# Nucleic Acid Related Compounds. 42. A General Procedure for the Efficient Deoxygenation of Secondary Alcohols. Regiospecific and Stereoselective Conversion of Ribonucleosides to 2′-Deoxynucleosides[1]

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**Abstract:** Treatment of unhindered secondary alcohols with phenoxythiocarbonyl chloride (phenyl chlorothionocarbonate) in pyridine/dichloromethane, or in acetonitrile with 4-dimethylaminopyridine catalysis for hindered alcohols, gave clean conversion to their *O*-phenoxythiocarbonyl derivatives. Reductive deoxygenation of these phenyl thionocarbonate esters proceeded smoothly, using tri-*n*-butyltin hydride and a free radical initiator in warm toluene. Treatment of ribonucleosides with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane/pyridine afforded selective protection as their 3′,5′-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl) (3′,5′-*O*-TPDS) derivatives in high yields. Phenoxythiocarbonylation of the 2′-hydroxyl group of 3′,5′-*O*-TPDS-nucleosides, AIBN-initiated homolytic deoxygenation with tri-*n*-butyltin hydride, and deprotection with tetra-*n*-butylammonium fluoride completed the generally applicable four-stage biomimetic conversion of ribonucleosides to 2′-deoxynucleosides. Overall conversion yields ranged from 57 to 78% for the naturally occurring nucleosides, nucleoside antibiotics, and methyl β-D-ribofuranoside. Greater than 85% stereoselectivity with retention of configuration for the 2′-deoxygenation was attained with adenosine in comparison with the complete retention stereoselectivity executed by ribonucleotide reductase.

Ribonucleosides, as their 5′-di- or triphosphates, are biosynthetically converted to their 2′-deoxy counterparts by ribonucleotide reductases. These completely retention-stereoselective free radical mediated deoxygenations utilize a complex sequence of enzymatic reactions and cofactors to provide the sole de novo pathway to the DNA components.[2]

Chemical 2′-deoxygenation of ribonucleosides has been pursued for many years, but with variable success.[3] Intramolecular attack of the 2-oxo group of the naturally occurring pyrimidine nucleosides at C2′ of the sugar has provided anhydro intermediates that have been converted efficiently to 2′-deoxy compounds.[4] However, analogous treatment of purine nucleosides results in retention of an "unnatural" 8-oxo substituent whose removal can be troublesome. Utilization of purine thioanhydro intermediates has given 2′-deoxynucleosides.[5] Bimolecular displacements at C2′ of ribonucleosides are disfavored sterically and electronically.[6] Bridged 2′,3′-acyloxonium ions suffer predominant (~9:1) attack at C3′ with purine intermediates[7a,8a] and exclusive 3′ substitution with tubercidin (7-deazaadenosine).[7b,c,8b] Poor overall yields of 2′-deoxynucleosides have been reported for $S_N2$ displacement–reduction sequences.[3,6-9] Cationic ($S_N1$) approaches are precluded by the electron-deficient nature of C2′ (bonded to the *N*,*O*-acetal center at C1′).[6] Reductive generation of anionic character at C2′ results in elimination of the weakly basic heterocycle at C1′ to produce labile unsaturated furanosyl sugars.[10,11] Generation of 2′-deoxynucleosides from halogenated precursors was known to proceed smoothly using tri-*n*-butyltin hydride.[4c,d,6,7a,c] Barton has reported analogous homolytic deoxygenation of alcohol thiono esters.[13,14]

Regiospecific 2′-deoxygenation of ribonucleosides had been impeded by the difficulty in differentiating the secondary cis 2′ and 3′ hydroxyl groups.[3] Nucleoside 5′-monophosphates had been cyclized to give 3′,5′ cyclic monophosphates,[15] but their purification is often tedious and they are not compatible with usual organic solvents and methodology. Isolation of 3′,5′-di-*O*-acyl derivatives had been utilized.[16] The problem of selective 3′,5′ protection was solved by Markiewicz.[17] Treatment of nucleosides with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane results in initial attack at the primary 5′-hydroxyl to give the 3′,5′-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl)nucleoside derivatives in high yields. Deprotection of these 3′,5′-*O*-TPDS-nucleosides occurs with tetra-*n*-butylammonium fluoride.[18]

Barton and others have employed thionobenzoate,[13,19,20] *S*-methyl xanthate (*S*-methyl dithiocarbonate),[13,19,21] thio-

(1) (a) For the previous paper in this series, see: Robins, M. J.; Wilson, J. S.; Sawyer, L.; James, M. N. G. *Can. J. Chem.*, in press. (b) For a preliminary report of this work, see: Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932.

(2) See: (a) Thelander, L.; Reichard, P. *Annu. Rev. Biochem.* **1979**, *48*, 133. (b) Stubbe, J. A.; Ackels, D.; Segal, R.; Blakley, R. L. *J. Biol. Chem.* **1981**, *256*, 4843 and references therein.

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(11) See for examples involving uridine derivatives: (a) Jain, T. C.; Jenkins, I. D.; Russell, A. F.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 30. (b) Adachi, T.; Iwasaki, T.; Inoue, I.; Miyoshi, M. *Ibid.* **1979**, *44*, 1404.

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(16) See, for example: (a) Fromageot, H. P. M.; Griffin, B. E.; Reese, C. B.; Sulston, J. E. *Tetrahedron* **1967**, *23*, 2315. (b) Ishido, Y.; Sakairi, N.; Okazaki, K.; Nakazaki, N. *J. Chem. Soc., Perkin Trans. 1* **1980**, 563.

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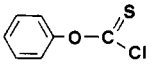
carbonylimidazolide,[13,22-24] and cyclic thionocarbonate[14] derivatives for deoxygenation of carbohydrate-type compounds. However, the basic conditions used for preparation of the xanthate esters[13,19] were inapplicable to 3′,5′-*O*-TPDS-nucleosides. Their[13,20] two-stage preparation of thionobenzoates employed noxious conditions (phosgene/*N*,*N*-dimethylbenzamide followed by hydrogen sulfide) and the chloroimminium chloride reagent was not chemospecific for the 2′-hydroxyl of nucleosides. Conversion of tri-*n*-butyltin hydride to hexa-*n*-butyldistannane was a reported side reaction catalyzed by imidazole released during sluggish reductions of thiocarbonylimidazolides.[13] Thionobenzoate and xanthate esters had been reported to give benzyl ether,[19] unidentified,[25] and starting alcohol[13,19] byproducts during reduction.

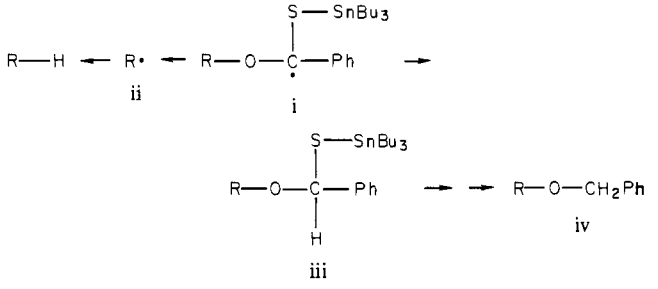
We sought a readily prepared thiocarbonyl reagent that would react with alcohols under mild conditions and whose esters would undergo clean homolytic hydrogenolysis. Phenoxythiocarbonyl chloride (phenyl chlorothionocarbonate) (PTC-Cl)[26,27] fulfills these



PTC - Cl

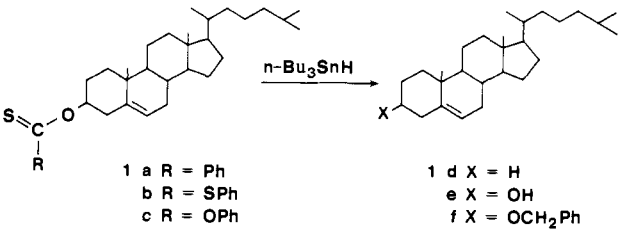
criteria. This thioacyl chloride is moderately active and converts unhindered secondary alcohols to their phenyl thionocarbonate esters in the presence of 3–4 equiv of pyridine in dichloromethane. However, hindered secondary alcohols, including the 3′,5′-*O*-TPDS-nucleosides, require catalysis by 4-dimethylaminopyridine[28] in acetonitrile. The phenyl substituent is a convenient spectral marker and controls unidirectional homolysis of the mixed thionocarbonate esters.

