Dideoxygenated Purine Nucleosides Substituted at the 8-Position: Chemical Synthesis and Stability[1]

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Synthesis of novel analogues of the largely unknown family of 8-substituted 2′,3′-dideoxyadenosines is described. Hydrolytic deamination of two of these analogues by mammalian adenosine deaminase was utilized for an enzymatic synthesis of 2′,3′-dideoxyinosine compounds. The glycosidic bond of 2′,3′-dideoxy-8-hydroxyadenosine is remarkably stable with respect to hydrolytic cleavage which is very unusual for a dideoxynucleoside.

2′,3′-Dideoxygenated analogues of the natural purine and pyrimidine nucleosides are known to be inhibitors of HIV reverse transcriptase, a key enzyme in the replication of the human immunodeficiency virus (HIV-1).[2,3] Recently, efforts have been made to increase the activity of dideoxynucleosides through selective modification of either the carbohydrate or base moieties. For example, dideoxypyrimidine analogues modified in both the ribose and pyrimidine base have been synthesized.[4-7] However, much more emphasis has been placed on carbohydrate modification due to the anti-HIV activity of 3′-azido-3′-deoxythymidine (AZT).[3] Dideoxypurine nucleosides are also of interest as 2′,3′-dideoxyadenosine (ddA) has a high anti-HIV selectivity index.[8] Modified dideoxyadenosines have been prepared in the quest for compounds with greater activity. Substituents introduced into the dideoxyribose moiety have generally resulted in decreased selectivity of the dideoxypurine analogues.[9] Dideoxyadenosine analogues with small group modifications at the 2- and 6-positions were found to retain anti-HIV activity.[8,10,11] Thus, in general, it appears that base modifications are better tolerated than changes in the dideoxyribose moiety. However, very little is known about dideoxynucleosides with specific modifications at the 8-position. With the exception of 8-bromo-2′,3′-dideoxyadenosine,[6] no 8-substituted dideoxyadenosine nucleoside is known. This paper reports on a generalized approach to novel dideoxyadenosine congeners with modifications at the 8-position. In addition, the enzymatic synthesis of two 8-substituted 2′,3′-dideoxyinosines is also described.

The key precursor for the syntheses was 8-bromoadenosine (**1**), prepared in high yield from adenosine.[12] The halogen atom in **1** is susceptible to displacement by appropriately chosen nucleophiles to provide 8-substituted adenosines.

