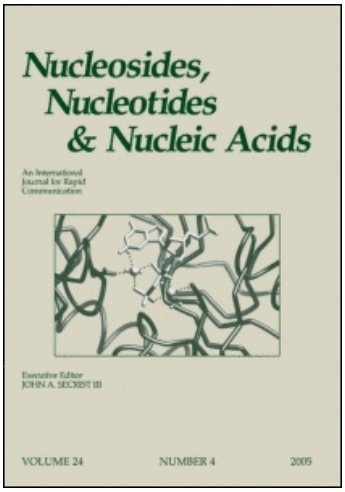

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A NEW SYNTHESIS OF 1-(2,3-DIDEOXY-β-D-GLYCERO-PENT-2-ENOFURANOSYL)- THYMINE. A HIGHLY POTENT AND SELECTIVE ANTI-HIV AGENT.

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*Abstract: A high yielding, straightforward synthesis of 1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (d4T) (**10**) is reported through a simple oxidation step of key intermediates such as, 1-(5-O-pivaloyl-3-deoxy-3(R)-phenylseleno-β-D-glycero-pentofuranosyl)thymine (**7**) [**1** →**3** →**5** →**7** →**9** →**10**], or 1-(5-O-(4-methoxytrityl)-3-deoxy-3(R)-phenylseleno-β-D-glycero-pentofuranosyl)thymine (**6**) [**1**→**2** →**4** →**6** →**8** →**10**]. The scope of this synthesis is also demonstrated by a simple preparation of a potential prodrug of d4T, 1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-5-methylcytosine (d4C^{5me}) (**15**), both from 1-(5-O-MMTr-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (**8**), and 1-(5-O-pivaloyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (**9**). Furthermore, 3',5'-dideoxy-3',5'-bis(phenylselenyl)thymidine (**19**) produced only 2-methylene-5-(R)-(thymin-1-yl)-2,5-dihydrofuran (**22**) through an oxidation followed by mild alkali treatment.*

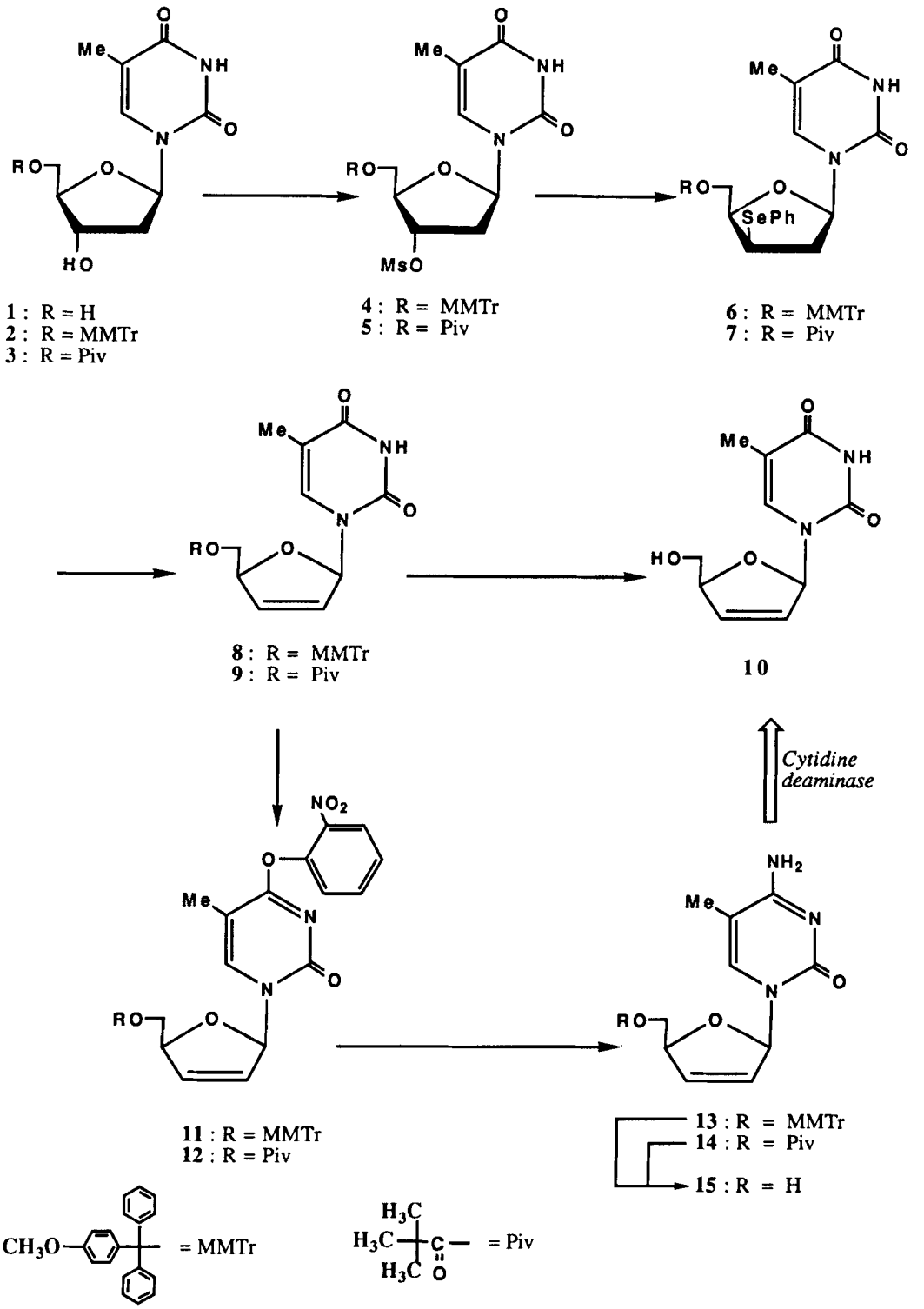
The discovery, that the human immunodeficiency virus (HIV) serves as the causative agent of acquired immunodeficiency syndrome,[1-3] has prompted synthesis of various 2',3'-dideoxy-3'-substituted, 2',3'-dideoxy- and 2',3'-didehydro-2',3'-dideoxy nucleosides.[5-8] Among these categories of nucleosides, 3'-azidothymidine(AZT),[9] 3'-fluorothymidine,[9] 2',3'-dideoxycytidine,[5] 2',3'-dideoxyadenosine,[5] 2',3'-dideoxy-5-fluorocytidine,[7] 2',3'-dideoxythymidine[8] can selectively suppress the replication of HIV through the inhibition of HIV-encoded reverse transcriptase in different cell models *in vitro*.

