A Short Synthesis of 5′-*O*-Trityl-Protected *threo*- and *erythro*-3′-Cyano-3′-deoxythymidine Epimers Using Free-Radical Chemistry

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A reinvestigation of a synthetic route to 5′-*O*-trityl-protected *erythro*-CNT that incorporates a modification of the Stork radical cyclization-cyanation reaction generates an unexpected *threo*-epimer.

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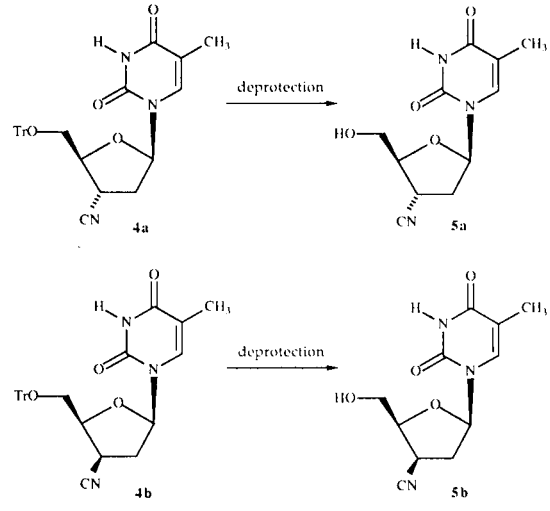
A recent report by Parkes and Taylor [1] describes a short, synthetic route to 1-(3′-cyano-2′,3′-dideoxy-5′-*O*-trityl-β-D-*erythro*-pentofuranosyl)thymine (**4a**). The reaction sequence (Scheme 1) includes free-radical methodology to introduce a nitrile function in fair to moderate yield. This modification of the Stork radical cyclization-cyanation reaction [2] is of considerable interest since it represents the first example of such a technique in nucleoside chemistry.

This route has distinct advantages for the synthesis of the deprotected species (*erythro*-CNT, **5a**) over others in the literature [3-5]. Interestingly, an investigation of this synthetic scheme led to similar, as well as different results, which are the focus of this report.

Results and Discussion.

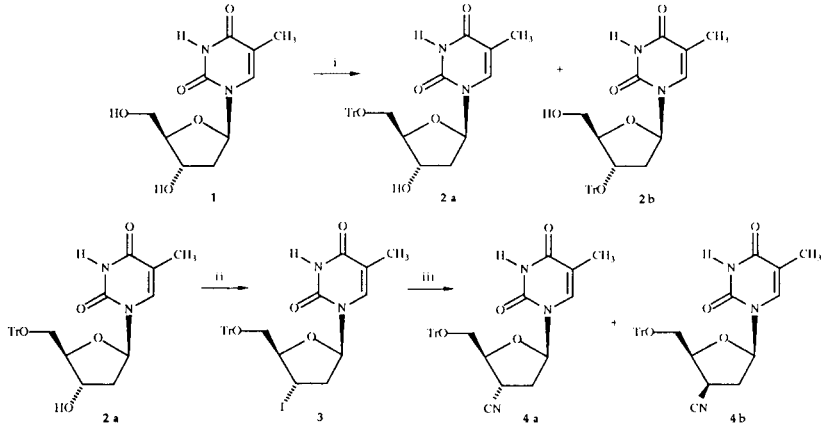
Tritylation of thymidine (**1**) in the presence of 3Å molecular sieves afforded 5′-*O*-tritylthymidine (**2a**, 84%) in high yield, as well as a small amount (1%) of 3′-*O*-tritylthymidine (**2b**) [6,7]. This isomeric mixture was easily separated by chromatography (silica gel, methanol/chloroform) or recrystallization (hexane/chloroform). Acidic hydrolysis [6] and hydrogenolysis [6] of 3′,5′-di-*O*-tritylthymidine [8] have given **2b** in 20 to 40% yields and have been the only known methods to obtain this intermediate; therefore, it is interesting that the reaction sequence discussed here provided even a trace amount of 3′-*O*-tritylthymidine. The utilization of molecular sieves may have dictated the course of this reaction.

Scheme 2



The conversion of **2a** to 1-(3′-iodo-2′,3′-dideoxy-5′-*O*-trityl-β-D-*erythro*-pentofuranosyl)thymine (**3**) [9-11] with methyltriphenoxyphosphonium iodide [11] in DMF pro-

Scheme 1



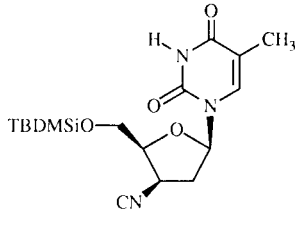
i: TrCl, pyridine, 3Å sieves, 100 °C, N_2; ii: $(PhO)_3MeP^+I^-$, DMF, RT, N_2; iii: Sn_2Me_6, *t*-BuNC, PhMe, AIBN, N_2, 80 °C.

ceeded smoothly, and the desired product was isolated (66 to 69%) after recrystallization from methanol/chloroform. This iodination was effected in 60% yield with hexamethyldisilane (HMDS)/iodine [12], but an attempt to prepare **3** with trimethylchlorosilane/sodium iodide [13] failed.