Barton[13] proposed attack of tributyltin radical at thionobenzoate sulfur to give the $\alpha$-stabilized benzylic radical (i). Unimolecular

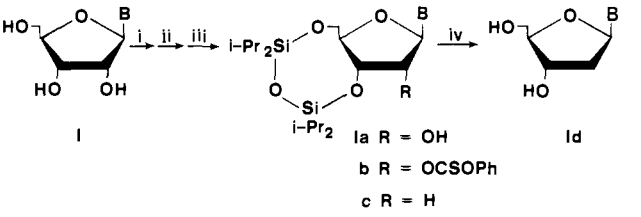


$\beta$-scission of i to give the desired alkyl radical (ii) competes with bimolecular hydrogen transfer from the stannane to give iii. Reversion of iii to starting alcohol presumably occurs. Others[19] and ourselves[33] have observed benzyl ether (iv) formation upon reductive treatment of thionobenzoates. Presumably homolytic

Scheme I



Scheme II[a]



[a](i) $(i\text{-}Pr_2SiCl)_2O$ / pyridine. (ii) PhOCSCl / DMAP / $CH_3CN$. (iii) $n\text{-}Bu_3SnH$ / AIBN / $PhCH_3$ / 75°C. (iv) $n\text{-}Bu_4N^+F^-$.

carbon–sulfur bond cleavage of iii followed by hydrogen transfer to the benzylic radical produces iv. Barton[13] and Cristol[34] outlined a mechanism involving loss of tributyltin methylmercaptide from the *S*-methyl xanthate esters. Loss of carbonoxy sulfide from the resulting (alkyloxy)thiocarbonyl radical would produce ii. Hydrogen transfer then would give the desired alkane. No route for reversion to starting alcohol was suggested.

We examined comparative reductions of the thionobenzoate (**1a**) (see Scheme I), *S*-phenyl xanthate (**1b**), and phenoxythiocarbonyl (**1c**) esters of cholesterol (**1e**).[33] At reflux in benzene, **1a** gave 3-*O*-benzylcholesterol (**1f**) as the major and cholesterol (**1e**) as a minor product in the absence or presence of AIBN.[35] At reflux in toluene, **1a** gave roughly equivalent amounts of **1f** and the deoxygenation product, $\Delta^5$-cholestene (**1d**), plus a minor quantity of **1e**. Slow addition of dilute solutions of the reactants to refluxing toluene gave **1d** as the major product, as observed by Barton.[13] However, minor amounts of **1e** and **1f** were detected in harmony with partitioning of the radical intermediate (**i**).[33]

Little or no reaction of **1b** with tributylstannane occurred at reflux in benzene. At reflux in toluene, **1b** gave **1d** plus **1e**. Artifactual deacylation of the stable xanthate (**1b**) to **1e** did not occur in toluene at reflux or upon addition of AIBN. However, addition of redistilled tributylstannane to a refluxing solution of **1b** in toluene produced **1d** plus a minor amount of **1e**. The **1c** derivative was essentially inert to the latter conditions, but noninitiated reaction of **1c** and tributylstannane did occur in xylene at 140 °C to give **1e** (major) and **1d** (minor).[33]

Thus, the activation energy for the noninitiated reactions increases from thionobenzoate to xanthate to thionocarbonate. Benzylic stabilization is the major factor with **1a**, and the ratio of products (**1d**,**e**,**f**) formed is dependent on the concentration of tributylstannane. The noninitiated Barton reduction of xanthate esters affords alkane plus starting alcohol. However, parallel initiated reductions of **1b** and **1c** in benzene at reflux gave **1d** without apparent dependence on the concentration of tributylstannane.[33] It appears that different activation and/or partitioning of intermediates occurs in the initiated (direct free radical chain) and noninitiated (electron-transfer chain initiation?)[36] reductions of xanthate esters. Reversion to starting alcohol occurs under noninitiated conditions. Preparative conversions of cholesterol

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(27) Available from Aldrich Chemical Co.
(28) The acylation of hindered alcohols using DMAP discovered by Steglich and Höfle[29] and numerous applications have been reviewed.[30] We reported dramatic catalysis of the acylation of secondary alcohols using highly hindered symmetrical amino acid anhydrides and DMAP.[31] Hassner has recently noted similar results.[32]
(29) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
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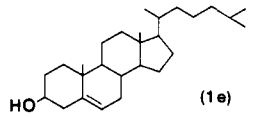
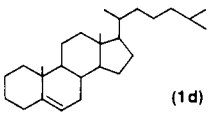
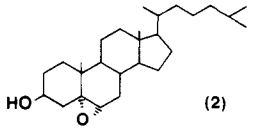
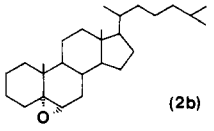
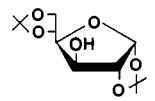
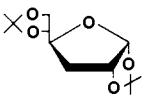
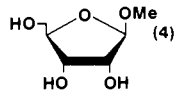
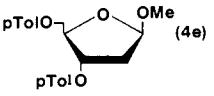
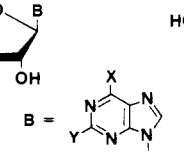
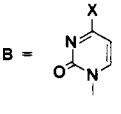
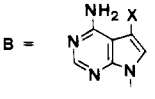
(35) Abbreviations used are as follows: AIBN for 2,2′-azobis(2-methylpropanitrile); DMAP for 4-*N*,*N*-dimethylaminopyridine; DMF for *N*,*N*-dimethylformamide; PTC-Cl for phenyl chlorothionocarbonate; TBAF for tetra-*n*-butylammonium fluoride; THF for tetrahydrofuran; and TPDS-$Cl_2$ for 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane.
(36) (a) Blackburn, E. V.; Tanner, D. D. *J. Am. Chem. Soc.* **1980**, *102*, 692. (b) Tanner, D. D.; Blackburn, E. V.; Diaz, G. E. *Ibid.* **1981**, *103*, 1557.

Table I

| entry | starting material | final product | overall yield, % |
|---|---|---|---|
| 1 |  (1e) |  (1d) | 85 |
| 2 |  (2) |  (2b) | 78 |
| 3 |  (3) |  (3b) | 85 |
| 4 |  (4) |  (4e) | 58 |
| 5 | Adenosine (5) | X = $NH_2$, Y = H | 2′-Deoxyadenosine (5d) | 78 |
| 6 | Guanosine (6) | X = OH, Y = $NH_2$ | 2′-Deoxyguanosine (6d) | 57 |
| 7 | Uridine (7) | X = OH | 2′-Deoxyuridine (7d) | 68 |
| 8 | Cytidine (8) | X = $NH_2$ | 2′-Deoxycytidine (8d) | 65 |
| 9 | Tubercidin (9) | X = H | 2′-Deoxytubercidin (9d) | 68 |
| 10 | Toyocamycin (10) | X = CN | 2′-Deoxytoyocamycin (10d) | 69 |
| 10a | 10 (X = CN) | X = $CONH_2$ | 2′-Deoxysangivamycin (11d) | 65 |







(**1e**) and its 5,6-$\alpha$-epoxide (**2**) (see Table I) to the 3-deoxy products (**1d** and **2b**) were effected smoothly[37] via their phenyl thionocarbonate esters (**1c** and **2a**).

Acylation of 1,2;5,6-di-*O*-isopropylidene-$\alpha$-D-glucofuranose (**3**) (see Table I) with PTC-Cl/DMAP[35] followed by the standard reduction using 1.5 equiv of tri-*n*-butyltin hydride and 0.2 equiv of AIBN gave 3-deoxy-1,2;5,6-di-*O*-isopropylidene-$\alpha$-D-*ribo*-hexofuranose (**3b**) in 85% overall yield. This compares favorably with conversions of **3** → **3b**, using *S*-methyl xanthate (56%)[13,38] and thiocarbonylimidazolide (69%)[22] approaches.

