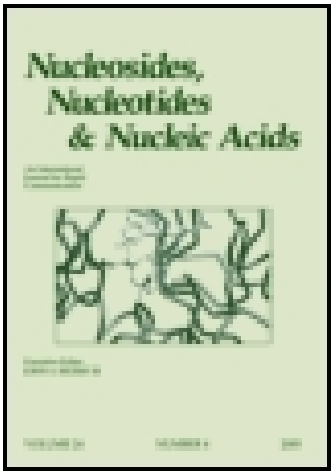

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SYNTHESIS OF PYRIMIDINE 2',3'-DIDEOXY-2-THIO-NUCLEOSIDES

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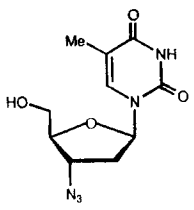
Abstract: 2'-Deoxyuridine **8a** and thymidine **8b** were converted in eight steps and in satisfactory overall yields into 2',3'-dideoxy-2-thiouridine (ddTU) **6a** and 3'-deoxy-2-thiothymidine (ddTT) **6b**, respectively. A three-step procedure is described for the conversion of ddTU **6a** and ddTT **6b** into the corresponding 2',3'-dideoxycytidine derivatives (ddTC **7a** and ddMTC **7b**, respectively) in good overall yield.

The discovery in the past decade that 3'-azido-3'-deoxythymidine (AZT, **1**) and a number of related 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine (ddC, **2**) and 2',3'-dideoxyinosine (ddI, **3**) possess high anti-HIV activity[1,2] has greatly stimulated work in the area of nucleoside analogue synthesis. The latter two compounds **2** and **3** have been approved[3] as alternative anti-AIDS drugs and both 3'-deoxythymidine **4** and 2',3'-dideoxyadenosine **5** also display powerful anti-HIV activity[1]. A very simple and obvious modification to make to a pyrimidine nucleoside is to replace *O*-2 by a sulfur atom. We now report the synthesis of four such nucleoside analogues: 2',3'-dideoxy-2-thiouridine



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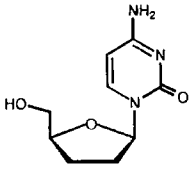

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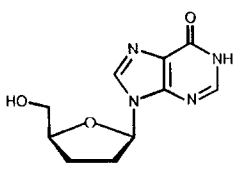

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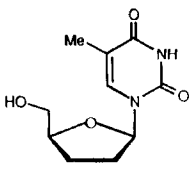

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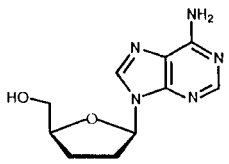

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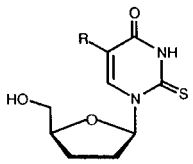
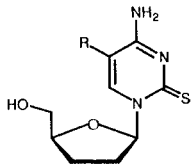


6 a; R = H
b; R = Me

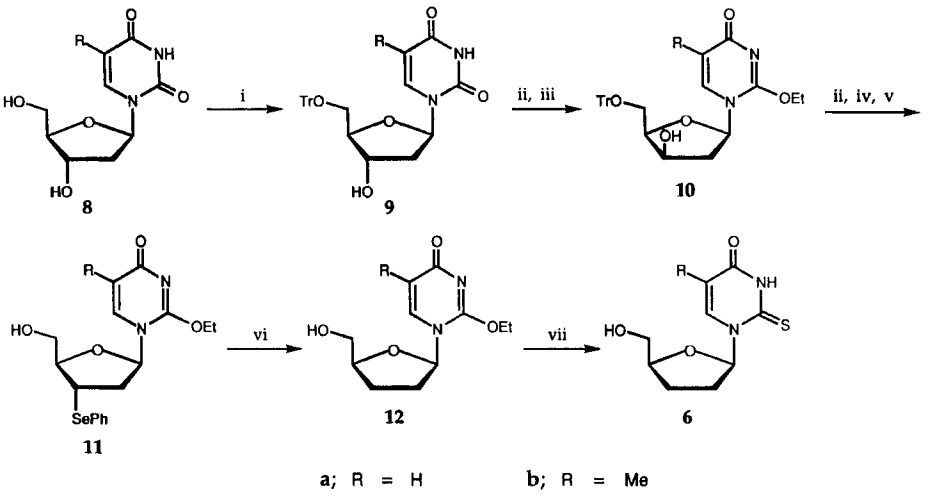


7 a; R = H
b; R = Me

(ddTU) **6a**, 3'-deoxy-2-thiothymidine (ddTT) **6b**, 2',3'-dideoxy-2-thiocytidine (ddTC) **7a** and 2',3'-dideoxy-5-methyl-2-thiocytidine (ddMTC) **7b**. To the best of our knowledge, none of these compounds has previously been described in the literature.

