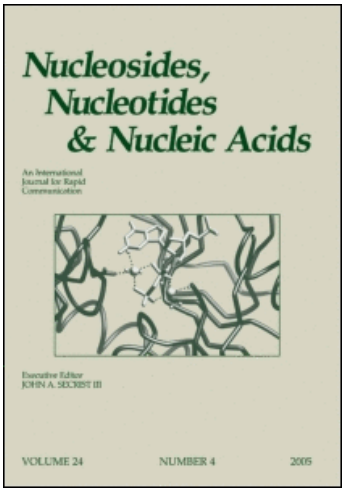

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Synthesis and Biological Activities of 3'-Deoxy-3'-Isocyano, -Isothiocyano, and -Isoselenocyano-thymidines

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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 3'-DEOXY-3'-ISOCYANO, -ISOTHIOCYANO, AND -ISOSELENOCYANO-THYMIDINES[1)]

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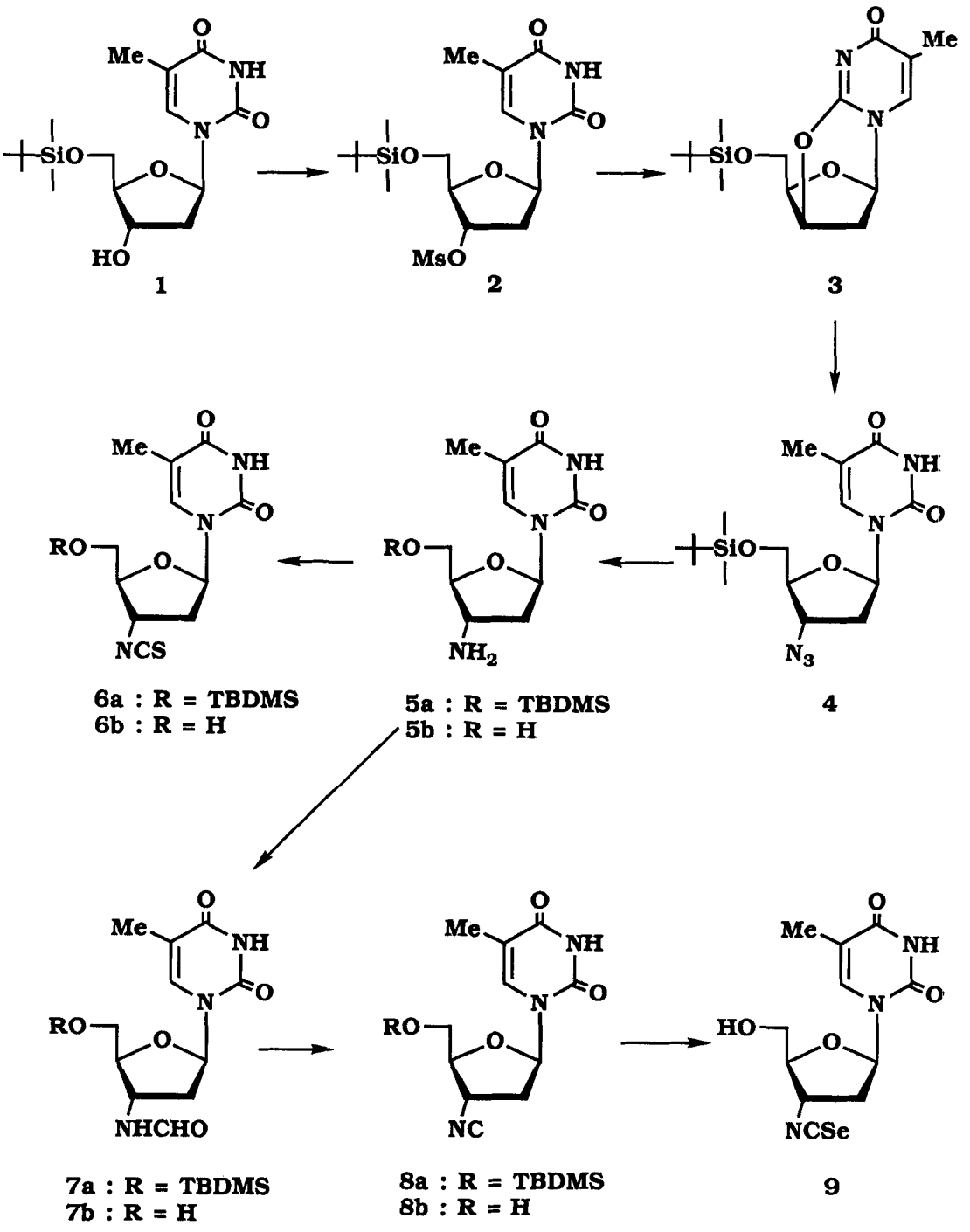
ABSTRACT: 2',3'-Dideoxy-3'-isothiocyano, -isocyano, and -isoselenocyanothymidines (**6b**, **8b**, and **9**) were synthesized from the corresponding 3'-amino derivatives (**5a**, **b**). These nucleosides were tested for inhibitory activity of the pathogenicity of HIV-1 and the growth inhibitory activity of mouse and human cancer cell lines.

