nitrogen atmosphere for 12 h and was then filtered over a pad of Celite. Standard workup afforded 135 mg (93% yield) of a yellow oil whose structure was assigned as **28** on the basis of its spectral properties: IR (neat) 2930, 2860, 1650, 1435, 1400, 1375, 1225, 1150, 1055, 830, 735, and 655 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.15–1.60 (m, 8 H), 2.08 (s, 3 H), 2.15 (m, 2 H), 2.66 (m, 2 H), 3.82 (m, 2 H), 5.65 (m, 1 H), and 5.73 (m, 1 H); HRMS for $C_{12}H_{19}NO$, calcd 193.1467, found 193.1466.

To a solution containing 44 mg of **28** in 5 mL of methanol was added 10 mg of 10% palladium on activated carbon. The resulting suspension was subjected to hydrogenation on the Parr shaker at 50 psi of hydrogen for 18 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give 0.44 mg (100% yield) of a yellow oil, whose structure was assigned as 1-acetyl-1-azaspiro[5.5]undecane (**29**) on the basis of its spectral properties: IR ($CHCl_3$) 2940, 2875, 1640, 1445, 1415, 1140, 915, and 795 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.15–1.75 (m, 14 H), 2.08 (s, 3 H), 2.82 (m, 2 H) and 3.33 (m, 2 H); HRMS for $C_{12}H_{21}NO$, calcd 195.1623, found 195.1630.

1-Acetyl-6,6-dimethyl-1,2,5,6-tetrahydropyridine (30). To a solution containing 0.83 g of **21c** in 20 mL of methylene chloride at 0 °C was added 0.69 g of triethylamine. After the mixture was stirred for 5 min, 0.54 g of acetyl chloride was added over a period of several minutes. The reaction was allowed to warm to 25 °C and was stirred for an additional 2 h. Standard workup gave 0.78 g (72% yield) of a yellow oil whose structure was assigned as 4-acetoxy-1-acetyl-6,6-dimethyl-3-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine on the basis of its spectral properties: IR (neat) 3080, 3020, 2975, 2935, 1780, 1730, 1660, 1585, 1410, 1310, 1195, 1150, 1020, 800, 765, 750, and 695 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.45 (s, 6 H), 2.00 (s, 3 H), 2.20 (s, 3 H), 2.50 (s, 2 H), 4.25 (s, 2 H), 7.65 (m, 3 H), and 8.00 (m, 2 H).

To a solution containing 1.38 g of the above compound in 50 mL of 1:1 tetrahydrofuran–methanol at 0 °C was added 0.74 g of sodium borohydride. The reaction was allowed to warm to 25 °C and was stirred for an additional 10 h. Standard workup gave 0.62 g (54% yield) of a white solid, mp 151–152 °C, whose structure was assigned as 1-acetyl-2,2-dimethyl-4-hydroxy-5-(phenylsulfonyl)piperidine on the basis of it spectral properties: IR ($CHCl_3$) 3540, 3075, 2980, 2935, 1655, 1450, 1400, 1310, 1170, 1150, 1085, 1060, 980, 795, 690, and 635 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 3 H), 1.48 (s, 3 H), 1.52 (dd, 1 H, J = 14.7 and 3.0 Hz), 1.84 (dd, 1 H, J = 14.7 and 5.0 Hz), 1.95 (s, 3 H), 3.18 (td, 1 H, J = 7.6 and 2.7 Hz), 3.50 (s, 1 H), 3.76 (d, 2 H, J = 7.6 Hz), 4.39 (m, 1 H), 7.56 (t, 2 H, J = 7.5 Hz), 7.67 (t, 1 H, J = 7.5 Hz), and 7.90 (d, 2 H, J = 7.5 Hz).

To a solution containing 70 mg of the above alcohol in 4 mL of methylene chloride at 0 °C was added 0.156 mL of triethylamine. To this solution was added dropwise 0.052 mL of methanesulfonyl chloride over a 10-min interval. The reaction was stirred at 0 °C for 30 min, after which time 0.185 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added. The reaction mixture was allowed to warm to 25 °C and was stirred for an additional 14 h. Standard workup gave 65 mg (98% yield) of a yellow oil whose structure was assigned as 1-acetyl-6,6-dimethyl-3-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine on the basis of its spectral properties: IR (neat) 3075, 2980, 2940, 1650, 1450, 1405, 1310, 1155, 1090, 920, 765, 730, 695, and 645 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 6 H), 1.82 (s, 3 H), 2.37 (d, 2 H, J = 4.7 Hz), 3.96 (s, 2 H), 7.14 (t, 1 H, J = 4.7 Hz), 7.53 (t, 2 H, J = 7.5 Hz), 7.64 (t, 1 H, J = 7.5 Hz), and 7.85 (d, 2 H, J = 7.5 Hz).