A number of reports from several laboratories have appeared that show that 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (d4T) (**10**) can *in vitro* selectively suppress the replication of HIV in several cell lines.[10] These observations have been recently confirmed and the activity of d4T compared with that of AZT.[11] The *in vitro* inhibitory activity of d4T was found to be equivalent to that of AZT in HIV-infected CEM cells. The triphosphates of d4T and AZT inhibited HIV reverse transcriptase with K_i values of 0.032 and 0.007 μM, respectively.[11] The *in vitro* toxicity of d4T and AZT measured by the reduction of the growth of normal human hematopoietic progenitor cells by 50 % are at a concentration of 100 μM and 1 μM respectively. With erythrocyte burst forming units, the *in vitro* toxicities for d4T and AZT have comparable ID50 values. These data suggest that d4T may offer a therapeutic advantage over AZT, which has prompted the Bristol-Myers investigators to take d4T to a first phase clinical trial in USA.

Ready availability of d4T has however been a problem because of the difficulties encountered in its synthesis.[11-13] Synthesis of d4T is based upon the base-promoted elimination of either 3′,5′-0-anhydro thymidine or appropriately 5′-protected 3′-0-mesyl thymidine (*threo* or *erythro*).[11-13] These syntheses by Horwitz et al.,[12,13] and a new report of an alternative work-up of Horwitz's procedure by Martin and co-workers[11] have shown that the KOtBu-DMSO base-solvent system is mandatory for the completion of the base-promoted elimination to give d4T. So the recovery of the final product involves: (i) the neutralization of the base generating more salt in the reaction mixture, (ii) tedious removal of the high-boiling DMSO (iii) the precipitation from the aqueous solution. All that results into a poor overall yield of d4T [11].

We herein report a simple straightforward synthesis of d4T, starting from 5′-O-(4-monomethoxytrityl) thymidine (**2**), or 5′-O-pivaloyl thymidine (**3**) which completely circumvents the need of any basic reagent or any high-boiling solvent in the key 2′,3′-elimination step (Scheme I).

The 5′-hydroxyl function of thymidine (**1**) was selectively protected with 4-monomethoxytrityl (MMTr) or pivaloyl (Piv) group by adding the reagent in slight excess over the stoichiometric amount in a dry pyridine solution of thymidine to give compounds (**2**) and (**3**) in 78 and 90 % yield respectively. These products were reacted in pyridine solution with methanesulphonyl (mesyl / Ms) chloride to give the corresponding 3′-0-mesylates (**4**) and (**5**) in 85 and 90 % yield, respectively. The 3′-0-



-Scheme I-

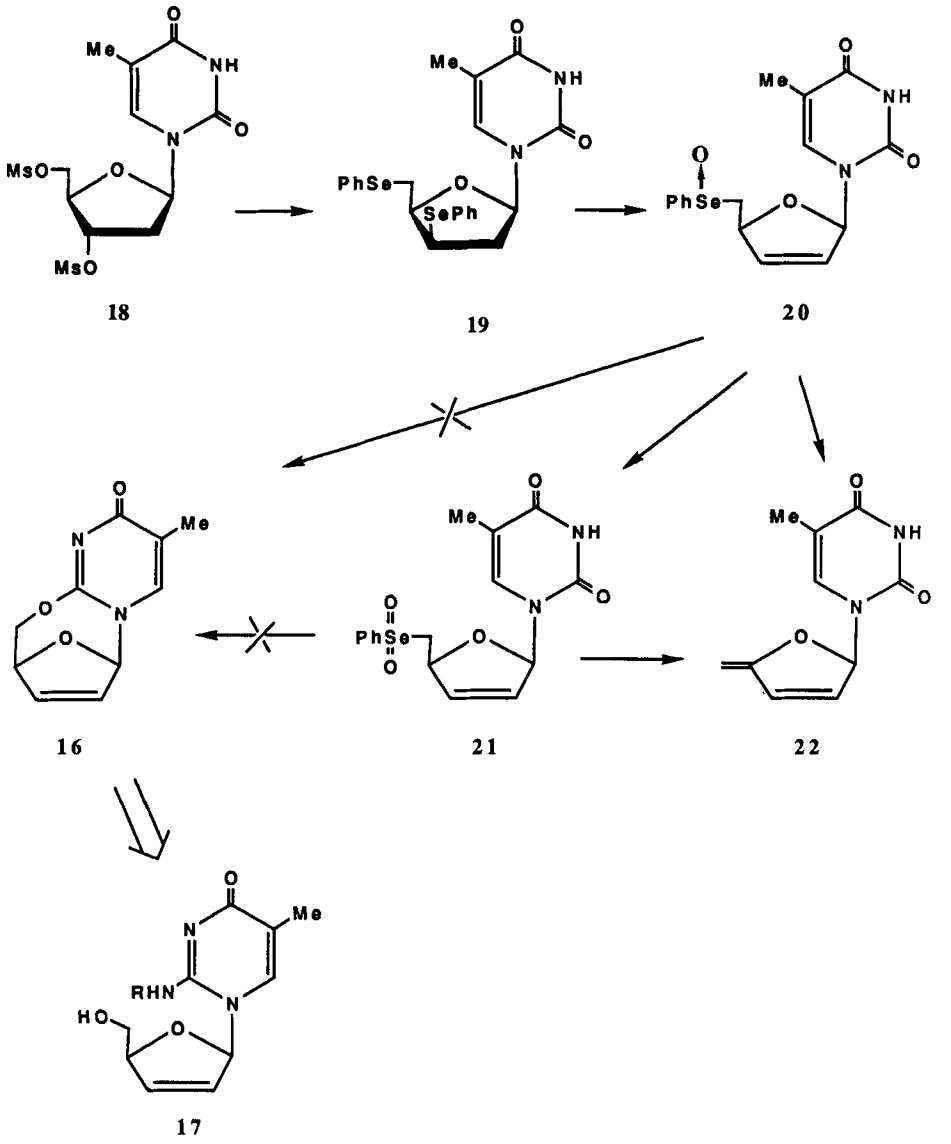
mesyl group in (**4**) and (**5**) was then displaced by $PhSe^-$ ion [$(PhSe)_2$ (3 equiv.) + $LiAlH_4$ (3.3 equiv) in dry THF] to give 5′-0-protected-3′-dideoxy-3′(R)-phenylseleno-glyceropentofuranosyl thymidine (**6**) and (**7**) in 90 and 96 % yield, respectively. From the later step the excess of expensive diphenyl diselenide is easily recoverable from the reaction mixture.[16] Pure (**6**) or (**7**) was then oxidized with an excess of *m*-chloroperbenzoic acid in dichloromethane. The intermediary 3′-phenylseleninyl-derivative formed from (**6**) or (**7**) immediately undergoes a *syn*-elimination reaction[16] by abstracting a β-hydrogen from the vicinal 2′-CH_2- to give the 5′-protected d4T (**8**) and (**9**) quantitatively, within about 20 min (T.l.c) at ~20 °C, which were isolated as pure products in excess of 90 % yield (experimental). The 5′-O-MMTr group from (**8**) was then removed by the treatment with 80 % aqueous acetic acid for 6 h at ~20 °C. A t.l.c examination showed d4T (**10**) as the major compound, which was purified by column chromatography and crystallized from methanol (56 % yield). On the other hand, the deprotection of the 5′-0-pivaloyl group from (**9**) was accomplished by an aqueous methylamine treatment for 24 h at ~20 °C. The reaction mixture was concentrated and the crude residue was dissolved in methanol whereupon pure d4T crystallized out in 56 % yield.

