Synthesis of 9-β-D-(Xylofuranosyl)adenine from Adenosine

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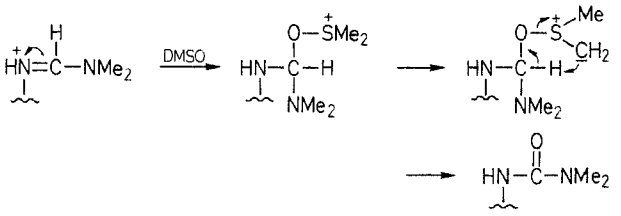
Protected adenosine **3** was oxidized using Moffatt reagent to give the 3'-ketoadenosine **4** in 60% yield. Stereospecific reduction of **4** with sodium borohydride in the presence of triethylamine at −18 °C followed by deprotection effects the inversion of configuration at C-4 affording 9-β-D-(xylofuranosyl)adenine (**7**).

The inversion of the configuration of hydroxy groups in nucleosides can be performed by reduction of the corresponding ketonucleosides. Moffatt and coworkers reported that 3',5'- and 2',5'-di-*O*-trityl uridine and cytidine derivatives were oxidized by dimethyl sulfoxide/dicyclohexylcarbodiimide to give the first reported furanosyl 2'- and 3'-ketonucleosides.[1,2] Treatment of these compounds with sodium borohydride gave epimers of the starting ribonucleosides. Garegg et al. described that protected carbohydrate derivatives can be oxidized selectively by chromium trioxide/pyridine/acetic anhydride.[3,4] Recently, Robins et al. examined oxidation of a number of protected nucleosides with this reagent and with dimethyl sulfoxide/acetic anhydride to obtain 3'- or 2'-ketonucleoside derivatives. Reduction of carbonyl functions with sodium borohydride gave the inverted arabino-, xylo-, or deoxy-*threo* isomers.[5] Although a derivative of 3'-ketoadenosine has been reported in the same literature, no effort was made to synthesize (xylofuranosyl)adenine. Crews and Baker also reported the same sequence of oxidation and reduction for epimerization, but the yield of such oxidation was low (26%), and a mixture of (xylofuranosyl)adenine and adenosine (3.5:1) was obtained after reduction.[6]

In this paper we report on the oxidation of protected adenosine using Moffatt reagent and its stereospecific reduction with sodium borohydride to give the derivative of (xylofuranosyl)adenine in good yield. In accordance with the unstability of 2'-ketonucleosides under alkaline conditions,[7] we also found that 2'-*O*-tosyl-5'-trityl-3'-ketoadenosine cannot be obtained in pure form by the oxidation of 2'-*O*-tosyl-5'-trityladenosine; adenine was very easily eliminated in this case. The protected nucleoside **3**, however, underwent the Moffatt oxidation (dicyclohexylcarbodiimide/pyridine/trifluoroacetic acid) rather smoothly under our conditions (see experimental) to give the 3'-ketoadenosine **4** in good yield.

When excess of trifluoroacetic acid was used for oxidation, compound **4** was obtained in 27% yield, besides the byproduct, compound **5** in 22% yield. A possible mechanism for the formation of the byproduct is given below.



In the presence of triethylamine, the reduction of compound **4** with sodium borohydride at −18 °C is stereospecific by attack at the less hindered α-face of sugar ring to form **6** exclusively. When this reduction was carried out at 0 °C, both the compounds **6** and **3** were obtained in a 1:1 ratio. Deprotection of **6** successively with dichloroacetic acid, ammonium hydroxide and tetra-*n*-butylammonium fluoride gave 9-β-D-(xylofuranosyl)adenine (**7**) in 70% yield.[8]

TLC is conducted on silica gel F_{254} by developing with 9:1:1 $CHCl_3$/MeOH/EtOAc. The column chromatography is performed on silica gel (100–200 mesh, purchased from Qing Dao Chemical Company, China). ^{1}H-NMR spectra are recorded with FX-90Q and VXR 300 spectrometers, with TMS as internal standard. UV spectra are recorded with DU-7 spectrophotometer. A ZAB-HS is used for fast atomic bombardement (FAB) mass spectra (glycerol matrix). IR spectra are obtained using a Perkin–Elmer IR 983G spectrophotometer. Microanalyses are obtained using a Perkin–Elmer 240c element analyser. Evaporations are carried out under reduced pressure with the bath temperature below 40 °C.

N^6-(*N*,*N*'-Dimethylaminomethylene)-5'-*O*-(4,4'-dimethoxytrityl)adenosine (2):

N^6-(*N*,*N*'-Dimethylaminomethylene)adenosine[9] (**1**; 5.7 g, 17.7 mmol) is stirred with 4,4'-dimethoxytrityl chloride (6.1 g, 18.0 mmol) in a mixture of dry DMF (50 mL) and pyridine (50 mL) for 10 h at room temperature. The mixture is poured into ice water (400 mL). The crude product is filtered, and then purified by column chromatography on silica gel with MeOH/$CHCl_3$ (1:100) to give **2** as a white foam; yield: 8.8 g (80%).