There are in principle two approaches to the synthesis of nucleoside analogues. The first approach involves the modification of a common (i.e. naturally-occurring or otherwise readily accessible) nucleoside starting material and the second involves the coupling together of appropriate derivatives of the sugar and aglycone moieties. In general, we consider the first approach to be preferable as it offers maximum control both of regio- and stereochemistry. We have recently reported[4] the synthesis of the 2',3'-didehydro-2',3'-dideoxynucleosides corresponding to the 2',3'-dideoxynucleosides **6a**, **6b**, **7a** and **7b** under consideration, but have not succeeded in effecting their hydrogenation. In order to convert a common pyrimidine nucleoside into the corresponding 2',3'-dideoxy-2-thionucleoside, modification both of the aglycone and sugar moieties is necessary. The two nucleoside starting materials used in this study were 2'-deoxyuridine **8a** and thymidine **8b**.

The procedure that we adopted for the conversion of 2'-deoxyuridine **8a** and thymidine **8b** into the corresponding 2',3'-dideoxy-2-thionucleosides [**6a** and **6b**, respectively] is indicated in outline in Scheme 1. Thus 2'-deoxyuridine **8a** was converted into its 5'-*O*-trityl derivative **9a** which was then mesylated on *O*-3' and the product heated, under reflux, with sodium ethoxide in ethanol solution to give[4] the 2-*O*-ethyl compound **10a**. The latter compound **10a** was obtained in 65% overall yield for the three steps. The intermediate 2,3'-anhydronucleoside derivative was not isolated. Thymidine **8b** was similarly converted into the corresponding 2-*O*-ethyl compound[5] **10b** in 59% overall yield for the three steps. The conversion of 1- [5-*O*-(triphenylmethyl)-2-deoxy-β-D-*threo*-pentofuranosyl]-2-*O*-ethyluracil **10a** into 2',3'-dideoxy-2-*O*-ethyl-3'-(phenylseleno)uridine **11a** also required three steps and proceeded in 63% overall yield. The conditions used for the mesylation of compound **10a** were the same as those used for compound **9a**. Sodium phenyl selenide was prepared[6] by treating diphenyl diselenide with sodium borohydride in ethanol solution, and the acid-catalyzed detritylation reaction was facilitated by the presence of pyrrole[7]. 1-[5-*O*-(Triphenylmethyl)-2-deoxy-β-D-*threo*-pentofuranosyl]-2-*O*-ethyl-

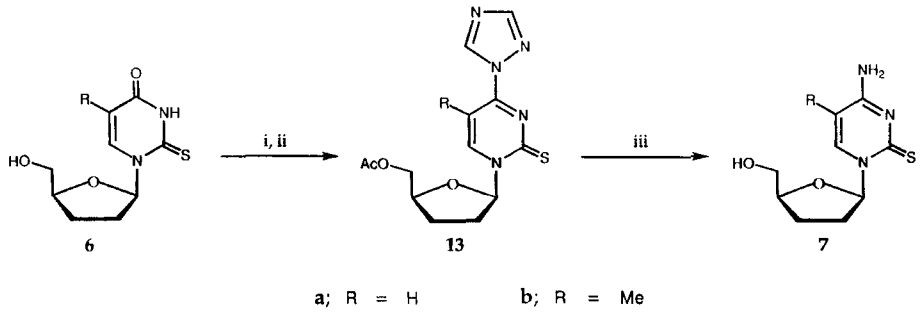


Scheme 1 *Reagents and conditions:* i, Ph_3CCl, C_5H_5N, 100 °C, 1 hr; ii, CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 1 hr; iii, NaOEt, EtOH, reflux, 10 min; iv, PhSeNa [from $(PhSe)_2$, $NaBH_4$, EtOH], EtOH, reflux, 10 - 30 min; v, pyrrole, CF_3CO_2H, CH_2Cl_2, 0 °C, 15 min; vi, nBu_3SnH, AIBN, C_6H_6, reflux, 20 min; vii, H_2S, $(Me_2N)_2C{=}NH$ (TMG), C_5H_5N, 0 °C to RT, 6 hr.

thymine **10b** was similarly converted into the corresponding 3'-(phenylseleno) derivative **11b** in 51% overall yield for the three steps.

The last two steps (Scheme 1, vi and vii) in the preparation of 2',3'-dideoxy-2-thiouridine (ddTU) **6a** proceeded in yields of 99 and 83%, respectively. The 3'-(phenylseleno) substituent was removed by tri-n-butyltin hydride reduction[8] initiated by 2,2'-azobis(2-methylpropionitrile) [AIBN]. The reaction conditions used for nucleophilic substitution (by HS^-) at C-2 were essentially the same as previously reported[4]. The corresponding steps in the conversion of 3'-deoxy-2-*O*-ethyl-3'-(phenylseleno)thymidine **11b** into 3'-deoxy-2-thiothymidine (ddTT) **6b** proceeded in yields of 98 and 63% respectively.

