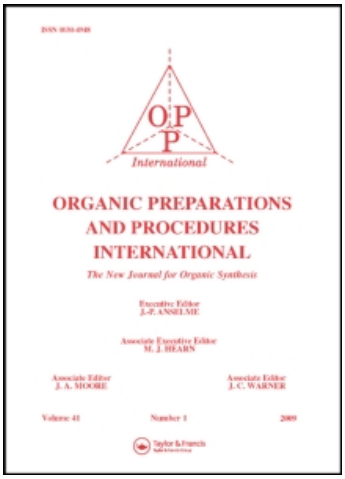


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN EFFICIENT SYNTHESIS OF 2',3'-DIDEOXYADENOSINE via THE COREY-WINTER REACTION

Russell L. K. Carr[a]; Thomas A. Donovan Jr.[a]; Mahendra N. Sharma[a]; C. Daniel Vizine[a]; Michael J. Wovkulich[a]
[a] Starks Associates, Inc., Buffalo, NY

To cite this Article Carr, Russell L. K. , Donovan Jr., Thomas A. , Sharma, Mahendra N. , Vizine, C. Daniel and Wovkulich, Michael J.(1990) 'AN EFFICIENT SYNTHESIS OF 2',3'-DIDEOXYADENOSINE via THE COREY-WINTER REACTION', Organic Preparations and Procedures International, 22: 2, 245 — 253
To link to this Article: DOI: 10.1080/00304949009458201
URL: http://dx.doi.org/10.1080/00304949009458201

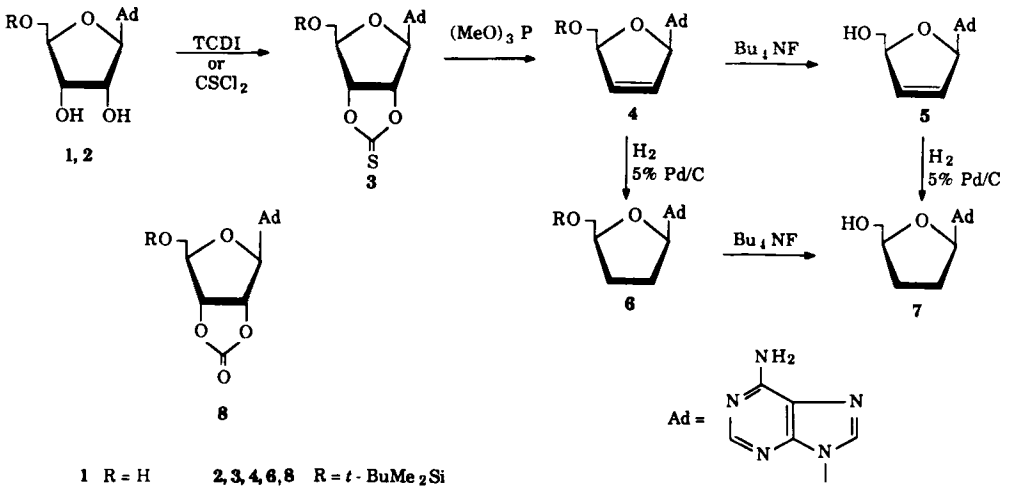
ORGANIC PREPARATIONS AND PROCEDURES INT. 22(2), 245-253 (1990)

AN EFFICIENT SYNTHESIS OF 2′,3′-DIDEOXYADENOSINE via THE COREY-WINTER REACTION

Russell L. K. Carr*, Thomas A. Donovan, Jr., Mahendra N. Sharma, C. Daniel Vizine, and Michael J. Wovkulich

Starks Associates, Inc.
1280 Niagara Street, Buffalo, NY 14213

Prior to 1989 there appeared reports that the application of the Corey-Winter[1] procedure to deoxygenate nucleosides was either wholly unsuccessful[2] or, at best yielded the desired olefin as a low yield minor reaction product.[3] During 1989 the use of the Corey-Winter synthesis to prepare 2′,3′-dideoxyuridine[4a], 2′,3′-dideoxyinosine and dideoxyadenosine[4b] was reported, albeit on a scale less than 5 g. We are, therefore, pleased to report the kilogram scale synthesis of 2′,3′-dideoxyadenosine (7) via the Corey-Winter route (Scheme 1). It has potential