Protection of a ribonucleoside (I) (see Scheme II) as its 3′,5′-*O*-TPDS derivative (Ia), phenoxythiocarbonylation of its 2′-hydroxyl group to give Ib, deoxygenation to give Ic, and deprotection using TBAF provides a mild and generally applicable four-stage conversion to the corresponding 2′-deoxynucleoside (Id).

(37) A minor amount of unknown steroid-containing byproduct (coupling?) formation occurred with AIBN initiation.[33] For the preparative steroid deoxygenations, di-*tert*-butyl peroxide initiation in toluene at reflux gave clean formation of the cholestene products.

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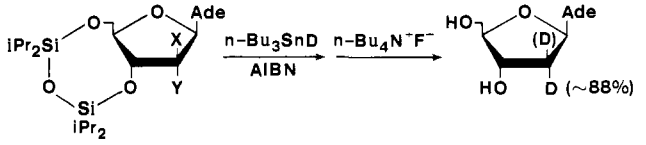
Scheme III



5b X = H, Y = OCSOPh
12b X = OCSOPh, Y = H
13a X = Cl, Y = H

14

Adenosine (**5**) (see Table I) was converted to 2′-deoxyadenosine (**5d**) in 78% overall yield. This represents the most efficient chemical 2′-deoxygenation of a ribonucleoside thus far reported and corresponds to an average yield of 94% for each of the four steps. Guanosine (**6**) was converted to 2′-deoxyguanosine (**6d**) in 57% yield. Its 3′,5′-*O*-TPDS derivative (**6a**) was obtained in 70% yield, the lowest of all the nucleosides examined, but the subsequent three stages proceeded smoothly in a combined 81% yield.

Uridine (**7**) was converted to 2′-deoxyuridine (**7d**) in 68% yield. No side reactions were encountered during reduction of 2′-*O*-phenoxythiocarbonyl-3′,5′-*O*-TPDS-uridine (**7b**). A 2′-*O*-thiocarbonyl-5′-*O*-trityluridine derivative was known to cyclize to the 2,2′-anhydro product in over 85% yield upon heating in toluene.[39] Cytidine (**8**) was converted to 2′-deoxycytidine (**8d**) in 65% yield. Owing to the known propensity of **8** to undergo acylation at the 4-amino group, it was protected by selective acetylation.[40] Conversion of 4-*N*-acetylcytidine (**8′**) to its 3′,5′-*O*-TPDS derivative (**8a′**) followed by treatment with PTC-Cl/DMAP gave the 2′-*O*-phenoxythiocarbonyl ester (**8b′**). The thioacylation step proceeded sluggishly and was incomplete under the usual conditions. However, increasing the quantity of DMAP to 6–9 equiv resulted in clean and rapid formation of **8b′**. Reductive deoxygenation followed by deprotection with TBAF and then methanolic ammonia (4-*N*-Ac) gave **8d**.

We previously had effected a seven-stage sequence to obtain 2′-deoxytubercidin in 27% overall yield from the parent antibiotic.[41] Blakely, Townsend, and co-workers have utilized enzymatic reduction to prepare the 2′-deoxynucleoside 5′-triphosphates. Tubercidin triphosphate was 2′-deoxygenated in ~76% yield by ribonucleotide reductase, but the corresponding toyocamycin conversion was ~30%.[42] Our overall yields of purified 2′-deoxytubericidin (**9d**) (68%) and 2′-deoxytoyocamycin (**10d**) (69%) correspond to average yields of 91% for each of the four stages. Passage of an aqueous solution of 2′-deoxytoyocamycin (**10d**) through a column of Dowex 1-X2 ($OH^-$) resin effected hydrolysis of the nitrile function[43] to give 2′-deoxysangivamycin (**11d**).

Methyl $\beta$-D-ribofuranoside (**4**) was subjected to the four-stage procedure without isolation of intermediates. The resulting 2-deoxy product (**4d**) was esterified to give the known[44] methyl 2-deoxy-3,5-di-*O*-*p*-toluyl-$\beta$-D-*erythro*-pentofuranoside (**4e**) in 58% yield for the five steps. No alcohol reversion byproduct (**4a**) was observed during the reduction of **4b**. This had been a significant side reaction reported in the 2-deoxygenation of a closely related sugar xanthate derivative,[19] using the noninitiated Barton reduction.

The 2′-*O*-phenoxythiocarbonyl esters (**5b** and **12b**) (see Scheme III) of 3′,5′-*O*-TPDS-adenosine (**5a**) and 3′,5′-*O*-TPDS-9-($\beta$-D-arabinofuranosyl)adenosine (**12a**) were reduced with tri-*n*-butyltin deuteride. Deprotection and then purification of the 2′-

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deuterio-2′-deoxyadenosine epimers (**14**) on a Dowex 1-X2 ($OH^-$) column was followed by 400-MHz $^1H$ NMR analysis. The ratio of ribo/arabino deuterium substitution was ~88:12 in both cases. Conversion of 9-(2-chloro-2-deoxy-β-D-arabinofuranosyl)-adenine[7a] (**13**) to its 3′,5′-*O*-TPDS derivative (**13a**) followed by the identical reduction, deprotection, and column purification sequence gave a 2′-deuterio-2′-deoxyadenosine epimer ratio indistinguishable from that of the above phenyl thionocarbonate (**5b** and **12b**) reductions. This provides corroborative evidence[36,45] for our suggested free radical chain process in which hydrogen transfer from the bulky tributylstannane to a "separated" C2′ radical occurs with >85% stereoselectivity on the less hindered α (ribo) face. Variable degrees of stereoselectivity have been reported in studies with epimeric carbohydrate derivatives.[21,22]

## Conclusions

Thioacylation of secondary alcohols is effected smoothly with phenyl chlorothionocarbonate.[27] Initiated homolytic deoxygenation of the resulting alkyl phenyl thionocarbonate esters occurs cleanly under mild reaction conditions with tri-*n*-butyltin hydride. Related *S*-phenyl dithiocarbonate (xanthate) esters appear to undergo deoxygenation under the same initiated conditions, but some reversion to starting alcohol occurs with the noninitiated Barton reduction.

An efficient and generally applicable four-stage biomimetic conversion of ribonucleosides to 2′-deoxynucleosides has been developed. Selective protection of a ribonucleoside as its 3′,5′-*O*-TPDS derivative, conversion to its 2′-(phenyl thionocarbonate) ester, AIBN-initiated homolytic deoxygenation with tri-*n*-butyltin hydride, and deprotection of the 3′,5′-*O*-TPDS product with tetra-*n*-butylammonium fluoride provides the 2′-deoxynucleoside in 57–78% overall yields. Stereoselectivity of over 85% for *ribo*-2′-deuterio-2′-deoxyadenosine was observed with reductions of the epimeric riko and arabino thionocarbonate esters in harmony with hydrogen transfer to a "separated" 2′ radical.

## Experimental Section

Melting points were determined on a Reichert microstage block and are uncorrected. Ultraviolet (UV) spectra were recorded on a Cary 15 spectrophotometer and infrared (IR) spectra on a Nicolet 7199 FT(IR) instrument. NMR spectra were determined as described in ref 1a. Electron impact mass spectra (MS) were determined by the mass spectrometry laboratory of this department with an AEI MS-50 instrument at 70 eV with computer processing. Direct probe sample introduction was employed. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter with a 10-cm 1-mL microcell. Elemental analyses were determined by the Microanalytical Laboratory of this department or by Schwarzkopf Microanalytical Laboratory. Evaporations were effected with a Buchler rotating evaporator equipped with a Dewar "dry-ice" condenser under water aspirator or mechanical oil pump vacuum at 40 °C or cooler.

