# 3'-(1,2,3-Triazol-1-yl)-2',3'-dideoxythymidine and 3'-(1,2,3-Triazol-1-yl)-2',3'-dideoxyuridine



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Cycloaddition of different acetylenic compounds on the azido function of 3'-azido-2',3'-dideoxythymidine and 3'-azido-2',3'-dideoxyuridine afforded products with a 1,2,3-triazol-1-yl substituent in the 3'-position. In contrast with the parent compounds, these triazolyl derivatives had no appreciable activity against human immunodeficiency virus (HIV-1).

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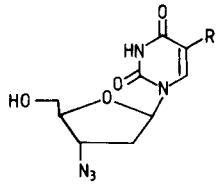
## Introduction.

Human immunodeficiency virus (HIV-1), the causative agent of the acquired immunodeficiency syndrome (AIDS) has been identified some 5 years ago [1,2], but except for 3'-azido-2',3'-dideoxythymidine [1-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)thymine, azidothymidine] no chemotherapeutic means have been formally licensed to treat this disease. The most potent anti-HIV-1 agents are 2',3'-dideoxynucleosides [3] and analogues thereof [4]. Especially compounds with a 3'-azido or 3'-fluoro substituent or a 2',3'-unsaturated linkage have proved to be potent and selective inhibitors of HIV-1 [5]. We first focussed our research work on the development of 2',3'-unsaturated nucleosides. This resulted in the discovery of 2',3'-dideoxy-2',3'-didehydrothymidine and 2',3'-dideoxy-2',3'-didehydrocytidine [6]. These compounds were later described by other research groups and are now generally referred to as D4T and D4C, respectively. Thereafter we explored the possibility of modulating the anti-HIV activity of 2',3'-dideoxynucleosides by introducing a 3'-fluoro substituent. This investigation led to the discovery of several fluorinated nucleosides as potent and selective inhibitors of HIV-1: viz. 3'-fluoro-2',3'-dideoxythymidine [7], 3'-fluoro-2',3'-dideoxyuridine [8] and more recently, 3'-fluoro-2',3'-dideoxy-5-chlorouridine [9].

Of the 3'-azido-2',3'-dideoxynucleosides, 3'-azido-2',3'-dideoxythymidine **1a** still ranks as the most active congener, although its profound toxicity for the bone marrows argues against the longterm use of this compound in patients. In our attempts to develop new 2',3'-dideoxynucleosides with superior activity and/or lesser toxicity, we synthesized various derivatives of 3'-azido-2',3'-dideoxythymidine in which the 3'-azido group was replaced by a five-membered heterocyclic ring containing 3 consecutive nitrogen atoms.

We also prepared some 2',3'-dideoxyuridine derivatives containing a (1,2,3-triazol-1-yl) group in the 3'-*erythro* position. These compounds could be considered as analogues of 3'-azido-2',3'-dideoxyuridine **1b**. These compounds were synthesized by a thermally induced 1,3-dipolar cycloaddition of acetylenic functions **2a-g** on the 3'-azido group of **1a** or **1b**. This classical approach for the synthesis of 1,2,3-triazol-1-yl derivatives functions very well with pyrimidine nucleosides and does not give rise to important side reactions.



1. a) R = $CH_3$
   b) R = H

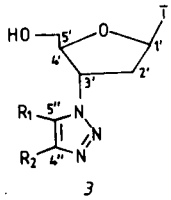
2. X—C≡C—Y

| | X | Y |
|---|---|---|
| a) | H | $SiMe_3$ |
| b) | H | $CH_2OH$ |
| c) | $CH_3$ | $SiMe_3$ |
| d) | $CH_2OH$ | $CH_2OH$ |
| e) | H | $COOCH_2CH_3$ |
| f) | H | phenyl |
| g) | H | $OCH_2CH_3$ |

## Chemistry.

3'-Azido-2',3'-dideoxythymidine **1a** was synthesized as previously described [10]. Reaction of **1a** with trimethylsilylacetylene **2a** in dichloromethane at 120° for 48 hours gave the expected triazolyl derivative **3a** in 60% yield together with the desilylated compound **3b** (10%) and unreacted **1a** (12%). These results are in agreement with literature data on this type of cycloaddition reaction [11]. The steric bulk of the silyl group determines the regiospecificity. The addition reaction gave the 4''-silylated compound **3a**. No 5''-silylated compound could be detected. *Ipso*-substitution of the trimethylsilyl group of **3a** by hydrogen could be performed in a mixture of acetic acid-methanol at 100° for 2 hours. The glycosidic bound of **3a** is stable enough to allow isolation of **3b** in 50% yield. This protodesilylation reaction could also be carried out with

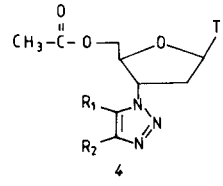
tetrabutylammonium fluoride monohydrate in tetrahydrofuran. Refluxing of **3a** in the presence of 1.5 equivalents of tetrabutylammonium fluoride for 6 hours yielded 87% of **3b**. Attempts to replace the trimethylsilyl group of **3a** with an halogen atom (I, Br, Cl) by using iodine, iodine monochloride or chlorine failed [12]. Also our efforts to halogenate **3b** with iodine, iodine monochlorine and bromine were not successful. In these cases, addition reaction occurred preferentially on the 5-6 unsaturated bound of the pyrimidine ring. The reaction of **1a** with propargyl



*3*

| | $R_1$ | $R_2$ |
|---|---|---|
| a) | H | $SiMe_3$ |
| b) | H | H |
| c) | $CH_2OH$ | H |
| d) | H | $CH_2OH$ |
| e) | $CH_2F$ | H |
| f) | H | $CH_2F$ |
| g) | $CH_2Cl$ | H |
| h) | H | $CH_2Cl$ |
| i) | $CH_3$ | H |
| j) | H | $CH_3$ |
| k) | $CH_3$ | $SiMe_3$ |
| l) | $CH_2OH$ | $CH_2OH$ |
| m) | H | $COOCH_2CH_3$ |
| n) | H |  |
| o) | H | $O-CH_2-CH_3$ |
| p) | H | $NO_2$ |

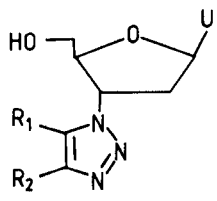
alcohol **2b** gave a mixture of **3c** and **3d** (ratio 1:2) in a total yield of 95%. These compounds could be readily separated by column chromatography. The ratio of **3c** to **3d** changed only marginally (3:5) when the 5′-hydroxyl group of 3′-azido-2′,3′-dideoxythymidine was first protected with an acetyl group before the reaction with propargyl alcohol was carried out. Prior protection of the 5′-hydroxyl group allowed us to selectively modify the hydroxymethyl substituent of the triazole ring. Reaction of **4a** and **4b** with diethylaminosulfur trifluoride in dichloromethane yielded the 4″- and 5″-fluoromethyl analogues **4c** and **4d** in about 50% yield. These compounds were completely identified after deacylation with ammonia in methanol giving **3e** and **3f**. Reaction of **4a** and **4b** with carbon tetrachloride and triphenylphosphine in dimethylformamide yielded the 4″- and 5″-chloromethyl derivatives **4e** and **4f** in 90% yield. During isolation, however, most part of **4e** was deacylated to **3g**. Deprotection of **4f** with methanol saturated with ammonia gave a mixture of 2 compounds. Only **3h** was obtained in pure form. The second compound is assumed to be the 4″-aminomethyl analogue. On the other hand, **4e** could be quantitatively deacylated in a mixture of methanol-water with potassium-carbonate at *p*H 10. Reaction of the free hydroxyl of **4a** with Rydon reagent (methyltriphenoxyphosphonium iodide) proceeded smoothly according to tlc analysis but compound **4g** was not stable. We were not able to obtain an analytically pure sample of **4g**. The latter was immediately converted into **4h** by hydrogenation on palladium on carbon and further converted into **3j** by 5′-*O*-deacylation. The other isomer **3i** was synthesized by a more direct route. Reaction of **1a** with 1-(trimethylsilyl)-1-propyne **2c** in toluene at elevated temperature gave **3k** which was desilylated to **3i** in the same manner as described for the synthesis of **3b**.