Subsequently, we have successfully carried out the following *two-step-one-pot* preparations for an optimized-high-yielding synthesis of d4T: **1** → **3** → **5** *[two-step-one-pot yield of 5 is 93% from thymidine in 20 mmol scale]*, **1** → **2** → **4** *[two-step-one-pot yield of 4 is 95% from thymidine in 20 mmol scale]*, **5** → **7** → **9** *[two-step-one-pot yield of 9 is 95% from 5 in 10 mmol scale]*, **4** → **6** → **8** *[3 steps, in 95% overall yield from 4]*. Preparation of d4T **10** was then performed using the above two routes in large scale (*vide supra* and experimental). The overall yield of d4T **10** using the 5′-O-MMTr group [**1** → **2** → **4** → **6** → **8** → **10**] was 45 % while with the 5′-O-pivaloyl group [**1** → **3** → **5** → **7** → **9** → **10**] the overall yield of d4T **10** was 65 %. Clearly, the 5′-O-pivaloyl group is recommended for the preparation of d4T **10**, both because of the fact that it gives high overall yield and also due to lower price of pivaloyl chloride (250 g for DM 23.9 from Aldrich) than 4-methoxytrityl chloride (100 g for DM 216.7 from Aldrich). It should be noted that the present synthesis of d4T in an overall yield of 65 % stands well against the overall yield of 34 % from thymidine carried out by Bristol-Myres laboratories[11]. After completion of this work our attention was drawn to a recent work by Chu *et al*[19] in which a new synthesis of d4T has been described in an overall yield of 38 % starting from 5-methyluridine which has to be synthesized from uridine by a multistep procedure.

We then turned our attention to the preparation of a suitable prodrug of d4T. It is known that 1-β-D-*arabino*furanosylcytosine (*ara*-C) or its 5-fluoro analogue are deaminated to the corresponding uracil derivatives at a much slower rate than that of cytidine, hence, they serve as depot for the cytostatic agents, such as *ara*-U or 5-fluoro *ara*-U, respectively, in chemotherapy.[17] These observations suggested to us that d4C^{5me} (**15**) may act as a prodrug of d4T.[10] Additionally, if the enzymatic phosphorylation of (**15**) to its 5′-triphosphate takes place before its enzymatic deamination, then it is cytidine kinase which might catalyze its 5′-phosphorylation in contrast with d4T which is 5′-triphosphorylated by thymidine kinase.[11] These different modes of formation of the corresponding 5′-triphosphates may influence the kinetics of the inhibitions of the HIV-specific cDNA synthesis by reverse transcriptase.

We envisioned the synthesis of d4C^{5me} (**15**) through the conversion of easily available 5′-0-MMTr d4T (**8**) to the O^4-aryl derivative (**11**), using our published procedures[18]. The subjection of (**11**) to a treatment of liquid ammonia should give 5′-0-MMTr-d4C^{5me} (**13**), which then should easily lead to (**15**). Conversion of (**8**) to (**11**) was performed satisfactorily in a one-pot preparation in 65 % yield (experimental). Compound (**11**) was then transformed into d4-(5-methylcytosine) derivative (**13**) by a treatment of liquid ammonia in 85 % yield. Unfortunately, in the last step, during the removal of 5′-O-MMTr group from (**13**) in 80 % aqueous acetic acid at room temperature, the deglycosylation reaction extensively took place, giving (**15**) in only 35 % yield. This made us search for an alternative procedure. We chose 5′-O-pivaloyl-d4T (**9**), which is also easily available through the procedure described herein, for the preparation of (**15**), since the steps from **9** → **12** → **14** → **15** involve only *non-acidic reaction conditions and reagents*. We therefore converted 5′-O-pivaloyl-d4T (**9**) to (**12**) in a one-pot preparation in 61 % yield. Compound (**12**) was then treated with liquid ammonia at room temperature to give 5′-0-Pivaloyl-d4C^{5me} (**14**) in 83 % yield. The 5′-O-pivaloyl group from (**14**) was then removed by a treatment with aqueous methylamine at room temperature to give (**15**) in 87 % yield [The overall yield of the synthesis of d4C^{5me} **15** from thymidine is 39 %].

Subsequently, we attempted to prepare a versatile intermediate such as 2,5′-O-anhydro-d4T derivative (**16**) which may be considered as an appropriate starting material for the preparation of various C-2 amino substituted d4T derivatives (**17**)[15] (Scheme II). A treatment of 3′,5′-bis(methanesulfonyl)thymidine (**18**)[13] with an excess of PhSe$^-$ ion in a heated dioxane solution gave 3′,5′-dideoxy-3′,5′-bis(phenylselenyl)thymidine (**19**) in 93 % yield. Compound (**19**) in dichloromethane solution was then oxidized with *m*-chloroperbenzoic acid (5 min at ~ 0 °C) to give a diastereomeric mixture of 5′-deoxy-5′-



- Scheme II-

phenylselenoxide of d4T (**20**) in 80 % yield. Compound (**20**) was then retreated with an excess of *m*-chloroperbenzoic acid (~ 0 °C for 6 h & then overnight at ~ 20 °C) to give 5′-deoxy-5′-phenylselenone of d4T (**21**) in 80 % yield. Both (**20**) and (**21**) under a mild alkaline condition (Et_3N in aqueous acetonitrile, reflux, overnight) gave exclusively 2-methylene-5-(R)-(thymin-1-yl)-2,5-dihydrofuran (**22**) which was identical to the product reported by Moffatt and Verheyden[14] from the reaction of 3′,5′-dideoxy-3′,5′-diiodothymidine and silver fluoride.

Experimentals

^{1}H-NMR spectra were recorded (in δ scale) with Jeol 90Q spectrometer at 90 MHz, using TMS (0.0 ppm). ^{13}C-NMR were recorded at 22.5 MHz using both ^{1}H-coupled and ^{1}H-decoupled or INEPT modes. UV absorption spectra were recorded with Varian-Cary 2200 instrument. Jeol DX 303 instrument was used for recording high resolution mass spectra. TLC was carried out using Merck pre-coated silica gel F_{254} plates. The column chromatographic separations were carried out using Merck G60 silica gel. The following solvent systems were used for t.l.c: system A : ethylacetate-hexane (2:1, v/v), system B: 10% ethanol in dichloromethane, system C : 15% ethanol in dichloromethane