Thin-layer chromatography (TLC) was performed on E. Merck 60-$F_{254}$ sheets with sample observation under 2537-Å light. Merck PF-254 silica on glass plates was used for preparative TLC. Mallinckrodt CC-7 (200 mesh) silica was used for column chromatography. Solvents used for column chromatography include the following: $S_1$, $CHCl_3$; $S_2$, 2% MeOH/$CHCl_3$; $S_3$, 1.5% MeOH/$CHCl_3$; $S_4$, 5% MeOH/$CHCl_3$; and $S_5$, hexane. Dowex 1-X2 ($OH^-$) resin was used for anion-exchange chromatography. Barnebey-Cheney AU-4 charcoal was used for carbon column chromatography. A bulk quantity of this charcoal was washed with MeOH and then $CHCl_3$, dried, refluxed with 1 N HCl/$H_2O$ until the supernatant remained colorless, with $H_2O$ to neutrality, with 10% NaOH/$H_2O$ until the supernatant remained colorless, with $H_2O$ to neutrality, with MeOH and $CHCl_3$, and air-dried at room temperature before use. Reagent grade solvents and reagents were redistilled prior to use. "Hexane" refers to the fraction of petroleum ether with bp 63–65 °C upon redistillation. Dried solvents were stored over Davison 4-Å molecular sieves (Fisher Scientific).

A general four-step reaction sequence was employed for the 2′-deoxygenation of nucleosides. Procedure A is the silylation of a nucleoside (I) to its 3′,5′-*O*-TPDS derivative (Ia); procedure B is the thioacylation of Ia to give the 3′,5′-*O*-TPDS-nucleoside 2′-(phenyl thionocarbonate) ester (Ib); procedure C is the reduction step with *n*-$Bu_3SnH$ to give the protected 2′-deoxynucleoside (Ic); and procedure D is the deprotection with *n*-$Bu_4N^+F^-$ to give the 2′-deoxynucleoside (**Id**). General procedures A–D are described in detail for the conversion of adenosine (**5**) to 2′-deoxyadenosine (**5d**).

The standard processing procedure refers to partitioning a reaction residue between ethyl acetate and water followed by successive washing of the organic phase with cold 1 N HCl/$H_2O$, $H_2O$, saturated $NaHCO_3$/$H_2O$, and saturated NaCl/$H_2O$ and then drying ($Na_2SO_4$), filtering, and evaporating the solution to dryness.

Limited characterization data are presented. See ref 33 for additional spectral data and interpretations, elemental analytical results (within ±0.4% of theory), etc.

**1,1,3,3-Tetraisopropyldisiloxane** was prepared by the general procedure of Gilman and Clark.[46] A 35–40% direct yield of the title product was obtained based on starting trichlorosilane. The byproduct diisopropylsilanol was converted to the title compound by addition of $P_2O_5$ and distillation of the supernatant. A combined yield of 75–85% of product was obtained: bp 104 °C (10 mmHg), 49 °C (0.5 mmHg); (lit.[17] bp 95 °C (15 mmHg)); $n^{20}_D$ = 1.4335; IR (neat film) 2110 $cm^{-1}$, ($CCl_4$) 2150 $cm^{-1}$, Si–H; MS, *m/z* 246.1836 (27, $M^+[C_{12}H_{30}OSi_2]$ = 246.1836), 203.1286 (100, M – *i*-Pr = 203.1287).

**1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (TPDS-$Cl_2$)** was prepared by an improvement of the procedure of Markiewicz.[17] A solution of 50 g (0.20 mol) of 1,1,3,3-tetraisopropyldisiloxane and 500 mL of $CCl_4$ in a three-neck round-bottom flask was dried by azeotropic distillation of ~20% of the volume at atmospheric pressure. The flask was then fitted with a gas delivery tube with a fine fritted disk and a discharge tube filled with Drierite (anhydrous $CaSO_4$) that could be attached to a water pump (aspirator). The solution was cooled in an ice bath and stirred vigorously while carefully dried $Cl_2$ was bubbled in at a rapid rate. The saturated solution was allowed to undergo the exothermic chlorination reaction for 15–30 min, chlorine flow was halted, and the aspirator vacuum (~20 mmHg) was attached to the Drierite-protected discharge tube. Dissolved HCl gas was evacuated for ~5 min. The introduction of $Cl_2$, chlorination, and evacuation of HCl was cycled until the solution remained yellow and the IR band at 2150 $cm^{-1}$ (Si–H) disappeared. Volatile materials were evaporated and the residue was distilled to give ~50 g (78%) of the title compound: bp 68–70 °C (0.05 mmHg) (lit.[17] bp 120 °C (15 mmHg)); $n^{20}_D$ = 1.4550; MS, *m/z* 314.1055 (6%, $M^+[C_{12}H_{28}{}^{35}Cl_2OSi_2]$ = 314.1055), 271.0502 (100, M – *i*-Pr = 271.0508). This product is now commercially available.[27]

**Phenyl chlorothionocarbonate (phenoxythiocarbonyl chloride) (PTC-Cl)** was prepared from thiophosgene and phenol as outlined[26] in 85% yield. This product is now commercially available.[27]

**3β-Cholesteryl Phenyl Thionocarbonate (1c).** To a stirred solution of 3.87 g (10 mmol) of cholesterol (**1e**) in 60 mL of $CH_2Cl_2$ was added 3 mL (2.94 g, 37 mmol) of dry pyridine and 2.0 mL (1.9 g, 11 mmol) of PTC-Cl. After 2 h the solvents were evaporated and the residue was subjected to the standard processing. Crystallization of the product from $Me_2CO$ gave 5.0 g (96%) of **1c**: mp 162–163.5 °C; MS, *m/z* 369.3493 (85, M – OCSOPh = 369.3521), 368.3436 (100, M – HOCSOPh). Anal. ($C_{34}H_{50}O_2S$) C, H, S.

**Cholest-5-ene (1d).** To 1.046 g (2 mmol) of **1c** was added 30 mL of $PhCH_3$, 800 μL (872 mg, 3 mmol) of *n*-$Bu_3SnH$, and 65 μL (0.4 mmol) of di-*tert*-butyl peroxide. The solution was refluxed under $N_2$ for 3 h and 3 mL of 1 M TBAF/THF was added. Refluxing was continued for 4 h, solvents were evaporated, and the residue was chromatographed on alumina (20 g, 3 × 15 cm) using $S_5$. Evaporation of the eluate and crystallization of the residue from EtOH gave 620 mg (84%) of **1d**: mp 92–94 °C (lit.[13] mp 90–92 °C); MS, *m/z* 370 (100, $M^+$) 371 (30, M + 1). Anal. ($C_{27}H_{46}$) C, H.

Conversion of **1e** → **1c** → **1d** without crystallization of **1c** proceeded in 85% yield.

**5,6-α-Epoxy-3β-cholesteryl Phenyl Thionocarbonate (2a).** To 2.01 g (5 mmol) of 5,6-α-epoxy-3β-cholesterol[47] (**2**) in 30 mL of $CH_2Cl_2$ was added 15 mL (19 mmol) of dry pyridine and 1.0 mL (5.5 mmol) of PTC-Cl. The solution was stirred for 2 h and solvents were evaporated. The residue from the standard processing was crystallized from $Me_2CO$ to give 2.48 g (92%) of **2a**: mp 191–194 °C; MS, *m/z* 385.3453 (77, M – OCSOPh), 384.3398 (100, M – HOCSOPh). Anal. ($C_{34}H_{50}O_3S$) C, H, S, O.

**5,6-α-Epoxycholestane (2b).** To 1.078 g (2 mmol) of **2a** in 30 mL of $PhCH_3$ was added 800 μL (3 mmol) of *n*-$Bu_3SnH$ and 65 μL (0.4 mmol) of di-*tert*-butyl peroxide. The solution was refluxed under $N_2$ for 3 h and then evaporated. The residue was chromatographed on alumina (20 g, 3 × 15 cm) with $S_5$. Evaporation of the appropriate fractions and crystallization of the residue from $Me_2CO$ gave 603 mg (78%) of **2b**: mp

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74–75 °C (lit.[48] mp 74–75 °C); MS, *m/z* 386.3552 (100, $M^+$ = 386.3549). Anal. ($C_{27}H_{46}O$) C, H, O.

Conversion of **2** → **2a** → **2b** without crystallization of **2a** gave **2b** in 78% yield.

