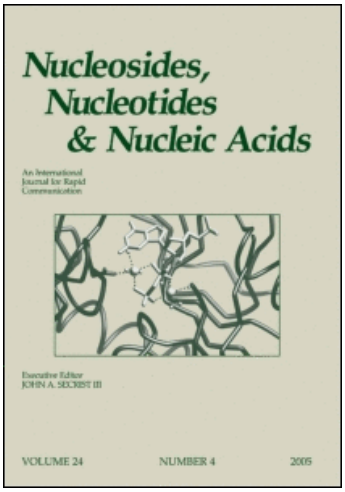

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Efficient Transformation of Thymidine into 2',3'-Didehydro-2',3'-Dideoxy-Thymidine (D4T) Involving Opening of a 2,3'-Anhydro Derivative by Phenylselenol

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EFFICIENT TRANSFORMATION OF THYMIDINE INTO 2',3'-DIDEHYDRO-2',3'-DIDEOXY-THYMIDINE (D4T) INVOLVING OPENING OF A 2,3'-ANHYDRO DERIVATIVE BY PHENYLSELENOL

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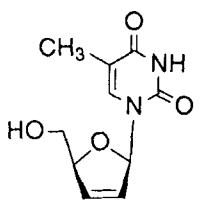
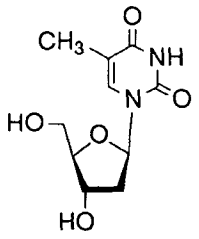
Abstract. A new, high-yielding method for introduction of the selenophenyl residue at the 3'- position of thymidine is reported. This reaction avoided any strongly basic or reductive reagent, thus allowing the use of benzoate ester as a protective group at O-5'. Further oxidation-elimination sequence followed by basic deprotection afforded 2',3'-didehydro-2',3'-dideoxythymidine (D4T) in 67.5 % overall yield from thymidine.

Since the discovery of human immunodeficiency virus (HIV) as the causative agent of AIDS,[1] much efforts were devoted to the synthesis of modified nucleosides as potential anti-HIV agents.[2,3] Among them, 3'-azido-2',3'-dideoxy-thymidine (AZT) is employed in the treatment of patients with AIDS and several have also exhibited promising results in vitro activity.[4] The unsaturated nucleoside 1-(2,3-dideoxy-β-**D**-*glycero*-pent-2-enofuranosyl)thymine (D4T, **1**) is of particular interest because it has been reported to show *in vitro* an anti-HIV activity comparable to AZT[5] and a lower toxicity.[5,6]

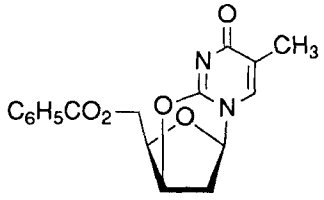
We report herein a short and efficient synthesis of D4T from thymidine **2** in which the key step is the opening by phenylselenol of protected 2,3'-anhydro derivative **3** prepared from thymidine by a tandem Mitsunobu reaction.[7]



D4T **1**



2



3

Because the introduction of the double bond in the sugar moiety of thymidine by base mediated elimination reactions was not very efficient,[5,8,9] other approaches were studied. They involved reductive elimination of vicinal 2',3'-functionalities of 5-methyluridine derivatives, but these ones have to be prepared via a multistep sequence.[10,11]

Consequently the problem of efficient transformation of thymidine into D4T was still to be solved and was recently addressed by several groups and new syntheses were reported.[6,12,13]