5'-O-Monomethoxytrityl-3'-O-methanesulfonyl-thymidine (4). Thymidine (4.84 g, 20 mmol) was coevaporated with dry pyridine and redissolved in the same solvent (200 ml). 4-Monomethoxytrityl chloride (9.26 g, 30 mmol) was added and the reaction allowed to proceed overnight at room temperature. Methanesulfonyl chloride (2.3 ml, 30 mmol) was added and reaction was allowed to proceed for another 6 h at room temperature. After a standard work-up and purification by short column chromatography, the title compound was isolated in 95% yield (11.3 g). ^{1}H-NMR ($CDCl_3$): 6.70 to7.60 (m, 15H including H-6); 6.43 (dd, 1H, $J_{1',2'}$ = 8.4 Hz, $J_{1',2''}$ = 5.6 Hz) H-1'; 5.38 (m, 1H) H-3'; 4.32 (m, 1H) H-4'; 3.80 (s, 3H) OCH_3; 3.49 (m, 2H) H-5'; 3.02 (s, 3H) methanesulfonyl; 2.60 (m, 2H) H-2' and H-2''; 1.46 (s, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$): 163.7 (m) C-4; 158.7 (s) OCH_3-bearing carbon of MMTr; 150.4 (d, J_{CH} = 8.5 Hz) C-2; 134.2 (d, J_{CH} = 178.2 Hz) C-6; 145.3, 134.2, 130.2, 128.1, 127.9, 127.2, aromatic carbons; 113.2 (dd, J_{CH} = 161.0 Hz, $^2J_{CH}$ = 5.0 Hz) carbons ortho to OCH_3; 111.6 (s) C-5; 87.4 (s) quaternary carbon of MMTr; 84.1 (d, J_{CH} = 172.1 Hz) C-1'; 83.5 (d, J_{CH} = 150.2 Hz) C-4'; 79.7 (d, J_{CH} = 159.9 Hz) C-3'; 62.8 (t, J_{CH} = 145.3 Hz) C-5'; 55.1 (q, J_{CH} = 144.1 Hz) OCH_3; 38.4 (q, J_{CH} = 139.1 Hz) methanesulfonyl; 38.2 (t, J_{CH} = 134.9 Hz) C-2'; 11.6 (q, J_{CH} = 129.4 Hz) 5-CH_3. UV (ethanol): λ_{max} 266 nm.

5'-O-Pivaloyl-3'-O-methanesulfonyl-thymidine (5). Thymidine (4.84 g, 20 mmol) was coevaporated with dry pyridine and redissolved in the same solvent (200 ml). The solution was cooled down to -15 °C in a salt-ice bath and pivaloyl chloride (3.8 ml, 30 mmol) added in one portion. The temperature was kept between -5 to -15 °C for 6 h. At that time t.l.c (system B) showed all thymidine had been consumed. Methanesulfonyl chloride (4 ml, 50 mmol) was added and the reaction was allowed to proceed further for 10 h. After the usual work-up and concentration of the volatile matters in vacuo, the residue was redissolved in small volume of dichloromethane and the title compound was precipitated from diethylether (4.7 g, 11.6 mmol). An aditional 2.8 g (6.9 mmol) was obtained upon chromatography of the mother liquor. Total yield:

18.5 mmol (93 %). R_f 0.15 (system A). ^{1}H-NMR ($CDCl_3$): 8.92 (bs, 1H) H-3; 7.18 (d, 1H) H-6; 6.24 (dd, $J_{1',2'}$ = 8.0 Hz, $J_{1',2''}$ = 5.3 Hz) H-1'; 5.23 (m, 1H) H-3'; 4.45 (m, 1H) H-4'; 4.36 (m, 2H) H-5'; 3.11 (s, 3H) methanesulfonyl, 2.62 (ddd, 1H, $J_{2'',3'}$ = 1.9 Hz, $J_{2',2''}$ = 14.4 Hz) H-2''; 2.29 (ddd, 1H, $J_{2',3'}$ = 6.6 Hz) H-2'; 1.92 (d, 3H, $J_{5\text{-}CH3,H6}$ = 1.2 Hz) 5-CH_3; 1.23 (s, 9H) Pivaloyl. ^{13}C-NMR ($CDCl_3$) : 177.7 (s) pivaloyl carbonyl; 163.7 (q) C-4; 150.3 (d, J_{CH} = 6.1 Hz) C-2; 134.4 (d, J_{CH} = 178.2 Hz) C-6; 111.4 (s) C-5; 84.9 (d, J_{CH} = 169.7 Hz) C-1'; 81.9 (d, J_{CH} = 150.7 Hz) C-4'; 78.4 (d, J_{CH} = 160 Hz) C-3'; 62.9 (t, J_{CH} = 143.7 Hz) C-5'; 38.7 (t, J_{CH} = 136 Hz) C-2';38.5 (q, J_{CH} = 140.4 Hz) methanesulfonyl; 37.8 (m) pivaloyl quaternary carbon; 27.0 (q, J_{CH} = 127 Hz) pivaloyl; 12.3 (q, J_{CH} = 128.3 Hz) 5-CH_3. UV (ethanol): λ_{max} 265 nm.

1-(5-O-Monomethoxytrityl-3-deoxy-3(R)-phenylseleno-β-D-*glycero*-pentofuranosyl)thymine (6). Compound **4** (12.13 g, 20.4 mmol) was reacted with phenylselenide ion (1.1 equiv.) in the same manner as described for compound **7**. Identical wok-up followed by short column chromatography gave the title compound in 90 % yield (11.8 g). R_f 0.45 (system A). ^{1}H-NMR ($CDCl_3$) : 8.35 (bs, 1H) H-3; 7.80 to 6.60 (m, 15H) H-6 and monomethoxytrityl protons; 6.06 (t, 1H, $J_{1',2'}$ = $J_{1',2''}$ = 6.6 Hz) H-1'; 4.32 (m, 1H) H-4'; 3.74 (m, 4H) OCH_3 and H-3'; 3.48 (m, 2H) H-5'; 2.77 (m, 1H) H-2''; 2.27 (m, 1H) H-2'; 1.41 (s, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$) : 164.0 (s) C-4; 158.7 (s) C-2; 135.8 (d, J_{CH} = 180.7 Hz) C-6; 150.5, 143.4, 134.6, 133.8, 130.5, 129.2, 128.6, 127.7, 127.1, aromatic carbons; 113.0 (dd, J_{CH} = 159.9 Hz and J_{CH} = 4.9 Hz) carbons ortho to OCH_3; 110.8 (s) C-5; 87.4 (s) quaternary carbon of monomethoxytrityl; 83.9 (d, J_{CH} = 166 Hz) C-1'; 80.8 (d, J_{CH} = 147.7 Hz) C-4'; 65.0 (t, J_{CH} = 140.4 Hz) C-5'; 41.0 (d, J_{CH} = 148.9 Hz) C-3'; 40.0 (t, J_{CH} = 135.5 Hz) C-3'; 11.7 (q, J_{CH} = 129.4 Hz) 5-CH_3. MS (FAB$^-$): calculated for $(M-H)^-$ 653.1555, found 653.1592. UV (ethanol): λ_{max} 269 nm.