**Procedure A. 3′,5′-*O*-TPDS-adenosine (5a).** To 267 mg (1 mmol) of dried adenosine (**5**) suspended in 10 mL of dry pyridine was added 320 μL (316 mg, 1 mmol) of TPDS-$Cl_2$, and the mixture was stirred at room temperature for 3 h. Pyridine was evaporated and the residue was partitioned between EtOAc and $H_2O$. The organic phase was washed with 2 × 20 mL of cold 1 N HCl/$H_2O$, $H_2O$, saturated $NaHCO_3/H_2O$, and saturated NaCl/$H_2O$, dried ($Na_2SO_4$), filtered, and evaporated. The resulting amorphous product was of sufficient purity for direct use in subsequent reactions.

For characterization, this material was chromatographed on silica (10 g, 2 × 10 cm) with $S_1$ and $S_2$. Evaporation of appropriate fractions and crystallization of the residue from $CH_3CN$ gave 433 mg (85%) of **5a**: mp 98–99.5 °C; UV (0.1 N HCl) max 257 nm (ε 14900), (0.1 N NaOH) max 259 nm (ε 15100); MS, *m/z* 509.2485 (8.8, $M^+$ = 509.2490), 466.1924 (100, M − *i*-Pr). Anal. ($C_{22}H_{39}N_5O_5Si_2$) C, H, N.

**Procedure B. 2′-*O*-Phenoxythiocarbonyl-3′,5′-*O*-TPDS-adenosine (5b).** To a vacuum-dried residue of total crude **5a** was added 15 mL of anhydrous $CH_3CN$, 250 mg (2.05 mmol) of DMAP, and 200 μL (1.1 mmol) of PTC-Cl. The solution was stirred at room temperature for 16 h. Solvent was evaporated and the residue was subjected to the standard processing. The resulting product was sufficiently pure to be used directly in the reduction step.

Purification of this material was achieved by chromatography on silica (10 g, 2 × 10 cm) with $S_1$ and $S_3$. Evaporation of appropriate fractions gave 586 mg (91%) of **5b** as an oil: UV (EtOH) max 259 and 228 nm, min 245 nm; MS, *m/z* 602.1924 (6.1, M − *i*-Pr[$C_{26}H_{36}N_5O_6SSi_2$] = 602.1927), 492.2471 (12, M − OCSOPh).

**Procedure C. 2′-Deoxy-3′,5′-*O*-TPDS-adenosine (5c).** The above total crude **5b** was dissolved in 20 mL of distilled $PhCH_3$ and 32 mg (0.2 mmol) of AIBN and 400 μL (1.5 mmol) of *n*-$Bu_3SnH$ were added. The solution was degassed with oxygen-free $N_2$ for 20 min and then heated at 75 °C for 3 h. Solvent was evaporated and the residue was chromatographed on silica (10 g, 2 × 10 cm) with $S_1$. Evaporation of appropriate fractions and crystallization of the residue from EtOH gave 370 mg (75%) of **5c**: mp 113–114.5 °C; UV (MeOH) max 259 nm (ε 14000); MS, *m/z* 493.2538 (18, $M^+$ = 493.2544), 450.1986 (100, M − *i*-Pr). Anal. ($C_{29}H_{39}N_5O_4Si_2$) C, H, N.

**Procedure D. 2′-Deoxyadenosine (5d).** Deprotection of crude **5c** was effected by addition of 2 molar equiv of 1 M TBAF/THF directly to the above reduction mixture. The solution was heated for an additional hour at 75 °C. Solvent was evaporated and the residue was partitioned between $Et_2O$ and $H_2O$. The aqueous phase was concentrated and applied to a column of Dowex 1-X2 ($OH^-$) resin. Elution of the product with $H_2O$, evaporation, and crystallization of the residue from $Et_2O$/EtOH gave 195 mg (78%) of **5d**: mp 191–192 °C (lit.[49] mp 187–189 °C); MS, *m/z* 251.1073 (7.1, $M^+$[$C_{10}H_{13}N_5O_3$] = 251.1082), 162.0827 (100, BHCH=$CH_2$). This product was identical with naturally occurring 2′-deoxyadenosine by the usual criteria.

Treatment of 1.068 g (4 mmol) of **5** by the four-step sequence (**5** → **5a** → **5b** → **5c** → **5d**) without isolation of intermediates gave 780 mg (78%) of recrystallized (**5d**).

**3′,5′-*O*-TPDS-Guanosine (6a).** To 1.132 g (4 mmol) of dried guanosine (**6**) suspended in 60 mL of anhydrous DMF was added 4 mL of dry pyridine and 1.3 mL (4.1 mmol) of TPDS-$Cl_2$. The mixture was stirred for 5 h and then added slowly to 1 L of vigorously stirred ice water. The resulting precipitate was collected by filtration and washed thoroughly with $H_2O$. Rapid crystallization from 95% EtOH gave 1.47 g (70%) of **6a**: mp >250 °C dec; UV (MeOH) max 256 nm (ε 14300); MS, *m/z* 525.2443 (24, $M^+$ = 525.2435), 526.2464 (9, M + 1), 482.1876 (91, M − *i*-Pr). Anal. ($C_{22}H_{39}N_5O_6Si_2$) C, H, N.

**2′-*O*-Phenoxythiocarbonyl-3′,5′-*O*-TPDS-guanosine (6b).** Procedure B was applied to 1.05 g (2 mmol) of **6a**. Crystallization of the product from 95% EtOH gave 1.25 g (94%) of **6b**: mp 255–258 °C; UV (EtOH) max 250 nm (ε 16700); MS, *m/z* 661.2436 (3.8, $M^+$ = 661.2414), 662.2465 (1.6, M + 1), 507.2347 (19, M − OCSOPh). Anal. ($C_{29}H_{43}N_5O_7SSi_2$) C, H, N, S.

**2′-Deoxyguanosine (6d).** A 1.0 g (1.5 mmol) sample of **6b** was subjected to procedure C. Deblocking procedure D was performed directly on the reaction solution. Solvents were evaporated and the residue was partitioned between $Et_2O$ and $H_2O$. The aqueous phase was concentrated and applied to a column of Dowex 1-X2 ($OH^-$) resin (10 mL, 2 × 5 cm). The column was washed well with $H_2O$ before elution was effected with 0.25 M $Et_4N^+HCO_3^-$ (TEAB) buffer (pH 9.0). After evaporation of the eluate, the residue was treated with 10 mL of $H_2O$ and reevaporated. This procedure was repeated four times to remove residual TEAB. Crystallization of the residue from $H_2O$ gave 345 mg (86%) of **6d**: mp 251–252 °C (lit.[49] mp 250 °C); MS, *m/z* 249.0864 (0.8, $M^+$[$C_{10}H_{13}N_5O_4$] − 18 = 249.0853), 151.0498 (13, B + H), 117.0553 (41, sugar ion).

**3′,5′-*O*-TPDS-uridine (7a).** Procedure A was followed with 972 mg (4 mmol) of dried uridine (**7**) to give an oil: UV (MeOH) max 262 nm (ε 9600); MS, *m/z* 486.2262 (12, $M^+$[$C_{21}H_{38}N_2O_7Si_2$] = 486.2268), 443.1718 (100, M − *i*-Pr).

**2′-*O*-Phenoxythiocarbonyl-3′,5′-*O*-TPDS-uridine (7b).** Procedure B was applied to the residue of crude **7a** to give an oil: UV (MeOH) max 262, 232 nm, min 245 nm; MS, *m/z* 469.2206 (0.5, M − OCSOPh-[$C_{21}H_{37}N_2O_6Si_2$] = 469.2172), 426.1577 (32, M − OCSOPh − *i*-Pr).

**2′-Deoxyuridine (7d).** The crude **7b** was subjected to procedure C and deblocking procedure D was performed directly. Solvents were evaporated and the residue was partitioned between $Et_2O$ and $H_2O$. The aqueous phase was stirred with 10 g of carbon. To a column (2 × 30 cm) was added 3 g of carbon followed by the slurry of carbon containing the absorbed nucleoside. The column was washed thoroughly with $H_2O$ and then a stepwise gradient from 20% to 40% EtOH/$H_2O$ was applied. Evaporation of appropriate fractions and crystallization of the residue from $Et_2O$/EtOH gave 620 mg (68% overall from **7**) of **7d**: mp 162–163 °C (lit.[49] mp 163 °C); MS, *m/z*, 228.0742 (4.1, $M^+$[$C_9H_{12}N_2O_5$] = 228.0746), 139.0726 (2.5, BHCH=$CH_2$).