Scheme 1

application to the large scale synthesis of other 2′,3′-dideoxynucleosides as well as their olefin analogs, the 2′,3′-didehydro-2′,3′-dideoxynucleosides. These have been shown to have activity against the acquired immune deficiency syndrome (AIDS) virus (HIV),[5] and efficient synthetic routes to these materials have recently been sought.[6-12]

The Corey-Winter deoxygenation of cyclic thionocarbonates for the preparation of dideoxynucleosides appeared attractive because: it started with the more readily available ribonucleoside (versus the 2′-deoxyribonucleoside), the other raw materials for each of the chemical steps were readily available, the process did not involve the separation of α-and β- anomers, and, importantly, the reaction seemed susceptible to practical and efficient scale up to kilogram levels.

While we found it desirable to block the 5′-hydroxyl of adenosine **(1)** we found it neither necessary nor desirable to block the amino group;[13] if the amino group was first blocked (with a benzoyl group) it tended to be lost during later reactions leading to problems in work-up. Also, the free amino group gave no problems in the subsequent reaction with thiophosgene. Treatment of **1** with tert-butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazole gave 5′-O-tert-butyldimethylsilyladenosine **(2)**[14] in 70% yield. The 5′-protected intermediate **2** was then converted to 5′-O-tert-butyldimethylsilyl-2′,3′-O-thionocarbonyladenosine **(3)** in one of two ways. The first method involved reaction of the 5′-protected species with 1,1′-thiocarbonyldiimidazole (TCDI)[1] to give the cyclic thionocarbonate **3** in 85-99% yield (inversely dependent on scale). An alternate route to the thionocarbonate **3** was the reaction of the 5′-protected diol **2** with thiophosgene in the presence of 4-dimethylaminopyridine (4-DMAP)[15] to give the desired product **3** in 88-93% yield on a 1-1.5 kilogram scale. The thiophosgene/4-DMAP route to the thionocarbonate **3** became our method of choice because of the smoothness of the reaction, the ease of manipulation, and the relatively small amount of material shown to be cyclic carbonate **8**[16] which was formed as the principal side-product. The material **8**, present in 5-7% of the total, did not appear to interfere with the succeeding step and its separation from the olefin **4** was significantly easier than its separation from the

thionocarbonate **3**. Desulfurization with concommitant deoxygenation of the thionocarbonate **3** was effected smoothly by reaction with excess trimethyl phosphite[1] at 85°. Higher temperatures (up to reflux, 110°) gave increased amounts of side products, and at lower temperatures (65°) the reaction rate was unsatisfactorily slow. The 5′-O-blocked olefin **4** was obtained in crude yields of 87-93% on a 1 to 2 kg scale. It was found necessary to purify crude **4** by silica gel column chromatography in order to obtain **4** of sufficient purity to hydrogenate smoothly and completely; the first fractions collected from the silica gel column invariably contained varying amounts of a phosphorus containing material with a vile odor. The overall yield of purified **4** was 60-61%.[17]

Conversion of **4** to ddA (**7**) is possible by two routes: a) by deblocking first to 2′,3′-didehydro-2′,3′-dideoxyadenosine (**5**) followed by hydrogenation, or b) by hydrogenation to 5′-O-tert-butyldimethylsilyl-2′,3′-dideoxyadenosine (**6**) and then deblocking. Because of the poor solubility characteristics of the deblocked olefin **5**, it was advantageous to first hydrogenate to give the saturated compound **6** (94.6% yield) and then deblock using Bu_4NF/THF to give 2′,3′-dideoxyadenosine (**7**). The product was then recrystallized from EtOH to give purified product in 59.5% yield.

The present synthesis provides a new and improved method of preparing 2′,3′-dideoxynucleosides, in this instance, 2′,3′-dideoxyadenosine; the scale is variable, from a few grams to several kilograms or more. We are currently working on a multi-kilogram synthesis of 2′,3′-dideoxyinosine.

EXPERIMENTAL SECTION

Melting points were measured with a Mel-Temp apparatus and are uncorrected. UV spectra were recorded on a Beckman Acta CV. Thin layer chromatography was done on silica gel using E. Merck 60 F-254 glass plates. Optical rotations were obtained on a Perkin Elmer model 141 polarimeter. ^{1}H NMR spectra were obtained on Varian GEMINI-300 or Bruker AM-500 spectrometers and are reported as ppm values downfield from TMS. High resolution mass spectra were obtained on a VG Analytical Instruments 70-SE instrument. Elemental analyses were obtained from Galbraith Laboratories or Atlantic Microlab, Inc.