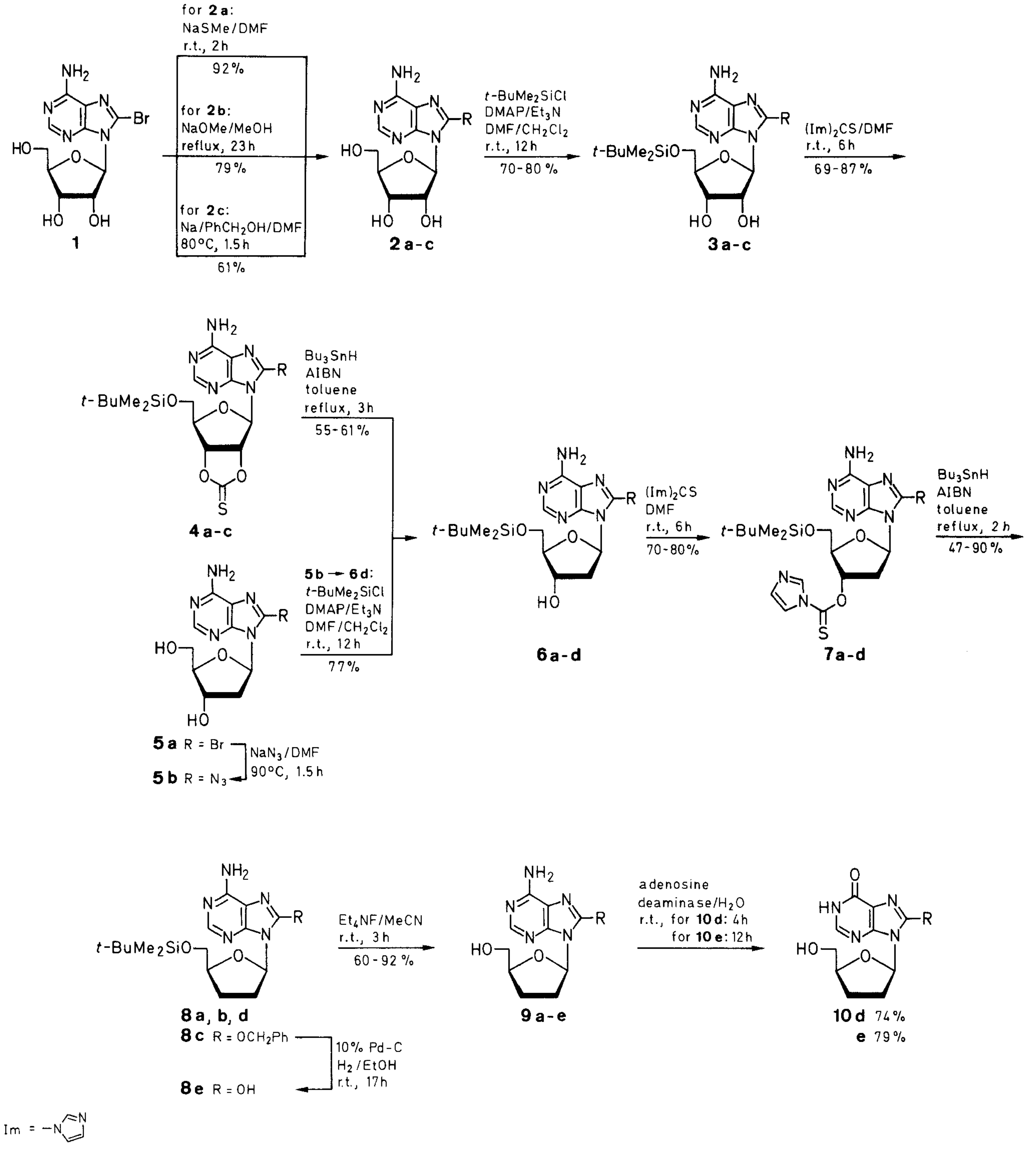
For example, 8-bromoadenosine underwent a very facile substitution when treated with sodium methanethiolate in dimethylformamide to give 8-methylthioadenosine (**2a**).[13] Compound **2a** was then dideoxygenated utilizing an approach recently described.[14] Thus, the 5′-hydroxyl group of 8-methylthioadenosine was selectively silylated and the hydroxyl groups at the 2′- and 3′-positions converted to the cyclic thiocarbonate **4a**. Radical deoxygenation of the thiocarbonate with tributyltin hydride and 2,2′-azobis(2-methylpropionitrile)[15] in refluxing toluene provided the 2′-deoxygenated compound **6a** as the major product. The 3′-hydroxyl group was then deoxygenated via the imidazolide **7a** to provide the protected dideoxynucleoside **8a**. Desilylation of **8a** with tetraethylammonium fluoride in acetonitrile gave 2′,3′-dideoxy-8-methylthioadenosine (**9a**). The dideoxynucleoside **9a** and the other dideoxynucleosides synthesized in this paper were fully characterized by FTIR, UV, and high-field NMR spectroscopy (see Table).

Oxygen nucleophiles also displace the halogen of **1**. 8-Methoxyadenosine (**2b**) was prepared by heating compound **1** with sodium methoxide in methanol.[16] Dideoxygenation of **2b** provided 2′,3′-dideoxy-8-methoxyadenosine (**9b**) in 15 % overall yield. The benzyloxy group was introduced at the 8-position by heating **1** with the sodium salt of benzyl alcohol to give 8-benzyloxyadenosine (**2c**) in good yield after purification by silica gel chromatography. Compound **2c** was dideoxygenated to the silylated dideoxynucleoside **8c** using the procedure outlined previously. Desilylation of **8c** gave 8-benzyloxy-2′,3′-dideoxyadenosine (**9c**).