**4-*N*-Acetylcytidine (8′).** The general procedure of Fox and coworkers[40] was applied to 486 mg (2 mmol) of cytidine (**8**) in 50 mL of MeOH at reflux. After 5 successive hourly additions of acetic anhydride, the solution was evaporated and coevaporated with 2 × 50 mL of $PhCH_3$. MeOH (50 mL) was added and 2 further additions of acetic anhydride to the solution at reflux gave complete conversion (TLC) to **8′**. The solution was evaporated and again coevaporated with $PhCH_3$ to remove all volatile materials. The colorless product was dried at 110 °C over $P_2O_5$ in vacuo.

**4-*N*-Acetyl-3′,5′-*O*-TPDS-cytidine (8a′).** The dried residue of **8′** was treated by procedure A. The residue was crystallized from EtOH to give 975 mg (92%) of **8a′**: mp 111–113 °C; UV (MeOH) max 297, 247 nm (ε 8200, 15000), min 270 nm (ε 4200); MS, *m/z* 527.2524 (0.3, $M^+$[$C_{23}H_{41}N_3O_7Si_2$] = 527.2533), 484.2006 (7.4, M − *i*-Pr).

**4-*N*-Acetyl-2′-*O*-phenoxythiocarbonyl-3′,5′-*O*-TPDS-cytidine (8b′).** The total crude residue of **8a′** was dried at room temperature in vacuo, dissolved in 20 mL of dry $CH_3CN$, and 2 g (16.4 mmol) of DMAP was added. The solution was cooled in ice water and 400 μL (2.2 mmol) of PTC-Cl was added. Stirring was continued for 5 min in the cold and 45 min at room temperature. After the standard processing, the residue was subjected to addition and evaporation of 3 × 10 mL of $PhCH_3$, 20 mL of $CHCl_3$, and 15 mL of $Et_2O$ followed by drying of the crisp slightly yellow glass at room temperature for 5 h in vacuo. This amorphous **8b′** showed the following: UV (MeOH) max 298, 234 nm, min 270 nm; MS, *m/z* 467.1835 (3.9, M − *i*-Pr − OCSOPh), 466.1841 (10, M − *i*-Pr − HOCSOPh).

**4-*N*-Acetyl-2′-deoxy-3′,5′-*O*-TPDS-cytidine (8c′).** The total crude **8b′** was dissolved in 20 mL of $PhCH_3$ and heated at 75 °C for 14 h under $N_2$ with 1.26 mL (4.7 mmol) of *n*-$Bu_3SnH$ and 50 mg (0.3 mmol) of AIBN.

A small aliquot was evaporated and the residue chromatographed on silica to give **8c′** as an oil: UV (MeOH) max 298, 247 nm, min 270 nm; MS, *m/z* 511.2524 (0.3, $M^+$[$C_{23}H_{41}N_3O_6Si_2$] = 511.2533), 468.2001 (9.2, M − *i*-Pr).

**2′-Deoxycytidine (8d).** To the above solution of **8c′** was added 4.5 mL of 1 M TBAF/THF and stirring was continued for 3 h at 75 °C. Volatile materials were evaporated and the residue was treated with 25 mL of saturated $NH_3$/MeOH. This solution was stirred overnight at room temperature and evaporated. The residue was partitioned between $Et_2O$ and $H_2O$. The aqueous phase was washed with $Et_2O$, concentrated, and applied to a column (2 × 25 cm) of Dowex 1-X2 ($OH^-$) resin. Elution with $H_2O$ and evaporation of appropriate fractions gave a colorless homogeneous product that was recrystallized from absolute MeOH to give 294 mg (65% from starting **8**) of **8d**: mp 203–206 °C (lit.[49] mp 200–201 °C); MS, *m/z* 227.0906 (1.8, $M^+$[$C_9H_{13}N_3O_4$] = 227.0907), 138.0668 (18, BHCH=$CH_2$).

**4-Amino-7-(3,5-*O*-TPDS-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3′,5′-*O*-TPDS-tubercidin) (9a).** Procedure A was followed with 266 mg (1 mmol) of dried tubercidin (**9**) to give **9a** as colorless platelets: mp 238–242 °C; UV (MeOH) max 270, 227 nm (ε 10800, 20000), min 245 nm (ε 3800); MS, *m/z* 508.2547 (8, $M^+$[$C_{23}H_{40}N_4O_5Si_2$] = 508.2528), 509.2598 (7.4, M + 1), 465.1980 (60, M − i-Pr).

**2′-*O*-Phenoxythiocarbonyl-3′,5′-*O*-TPDS-tubercidin (9b).** Procedure B was applied to the residue of crude **9a** to give an oil: UV (MeOH) max

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271, 232 nm, min 245 nm; MS, *m/z* 491.2460 (12, M - OCSOPh-[$C_{23}H_{39}N_4O_4Si_2$] = 491.2562), 448.1905 (3.1, M - OCSOPh - *i*-Pr).

**2′-Deoxy-3′,5′-*O*-TPDS-tubercidin (9c).** Crude **9b** was reduced according to Procedure C to give an oil: UV (MeOH) max 271, 227 nm, min 245 nm; MS, *m/z* 492.2488 (13, $M^+$[$C_{23}H_{40}N_4O_4Si_2$] = 492.2467), 449.1923 (100, M - *i*-Pr), 161.0820 (1.5, BHCH=$CH_2$).

**4-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (2′-Deoxytubercidin) (9d).** The above reaction solution of **9c** was subjected to deblocking procedure D. The column was washed with $H_2O$ prior to elution of the product with 10% MeOH/$H_2O$. Evaporation of the eluate and crystallization of the residue from EtOH gave **9d**: mp 217–218.5 °C (lit.[41] mp 217–218 °C); $[\alpha]^{24}_D$ -43.8° (*c* 0.34, MeOH) (lit.[41] $[\alpha]^{24}_D$ -43° (*c* 0.58, EtOH)); UV (MeOH) max 271, 227 nm (ε 13 600, 24 200), min 239 nm (ε 2700); MS, *m/z* 250.1070 (5%, $M^+$ = 250.1066), 161.0826 (14, BHCH=$CH_2$). Anal. ($C_{11}H_{14}N_4O_3$) C, H, N.

Treatment of 1.064 g (4 mmol) of **9** by the four-step sequence (**9** → **9a** → **9b** → **9c** → **9d**) without isolation of intermediates gave 680 mg (68%) of recrystallized **9d**.

**4-Amino-5-cyano-7-(3,5-*O*-TPDS-β-D-ribofuranosyl)pyrrolo[2,3-*d*]-pyrimidine (3′,5′-*O*-TPDS-toyocamycin) (10a).** Procedure A was applied to 582 mg (2 mmol) of dried toyocamycin (**10**) to give 945 mg (89%) of **10a**: mp 171–172 °C; UV (MeOH) max 280, 232 nm (ε 17 400, 11 900), min 247 nm (ε 4700); MS, *m/z* 533.2478 (4.1, $M^+$ = 533.2492), 534.2514 (1.7, M + 1), 490.1938 (100, M - *i*-Pr). Anal. ($C_{24}H_{39}N_5O_5Si_2$) C, H, N.

**2′-*O*-Phenoxythiocarbonyl-3′,5′-*O*-TPDS-toyocamycin (10b).** Procedure B was applied to 800 mg (1.5 mmol) of **10a**. Crystallization of the residue from EtOH gave **10b**: mp 136–139 °C; UV (MeOH) max 278, 230 nm (ε 16 600, 17 000), min 250 nm (ε 8400); MS, *m/z* 626.1904 (11, M - *i*-Pr = 626.1925), 516.2407 (46, M - OCSOPh). Anal. ($C_{31}H_{43}N_5O_6SSi_2$) C, H, N, S.