To a solution containing 90 mg of the above vinyl sulfone in 30 mL of a 30% tetrahydrofuran–methanol mixture was added 960 mg of sodium phosphate dibasic at 25 °C. The solution was vigorously stirred while 1.31 g of freshly prepared 6% sodium amalgam was added all at once. Standard workup gave 43 mg (91% yield) of a clear oil whose structure was assigned as 1-acetyl-6,6-dimethyl-1,2,5,6-tetrahydropyridine (**30**) on the basis of its spectral properties: IR ($CHCl_3$) 2980, 2855, 1645, 1385, and 1025 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 6 H), 2.07 (s, 3 H), 2.12 (m, 2 H), 3.84 (m, 2 H), 5.81 (m, 1 H), and 5.89 (m, 1 H); HRMS for $C_9H_{15}NO$, calcd 153.1154, found 153.1158. Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.41; H, 9.80; N, 8.78.

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Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra (75 MHz) for all compounds with high-resolution mass spectra (9 pages). Ordering information is given on any current masthead page.

Selenium Nucleophiles for the Preparation of Antiviral Nucleosides

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The reactivity of nucleophilic selenium species toward nucleoside derivatives has been examined. A number of new 2′-deoxyribose nucleosides have been synthesized using this methodology. The cis elimination of the selenoxide obtained from the oxidation of the corresponding phenylselenide has been shown to be an efficient method for the preparation of the 2′,3′-unsaturated antiviral nucleoside 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (D4T).

Introduction

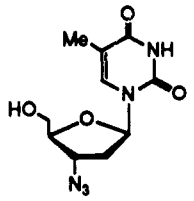
Acquired immunodeficiency syndrome (AIDS) is a consequence of infection by the human immunodeficiency virus (HIV).[1] Several 2′,3′-dideoxynucleosides have been shown to be effective in the treatment of cells infected with HIV, and one compound, 3′-azido-3′-deoxythymidine (AZT, 1), has been approved by the Food and Drug Administration (FDA) for the treatment of individuals with AIDS.[2] These compounds, as their 5′-triphosphates, are

(1) (a) Barre-Sinoussi, F.; Chermann, J. C.; Rey, R.; Nugeyre, M. T.; Chamaret, S.; Gruest, C.; Dauguet, C.; Axler-Blin, C.; Rouzioux, C.; Rosenbaum, W.; Montagnier, L. *Science (Washington, D.C.)* **1983**, *220*, 868. (b) Broder, S.; Gallo, R. C. *New. Engl. J. Med.* **1984**, *311*, 1292. (c) Broder, S.; Gallo, R. C. *Annu. Rev. Immunol.* **1985**, *3*, 321.

(2) (a) Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533. (b) Schinazi, R. F. In *AIDS in Children, Adolescents, and Heterosexual Adults*; Schinazi, R. F., Nahmias, A. J., Eds.; Elsevier: New York, 1988; p 126. (c) Fischl, M. A.; Richman, D. D.; Grieco, M. H.; Gottlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Schooley, R. T.; Jackson, G. G.; Durack, D. T.; King, D. *New. Engl. J. Med.* **1987**, *317*, 185.

0022-3263/91/1956-2161$02.50/0

believed to inhibit viral reverse transcriptase by competing with the natural substrates at the nucleotide binding site on the enzyme and can be incorporated into proviral DNA. The unsaturated nucleoside 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (D4T, 2) has been reported



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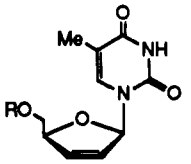


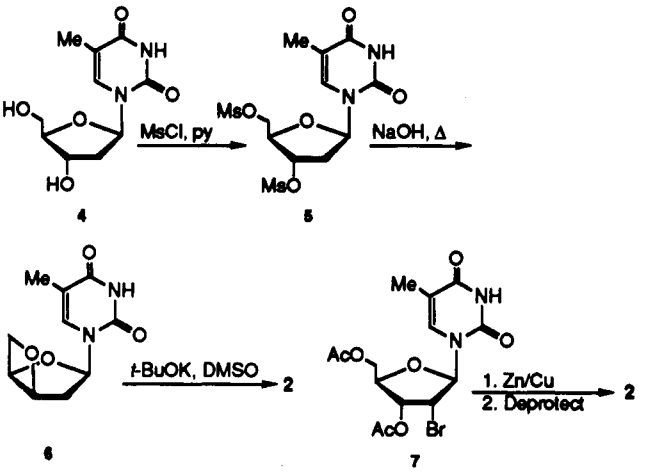
2 R = H
3 R = Tr

to have a comparable potency with AZT against HIV in culture and is currently in clinical trials.[3] Modifications of this synthetic target are currently under investigation by several groups, and various approaches toward an efficient preparation of D4T have been reported.[4a-c,5,7a] In this study, nucleophilic selenium reagents, species which are reactive under mild conditions, have been used to prepare several new thymidine derivatives. The selenoxide elimination reaction has been used to produce the desired unsaturation at the 2′,3′-position of the sugar.

