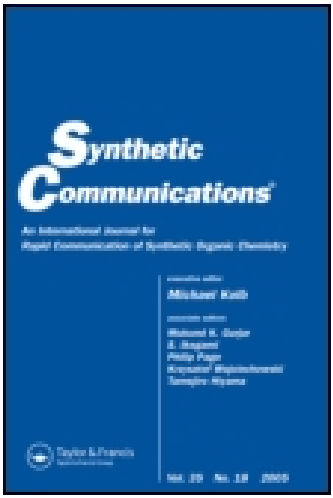

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1-Chloro-2-deoxy-3,5-di-p-toluoyl-D-erythro-pentosyl Chloride - A Versatile Synthetic Intermediate

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1-CHLORO-2-DEOXY-3,5-DI-P-TOLUOYL-D-ERYTHRO-PENTOSYL CHLORIDE - A VERSATILE SYNTHETIC INTERMEDIATE

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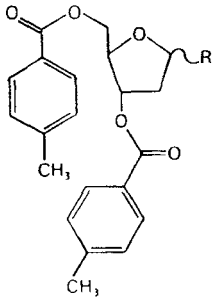
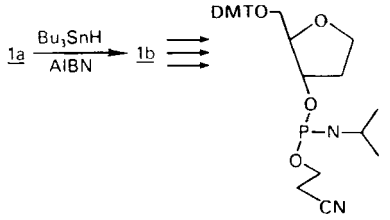
Abstract: Syntheses of **1b-d** is described using 1-chloro-2-deoxy-3,5-di-*p*-toluoyl-D-*erythro*-pentosyl chloride.

Preparation and use of 1-chloro-2-deoxy-3,5-di-*p*-toluoyl-D-*erythro*-pentosyl chloride **1a** in the synthesis of 2'-deoxyribonucleosides has been extensively documented in the literature.[1] Typically, these syntheses involve the substitution of the chloro group in **1a** for the N-9 of purines or the N-3 of pyrimidines, *via* the Hilbert-Johnson reaction or some modification thereof.[2] In connection with our ongoing research in the development of agents against the human immunodeficiency virus (HIV), we wished access to various "abasic"



1a R = -Cl
1b R = -H
1c R = -CN
1d R = -CH_2NH_2

2′-deoxyribonucleoside analogs, which could be readily converted to the corresponding 5′-*O*-dimethoxytrityl-3′-*O*-ß-cyanoethyl-*N,N*-di-isopropylamino phosphoramidite monomers such as **2**. Reported herein is the realization

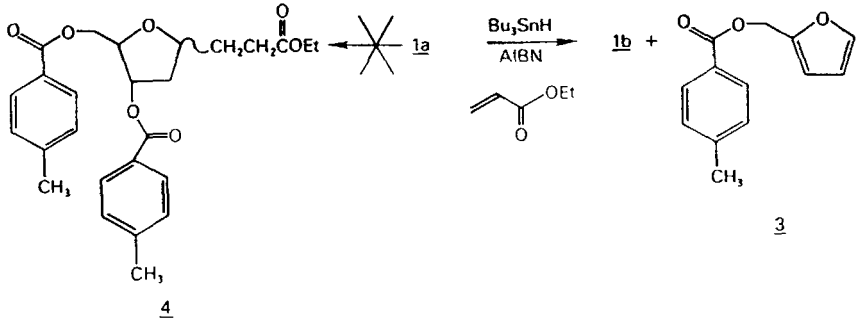


2

of some of our goals, using **1a** as a key intermediate.

