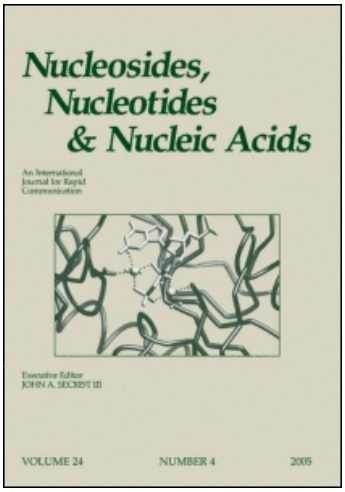

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A Short Synthesis of 2',3'-Didehydro-3'-deoxythymidine

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A SHORT SYNTHESIS OF 2',3'-DIDEHYDRO-3'-DEOXYTHYMIDINE

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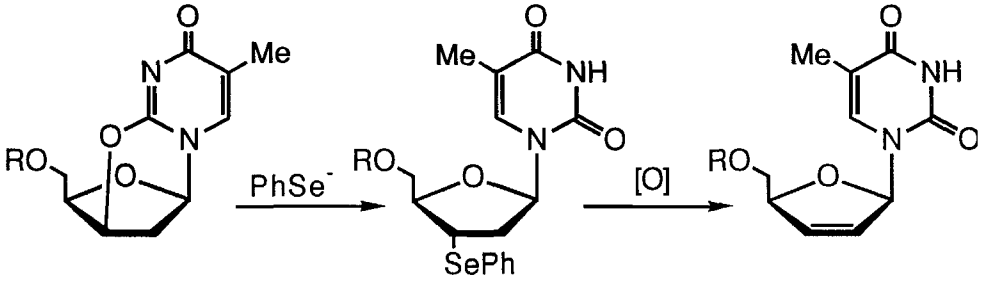
Abstract: Reaction of sodium metal in HMPA-THF with 2,3'-anhydrothymidine **1a** results in an elimination to give the 2',3'-unsaturated nucleoside **3a**. This process was utilized in a synthesis of the antiviral drug D4T from thymidine.

2',3'-Didehydro-3'-deoxythymidine (D4T) **3b** is a potent and selective antiviral agent that is currently in clinical trials for the treatment of acquired immunodeficiency syndrome (AIDS) and infections caused by human immunodeficiency virus type 1.[1-4] The clinical relevance of this compound has generated interest and recently several synthetic routes to this compound have been published. The original synthesis of D4T was that of Horwitz[5] and recently other groups have examined alternatives to this procedure.[6-9] We now report an extension to an earlier study from this laboratory[10] which provides a facile synthesis of D4T in four steps from thymidine.

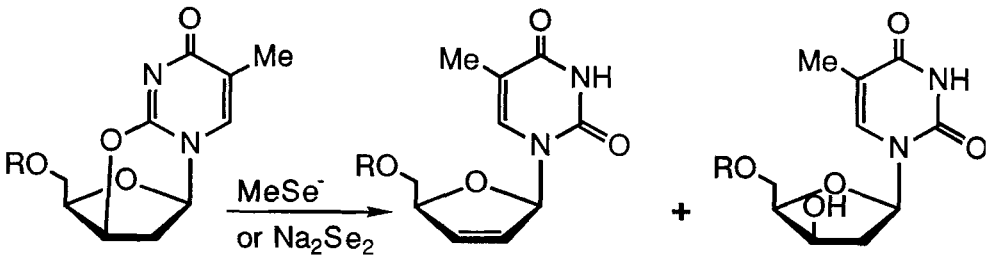


1a R = Tr
1b R = H

2a R = Tr
2b R = H

3a R = Tr
3b R = H

SCHEME 1



1a R = Tr
1b R = H

3a R = Tr
3b R = H

4

SCHEME 2

Our group has for some time been interested in the preparation of organometallic nucleosides as potential antiviral and anticancer agents.[11-14] For example, we have recently demonstrated that the addition of phenylselenide anion to 2,3'-anhydro-1-(2-deoxy-5-*O*-trityl-β-D-furanosyl)thymine **1a** followed by elimination of selenoxide under mild conditions is a facile route to D4T **3b** (Scheme 1).[10] Since the nucleophilic addition of phenylselenide to **1a** proceeded smoothly we reasoned that methylselenide anion would add in a similar manner to give the 3'-selenomethyl derivative **2**. Interestingly, however, reaction of lithium methylselenide (MeLi, Se, THF, Δ)[15] with **1a** gave none of the expected product and instead the elimination product **3a** and the lyxo compound **4** were isolated in 27% and 20% yields, respectively (Scheme 2). Furthermore, when **1a** was reacted with sodium selenide (Na, Se, HMPA-THF, Δ)[16] in an attempt to form the 3'-selenol, the unsaturated nucleoside **3a** was the sole product (60%). An identical reactivity toward sodium selenide was observed for the deprotected anhydro derivative **1b** and in this case D4T **3b** was isolated, although in reduced yield (33%). These results led us to examine the elimination reaction of **1a** in more detail, since the novel reaction conditions discovered for this process could be readily incorporated into a synthesis of D4T **3b**. The conditions which have previously been employed for the elimination of **1a** are strongly basic *i.e.*, *t*BuOK-DMSO[4] or CsF-DMSO.[17] The disadvantage of these procedures is that the solvent of choice is DMSO and its removal has proved to be problematic on a large scale. Mansuri and coworkers were able to circumvent this by using an alternative work-up procedure.[21] Thus, the potassium salt of D4T was precipitated from DMSO with toluene and when the solid was collected and acidified the desired compound was eventually isolated in 57% yield. By contrast our method employs a relatively small quantity of the high boiling solvent HMPA and this is readily removed during work-up (see Experimental Section).