*4*

| | $R_1$ | $R_2$ |
|---|---|---|
| a) | $CH_2OH$ | H |
| b) | H | $CH_2OH$ |
| c) | $CH_2F$ | H |
| d) | H | $CH_2F$ |
| e) | $CH_2Cl$ | H |
| f) | H | $CH_2Cl$ |
| g) | H | $CH_2I$ |
| h) | H | $CH_3$ |
| i) | H | OEt |

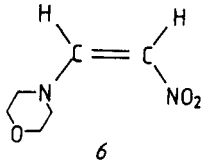
Also other cycloaddition reactions could be readily carried out with AZT. Reaction with 2-butyn-1,4-diol **2d** in a mixture of toluene-pyridine (9:1) gave **3l** in 70% yield. Reaction of **1a** with ethylpropiolate **2e** in ethanol gave **3m** in 57% yield and with phenylacetylene **2f** in the same solvent gave **3n** in 71% yield. The reaction was not so clean with **2g**. When **1a** was heated with ethoxyacetylene in toluene, we obtained a complex reaction mixture. The main reaction compound was identified as **4i** and isolated in 15% yield only. Apparently cycloaddition was accomplished by acetylation of the 5′-hydroxyl group with ethoxyacetylene. Therefore we first acetylated the 5′-OH group and repeated the cycloaddition reaction. After 2 days refluxing to toluene, followed by deprotection with ammonia in methanol, about 34% of **3o** and 60% of unreacted **1a** were isolated. Finally, we tried to modulate the electron distribution of the triazole ring by introducing the strong electron withdrawing nitro group. Compound **3p** was synthesized following the method of Maiorana *et al.* [13] for the addition on aromatic azides. The reagent 1-morpholino-2-nitroethene **6** was synthesized according to Neuman *et al.* [14]; **1a** was treated with an excess of 1-morpholino-2-nitroethene in toluene at 110° for 1 week giving **3p** in 15% yield only.



5

| | $R_1$ | $R_2$ |
|---|---|---|
| a) | H | $SiMe_3$ |
| b) | H | H |
| c) | $CH_2OH$ | H |
| d) | H | $CH_2OH$ |

The reaction procedure established for the synthesis of **3a**, **3b**, **3c** and **3d** was repeated for the synthesis of the analogues with uracil as base giving **5a**, **5b**, **5c** and **5d**, respectively. Most of these compounds **3a**, **3b**, **3c**, **3d**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, **3m**, **3n**, **5a**, **5b**, **5c** and **5d** were obtained as crystalline solids. The compounds **3e**, **3f**, **3o**, and **3p** were obtained only in small amounts and these were finally purified by preparative thin layer chromatography. The compounds were fully identified by their $^1H$ nmr, $^{13}C$ nmr, mass spectrum, uv spectrum and by elemental analyses. For every compound the molecular ion ($M^+$) could be detected except of **3g** and **3h**.



6

When the $^1H$ nmr spectrum of compound **3b** is compared with that of **1a** we notice the expected downfield shift for the H-3' (from $\delta$ 3.94 to $\delta$ 5.40), H-4' (from $\delta$ 3.40 to $\delta$ to 4.22), and H-2' (from $\delta$ 1.90 to $\delta$ 2.70) protons. The influence of the triazole ring on the chemical shift values of H-1' and H-5' is negligible. The aromatic area of the $^1H$ nmr spectrum of **3b** shows two additional doublets (J = 1 Hz) at $\delta$ 7.80 and $\delta$ 8.30 ppm. These values correspond well with those reported for 1-methyl-1,2,3-triazole: $\delta$ 7.72 (H-4) and $\delta$ 8.08 (H-5) [15]. When introducing in the 4''-position a substituent like nitro, fluoromethyl, phenyl or an ethoxycarbonyl, the 5''-H signal shifts downfield. Electron donating substituents like ethoxy, methyl or hydroxymethyl give an upfield shift. The influence of the trimethylsilyl and chloromethyl group is marginal. Analogous shifts for the H-4'' were found when these substituents, **3c**, **3e**, **3g** and **3i**, are introduced in the 5''-position. Methyl and hydroxymethyl give an upfield shift, fluoromethyl gives a downfield shift, and the influence of chloromethyl is very small.

The $^{13}C$ nmr data for the sugar moiety and pyrimidine base of **3b** resemble those of 3'-azido-2',3'-dideoxythymidine. The aromatic part of the spectrum shows 2 additional signals at 124.5 and 133.5; these values correspond very well to those reported for 1-methyl-1,2,3-triazole: C-5 at 124.8 and C-4 at 132.6 [16]. Introduction of substituents at C-4'' and/or C-5'' influences the position of these carbon atoms in the same manner as they do for mono-substituted benzene analogues [17]. The $^{13}C$ spectrum of **3n** shows 6 additional signals compared to the spectrum of **1a**. We assigned these signals according to Radios *et al.* [18], who described the $^{13}C$ spectrum of 1-(*n*-arylidene)amino-4-phenyl-1,2,3-triazole.

Biological Activity.

The 3'-(1,2,3-triazol-1-yl)-2',3'-dideoxythymidine **3a-p** and 3'-(1,2,3-triazol-1-yl)-2',3'-dideoxyuridine **5a-d** derivatives were examined for their inhibitory effect HIV-1-induced cytopathogenicity in human T lymphocyte MT-4 cells and Moloney murine sarcoma virus (MSV)-induced transformation of murine C3H/3T3 embryo fibroblasts.

In contrast to 3'-azido-2',3'-dideoxythymidine, none of the 3'-(1,2,3-triazol-1-yl) derivatives of either 2',3'-dideoxythymidine and 2',3'-dideoxyuridine showed an appreciable activity against MSV or HIV-1 replication *in vitro*. The 50% antiviral effective doses ($ED_{50}$) of compounds **3a-p** and **5a-d** were at least 1000 to 10000 fold higher than the $ED_{50}$ values obtained for 3'-azido-2',3'-dideoxythymidine.