Results and Discussion

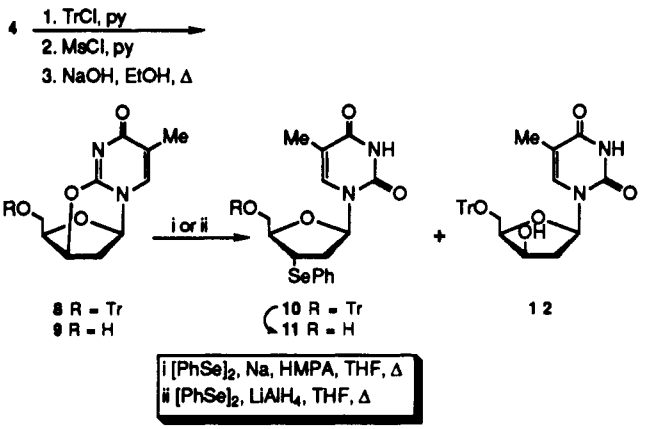
The introduction of 2′,3′-unsaturation into the sugar moiety of pyrimidine nucleosides has in the past been accomplished by base mediated elimination reactions. For example, the method most widely used for the production of D4T was first described by Horwitz et al.[4d] and involves the ring opening of the oxetane 6 (Scheme I) (*t*BuOK, DMSO). Unfortunately, yields are generally poor due to the instability of D4T under strongly basic conditions, and the difficulties associated with the removal of DMSO during workup. Because of these drawbacks, other approaches have been examined, such as the use of the Corey–Winter reaction, the deoxygenation of 2-alkoxy-1,3-dioxolanes, and the reductive elimination of 2′,3′-haloacetates 7.[5] However, the latter processes although practical, are not highly efficient. For example, the elimination of bromoacetate from compound 7 to give the unsaturated derivative proceeds in only 38% yield from thymine riboside, and the reaction results in the isolation

Scheme I



4 5 6 7

Scheme II



of thymine as a major side product (40%). Further, these reactions require thymine riboside derivatives as starting materials, and these must be prepared via a multistep sequence. Naturally occurring thymidine 4, a 2′-deoxyribose sugar nucleoside, is therefore a more attractive precursor than thymine riboside. We envisaged a novel procedure employing 3′-selenenylated thymidine derivatives which could be transformed to the corresponding alkene under extremely mild conditions. In addition, such 3′-substituted nucleosides might possess antiviral activity in themselves since they are structurally analogous to active compounds such as AZT, 1.

Despite the volume of literature published in recent years describing the use of selenium reagents in organic synthesis,[6] until recently there were few reports involving nucleosides.[7] This may be because of the problems associated with the introduction of a selenium species into nucleosides via an efficient process. Our initial studies were directed at determining the conditions required for the preparation of 10 directly from a nucleoside derivative. During the course of this work, Chu et al.[7a] and Liotta et al.[4c] have independently reported that glycosylation of 2-phenylselenylated or 2-arylsulfinylated 2,3-dideoxyribosides with silylated thymine followed by thermal elimination of the respective selenoxide and sulfoxide derivatives is an efficient entry into 2′,3′-unsaturated nucleosides. Whilst this approach allows access to the 2′-phenylselenylated or 2′-arylsulfinylated nucleosides, we wished to develop a method which would produce the 3′-substituted selenium derivatives 11 and 18 both as potential antiviral agents and as precursors to D4T. The substrate initially employed in this study, the 3′-anhydro

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(4) (a) Mansuri, M. M.; Starrett, J. E.; Ghazzouli, I.; Hitchcock, M. J. M.; Sterzycki, R. A.; Brankovan, V.; Lin, T. S.; August, E. M.; Prusoff, W. H.; Sommadossi, J.-P.; Martin, J. C. *J. Med. Chem.* **1989**, *32*, 461. (b) Martin, J. C.; Mansuri, M. M.; Starrett, J. E.; Sommadossi, J.-P.; Brankovan, V.; Ghazzouli, I.; Ho, H.-T.; Hitchcock, M. J. M. *Nucleosides Nucleotides* **1989**, *8*, 841. (c) Wilson, L. J.; Liotta, D. *Tetrahedron Lett.* **1990** *31*, 1815. (d) Horwitz, J. P.; Chua, J.; Da Rooge, M.; Noel, M.; Klundt, I. L. *J. Org. Chem.* **1966**, *31*, 205.

(5) (a) Mansuri, M. M.; Starrett, J. E.; Wos, J. A.; Tortolani, D. R.; Brodfuehrer, P. R.; Howell, H. G.; Martin, J. C. *J. Org. Chem.* **1989**, *54*, 4780. (b) Dudycz, L. *Nucleosides Nucleotides* **1989**, *8*, 3. (c) Shiragami, M.; Irie, Y.; Shirae, H.; Yokozeki, K.; Yasuda, N. *J. Org. Chem.* **1988**, *53*, 5179.

(6) (a) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1986. (b) Liotta, D. *Organoselenium Chemistry*; Wiley: New York, 1987.

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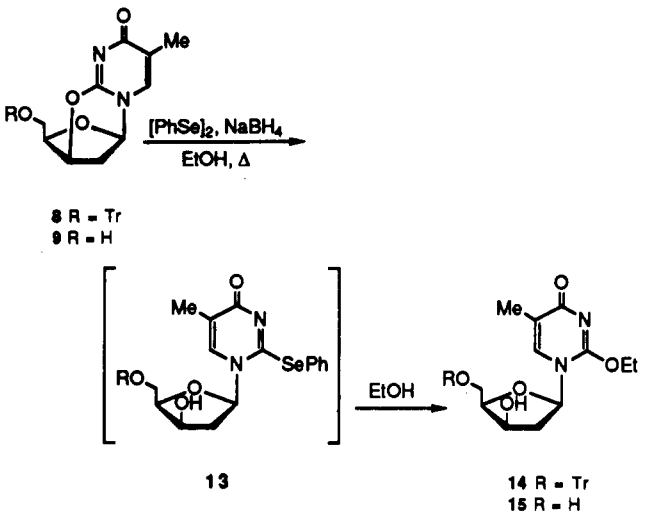
Scheme III