The benzyloxy group can be considered as the protected form of the corresponding alcohol. Thus, catalytic hydrogenation (10% Pd–C, H_2, EtOH) of **8c** cleanly removed the benzyl group to produce the 8-hydroxy nucleoside **8e**. This compound was desilylated to the novel 2′,3′-dideoxy-8-hydroxyadenosine (**9e**). The FTIR (1711 cm^{-1}, lactam carbonyl) and NMR data (Table) suggest that 2′,3′-dideoxy-8-hydroxyadenosine exists entirely in the 8-carbonyl form. It should be mentioned that hydrogenation of the ribonucleoside, 8-benzyloxyadenosine (**2c**), provides an alternative route for the synthesis of 8-hydroxyadenosine.[16,17]

8-Bromo-2′-deoxyadenosine (**5a**)[12] served as the starting material for the preparation of 8-amino-2′,3′-dideoxyadenosine (**9d**). Compound **5a** was heated with sodium azide in dimethylformamide to give the 8-azidonucleoside **5b** in 91% yield.[16,18] Silylation of the 5′-hydroxyl group was followed by formation of the imidazolide **7d** as previously described. This nucleoside was subjected to the radical deoxygenation reaction which accomplished two things: firstly, the 3′-position was deoxygenated; and secondly, the azido functional group was reduced.[19] Desilylation of the resulting product, **8d**, provided the target molecule, 8-amino-2′,3′-dideoxyadenosine, **9d**, in good yield.

The stability of these new dideoxynucleosides with respect to deamination by the mammalian enzyme, adenosine deaminase, was investigated. This enzyme normally catalyzes the hydrolytic deamination of adenosine to inosine.[20,21] Adenosine deaminase is known to tolerate some substitution at the 8-position of adenosine with retention of minimal substrate activity.[22,23] It was found



2-4, 6, 7	R	5	R	8, 9	R	10	R
a	SMe	a	Br	a	SMe	d	NH_2
b	OMe	b	N_3	b	OMe	e	OH
c	OCH_2Ph			c	OCH_2Ph		
d	N_3			d	NH_2		
				e	OH		

that 8-amino ddA (**9d**) and 8-hydroxy ddA were deaminated by adenosine deaminase to the corresponding 8-substituted dideoxyinosine analogues **10d** and **10e**. The 8-substituent slows the rate of deamination to about 2% of the rate for the deamination of the natural substrate, adenosine. The methylthio, methoxy, and benzyloxy groups at the 8-position gave ddA analogues which were totally resistant to deamination by adenosine deaminase. Finally, it should be mentioned that the glycosidic bond of 2′,3′-dideoxy-8-hydroxyadenosine (**9e**) is stable towards hydrolytic cleavage even at pH 1 which is very unusual for a dideoxynucleoside. This remarkable stability of **9e** may be a result of the preferred lactam structure of the imidazole ring.

Melting points reported are uncorrected and were determined on a Thomas-Hoover apparatus fitted with a microscope. NMR spectra were recorded on JEOL Model FX 90Q and Bruker Model WM 360 and MSL 300 instruments. FTIR spectra were recorded on a Mattson Cygnus 25 Fourier transform instrument. UV data were determined using a Gilford Response spectrophotometer. Preparative layer chromatography plates were prepared by coating six 20 cm x 20 cm plates with a slurry made from 140 g of E. Merck PF_{254} silica gel in 400 mL of H_2O. The silica gel plates were allowed to dry slowly and were then activated for 3 h at 135 °C. Flash chromatography was carried out in glass columns packed with 230–400 mesh silica gel. Elemental analyses were determined by Galbraith Laboratories, Inc., Knoxville, TN.

2′,3′-Dideoxy-8-methylthioadenosine (8a):

8-Methylthioadenosine (**2a**):[13] To a solution of 8-bromoadenosine[12] (**1**; 0.502 g, 1.45 mmol) in dry DMF (10 mL) is added MeSNa (0.203 g, 2.90 mmol) and the solution is stirred for 2 h at r.t. The mixture is neutralized with 1 N HCl and the solvent evaporated under reduced pressure. The residue is purified by preparative layer chromatography using 10% MeOH/$CHCl_3$ as the eluting solvent to give **2a**; yield: 0.417 g (82%); mp 235–237 °C (Lit.[13] mp 230–233 °C).