## EXPERIMENTAL

Melting points were determined in capillary tubes with a Büchi-Tottoli apparatus and are uncorrected. Ultraviolet spectra were recorded with a Philips PU 8700 spectrophotometer. The $^1H$ nmr and $^{13}C$ nmr spectra were determined with a JEOL FX 90Q spectrometer with tetramethylsilane as internal standard for the $^1H$ nmr spectra and DMSO-$d_6$ (39.6 ppm) for the $^{13}C$ nmr spectra (s = singlet, d = doublet, t = triplet, br s = broad signal, m = multiplet). Mass spectra were determined with an AEI MS-12 apparatus. Precoated Merck silica gel F254 plates were used for tlc, and the spots were examined with uv light and sulfuric acid-anisaldehyde spray. Column chromatography was performed on Merck silica gel (0.063-0.200 $\mu$m). Anhydrous solvents were obtained as follows: tetrahydrofuran was obtained by distillation after refluxing overnight on lithium aluminium hydride; pyridine was refluxed overnight on potasium hydroxide and distilled; dichloromethane was stored for 1 week on anhydrous calcium chloride, filtered, and distilled; water was removed from *N,N*-dimethylformamide by distillation with benzene followed by distillation *in vacuo*.

3'-(4-Trimethylsilyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3a**).

A mixture of 250 mg (0.94 mmole) of **1a** and 1 ml (10 mmoles) of trimethylsilylacetylene **2a** in 10 ml of dichloromethane was heated in a sealed vessel at 120° for 48 hours. The reaction mix-

ture was evaporated, coevaporated (2x) with toluene and then purified by column chromatography [silica gel-ethyl acetate-methanol (95:5)]. Three products were isolated: 33 mg (13%) of unreacted **1a**, 250 mg (68%) of **3a** and 34 mg (10%) of **3b**; **3a** was crystallized from a mixture of methanol and ether, mp 98-100°; uv (methanol): λ max 266 nm (log ε = 4.08); $^1$H nmr (DMSO-$d_6$): δ 0.27 [s, 9H, $Si(CH_3)_3$], 1.81 (s, 3H, $CH_3$), 2.71 (m, 2H, H-2'), 3.65 (br s, 2H, H-5'), 4.20 (m, 1H, H-4'), 5.23 (t, 1H, OH), 5.42 (m, 1H, H-3'), 6.43 (t, 1H, H-1'), 7.82 (s, 1H, H-6), 8.33 (s, 1H, H-5''), 11.30 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 1.0 [$Si(CH_3)_3$], 12.2 ($CH_3$), 33.4 (C-2'), 58.7 and 60.9 (C-3' and C-5'), 83.9 and 84.6 (C-4' and C-1'), 109.7 (C-5), 130.0 (C-5''), 136.3 (C-6), 147.3 (C-4''), 150.4 (C-2), 163.7 (C-4) ppm; ms: (m/e) 365 ($M^+$).

*Anal.* Calcd. for $C_{15}H_{23}N_5O_4Si\cdot\frac{1}{2}H_2O$: C, 48.1; H, 6.5; N, 18.7. Found: C, 48.2; H, 6.3; N, 18.5.

3'-(1,2,3-Triazol-1-yl)-2',3'-dideoxythymidine (**3b**).

A. A solution of 290 mg (0.79 mmole) of **3a** in 20 ml of a mixture of acetic acid-methanol (8:2) was heated for 2 hours at 100°. The solvents were evaporated and coevaporated with toluene. The reaction mixture was purified by column chromatography [silica gel-chloroform-methanol: 1. (95:5); 2. (85:15)], yielding 120 mg (52%) of 3'-(1,2,3-triazol-1-yl)-2',3'-dideoxythymidine, which was crystallized from methanol, mp 213-215°; uv (methanol): λ max 266 nm (log ε = 4.01); $^1$H nmr (DMSO-$d_6$): δ 1.81 (s, 3H, $CH_3$), 2.70 (m, 2H, H-2'), 3.67 (br s, 2H, H-5'), 4.22 (m, 1H, H-4'), 5.25 (t, 1H, OH), 5.40 (m, 1H, H-3'), 6.43 (t, 1H, H-1'), 7.75 (s, 1H, H-6), 7.80 (d, 1H, J = 1 Hz, H-4''), 8.30 (d, 1H, J = 1 Hz, H-5''), 11.30 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.2 ($CH_3$), 37.3 (C-2'), 59.1 and 60.8 (C-3' and C-5'), 84.0 and 84.6 (C-1' and C-4'), 109.7 (C-5), 124.5 (C-5''), 133.5 (C-4''), 136.3 (C-6), 150.5 (C-2), 163.7 (C-4) ppm; ms: (m/e) 293 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{15}N_5O_4\cdot\frac{1}{2}H_2O$: C, 47.7; H, 5.3; N, 23.2. Found: C, 47.6; H, 5.0; N, 22.9.

B. A mixture of 100 mg (0.27 mmole) of **3a** and 0.4 ml of a 1 *M* solution of tetrabutylammonium fluoride monohydrate in tetrahydrofuran was refluxed for 6 hours in 10 ml of tetrahydrofuran. Tlc analysis (silica gel-ethyl acetate) revealed almost complete disappearance of all starting material. The solvent was evaporated and the mixture purified by column chromatography [silica gel-ethyl acetate-methanol: 1. (100.0); 2. (95.5)] yielding 70 mg (87%) of **3b**.

3'-(4-Hydroxymethyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3d**) and 3'-(5-hydroxymethyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3c**).

A mixture of 450 mg of **1a** (1.7 mmoles) and 3 ml (51 mmoles) of propargyl alcohol **2b** was heated for 72 hours at 70° in 45 ml of toluene; tlc (ethyl acetate and chloroform-methanol (8:2)] of the reaction mixture indicated that all starting material had been transformed in two compounds. These could be separated chromatographically [silica gel-chloroform-methanol (90:10)] after evaporation of the solvents. The less polar product was obtained in 29% yield (160 mg) and identified as the 5''-hydroxymethyl isomer **3c**; this product was crystallized from methanol, mp 190-192°; uv (methanol): λ max 266 nm (log ε = 4.03); $^1$H nmr (DMSO-$d_6$): δ 1.83 (s, 3H, $CH_3$), 2.67 (m, 2H, H-2'), 3.70 (br s, 2H, H-5'), 4.24 (m, 1H, H-4'), 4.66 (d, 2H, $CH_2$-5''), 5.11-5.67 (m, 3H, 2 x OH and H-3'), 6.56 (t, 1H, H-1'), 7.67 (s, 1H, H-4''), 7.85 (s, 1H, H-6), 11.26 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.3 ($CH_3$), 37.4 (C-2'), 51.7 ($CH_2$-5''), 58.1 and 61.4 (C-3' and C-5'), 84.7 and 85.1 (C-1' and C-4'), 109.7 (C-5), 132.4 (C-4''), 136.1 (C-6), 137.5 (C-5''), 150.5 (C-2), 163.7 (C-4) ppm; ms: (m/e) 323 ($M^+$).

*Anal.* Calcd. for $C_{13}H_{17}N_5O_5$: C, 48.3; H, 5.3; N, 21.7. Found: C, 48.0; H, 5.2; N, 21.5.