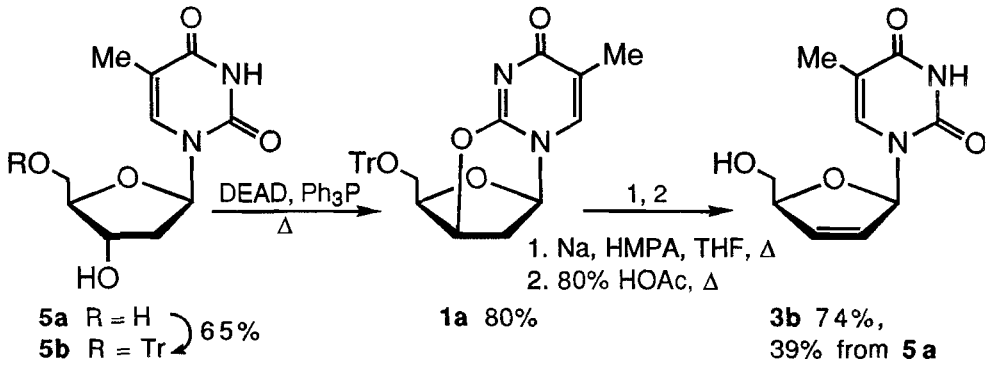
It is conceivable that the observed elimination might occur as a result of the presence of adventitious water in the solvents. This would react with the elemental sodium or methyllithium to form hydroxide ion which then elicits basic elimination. To rule out this possibility **1a** was heated with 1 M NaOH in HMPA-THF. After standard work-up and column chromatography the only product formed in this reaction was the nucleoside **4**, the expected product from the basic hydrolysis of **1a**. In the case of the reaction with lithium methylselenide, there was also the possibility that methyllithium itself might be responsible for the observed elimination. Therefore, as a check **1a** was stirred with *n*BuLi at -78°C, 0°C, 25°C and finally at 70°C. At low temperature no reaction was observed and at high temperature decomposition occurred. Finally, we surmised that in the Na/Se reaction the selenium metal may be unnecessary for the reaction to proceed. This would provide a more synthetically useful process since the toxicity of selenium limits its use in the preparation of bioactive compounds. Thus, heating **1a** with Na in HMPA-THF followed by detritylation gave D4T **3b** (74% over 2 steps). These results are consistent with a mechanism which involves either a single electron transfer process or an elimination induced by a strong base formed from the interaction of sodium with HMPA.[18] Interestingly, the group at Hoffmann-La Roche observed elimination of the anhydro nucleoside **1a** when it was exposed to LiCN/DMF giving the unsaturated nucleoside **3a** in 40% yield.[22] Lithium cyanide in DMF has been shown to elicit electron transfer processes,[23] providing evidence supporting this type of mechanism for the Na-HMPA elimination conditions.

The methodology was incorporated into a short synthesis of D4T starting from thymidine **5a** (Scheme 3). Thus, tritylation (65%)[19] followed by treatment of 5'-*O*-tritylthymidine **5b** with DEAD-PPh_3[20] gave the 2,3'-anhydrothymidine **1a** (80%). This compound was subjected to elimination conditions (Na, HMPA-THF, 70°C, 2-3 h) and deprotection (80% HOAc, 90°C, 1 h) afforded D4T **3b** (39% from thymidine).

Thus, we have demonstrated that the elimination of the important nucleoside intermediate **1a** may be achieved in good yield under mild conditions which avoid the use of either strong base such as *t*BuOK or large amounts of high boiling solvent (DMSO). The yield of D4T from thymidine obtained in the reaction sequence (39%) compares favorably with that previously reported (34%) in a similar reaction sequence.[21] While the merits of this method for the large scale preparation of D4T remain to be established, the new procedure does provide a potentially useful alternative to the standard conditions.

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-



SCHEME 3

300 (300 MHz) spectrometer. 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.

