-O-ethoxycarbonyl-3-[1-(ethoxycarbonyloxy)ethyl]thymidine (**23b**). 3'-Azido-3'-deoxy-5'-*O*-ethoxycarbonylthymidine (304 mg, 0.90 mmol) was dissolved in DMF (15 ml), dry potassium carbonate (148 mg, 1.07 mmol) added and the suspension was stirred for 1 h. 1-Chloroethyl ethyl carbonate (0.14 ml, 1.05 mmol) was added. The reaction mixture was stirred at 60 °C for 14 h under dry nitrogen. The solvent was removed at reduced pressure and the residue purified by flash chromatography using chloroform/diethyl ether (1 : 1) as eluent. Yield 134 mg (33 %); colourless oil. ^{1}H NMR (300 MHz): δ 1.29 (t, *J* 7 Hz, 3H, CH_3), 1.33 (t, *J* 7 Hz, 3H, CH_3), 1.85 (d, *J* 7 Hz, 3H, CH_3), 1.93 (d, *J* 1 Hz, 3H, CH_3), 2.42 (m, 2H, H-2'), 4.04–4.43 (m, 8H, 2 × CH_2, H-3', H-4', H-5'), 6.25 (dd, *J* 4 Hz, 4 Hz, 1H, H-1'), 7.22 (m, 1H, CH), 7.37 (d, *J* 1 Hz, 1H, H-6). ^{13}C NMR (75 MHz): δ 13.15, 14.14, 14.23, 17.88, 17.91,

37.81, 37.90, 59.77, 59.86, 64.39, 64.78, 65.96, 66.00, 77.47, 81.64, 81.68, 85.26, 85.38, 110.66, 133.87, 149.72, 153.85, 154.58, 162.38. MS(EI): 455 (3.2, M^+), 232 (14), 199 (7), 154 (9), 153 (100), 152 (81), 127 (34), 110 (59). HR-MS: mol. wt. obs.: 455.1640. Calc. for $C_{18}H_{25}N_5O_9$: 455.1652.

3'-Azido-3'-deoxy-5'-O-diethylcarbamoyl-3-[1-(ethyloxycarbonyloxy)ethyl]-thymidine (**23c**). 3'-Azido-3'-deoxy-5'-*O*-diethylcarbamoylthymidine (726 mg, 2.00 mmol) was dissolved in DMF (10 ml) under dry nitrogen, dry potassium carbonate (299 mg, 2.20 mmol) added and the suspension was stirred at ambient temperature for 1 h. 1-Chloroethyl ethyl carbonate (0.30 ml, 2.20 mmol) was added and the reaction mixture was stirred at 60 °C for 16 h. The solvent was removed at reduced pressure, and the residue was purified by chromatotron chromatography using hexane/ethyl acetate (2:1) as eluent. Yield 536 mg (55%); yellow oil. Anal. $C_{20}H_{30}N_6O_8$: C, H. ^{1}H NMR (300 MHz): δ 1.14 (t, *J* 7 Hz, 6H, 2 × CH_3), 1.29 (t, *J* 7 Hz, 3H, CH_3), 1.84 (d, *J* 7 Hz, 3H, CH_3), 1.92 (d, *J* 1 Hz, 3H, CH_3), 2.20, 2.50 (m, 2H, H-2'), 3.28 (m, 4H, 2 × CH_2), 4.05–4.36 (m, 6H, CH_2, H-3', H-4', H-5'), 6.08 (m, 1H, H-1'), 7.12 (m, 1H, CH), 7.61 (d, *J* 1 Hz, 1H, H-6). ^{13}C NMR (75 MHz): δ 12.22, 13.41, 14.13, 19.46, 38.62, 38.65, 41.29, 42.11, 60.90, 64.21, 64.53, 77.47, 82.25, 82.31, 85.67, 85.77, 110.59, 133.55, 149.62, 153.11, 155.10, 162.35. FAB-MS: 483 (M+H).