2',3'-Dideoxy-3'-substituted analogues of ribonucleosides have elicited considerable anticancer and antiviral interests. 3'-Amino-3'-deoxythymidine[2-4)] has been shown to have a potent antileukemic activity. 3'-Azido-3'-deoxy-pyrimidine nucleosides[5,6)] and 2',3'-dideoxy-3'-fluoro-pyrimidine nucleosides[6)] have been recently found to inhibit the cytopathic effect of the human immunodeficiency virus type-1 (HIV-1), the causative agent of acquired immunodeficiency syndrome (AIDS). These nucleosides should be phosphorylated to the corresponding 5'-triphosphates by the cellular kinases and they are inhibitors of HIV-1 reverse transcriptase, which plays an important role of the transcription of the viral RNA to the corresponding DNA. In either cases, the cellular thymidine kinase plays a crucial role for the initial phosphorylation of the nucleosides. Recently, Chu *et al.*,



reported that the 3'-exo-sugar ring conformation of the nucleoside analogues is the most important factor for the substrate of the kinase and the inhibitor of the reverse transcriptase, based on evidence from the crystallographic data of the nucleosides exhibiting anti-HIV-1 activity.[7] From this consideration, an electron-withdrawing substituent at the 3'-α-position, would be suitable. However, 3'-cyano-2',3'-dideoxythymidine synthesized by us[8] and by others[9-11] did not show any inhibitory activity of HIV-1 cytopathogenicity. We designed thymidine derivatives bearing not only electron-withdrawing but also somewhat reactive functionalities at the 3'-position, such as 3'-isocyano, -isothiocyano and -isoselenocyano derivatives. In this paper we describe the synthesis of such thymidine derivatives and their anti-HIV-1 and antineoplastic activities.

As a starting material introducing isocyano, isothiocyano or isoselenocyano group to the 3'-position, 3'-amino-2',3'-dideoxy derivative of thymidine was first synthesized. In consideration of the instability of the 3'-substituents, we chose *tert*-butyldimethylsilyl (TBDMS) group for protection of the 5'-hydroxy. Treatment of 5'-*O*-TBDMS thymidine (**1**) with methanesulfonyl chloride in pyridine gave the corresponding 3'-*O*-mesylate (**2**). This was cyclized to the 2,3'-anhydro derivative (**3**) by treatment with 1,5-diazabicyclo[5.4.0]-undecene-5 (DBU) in acetonitrile. The anhydro nucleoside (**3**) was treated with lithium azide in the presence of a catalytic amount of benzoic acid in *N,N*-dimethylformamide (DMF) to give 5'-*O*-TBDMS-AZT (**4**) in good yield. Catalytic hydrogenation of **4** in the presence of 10% Pd/C in MeOH afforded the amino derivative (**5a**) in 66% yield.