2,3'-Anhydro-1-(2-deoxy-5-*O*-trityl-β-D-furanosyl)thymine 1a. A suspension of 5'-*O*-tritylthymidine (2.05 g, 4.2 mmol) and triphenylphosphine (1.27 g, 4.9 mmol) in toluene (15 mL) was heated to 80°C and then THF (10 mL) was added to afford a clear solution. Diethyl azodicarboxylate (DEAD) (0.77 mL, 4.9 mmol) was added and after 0.5 h TLC analysis indicated the reaction had gone to completion. The reaction mixture was allowed to cool and was stored overnight at 4°C. The solvents were removed *in vacuo* and the residue chromatographed on silica gel eluting with EtOAc-petroleum ether (1:1) and then EtOAc to give the title compound **1a** (1.56 g, 80%) as a solid mp 226-229°C (lit.[5] 218-222°C) ^{1}H NMR ($CDCl_3$) δ 1.93 (3 H, s, CH_3), 2.40 (1H, dm, J = 13.4 Hz, 2'-H), 2.60 (1H, 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 (1H, s, 6-H), 7.16-7.44 (15 H, m, Ar).

Reaction of lithium methylselenide with 1a. Methyllithium (1 mL of a 1.4 M solution in diethyl ether, 1.4 mmol) was added dropwise to a stirred suspension of selenium powder (111 mg, 1.4 mmol) in anhydrous THF (10 mL) at room temperature under nitrogen. After 15 min the selenium was consumed and a colorless suspension of lithium methyl selenide obtained. The anhydro compound **1a** (605 mg, 1.3 mmol) was added and the mixture heated at reflux for 3 h. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL), extracted with ethyl acetate (3 x 20 mL), and the

combined organic phases were washed (brine), dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with EtOAc:hexane (1:3) as eluent to yield 1-(2,3-dideoxy-β-D-glyceropent-2-enofuranosyl-5-*O*-trityl)thymine **3a** (162 mg, 27%) R_f= 0.5 (EtOAc:hexane 1:1) mp 107-111°C (lit.[5] 92-109°C) ^1H NMR ($CDCl_3$) δ 2.03 (3 H, s, C*H*$_3$), 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, N*H*). A second product isolated as a colorless solid was identified as 1-(2-deoxy-5-*O*-trityl-β-D-*threo*-furanosyl)thymine **4** (127 mg, 20%) mp 240-244°C (lit.[5] mp 240-241°C) ^1H NMR ($CDCl_3$) δ 1.80 (3 H, s, C*H*$_3$), 2.08 (1 H, d, *J* = 15.3 Hz, 2'-H), 2.60 (1 H, m, 2'-H), 2.86 (1 H, s exch, O*H*), 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, N*H*). 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%.

Reaction of sodium selenide with 1a. Freshly cut pieces of sodium (32 mg, 1.4 mmol) were added to HMPA (1 mL) and this was warmed to 50°C to afford a deep blue solution. Selenium powder (111 mg, 1.4 mmol), anhydrous THF (10 mL), and **1a** (500 mg, 1.1 mmol) were added and the mixture was heated at reflux for 2 h. The reaction was quenched with saturated NH_4Cl solution (10 mL) and EtOAc (30 mL) was added and the mixture was filtered through celite and the solvents removed *in vacuo*. Water (10 mL) was added and the mixture extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with EtOAc:hexane (1:3) as eluent to yield 1-(2,3-dideoxy-β-D-glyceropent-2-enofuranosyl-5-*O*-trityl)thymine **3a** (310 mg, 60%).

5'-*O*-Tritylthymidine 5b. This was prepared according to the published procedure[19] in 65% yield.

2',3'-Didehydro-3'-deoxythymidine, D4T 3b. Freshly cut pieces of sodium (23 mg, 1 mmol) were added to anhydrous HMPA (0.5 mL) while stirring at 25°C under N_2 (g) to afford a deep blue solution. After 0.5 h, dry THF (10 mL) and **1a** (233 mg, 0.5 mmol) were added and the mixture was heated at 70°C for 2-3 h until TLC analysis (Si, $CHCl_3$:MeOH 9:1) indicated completion. The cooled mixture was quenched with MeOH and the solvents removed *in vacuo*. The residue was dissolved in glacial HOAc (4 mL) and water (1 mL) and heated at 90°C for 1 h. The reaction mixture was concentrated under reduced pressure, re-evaporated with MeOH, and the residue dissolved in water (10 mL). The aqueous phase was washed with $CHCl_3$ (3 x 5 mL) to remove HMPA, concentrated *in vacuo*, re-evaporated twice with MeOH, and the residue chromatographed

on a silica gel column with EtOAc as eluent to give D4T **3b** (74% over 2 steps) as a solid. This material was identical to an authentic sample of D4T obtained from Dr. T.-S. Lin, Yale University, New Haven, CT, mp 164-166°C (lit.[5] 164-165°C).[1]

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