The slower moving product was obtained in 66% yield (360 mg) and was identified as the 4''-hydroxymethyl isomer **3d**; it was crystallized from methanol, mp 184-186°; uv (methanol): λ max 266 nm (log ε = 4.04); $^1$H nmr (DMSO-$d_6$): δ 1.81 (s, 3H, $CH_3$), 2.67 (m, 2H, H-2'), 3.65 (br s, 2H, H-5'), 4.21 (m, 1H, H-4'), 4.53 (d, 2H, $CH_2$-4''), 5.05-5.45 (m, 3H, 2 x OH and H-3'), 6.39 (t, 1H, H-1'), 7.80 (s, 1H, H-6), 8.14 (s, 1H, H-5''), 11.26 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.3 ($CH_3$), 37.3 (C-2'), 55.2 ($CH_2$-4''), 59.2 and 60.8 (C-3' and C-5'), 84.1 and 84.4 (C-1' and C-4'), 109.7 (C-5), 122.5 (C-5''), 136.3 (C-6), 148.3 (C-4''), 150.5 (C-2), 163.8 (C-4) ppm; ms: (m/e) 323 ($M^+$).

*Anal.* Calcd. for $C_{13}H_{17}N_5O_5\cdot\frac{1}{2}H_2O$: C, 47.0; H, 5.5; N, 21.1. Found: C, 47.1; H, 5.4; N, 20.7.

5'-*O*-Acetyl-3'-(4-hydroxymethyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**4b**) and 5'-*O*-Acetyl-3'-(5-hydroxymethyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**4a**).

To a solution of 1 g (3.8 mmoles) of **1a** in 10 ml of pyridine was added 2 ml of acetic anhydride. The mixture was kept overnight at 4°, evaporated and coevaporated three times with toluene. The residual foam was dissolved in a mixture of 25 ml of toluene and 2.5 ml of propargyl alcohol **2b**. The solution was kept for 3 days at 75°. The liquids were evaporated to an oil and this oil was purified by column chromatography. Two products were isolated. The compound with the highest Rf on tlc was obtained in 32% yield (450 mg) and identified as 5'-*O*-acetyl-3'-(5-hydroxymethyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine: uv (methanol): λ max 266 nm; $^1$H nmr (DMSO-$d_6$): δ 1.86 (s, 3H, $CH_3$-5), 2.09 (s, 3H, $CH_3$-Ac), 2.70 (m, 2H, H-2'), 4.33 (d, 2H, H-5'), 4.51 (m, 1H, H-4'), 4.67 (d, 2H, $CH_2$-5''), 5.11-5.70 (m, 2H, OH and H-3'), 6.56 (t, 1H, H-1'), 7.63 (s, 1H, H-6), 7.70 (s, 1H, H-4''), 11.28 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.6 ($CH_3$-5), 20.9 ($CH_3$-Ac), 37.3 (C-2'), 51.8 ($CH_2$-5'') 58.1 (C-3'), 64.3 (C-5'), 82.0 and 85.6 (C'-4 and C'-1), 110.5 (C-5), 133.0 (C-4''), 136.5 (C-6), 138.0 (C-5''), 150.8 (C-2) 164.2 (C-4), 170.7 (C=O-Ac) ppm.

The second compound was obtained in 51% yield (720 mg) and was identified as 5'-*O*-acetyl-3'-(4-hydroxymethyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine; uv (methanol): λ max 267 nm; $^1$H nmr (DMSO-$d_6$): δ 1.83 (s, 3H, $CH_3$-5), 2.03 (s, 3H, $CH_3$-Ac), 2.75 (m, 2H, H-2'), 4.27 (d, 2H, H-5'), 4.44 (m, 1H, H-4'), 4.57 (d, 2H, $CH_2$-4''), 5.15-5.63 (m, 2H, OH and H-3'), 6.42 (t, 1H, H-1'), 7.63 (s, 1H, H-6), 8.20 (s, 1H, H-5''), 11.32 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.2 ($CH_3$-5), 20.7 ($CH_3$-Ac), 36.7 (C-2'), 55.1 ($CH_2$-4''), 59.4 (C-3') 63.5 (C-5'), 81.2 and 84.5 (C-4' and C-1'), 110.2 (C-5), 122.6 (C-5''), 136.6 (C-6), 148.5 (C-4''), 150.6 (C-2) 163.9 (C-4), 170.4 (C=O-Ac).

3'-(4-Fluoromethyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3f**).

To a stirred suspension of 220 mg (0.57 mmole) of **4b** at -78° was added 90 μl (0.6 mmole) of diethylaminosulfur trifluoride in 10 ml of dichloromethane. The mixture was warmed up to 0°. After 1 hour 150 mg of sodium bicarbonate was added, tlc [chloroform-methanol, (9:1)] of the reaction mixture revealed one compound with a higher mobility than the starting material **4b**. The solvent was evaporated and the reaction mixture was purified by column chromatography, yielding 100 mg (45%) of an oil which was kept overnight in methanol saturated with ammonia. Evaporation of the reaction mixture and chromatographic

purification [silica gel-dichloromethane-methanol: (90:10)] yielded 60 mg (31% from **4b**). This compound was obtained as a white foam: uv (methanol): λ max 266 nm; (log ε = 4.00); $^1$H nmr (DMSO-$d_6$): δ 1.83 (s, 3H, $CH_3$), 2.71 (m, 2H, H-2'), 3.70 (br s, 2H, H-5'), 4.27 (m, 1H, H-4'), 5.41 (m, 1H, H-3'), 5.48 (d, 2H, $J_{H,F}$ = 48.8 Hz, $CH_2$-F), 6.44 (t, 1H, H-1'), 7.82 (s, 1H, H-6), 8.50 (d, 1H, $J_{H,F}$ = 2.9 Hz, H-5''), 11.30 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.4 ($CH_3$), 37.4 (C-2'), 59.6 and 60.5 (C-3' and C-5'), 75.5 (d, $J_{C,F}$ = 159.9 Hz, $CH_2$F), 84.2 and 84.6 (C-1' and C-4'), 109.9 (C-5), 125.5 (C-5''), 136.4 (C-6), 142.6 (d, $J_{C,F}$ = 20.8 Hz, C-4''), 150.6 (C-2), 164.4 (C-4) ppm; ms: (m/e) 325 ($M^+$).

*Anal.* Calcd. for $C_{13}H_{16}N_5O_4F\cdot\frac{1}{2}H_2O$: C, 46.7; H, 5.1; N, 21.0. Found: C, 47.1; H, 4.9; N, 21.4.

3'-(5-Fluoromethyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3e**).