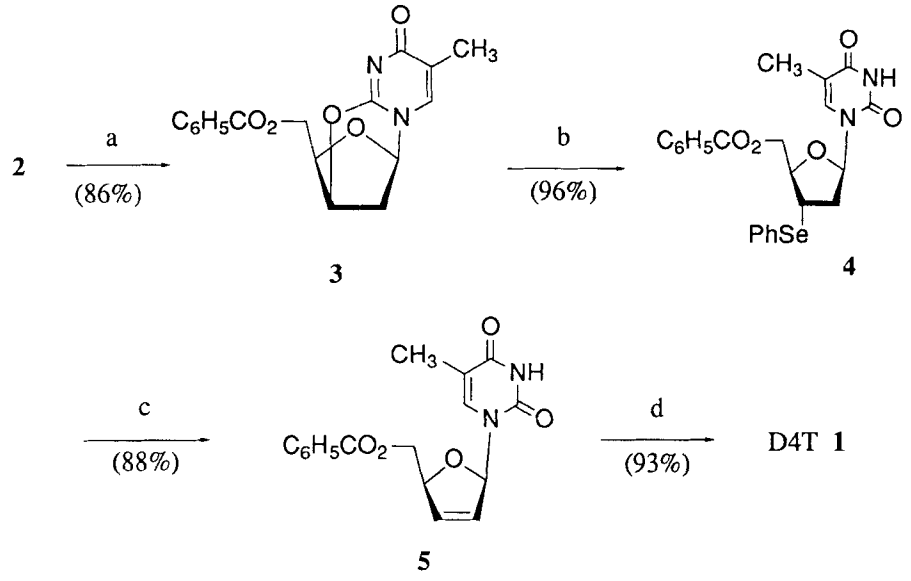
Except for one,[13] in which the double bond was formed by treatment of 5'-*O*-triphenylmethyl-2,3'-anhydrothymidine with sodium in HMPA-THF at 70° C, in all these recent approaches the double bond was created by elimination of a selenoxide. This reaction which is well documented,[14] was recently employed for the synthesis of unsaturated nucleosides.[15] It can be carried out under mild conditions but the problem lays in the preparation of the required 2' or 3'-phenylseleno nucleoside derivatives.

The introduction of the phenylselenyl group on the carbohydrate residue was generally achieved by nucleophilic substitution of methylsulfonate[6] or opening of 2,3'-anhydro nucleosides[12,15] as well as 2,2'-anhydro derivatives[16] with phenylselenide anion generated by reduction of diphenyldiselenide by sodium in HMPA-THF[12] or lithium aluminumhydride.[6,12,15,16] One disadvantage of this method is the limited choice of hydroxyl-protecting group that has to be compatible with the basic and reductive conditions. The other one stands in the fact that in opening 2,2'- and 2,3'-anhydro derivatives by phenylselenide anion a by product is formed by nucleophilic attack at C-2 of the heterocyclic base.[12,15]

To overcome this two difficulties we decided to promote an electrophilic assistance process for the opening of a 2,3'-anhydro derivative and we anticipated that phenylselenol itself could be suitable, due to its own acidity. Since no basic or reductive conditions would be required, a benzoate ester could be used as the primary hydroxyl protecting group.

Actually treatment of **3** with phenylselenol (1.5 equiv) in DMF (1h at reflux temperature) yielded the phenylseleno nucleoside **4** in 96 % yield.

Oxidation under basic conditions of such phenylseleno nucleosides was reported to be accompanied by reverse formation of 2,3'-anhydro derivative due to intramolecular nucleophilic substitution.[12] Consequently, the oxidation was carried out with H_2O_2 in the presence of acetic acid,[17] and no 2,3'-anhydro derivative was formed. The resulting transient selenoxide spontaneously decomposed and protected D4T was formed as the sole product (88 % yield). The high degree of regioselectivity which was obtained was already observed and rationalized by other authors.[15]



a: C_6H_5COOH, PPh_3, DIAD / DMF then PPh_3, DIAD / DMF; b: C_6H_5SeH / DMF, reflux; c: H_2O_2, CH_3COOH / THF; d: 1.1 equiv. NaOMe / MeOH then IRN 77 resin (H^+ form).

The other further advantage of our approach stands in the fact that the final deprotection of the 5'-hydroxyl group proceeded under mild basic conditions which are the most favourable ones according to the instability of D4T towards acidic reagents.[10,12]

In summary, very efficient experimental conditions have been determined for the incorporation of the phenylselenyl group at the 3'- position of 2',3'-dideoxythymidine. Under these conditions a benzoate can be used as protecting group at O-5', thus allowing mild basic deprotection for the ultimate step of the synthesis of the antiviral nucleoside D4T.