Our initial objective was to have analogs derived from **1a**, wherein Cl would be replaced by H (**1b**), CN (**1c**) or an aminomethyl group (**1d**). Prompted by literature reports[2] about the generation and trapping of radicals derived from various alkyl and aryl halides using tri-n-butyltin hydride and azaisobutyronitrile (AIBN), we and others[3,4] have carried out such studies on **1a**. Thus, exposing **1a** to tri-n-butyltin hydride and AIBN at 50-60 °C resulted in its facile reductive dehydrogenation giving **1b** in greater than 95% yield. The structure of **1b** was confirmed through extensive use of 1D and 2D NMR experiments. The conversion of **1b** to the phosphoramidite **2** and subsequent syntheses of homo-oligodeoxyribonucleotides and oligodeoxyribonucleotides have been reported by us elsewhere.[3]

Led by our experience in such radical-mediated reductive dehalogenations, we attempted to trap the incipient radical derived from **1a** with various nitriles and α,β-unsaturated esters. However, the major isolable product from the reaction of **1a** with tri-n-butyltin hydride/AIBN was the furan derivative **3**. Similarly, reaction of **1a** with tri-n-butyltin hydride/AIBN, in the presence of a large excess of ethyl acrylate, under a variety of conditions, gave only the furan **3** and the ditoluate **1b** as the major isolable products, but no trace

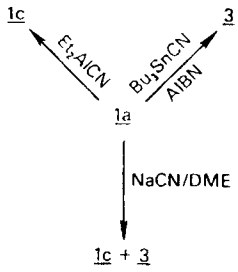


4 3

of the desired **4** was detected. Evidently the propensity for the intermediate, either to capture an H radical or to induce aromatization by loss of the 3′-*p*-toluoyl group, predominated giving rise to **1b** or **3** respectively. It should be pointed out that successful trapping of radicals derived from glucopyranosyl-1-bromides and *erythro* pentofuranosyl bromides with various Michael acceptors have been reported.[5,6] Presumably, in these instances, the presence of the 2′-hydroxy substituent or

its derivative may influence the course of the reaction.

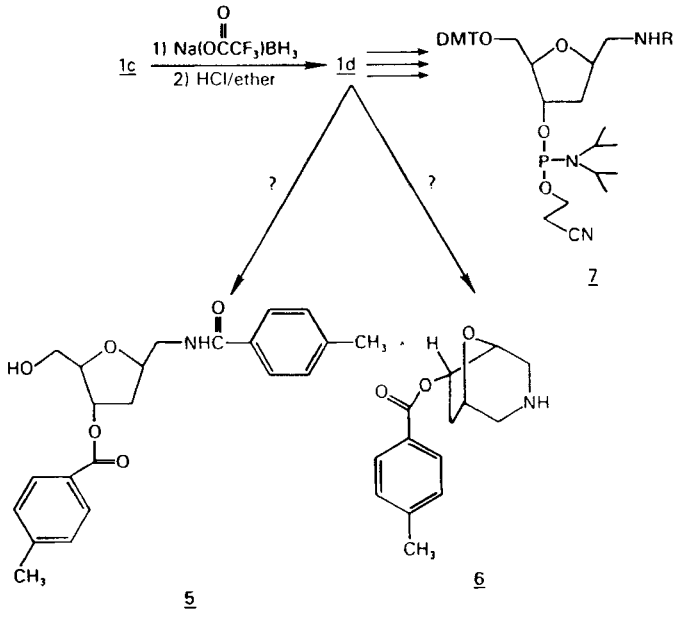
It then appeared to us that since **1a** is a reactive α-halo ether derivative, the halogen may be readily replaced by a cyano group under ionic reaction conditions. However, our attempts to convert **1a** to **1c** using NaCN/DME according to a published report[7] were



unsuccessful. In our hands, the major isolable product was **3**. It was then reasoned that the desired conversion could be effected if one uses a reagent which would function as a Lewis acid, causing polarization of the C-Cl bond, and also behave as a nucleophile to deliver a cyano group to the transient electrophilic center. Diethylaluminum cyanide,[8] a commonly used hydrocyanation reagent for ketones and aldehydes, seemed to fulfill these requirements. As expected, the reaction of **1a** with diethylaluminum cyanide in toluene gave the cyano compound **1c** as an anomeric mixture (ca. 1:1) in isolated yields in excess of 90% after flash chromatography. Stereochemical configuration was assigned on the basis of selected 1D and 2D NMR experiments.