The method used for the conversion ddTU **6a** and ddTT **6b** into 2',3'-dideoxy-2-thiocytidine (ddTC) **7a** and 2',3'-dideoxy-5-methyl-2-thiocytidine (ddMTC) **7b**, respectively, is indicated in outline in Scheme 2. First, ddTU **6a** was converted by the standard procedure[9] into the 5'-*O*-acetyl-4-triazolo derivative **13a** in 80% overall yield. When the latter compound **13a** was treated with methanolic ammonia[4,9] at room temperature overnight, deacetylation and displacement of the triazolo residue occurred, and 2',3'-dideoxy-2-thiocytidine (ddTC) **7a** was obtained in 91% yield. In the same way ddTT



Scheme 2 *Reagents and conditions:* i, Ac_2O, C_5H_5N, 0 °C to RT, 4 hr; ii, 1,2,4-triazole, $POCl_3$, Et_3N, MeCN, 0 °C to RT, 4 hr; iii, *ca.* 6 M NH_3, MeOH, RT, 16 hr.

6b was converted *via* the intermediate triazolo-compound **13b** into 2',3'-dideoxy-5-methyl-2-thiocytidine (ddMTC) **7b** in 72% overall yield for the three steps.

Although none of the newly synthesized 2',3'-dideoxynucleosides [**6a**, **6b**, **7a** and **7b**] proved to be particularly cytotoxic [all had $TC_{50} > 1000$ μm], their anti-HIV activities were disappointing. The most active of the four compounds, ddTC **7a** has an EC_{50} of 100μm and is therefore considerably less active than the corresponding 2-oxy derivative, ddC **2**. The remaining three compounds ddTU **6a**, ddTT **6b** and ddMTC **7b** were found to have EC_{50} = 200, 250 and 200 μm, respectively.

EXPERIMENTAL

M.p.s. were measured with a Büchi melting point apparatus and are uncorrected. ^1H NMR spectra, unless otherwise stated, were measured at 360 MHz with a Bruker AM 360 spectrometer; ^{13}C NMR spectra were measured at 90.6 MHz with the same spectrometer. Tetramethylsilane was used as an internal standard, and *J*-values are given in Hz. UV spectra were measured with a Perkin-Elmer Lambda-3 spectrophotometer. Merck silica gel 60 F_{254} TLC plates were developed in solvent systems A [chloroform-methanol (9:1 v/v)] and B [chloroform-methanol (19:1 v/v)]. Merck silica gel H was used for short column chromatography. Acetonitrile, triethylamine and pyridine were dried by heating, under reflux, over calcium hydride and were then distilled; benzene was dried over sodium wire and was then distilled; N^1, N^1, N^3, N^3- tetramethylguanidine (TMG) was dried by distillation over calcium hydride under reduced pressure.

*1-[5-O-(Triphenylmethyl)-2-deoxy-*β*-D-threo-pentofuranosyl]-2-O-ethyluracil* **10a**. - A solution of 2'-deoxyuridine (4.25 g, 18.6 mmol) and chlorotriphenylmethane (5.72 g, 20.5 mmol) in dry pyridine (185 mL) was stirred at 100°C. After 1 hr, the cooled products