EXPERIMENTAL SECTION

Microanalyses were performed at the Service de Microanalyse of Pierre et Marie Curie University. Melting points were determined with Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. The ^{1}H-NMR spectra were recorded on a Bruker AC-200 spectrometer with TMS as internal standard. Reactions were monitored by analytical TLC using 2x5 cm precoated aluminum plates silica gel 60 F_{254} (Merck) and detection by UV light and charring with H_2SO_4. For column chromatography, Merck silica gel 60 (230-400 Mesh) and anhydrous solvents were used. Solvents and reagents were purified and dried by standard procedures.

2,3'-Anhydro-5'-*O*-benzoyl-2'-deoxythymidine (3).

Thymidine (**2**; 3.63 g, 15 mmol) and Ph_3P (5.9 g, 22.5 mmol, 1.5 equiv) were dissolved in DMF (30 mL). To this mixture a solution of diisopropyl azodicarboxylate (DIAD, 4.4 mL, 22.5 mmol, 1.5 equiv) and benzoic acid (2.74 g, 22.5 mmol, 1.5 equiv) in DMF (7 mL) was added drop by drop under stirring. After 15 min. at r.t. the same quantity of Ph_3P and DIAD was added and after further 30 min. at r.t. the resulting heterogeneous mixture was poured in Et_2O (370 mL). The resulting suspension was chilled for 2 h. The white crystalline precipitate was isolated by suction, washed with Et_2O and air-dried to yield **3** (4.23 g, 86%). mp 242°C.

$C_{17}H_{16}N_2O_5$	calc.	C, 62.18	H, 4.91	N, 8.53
(328.32)	found	62.02	4.90	8.56

^{1}H-NMR ($CDCl_3$): d= 7.95, 7.55 and 7.40 (3 m, 2H, 1H and 2H, H_{Arom}); 6.95 (s, 1H, H-6); 5.50 (d, 1H, $J_{1',2'b} \approx 3.5$ Hz, H-1'); 5.25 (m., 1H, H-3'); 4.65 (dd, 1H, $J_{5'a,5'b}$ = 10.5, $J_{4',5'a}$ = 5.5 Hz, H-5'a); 4.55 (m, 1H, $J_{3',4'}$ = 2.2 Hz, H-4'); 4.45 (dd, 1H, $J_{4',5'b}$ = 5 Hz, H-5'b); 2.70 (d, 1H, $J_{2'a,2'b}$ = 12.9 Hz, H-2'b); 2.50 (m, 1H, $J_{1',2'b} \approx J_{3',2'b} \approx 3.5$ Hz, H-2'b); 1.90 (s, 3H, 5-Me).

5'-*O*-benzoyl-2',3'-dideoxy-3'-phenylselenothymidine (4).

To a suspension of **3** (1.64 g, 5 mmol) in DMF (5 mL), selenophenol (0.8 mL, 7.5 mmol, 1.5 equiv) was added and the mixture was heated at 140°C. After completion of the reaction (1 h.), the solvent was evaporated under reduced pressure (1 torr) and the residue dissolved in $CHCl_3$ (50 mL). The organic phase was washed with saturated aqueous Na_2CO_3, with H_2O to neutral pH and dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography. Elution with $CHCl_3$ and $CHCl_3$-acetone (30:1) afforded **4** as white crystals (2.33 g, 96%): mp 64-65°C; R_f 0.55 (CH_2Cl_2- acetone, 4:1); $[\alpha]_D$ + 45.5° (*c* 1, $CHCl_3$).

$C_{23}H_{22}N_2O_5Se$	calc.	C, 56.91	H, 4.56	N, 5.77
(485.39)	found	56.91	4.57	5.81

^{1}H-NMR ($CDCl_3$): d= 8.45 (s, 1H, H-3); 8.0-7.30 (m, 11H, H_{Arom}, H-6); 6.05 (t, 1H, $J_{1',2'a} = J_{1',2'b}$ = 5.3 Hz, H-1'); 4.75 (dd, 1H, $J_{5'a,5'b}$ = 12.5, $J_{4',5'a}$ = 2.5 Hz, H-5'a); 4.45 (dd, 1H, $J_{4',5'b}$ = 3.7 Hz, H-5'b); 4.30 (ddd, 1H, $J_{3',4'}$ = 8.5 Hz, H-4'); 3.70 (ddd, 1H, $J_{2'a,3'} = J_{2'b,3'}$ = 8.5 Hz, H-3'); 2.55 (m, 2H, H-2'a, H-2'b); 1.65 (s, 3H, 5-Me).