To 467 mg (1.21 mmoles) of a mixture of **4a** and **4b** in 20 ml of dichloromethane at -78° was added 170 μl of (1.06 mmoles) diethylaminosulfur trifluoride. The mixture was warmed up to 0°, stirred for 1 hour and poured into 20 ml of a 5% sodium bicarbonate solution in water. The aqueous solution was extracted with dichloromethane (2 x 20 ml). The organic layer was dried, evaporated and treated overnight with methanol saturated with ammonia. The reaction mixture was evaporated and purified by column chromatography; 70 mg of 3'-(5-fluoromethyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymine was obtained. Finally the product was purified by preparative tlc; uv (methanol): λ max 266 nm; (log ε = 4.03); $^1$H nmr (DMSO-$d_6$): δ 1.83 (s, 3H, $CH_3$), 2.67 (m, 2H, H-2'), 3.70 (br s, 2H, H-5'), 4.25 (m, 1H, H-4'), 5.23 (m, 2H, H-3' and OH), 5.75 (d, 2H, $J_{H,F}$ = 47.9 Hz, $CH_2$-F), 6.56 (t, 1H, H-1'), 7.83 (s, 1H, H-6), 7.97 (d, 1H, $J_{H,F}$ = 3.1 Hz, H-4''), 11.35 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.2 ($CH_3$), 37.3 (C-2'), 58.4 and 61.2 (C-3' and C-5'), 71.5 (d, $J_{C,F}$ = 159.9 Hz, $CH_2$F), 84.7 and 84.9 (C-1' and C-4'), 109.7 (C-5), 133.6 (d, $J_{C,F}$ = 18.3 Hz, C-5''), 135.0 (C-4''), 136.0 (C-6), 150.4 (C-2), 163.7 (C-4) ppm; ms: (m/e) 325 ($M^+$).

*Anal.* Calcd. for $C_{13}H_{16}N_5O_4F\cdot\frac{1}{2}H_2O$: C, 46.7; H, 5.1; N, 21.0. Found: C, 46.6; H, 5.1; N, 20.6.

3'-(5-Chloromethyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3g**).

To a solution of 310 mg (0.83 mmole) of **4a** in 10 ml of dimethylformamide was added 0.075 ml (0.85 mmole) of carbon tetrachloride and 275 mg (1 mmole) of triphenylphosphine. The mixture was stirred overnight at room temperature; tlc [ethyl acetate-methanol (9:1)] revealed that half of the starting material had been transformed to a more lipophilic compound. Another 0.075 ml of tetrachlorocarbon and 275 mg of triphenylphosphine was added. The reaction was completed after 48 hours (tlc). The solvent was removed by evaporation and the residual oil was purified chromatographically. Two products were obtained: 170 mg (60% yield) of **3g** and 100 mg of **4e** (31% yield); **4e** was taken up in 50 ml of a 1-1 mixture of methanol and water; the *p*H was brought to 10 with potassium carbonate. After 2 hours **4e** was converted quantitatively into **3g**.

This compound was crystallized from methanol, mp 182-184°; uv (methanol): λ max 266 nm; (log ε = 3.98); $^1$H nmr (DMSO-$d_6$): δ 1.82 (s, 3H, $CH_3$), 2.66 (m, 2H, H-2'), 3.72 (br s, 2H, H-5'), 4.28 (m, 1H, H-4'), 5.07 (s, 2H, $CH_2$Cl), 5.15-5.48 (m, 2H, OH and H-3'), 6.56 (t, 1H, H-1'), 7.86 (br s, 2H, H-6 and H-4''), 11.30 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.7 ($CH_3$), 32.2 ($CH_2$Cl), 38.0 (C-2'), 58.7 and 61.8 (C-3' and C-5'), 85.3 (C-1' and C-4'), 110.4 (C-5), 134.3 and 134.6 (C-4'' and C-5''), 136.7 (C-6), 150.9 (C-2), 164.4 (C-4) ppm.

*Anal.* Calcd. for $C_{13}H_{16}N_5O_4Cl$: C, 45.7; H, 4.7; N, 20.5. Found: C, 45.5; H, 4.7; N, 20.6.

3'-(4-Chloromethyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3h**).

To a solution of 200 mg (0.53 mmole) of **4b** in 10 ml of dimethylformamide was added 0.05 ml of carbon tetrachloride (0.55 mmole) and 300 mg (1.1 mmoles) of triphenylphosphine. The mixture was kept for 72 hours at room temperature, tlc [ethyl acetate-methanol (9:1)] revealed that all of **4b** had been transformed to a more lipophilic product. The solvent was evaporated and the residual oil was taken up in methanol saturated with ammonia. Two compounds were formed according to tlc analysis. Only the one with the highest mobility was obtained in pure form and identified as **3h** in 106 mg yield (58% from **4b**). This compound was crystallized from methanol-ether, mp 148-150°; uv (methanol): λ max 266 nm (log ε = 4.01); $^1$H nmr (DMSO-$d_6$): δ 1.84 (s, 3H, $CH_3$), 2.74 (m, 2H, H-2'), 3.71 (br s, 2H, H-5'), 4.27 (m, 1H, H-4'), 4.86 (s, 2H, $CH_2$Cl), 5.28-5.57 (m, 2H, OH and H-3'), 6.44 (t, 1H, H-1), 7.84 (s, 1H, H-6), 8.40 (s, 1H, H-5''), 11.29 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.5 ($CH_3$), 36.5 and 37.2 ($CH_2$Cl and C-2'), 59.5 and 60.9 (C-3' and C-5'), 84.0 and 84.5 (C-1' and C-4'), 109.8 (C-5), 124.0 (C-5''), 136.3 (C-6), 143.7 (C-4''), 150.5 (C-2), 163.8 (C-4) ppm.

*Anal.* Calcd. for $C_{13}H_{16}N_5O_4Cl$: C, 45.7; H, 4.7; N, 20.5. Found: C, 45.8; H, 4.8; N, 20.5.

3'-(5-Methyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3i**).

To a solution of 190 mg (0.5 mmole) of **3k** in 20 ml of tetrahydrofuran was added 0.8 ml of 1 *M* solution of tetrabutylammonium fluoride monohydrate in tetrahydrofuran. The mixture was refluxed overnight. The solvent was evaporated and the reaction mixture was purified by column chromatography giving 120 mg (80% yield) of **3i** which was crystallized from methanol, mp 222-224°; uv (methanol): λ max 266 nm (log ε = 3.97); $^1$H nmr (DMSO-$d_6$): δ 1.82 (s, 3H, $CH_3$-5), 2.34 (s, 3H, $CH_3$-5''), 2.66 (m, 2H, H-2'), 3.65 (br s, 2H, H-5'), 4.20 (m, 1H, H-4'), 5.17 (m, 1H, H-3'), 5.34 (t, 1H, OH), 6.50 (t, 1H, H-1'), 7.55 (s, 1H, H-4''), 7.87 (s, 1H, H-6), 11.33 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 8.1 ($CH_3$-5''), 12.5 ($CH_3$-5), 37.2 (C-2'), 57.4 and 61.4 (C-3' and C-5'), 84.8 and 85.1 (C-1' and C-4'), 110.2 (C-5), 132.9 (C-5''), 134.0 (C-4''),136.5 (C-6), 150.7 (C-2), 164.1 (C-4); ms: (m/e) 307 ($M^+$).

*Anal.* Calcd. for $C_{13}H_{17}N_5O_4\cdot\frac{1}{4}H_2O$: C, 50.1; H, 5.7; N, 22.8. Found: C, 50.2; H, 5.5; N, 22.4.

3'-(4-Methyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3j**).