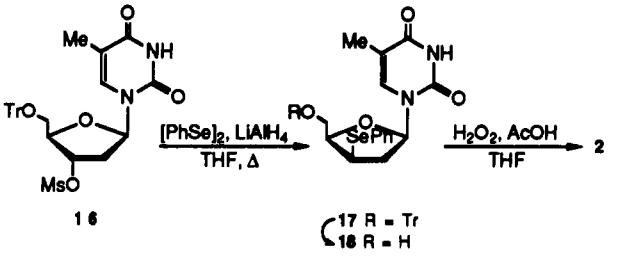
derivative 8, was readily prepared from thymidine by known methods in three steps, Scheme II (62% overall yield).[4d,8]

The reactivity of 8 is characterized by two modes of nucleophilic attack depending on the reaction conditions: (1) addition from the α-face of the sugar to give 3′-substitution, and (2) ring opening at the 2-position to give substitution at the base. Using the method of Liotta and co-workers[9] for generating sodium phenylselenolate using $(PhSe)_2$, Na, HMPA, and THF, it was possible to isolate **10**, but only in 46% yield, and with a substantial amount (35%) of the 3′-lyxo derivative **12**. A related method,[10] which used $(PhSe)_2$ and NaH in the same solvents, resulted in the formation of **12** as the sole product (58%). Interestingly, these results are in agreement with other workers who have reported the production of an arabinofuranosyl derivative when 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil is subjected to the same conditions.[7d] The most likely explanation for these observations is that residual moisture in the solvent in the presence of Na or NaH formed NaOH, and this resulted in the formation of the hydrolysis product. The authors have observed that when **8** was heated in NaOH/HMPA/THF the 3′-lyxo compound **12** was the sole reaction product.

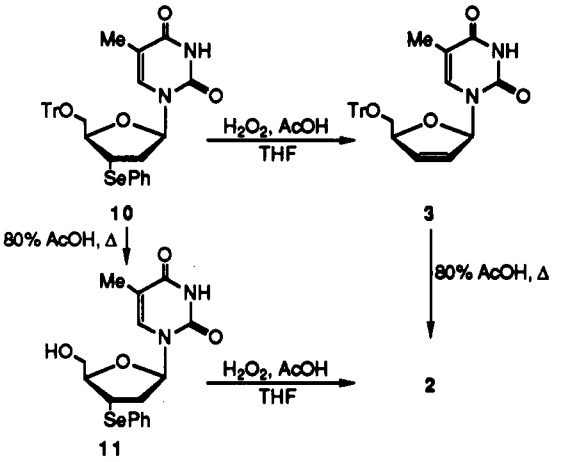
Changing the nucleophilic character of the selenium species by generating the complexed anion, $[PhSeBH_3]Na$ using $(PhSe)_2$ and $NaBH_4$ in EtOH can, in some cases, alter its reactivity.[9] Under these conditions, **10** was isolated (24%), as well as **14** (18%). The latter product arises from attack by the selenide anion to give an intermediate selenium species **13**, followed by an addition–elimination sequence to afford **14** (Scheme III).[11] Since the 5′-*O*-trityl group could be a source of steric hindrance, the reaction with the deprotected 3′-anhydro compound **9** (80% HOAc, Δ) was performed under the same conditions. The sole product isolated from this reaction was the product **15** (61%) arising from ring opening at position 2.

A less widely employed method of generating phenyl selenide anion utilizes $(PhSe)_2/LiAlH_4$ in THF as the reducing agent.[7b-d] Treatment of **8** with a slight excess of

Scheme IV



Scheme V



these reagents in THF at reflux gave the desired compound **10** in 70% yield, with no trace of the lyxo adduct **12**. Furthermore, it was also possible to convert the mesylate **16** into the β-phenylselenenyl isomer **17** (61%) using the same conditions (Scheme IV). The selenium species involved in these processes is assumed to be $[PhSeAlH_3]Li$, and this reagent exhibits the necessary reactivity to ring open the anhydro compound **8** selectively at the 3′-position. It seems likely that increasing the soft nature of the nucleophile by complexation with AlH_3 enables it to attack the 3′-position rather than the harder sp^2 aromatic C2 position. This may be contrasted with the reactivity of **8** with the uncomplexed species PhSeLi, generated from phenyllithium and selenium metal in THF, which produced an inseparable mixture of products, rather than the clean reaction observed with $[PhSeAlH_3]Li$. Thus, it appears that there is a considerable difference in the reactivity of the selenium nucleophile species depending on the type of complexation present.