^{1}H-NMR (DMSO-d_6): $\delta = 2.72$ (s, 3 H); 3.55 (m, 2 H), 3.96 (m, 1 H), 4.10 (m, 1 H); 4.95–5.14 (m, 2 H), 5.35–5.69 (m, 3 H), 7.23 (br s, 2 H), 8.05 (s, 1 H).

UV (EtOH): $\lambda_{max} = 279$ nm.

5′-O-tert-Butyldimethylsilyl-8-methylthioadenosine (**3a**): To a flask containing **2a** (0.809 g, 2.58 mmol) is added *t*-$BuMe_2SiCl$ (0.467 g, 3.09 mmol), *N*,*N*-dimethylaminopyridine (DMAP, 0.0407 g, 0.39 mmol), NEt_3 (0.37 mL, 2.66 mmol), CH_2Cl_2 (10 mL), and DMF (20 mL), and the resulting mixture is stirred for 12 h at r.t. The solvents are evaporated and the residue is purified by flash chromatography (5% MeOH/$CHCl_3$) to give **3a** as a low melting solid; yield: 0.863 g (78%).

^{1}H-NMR (DMSO-d_6): $\delta = -0.03$ (s, 6 H), 0.81 (s, 9 H), 2.71 (s, 3 H), 3.85 (m, 3 H), 4.31 (m, 1 H); 5.13–5.35 (m, 3 H), 5.73 (d, 1 H), 7.09 (br s, 2 H), 8.05 (s, 1 H).

5′-O-tert-Butyldimethylsilyl-8-methylthio-2′,3′-O-thiocarbonyladenosine (**4a**): A solution of **3a** (0.863 g, 2.02 mmol) and 1,1′-thiocarbonyldiimidazole (0.680 g, 3.43 mmol) in dry DMF (15 mL) is stirred for 6 h at r.t. The solvent is evaporated and the residue is purified by flash chromatography using 0–5% MeOH/$CHCl_3$ to provide **4a** as a low melting solid; yield: 0.821 g (87%).

^{1}H-NMR (DMSO-d_6): $\delta = -0.11$ (s, 6 H), 0.78 (s, 9 H), 2.72 (s, 3 H), 3.64 (m, 2 H), 4.48 (m, 1 H), 5.85 (m, 1 H), 6.27 (m, 1 H), 6.53 (m, 1 H), 7.27 (br s, 2 H), 8.07 (s, 1 H).

UV (EtOH): $\lambda_{max} = 279$ nm.

5′-O-tert-Butyldimethylsilyl-2′-deoxy-8-methylthioadenosine (**6a**): A nitrogen-purged solution of Bu_3SnH (1.64 mL, 6.11 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN, 0.229 g, 1.39 mmol) in toluene (30 mL) is added dropwise over 40 min to a refluxing solution of **4a** (0.820 g, 1.75 mmol) in toluene (40 mL). The reaction mixture is stirred at reflux for 2.5 h. The solvent is then evaporated under reduced pressure. The residue is purified by flash chromatography using hexane followed by 0–5% MeOH/$CHCl_3$ to give **6a** as an oil; yield: 0.442 g (61%).

^{1}H-NMR (DMSO-d_6): $\delta = -0.06$ (s, 6 H), 0.81 (s, 9 H), 2.25 (m, 2 H), 2.71 (s, 3 H), 3.74 (m, 3 H), 4.36 (m, 1 H), 5.30 (m, 1 H), 6.21 (m, 1 H), 7.06 (br s, 2 H), 8.05 (s, 1 H).

5′-O-tert-Butyldimethylsilyl-2′-deoxy-3′-O-(1-imidazolylthiocarbonyl)-8-methylthioadenosine (**7a**): A solution of **6a** (0.442 g, 1.07 mmol) and 1,1′-thiocarbonyldiimidazole (0.361 g, 1.82 mmol) in dry DMF (10 mL) is stirred for 5 h at 90 °C. Evaporation of the solvent gives a residue which is purified on silica gel with 0–5% MeOH/$CHCl_3$ to give **7a** as a low melting solid; yield: 0.420 g (76%).