In order to access the amino di-toluate **1d**, chemoselective reduction of the nitrilic function of **1c** had to be carried out while maintaining the integrity of the toluoyl groups. We were also concerned about the

potential of the intermediate **1d** converting to the amide **5** or the amine **6** by intramolecular reactions. Access to **1d** was specifically required because we wanted to use the amino group as a nucleophile in reactions with other electrophiles. Among the various reagents we investigated to effect the transformation of **1c** to **1d**, the best results were obtained using sodium trifluoroacetoxy borohydride.[9,10] Thus, reaction of **1c** with sodium trifluoroacetoxy borohydride for 6 hours at ambient temperature gave the amino toluate **1d** in greater than 70% isolated yield, which we immediately converted to its hydrochloride salt. No detectable epimerization or formation of side products such as **5** or **6** had occurred under these reaction conditions, as seen by NMR. Studies in the conversion of **1d** to **7** and synthesis of oligodeoxy-



ribonucleotides derived from **7** are in progress, the results of which will be reported elsewhere.

Experimental Section

Tetrahydrofuran (THF) was freshly distilled from lithium tetrahydroaluminate ($LiAlH_4$) just prior to use. Other reagents and anhydrous solvents were obtained from commercial suppliers and were used as received.

Flash column chromatography was performed on silica gel (10 ± 4μ, Analtech). Thin layer chromatography (TLC) was performed on plastic plates coated with a 0.2 mm thick layer of silica gel 60 F_{254} (EM Science).

Melting points are uncorrected and were determined using a Buchi 510 melting point apparatus.

Normal Fourier transform (F.t.) ^1H and ^1H-homonuclear spin-decoupled nuclear magnetic resonance (NMR) spectra were acquired using a General Electric GN-300 spectrometer. ^{13}C-NMR spectra were acquired in the presence of broad-band decoupling at 7.05 T. Samples were dissolved in $CDCl_3$ (ca. 50 mg in 0.6 mL) containing 1% tetramethylsilane (TMS).

Electron-ionization (EI) mass spectra were recorded with a Hewlett-Packard 5995 gas chromatograph/mass spectrometer equipped with an HP 59970C MS ChemStation data system. The ionization potential was 70 eV and the ionizing current was 220 μA.

Synthesis of 1c. Dry toluene (35 mL) was added to **1a**[11] (9.4 g, 23.7 mmol) in an argon atmosphere. The resulting solution was cooled and diethylaluminum cyanide (35 mL, 35 mmol) was added (at 0°C) with stirring over a period of 30 minutes. The reaction mixture was stirred and allowed to warm to room temperature. After about 14 hours, methanol (20 mL) was slowly introduced into the cooled (0°C) reaction mixture, in order to decompose the excess diethylaluminum cyanide (*CAUTION! HCN may be evolved during this operation!*). The resulting thick mass was diluted with chloroform and the slurry (400 mL) was evaporated under reduced pressure to remove most of the solvents. Additional chloroform was then added to the residue and the resulting mixture was stirred vigorously. The suspension was then filtered through a column of anhydrous sodium sulfate layered with silica gel. The filter cake was washed with chloroform. The filtrate and washings (400 mL) were evaporated under reduced pressure to give a pale yellow oil. On keeping at room temperature for 15 minutes, the oil solidified to a white crystalline mass. The crystalline mass was then triturated with hexane (40 mL) and filtered to give the α,ß anomeric mixture of **1c** as a white solid: yield 8 g (85-90%). Additional product (5-10%) may be recovered after resuspending the filter cake in water, extraction with chloroform, drying and concentration to dryness. The α,ß anomeric mixture was separated by flash

chromatography (45 X 4 cm, silica gel) using a stepped gradient of toluene and toluene:EtOAc (99:1).