$C_{34}H_{36}N_6O_6$	calc.	C 65.38	H 5.77	N 13.46
(624.3)	found	65.21	5.76	13.35

UV (EtOH): λ_{max} = 310 nm.

^{1}H-NMR ($CDCl_3$): δ = 3.2 (d, 6H, NMe_2); 3.40 (m, 2H, H-5'); 3.76 (s, 6H, $ArOCH_3$); 4.25 (m, 1H, H-4'); 4.45 (m, 1H, H-2'); 4.65 (m, 1H, H-3'); 6.12 (d, 1H, *J* = 0.6 Hz, H-1'); 6.8–7.4 (m, 13 H_{arom}); 8.26 (s, 1H, H-1'); 8.34 (s, 1H, H-2); 8.92 (s, 1H, =CHN).

N^6-(*N*,*N*'-Dimethylaminomethylene)-2'-*O*-*tert*-butyldimethylsilyl-5'-*O*-(4,4'-dimethoxytrityl)adenosine (3):

A mixture of compound **2** (0.312 g, 0.5 mmol), $AgNO_3$ (0.102 g, 0.6 mmol), *tert*-butyldimethylsilyl chloride (0.09 g, 0.6 mmol), pyridine (0.2 mL), and THF (2.0 mL) is stirred at room temperature for 2 h. After evaporation of the solvent, the material is poured into ice water (40 mL), the aqueous solution is extracted with EtOAc (3 × 10 mL), and dried (Na_2SO_4). The solvent is evaporated, and the crude product is

purified by column chromatography on silica gel with CH_2Cl_2/MeOH (95:5) as eluent to give compound **3** as a white foam; yield: 0.36 g (80%); $R_f = 0.65$ (TLC).

$C_{40}H_{50}N_6O_6Si$	calc.	C 65.00	H 6.83	N 11.30
(738.4)	found	65.39	7.13	11.26

UV (EtOH): $\lambda_{max} = 310.5$ nm.

^{1}H-NNR ($CDCl_3$): $\delta = 0.44$ (s, 6H, $SiMe_2$); 1.04 (s, 9H, SiC_4H_9-*t*); 3.00 (m, 1H, H-5'); 3.48 (d, 6H, NMe_2); 3.72 (m, 1H, H-4'); 4.04 (s, 6H, OCH_3); 4.52 (m, 1H, H-3'); 5.32 (m, 1H, H-2'); 6.32 (d, 1H, $J = 0.8$ Hz, H-1'); 7.00–7.68 (m, 13 H_{arom}); 8.36 (s, 1H, H-8); 8.76 (s, 1H, H-2); 9.24 (s, 1H, =CHN).

Moffat Oxidation of Compound 3:

Method A: Compound **3** (0.35 g, 0.47 mmol) is dissolved in a mixture of DMSO (20 mL), benzene (2 mL) and pyridine (40 µL) CF_3CO_2H (20 µL) and dicyclohexylcarbodiimide (0.4 g) are added. The mixture is stirred at 13 °C for 4 h, then oxalic acid (0.15 g) is added. After 30 min, the mixture is extracted with EtOAc (2 × 10 mL). The organic phase is washed with water (2 × 10 mL) and dried (Na_2SO_4). The solvent is evaporated, and the crude product is purified by column chromatography on silica gel using EtOAc as eluent to give **4** as a white foam; yield: 0.21 g (60%); $R_f = 0.63$ (TLC).

$C_{40}H_{48}N_6O_6Si$	calc.	C 65.18	H 6.57	N 11.40
(736.4)	found	65.12	6.67	11.76

UV (EtOH): $\lambda_{max} = 310$ nm.

IR (KBr): $\nu = 1783$ cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$): $\delta = 0.05$ (s, 6H, $SiMe_2$); 0.73 (s, 9H, SiC_4H_9-*t*); 3.24 (d, 6H, NMe_2); 3.47 (d, 2H, $J = 4.7$ Hz, H-5'); 3.72 (d, 6H, OCH_3); 4.28 (m, 1H, H-4'); 5.84 (d, 1H, $J = 2.9$ Hz, H-2'); 6.08 (d, 1H, H-1'); 6.70–7.60 (m, 13 H_{arom}); 8.04 (1H, H-8); 8.37 (s, 1H, H-2); 8.91 (s, 1H, =CHN).

^{13}C-NMR ($CDCl_3$): $\delta = 4.07$ ($SiCH_3$); 18.00 [$SiC(CH_3)_3$]; 25.33 [$SiC(CH_3)_3$]; 33.87 (NCH_3); 55.11 (OCH_3); 62.74 (C-5'); 76.50 (C-2'); 85.26 (C-4'); 86.53 (C-1'); 118.00 (C-5); 144.30 (C-8); 152.08 (C-4); 153.40 (C-2); 158.1(N=C); 158.60 (C-6); 208.56 (C-3').

MS (FAB): $m/z = 737$ ($M^+ + 1$).

Method B: Compound **3** is oxidized using the Moffat reagent as described in Method A, but in the presence of 3 fold excess of CF_3CO_2H at room temperature to give **4** and **5**.

4; yield: 0.094 g (27%), for analytical and spectral data, see above.