5′-O-tert-Butyldimethylsilyladenosine (2). - To an argon blanketed suspension of

adenosine (80.0 g, 0.299 mol) and imidazole (45.6 g, 0.670 mol) in dimethylformamide (DMF) (1.5 L) was added a solution of TBDMSCl (47.2 g, 0.313 mol) in DMF (200 mL) dropwise. The solution was stirred overnight, then spin-evaporated in vacuo to an oil. This oil was dissolved in THF-$CHCl_3$ (1:1)(1.0 L), washed with H_2O (2 x 500 mL) and spin-evaporated in vacuo to a solid. The solid was triturated with ethyl acetate (EtOAc) (750 mL) and dried to constant weight in vacuo at 50° to give 85.8 g (75.2%) of analytically pure material; mp 178-180°C. TLC R_f (THF/$CHCl_3$ 2/1) 0.41; λ_{max} (EtOH) 259 nm (log ε 4.127); ^{1}H NMR (300 MHz)(DMSO-d_6); δ 8.36 (s, 1H, H-2); 8.20 (s, 1H, H-8); 7.38 (s, 2H, -NH_2); 5.97 (d, 1H, H-1′); 5.63 (d, 1H, 2′-OH); 5.28 (d, 1H, 3′-OH); 4.59 (q, 1H, H-2′); 4.25 (q, 1H, H-3′); 4.00 (m, 1H, H-4′); 3.96-3.68 (m, 2H, H-5′, H-5″); 0.90 (s, 9H, t-Bu); 0.10 (s, 6H, -CH_3).

Anal. Calcd. for $C_{16}H_{27}N_5O_4Si$: C, 50.36; H, 7.15; N, 18.36; Si, 7.36
Found: C, 50.51; H, 7.24; N, 18.49; Si, 7.11

Larger runs were also made exactly as described above. For example, adenosine (1250 g, 4.677 mol) gave 1251 g, 3.280 mol of (2); 70.1% yield, mp 176-179°C.

5′-O-tert-Butyldimethylsilyl-2′,3′-O-thionocarbonyladenosine (3). - Method A. A solution of 2 (80.0 g, 0.210 mol) and TCDI (40.9 g, 0.230 mol) in toluene (800 mL) was heated at reflux for 2 h. The mixture was cooled and triturated with H_2O (700 mL). The resulting precipitate was collected, azeotropically dried in toluene (300 mL), and the solution was stored at -20° for 20 h. The resulting precipitate was collected by filtration, and dried to constant weight in vacuo at 50° to give 87.7 g (98.5%) of product. An analytical sample was obtained by chromatography (EtOAc/silica gel); mp 202-203°C. TLC R_f (THF/$CHCl_3$ 2/1) 0.64; λ_{max} (EtOH) 240 nm (log ε 4.310); ^{1}H NMR (300 MHz)(DMSO-d_6): δ 8.47 (s, 1H, H-2); 8.35 (s, 1H, H-8); 7.64 (s, 2H, -NH_2); 6.78 (s, 1H, H-1′); 6.57 (d, 1H, H-2′); 6.01 (d, 1H, H-3′); 4.73 (m, 1H, H-4′); 3.92 (br m, 2H, H-5′, H-5″); 0.95 (s, 9H, t-Bu); 0.10 (s, 6H, -CH_3).

Anal. Calcd. for $C_{17}H_{25}N_5O_4SSi$: C, 48.20; H, 5.96; N, 16.54; S, 7.57
Found: C, 48.51; H, 5.97; N, 16.53; S, 7.84

Method B. This compound was also prepared by the dropwise addition of thiophosgene (556 g, 4.84 mol) to a stirred mixture of **2** (1628 g, 4.267 mol) and 4-DMAP (1182 g, 9.675 mol) in dry CH_2Cl_2 (19.0 L) at 20°, with cooling. After stirring for 2.5 h, H_2O (38.5 L) was added and the mixture stirred rapidly for 15 min. The mixture was then diluted with hexanes (19.0 L) and stirred for 1 h. The resulting precipitate was collected, washed by resuspension in H_2O (2 x 4.0 L), hexanes (2 x 4.0 L) and air-dried. The resulting solid was dissolved in THF (13.0 L), washed with brine (2 x 4.0 L), dried over Na_2SO_4 (400 g) and spin-evaporated in vacuo to a semi-solid. This material was triturated with Et_2O (7.0 L), collected by filtration, washed with Et_2O (3 x 700 mL) and dried to constant weight in vacuo to give 1362 g (75.3%) of product. Additional product was obtained from the Et_2O filtrates to give a total of 1673 g (92.5%) of product containing 5-7% 5′-O-tert-butyldimethylsilyl-2′,3′-O-carbonyladenosine **(8)**.