When **5a** was treated with carbon disulfide and dicyclohexyl-carbodiimide (DCC) in pyridine the desired 3'-isothiocyano derivative (**6a**) was obtained in 87% yield. However, the deblocking of **6a** with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) resulted in a formation of a complex mixture probably due to the instability of the isothiocyano group. 3'-Amino-3'-deoxythymidine hydrochloride (**5b**)[12] which was readily obtained from **5a**, was then reacted with carbon disulfide and DCC in pyridine to furnish the desired 3'-deoxy-3'-isothiocyanothymidine (**6b**)[11,13] in 96% yield as hygroscopic crystals after purification by a silica gel column.

TABLE 1. Inhibitory Effects of 3'-Deoxy-3'-Substituted Thymidine Derivatives on the Growth of Tumor Cells *In Vitro*

Cell lines / Compds	IC_{50} (μg / ml)		
	L5178Y	**L1210**	**KB**
7b	> 100	> 10	> 10
8b	37.2	> 10	> 10
6b	3.9	28.5% (10μg/ml)	7.6% (10μg/ml)
9	1.2	4.8	6.2

Treatment of **5a** with acetic formic anhydride in dichloromethane gave the 3'-formamido derivative (**7a**) in 91% yield. Deprotection of **7a** with TBAF in THF furnished 3'-deoxy-3'-formamidothymidine (**7b**) in quantitative yield. Treatment of **7a** with a mixture of triphenylphosphine, carbon tetrachloride, and triethyamine in hot dichloromethane gave the desired isocyano derivative (**8a**) in 81% yield. The dehydration reaction of **7a** with diethyl azodicarboxylate and triphenylphosphine in THF also afforded **8a** in 81% yield. Conversion of **7a** to **8a** by the use of tosyl chloride in pyridine proceeded rather sluggishly. Compound **8a** was then desilylated with TBAF in THF giving 3'-deoxy-3'-isocyanothymidine (**8b**)[13-15] in 48% yield.

Compound **8b** was heated with selenium metal in anhydrous pyridine to furnish 3'-deoxy-3'-isoselenocyanothymidine (**9**) which was obtained as colorless crystals from hexane after purification by a silica gel column. However, this compound (**9**) was very sensitive to air, even on standing at room temperature, the selenium metals released quickly.

Inhibition of the cytopathogenicity of HIV-1 with the compounds (**6b**, **7b** and **8b**) was tested by using HTLV-1-carrying MT-4 cells. None of them exhibited any inhibitory activity up to 100 μg/ml concentrations.[16] Instead, compounds **6b** and **9** were rather cytotoxic to mouse leukemic cell lines, L5178Y and L1210 cells.

Compound **9** also showed the growth inhibition to human oral epidermoid carcinoma (KB) cells (Table 1). It is not clear whether the toxicity is due to the isoselenocyano function of **9** or the selenium metals released therefrom. Preliminary *in vivo* test of **6b** (ip. qd x 9, 50 mg/kg) using female BDF_1 mice bearing P388 leukemia was also performed. Compound **6b** was found to be also toxic to the mouse and the ILS value was -10.6 %, whereas the mean values for the control was 11.3 days. The precise analysis of the sugar-puckering of these 3'-substituted thymidines is a future subject.

EXPERIMENTAL

Melting points were determined on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL FT100FT or FX-270FT spectrometer with tetramethylsilane as internal standard. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were confirmed by addition of D_2O. IR spectra were recorded on JASCO IR report 100 spectrometer. Mass spectra (MS) were measured on a JEOL JMX-DX303 spectrometer. TLC was performed on Merck Kieselgel F254 precoated plates. Silica gel used for column chromatography was YMC gel 60A (70-230 mesh).

5'-*O*-*t*-Butyldimethylsilyl-3'-*O*-mesylthymidine (2).
Methanesulfonyl chloride (2.5 ml, 15 mmol) was added to a mixture of 5'-*O*-TBDMS thymidine (**1**, 3.5 g, 10 mmol) and triethylamine (1.5 ml, 15 mmol) in dry CH_2Cl_2 (50 ml) at 0°C. The mixture was stirred for 2 h, then washed successively with sat. aqueous $NaHCO_3$ (20 ml) and H_2O (20 ml). The separated organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was chromatographed over a silica gel column with 30% hexane in EtOAc to give **2** (3.6 g, 82%, Et_2O-hexane); mp 148-9°C. MS *m/z*: 419 (M^+-t-Bu). ^{1}H-NMR ($CDCl_3$): 0.14 (6H, s, $SiMe_2$), 0.93 (9H, s, Si-t-Bu), 1.86 (3H, d, 5-Me, $J_{Me,6}$ = 1.1 Hz), 3.10 (3H, s, OMs), 2.32-2.86 (2H, m, H-2',2''), 3.91 (2H, m, H-5',5''), 4.34 (1H, m, H-4'), 5.26 (1H, m, H-3'), 6.31 (1H, dd, H-1', $J_{1',2'}$ = Hz), 7.44 (1H, d, H-6), 8.23