1-(5-O-Pivaloyl-3-deoxy-3(R)-phenylseleno-β-D-*glycero*-pentofuranosyl)thymine (7). To a THF (30 ml) solution of diphenyldiselenide (3.45 g, 11 mmol), $LiAlH_4$ (392 mg, 10 mmol) was added portionwise. After addition, the suspension was heated under reflux for 5 min. Compound **5** (2.24 g, 3.7 mmol), previously coevaporated with dry THF and redissolved in the same solvent (10 ml / mmol) was added dropwise. The reaction was allowed to proceed at reflux temperature for 1.5 h. The reaction mixture was worked-up with diluted acetic acid, extracted with ethylacetate, extracts were pooled and thoroughly washed with water, lipophilic phase was concentrated and purified by short-column chromatography to give the title compound in 96% yield (1.65 g). R_f 0.40 (system A). ^{1}H-NMR ($CDCl_3$) : 9.17 (bs, 1H) H-3; 7.68 to 7.22 (m, 6H) H-6 and phenylselenyl protons; 6.04 (dd, 1H, $J_{1',2'}$ = 7.1 Hz, $J_{1',2''}$ = 6.1 Hz) H-1'; 4.46 (m, 3H) H-4' and H-5'; 3.94 (m, 1H) H-3'; 2.91 (m, 1H, $J_{2'',3'}$ = 7.1 Hz) H-2''; 2.16 (m, 1H, $J_{2',3'}$ = 8.8 Hz) H-2'; 1.97 (d, 3H) 5-CH_3; 1.24 (s, 9H) pivaloyl. ^{13}C-NMR ($CDCl_3$) : 177.6 (s) pivaloyl carbonyl; 163.9 (d, J_{CH} = 6.1 Hz) C-4; 150.4 (d, J_{CH} = 7.3 Hz) C-2; 134.7 (d, J_{CH} = 178.2 Hz) C-6; 133.6, 129.2, 128.5, 127.8 phenylselenyl carbons, 110.5 (s) C-5; 84.2 (d, J_{CH} = 171.9 Hz) C-1'; 78.6 (d, J_{CH} = 151.4 Hz) C-4'; 65.4 (t, J_{CH} = 143.9 Hz) C-5'; 40.2 (d, J_{CH} = 147.7 Hz) C-3'; 39.5 (t, J_{CH} = 136.1 Hz) C-2'; 38.3 (s) pivaloyl quaternary carbon; 27.0 (q, J_{CH} = 138.1 Hz) pivaloyl; 12.2 (qd, J_{CH} = 121.2 Hz and J_{CH} = 3.7 Hz) 5-CH_3 . MS (FAB$^-$): calculated for $(M-H)^-$ 465.0929, found 465.0900. UV (ethanol): λ_{max} 269 nm.

1-(5-O-Monomethoxytrityl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (8). Compound **6** (12.7 g, 18.8 mmol) was dissolved in dichloromethane (10 ml / mmol) and treated with *m*-chloroperbenzoic acid (6.24 g., 56.4 mmol)) for 10 min . After a standard work-up and the usual column chromatographic purification step, the title product was isolated in 95 % yield (8.68 g). R_f 0.33 (system A). ^{1}H-NMR ($CDCl_3$) : 8.35 (bs, 1H) H-3; 7.80 - 6.60 (m, 15H) H-6 and monomethoxytrityl protons; 6.98 (m, 1H) H-1'; 6.31 (m, 1H) H-3'; 5.83 (m, 1H) H-2'; 4.91 (m, 1H) H-4'; 3.72 (s, 3H) OCH_3; 3.32 (m, 2H) H-5'; 1.17 (d, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$) : 164.1 (m) C-4; 158.6 (s) OCH_3-bearing carbon of MMTr; 150.7 (d, J_{CH} = 8.5 Hz) C-2; 134.4 (d, J_{CH} = 173.3 Hz) C-6; 143.5, 143.4, 136.0, 134.6, 130.3, 128.3, 127.7, 127.1, 126.1, C-2', C-3' and aromatic carbons; 113.0 (dd, J_{CH} = 159.9 Hz and J_{CH} = 4.9 Hz) carbons ortho to OCH_3; 111.1 (s) C-5; 89.5 (d, J_{CH} = 171.0 Hz) C-1'; 86.5 (s) quaternary carbon of monomethoxytrityl; 85.6 (d, J_{CH} = 150.1 Hz) C-4'; 64.6 (t, J_{CH} = 142.4 Hz) C-5'; 55.1 (q, J_{CH} = 144.0 Hz) OCH_3; 11.1 (q, J_{CH} = 129.4 Hz) 5-CH_3. MS (FAB^-): calculated for $(M-H)^-$ 495.1920, found 495.1929. UV (ethanol): λ_{max} 265 nm.

1-(5-O-Pivaloyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (9). *Method 1*: Compound **7** (1.45 g, 3.1 mmol) was dissolved in dichloromethane (10 ml / mmol) and treated for 10 min with *m*-chloroperbenzoic acid (3 equiv.). After a standard work-up, the title product readily crystallized out in diethylether-dichloromethane mixture and the overall yield of (**9**) from 1-(5-O-pivaloyl-3-deoxy-3(R)-phenylseleno-β-D-*glycero*pentofuranosyl)thymine (**7**) was 935 mg (98 %). *Method 2*: Diphenyldiselenide (3.43 g, 11 mmol) was dissolved in dry THF (30 ml) and lithiumaluminium hydride (417 mg, 11 mmol) was added portionwise. The dark green solution was heated under reflux for 15 min. Then, **5** (4.04 g, 10 mmol), previously coevaporated with dry THF and redissolved in the same solvent (100 ml) was added dropwise in about 10 min. After a reflux for 6 h the reaction was worked up as described for (**7**). The crude reaction mixture was then dissolved in dichloromethane (100 ml) and *m*-chloroperbenzoic acid (6.7 g, 60 mmol) was added in two portions. Twenty minutes later the reaction was worked up as usual. A first crystallization in diethylether-dichloromethane mixture gave 2.05 g (66%) of (**9**). Subsequent chromatography of the mother liquor gave an additional 880 mg (29%) of (**9**). R_f 0.26 (system A). ^{1}H-NMR ($CDCl_3$) : 8.35 (bs, 1H) H-3; 7.14 (d, 1H, J = 1.3 Hz) H-6; 6.94 (m, 1H) H-1'; 6.27 (dt, 1H, $J_{2',3'}$ = 5.9 Hz, $J_{3',4'}$ = $J_{1',3'}$ = 1.5 Hz) H-3'; 5.92 (dq, 1H, $J_{1',2'}$ = 1.3 Hz, $J_{2',4'}$ = 2.4 Hz) H-2'; 5.03 (m, 1H) H-4'; 4.35 (dd, 1H, $J_{4',5''}$ = 4.9 Hz and $J_{5',5''}$ = 12 Hz) H-5''; 4.22 (dd, 1H, $J_{4',5'}$ = 3.7 Hz) H-5'; 1.91 (d, 1H) 5-CH_3; 1.20 (s, 9H) pivaloyl.^{13}C-NMR ($CDCl_3$) : 178.2 (s) pivaloyl carbonyl; 164.0 (s) C-4; 150.7 (s) C-2; 135.0 (d, J_{CH} = 179.4 Hz) C--6; 133 (d, J_{CH} = 173.3 Hz) C-3'; 127.0 (d, J_{CH} = 180.1 Hz) C-2'; 111.0 (s) C-5; 89.9 (d, J_{CH} = 170.9 Hz) C-1'; 84.1 (d, J_{CH} = 152.6 Hz) C-4'; 64.7 (t, J_{CH} = 145.3 Hz) C-5'; 38.6 (s) quaternary carbon of pivaloyl; 26.9 (q, J_{CH} = 128.2 Hz) pivaloyl; 12.2 (q, J_{CH} = 129.4 Hz) 5-CH_3. MS (FAB^-): calculated for $(M-H)^-$ 307.1294, found 307.1320. UV (ethanol): λ_{max} 265 nm. Mp 206-207°.