were evaporated under reduced pressure and the residual gum was partitioned between chloroform (200 mL) and 2.0 M sulfuric acid (400 mL). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (200 mL), and then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel: the appropriate fractions were combined and evaporated under reduced pressure to give a glass (7.85 g). Triethylamine (3.20 mL, 23.0 mmol) was added to a solution of the latter material (7.22 g) in dichloromethane (125 mL). Then methanesulfonyl chloride (1.42 mL, 18.3 mmol) was added dropwise with stirring to the reaction solution at 0°C (ice-water bath). After the reaction had been allowed to proceed for a further period of 1 hr at 5°C, chloroform (150 mL) was added and the products were extracted with saturated aqueous sodium hydrogen carbonate (125 mL). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure to give a glass (8.40 g). A solution of sodium ethoxide [prepared by dissolving sodium metal (0.705 g, 0.031 g atom) in anhydrous ethanol (25 mL)] was added to a solution of the latter material (7.64 g) in anhydrous ethanol (40 mL) and the reactants were heated, under reflux, for 10 min. The cooled products were neutralized (to *ca.* pH 8) with solid carbon dioxide and the resulting mixture was evaporated under reduced pressure. The residue was partitioned between chloroform (300 mL) and water (300 mL). The chloroform layer was separated, washed with saturated brine (2 x 250 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, eluted with chloroform - ethanol (95:5 v/v), were combined and evaporated under reduced pressure to give the *title compound* **10a** (5.08 g, 65% overall yield for the 3 steps starting from 2'-deoxyuridine **8a**) as a colourless solid [Found, in material crystallized from ethyl acetate - petroleum ether (b.p. 60-80°C) : C, 71.7; H. 6.1; N, 5.4. $C_{30}H_{30}N_2O_5 \cdot 0.2\ H_2O$ requires: C, 71.75; H, 6.1; N, 5.6%], m.p. 199°C; R_f 0.30 (system B); δ_H [$(CD_3)_2SO$] 1.33 (3 H, t, *J* 7.1), 1.99 (1 H, d, *J* 14.5), 2.56 (1 H, m), 3.25 (1 H, dd, *J* 2.9 and 10.4), 3.44 (1 H, dd, *J* 8.0 and 10.4), 4.18 (2 H, m), 5.18 (1 H, d, *J* 3.1), 5.70 (1 H, d, *J* 7.7), 6.08 (1H, d, *J* 6.7), 7.29 (9 H, m), 7.43 (6 H, m), 7.71 (1 H, d, *J* 7.7); δ_C [$(CD_3)_2SO$] 13.9, 41.4, 62.6, 63.9, 68.6, 84.3, 86.0, 86.2, 106.7, 126.8, 127.6, 128.2, 138.4, 143.5, 154.5, 170.2.

*1-[5-O-(Triphenylmethyl)-2-deoxy-*β*-D-*threo*-pentofuranosyl]-2-O-ethylthymine* **10b**. - A solution of thymidine (9.12 g, 37.65 mmol) and chlorotriphenylmethane (12.276 g, 44.0 mmol) in dry pyridine (400 mL) was stirred at 100°C. After 1 hr, the products were worked-up and fractionated as in the above preparation of the corresponding 2-*O*-ethyluracil derivative to give a colourless solid (17.10 g). The latter material was dissolved in dichloromethane (200 mL) and triethylamine (7.41 mL, 53.2 mmol) was added. The resulting solution was cooled to 0°C, treated with methanesulfonyl chloride (3.27 mL, 42.2 mmol) and the products worked up as above to give a residual glass (19.65 g). The latter material (18.0 g) was heated, under reflux, with a solution of sodium ethoxide [prepared from sodium metal (1.62 g, 0.07 g atom)] in anhydrous ethanol (200 mL) for 10 min. The reaction mixture was then worked-up and the products were fractionated as in the above preparation of the corresponding 2-*O*-ethyluracil derivative **10a** to give the *title compound* **10b** (10.50 g, 59% overall yield for the 3 steps starting from thymidine **8b**) [Found, in

material crystallized from ethanol - ethyl acetate : C, 71.7; H, 6.1; N, 5.4. $C_{31}H_{32}N_2O_5 \cdot 0.4\ H_2O$ requires : C, 71.6; H, 6.4; N, 5.4%], m.p. 176°C; R_f 0.32 (system B); δ_H [$(CD_3)_2SO$ - $CDCl_3$] 1.37 (3 H, t, *J* 7.1), 1.74 (3 H, d, *J* 0.8), 2.01 (1 H, d, *J* 14.7), 2.58 (1 H, m), 3.26 (1 H, dd, *J* 2.7 and 10.5), 3.53 (1 H, m), 4.21 (2 H, m), 4.42 (2 H, quart, *J* 7.0), 5.20 (1H, d, *J* 3.1), 6.12 (1 H, m), 7.28 (9 H, m), 7.47 (6 H, m), 7.66 (1 H, m); δ_C [$(CD_3)_2SO$] 13.7, 14.1, 41.7, 62.9, 64.1, 68.9, 84.4, 86.2, 114.9, 126.9, 127.7, 128.4, 134.6, 143.6, 154.4, 171.4.