^{1}H-NMR (DMSO-d_6): $\delta = -0.05$ (s, 6 H), 0.79 (s, 9 H), 2.73 (s, 3 H), 3.87 (m, 2 H), 4.25 (m, 1 H), 6.37 (m, 1 H), 7.12 (br s, 3 H), 7.89 (s, 1 H), 8.08 (s, 1 H), 8.58 (s, 1 H).

5′-O-tert-Butyldimethylsilyl-2′,3′-dideoxy-8-methylthioadenosine (**8a**): To a refluxing solution of **7a** (0.420 g, 0.81 mmol) in toluene (40 mL) is added dropwise over 30 min a solution of Bu_3SnH (0.65 mL, 2.42 mmol) and AIBN (0.105 g, 0.64 mmol) in toluene (30 mL). The mixture is stirred for 1.5 h at toluene reflux. The

Table. 8-Substituted 2′,3′-Dideoxyadenosines **9** Prepared

Product	Yield[a] (%)	mp[c] (°C)	Molecular Formula[d]	UV (H_2O) λ_{max} (ε)	IR (KBr)[e] ν (cm^{-1})	^{1}H-NMR[f] δ	^{13}C-NMR[f] δ
9a	10	197–199	$C_{11}H_{15}N_5O_2S$ (281.3)	277 (15300)	1651, 1600, 1292, 1052	2.20 (m, 4 H), 2.71 (s, 3 H), 3.51 (m, 2 H), 4.09 (m, 1 H), 5.11 (m, 1 H), 6.09 (m, 1 H), 7.12 (br s, 2 H), 8.06 (s, 1 H)	14.5, 26.9, 29.1, 63.9, 81.1, 85.3, 119.4, 149.2, 150.8, 151.3, 154.3
9b	15	197–199	$C_{11}H_{15}N_5O_3$ (265.3)	260 (11040)	1643, 1610, 1393, 1055	2.16 (m, 4 H), 3.51 (m, 2 H), 4.10 (m, 4 H), 5.01 (m, 1 H), 6.08 (m, 1 H), 6.85 (br s, 2 H), 8.03 (s, 1 H)	27.0, 28.9, 57.2, 64.0, 81.1, 83.3, 114.8, 148.8, 150.7, 153.9, 154.3
9c	16	149–151	$C_{17}H_{19}N_5O_3$ (341.4)	261 (13900)	1655, 1612, 1556, 1354	2.08 (m, 4 H), 3.43 (m, 2 H), 4.05 (m, 1 H), 4.94 (m, 1 H), 5.54 (s, 2 H), 6.10 (m, 1 H), 6.84 (br s, 2 H), 7.44 (m, 5 H), 8.04 (s, 1 H)	26.9, 28.8, 63.9, 71.2, 81.0, 83.1, 114.7, 128.4, 128.5, 135.4, 148.7, 150.7, 153.5, 153.9
9d	39[b]	177–179	$C_{10}H_{14}N_6O_2$ (251.2)	273.5 (13900)	3329, 3184, 1643	2.16 (m, 4 H), 3.61 (m, 2 H), 4.11 (m, 1 H), 5.54 (m, 1 H), 6.10 (m, 1 H), 6.40 (br s, 2 H), 6.52 (br s, 2 H), 7.89 (s, 1 H)	26.0, 29.0, 63.1, 79.5, 83.9, 117.1, 148.4, 148.9, 151.4, 152.3
9e	8	204–206	$C_{10}H_{13}N_5O_3$ (251.2)	265 (9500)	1711, 1653	2.10 (m, 4 H), 3.51 (m, 2 H), 4.01 (m, 1 H), 4.90 (m, 1 H), 5.99 (m, 1 H), 6.48 (br s, 2 H), 7.24 (br s, 1 H), 8.02 (s, 1 H)	27.0, 28.0, 64.1, 80.6, 82.3, 103.5, 146.6, 147.1, 150.7, 151.4

[a] Overall yield of isolated product from **1**.