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (10). *Method 1* Compound **9** (1.89 g, 6.14 mmol) was treated for 24 h with 40% aqueous methylamine (d = 0.9, 65 ml) at room temperature. The product crystallized out from methanol (1.89 g, 74%). m.p 162 - 164 °C [lit.[11] m.p 164 - 166 °C]. *Method 2:* Compound **8** (8.68 g, 17.9 mmol) was treated with 80% aqueous acetic acid for 6 h at room temperature. The reaction mixture was concentrated and coevaporated with dioxane several times.

The reaction mixture was then purified by column chromatography on silica gel. Appropriate fractions were pooled and concentrated to give a glass which was crystallized from methanol to give d4T **10** (2.245 g, 56%). ^{1}H-NMR (CD_3OD) : 7.84 (d, 1H) H-6; 7.04 (m, 1H) H-1'; 6.49 (dt, $J_{2',3'}$ = 5.9 Hz, $J_{1',3'} = J_{3',4'}$ = 1.7 Hz) H-3'; 5.99 (dq, 1H, $J_{1',2'}$ = 1.0 Hz, $J_{2',4'}$ = 2.4 Hz) H-2'; 4.71 (bs, 1H) H4'; 3.85 (d, 1H, $J_{4',5'}$ = 3 Hz) H-5'; 1.93 (d, 3H, J = 1.2 Hz) 5-CH_3 ^{13}C-NMR (CD_3OD) : 166.6 (s) C-4; 153 (s) C-2; 139.2 (d, J_{CH} = 180.7 Hz) C-6; 136.3 (d, J_{CH} = 173.3 Hz) C-3'; 127.6 (d, J_{CH} = 174.6 Hz) C-2'; 111.6 (s) C-5; 91.4 (d, J_{CH} = 172.1 Hz) C-1'; 89.3 (d, J_{CH} = 148.9 Hz) C-4'; 64.1 (t, J_{CH} = 141.0 Hz) C-5'; 12.7 (qd, J_{CH} = 124.5 Hz and J_{CH} = 4.6 Hz) 5-CH_3. UV (water) : λ_{max} 265 nm (pH 7), λ_{max} 265 nm (pH 1), λ_{max} 266 nm (pH 13). MS (FAB$^-$): calculated for (M-H)$^-$ 223.0719, found 223.0740. $[\alpha]_D$ = -22.9° (25 °C, c = 3.11).

1-[(5-O-Monomethoxytrityl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-4-O-(*o*-nitrophenyl)]-thymine (11). Compound **8** (410 mg, 0.84 mmol) was dissolved in dry dichloromethane (10 ml / mmol), triethylamine (1.2 ml, 8.5 mmol) was added, followed by N,N-dimethylaminopyridine (26 mg, 0.21 mmol) and 1-mesitylenesulfonyl chloride (354 mg, 2.55 mmol). The reaction was allowed to proceed at room temperature for 36 h. Additional triethylamine (0.6 ml, 4.2 mmol), and 2-nitrophenol (587 mg, 4.2 mmol) were added. One hour later the reaction mixture was diluted with chloroform, washed with aqueous saturated sodium bicarbonate, water, citric acid and water again. Purification by short column chromatography gave the title product (331 mg) in 65% yield. R_f 0.27 (system A), 0.60 (system B). ^{1}H-NMR ($CDCl_3$) : 8.26 - 6.89 (m, 18H) aromatic protons; 8.01 (d, 1H) H-6; 7.09 (m, 1H) H1'; 6.35 (m, 1H) H-3'; 6.10 (m, 1H) H-2'; 5.07 (m, 1H) H-4'; 3..85 (s, 3H) OCH_3; 3.49 (m, 2H, $J_{4',5'}$ = 2.9 Hz, $J_{4',5''}$ = 2.4 Hz, $J_{5',5''}$ = 10.3 Hz) H-5' and H-5''; 1.48 (d, 3H, J = 1 Hz) 5-CH_3. ^{13}C-NMR ($CDCl_3$) : 169.7 (s) C-4; 158.6 (s) OCH_3-bearing carbon; 155.1 (d, J_{CH} = 7.3 Hz) C-2; 145.3, 143.6, 143.4, 142.5, 141.3, 134.7, 134.5, 130.2, 128.3, 127.8, 127.1, 126.3, 125.8, 125.6, C-2', C-3' and aromatic carbons; 133 0 (d, J_{CH} = 173.4 Hz) C-6; 113.0 (dd, J_{CH} = 159.9 Hz and J_{CH} = 4.9 Hz) carbons ortho to OCH_3; 104.3 (s) C-5; 91.4 (dt,J_{CH} = 170.1 Hz and J_{CH} = 11 Hz) C-1'; 86.5 (s) quaternary carbon of MMTr; 86.1 (dt, J_{CH} = 147.7 Hz and J_{CH} = 9.8 Hz) C-4'; 64.2 (t, J_{CH} = 142.8 Hz) C-5'; 55.1 (q, J_{CH} = 144 Hz) OCH_3; 11.0 (qd, J_{CH} = 129.4 Hz and J_{CH} = 3.7 Hz) 5-CH_3.