2', 3'-Dideoxy-2-O-ethyl-3'-(phenylseleno)uridine **11a**. - Triethylamine (1.30 mL, 9.3 mmol) and then methanesulfonyl chloride (0.57 mL, 7.4 mmol) were added to a stirred solution of 1-[5-*O*-(triphenylmethyl)-2-deoxy-β-D-*threo*-pentofuranosyl]-2-*O*-ethyluracil (3.08 g, 6.18 mmol) in dichloromethane (100 mL) at 0°C (ice-water bath). The reaction mixture was allowed to warm up to room temperature. After 1 hr, chloroform (100 mL) was added and the products were extracted with saturated aqueous sodium hydrogen carbonate (120 mL). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure and the residue was dissolved in anhydrous ethanol (15 mL). A freshly prepared solution of sodium phenyl selenide, obtained by adding sodium borohydride to a solution of diphenyl diselenide (1.922 g, 6.15 mmol) in ethanol (15 mL) until the yellow colour was discharged, was added and the reactants were heated, under reflux, for 10 min. The cooled products were evaporated under reduced pressure and the residue was partitioned between ethyl acetate (200 mL) and water (150 mL). The organic layer was separated, washed with brine (2 x 150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The syrupy residue was fractionated by short column chromatography on silica gel; the appropriate fractions, eluted with chloroform - ethanol (95:5 v/v), were combined and evaporated under reduced pressure to give a colourless glass (2.63 g); R_f 0.38 (system B).

Pyrrole (2.93 mL, 42 mmol) and trifluoroacetic acid (1.63 mL, 21 mmol) were added to a stirred solution of the latter material in dichloromethane (12 mL) at 0°C. After the reaction had been allowed to proceed for 15 min at 5°C, the products were evaporated under reduced pressure (oil-pump) and redissolved in chloroform (150 mL). The resulting solution was washed with saturated aqueous sodium hydrogen carbonate (150 mL), water (2 x 150 mL) and brine (150 mL). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure and the residue was fractionated by short column chromatography on silica gel: the appropriate fractions eluted with ethyl acetate - ethanol (95:5 v/v) were combined and evaporated under reduced pressure to give the *title compound* **11a**. (1.55 g, 63% overall yield for the 3 steps) [Found, in material crystallized from ethyl acetate: C, 51.5; H, 5.1; N, 7.1. $C_{17}H_{20}N_2O_4Se$ requires: C, 51.65; H, 5.1; N 7.1%] as a colourless solid, m.p. 130°C; R_f 0.19 (system A); δ_H [$(CD_3)_2SO$] 1.29 (3 H, t, *J* 7.1), 2.43 (1 H, m), 2.61 (1 H, m), 3.62 (1 H, m), 3.78 (2 H, m), 3.97 (1 H, m), 4.32 (2 H, quart, *J* 7.1), 5.24 (1 H, t, *J* 5.1), 5.79 (1 H, d, *J* 7.7), 5.94 (1 H, dd *J* 3.2 and 6.9), 7.36 (3 H, m), 7.59 (2 H, m), 8.07 (1 H, d, *J* 7.7); δ_C [$(CD_3)_2SO$] 13.9, 35.7, 39.8, 59.6, 64.1, 85.7, 86.7, 107.3, 127.5, 127.9, 129.4, 134.1, 138.2, 154.6, 169.8.

3'-Deoxy-2-O-ethyl-3'-(phenylseleno)thymidine **11b**. - Triethylamine (1.05 mL, 7.5 mmol) and then methanesulfonyl chloride (0.46 mL, 5.9 mmol) were added to a stirred

solution of 1-[5-*O*-(triphenylmethyl)-2-deoxy-β-D-*threo*-pentofuranosyl]-2-*O*-ethylthymine (2.575 g, 5.02 mmol) in dichloromethane (100 mL) at 0°C (ice-water bath). The reaction mixture was allowed to warm up to room temperature and, after 1 hr, the products were worked-up as in the above preparation of the corresponding 2-*O*-ethyluracil derivative **11a**. A solution of the residue obtained in anhydrous ethanol (15 mL) was treated with a solution of sodium phenyl selenide, prepared by adding sodium borohydride to a solution of diphenyl diselenide (1.56 g, 5.0 mmol) in ethanol (15 mL). The reactants were then heated, under reflux, for 30 min. The products were worked-up and fractionated as above to give a colourless glassy solid (2.05 g); R_f 0.40 (system B).

Pyrrole (2.07 mL, 29.8 mmol) and trifluoroacetic acid (1.15 mL, 14.9 mmol) were added to a stirred solution of the latter material (1.95 g) in dichloromethane (15 mL) at 0°C. After the reaction had been allowed to proceed at 0°C for 15 min, the products were worked-up and fractionated as in the above preparation of the corresponding 2-*O*-ethyluracil derivative **11a** to give the *title compound* **11b** (1.00 g, 52% overall yield for the three steps)[Found, in material recrystallized from ethyl acetate: C, 52.9; H, 5.6; N, 6.9. $C_{18}H_{22}N_2O_4Se$ requires: C, 52.8; H, 5.4; N, 6.8%] as a colourless solid, m.p. 151°C; R_f 0.24 (system B); δ_H [$CDCl_3$] 1.34 (3 H, t, *J* 7.1), 1.90 (3 H, d, *J* 1.0), 3.45 (2 H, m), 3.86 (2 H, m), 4.06 (3 H, m), 4.45 (2 H, quart, *J* 7.1), 5.97 (1 H, dd, *J* 4.1 and 6.1), 7.33 (3 H, m), 7.59 (2 H, m), 8.03 (1 H, m); δ_C [$CDCl_3$] 13.8, 14.3, 35.5, 41.1, 60.6, 64.9, 85.7, 87.0, 116.8, 126.6, 128.6, 129.4, 134.1, 135.6, 154.6, 172.6.