3'-Azido-3'-deoxy-3-[1-(ethyloxycarbonyloxy)ethyl]-5'-O-hemisuccinylthymidine (**23d**). 3'-Azido-3'-deoxy-5'-*O*-hemisuccinylthymidine (360 mg, 0.98 mmol) was dissolved in DMF (15 ml) under dry nitrogen. Dry potassium carbonate (168 mg, 1.22 mmol) was added, and the suspension was stirred for 1.5 h at ambient temperature. 1-Chloroethyl ethyl carbonate (0.14 ml, 1.05 mmol) was added, and the reaction mixture was stirred at 60 °C. The solvent evaporated at reduced pressure after 14 h. The residue was purified by chromatotron chromatography using chloroform/diethyl ether/ethanol (10:9:1) as eluent. Yield 278 mg (58%); yellowish oil. Anal. $C_{19}H_{25}N_5O_{10}$: C, H. ^{1}H NMR (300 MHz): δ 1.29 (t, *J* 7 Hz, 3H, CH_3), 1.85 (d, *J* 6 Hz, 3H, CH_3), 1.93 (s, 3H, CH3), 2.45 (m, 2H, H-2'), 2.70 (m, 4H, 2 × CH_2), 4.03–4.51 (m, 6H, CH2, H-4', H-3', H-5'), 6.12 (dd, *J* 6 Hz, 5 Hz, 1H, H-1'), 6.76 (q, *J* 5 Hz, 1H, CH), 8.80 (s, 1H, NH). ^{13}C NMR (75 MHz): δ 13.26, 14.13, 17.85, 28.58, 28.74, 37.56, 60.28(60.33), 63.35, 64.48, 77.46, 81.80, 81.91, 85.86, 85.89, 110.44, 110.63, 134.03, 134.10, 149.59, 153.83, 153.95, 162.45, 171.78, 171.82, 176.64, 176.78. MS(CI): 484 (8.5, M^++1), 458 (8), 396 (14), 350 (37), 251 (13), 250 (100), 207 (14), 155 (26), 127 (79), 101 (51).

N^6-Benzyloxycarbonyl-2',3'-dideoxy-5'-O-pivaloyloxymethyladenosine (**24**). *N*^{6}-Benzyloxycarbonyl-2',3'-dideoxyadenosine (828 mg, 2.24 mmol) in DMF (70 ml) was added sodium hydride [246 mg, 6.15 mmol, (60–65% in oil)] at −20 °C, the suspension stirred at ambient temperature for 10 min, cooled to −20 °C and chloromethyl pivalate (0.41 ml, 2.86 mmol) added dropwise before the mixture was allowed to reach ambient temperature. Saturated ammonium chloride solution (15 ml) was added after 4 h. The aqueous phase was extracted with chloroform (3 × 100 ml). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography using chloroform and chloroform/diethyl ether/ethanol (5:4:1) as eluents. Yield 410 mg (50%); yellow oil. ^{1}H NMR (200 MHz): δ 1.18 (s, 9H, 3 × CH_3), 2.13 (m, 2H, H-3'), 2.49 (m, 2H, H-2'), 3.85 (ABX, 2H, H-5'), 4.34 (m, 1H, H-4'), 5.29 (bs, 4H, 2 × CH_2), 6.34 (m, 1H, H-1'), 7.34 (m, 5H, 5 × CH), 8.34 (s, 1H, H-2 or H-8), 8.73 (s, 1H, H-2 or H-8), 8.80 (s, 1H, NH). ^{13}C NMR (50 MHz): δ 25.57, 26.94, 32.89, 38.85, 67.65, 70.49, 80.21, 85.59, 88.71, 122.41, 128.40, 128.53, 135.40, 141.43, 149.22, 150.97, 152.48, 177.85. MS(EI): 274 (19), 185 (14), 162 (38), 161 (46), 113 (23), 108 (45), 107 (32). HR-MS: mol. wt. obs., 483.4931. Calc. for $C_{24}H_{29}N_5O_6$: 483.4930.

2',3'-Dideoxy-5'-O-pivaloyloxymethyladenosine (**25**). *N*^{6}-Benzyloxycarbonyl-2',3'-dideoxy-5'-O-pivaloyloxymethyladenosine (281 mg, 0.58 mmol) was dissolved in dry ethanol (70 ml) and palladium on charcoal (54 mg, 10%) was added. This mixture was kept under an atmosphere of hydrogen for 14 h. After removal of the solvent, the product was purified by flash chromatography using chloroform/ethanol (4:1) as eluent. Yield 100 mg (49%); colourless oil. ^{1}H NMR (200 MHz): δ 1.20 (s, 9H, 3 × CH_3), 2.12 (m, 2H, H-3'), 2.48 (m, 2H, H-2'), 3.87 (ABX, 2H, H-5'), 4.31 (m, 1H, H-4'), 5.32 (dd, 2H, CH_2), 6.32 (m, 1H, H-1'), 6.42 (s, 2H, NH2), 8.22 (s, 1H, H-2 or H-8), 8.33 (s, 1H, H-2 or H-8). ^{13}C NMR (50 MHz): δ 25.56, 26.97, 33.03, 38.89, 70.50, 80.06, 85.43, 88.68, 122.41, 139.17, 149.09, 152.08, 155.21, 177.96. MS(EI): 349 (3, M^+), 248 (25), 218 (23), 136 (50), 135 (72), 108 (19), 85 (14). HR-MS: mol. wt. obs., 349.1748. Calc. for $C_{16}H_{23}N_5O_4$: 349.1750.

Acknowledgement. The chemical stability and partition coefficient measurements were carried out by Dr. Hermann Ruckendorfer, Hafslund Nycomed Pharma AG, Linz, Austria.

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Received September 20, 1995.