To a solution of 150 mg of **4b** (0.41 mmole) in 5 ml of dimethylformamide was added under nitrogen atmosphere 210 mg (0.46 mmole) of methyltriphenoxyphosphonium iodide. The mixture was kept at room temperature for 1 hour and poured into 50 ml of water. Sodium thiosulfate was added until the solution discolored. The reaction mixture was extracted with 3 x 50 ml of ethyl acetate. The organic layer was dried, evaporated and taken up in 20 ml of methanol. An amount of 30 mg of 10% of palladium on carbon and 136 mg (1.66 mmoles) of sodium acetate were added. The solution was hydrogenated for 16 hours at 50 psi. After filtration, the solvent was evaporated and the resulting oil was purified chromatographically; 75 mg (52%) of **4h** was obtained as a colourless foam; $^1$H nmr (DMSO-$d_6$): δ 1.84 (s, 3H, $CH_3$-5), 2.04 (s, 3H, $CH_3$-Ac), 2.27 (s, 3H, $CH_3$-4''), 2.78 (m, 2H, H-2'), 4.30 (br s, 2H, H-5'), 4.55 (m, 1H, H-4'), 5.41 (m, 1H, H-3'), 6.42 (t, 1H, H-1'), 7.60 (s, 1H, H-6), 8.03 (s, 1H, H-5''), 11.35 (br s,

1H, NH) ppm; $^{13}$C nmr: δ 10.5 ($CH_3$-4'), 12.0 ($CH_3$-5), 20.5 ($CH_3$-Ac), 36.4 (C-2'), 59.1 (C-3'), 69.8 (C-5'), 80.9 and 84.2 (C-4' and C-1'), 109.9 (C-5), 121.7 (C-5''), 136.3 (C-6), 142.3 (C-4''), 150.3 (C-2), 163.6 (C-4), 170.0 (CO-Ac) ppm. Then 75 mg (0.2 mmole) of **4h** was dissolved in methanol saturated with ammonia and kept overnight at room temperature. The solvent was evaporated and the product was isolated after chromatographic purification, yield 60 mg (93%). This product was crystallized from methanol, mp 237-239°; uv (methanol): λ max 266 nm; (log ε = 4.02); $^1$H nmr (DMSO-$d_6$): δ 1.82 (s, 3H, $CH_3$-5), 2.28 (s, 3H, $CH_3$-4''), 2.67 (m, 2H, H-2'), 3.63 (br s, 2H, H-5'), 4.55 (m, 1H, H-4'), 5.26 (t, 1H, OH), 5.41 (m, 1H, H-3'), 6.42 (t, 1H, H-1'), 7.60 (s, 1H, H-6), 8.03 (s, 1H, H-5''), 11.27 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 10.4 ($CH_3$-4''), 12.1 ($CH_3$-5), 36.8 (C-2'), 58.9 and 60.7 (C-3' and C-5'), 84.0 and 84.5 (C-1' and C-4'), 109.6 (C-5), 121.7 (C-5''), 136.2 (C-6), 142.2 (C-4''), 150.4 (C-2), 163.6 (C-4) ppm; ms: (m/e) 307 ($M^+$).

*Anal.* Calcd. for $C_{13}H_{17}N_5O_4$: C, 50.8; H, 5.6; N, 22.8. Found: C, 50.9; H, 5.7; N, 22.7.

3'-(4-Trimethylsilyl-5-methyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3k**).

A mixture of 310 mg of **1a** (1.16 mmoles), 0.3 ml of 1-(trimethylsilyl)-1-propyne **2c**, 1 ml of pyridine and 10 ml of toluene was heated for 48 hours at 100°. After addition of another 0.2 ml of **2c**, the reaction was heated for another 4 days. The solvents were evaporated, and the title compound was isolated after chromatographic purification. The compound was crystallized from a mixture dichloromethane-ether, mp 80-85°; uv (methanol): λ max 266 nm (log ε = 3.98); $^1$H nmr (DMSO-$d_6$): δ 0.43 [s, 9H, $Si(CH_3)_3$], 1.82 (s, 3H, $CH_3$-5), 2.37 (s, 3H, $CH_3$-5''), 2.65 (m, 2H, H-2'), 3.66 (br s, 2H, H-5'), 4.21 (m, 1H, H-4'), 5.06 (m, 1H, H-3'), 5.28 (t, 1H, OH), 6.50 (t, 1H, H-1'), 7.81 (s, 1H, H-6), 11.30 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 0.6 [$Si(CH_3)_3$], 9.0 ($CH_3$-5''), 12.4 ($CH_3$-5), 37.4 (C-2'), 57.1 and 61.4 (C-3' and C-5'), 84.9 and 85.1 (C-4' and C-1'), 110.1 (C-5), 136.4 (C-6), 139.4 (C-5''), 142.3 (C-4''), 150.7 (C-2), 164.1 (C-4) ppm; ms: (m/e) 379 ($M^+$).

*Anal.* Calcd. for $C_{16}H_{26}N_5O_4Si$: C, 48.3; H, 6.8; N, 17.6. Found: C, 48.4; H, 6.5; N, 17.6.

3'-[4,5-Di(hydroxymethyl)-1,2,3-triazol-1-yl]-2',3'-dideoxythymidine (**3l**).

A solution of 250 mg (0.94 mmole) of **1a** and 430 mg (5 mmoles) of 2-butyne-1,4-diol **2d** in 10 ml of a mixture of toluene-pyridine (10:1) was refluxed overnight, tlc revealed that all starting material was transformed into a less lipophilic compound. This product was isolated by column chromatography [silica gel-ethyl acetate-methanol: 1. (100:0); 2. (90:10)] and crystallised from methanol, mp 151-153°; uv (methanol): λ max 226 nm (log ε = 4.02); $^1$H nmr (DMSO-$d_6$): δ 1.81 (s, 3H, $CH_3$), 2.61 (m, 2H, H-2'), 3.69 (2H, br s, H-5'), 4.24 (m, 1H, H-4'), 4.54 and 4.66 (2 x d, each 2H, $CH_2$-4'' and $CH_2$-5''), 5.08 (t, 1H, OH), 5.32 (m, 3H, 2 x OH and H-3'), 6.54 (t, 1H, H-1'), 11.33 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.4 ($CH_3$), 50.8 ($CH_2$-5''), 54.5 ($CH_2$-4''), 58.6 and 61.7 (C-3' and C-5'), 85.2 and 85.4 (C-1' and C-4'), 110.2 (C-5'), 134.8 (C-5''), 136.6 (C-6), 145.1 (C-4''), 150.5 (C-2), 164.2 (C-4) ppm; ms: (m/e) 353 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{13}N_5O_6 \cdot H_2O$: C, 45.3; H, 5.7; N, 18.9. Found: C, 45.6; H, 5.6; N, 18.9.

3'-(4-Ethoxycarbonyl-1,2,3-triazole-1-yl)-2',3'-dideoxythymidine (**3m**).