*2', 3'-Dideoxy-2-*O*-ethyluridine* **12a**. - 2,2'-Azobis(2-methylpropionitrile) (0.066 g, 0.4 mmol) and freshly prepared tri-n-butyltin hydride[10] (3.27 mL, 12.15 mmol) were added to a suspension of 2',3'-dideoxy-2-*O*-ethyl-3'-(phenylseleno)uridine **11a** (1.60 g, 4.05 mmol) in dry benzene (25 mL). The reactants were heated, under reflux, for 20 min and the cooled products were then evaporated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, eluted with chloroform containing increasing proportions of ethanol (0 - 10% v/v) were combined and evaporated under reduced pressure, to give the *title compound* **12a** as a colourless solid (0.97 g, *ca.* 99%)[Found, in material crystallized from ethyl acetate - benzene: C, 55.1; H, 6.7; N, 11.5. $C_{11}H_{16}N_2O_4$ requires: C, 55.0; H, 6.7; N, 11.7%], m.p. 110°C; R_f 0.12 (system B); δ_H [$(CD_3)_2SO$] 1.31 (3 H, t, *J* 7.1), 1.85 (2 H, m), 2.05 (1 H, m), 2.35 (1 H, m), 3.55 (1 H, m), 3.71 (1 H, m), 4.07 (1 H, m), 4.35 (2 H, m), 5.08 (1 H, t, *J* 5.3), 5.79 (1 H, d, *J* 7.7), 5.93 (1 H, dd, *J* 3.0 and 6.8), 8.04 (1 H, d, *J* 7.7); δ_C [$(CD_3)_2SO$] 13.9, 24.4, 32.5, 61.7, 63.9, 82.3, 86.9, 107.2, 138.2, 154.7, 169.9.

*3'-Deoxy-2-*O*-ethylthymidine* **12b**. - 2,2'-Azobis(2-methylpropionitrile) (0.028 g, 0.17 mmol) and freshly prepared tri-n-butyltin hydride (1.38 mL, 5.13 mmol) were added to a suspension of 3'-deoxy-2-*O*-ethyl-3'-(phenylseleno)thymidine (0.70 g, 1.71 mmol) in dry benzene (25 mL). The reactants were heated, under reflux, for 20 min. The products were worked-up and fractionated as in the above preparation of 2',3'-dideoxy-2-*O*-ethyluridine **12a** to give the *title compound* **12b** as a colourless solid (0.43 g, *ca.* 98%) [Found, in material crystallized from ethyl acetate - benzene: C, 56.7; H, 7,1; N. 11.0.

$C_{12}H_{18}N_2O_4$ requires: C, 56.7; H, 7.1; N. 11.0%] m.p. 128°C; R_f 0.16 (system B); δ_H [$(CD_3)_2SO$] 1.29 (3 H, t, *J* 7.1), 1.78 (3 H, d, *J* 1.0), 1.85 (2 H, m), 2.03 (1 H, m), 2.32 (1 H, m), 3.55 (1, H, m), 3.71 (1 H, m), 4.04 (1 H, m), 4.32 (2 H, m), 5.12 (1 H, t, *J* 5.3), 5.13 (1 H, dd, *J* 3.2 and 6.8), 7.93 (1 H, m); δ_C [$(CD_3)_2SO$] 13.5, 14.1, 24.6, 32.3, 61.8, 63.9, 82.1, 86.5, 115.3, 134.1, 154.4, 170.5.