The cis elimination of selenoxide from **10** was anticipated to provide a facile entry into 2′,3′-unsaturated compounds. Elimination to give the 3′,4′-unsaturated derivative, although possible, is less likely because of the adjacent ring oxygen. Thus, under mildly acidic conditions[12] (30% H_2O_2, trace HOAc, THF) **10** was converted to 5′-*O*-trityl D4T **3** (61%) and deprotection afforded the desired compound **2** (67%) (Scheme V). The relatively low yield of the latter step may be attributable to the instability of D4T to the acidic conditions required for the removal of the trityl group. This can be overcome by the simple deprotection of the phenylselenenyl nucleoside **10** prior to selenoxide elimination. Thus, treatment of **10** with 80% acetic acid at 90 °C for 1 h afforded **11** (81%), and selenoxide elimination of this compound to D4T proceeded in 86% yield. The overall yield of D4T from thymidine via the 3′-(phenylselenenyl)-3′-deoxythymidine **10** is

(8) Chu, C. K.; Schinazi, R. F.; Ahn, M. K.; Ullas, G. V.; Gu, Z. P. *J. Med. Chem.* **1989**, *32*, 612.
(9) Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4365.
(10) Dowd, P.; Kennedy, P. *Synth. Commun.* **1981**, *11*, 935.
(11) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831.
(12) Grieco, P. A.; Miyashita, M. *J. Org. Chem.* **1974**, *39*, 120.

therefore 30% by this route. Similarly, the β-isomer 17 was detritylated in 85% yield to give 18, and selenoxide elimination of this compound proceeded almost quantitatively to afford D4T 2 (99%). The overall yield from thymidine via this synthetic route is therefore 28%. Interestingly, oxidation of 10 in the presence of base[13] (30% H_2O_2, C_5H_5N, CH_2Cl_2, H_2O) gave the 2',3'-anhydro compound 8 (24%) as the sole product. Phenyl selenoxide is a good leaving group and deprotonation at N3 by pyridine followed by O2 anion formation leads to production of the anhydro compound 8. It appears therefore that basic conditions favor cyclization of the thymine oxygen over syn elimination of the selenoxide.

In summary, experimental conditions have been determined for the incorporation of a phenylselenenyl group into a 2',3'-dideoxynucleoside. Alternative modes of attack have been observed depending on the nature of the nucleophilic species employed. Cis elimination under oxidative conditions leads smoothly to the 2',3'-unsaturated derivatives, and hence to the antiviral nucleoside D4T, 2.

Experimental Section

Melting points were determined on an Electrothermal IA 8100 digital melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a General Electric QE-300 (300 MHz) spectrometer. Mass spectra were obtained by using a Varian MAT 112S spectrometer interfaced with an SS 200 data system. Microanalyses were performed at Atlantic Microlabs, Atlanta, GA. Experiments were monitored using TLC analysis performed on Kodak Chromagram sheets precoated with silica gel and a fluorescent indicator, while column chromatography, employing either silica gel (60–200 mesh, available from Fisher Scientific) or Merck 60 H silica gel, was used for the purification of products.

3'-*O*-Mesyl-5'-*O*-tritylthymidine (16). This was prepared according to the published method[13] (84%), mp 137–139 °C.

2,3'-Anhydro-1-(2-deoxy-5-*O*-trityl-β-D-furanosyl)thymine (8). This compound was prepared according to literature procedures[4d,8] (17.3 g, 62% from thymidine): mp 226–229 °C (lit.[4d] mp 218–222 °C); ^1H NMR ($CDCl_3$) δ 1.93 (3 H, s, CH_3), 2.40 (1 H, dm, J = 13.4 Hz, 2'-H), 2.60 (1 H, d, J = 13.4 Hz, 2'-H), 3.35 (2 H, d, J = 6.7 Hz, 5'-H_2), 4.25 (1 H, m, 4'-H), 5.14 (1 H, s, 3'-H), 5.43 (1 H, d, J = 3.4 Hz, 1'-H), 6.90 (1 H, s, 6-H), 7.16–7.44 (15 H, m, Ar).

2,3'-Anhydro-1-(2-deoxy-β-D-furanosyl)thymine (9). This was prepared by detritylation of 8 using the method of Verheyden and Moffatt[15] (91%), mp 231–233 °C (lit.[14] mp 230 °C).

3'-α-(Phenylselenenyl)-5'-*O*-trityl-3'-deoxythymidine (10). Method A. To a solution of diphenyl diselenide (156 mg, 0.5 mmol) in anhydrous THF (10 mL) under N_2(g) was added sodium metal (23 mg, 1 mmol), and the mixture was heated under reflux for 4 h. Addition of anhydrous HMPA (0.5 mL) afforded a red orange solution, and heating was continued for 3 h. The anhydrothymidine 8 (213 mg, 0.46 mmol) was added, and the mixture was heated for a further 8 h. After cooling, the reaction was quenched with MeOH (5 mL) and the solvents were removed in vacuo. The residue was treated with water (20 mL) and extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), concentrated, and chromatographed on silica gel with EtOAc–petroleum ether (1:4) as eluant to yield the title compound 10 (130 mg, 46%) as a colorless glass: R_f = 0.47 (EtOAc–hexane, 1:1); ^1H NMR ($CDCl_3$) δ 1.39 (3 H, s, CH_3), 2.51 (2 H, m, 2'-H_2), 3.39 (1 H, d, J = 10 Hz, 5'-H), 3.56 (1 H, d, J = 10 Hz, 5'-H), 3.85 (1 H, dd, J = 17, J = 7.6 Hz, 3'-H), 4.03 (1 H, m, 4'-H), 6.06 (1 H, dd, J = 6.3, J = 3.8 Hz, 1'-H), 7.18–7.5 (20 H, m, Ar), 7.68 (1 H, s, 6-H), 8.02 (1 H, bs exch, NH); MS m/z (relative intensity) 624 (M + 1, 20), 623 (M, 12), 381 (M – CPh_3, 32), 243 (CPh_3, 100). Anal. Calcd for $C_{35}H_{32}N_2O_4Se$: C, 67.42; H, 5.17; N, 4.49. Found: C, 67.33; H, 5.54; N, 4.32.