[b] Overall yield of isolated product from **5a**.

[c] Uncorrected.

[d] Satisfactory microanalyses obtained: C ±0.33, H ±0.18, N ±0.50

[e] Recorded on a Mattson Cygnus 25 FTIR spectrophotometer.

[f] In DMSO-d_6, with TMS as internal reference.

solvent is evaporated and the residue purified by preparative layer chromatography (5% MeOH/$CHCl_3$) to give **8a** as a low melting solid; yield: 0.151 g (47%).

^{1}H-NMR (DMSO-d_6): $\delta = -0.10$ (s, 6H), 0.78 (s, 9H), 2.20 (m, 4H), 2.70 (s, 3H), 3.70 (m, 2H), 4.01 (m, 1H), 6.08 (m, 1H), 7.02 (br s, 2H), 8.05 (s, 1H).

UV: $\lambda_{max} = 278$ nm.

2',3'-Dideoxy-8-methylthioadenosine (**9a**): To a solution of **8a** (0.150 g, 0.38 mmol) in MeCN (15 mL) is added Et_4NF (0.5 M, 2.30 mL) and the resulting solution is stirred for 3 h at r.t.

Evaporation of the solvent gives a residue which is purified by preparative layer chromatography (10% MeOH/$CHCl_3$) to give **9a**; yield: 0.080 g (74%).

$C_{11}H_{15}N_5O_2S$	calc.	C 46.93	H 5.37	N 24.89
(281.3)	found	46.31	5.16	24.54

2',3'-Dideoxy-8-methoxyadenosine (9b):

8-Methoxyadenosine **2b**:[16] A solution of 8-bromoadenosine (**1**; 1.679 g, 4.85 mmol) and MeONa (0.688 g, 12.73 mmol) in MeOH (60 mL) is stirred at reflux for 23 h. The solvent is evaporated and the residue is purified by flash chromatography using 10% MeOH/$CHCl_3$ to give **2b**; yield: 1.145 g (79%); mp 205–207 °C (Lit.[16] mp 206–208 °C).

^{1}H-NMR (DMSO-d_6): $\delta = 3.59$ (m, 2H), 3.92 (m, 1H), 4.11 (m, 4H), 5.10 (d, 1H), 5.30–5.48 (m, 2H), 5.71 (d, 1H), 6.95 (br s, 2H), 8.03 (s, 1H).

UV (EtOH): $\lambda_{max} = 261$ nm.

5'-O-tert-Butyldimethylsilyl-8-methoxy-2',3'-O-thiocarbonyladenosine (**4b**): Using the procedures described for the preparation of **4a** from **2a**, 8-methoxyadenosine (**2b**; 1.132 g, 3.81 mmol) is silylated and converted to the thiocarbonate **4b** as a low melting solid; yield: 0.832 g (48%, 2 steps).

^{1}H-NMR (DMSO-d_6): $\delta = -0.09$ (s, 6H), 0.79 (s, 9H), 3.63 (d, 2H, $J = 6.8$ Hz), 4.12 (s, 3H), 4.42 (m, 1H), 5.80 (dd, 1H, $J = 2.9$, 7.8 Hz), 6.21 (d, 1H, $J = 1.5$ Hz), 6.45 (dd, 1H, $J = 1.5$, 7.3 Hz), 7.02 (br s, 2H), 8.04 (s, 1H).

5'-O-tert-Butyldimethylsilyl-2',3'-dideoxy-8-methoxyadenosine (**8b**): Compound **4b** (0.830 g, 1.83 mmol) is dideoxygenated as previously described to give **8b** as a low melting solid; yield: 0.358 g (51.5%, 3 steps).

^{1}H-NMR (DMSO-d_6): $\delta = -0.07$ (s, 6H), 0.79 (s, 9H), 2.21–2.77 (m, 4H), 3.64 (m, 2H), 4.09 (m, 4H), 6.10 (m, 1H), 6.79 (br s, 2H), 8.03 (s, 1H).

UV (EtOH): $\lambda_{max} = 260$ nm.