1-(5-*O*-Benzoyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (5).

To a cooled (0°C) solution of **4** (1.21 g, 2.5 mmol) in THF (10 mL), AcOH (0.5 mL) and H_2O_2 (30% in H_2O, 0.6 mL) were successively added. The mixture was stirred at r.t until completion of the reaction (3 h.) then dissolved in EtOAc (100 mL). The solution was washed with 5% aqueous $NaHCO_3$ (30 mL) and H_2O (30 mL) to neutral pH. The organic phase was dried ($MgSO_4$) and the solvent evaporated. The residue was

purified by flash chromatography. Elution with CH_2Cl_2-acetone (9:1) afforded **5** as white crystals (720 mg, 88%): mp 158-159°C; Rf 0.46 (CH_2Cl_2- acetone, 4:1); $[\alpha]_D$ -117° (*c* 1, $CHCl_3$).

$C_{17}H_{16}N_2O_5$	calc.	C, 62.19	H, 4.91	N, 8.53
(328.32)	found	62.31	5.01	8.48

^{1}H-NMR ($CDCl_3$): d = 8.85 (s, 1H, H-3); 8.05-7.4 (m, 5H, H_{Arom}); 7.05 (s, 1H, H-6); 6.40 (dt, $J_{2',3'}$ = 5.8, $J_{1',3'}$ = $J_{3',4'}$ = 1.7 Hz, H-3'); 5.95 (dt, 1H, $J_{1',2'}$ = $J_{2',4'}$ = 1.7 Hz, H-2'); 5.15 (m, 1H, H-4'); 4.65 (dd, 1H, $J_{5'a,5'b}$ = 12.4, $J_{4',5'a}$ = 6.6 Hz, H-5'a); 4.55 (dd, 1H, $J_{4',5'b}$ = 3.2 Hz, H-5'b); 1.52 (s, 3H, 5-Me).

1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (1).

Compound **5** (330 mg, 1 mmol) was suspended in MeOH (4 mL) and 1 M NaOMe in MeOH (1.15 mL, 1.15 equiv) was added. The mixture was stirred at r.t. overnight. H_2O (20 mL) was added and MeOH evaporated under reduced pressure. The aqueous solution was extracted with toluene (2x3 mL), then Amberlite IRN 77 (H^+ form, 420 mg) was added and the mixture slowly stirred at r.t. for 15 min. The resin was filtered, washed with H_2O and the filtrate concentrated under reduced pressure to give **1** as white crystals (206 mg, 92%): mp 164-165°C [litt.[8] mp 165-166°C]; R_f 0.42 (EtOAc-EtOH, 9:1); $[\alpha]_D^{20}$ - 32.5 (*c* 0.7, H_2O) [litt.[8] $[\alpha]_D^{25}$ - 42 (*c* 0.69, H_2O)].

$C_{10}H_{12}N_2O_4$	calc.	C, 53.56	H, 5.39	N, 12.49
(224.22)	found	53.44	5.34	12.44

^{1}H-NMR (CD_3OD): d = 7.75 (d, 1H, $J_{6,5Me}$ = 1.1 Hz, H-6), 6.95 (m, 1H, H-1'), 6.41 (dt, 1H, $J_{2',3'}$ = 5.8, $J_{1',3'}$ = $J_{3',4'}$ = 1.7 Hz, H-3'); 5.90 (dq, 1H, $J_{2',4'}$ = 2.4, $J_{1',2'}$ = 1.2 Hz, H-2'); 4.85 (m, 1H, H-4'); 4.80 (m,2H, H-5'a and H-5'b); 1.84 (d, 3H, 5-Me).

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