(1H, brs, NH). *Anal.* Calcd for $C_{17}H_{30}N_2O_7SSi$: C, 46.99; H, 6.96; N, 6.45. Found: C, 46.51; H, 7.02; N, 6.20.

5'-*O*-*t*-Butyldimethylsilyl-2,3'-anhydrothymidine (3).

A mixture of **2** (2.61 g, 6 mmol) and DBU (0.98 ml, 6.6 mmol) in dry CH_3CN (25 ml) was heated under reflux for 1 h, and the solvent was concentrated to dryness *in vacuo*. The residue was partitioned between $CHCl_3$ (80 ml) and H_2O (30 ml) and the organic phase was dried (Na_2SO_4) and concentrated to dryness. The residue was purified over a silica gel column (3.6 x 23.5 cm) with 8% EtOH in $CHCl_3$ to give **3** (1.9 g, 87%, $CHCl_3$-hexane); mp 164-167°C. MS *m/z*: 339 (M^+), 281 (M^+-t-Bu). ^{1}H-NMR ($CDCl_3$): 0.06 (6H, d, $SiMe_2$), 0.87 (9H, s, Si-t-Bu), 1.95 (3H, d, 5-Me, $J_{Me,6}$ = 1.2 Hz), 2.45-2.57 (2H, m, H-2'), 3.77 (2H, dd, H-5',5''), 4.28 (1H, m, H-4'), 5.19 (1H, m, H-3'), 5.75 (1H, d, H-1', $J_{1',2'}$ = 3.9 Hz), 6.93 (1H, d, H-6). *Anal.* Calcd for $C_{16}H_{26}N_2O_4Si$: C, 56.78; H, 7.74; N, 8.28. Found: C, 56.48; H, 7.83; N, 8.16.

3'-Azido-5'-*O*-*t*-butyldimethylsilyl-3'-deoxythymidine (4).

A mixture of **3** (339 mg, 1 mmol), benzoic acid (24 mg, 0.2 mmol) and lithium azide (73 mg, 1.5 mmol) in dry DMF (10 ml) was heated under reflux for 1.5 h and the cooled mixture was partitioned between EtOAc (50 ml) and H_2O (10 ml x 4). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified over a silica gel column (2.1 x 13 cm) with $CHCl_3$ to give **4** (298 mg, 78.2%, hexane); mp 79-82°C. MS *m/z*: 324 (M^+-t-Bu). IR vmax KBr cm^{-1}: 2200 (N_3). ^{1}H-NMR ($CDCl_3$): 0.13 (6H, s, $SiMe_2$), 0.94 (9H, s, Si-t-Bu), 1.92 (3H, d, 5-Me, $J_{Me,6}$ = 1.2 Hz), 2.28 (2H, m, H-2',2''), 3.74-4.04 (3H, m, H-4',5',5''), 4.24 (1H, m, H-3'), 6.22 (1H, t, H-1', $J_{1',2'}$ = $J_{1',2''}$ = 6.6 Hz), 7.44 (1H, d, H-6), 8.24 (1H, brs, NH). *Anal.* Calcd for $C_{16}H_{27}N_5O_4Si$: C, 50.37; H, 7.13; N, 18.36. Found: C, 50.32; H, 7.08; N, 18.24.

3'-Amino-5'-*O*-*t*-butyldimethylsilyl-3'-deoxythymidine (5a).