2',3'-Dideoxy-8-methoxyadenosine (**9b**): Compound **8b** (0.152 g, 0.40 mmol) is desilylated as described for the preparation of **9a** to give **9b**; yield: 0.0825 g (79%).

$C_{11}H_{15}N_5O_3$	calc.	C 49.81	H 5.70	N 26.40
(265.3)	found	49.52	5.81	26.19

8-Benzyloxy-2',3'-dideoxyadenosine (9c):

8-Benzyloxy-5'-O-tert-butyldimethylsilyl-2',3'-thiocarbonyladenosine (**4c**): 8-Bromoadenosine (**1**; 2.122 g, 6.13 mmol) is added to a mixture of Na (0.500 g, 21.7 mmol) in $PhCH_2OH$ (12.5 mL) and DMF (40 mL) and the resulting mixture stirred for 1.5 h at 80 °C. The mixture is neutralized with conc. AcOH and the solvents evaporated. The residue is purified on silica gel with 5–10% MeOH/$CHCl_3$ to provide **2c**; yield: 1.40 g (61%).

Compound **2c** (1.333 g, 3.57 mmol) is then silylated and converted to the thiocarbonate as previously described to give **4c** as a low melting solid; yield: 1.225 g (65%).

^{1}H-NMR (DMSO-d_6): $\delta = -0.13$ (s, 6H), 0.77 (s, 9H), 3.60 (d, 2H), 4.36 (m, 1H), 5.55 (s, 2H), 5.71 (dd, 1H), 6.25 (m, 1H), 6.48 (m, 1H), 7.02 (br s, 2H), 7.45 (m, 5H), 8.05 (s, 1H).

8-Benzyloxy-5'-O-tert-butyldimethylsilyl-2',3'-dideoxyadenosine (**8c**): Compound **4c** (1.225 g, 2.31 mmol) is dideoxygenated as described previously to give **8c** as a low melting solid; yield: 0.534 g (51%).

^{1}H-NMR (DMSO-d_6): $\delta = -0.10$ (s, 6H), 0.78 (s, 9H), 2.12 (m, 4H), 3.55 (d, 2H), 4.00 (m, 1H), 5.54 (s, 2H), 6.14 (m, 1H), 6.79 (br s, 2H), 7.44 (m, 5H), 8.05 (s, 1H).

UV (EtOH): $\lambda_{max} = 259$ nm.

8-Benzyloxy-2,3-dideoxyadenosine (**9c**): Compound **8c** (0.099 g, 0.22 mmol) is desilylated following the procedure for preparing **9a** to give **9c**; yield: 0.061 g (82%).

$C_{17}H_{19}N_5O_3 \cdot 0.5\ H_2O$	calc.	C 58.28	H 5.75	N 19.99
(341.4)	found	58.30	5.60	19.58

2',3'-Dideoxy-8-hydroxyadenosine (9e):

5'-O-tert-Butyldimethylsiloxy-2',3'-dideoxy-8-hydroxyadenosine (**8e**): To a solution of **8c** (0.429 g, 0.94 mmol) in absolute EtOH (75 mL) is added 10% Pd-C (0.290 g) and the resulting mixture is shaken under H_2 (36 psi) for 17 h. The catalyst is removed by filtration and the solvent evaporated. Purification of the residue by preparative layer chromatography (7% MeOH/$CHCl_3$) provides **8e** as a low melting solid; yield: 0.226 g (66%).

^{1}H-NMR (DMSO-d_6): $\delta = -0.04$ (s, 6H), 0.82 (s, 9H), 2.22 (m, 4H), 3.70 (m, 2H), 3.99 (m, 1H), 6.01 (m, 1H), 6.43 (br s, 2H), 8.01 (s, 1H).

UV (EtOH): $\lambda_{max} = 270$ nm, 256 nm.

2',3'-Dideoxy-8-hydroxyadenosine (**9e**): Compound **8e** (0.223 g, 0.61 mmol) is desilylated via the procedure previously described for **9a** to give **9e**; yield: 0.0922 g (60%).

$C_{10}H_{13}N_5O_3$	calc.	C 47.81	H 5.22	N 27.88
(251.2)	found	47.33	5.16	26.77

FAB HRMS: calc. ($M^+ + H$) 252.1097, found 252.1071.