5′-O-tert-Butyldimethylsilyl-2′,3′-O-carbonyladenosine (8). - A **mixture** of **4** and **8** (153g) from the purification of **4** was dissolved in EtOH (150mL) and a mixture of hexanes (300mL) was added. The resulting white precipitate was collected by filtration, recrystallized twice from EtOH and dried to constant weight in vacuo to give 9.2g of **8**; mp 185-186°C. TLC R_f (EtOH/MeOH 25/1) 0.62. ^{1}H NMR (300 MHz)(DMSO-d_6): δ 8.47 (s, 1H, H-2); 8.34 (s, 1H, H-8); 7.42 (s, 2H, -NH_2); 6.67 (s, 1H, H-1′); 6.21 (d, 1H, H-2′); 5.65 (dd, 1H, H-3′); 4.54 (d, 1H, H-4′); 3.91 (t, 1H, H-5′); 0.97 (s, 9H, t-Bu); 0.19 (s, 6H, -CH_3). MS/CI (high resolution) calc. for ($C_{12}H_{25}N_5O_5Si+H^+$): 408.1703 found: 408.1694.

Anal. Calcd. for $C_{12}H_{25}N_5O_5Si$: C, 50.10; H, 6.20; N, 17.19; Si, 6.89

Found: C, 50.21; H, 5.79; N, 17.54; Si, 6.25

5′-O-tert-Butyldimethylsilyl-2′,3′-didehydro-2′,3′-dideoxyadenosine (4). - Method A. An argon blanketed mixture of **3** (10.0 g, 0.0236 mol) and $(CH_3O)_3P$ (100 mL, 0.848 mol) was heated at reflux for 4 h then spin-evaporated in vacuo to a solid. This material was chromatographed twice (silica gel/EtOAc) to give 3.7 g (45.1%) of analytically pure product; mp 131-132°C. TLC R_f (EtOAc) 0.32; λ_{max} (EtOH) 259 nm (log ε 4.130); ^{1}H NMR (300 MHz)(DMSO-d_6): δ 8.30 (s, 1H, H-2); 8.25 (s, 1H, H-8); 7.45 (s, 2H, -NH_2); 7.08 (s, 1H, H-1′); 6.50 (d, 1H, H-3′); 6.32 (d, 1H, H-2′);

5.05 (s, 1H, H-4′); 3.92 (m, 2H, H-5′, H-5″); 0.96 (s, 9H, t-Bu); 0.10 (s, 6H, -CH_3).

Anal. Calcd. for $C_{16}H_{25}N_5O_2Si$: C, 55.29; H, 7.27; N, 20.16; Si, 8.08

Found: C, 55.18; H, 7.31; N, 20.00; Si, 7.85

Method B. An argon blanketed mixture of **3** (2,102 g, 4.962 mol) and $(CH_3O)_3P$ (15.00 kg, 120.9 mol) was stirred at 85° for 24 h and spin-evaporated in vacuo to a thick slurry which was dissolved in EtOAc (15.0 L). The turbid solution was washed successively with H_2O (2 x 2.5 L), 5% aqueous NaOH (2 x 2.5 L), H_2O (2 x 2.5 L) and saturated brine (4.0 L), and the resulting organic phase dried over $MgSO_4$ (650 g). The EtOAc filtrate was spin-evaporated in vacuo to a solvent-wet solid which was triturated with hexanes (3.0 L) and filtered. Drying to constant weight at room temperature in vacuo gave 1599 g of crude **4** (92.7% yield). This material was purified by silica gel column chromatography with the use of 17.0 kg of silica gel (9" dia x 36"h column) per 800 g of crude **4**, eluted with EtOAc-MeOH (94/6, v/v)(110 L/column). In this way a combined total of 2809 g, 8.083 mol, overall yield, 60.5%, of pure **4** was obtained ready for hydrogenation.