A solution of **4** (3.81 g, 10 mmol) in MeOH (20 ml) was hydrogenated with 10% Pd/C (300 mg) under atmospheric hydrogen pressure at room temperature for 55 h. The insoluble materials were removed by filtration through a celite pad. The filtrate was concentrated to dryness and the residue was chromatographed over a silica gel column (2.7 x 15.5 cm) with 8% EtOH in $CHCl_3$ to give **5a** (2.35 g,

66%, Et_2O); mp 168-170°C. MS *m/z*: 355 (M^+), 340 (M^+-Me). ^{1}H-NMR ($CDCl_3$ + D_2O): 0.12 (6H, s, $SiMe_2$), 0.93 (9H, s, Si-t-Bu), 1.92 (3H, d, 5-Me, $J_{Me,6}$ = 1.2 Hz), 2.19 (2H, m, H-2',2''), 3.58-3.91 (4H, m, H-3',4',5',5''), 6.24 (1H, t, H-1', $J_{1',2'} = J_{1',2''}$ = 6.1 Hz), 7.50 (1H, d, H-6). *Anal.* Calcd for $C_{16}H_{29}N_3O_4Si$: C, 54.06; H, 8.22; N, 11.82. Found: C, 54.06; H, 8.27; N, 11.62.

3'-Amino-3'-deoxythymidine hydrochloride (5b).

A solution of **5a** (1.77 g, 5 mmol) in dry THF (20 ml) was treated with TBAF (1M THF solution, 6 ml) at room temperature for 1 h. The mixture was concentrated to dryness and the residue was crystallized from EtOH containing N HCl (6 ml) to give **5b** (1.1 g, 79%).

5'-*O*-*t*-Butyldimethylsilyl-3'-deoxy-3'-isothiocyanothymidine (6a).

A mixture of **5a** (120 mg, 0.33 mmol) and DCC (105 mg, 0.51 mmol) in dry pyridine (5 ml) containing carbon disulfide (0.2 ml) was stirred for 9 h at room temperature then concentrated to dryness *in vacuo*. The residue was purified by a silica gel column eluted with hexane / ethyl acetate (1 : 1). Evaporation of the UV absorbing fractions gave **6a** (117 mg, 87%, hexane); mp 147-149°C. MS *m/z*: 340 (M^+-t-Bu). IR νmax KBr (cm^{-1}): 2050 (NCS).

3'-Deoxy-3'-isothiocyanothymidine (6b).

Dicyclohexylcarbodiimide (77 mg, 0.37 mmol) was added to a suspension of **5b** (70 mg, 0.25 mmol) in dry pyridine (5 ml) containing carbon disulfide (0.1 ml). The mixture was stirred for 16 h at room temperature and the solvent was removed *in vacuo*. The residue was suspended in MeOH to which a small amount of silica gel was added and the mixture was concentrated to dryness. The residue was placed on top of a silica gel column (2.5 x 19 cm) which was eluted with 8% EtOH in $CHCl_3$ to give **6b** as hygroscopic crystal from hexane (71 mg, 96%); mp 110-112°C. MS *m/z*: 283 (M^+). IR νmax KBr (cm^{-1}): 2050 (NCS). ^{1}H-NMR (DMSO-d_6): 1.77 (3H, s, 5-Me), 2.28-2.73 (2H, m, H-2',2''), 3.67 (2H, m, H-5',5''), 4.05 (1H, m, H-4'), 4.62 (1H, m, H-3'), 5.23 (1H, t, 5'-OH, J = 5.1 Hz), 6.16 (1H, t, H-1', $J_{1',2'} = J_{1',2''}$ = 6.6 Hz), 7.62 (1H, s, H-6). *Anal.* Calcd for $C_{11}H_{13}N_3O_4S$ 0.5 H_2O: C, 45.30; H, 4.83; N, 14.38. Found: C, 45.38; H, 4.95; N, 14.15.

5'-*O*-*t*-Butyldimethylsilyl-3'-deoxy-3'-formamidothymidine (7a).