8-Amino-2',3'-dideoxyadenosine (9d):

8-Azido-2'-deoxyadenosine (**5b**): To a solution of 8-bromo-2'-deoxyadenosine (**5a**)[12] (0.403 g, 1.22 mmol) in DMF (25 mL) is added NaN_3 (0.278 g, 4.27 mmol) and the mixture stirred for 1.5 h at 90 °C. The solvent is removed and the residue purified by flash chromatography (10% MeOH/$CHCl_3$) to give **5b**; yield: 0.325 g (91%); mp dec > 185 °C.

UV (EtOH): $\lambda_{max} = 282.5$ nm.

FTIR (KBr): $\nu = 2155\ cm^{-1}$.

8-Azido-5'-O-tert-butyldimethylsilyl-2'-deoxy-3'-O-(1-imidazolylthiocarbonyl)adenosine (**7d**): Compound **7d** (low melting solid) is formed in 61% from **5b** via silylation of the 5'-hydroxyl group and formation of the 3'-imidazolide as previously described.

UV: $\lambda_{max} = 278$ nm.

FTIR (KBr): $\nu = 2145\ cm^{-1}$.

8-Amino-5'-O-tert-butyldimethylsilyl-2',3'-dideoxyadenosine (**8d**): Compound **7d** (0.193 g, 0.37 mmol) is deoxygenated as previously described to give **8d** as a low melting solid; yield: 0.1056 g (77%).

^{1}H-NMR (DMSO-d_6): $\delta = 0.00$ (s, 6H), 0.84 (s, 9H), 2.16 (m, 4H), 3.73 (m, 2H), 4.09 (m, 2H), 6.06 (m, 1H), 6.33 (br s, 4H), 7.89 (s, 1H).

UV (EtOH): $\lambda_{max} = 273.5$ nm.

8-Amino-2',3'-dideoxyadenosine (**9d**): Desilylation of **8d** (0.1014 g, 0.28 mmol) provides **9d**; yield: 0.064 g (92%).

$C_{10}H_{14}N_4O_2 \cdot 0.5\ H_2O$	calc.	C 46.33	H 5.83	N 32.41
(251.2)	found	46.56	5.48	31.98

8-Amino-2',3'-dideoxyinosine (10d):

Compound **9d** (0.0598 g, 0.24 mmol) is dissolved in H_2O and excess adenosine deaminase is added. The mixture is allowed to stand at r.t. for 4 h. The H_2O is evaporated and the residue purified by preparative layer chromatography (10% MeOH/$CHCl_3$) to give **10d**; yield: 0.044 g (74%); mp dec > 230 °C.

^{1}H-NMR (DMSO-d_6): $\delta = 2.22$ (m, 4H), 3.73 (m, 2H), 4.10 (m, 1H), 5.30 (m, 1H), 6.10 (m, 1H), 6.44 (br s, 2H), 7.78 (s, 1H).

UV (H_2O): $\lambda_{max} = 266.5$ nm.

FTIR (KBr): $\nu = 1684\ cm^{-1}$.

2′,3′-Dideoxy-8-hydroxyinosine (10e):
Compound **9e** (0.021 g, 0.08 mmol) is dissolved in H_2O and excess adenosine deaminase (Type 1 from calf intestinal mucosa, Sigma) is added. The reaction is allowed to stand at r. t. and is monitored by UV spectroscopy.[24] After 12 h the H_2O is evaporated and the residue is purified by preparative layer chromatography (10% $MeOH/CHCl_3$) to give **10e**; yield: 0.0166 g (79%); mp 181–183 °C.

^{1}H-NMR (DMSO-d_6): $\delta = 2.00$ (m, 1 H), 2.19 (m, 2 H), 2.59 (m, 1 H), 3.51 (m, 2 H), 3.98 (m, 1 H), 4.80 (br s, 1 H), 5.96 (m, 1 H), 7.96 (s, 1 H).

UV (H_2O): $\lambda_{max} = 256$ nm.

FTIR (KBr): $\nu = 1716, 1680\ cm^{-1}$.

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