2', 3'-Dideoxy-2-thiouridine **6a**. - Hydrogen sulfide gas was bubbled into a stirred solution of 2',3'-dideoxy-2-*O*-ethyluridine **12a** (0.97 g, 4.04 mmol) and TMG (5.07 mL, 40.4 mmol) in dry pyridine (20 mL) at 0°C (ice-water bath) for 30 min. The stirred reactants were allowed to warm up to room temperature. After 6 hr, the products were diluted with chloroform (20 mL) and nitrogen was bubbled through the solution. The products were then evaporated under reduced pressure and the residue was fractionated by short column chromatography on silica gel: the appropriate fractions, eluted with chloroform containing increasing proportions of ethanol (0 - 5% v/v), were combined and evaporated under reduced pressure to give the *title compound* **6a** as a colourless solid (0.769 g, 83%) [Found, in material crystallized from ethyl acetate: C, 47.4; H, 5.2; N, 12.1. $C_9H_{12}N_2O_3S$ requires: C, 47.4; H, 5.3; N, 12.3%], m.p. 156°C; R_f 0.38 (system A); δ_H [$(CD_3)_2SO$] 1.82 (2 H, m), 2.04 (1 H, m), 2.40 (1 H, m), 3.58 (1 H, m), 3.77 (1 H, m), 4.11 (1 H, m), 5.20 (1 H, t, *J* 4.8), 5.96 (1 H, d, *J* 8.0), 6.55 (1 H, dd, *J* 2.7 and 6.7), 8.26 (1 H, dd, *J* 0.6 and 8.1), 12.60 (1 H, br); δ_C [$(CD_3)_2SO$] 23.9, 32.6, 61.1, 82.8, 90.0, 105.9, 140.8, 159.8, 174.9.

3'-Deoxy-2-thiothymidine **6b**. - Hydrogen sulfide gas was bubbled into a stirred solution of 3'-deoxy-2-*O*-ethylthymidine **12b** (0.245 g, 1.0 mmol) and TMG (1.10 mL, 8.8 mmol) in dry pyridine (5 mL) at 0°C (ice-water bath) for 30 min. The stirred reactants were allowed to warm up to room temperature. After 5 hr, the products were worked up and fractionated as above in the preparation of 2',3'-dideoxy-2-thiouridine **6a** to give the *title compound* **6b** as a colourless solid (0.154 g, 63%) [Found, in material crystallized from ethyl acetate - benzene: C, 49.55; H, 5.5; N, 11.3. $C_{10}H_{14}N_2O_3S$ requires: C, 49.6; H, 5.8; N, 11.6%] , m.p. 159°C; R_f 0.53 (system A); δ_H [$(CD_3)_2SO$] 1.80 (3 H, d, *J* 1.1), 1.86 (2 H, m), 1.98 (1 H, m), 2.37 (1 H, m), 3.61 (1 H, m), 3.77 (1 H, m), 4.09 (1 H, m), 5.35 (1 H, t, *J* 5.1), 6.54 (1 H, dd, *J* 2.8 and 6.8), 8.20 (1 H, m), 12.53 (1 H, br); δ_C [$(CD_3)_2SO$] 12.6, 23.9, 32.6, 61.1, 82.7, 89.9, 114.5, 137.1, 160.8, 173.7.

*1-(5-*O*-Acetyl-2,3-dideoxy-*β*-*D*-pentofuranosyl)-4-(1,2,4-triazol-1-yl)-pyrimidin-2-(1*H*)-thione* **13a**. - Acetic anhydride (0.40 mL, 4.2 mmol) was added to a stirred solution of 2',3'-dideoxy-2-thiouridine **6a** (0.52 g, 2.28 mmol) in anhydrous pyridine (12 mL) at 0°C (ice-water bath). The reactants were allowed to warm up to room temperature. After 4 hr, methanol (5 mL) was added, and after a further period of 10 min, the products were concentrated under reduced pressure. The residue was partitioned between chloroform (60 mL) and water (50 mL). The organic layer was separated, washed with brine (2 x 25 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, eluted with chloroform

- ethanol (98:2 v/v), were combined and concentrated under reduced pressure to give a glass (0.61 g). A solution of the latter material (0.57 g) in acetonitrile (6 mL) was added to the products obtained by stirring phosphoryl trichloride (0.36 mL, 3.86 mmol), 1,2,4-1*H*-triazole (1.24 g, 18.0 mmol) and triethylamine (2.52 mL, 18.1 mmol) together in acetonitrile (12 mL) for 15 min at 0°C (ice-water bath). The reactants were allowed to warm up to room temperature. After 4 hr, triethylamine (2.52 mL, 18.1 mmol) and water (0.4 mL) were added and, after a further period of 10 min, the products were concentrated under reduced pressure. The residue was extracted with chloroform (2 x 50 mL) at room temperature. The dried ($MgSO_4$) extract was evaporated under reduced pressure to give the *title compound* **13a** as a yellow solid (0.55 g, 80%) [Found, C, 48.6; H, 4.5; N, 21.5. $C_{13}H_{15}N_5O_3S$ requires: C, 48.6; H, 4.7; N, 21.8%], m.p. 112°C dec.; R_f 0.46 (system B); δ_H [$(CD_3)_2SO$] 1.67 (1 H, m), 1.98 (1 H, m), 2.11 (3 H, s), 2.21 (1 H, m), 2.62 (1 H, m), 4.39 (3 H, m), 6.54 (1 H, dd, *J* 1.9 and 6.8), 7.41 (1 H, d, *J* 7.2), 8.44 (1 H, s), 8.69 (1 H, d, *J* 7.3), 9.44 (1 H, s); δ_C [$(CD_3)_2SO$] 20.7, 24.3, 32.7, 64.2, 80.7, 92.5, 99.2, 143.7, 148.0, 153.1, 154.4, 170.3, 178.8.