A second product isolated as a colorless solid was identified as 1-(2-deoxy-5-*O*-trityl-β-D-threofuranosyl)thymine (12) (78 mg, 35%): mp 240–244 °C (lit.[4d] mp 240–241 °C); ^1H NMR ($CDCl_3$) δ 1.80 (3 H, s, CH_3), 2.08 (1 H, d, J = 15.3 Hz, 2'-H), 2.60 (1 H, m, 2'-H), 2.86 (1 H, s, exch, OH), 3.48 (1 H, dd, J = 9.8, J = 4.9 Hz, 5'-H), 3.63 (1 H, dd, J = 9.8, J = 4.9 Hz, 5'-H), 4.03 (1 H, m, 4'-H), 4.46 (1 H, m, 3'-H), 6.19 (1 H, dd, J = 8.5, J = 2.4 Hz, 1'-H), 7.20–7.50 (15 H, m, Ar), 7.65 (1 H, s, 6-H), 8.05 (1 H, bs exch, NH). Anal. Calcd for $C_{29}H_{28}N_2O_5$: C, 71.89; H, 5.82; N, 5.78. Found: C, 71.53; H, 5.84; N, 5.63.

3'-α-(Phenylselenenyl)-5'-*O*-trityl-3'-deoxythymidine (10). Method B. A solution of diphenyl diselenide (2.49 g, 8 mmol) in anhydrous THF (50 mL) under N_2(g) was cooled to 0 °C, and $LiAlH_4$ (230 mg, 6 mmol) was added carefully. This was allowed to warm to room temperature over 0.25 h. To the clear solution thus formed was added the anhydrothymidine 8 (2.33 g, 5 mmol) with anhydrous THF (10 mL). The mixture was heated under reflux for 3 h, allowed to cool, and quenched with MeOH (10 mL). The solvents were removed in vacuo, the residue was treated with saturated NH_4Cl solution (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated to afford a yellow oil. This was chromatographed on silica gel with EtOAc–hexane (1:3) as eluant to give the title compound 10 (2.18 g, 70%).

2-Ethoxy-1-(2-deoxy-5-*O*-trityl-β-D-threofuranosyl)thymine (14). To a solution of diphenyl diselenide (156 mg, 0.5 mmol) in absolute ethanol (10 mL) under N_2(g) was added $NaBH_4$ (45 mg, 1.2 mmol). Anhydrothymidine 8 (448 mg, 0.9 mmol) was added to the colorless solution, and this was heated under reflux for 16 h. The reaction mixture was allowed to cool, and the solvents were removed in vacuo. The crude mixture was chromatographed on silica gel with EtOAc–petroleum ether (1:4), followed by EtOAc, and then 5% MeOH in EtOAc as eluants to afford 3'-α-(phenylselenenyl)-5'-*O*-trityl-3'-deoxythymidine (10) (142 mg, 24%) as a colorless glass and the title compound 14 as a solid (87 mg, 18%): R_f = 0.14 (EtOAc); mp 182–184 °C; ^1H NMR ($CDCl_3$) δ 1.35 (3 H, t, J = 7 Hz, OCH_2CH_3), 1.80 (3 H, s, CH_3), 2.22 (1 H, d, J = 14 Hz, 2'-H), 2.56 (1 H, m, 2'-H), 3.18 (1 H, bs exch, OH), 3.49 (1 H, dd, J = 10.5, J = 5.3 Hz, 5'-H), 3.65 (1 H, dd, J = 10.5, J = 5.3 Hz, 5'-H), 4.08 (1 H, m, 4'-H), 4.46 (3 H, m, 3'-H and OCH_2CH_3), 6.1 (1 H, d, J = 8.7 Hz, 1'-H), 7.22–7.49 (15 H, m, Ar), 7.66 (1 H, s, 6-H). Anal. Calcd for $C_{31}H_{33}N_2O_5 \cdot 0.5H_2O$: C, 71.25; H, 6.55; N, 5.36. Found: C, 71.20; H, 6.51; N, 5.38.