Iodide **3** was heated to reflux overnight in degassed anhydrous toluene in the presence of hexamethylditin, *t*-butyl isocyanide, and AIBN under a nitrogen atmosphere. The desired nitrile **4b** was isolated in 57% yield after chromatographic purification (silica gel, hexane/-ethyl acetate). Quite unexpectedly, a 6% yield of the *threo*-nitrile **4b** [4] was realized as well. Parkes and Taylor [1] did not discuss the isolation of **4b** in their report; this result suggests that this free-radical methodology can be modified to favor, or at least increase, the yield of the *threo*-epimer.

Spectroscopic examination of iodide **3** confirmed its identity as the *erythro*-isomer, therefore, inversion-of-configuration must have occurred during the free-radical cyanation and it is proposed that this isomerization followed a mechanistic path similar to that of a Rydon reaction [9,14].

Nuclear Overhauser effect (nOe) experiments, and ir, elemental, and mass-spectral data supported the assignment of **4b** as the trityl-protected *threo*-epimer. It is interesting that this information was not previously described in the literature; however, spectral data are available [3] for 1-(3′-cyano-2′,3′-dideoxy-5′-*O*-*t*-butyldimethylsilyl)-β-D-*threo*-pentofuranosyl)thymine (**6**).



6
TBDMSi = *t*-Butyldimethysilyl

Deprotection of **4a** and **4b** (Scheme 2) can be accomplished with diethylaluminum chloride [16] or formic acid [4]; nevertheless, TFA/methanol [17] and TFA/dichloromethane are presently being investigated as effective reagents for this purpose. The latter reagent appears to be more effective for the deprotection of **4b** because the *threo*-epimer is not very soluble in methanol. The isolation of *threo*-CNT (**5b**) [4] by this route was achieved in 62% yield after chromatographic purification (silica gel, methanol/dichloromethane): however, further experimentation may optimize this step. Attempted deprotection of **4a** or **4b** with methanolic hydrogen chloride or aqueous methanolic hydrogen chloride was futile and only provided products of decomposition; but substrate decomposition was minimized with the use of TFA.

In conclusion, the free-radical chemistry discussed here provides *threo*- and *erythro*-CNT. Further scrutiny of this route may result in optimized yields of the minor isomer and could lead to a general method for other systems in which a *threo*-epimer is desired.

EXPERIMENTAL

The ^{1}H-nmr spectra were obtained in deuteriochloroform on a Varian 300-MHz spectrophotometer. Atlantic Microlab, Inc. provided elemental analyses and mass spectral data were obtained in-house or from Oneida.

Preparation of **2a**.

A mixture of thymidine (20 g, 82.57 mmoles) and 3 Å molecular sieves in 200 ml of pyridine was treated with triphenylmethyl chloride (25 g, 89.68 mmoles), and the mixture was heated to ~100° under a nitrogen atmosphere for 90 minutes. The mixture was cooled to room temperature and filtered, and the filtrate was rotary evaporated. The residue was dissolved in 800 ml of methylene chloride and washed with water (3 x 150 ml). The organic phase was concentrated and chromatographed (silica gel, 4.0% methanol/chloroform) to provide 36.7 g (67.68 mmoles, 82%) of **2a** as a white, crystalline solid; ^{1}H-nmr (deuteriochloroform): δ 1.48 (s, 3H, CH_3), 2.30 (d, J = 4.2 Hz, 1H, OH), 2.36 (m, 2H, 2′), 3.38 (dd, J = 3.1, 10.5 Hz, 1H, 5′), 3.48 (dd, J = 3.1, 10.5 Hz, 1H, 5′), 4.06 (m, 1H), 4.58 (m, 1H), 6.41 (dd, J = 6.0, 7.8 Hz, 1H, 1′), 7.29 (m, 9H, trityl), 7.40 (m, 6H, trityl), 7.56 (s, 1H, 6), 8.61 (s, 1H, NH).

Anal. Calcd. for $C_{29}H_{28}N_2O_5 \cdot 0.40CHCl_3 \cdot 0.20H_2O$: C, 65.89; H, 5.42; N, 5.23. Found: C, 65.91; H, 5.30; N, 5.25.

Preparation of **3**.