1-[(5-O-Pivaloyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)4-O-(*o*-nitrophenyl]-thymine (12). Compound (**9**) (1.35 g, 4.4 mmol) was dissolved in dry dichloromethane (45 ml), triethylamine (6.1 ml, 44 mmol), N,N-dimethylaminopyridine (134 mg, 1.1 mmol) and 1-mesitylenesulfonyl chloride (1.84 g, 13.2 mmol) were sequentially added. The reaction was allowed to stand at room temperature for 3 days and then 2-nitrophenol (3.06 g, 15.5 mmol) was added. After 1.5 h, the reaction mixture was worked-up in the usual manner. Subsequent purification by short column chromatography gave the title product (1.148 g) in 61% yield. R_f 0.19 (system A). ^{1}H-NMR ($CDCl_3$): 8.22 - 7.25 (m, 5H) arom.; 6.81 (d, 1H, $J_{1',4'}$ = 3.5 Hz) H-1'; 6.14 (d, 2H, J = 0.6 Hz) H-2' and H-3'; 5.13 (m, 1H) H-4'; 4.58 (dd, 1H, $J_{4',5''}$ = 3.1 Hz, $J_{5',5''}$ = 12.3 Hz) H-5''; 4.17 (dd, 1H, $J_{4',5'}$ = 4.8 Hz) H-5'; 2.15 (d, 3H, J = 1.1 Hz) 5-CH_3; 1.19 (s, 9H) pivaloyl. ^{13}C-NMR ($CDCl_3$): 177.8 (s) carbonyl of pivaloyl; 169.8 (s) C-4; 154.9 (d, J_{CH} = 6.1 Hz) C-2; 134.8 (dq, J_{CH} = 183.2 Hz, J_{CH} = 9.5 Hz) C-6; 131.1 (d, J_{CH} = 172.1 Hz) C-3'; 128.0 (d, J_{CH} = 178.2 Hz) C-2'; 145.2, 141.1, 126.4, 125.8, 125.5, aromatic carbons; 103.9 (qd, J_{CH} = 6.1 Hz, J_{CH} = 2.4 Hz) C-5; 92.2 (dt, J_{CH} = 168.5 Hz, J_{CH} = 10.0 Hz) C-1'; 85.2 (m, J_{CH} = 145.9

Hz, J_{CH} = 11.0Hz, J_{CH} = 3.7 Hz) C-4'; 64.4 (td, J_{CH} = 147.7 Hz, J_{CH} = 3.7 Hz) C-5'; 38.6, s, quaternary carbon of pivaloyl; 28.9 (q, J_{CH} = 128.2 Hz) pivaloyl; 12.2 (qd, J_{CH} = 129.4 Hz, J_{CH} = 3.6 Hz) 5-CH_3. UV (ethanol): λ_{max} 267nm.

1-(5-O-Monomethoxytrityl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-5-methyl- cytosine (13). Compound **11** (1 g, 1.65 mmol) was dissolved in dry THF (17 ml) and treated with liquid ammonia under pressure (8 atmosphere) for two days at room temperature. After column chromatography the title product was isolated in 85% yield (677 mg). R_f 0.37 (system B). ^{1}H-NMR ($CDCl_3$) : 7.57 (d, J = 1 Hz) H-6; 7.48 to 6.71 (m, 14H) aromatic protons; 7.14 (m,1H) H-1'; 6.26 (m, 1H, $J_{2',3'}$ = 6.4 Hz, $J_{1',3'} = J_{1',4'}$ = 2.0 Hz) H-3'; 5.96 (m, 1H) H-2'; 4.97 (m, 1H) H-4'; 3.78 (s, 3H) OCH_3; 3.38 (m, 2H) H-5'; 1.20 (d, 3H) 5-CH_3. ^{13}C-NMR ($CDCl_3$) : 165.6 (s) C-4; 158.4 (s) OCH_3-bearing carbon of MMTr; 156.1 (d, J_{CH} = 4.9 Hz) C-2; 143.6, 143.5, 134.6, 132.8, 130.2, 128.2, 127.6, 127.3, 126.9, C-2', C-3' and aromatic carbons; 138.4 (d, J_{CH} = 175.8 Hz) C-6; 112.9 (dd, J_{CH} = 159.9 Hz and J_{CH} = 4.9 Hz) carbons ortho to OCH_3; 102.0 (q, J_{CH} = 4.9 Hz) C-5; 90.3 (dt, J_{CH} = 170.2 Hz, J_{CH} = 11 Hz) C-1'; 86.3 (s) quaternary carbon of MMTr; 85.3 (dt, J_{CH} = 148.9 Hz, J_{CH} = 11 Hz) C-4'; 64.7 (t, J_{CH} = 145.3 Hz) C-5'; 55.0 (q, J_{CH} = 144.1 Hz) OCH_3; 11.9 (qd, J_{CH} = 128.2 Hz, J_{CH} = 5.1 Hz) 5-CH_3. MS (FAB$^-$): calculated for $(M-H)^-$ 494.2080, found 494.2049.

1-(5-O-Pivaloyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-5-methylcytosine (14). Compound **12** (1.048 g, 2.44 mmol) was coevaporated with dry THF, redissolved in the same solvent (10 ml) and treated with liquid ammonia for 3 days at room temperature. After evaporation of volatile matters, the crude reaction mixture was redissolved in dichloromethane. Precipitation in diethylether afforded the title product in 83% yield (623 mg, 2.03 mmol). R_f 0.24 (system B). ^{1}H-NMR ($CDCl_3$): 7.30 (d, 1H) H-6; 6.95 (m, 1H, $J_{1',4'}$ = 3.2 Hz) H-1'; 6.10 (m, 2H) H-2' and H-3'; 5.07 (m, 1H) H-4'; 4.45 (dd, 1H, $J_{4',5''}$ = 4.5 Hz, $J_{5',5''}$ = 12 Hz) H-5''; 4.15 (dd, $J_{4',5'}$ = 3.4 Hz) H-5'; 1.94 (d, 3H, J = 1.0 Hz) 5-CH_3; 1.19 (s, 9H) pivaloyl protons.^{13}C-NMR ($CDCl_3$): 165.7 (s) C-4; 156.1 (s) C-2; 134.5 (d, J_{CH} = 176.4 Hz) C-6; 131.2 (d, J_{CH} = 174.1 Hz) C-3'; 128.5 (d, J_{CH} = 176.4 Hz) C-2'; 101.9 (s) C-5; 91.1 (d, J_{CH} = 173.0 Hz) C-1'; 84.2 (d, J_{CH} = 146.1 Hz) C-4'; 64.9 (t, J_{CH} = 149.9 Hz) C-5'; 39.6 (s) quaternary carbon of pivaloyl; 27.0 (q, J_{CH} = 129.2 Hz) pivaloyl; 13.1 (q, J_{CH} = 128.0Hz) 5-CH_3. UV (water) : λ_{max} 276 nm (pH 7), λ_{max} 285 nm (pH 1), λ_{max} 276 nm (pH 13). MS (FAB$^-$): calculated for $(M-H)^-$ 306.1454, found 306.1457.

1-(2',3'-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-5-methylcytosine (15). Compound **12** (150 mg, 0.31 mmol) was dissolved in a minimum of dioxane and treated with 80% aqueous acetic acid for 4 h at room temperature, *5-methylcytosine* was formed and (**15**) was isolated in only 35 % yield.