2-Ethoxy-1-(2-deoxy-β-D-threofuranosyl)thymine (15). To a solution of diphenyl diselenide (35 mg, 0.11 mmol) in absolute ethanol (5 mL) under N_2(g) was added $NaBH_4$ (10 mg, 0.26 mmol), affording a colorless solution. After the addition of anhydrothymidine 9 (44 mg, 0.2 mmol), the mixture was heated under reflux for 3 h and then stirred at room temperature overnight. The solvents were removed in vacuo, and the residue was chromatographed on silica gel with $CHCl_3$–MeOH (9:1), increasing to $CHCl_3$–MeOH (5:1) as eluant to yield the title compound 15 (33 mg, 61%) as a colorless solid: R_f = 0.75 ($CHCl_3$–MeOH, 5:1); mp 134–137 °C; ^1H NMR ($[CD_3]_2SO$) δ 1.25 (3 H, t, J = 6.6 Hz, OCH_2CH_3), 1.71 (3 H, s, CH_3), 1.91 (1 H, d, J = 15 Hz, 2'-H), 2.51 (1 H, m, 2'-H), 3.65 (2 H, m, 5'-H), 3.80 (1 H, m, 4'-H), 4.19 (1 H, m, 3'-H), 4.29 (2 H, q, J = 6.6 Hz, OCH_2CH_3), 4.66 (1 H, t, exch, 5'-OH), 5.18 (1 H, bd exch, 3'-OH), 5.97 (1 H, d, J = 7.6 Hz, 1'-H), 7.79 (1 H, s, 6-H). Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 52.98; H, 6.77; N, 10.63.

3'-α-(Phenylselenenyl)-3'-deoxythymidine (11). The 5'-*O*-trityl nucleoside 10 (197 mg, 0.316 mmol) was dissolved in a solution of water (1 mL) in glacial HOAc (4 mL), and the mixture was heated to 80–90 °C for 1.5 h. After cooling, the solvents were removed under reduced pressure and the residue was dissolved in methanol. This was evaporated and further portions of methanol were added and reevaporated. The residue was chromatographed on silica gel with EtOAc–hexane (1:3) as eluant to yield the title compound 11 as a colorless gum (97 mg, 81%): R_f = 0.16 (EtOAc–hexane, 1:1); ^1H NMR ($CDCl_3$) δ 1.88 (3 H, s, CH_3), 2.13 (1 H, t, exch, J = 4.8 Hz, 5'-OH), 2.50 (2 H, m, 2'-H_2), 3.78 (2 H, m, 5'-H_2), 3.98 (2 H, m, 3'-H, 4'-H), 5.99 (1 H, dd, J = 6.9,

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J = 2.8 Hz, 2'-H), 7.30–7.60 (6 H, m, Ph, 6-H), 8.31 (1 H, bs exch, NH); MS m/z (relative intensity) 382 (M + 1, 15), 257 (M – thymine, 49), 157 (HSePh, 39). Anal. Calcd for $C_{16}H_{18}N_2O_4Se$: C, 50.40; H, 4.75; N, 7.35. Found: C, 50.21; H, 4.82; N, 7.19.

3'-β-(Phenylselenenyl)-5'-*O*-trityl-3'-deoxythymidine (17). A solution of diphenyl diselenide (250 mg, 0.8 mmol) in anhydrous THF (10 mL) under N_2(g) was cooled to 0 °C, and $LiAlH_4$ (23 mg, 0.6 mmol) was added carefully. This was allowed to warm to room temperature (0.25 h), giving a clear solution, and the methanesulfonate **16** (281 mg, 0.5 mmol) was added in anhydrous THF (5 mL). The mixture was heated under reflux for 2 h and allowed to cool. The reaction was quenched with MeOH (5 mL), and the solvents were removed in vacuo. The residue was treated with saturated NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with water and then brine, dried ($MgSO_4$), and concentrated to afford a yellow oil. This was chromatographed on silica gel with EtOAc–hexane (1:3) as eluant to yield the title compound **17** (190 mg, 61%) as a solid: R_f = 0.49 (EtOAc–hexane, 1:1); mp 139–141 °C; ^1H NMR ($CDCl_3$) δ 1.48 (3 H, s, CH_3), 2.34 (1 H, m, 2'-H_1), 2.82 (1 H, m, 2'-H_1), 3.48 (1 H, dd, J = 11, J = 4.6 Hz, 5'-H_1), 3.61 (1 H, dd, J = 11, J = 3.5 Hz, 5'-H_1), 3.85 (1 H, dd, J = 16.6, J = 7.4 Hz, 3'-H), 4.39 (1 H, m, 4'-H), 6.11 (1 H, t, J = 7.1 Hz, 1'-H), 7.15–7.45 (20 H, m, Ar), 7.69 (1 H, s, 6-H), 8.10 (1 H, bs exch, NH). Anal. Calcd. for $C_{35}H_{32}N_2O_4Se$·0.5EtOAc: C, 66.57; H, 5.43; N, 4.20. Found: C, 66.32; H, 5.31; N, 4.34.

3'-β-(Phenylselenenyl)-3'-deoxythymidine (18). The 5'-*O*-trityl nucleoside **17** (163 mg, 0.26 mmol) was dissolved in a solution of water (1 mL) in glacial HOAc (4 mL), and the mixture was heated at 80–90 °C for 1 h. After cooling, the solvents were removed under reduced pressure and the residue was dissolved in methanol. This was evaporated, and further portions of methanol were added and reevaporated. The residue was chromatographed on silica gel with EtOAc–hexane (1:3), increasing to (1:1) to yield **18** as a solid (84 mg, 85%): R_f = 0.41 (EtOAc–hexane, 1:1); mp 176–178 °C; ^1H NMR ($CDCl_3$) δ 1.94 (3 H, s, CH_3), 2.14 (1 H, t exch, J = 6.2 Hz, 5'-OH), 2.27 (1 H, m, 2'-H_1), 2.78 (1 H, m, 2'-H_1), 3.95 (3 H, m, 3'-H, 5'-H_2), 4.32 (1 H, m, 4'-H), 6.10 (1 H, t, J = 6.9 Hz, 1'-H), 7.27–7.56 (5 H, m, Ph), 7.77 (1 H, s, 6-H), 8.19 (1 H, bs exch, NH). Anal. Calcd for $C_{16}H_{18}N_2O_4Se$: C, 50.40; H, 4.75; N, 7.35. Found: C, 50.20; H, 4.87; N, 7.21.