2', 3'-Dideoxy-2-thiocytidine **7a**. - Methanolic ammonia (*ca.* 8 M, 4 mL) was added to a stirred solution of 1-(5-*O*-acetyl-2,3-dideoxy-β-D-pentofuranosyl)-4-(1,2,4-triazol-1-yl)-pyrimidin-2(1*H*)-thione **13a** (0.25 g, 0.78 mmol) in dry methanol (1 mL) at room temperature. After 16 hr, the products were concentrated under reduced pressure and the residue was fractionated by short column chromatography on silica gel: elution of the column with chloroform - methanol (95:5 v/v) and concentration of the appropriate fractions gave the *title compound* **7a** (0.162 g, 91%) [Found, in material crystallized from ethyl acetate - methanol : C, 47.7; H, 5.8; N,18.4. $C_9H_{13}N_3O_2S$ requires: C, 47.6; H, 5.8; N, 18.5%], m.p. 176°C; R_f 0.15 (system A); δ_H [$(CD_3)_2SO$] 1.79 (2, H, m), 1.96 (1 H, m), 2.42 (1 H, m), 3.59 (1 H, m), 3.77 (1 H, m), 4.10 (1 H, m), 5.13 (1 H, t, *J* 5.3), 6.06 (1 H, d, *J* 7.5), 6.68 (1 H, d, *J* 2.7 and 6.6), 7.51 (1 H, br s), 7.74 (1 H, br s), 8.27 (1 H, d, *J* 7.5); δ_C [$(CD_3)_2SO$] 24.0, 33.2, 61.4, 82.6, 90.3, 97.3, 141.3, 160.4, 178.8.

2', 3'-Dideoxy-5-methyl-2-thiocytidine **7b**. - Acetic anhydride (0.094 mL, 1.0 mmol) was added to a stirred solution of 3'-deoxy-2-thiothymidine **6b** (0.121 g, 0.5 mmol) in anhydrous pyridine (2.5 mL) at room temperature. After 6 hr, ethanol (1 mL) was added and, after a further period of 15 min, the products were concentrated under reduced pressure. The residue was extracted with chloroform (25 mL) at room temperature and the resulting extract was washed with water (2 x 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. A solution of the residue in acetonitrile (2 mL) was added to the products obtained by stirring 1,2,4-1*H*-triazole (0.276 g, 4.0 mmol), phosphoryl trichloride (0.093 mL, 1.0 mmol) and triethylamine (0.56 mL, 4.0 mmol) for 30 min at 0°C (ice-water bath). The reactants were then allowed to warm up to room temperature. After 6 hr, triethylamine (0.56 mL, 4.0 mmol) and water (0.5 mL) were added and, after a further period of 10 min, the products were concentrated under reduced pressure. The residue was redissolved in chloroform (30 mL) and the solution was washed with saturated aqueous sodium hydrogen carbonate (2 x 10 mL). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure. The pale yellow residue was dissolved in methanolic ammonia (6 M, 3 mL) at

room temperature. After 12 hr, the products were concentrated under reduced pressure and the residue was fractionated by short column chromatography on silica gel: elution of the column with chloroform - ethanol (85:15 v/v) and concentration of the appropriate fractions gave the *title compound* **7b** as a colourless solid (0.087 g, 72% overall yield for the 3 steps) [Found, in material crystallized from ethanol - ethyl acetate: C, 49.2; H, 6.3; N, 17.1. $C_{10}H_{15}N_3O_2S \cdot 0.15\ H_2O$ requires: C, 49.2; H, 6.3; N, 17.2%], m.p. 235°C dec.; R_f 0.26 (system A); δ_H [$(CD_3)_2SO$] 1.79 (2 H, m), 1.87 (3 H, d, *J* 0.8), 1.92 (1 H, m), 2.41 (1 H, m), 3.57 (1 H, m), 3.77 (1 H, m), 4.07 (1 H, m), 5.43 (1 H, t, *J* 5.2), 6.61 (1 H, dd, *J* 2.7 and 6.7), 7.12 (1 H, br), 7.51 (1 H, br), 8.21 (1 H, m); δ_C [$(CD_3)_2SO$] 13.7, 23.9, 33.5, 61.5, 82.8, 90.5, 105.7, 139.6, 160.7, 177.2.

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