A solution of **2a** (25 g, 51.59 mmoles) and methyltriphenoxyphosphonium iodide (50 g, 110.00 mmoles) in 500 ml of anhydrous *N,N*-dimethylformamide was stirred at room temperature under a nitrogen atmosphere. After 21 hours the mixture was cooled to 0° and treated with aqueous sodium thiosulfate, followed by additional water to effect precipitation of an oil. The solvent was carefully decanted, and the oily residue was dissolved in 300 ml of chloroform. The organic medium was washed with water, filtered over phase-separator paper, and concentrated. Recrystallization from chloroform-methanol provided 20.7 g (35.82 mmoles, 67%) of **3**, mp 148-152°; ^{1}H-nmr (deuteriochloroform): δ 1.46 (s, 3H, CH_3), 2.77 (m, 2H, 2′), 3.50 (m, 2H, 5′), 4.31 (m, 1H, 4′), 4.48 (q, J = 8.4 Hz, 1H, 3′), 6.14 (t, J = 4.5 Hz, 1H, 1′), 7.30 (m, 15H, trityl), 7.66 (s, 1H, 6), 8.25 (brs, 1H, NH).

Anal. Calcd. for $C_{29}H_{27}N_2O_4I \cdot 0.20CH_3OH$: C, 58.37; H, 4.66; N, 4.66; I, 21.12. Found: C, 58.31; H, 4.95; N, 4.61; I, 21.41.

Preparation of **4a/4b**.

To a mixture of **3** (10 g, 16.82 mmoles), *t*-butyl isocyanide (18.8 g, 226.62 mmoles), and hexamethylditin (5.6 g, 17.09 mmoles) was added 300 ml of degassed toluene followed by AIBN (0.5 g). The contents were heated to ~70° under a nitrogen atmosphere for 24 hours, concentrated, and chromatographed on silica gel with 20% ethyl acetate/hexane to provide 4.90 g (9.93 mmoles, 59%) of **4a** (*erythro*-epimer) and crude **4b** (*threo*-epimer). Subsequent chromatography (silica gel, 2% methanol/methylene chloride) provided 0.48 g (0.97 mmoles, 6%) of pure **4b**; ^{1}H-nmr (deuteriochloroform): δ 1.67 (s, 3H, CH_3), 2.41 (ddd, J = 5.5, 5.5, 14.0 Hz,

1H, 2′), 2.77 (ddd, J = 6.9, 8.4, 14.0 Hz, 1H, 2′), 3.36 (ddd, J = 5.5, 6.9, 8.4 Hz, 1H, 3′), 3.57 (dd, J = 5.2, 10.4 Hz, 1H, 5′), 3.68 (dd, J = 4.9, 10.4 Hz, 1H, 5′), 4.18 (ddd, J = 5.2, 4.9, 6.9 Hz, 1H, 4′), 6.20 (dd, J = 5.5, 6.9 Hz, 1H, 1′), 7.31 (m, 9H, trityl), 7.39 (s, 1H, 6); 7.47 (m, 6H, trityl), 8.44 (brs, 1H, NH); ir (potassium bromide): ν (CN) 2247 cm^{-1}; the nOe was observed at the H-1′ position upon irridiation of H-3′; ms: (FAB^+): m/e 494 (m+1, 15%); 243 (trityl, 100%).

Anal. Calcd. for $C_{30}H_{27}N_3O_4 \cdot 0.30CH_2Cl_2 \cdot 0.40H_2O$: C, 69.16; H, 5.44; N, 7.98. Found: C, 69.15; H, 5.41; N, 8.00.

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[15] ^{1}H-nmr (300 MHz, deuteriochloroform): δ 1.67 (s, 3H, CH_3); 2.41 (ddd, J = 5.5, 5.5, 14.0 Hz, 1H, 2′); 2.77 (ddd, J = 6.9, 8.4, 14.0 Hz, 1H, 2′); 3.36 (ddd, J = 5.5, 6.9, 8.4 Hz, 1H, 3′); 3.57 (dd, J = 5.2, 10.4 Hz, 1H, 5′); 3.68 (dd, J = 4.9, 10.4 Hz, 1H, 5′); 4.18 (ddd, J = 5.2, 4.9, 6.9 Hz, 1H, 4′); 6.20 (dd, J = 5.5, 6.9 Hz, 1′); 7.31 (m, 9H, trityl); 7.39 (s, 1H, 6); 7.47 (m, 6H, trityl); 8.44 (br s, 1H, NH); ir (potassium bromide): λ (CN): 2247 cm^{-1}; the nOe was observed at the H-1′ position upon irradiation of H-3′; mass spectrum (FAB^+): m/e 494 (M+1, 15%), 243 (trityl, 100%). *Anal.* Calcd. for $C_{30}H_{27}N_3O_4 \cdot 0.30CH_2Cl_2 \cdot 0.40H_2O$: C, 69.16; H, 5.44; N, 7.98. Found: C, 69.15; H, 5.41; N, 8.00.

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