1c (ß isomer) mp 110-111°C (lit.[7] 110-111°C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.4 (s, 3H), 2.6-2.7 (m, 2H), 4.5-4.6 (m, 3H), 4.9 (t, J = 7 Hz, 1H), 5.6 (d, J = 5 Hz, 1H), 7.2 (d, J = 8 Hz, 4H), 7.9 (d, J = 8 Hz, 2H), 8.0 (d, J = 8 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) ppm 21.5, 37.6, 63.6, 65.7, 75.2, 83.6, 117.8, 126.1, 126.5, 129.1, 129.5, 143.9, 144.4, 165.5, 165.9; MS (electron ionization) m/z (%) 379 ($M^{+\cdot}$, 1), 243 (19), 230 (12), 136 (7), 119 (100), 91 (83), 81 (4), 65 (29), 51 (5); MS (chemical ionization, NH_3) m/z 380 ($M+H^+$).

1c (α isomer) mp 142-143°C (lit.[7] 145-146°C); ^{1}H-NMR (300 Mhz, $CDCl_3$) δ 2.4 (s, 6H), 2.6-2.7 (m, 2H), 4.5-4.6 (m, 2H), 4.7 (bs, 1H), 5.0-5.1 (m, 1H), 5.60-5.62 (m, 1H), 7.2-7.3 (m, 4H), 7.9-8.0 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) ppm 21.6, 37.8, 63.6, 66.5, 74.8, 84.2, 118.4, 126.2, 126.6, 129.2, 129.25, 129.6, 129.9, 144.1, 144.4, 165.9; MS (electron ionization) m/z (%) 379 ($M^{+\cdot}$, 1), 243 (18), 230 (5), 136 (5), 119 (100), 91 (55), 81 (4), 65 (18), 51 (4); MS (chemical ionization, NH_3) m/z 380 ($M+H^+$).

Synthesis of 1d. To anhydrous tetrahydrofuran (5 mL), under argon, was added sodium borohydride (125 mg, 3.30 mmoles). The contents were cooled to 0°C and a solution of dry trifluoroacetic acid (254 μL, 375 mg, 3.30 mmoles) in anhydrous THF (20 mL) was added dropwise

with stirring over a period of 15 minutes. After the vigorous reaction had subsided, a solution of **1c** (1.25 g, 3.30 mmoles) in anhydrous THF (mL) was added, with stirring, over a period of 10 minutes. The reaction mixture was stirred for 12 hours at 25°C and an additional amount of $NaBH_4$ (125 mg) followed by TFA (254 μL) was introduced to ensure completion of the reaction (as monitored by TLC on silica gel using $CHCl_3$ as a solvent). After an hour of additional stirring, the reaction mixture was then concentrated under reduced pressure and diluted with saturated sodium chloride solution (30 mL). Extraction of the reaction mixture with methylene chloride (3 X 40 mL), drying of the combined organic layers and concentration to dryness under reduced pressure gave an oil. Column chromatography (silica gel) and elution with chloroform:methanol (95:5) gave **1d** as an oil (TLC, silica gel, $CHCl_3$:MeOH, 9:1, R_f 0.2). This oil was immediately dissolved in a mixture of anhydrous methanol and ether (1:9) and was then saturated with dry HCl gas. Concentration of the reaction mixture, followed by drying of the residue *in vacuo* (0.5 mm) gave a foamy white solid (mp 145-147°C). This material was somewhat hygroscopic and had to be stored dry, in a dessicator, and protected from light. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.1-2.3 (m, 2H), 2.36 (s, 3H), 2.4 s, 3H), 3.0-3.1 (m, 1H), 3.27-3.32 (m, 1H), 4.4-4.69 (m, 4H), 5.46-5.48 (m, 1H), 6.0 (bs, 3H),

7.2-7.3 (m, 4H), 7.88-7.91 (m, 4H); ^{13}C-NMR (75 Mhz, $CDCl_3$) ppm 166.5, 165.9, 144.0, 143.9, 129.7, 129.1, 126.8, 126.7, 82.9, 76.8, 76.6, 64.5, 43.5, 35.4, 21.6.

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