Acetic formic anhydride (prepared from 0.56 ml of acetic anhydride and 0.11 ml of 98% formic acid) was added to a solution of **5a** (355

mg, 1 mmol) in CH_2Cl_2 (10 ml) at 0°C. The mixture was stirred for 5 min and was diluted with $CHCl_3$ (30 ml). The whole was washed with sat. aqueous Na_2CO_3 and H_2O and the organic phase was dried (Na_2SO_4) and concentrated to dryness. The residue was crystallized from Et_2O to give **7a** (347 mg, 91%); mp 187-190°C. MS *m/z*: 368 (M^+-Me). ^{1}H-NMR ($CDCl_3$): 0.14 (6H, s, $SiMe_2$), 0.94 (9H, s, Si-t-Bu), 1.93 (3H, d, 5-Me, $J_{Me,6}$ = 1.1 Hz), 2.33 (2H, m, H-2',2''), 3.90 (2H, m, H-5',5''), 4.06 (1H, m, H-4'), 4.56 (1H, m, H-3'), 6.33 (1H, t, H-1'), 7.58 (1H, d, 3'-NH), 8.25 (1H, s, 3'-NHC<u>H</u>O), 9.45 (1H, brs, 3-NH). *Anal.* Calcd for $C_{17}H_{29}N_3O_5Si$: C, 53.24; H, 7.62; N, 10.96. Found: C, 53.30; H, 7.58; N, 10.84.

3'-Deoxy-3'-formamidothymidine (7b).

A solution of **7a** (200 mg, 0.52 mmol) in dry THF (10 ml) was treated with TBAF (1M THF solution, 0.6 ml) for 30 min at room temperature. Silica gel was added to the reaction mixture and the whole was concentrated to dryness *in vacuo*. The residue was placed on top of a silica gel column (2.1 x 7 cm) which was eluted with 30% EtOH in $CHCl_3$ to give **7b** (136 mg, 98%, EtOH); mp 197-199°C. MS *m/z*: 269 (M^+). ^{1}H-NMR (DMSO-d_6): 1.78 (3H, d, 5-Me, $J_{Me,6}$ = 1.2 Hz), 2.08-2.26 (2H, m, H-2',2''), 3.57 (2H, m, H-5',5''), 3.76 (1H, m, H-3'), 4.33 (1H, m, H-4'), 5.08 (1H, t, 5'-OH), 6.17 (1H, t, H-1', $J_{1',2'}$ = $J_{1',2''}$ = 6.6 Hz), 7.76 (1H, d, H-6), 8.25 (1H, s, 3'-NHC<u>H</u>O), 8.48 (1H, d, 3'-NH). *Anal.* Calcd for $C_{11}H_{15}N_3O_5$: C, 49.07; H, 5.62; N, 15.61. Found: C, 49.11; H, 5.67; N, 15.49.

5'-*O*-*t*-Butyldimethyl-3'-deoxy-3'-isocyanothymidine (8a).

a) A solution of **7a** (200 mg, 0.52 mmol), triphenylphosphine (272 mg, 1.04 mmol), Et_3N (0.14 ml) and carbon tetrachloride (0.1 ml) in CH_2Cl_2 (10 ml) was heated under reflux for 6 h and the cooled mixture was concentrated to dryness *in vacuo*. The residue was chromatographed over a silica gel column (2.1 x 10 cm) with 25% EtOAc in hexane to give **8a** (183 mg, 81%, Et_2O/hexane); mp 106-109°C. MS *m/z*: 350 (M^+-Me), 308 (M^+-t-Bu). IR vmax KBr (cm^{-1}): 2120 (NC). ^{1}H-NMR ($CDCl_3$): 1.92 (3H, d, 5-Me, $J_{5\text{-}Me,6}$ = 1.2 Hz), 2.40--2.66 (2H, m, H-2',2''), 3.88-3.95 (2H, m, H-5',5''), 4.11-4.32 (2H, m, H-3',4'), 6.31 (1H, t, H-1', $J_{1',2'}$ = $J_{1',2''}$ = 6.6 Hz), 7.34 (1H, d, H-6, $J_{6,5\text{-}Me}$ = 1.2 Hz). *Anal.* Calcd for $C_{17}H_{27}N_3O_4Si$ 0.5 H_2O: H, 54.52; H, 7.53; N, 11.22. Found: C, 54.32; H, 7.32; N, 11.49. b) A