A solution of 330 mg of **1a** (1.24 mmoles), 2 ml (20 mmoles) of ethyl propiolate **2e** in 20 ml of ethanol was refluxed for 72 hours, tlc (ethylacetate) revealed the formation of one major product. The solvent was evaporated and coevaporated with toluene twice. The mixture was purified chromatographically (silica gel-ethyl acetate) and 260 mg (57% yield) of pure **3m** was obtained; the compound was crystallized from a mixture of methanol and ether, mp 198-200°; uv (methanol): λ max 266 (log ε = 4.02); $^1$H nmr (DMSO-$d_6$): δ 1.31 (t, 3H, $CH_3$-Et), 1.81 (s, 3H, $CH_3$-5), 2.67 (m, 2H, H-2'), 3.69 (br s, 2H, H-5'), 4.11-4.53 (m, 3H, H-4' and $CH_2$-Et), 5.26 (t, 1H, OH), 5.44 (m, 1H, H-3'), 6.44 (t, 1H, H-1'), 7.81 (s, 1H, H-6), 8.98 (s, 1H, H-5''), 11.29 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.6 ($CH_3$-5), 14.6 ($CH_3$-Et), 60.7, 61.2 and 61.4 (C-3', C-5' and $CH_2$-Et), 84.7 and 84.8 (C-1' and C-4'), 110.5 (C-5), 129.2 (C-5''), 137.0 (C-6), 139.6 (C-4''), 150.9 (C-2), 161.0 (C=O-COOEt) 164.5 (C-4) ppm; ms: (m/e) 365 ($M^+$).

*Anal.* Calcd. for $C_{15}H_{19}N_5O_6 \cdot \frac{1}{2}H_2O$: C, 48.2; H, 5.4; N, 18.7. Found: C, 48.2; H, 5.2; N, 19.0.

3'-(4-Phenyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3n**).

To a solution of 300 mg (1.1 mmoles) of **1a** in ethanol was added 1 ml (0.91 mmole) of phenylacetylene **2f**. The solution was refluxed for 24 hours. Then another 2 ml of **2f** was added and the mixture was further refluxed for 48 hours. At that moment almost 80% of **1a** was transformed; another 1 ml of **2f** was added and the solution was refluxed for 72 hours. The solvent was evaporated and coevaporated with toluene (3 x). The residual oil was diluted with dichloromethane. The title compound crystallized from this solvent. The filtrate was evaporated and purified chromatographically (silica gel-ethyl acetate), total yield 71% (290 mg), mp 232-234°; uv (methanol): λ max 252 nm (log ε = 4.64); $^1$H nmr (DMSO-$d_6$): δ 1.83 (s, 3H, $CH_3$), 2.76 (m, 2H, H-2'), 3.72 (br s, 2H, H-5'), 4.82 (m, 1H, H-4'), 5.23 (t, 1H, OH), 5.41 (m, 1H, H-3'), 6.45 (t, 1H, H-1'), 7.26-7.62 and 7.71-8.03 (2 x m, each 3H, phenyl and H-6), 8.77 (s, 1H, H-5''), 11.34 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 10.29 ($CH_3$), 37.3 (C-2'), 59.6 and 60.9 (C-3' and C-5'), 84.3 and 84.6 (C-1' and C-4'), 109.8 (C-5), 121.1 (C-5''), 125.4, 128.1, 129.1 and 130.7 (phenyl), 136.4 (C-6), 146.8 (C-4''), 150.5 (C-2), 163.8 (C-4) ppm; ms: (m/e) 369 ($M^+$).

*Anal.* Calcd. for $C_{18}H_{19}N_5O_4$: C, 58.5; H, 5.2; N, 19.0. Found: C, 58.2; H, 5.2; N, 19.1.

3'-(4-Ethoxy-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3o**).

To a solution of 300 mg (1.13 mmoles) of **1a** in 10 ml of pyridine was added 2 ml of acetic anhydride. The solution was kept overnight at 4°. The liquids were removed by evaporation. The residual oil was taken up in 20 ml of toluene and 1 g of a 50% solution of ethyl ethinyl ether **2g** in hexane was added. The mixture was refluxed for 2 days, cooled and poured into 200 ml of ethyl acetate. The organic layer was washed with 200 ml of a 5% sodium bicarbonate solution in water and with 200 ml of water. The organic layer was dried and evaporated. The residual oil was taken up in 20 ml of methanol saturated with ammonia. Chromatographic purification [silica gel-ethyl acetate] gave 180 mg of unreacted **1a** (60%) and 130 mg (34%) of **3o**. This compound was further purified by preparative tlc to obtain an analytical pure compound; uv (methanol): λ max 266 nm (log ε = 4.06); $^1$H nmr (DMSO-$d_6$): δ 1.30 (t, 3H, $CH_3$-Et), 1.74 (s, 3H, $CH_3$-5), 3.60 (br s, 2H, H-5'), 4.10-4.30 (m, 3H, H-4' and $CH_2$-Et), 5.00 (t, 1H, OH), 5.20 (m, 1H, H-3'), 6.36 (t, 1H, H-1'), 7.26 (s, 1H, H-5''), 7.74 (s, 1H, H-6), 11.29 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.7 ($CH_3$-5), 14.9 ($CH_3$-Et), 29.7 (C-2'), 56.7 and 61.8 (C-3' and C-5'), 69.8 ($CH_2$-Et),

84.6 and 85.1 (C-1' and C-4'), 110.6 (C-5), 115.1 (C-5''), 137.0 (C-6), 151.1 (C-2), 152.0 (C-4''), 164.6 (C-4) ppm; ms: (m/e) 337 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{19}N_5O_4 \cdot \frac{1}{2}H_2O$: C, 48.6; H, 5.8; N, 20.2. Found: C, 48.3; H, 5.5; N, 20.1.

3'-(4-Nitro-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**3p**).

To a solution of 300 mg (1.13 mmoles) of **1a** in pyridine was added 150 mg (0.95 mmole) of 1-morpholino-2-nitroethene **6**. The mixture was refluxed for 1 week. Every day 150 mg of **6** was added. After 1 week the reaction was stopped. The solvent was evaporated and the reaction mixture purified by column chromatography [silica gel-dichloromethane-methanol: 1. (100:0); 2. (97:3); 3. (95.5)]; 60 mg (15%) of **3p** was obtained. An analytically pure sample was obtained by preparative tlc; uv (methanol): λ max 266 nm (log ε = 4.24); $^1$H nmr (DMSO-$d_6$): δ 1.81 (s, 3H, $CH_3$), 2.79 (m, 2H, H-2'), 3.71 (br s, 2H, H-5'), 4.35 (m, 1H, H-4'), 5.28 (t, 1H, OH), 5.52 (m, 1H, H-3'), 6.44 (t, 1H, H-1'), 7.81 (s, 1H, H-6), 9.52 (s, 1H, H-5''), 11.29 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 12.2 ($CH_3$), 37.0 (C-2'), 60.7 and 61.1 (C-3' and C-5'), 84.0 (C-1' and C-4'), 109.8 (C-5), 124.8 (C-5''), 136.3 (C-6), 151.1 (C-2), 153.1 (C-4''), 163.7 (C-4) ppm; ms: (m/e) 338 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{14}N_6O_6 \cdot \frac{1}{4}H_2O$: C, 41.9; H, 4.5; N, 24.4. Found: C, 42.2; H, 4.2; N, 24.1.

3'-(4-Trimethylsilyl-1,2,3-triazol-1-yl)-2',3'-dideoxythymidine (**5a**).