2′,3′-Didehydro-2′,3′-dideoxyadenosine (5). - A mixture of **4** (73.9 g, 0.213 mol) and 1.0M Bu_4NF in THF (550 mL, 0.550 mol) was stirred at 25° for 1 h. The solution was filtered through a silica gel pad with THF and spin-evaporated in vacuo to an oil. The oil was dissolved in EtOH (300 mL) and stored at 0° for 72 h. The resulting precipitate was collected and dried to constant weight in vacuo to give 45.2 g (90.9%) of analytically pure product; mp 194-196°C; literature[11] mp 194-196°C. TLC R_f (THF) 0.63; λ_{max} (EtOH) 259 nm (log ϵ 4.141); ^1H NMR (300 MHz)(DMSO-d_6): δ 8.17 (s, 1H, H-2); 8.15 (s, 1H, H-8); 7.29 (s, 2H, -NH_2); 6.94 (s, 1H, H-1′); 6.46 (d, 1H, H-3′); 6.13 (d, 1H, H-2′)(see reference 11); 5.05 (s, 1H, -OH); 4.88 (s, 1H, H-4′); 3.57 (s, 2H, H-5′, H-5″).

Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 51.49; H, 4.76; N, 30.03; O, 13.72

Found: C, 51.45; H, 4.87; N, 29.81; O, 13.81

5′-O-tert-Butyldimethylsilyl-2′,3′-dideoxyadenosine (6). - A mixture of **4** (4.1 g, 0.012 mol) and 5% Pd/C (0.5 g) in EtOAc (100 mL) was shaken under H_2 (50 psig) for 24 h. The solution was filtered and spin-evaporated in vacuo to a solid. The solid was

recrystallized from hexanes-toluene (2:1)(180 mL) and dried to constant weight in vacuo at 40° to give 2.9 g (69.0%) of analytically pure product; mp 144-145°C. TLC R_f (EtOAc) 0.31; λ_{max} (EtOH) 260 nm (log ε 4.151); ^{1}H NMR (300 MHz)(DMSO-d_6): δ 8.39 (s, 1H, H-2); 8.20 (s, 1H, H-8); 7.35 (s, 2H, -NH_2); 6.32 (m, 1H, H-1′); 4.23 (m, 1H, H-4′); 3.95-3.76 (m, 2H, H-5′, H-5″); 2.57-2.10 (complex m, 4H, H-2′, H-2″, H-3′, H-3″); 0.94 (s, 9H, t-Bu); 0.10 (s, 6H, -CH_3).

Anal. Calcd. for $C_{16}H_{27}N_5O_2Si$: C, 54.97; H, 7.80; N, 20.04

Found: C, 54.91; H, 7.67; N, 20.06

On a larger scale purified **4** (2771 g, 7.974 mol) in absolute EtOH (29.8 L) was hydrogenated at room temperature and 30-60 psig with 5% Pd/C. After removal of the catalyst by filtration, the ethanolic solutions were stirred with decolorizing carbon and the clear filtrates spin-evaporated to dryness in vacuo at 40°, to give **6** as a white solid, 2638 g (94.6% yield).

2′,3′-Dideoxyadenosine (7). - To a stirred solution of **6** (750.0 g, 2.146 mol) in dry THF (4.0 L) was added 1.0M Bu_4NF in THF (2.241 L, 2.241 mol) in one portion. After 2 h the precipitate was collected by filtration, washed with THF (2 x 750 mL) and dried in vacuo at 40° to give 500.3 g (99.1%) of crude product. This material was recrystallized from EtOH to give 300.6 g (59.5%) of purified product; mp 186-188°C (corr.); literature[11,18] mp, 185-187°C, 183-185°C. TLC R_f ($CHCl_3$/MeOH 4/1) 0.48; λ_{max} (H_2O) 260 nm (log ε 4.1480); literature[18] λ_{max} (CH_3OH) 259.5 nm (log ε 4.1644); ^{1}H NMR (500 MHz)(DMSO-d_6): δ 8.39 (s, 1H, H-2); 8.19 (s, 1H, H-8); 7.28 (s, 2H, -NH_2); 6.27 (t, 1H, J=5.6, H-1′); 5.08 (t, 1H, J=5.8, -OH); 4.16 (m, 1H, C-4′); 3.68-3.56 (m, 2H, H-5′, H-5″); 2.47 (m, 2H, H-2′, H-2″); 2.11 (m, 2H, H-3′, H-3″); $[\alpha]_D^{22}$ -26.3°, (c=1, H_2O) literature[18] $[\alpha]_D^{23}$ -26.8°, (c=1, H_2O).