solution of diethyl azodicarboxylate (0.2 ml, 1.3 mmol) in THF (5 ml) was added dropwise over a period of 5 min to a mixture of **7a** (82 mg, 0.21 mmol) and triphenylphosphine (330 mg, 1.3 mmol) in THF (5 ml). The reaction mixture was heated under reflux for 30 h and the cooled mixture was concentrated to dryness. The residue was chromatographed over a silica gel column (2.1 x 10 cm) with 25% EtOAc in hexane to give **8a** (62 mg, 81%). c) A solution of **7a** (38 mg, 0.1 mmol) and tosyl chloride (56 mg, 0.25 mmol) in pyridine (5 ml) was heated under reflux for 2 h and was concentrated to dryness. The residue was purified by silica gel column chromatography to give **8a** (13 mg, 36%).

3'-Deoxy-3'-isocyanothymidine (8b).

A solution of **8a** (290 mg, 0.79 mmol) in THF (5 ml) was treated with TBAF (1M THF solution, 1 ml) for 10 min at room temperature. Silica gel was added to the mixture and the whole was evaporated to dryness. The residue was placed on a silica gel column (2.1 x 7 cm) which was eluted with 50% EtOAc in hexane then EtOAc to give **8b** (95 mg, 48%); mp 154-155°C (lit.[14] 154°C; dec, lit.[15] 150°C). MS *m/z*: 251 (M^+). IR νmax KBr (cm^{-1}): 2120 (NC). ^{1}H-NMR (DMSO-d_6): 1.76 (3H, d, 5-Me, $J_{Me,6}$ = 1.1 Hz), 3.64 (2H, m, H-5',5''), 4.05 (1H, ddd, H-3', $J_{2',3'} = J_{2'',3'}$ = 3.8, $J_{3',4'}$ = 6.6 Hz), 4.44 (1H, dd, H-4', $J_{4',5'}$ = 13.1 Hz), 5.26 (1H, t, 5'-OH), 6.19 (1H, t, H-1', $J_{1',2'} = J_{1',2''}$ = 6.6 Hz), 7.60 (1H, d, H-6), 11.35 (1H, brs, NH). *Anal.* Calcd for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.33; H, 5.21; N, 16.44.

3'-Deoxy-3'-isoselenocyanothymidine (9).

A mixture of **8b** (51 mg, 0.2 mmol) and selenium (32 mg, 0.4 mmol) in anhydrous pyridine (5 ml) was heated at 80°C for 4 h and the solvent was removed under reduced pressure. The residue was dissolved in acetone and mixed with silica gel (ca. 5 g). The suspension was evaporated to dryness and the resulting silica gel was placed on a top of a silica gel (1.5 x 5 cm) which was eluted with ethyl acetate/hexane (3 : 1). Concentration of the appropriate fractions *in vacuo* gave the pale yellow solid which was crystallized from hexane to afford **9** (32 mg, 48%); mp 121-123°C. MS *m/z*: 331 (M^+, this number is for ^{80}Se), the corresponding peaks for $^{74, 76, 77, 78, 82}$Se were also observed. High-resolution MS *m/z*: M^+ Calcd for

$C_{11}H_{13}N_3O_4Se$: 331.0071. Found: 331.0085. IR νmax nujol (cm^{-1}): 2150 (NCSe). ^{1}H-NMR (DMSO-d_6): 1.78 (3H, d, 5-Me), 2.52-2.64 (2H, m, 2',2"-H, partially overlapped with DMSO), 3.49 (1H, m, 5'-H, $J_{4',5'}$ = 3.3 Hz, $J_{5',5"}$ = 12.1 Hz), 3.65 (1H, m, 5"-H, $J_{4',5"}$ = 3.3 Hz), 4.09 (1H, m, 4'-H), 4.72 (1H, m, 3'-H), 5.26 (1H, t, 5'-OH), 6.19 (1H, t, 1'-H, $J_{1',2'}$ = $J_{1',2"}$ = 6.0 Hz), 7.61 (1H, d, 6-H, $J_{5\text{-Me},6}$ =1.1 Hz), 11.35 (1H, brs, NH).

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