A mixture of 300 mg of **1b** (1.4 mmoles) and 1 ml (10 mmoles) of trimethylsilylacetylene **2a** in 10 ml of dichloroethane was heated for 24 hours at 120° in a sealed vessel. After cooling, the mixture was poured into 50 ml of methanol and stirred overnight at room temperature. The liquids were evaporated and mixture was separated by column chromatography to obtain 340 mg of **5a** (yield 71%). It was crystallized from dichloromethane, mp 211-213°: uv (methanol): λ max 260 nm (log ε = 4.07); $^1$H nmr (DMSO-$d_6$): δ 0.56 [s, 9H, $Si(CH_3)_3$], 2.67 (m, 2H, H-2'), 3.97 (br s, 2H, H-5'), 4.54 (m, 1H, H-4'), 5.33 (m, 1H, H-3'), 5.62 (t, 1H, OH), 6.00 (d, 1H, J = 8.35 Hz, H-5), 6.70 (t, 1H, H-1'), 8.27 (d, 1H, J = 8.35 Hz, H-6), 8.60 (s, 1H, H-5''), 11.55 (br s, 1H, NH) ppm; $^{13}$C nmr: δ 0.6 [$Si(CH_3)_3$], 37.3 (C-2'), 59.4 and 61.2 (C-3' and C-5'), 85.2 (C-4' and C-1'), 102.3 (C-5), 130.5 (C-5''), 141.3 (C-6), 149.9 (C-4''), 150.8 (C-2) 163.8 (C-4) ppm; ms: (m/e) 351.

*Anal.* Calcd. for $C_{14}H_{21}N_5O_4Si$: C, 47.8; H, 6.0; N, 19.9. Found: C, 47.4; H, 5.9; N, 19.7.

3'-(1,2,3-Triazol-1-yl)-2',3'-dideoxyuridine (**5b**).

To a solution of 250 mg (0.71 mmole) of **5a** in 20 ml of tetrahydrofuran was added 1 ml of a 1*M* solution of tetrabutylammonium fluoride monohydrate in tetrahydrofuran. The mixture was refluxed for 6 hours. The solvent was removed and the title compound was obtained in pure form after column chromatographic purification [dichloromethane-methanol: 1. (95:5), 2. (90:10)] giving 200 mg of **5b** as a white foam, The product was crystallized from methanol, mp 210-213°; uv (methanol): λ max 261 (log ε = 4.07); $^1$H nmr: δ 2.71 (m, 2H, H-2'), 3.67 (br s, 2H, H-5'), 4.21 (m, 1H, H-4'), 5.21 (t, 1H, OH), 5.34 (m, 1H, H-3'), 5.70 (d, 1H, J = 7.9 Hz, H-5), 6.40 (t, 1H, H-1'), 7.79 (s, 1H, H-4''), 7.99 (d, 1H, J = 7.9 Hz, H-6), 8.29 (s, 1H, H-5''), 11.31 (br s, 1H, NH) ppm; $^{13}$C nmr: δ (C-2' hidden by DMSO-signal) 59.5 and 61.0 (C-3' and C-5'), 84.9 and 85.0 (C-4' and C-1'), 102.3 (C-5), 124.8 (C-5''), 133.9 (C-4''), 141.1 (C-6), 150.6 (C-2), 163.5 (C-4) ppm; ms: (m/e) 279 ($M^+$).

*Anal.* Calcd. for $C_{11}H_{13}N_5O_4 \cdot \frac{1}{4}H_2O$: C, 46.6; H, 4.8; N, 24.7. Found: C, 46.9; H, 4.7; N, 25.0.

3'-(5-Hydroxymethyl-1,2,3-triazol-1-yl)-2',3'-dideoxyuridine (**5c**) and 3'-(4-Hydroxymethyl-1,2,3-triazol-1-yl)-2',3'-dideoxyuridine (**5d**).

A solution of 600 mg (2,8 mmoles) of **1b** in mixture of 20 ml of toluene, 2 ml of pyridine and 2 ml of propargyl alcohol **2b** was refluxed overnight; tlc [chloroform-methanol: (80:20)] revealed that the reaction was completed. The compounds **4a** and **4b** were readily separated by column chromatography [silica gel, dichloromethane-methanol: 1. (88:12); 2. (85:15)]. The fast eluting product was obtained in 170 mg yield (23%) and was identified as the 5''-hydroxymethyl isomer **5c**; it was crystallized from methanol, mp 224-226°; uv (methanol): λ max 262 nm (log ε = 3.97); $^1$H nmr (DMSO-$d_6$): δ 2.66 (m, 2H, H-2'), 3.67 (m, 2H, H-5'), 4.24 (m, 1H, H-4'), 4.66 (d, 2H, $CH_2$-5''), 5.31-5.60 (m, 3H, 2 x OH and H-3'), 5.68 (d, 1H, J = 7.9 Hz, H-5), 6.32 (t, 1H, H-1'), 7.66 (s, 1H, H-4''), 7.99 (d, 1H, J = 7.9 Hz, H-6), 11.33 (s, 1H, NH) ppm; $^{13}$C nmr: δ 30.7 (C-2'), 51.6 ($CH_2$-5''), 58.1 and 61.3 (C-3' and C-5'), 85.0 and 85.3 (C-4' and C-1'), 102.0 (C-5), 132.5 (C-4''), 137.5 (C-5''), 140.5 (C-6) 150.5 (C-2), 163.0 (C-4) ppm; ms: (m/e) 209 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{15}N_5O_5$: C, 46.6; H, 4.9; N, 22.6. Found: C, 46.4; H, 4.8; N, 22.2.

The second product **5d** was obtained in 230 mg yield (31%) and was crystallized from a mixture of methanol and ether, mp 180-183°; uv (methanol): λ max 261 nm (log ε = 4.01). $^1$H nmr (DMSO-$d_6$): δ 2.69 (br s, 2H, H-2'), 3.65 (br s, 2H, H-5'), 4.26 (m, 1H, H-4'), 4.54 (s, 2H, $CH_2$-4''), 4.92-5.53 (br s, 3H, 2 x OH and H-3'), 5.66 (d, 1H, J = 7.9 Hz, H-5), 6.35 (t, 1H, H-1'), 7.96 (d, 1H, J = 7.9 Hz, H-6), 8.13 (s, 1H, H-5''), 11.41 (s, 1H, NH) ppm; $^{13}$C nmr: δ 37.5 (C-2'), 55.0 ($CH_2$-4''), 57.1 and 60.7 (C-3' and C-5'), 84.4 and 84.7 (C-4' and C-1'), 101.9 (C-5), 122.3 (C-5''), 140.6 (C-6), 148.3 (C-4''), 150.4 (C-2), 163.1 (C-4) ppm; ms (m/e) 369 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{15}N_5O_5$: C, 44.6; H, 4.9; N, 22.6. Found: C, 46.6; H, 4.9; N, 22.4.

Antiviral Assay Procedures.

The anti-HIV-1 assays were carried out with the HTLV-III$_B$ strain (kindly provided by Dr. R. C. Gallo, National Cancer Institute, Bethesda, MD). These assays were based on the inhibition of HIV-1 induced cytopathogenicity in human MT4 lymphocyte cells. The anti-MSV assays were based on the inhibition of Moloney murine sarcoma virus (MSV)-induced transformation of murine embryo fibroblast C3H/3T3 cells. Both assay procedures have been previously described [19].

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