When **14** (455 mg, 1.48 mmol)was treated with 40% aqueous methylamine (d = 0.9, 30 ml) for 24 h, a t. l. c examination (system C) showed a clean conversion of (**14**) to (**15**). The reaction mixture was concentrated and the title product was crystallized out from *iso*-butylalcohol in 68% yield (222 mg, 1 mmol). Purification of (**15**) from the the mother liquors by preparative t.l.c (system C) gave an additional 62 mg (0.28 mmol, 19%). Total yield: 87%. M.p : 165 °C (decomp). R_f 0.15 (system C). ^{1}H-NMR (CD_3OD): 7.86 (m, 1H) H-6; 7.08 (m, 1H, $J_{1',4'}$ = 3.4 Hz) H-1'; 6.43 (dt, 1H, $J_{2',3'}$ = 6.1 Hz, $J_{1',3'} = J_{3',4'}$ = 1.7 Hz) H-3'; 5.99 (dq, $J_{1',2'}$ = 1.5 Hz, $J_{2',4'}$ = 2.5 Hz) H-2';

4.96 (m, 1H) H-4'; 3.84 (d, 2H, $J_{4',5'}$ = 3.7 Hz) H-5'; 2.01 (d, 3H, $J_{6,5\text{-Me}}$ = 1.0 Hz) 5-CH_3. ^{13}C-NMR (CD_3OD): 165.6 (s) C-4; 155.5 (d, J_{CH} = 6.1 Hz) C-2; 139.0 (d, J_{CH} = 175.8 Hz) C-6; 134.0 (d, J_{CH} = 172.1 Hz) C-3'; 127.0 (d, J_{CH} = 177 Hz) C-2'; 101.4 (s) C-5; 89.7 (dt, J_{CH} = 169.7 Hz, J_{CH} = 9.8 Hz) C-1'; 87.1 (dt, J_{CH} = 146.5 Hz, J_{CH} = 10.0 Hz) C-4'; 62.7 (t, J_{CH} = 141.6 Hz) C-5'; 13.4 (qd, J_{CH} = 127.0 Hz, J_{CH} = 4.9 Hz) 5-CH_3. UV (water) : λ_{max} 276 nm (pH 7), λ_{max} 285 nm (pH 1), λ_{max} 277 nm (pH 13). MS (FAB^-): calculated for $(M-H)^-$ 222.0879, found 222.0906. $[\alpha]_D$ = +71.7° (25 °C, c = 1.08).

3',5'-Dideoxy-3',5'-bis(phenylselenyl)thymidine (19). A solution of diphenyl diselenide (0.75 g. 2.4 mmol) in 1,4-dioxane (6 ml) was treated with $LiAlH_4$ (81 mg, 2.13 mmol) at 100 °C for 30 min. To this a 1,4-dioxane (6 ml) solution of **18** (0.198 g, 0.5 mmol) was added and the mixture was heated under reflux for 3 h. The reaction mixture was then allowed to cool to room temperature and then quenched with 10 % aqueous acetic acid and extracted with CH_2Cl_2 (3 x 20 ml). the organic phase was washed with water, dried ($MgSO_4$), evaporated and purified by silical gel column chromatography to give a syrup. Yield 0.24 g (93 %). R_f 0.62 (system B) ^{1}H-NMR ($CDCl_3$): 9.71 (s, 1H) N-H; 7.64 - 7.15 (m, 11H) arom., H-6; 6.09 (t, 1H) H-1'; 4.42 (m, $J_{3',4'}$ = 5.8 Hz. 1H) H-4'; 4.03 (m, 1H) H-3'; 3.28 (2 x d, 2H) H-5', H-5''; 2.87 and 2.28 (2 x m, 2H) H-2', H-2''; 1.66 (s, 3H) CH_3. UV (EtOH): λ_{max} 272 nm. MS (FAB^-): calculated for $(M-H)^-$ 520.9883, found 520.9844.

5'-Deoxy-5'-phenylselenoxide of d4T (20). A solution of **19** (0.175 g, 0.34 mmol) in dichloromethane (3 ml) solution was cooled in an ice-water bath and *m*-chloroperbenzoic acid (0.16 g, 0.95 mmol) was added. The mixture was stirred for 5 min at ~ 0 °C and then methanolic ammonia was added. The mixture was evaporated and purified by silica gel column chromatography to give a diastereomeric mixture of **20** Yield 0.121 g (95 %). R_f 0.10 (system B) ^{1}H-NMR ($CDCl_3$): 8.00 - 7.40 (m. 5H) arom.; 7.22 and 6.80 (2 x d, $J_{6,CH3}$ = 1.2.Hz, 1H) H-6; 6.93 (m, $J_{1',2'}$ = 2.6 Hz, 1H) H-1'; 6.41 (m, $J_{2',3'}$ = 5.9 Hz, 1H) H-3'; 5.89 (m, 1H) H-2'; 5.41 and 4.95 (2 x br.s, 1H) H-4'; 3.29 (m, 2H) H-5', H-5''; 1.92 and 1.75 (2 x d, 3H) CH_3. UV (EtOH): λ_{max} 262 nm. MS (FAB^-): calculated for $(M-H)^-$ 381.0354, found 381.0393.

5'-Deoxy-5'-phenylselenone of d4T (21). Compound **20** (0.129 g, 0.34 mmol) in dichloromethane (4 ml) solution was cooled in an ice-water bath and *m*-chloroperbenzoic acid (0.12 g, 0.7 mmol) was added. The mixture was stirred at O °C for 6 h and then at room temperature overnight. Methanolic ammonia was added and the mixture was evaporated and purified by silica gel column chromatography. Yield 0.106 g (80 %). R_f 0.24 (system B). ^{1}H-NMR ($CDCl_3$): 8.09 - 7.85 and 7.68 - 7.25 (m, 5H) arom.; 6.83 (d, $J_{6,CH3}$ = 1.2.Hz, 1H) H-6; 6.76 (t, $J_{1',2'}$ = 2.7 Hz, $J_{1',3'}$ = 1.8 Hz, 1H) H-1'; 6.42 (2 x t, $J_{2',3'}$ = 5.9 Hz, 1H) H-3'; 5.92 (2 x t, $J_{2',4'}$ = 2.3 Hz, 1H) H-2'; 5.48 (br.s, 1H) H-4'; 3.92 (m, 2H) H-5', H-5''; 1.78 (d, 3H) CH_3. UV (EtOH): λ_{max} 276 nm.

2-Methylene-5-(R)-(thymin-1-yl)-2,5-dihydrofuran (22). *Method 1*: Compound **20** (50 mg, 0.13 mmol) was dissolved in acetonitrile (10 ml) and water (0.5 ml). Triethylamine was added (0.3 ml, 2 mmol) and the mixture was stirred at 70 °C overnight. The mixture was then cooled to room temperature, evaporated and purified by silica gel column chromatography. Yield 25 mg (92 %). R_f 0.56 (system B) ^{1}H-NMR ($CDCl_3$): 7.30 (dd, $J_{1'-2'}$ = 1.6 Hz, 1H) H-1', 6.77 ($J_{6,CH3}$ = 1.2.Hz, 1H) H-6,

H-1′, 6.59 (2 x d, $J_{2',3'}$ = 5.6 Hz, 1H) H-3′, 6.15 (m, 1H) H-2′, 4.59, 4.29 (2 x m, 2H) H-5, H-5", 1.90 (d, 3H) CH_3. UV (EtOH): λ_{max} 278 nm. MS (FAB^+): calculated for $(M+H)^+$ 207.0844 found 207.0769.

Method 2: Compound **21** was treated in the same manner as described in *Method 1* to give **22** (23 mg, 90 %)

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