**2′-Deoxy-3′,5′-*O*-TPDS-toyocamycin (10c).** Procedure C was applied to the crude residue of **10b**. Crystallization of the residue from $CH_3CN$ gave 675 mg (87%) of **10c**: mp 174–177 °C; UV (MeOH) max 279, 230 nm (ε 16 400, 11 700), min 246 nm (ε 4000); MS, *m/z* 517.2548 (6.4, $M^+$ = 517.2543), 518.2568 (2.8, M + 1), 474.2001 (78 M - *i*-Pr). Anal. ($C_{24}H_{39}N_5O_4Si_2$) C, H, N.

**4-Amino-5-cyano-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (2′-Deoxytoyocamycin) (10d).** Procedure D was applied to 517 mg (1 mmol) of **10c** dissolved in 20 mL of $PhCH_3$, using 2 mL of 1 M TBAF/THF and stirring at 80 °C for 2 h. Solvents were evaporated and the residue was partitioned between $Et_2O$ and $H_2O$. The aqueous phase was applied to a column of carbon (2 g, 1 × 5 cm) and the column was washed with 50 mL of $H_2O$ and then 50 mL of EtOH. Washing was continued with $CHCl_3$ and elution of the product was effected with 20% PhH/$CHCl_3$. Evaporation of the appropriate fractions and crystallization of the residue from $Et_2O$/EtOH gave 245 mg (89%) of **10d**: mp 208–209 °C; $[\alpha]^{24}_D$ -24.6° (*c* 0.28, MeOH); UV (MeOH) max 278, 229 nm (ε 15 700, 12 700), min 247, 221 nm (ε 4700, 11 800); (0.1 N HCl) max 273, 231 nm (ε 12 400, 17 600), min 247 nm (ε 5200); (0.1 N NaOH) max 278, 231 nm (ε 15 100, 12 000), min 246 (ε 4800); 200-MHz NMR ($Me_2SO$-$d_6$, $Me_4Si$) δ 2.28 (d of d of d, $J_{2''-2'}$ = 13.1 Hz, $J_{2''-1'}$ = 6.1 Hz, $J_{2''-3'}$ = 3.2 Hz, 1, H2″), 2.48 (d of d of d, $J_{2'-1'}$ = 7.2 Hz, $J_{2'-3'}$ = 5.8 Hz, 1, H2′), 3.58 (m, 2, H5′,5″), 3.87 (m, 1, H4′), 4.38 (m, 1, H3′), 5.06 (t, $J_{OH-5',5''}$ = 5.5 Hz, 1, 5′-OH), 5.32 (d, $J_{OH-3'}$ = 4.1 Hz, 1, 3′-OH), 6.53 (d of d, $J_{1'-2'}$ = 7.2 Hz, $J_{1'-2''}$ = 6.1 Hz, 1, H1′), 6.88 (br s, 2, $NH_2$), 8.26 (s, 1, H6), 8.44 (s, 1, H2); MS, *m/z* 275.1020 (6.6, $M^+$ = 275.1012), 245.0933 (2.2, M - $CH_2O$), 186.0780 (21, BHCH=$CH_2$), 159.0544 (100, B + H). Anal. ($C_{12}H_{13}N_5O_3$) C, H, N.

**4-Amino-5-carboxamido-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (2′-Deoxysangivamycin) (11d).** A 550 mg (2 mmol) sample of **10d** was dissolved in $H_2O$ and applied to a column of Dowex 1-X2 ($OH^-$) resin (2 × 10 cm). The resin was washed with 200 mL of $H_2O$ and then with a mixture of MeOH/$H_2O$ (1:9). The ratio of MeOH in $H_2O$ was gradually increased to 2:3 which eluted the product. Evaporation of the eluate and crystallization of the residue from EtOH gave 551 mg (94%) of **11d**: mp 272–275 °C; $[\alpha]^{24}_D$ -22.3° (*c* 0.26, MeOH); UV (MeOH) max 279, 231 nm (ε 14 800, 10 200), min 255 nm (ε 6500); (0.1 N HCl) max 274, 230 nm (ε 12 500, 14 400), min 253 nm (ε 6900); (0.1 N NaOH) max 278 nm (ε 14 800), min 255 nm (ε 7400); 200-MHz NMR ($Me_2SO$-$d_6$, $Me_4Si$) δ 2.27 (d of d of d, $J_{2''-1'}$ = 6.1 Hz, $J_{2''-2'}$ = 12.9 Hz, $J_{2''-3'}$ = 3.4 Hz, 1, H2″), 2.42 (d of d of d, $J_{2'-1'}$ = 7.5 Hz, $J_{2'-3'}$ = 5.8 Hz, 1, H2′), 3.56 (m, 2, H5′, 5″), 3.86 (m, 1, H4′), 4.39 (m, 1, H3′), 5.00 (t, $J_{OH-5',5''}$ = 5.7 Hz, 1, 5′-OH), 5.31 (d, $J_{OH-3'}$ = 4.4 Hz, 1, 3′-OH), 6.53 (d of d, $J_{1'-2'}$ = 7.5 Hz, $J_{1'-2''}$ = 6.1 Hz, 1, H1′), 7.36 (br s, 2, $NH_2$), 7.94 (br s, 2, $CONH_2$), 8.10 (s, 1, H6), 8.15 (s, 1, H2); MS, *m/z* 293.1128 (5.9, $M^+$ = 293.1124), 204.0886 (12, BHCH=$CH_2$), 177.0649 (100, B + H). Anal. ($C_{12}H_{15}N_5O_4$) C, H, N.

**Methyl 3,5-*O*-TPDS-β-D-ribofuranoside (4a).** Procedure A was applied to 164 mg (1 mmol) of methyl β-D-ribofuranoside (**4**). The standard processing (excluding the acid wash) gave a crude residue that was chromatographed on ammonia-impregnated silica (10 g, 2 × 10 cm). The column was developed quickly (to reduce hydrolysis) with $S_5$ and then $S_1$. Evaporation of the appropriate fractions gave 325 mg (80%) of **4a** as an oil: MS, *m/z* 363.1686 (3.5, M - *i*-Pr[$C_{15}H_{31}O_6Si_2$] = 363.1661), 332.1426 (3.5%, M - *i*-Pr - $OCH_3$).

**Methyl 2-*O*-Phenoxythiocarbonyl-3,5-*O*-TPDS-β-D-ribofuranoside (4b).** Procedure B was applied to 300 mg (0.74 mmol) of **4a**. The standard processing (excluding the acid wash) gave a residue that was chromatographed on ammonia-impregnated silica (10 g, 2 × 10 cm) with $S_5$ and then 50% hexane/$CHCl_3$. Evaporation of appropriate fractions gave 300 mg (75%) of **4b** as an oil: MS, *m/z* 390.2275 (2.1, M - OCSOPh [$C_{18}H_{38}O_5Si_2$] = 390.2259), 359.2086 (9.2%, M - OCSOPh - OMe).

**Methyl 2-Deoxy-3,5-di-*O*-*p*-toluyl-β-D-*erythro*-pentofuranoside (4e).** To 270 mg (0.5 mmol) of **4b** dissolved in 10 mL of $PhCH_3$ was added 200 μL (0.75 mmol) of *n*-$Bu_3SnH$ and 15 mg (0.09 mmol) of AIBN. The reduction was effected according to procedure C followed by deprotection with procedure D. Solvents were evaporated and the residue was partitioned between $Et_2O$ and $H_2O$. The aqueous phase was evaporated, coevaporated several times with pyridine, and dissolved in 15 mL of anhydrous pyridine. A 5-fold molar excess of *p*-toluyl chloride was added to the stirred solution at room temperature. After 3 h the solvent was evaporated and the residue was partitioned between $Et_2O$ and $H_2O$. The organic phase was washed with 2 × 10 mL of $H_2O$, saturated $NaHCO_3$/$H_2O$, and saturated NaCl/$H_2O$, dried ($Na_2SO_4$), filtered, and evaporated. The residue was chromatographed on silica (5 g, 1.5 × 7 cm) with $S_5$ and then 10% $Et_2O$/hexane. Evaporation of appropriate fractions and crystallization of the residue from EtOH gave 120 mg (62%) of **4e**: mp 76–78 °C (lit.[44b] mp 76.5–78 °C); $[\alpha]^{25}_D$ -9.4° (*c* 1.0, $CHCl_3$) (lit.[44b] $[\alpha]^{20}_D$ -8.1° (*c* 2.5, $CHCl_3$)).