5; yield: 0.078 g (22%); $R_f = 0.48$ (TLC).

$C_{40}H_{48}N_6O_7Si$	calc.	C 63.80	H 6.43	N 11.17
(752.4)	found	63.63	6.73	11.40

UV (EtOH): $\lambda_{max} = 286$ nm.

IR (KBr): $\nu = 1780$ (C=O); 1607 cm^{-1} (HN–C=O).

^{1}H-NMR ($CDCl_3$): $\delta = 0.06$ (s, 6H, $SiMe_2$); 0.76 (s, 9H, SiC_4H_9-*t*); 2.88 (s, 6H, NMe_2); 3.50 (d, 2H, $J = 4.7$ Hz, H-5'); 3.78 (s, 6H, OCH_3); 4.23 (m, 1H, H-4'); 5.48 (d, 1H, $J = 2.9$ Hz, H-2'); 6.05 (d, 1H, $J = 2.9$ Hz, H-1'); 6.60–7.40 (m, 13 H_{arom}); 7.95 (s, 1H, H-8); 8.19 (s, 1H, H-2).

^{13}C-NMR ($CDCl_3$): $\delta = -4.76$ ($SiCH_3$); -5.37 ($SiCH_3$); 18.00 [$SiC(CH_3)_3$]; 25.39 [$SiC(CH_3)_3$]; 33.02 (NCH_3); 55.05 (OCH_3); 62.80 (C-5'); 76.54 (C-2'); 85.14 (C-4'); 86.67 (C-1'); 124.4 (C-5); 144.4 (C-8); 149.5 (C-4); 152.5 (C-2); 158.4 (C-6); 161.68 (NHCON); 208.85 (C-3').

MS (FAB): $m/z = 753$ ($M^+ + 1$).

5'-*O*-(4,4'-Dimethoxytrityl)-2'-*O*-*tert*-butyldimethylsilyl-β-D-xylofuranosyl-N^6-(*N*,*N*'-dimethylaminomethylene)adenine (6):

Compound **4** (0.2 g, 0.27 mmol) is dissolved in a mixture of THF (20 mL) and Et_3N (3 mL), then $NaBH_4$ (41 mg, 1.1 mmol) is added at −18 °C. The mixture is stirred at −18 °C for 2 h, and acetone (1 mL) is added. After 10 min, the solution is extracted with EtOAc (30 mL), the extract is washed with water (10 mL) and dried (Na_2SO_4). The solvent is evaporated, and the crude material is purified by column chromatography on silica gel using $CHCl_3$ as eluent to give **6** as a white foam; yield: 0.122 g (61%); $R_f = 0.45$ (TLC).

$C_{40}H_{50}N_6O_6Si$	calc.	C 65.00	H 6.83	N 11.30
(738.4)	found	65.39	7.13	11.78

UV (EtOH): $\lambda_{max} = 310$ nm.

^{1}H-NMR ($CDCl_3$): $\delta = 0.02$ (s, 6H, $SiMe_2$); 0.87 (s, 9H, SiC_4H_9-*t*); 3.25 (d, 6H, NMe_2); 3.57 (m, 2H, H-5'); 3.74 (s, 6H, OCH_3); 3.96 (d, 1H, $J = 2.4$ Hz, H-3'); 4.30 (m, 1H, H-4'); 4.47 (s, 1H, H-2'); 5.75 (s, 1H, H-1'); 6.75–7.40 (m, 13 H_{arom}); 8.03 (s, 1H, H-8); 8.45 (s, 1H, H-2); 9.05 (s, 1H, =CHN).

MS (FAB): $m/z = 739$ ($M^+ + 1$).

9-β-D-(Xylofuranosyl)adenine (7):

Compound **6** (100 mg, 0.135 mmol) is dissolved in a 5% solution of dichloroacetic acid in CH_2Cl_2 (5 mL). The mixture is stirred at r.t., 10 min and then neutralized by K_2CO_3. The mixture is washed with water (2 × 5 mL) and dried (Na_2SO_4). The solvent is evaporated, and the residue is stirred with THF (5 mL) and NH_4OH (25%, 2 mL) at room temperature for 12 h. The solvent is evaporated, and a solution of tetrabutylammonium fluoride in THF (1 M, 2 mL) is added, and the mixture is stirred at room temperature for 24 h. The solvent is evaporated and the residue is purified by column chromatography on silica gel using EtOAc/MeOH (9:2) to give a white solid; yield: 25 mg (70%); mp 155 °C (MeOH/ether); Lit.[8] mp 154–156 °C.

UV (MeOH): $\lambda_{max} = 259$ nm; Lit.[8] $\lambda_{max} = 259$ nm.

^{1}H-NMR (DMSO-d_6): $\delta = 3.64$ (m, 1H, H-5'); 3.82 (m, 1H, H-5'); 4.05 (m, 1H, H-3'); 4.14 (m, 1H, H-4'); 4.31 (d, 1H, $J = 0.5$ Hz, H-2'); 5.88 (d, 1H, $J = 0.5$, H-1'); 7.33 (s, 2H, NH_2); 8.14 (s, 1H, H-8); 8.26 (s, 1H, H-2).

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