Anal. Calcd. for $C_{10}H_{13}N_5O_2$: C, 51.05; H, 5.57; N 29.77

Found: C, 51.12; H, 5.59; N, 29.74

An additional 607.8 g of identical material was prepared in the same way for a total of 905.0 g of **7**.

Acknowledgment.- This work was supported by NCI contract NO1-CM-67934. The NMR spectra reported were obtained at McMaster University, Ontario, Canada (500 MHz) or the State University of New York at Buffalo (300 MHz); the mass spectra at the State University of New York at Buffalo; and the optical rotations at Roswell

Park Memorial Institute.

REFERENCES

1. E. J. Corey and R. A. E. Winter, J. Am. Chem. Soc., 85, 2677 (1963).

2. G. L. Tong, W. W. Lee and L. Goodman, J. Org. Chem., 30, 2854 (1965).

3. K. Anzai and M. Matsui, Agr. Biol. Chem., 37, 345 (1973).

4. a) L. W. Dudycz, Nucleosides Nucleotides, 8, 35 (1989); b) C. K. Chu, V. S. Bhadti, B. Doboszewski, Z. P. Gu, Y. Kosugi, K. C. Pullaiah, and P. Van Roey, J. Org. Chem., 54 2217 (1989).

5. (a) V. E. Marquez, C. K. H. Tseng, S. P. Treanor and J. S. Driscoll, Nucleosides Nucleotides, 6, 239 (1987) and references cited therein; (b) E. De Clercq, J. Med. Chem., 29, 1561 (1986), and references cited therein; (c) P. Herdewijn, J. Balzarini, E. De Clercq, R. Pauwels, M. Baba, S. Broder, H. Vanderhaeghe, J. Med. Chem., 30, 1270 (1987).

6. V. Farina and D. A. Benigni, Tetrahedron Lett., 29, 1239 (1988).

7. I. Saito, H. Ikehira, R. Kasatani, M. Watanabe and T. Matsuura, J. Am. Chem. Soc., 108, 3115 (1986).

8. E. J. Prisbe and J. C. Martin, Synth. Commun., 15, 401 (1985).

9. V. V. Samukov and V. I. Ofitserov, Bioorg. Khim., 9, 52 (1983); Chem. Abstr. 98, 161094, (1983).

10. R. R. Webb, J. A. Wos, J. C. Martin and P. R. Brodfuehrer, Nucleosides Nucleotides, 7, 147 (1988).

11. M. J. Robins, F. Hansske, N. H. Low and J. I. Park, Tetrahedron Lett., 25, 367 (1984).

12. H. Shiragami, Y. Irie, H. Shirae, K. Yokozeki and N. Yasuda, J. Org. Chem., 53, 5170 (1988).

13. D. C. Baker, T. H. Haskell, and S. R. Putt, Nucleic Acid Chemistry, Part 2, L. B. Townsend and R. S. Tipson, Ed.; John Wiley & Sons, New York, 1978, p. 505.

14. K. K. Ogilvie, Can. J. Chem., 51, 3799 (1973).

15. E. J. Corey and P. B. Hopkins, Tetrahedron Lett., 23, 1979 (1982).

16. Carbonate by-products have been produced in the reaction of 1-O-methyl-2,6-anhydro-D-talo hexopyranosides with TCDI. P. Koell and F. S. Tayman, Chem. Ber., 112, 2296 (1979). ^{1}H NMR (300 MHz), MS(CI) and elemental (C, H, N, Si) analyses were consistent with structure **8**.

17. If any products isomeric with the final thionocarbonate **(3)** were produced (see Reference 4a.), such as, e.g., 2′-deoxy-2′-thio-5′-O-tert-butyldimethylsilyladenosine-2′,3′-S,O-carbonate, they were present in amounts which caused no difficulties in purification and use of **4**.

18. J. R. McCarthy, Jr., M. J. Robins, L. B. Townsend and R. K. Robins, J. Am. Chem. Soc., 88, 1549 (1966).

(Received September 20, 1989; in revised form November 13, 1989)

(Received September 20, 1989; in revised form November 13, 1989)