Preparation of 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl-5-*O*-trityl)thymine (3) from 3'-α-(Phenylselenenyl)-5'-*O*-trityl-3'-deoxythymidine (10). The 5'-*O*-trityl nucleoside **10** (73 mg, 0.11 mmol) was dissolved in THF (1.5 mL) containing 4 drops of glacial HOAc. The mixture was cooled to 0 °C, and 30% H_2O_2 (0.042 mL) was added. This was stirred at 0 °C for 0.25 h and then allowed to warm to room temperature over 1 h. TLC analysis (EtOAc–hexane, 1:1) indicated complete conversion of the starting material, and the reaction mixture was poured into a saturated solution for Na_2CO_3 (3 mL) and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and evaporated in vacuo to afford a colorless foam. This was chromatographed on silica gel with EtOAc–hexane (1:3) as eluant to yield 5'-*O*-trityl D4T **3** (34 mg, 61%): R_f = 0.5 (EtOAc–hexane, 1:1): mp 107–111 °C (lit.[4d] mp 92–109 °C); ^1H NMR ($CDCl_3$) δ 2.03 (3 H, s, CH_3), 3.35 (1 H, dd, J = 9.7, J = 3.2 Hz, 5'-H_1), 3.41 (1 H, dd, J = 9.7, J = 3.2 Hz, 5'-H_1), 4.97 (1 H, bs, 4'-H), 5.90 (1 H, d, J = 5.9 Hz, 2'-H), 6.37 (1 H, d, J = 5.9 Hz, 3'-H), 7.02 (1 H, m, 1'-H), 7.2–7.45 (16 H, m, Ar, 6-H), 8.10 (1 H, bs exch, NH).

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (2). 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl-5-*O*-trityl)thymine **3** (130 mg, 0.28 mmol) was dissolved in a solution of water (1 mL) in glacial HOAc (4 mL), and the mixture was heated at 80–90 °C for 1 h. After cooling, the solvents were removed under reduced pressure and the residue was dissolved in methanol. This was evaporated, and further portions of methanol were added and reevaporated. The residue was chromatographed on silica gel with ethyl acetate as eluant to yield the title compound **2** (42 mg, 67%) as an off white solid, mp 165–167 °C (lit.[4d] mp 164–165 °C). The chemical and physical characteristics of this compound were identical to an authentic sample of D4T obtained from Dr. W. H. Prusoff (Yale University).

Oxidation of 3'-α-(Phenylselenenyl)-5'-*O*-trityl-3'-deoxythymidine (10) under Basic Conditions. 3'-α-(Phenylselenenyl)-5'-*O*-trityl-3'-deoxythymidine (**10**) (50 mg, 0.08 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.015 mL) was cooled to –50 °C, and 30% H_2O_2 was added. The mixture was stirred for 5 min and then allowed to warm to 0 °C. After 0.5 h the solvents were removed in vacuo, and the residue was dissolved in CH_2Cl_2, dried ($MgSO_4$), and concentrated to a gum. This was chromatographed on silica gel with EtOAc–hexane (1:1), increasing to MeOH–EtOAc (1:4) as eluant to yield 2,3'-anhydro-1-(2-deoxy-5-*O*-trityl-β-D-furanosyl)thymine **8** (9 mg, 24%), mp 222–226 °C (lit.[8b] mp 218–222 °C).

Preparation of 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (2) from 3'-α-(Phenylselenenyl)-3'-deoxythymidine (11). 3'-α-(Phenylselenenyl)-3'-deoxythymidine **11** (50 mg, 0.13 mmol) was dissolved in THF (2 mL) containing 2 drops of glacial HOAc. The mixture was cooled to 0 °C, and 30% H_2O_2 (0.03 mL) was added. This was stirred at 0 °C for 0.25 h and then allowed to warm to room temperature over 1 h. $NaHCO_3$ and MeOH were added, and the solvents were removed in vacuo. The residue was preadsorbed onto silica gel, applied to the top of the silica gel column, and chromatographed with $CHCl_3$–MeOH (9:1) as eluant to yield **2** (25 mg, 86%), mp 164–166 °C (lit.[4d] mp 164–165 °C).

Preparation of 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (2) from 3'-β-(Phenylselenenyl)-3'-deoxythymidine (18). 3'-β-(Phenylselenenyl)-3'-deoxythymidine (**18**) (40 mg, 0.1 mmol) was treated as described for the preparation of **2** from **11** (23 mg, 99%), mp 163–165 °C (lit.[4d] mp 164–165 °C).

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