Treatment of 328 mg (2 mmol) of **4** by the 5-step sequence (**4** → **4a** → **4b** → **4c** → **4d** → **4e**) without isolation of intermediates gave 445 mg (58%) of **4e**.

**1,2;5,6-Di-*O*-isopropylidene-3-*O*-phenoxythiocarbonyl-α-D-glucofuranose (3a).** Procedure B was applied to 260 mg (1 mmol) of 1,2;-5,6-di-*O*-isopropylideneglucose (**3**). Crystallization of the residue from MeOH/$H_2O$ gave 340 mg (86%) of **3a**: mp 108–110 °C; MS, *m/z* 396.1251 (0.3, $M^+$ = 396.1230), 381.1010 (23, M - $CH_3$), 243.1241 (20, M - OCSOPh). Anal. ($C_{19}H_{24}O_7S$) C, H, S.

**3-Deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (3b).** Procedure C was applied to 792 mg (2 mmol) of **3a**. The residue was chromatographed on silica (10 g, 2 × 10 cm) with $S_5$. Concentration of appropriate fractions gave 425 mg (87%) of **3b** as an oil: 100-MHz NMR ($CDCl_3$, $Me_4Si$) δ ~1.4 (4 × s, 12, $CH_3$'s), 1.78 (m, 1, H3′), 2.20 (d of d, $J_{3-3'}$ = 13.0 Hz, $J_{2-3}$ = 4.0 Hz, 1, H3), 3.80 (m, 1, H5), 4.10 (m, 3, H4,6,6′), 4.75 (t, $J_{1-2}$ = $J_{2-3'}$ = 4.0 Hz, 1, H2), 5.78 (d, 1, H1); MS, *m/z* 229 (47%, M - $CH_3$). Anal. ($C_{12}H_{20}O_5$) C, H.

Treatment of 520 mg (2 mmol) of **3** by the two-step sequence without isolation of **3a** gave 415 mg (85%) of **3b**.

**2′-Deuterio-2′-deoxyadenosines (14).** (a) Reduction of a 65 mg (0.1 mmol) sample of **5b** was effected by procedure C (as described for **5c**) with *n*-$Bu_3SnD$ substituted for *n*-$Bu_3SnH$. The product obtained had identical chromatographic mobility with that of **5c**. Deprotection procedure D was applied directly to the reduction solution and analogous processing was continued to give 22.5 mg (89%) of **14** as an oil: 400-MHz NMR ($Me_2SO$-$d_6$, $Me_4Si$) δ 2.30 (d of d, $J_{2''-1'}$ = 2.8 Hz, $J_{2''-3'}$ = 5.8 Hz, ~0.12, H2″ of the arabino-deuterio epimer), 2.71 (d of d, $J_{2'-1'}$ = 7.5 Hz, $J_{2'-3'}$ = 5.8 Hz, ~0.88, H2′ of the ribo-deuterio epimer), 3.57 (d of d, $J_{5''-4'}$ = 4.2 Hz, $J_{5''-5'}$ = 12.0 Hz, 1, H5″), 3.68 (d of d, $J_{5'-4'}$ = 4.2 Hz, 1, H5′), 3.94 (m, 1, H4′), 4.46 (d of d, $J_{3'-4'}$ = 2.8 Hz, 1, H3′), 5.35 (m, 2, OH's), 6.39 (d, $J_{1'-2'}$ = 7.5 Hz, ~0.9, H1′), 7.29 (s, 2, $NH_2$), 8.18 (s, 1, H2), 8.36 (s, 1, H8); MS, *m/z* 252.1075 (6.7, $M^+$[$C_{10}H_{12}DN_5O_3$] = 252.1082), 163.0835 (67, BHCH=CHD), 135.0662 (100, B + H).

(b) The four-step sequence outlined above in (a) (**5** → **5a** → **5b** → **14**) was applied to 53 mg (0.2 mmol) of 9-(β-D-arabinofuranosyl)adenine (**12**) without purification of the intermediates. A 34 mg (67%) yield of **14** was obtained as an oil with the identical spectral properties listed in part a.

(c) A 53-mg (0.1 mmol) sample of 9-(2-chloro-2-deoxy-3,5-*O*-TPDS-β-D-arabinofuranosyl)adenine (**13a**) was subjected to the reduction conditions of procedure C, using 10 mL of $PhCH_3$, 40 μL (0.15 mmol) of *n*-$Bu_3SnD$, and 5 mg of AIBN. Deprotection procedure D was performed directly on the reaction solution. A 22-mg (87%) yield of **14** was obtained as an oil with the identical spectral properties listed in part a.

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# Multiple Conformational States of a Pro-Pro Peptide. Solid-State and Solution Conformations of Boc-Aib-Pro-Pro-NHMe

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**Abstract:** The solid-state and solution conformations of the model peptide Boc-Aib-Pro-Pro-NHMe have been studied by X-ray diffraction and NMR. The peptide adopts a poly(proline II) conformation in the solid state. Two molecules are observed in the asymmetric unit differing in the geometry (cis/trans) of the urethane group. The molecules are held together in the crystal by a complex network of hydrogen bonds involving three molecules of water, which cocrystallize. Dissolution of single crystals at low temperature (~233 K) permits NMR observation of the solid-state conformer. In solution, the peptide undergoes a trans-cis isomerization of the Pro–Pro bond. Low-temperature NMR measurements allow the detection of three conformational states of the Pro–Pro segment. Both cis′ and trans′ rotational isomers about the $C^{\alpha}$–CO ($\psi$) bond of Pro-3 are detectable at low temperatures. Theoretical calculations suggest an appreciable activation barrier to $\psi$ rotation. Temperature and solvent dependence of NH chemical shifts provide evidence for an intramolecular hydrogen bond, involving the NHMe group in the cis Pro-Pro conformer. Energy calculations suggest the possibility of a type VI $\beta$-turn conformation stabilized by a 4 → 1 hydrogen bond between the Aib-1 CO and NHMe groups.

Proline peptides occupy a central position in the development of peptide conformational analysis.[1] The restrictions imposed on the available backbone conformations by the pyrrolidine ring,[2] the possibility of cis–trans isomerism about the X–Pro imide bond,[3] and conformational flexibility of the five-membered ring[4] have all been the focus of several investigations. The extensive occurrence of Pro residues in fibrous protein structures like collagen[5] and tropoelastin[6] has provided a stimulus for these studies. The suggestion that cis–trans isomerization about X–Pro bonds may constitute the rate-determining step in the folding of globular proteins[7] has evoked particular interest in the possibility that Pro residues may modulate the dynamics of polypeptide chain folding.[8] Studies in this laboratory have been directed toward the use of Pro residues in conjunction with stereochemically constrained $\alpha$-aminoisobutyryl (Aib)[9] residues in developing synthetic model peptides which will exemplify various folded conformations of acyclic peptides.[10] While there exist several examples of 4 → 1 hydrogen-bonded $\beta$-turn conformations with all trans peptide backbones,[11] there are, as yet, no examples of a 5 → 1 hydrogen-bonded classical $\alpha$-helical conformation ($\phi \sim \pm 55°$, $\psi \sim \pm 45°$)[12] in a small acyclic peptide. In an attempt to develop a suitably constrained model, we have examined the peptide Boc-Aib-Pro-Pro-NHMe. The Aib residue is largely restricted to conformations in the helical region ($\phi \pm 60 \pm 20°$, $\psi \sim \pm 30 \pm$

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(9) Abbreviations used: Boc, *tert*-butyloxycarbonyl; DCC, *N,N′*-dicyclohexylcarbodiimide; DMF, *N,N*-dimethylformaide; NHMe, *N*-methylamide.

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