A Convenient Preparation of 9-(3′-Deoxy-β-D-*threo*-pentofuranosyl)-adenine and 9-[3′-Deoxy-3′-(*S*)-deuterio-β-D-2′-(*S*)-pentofuranosyl]-adenine

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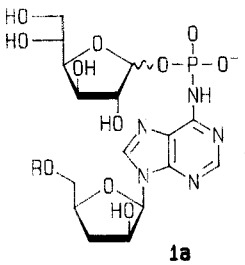
A new procedure is described for the synthesis of the title compounds by lithium aluminium hydride or deuteride reduction of appropriately protected 2′,3′-anhydro-*lyxo*-adenosine.

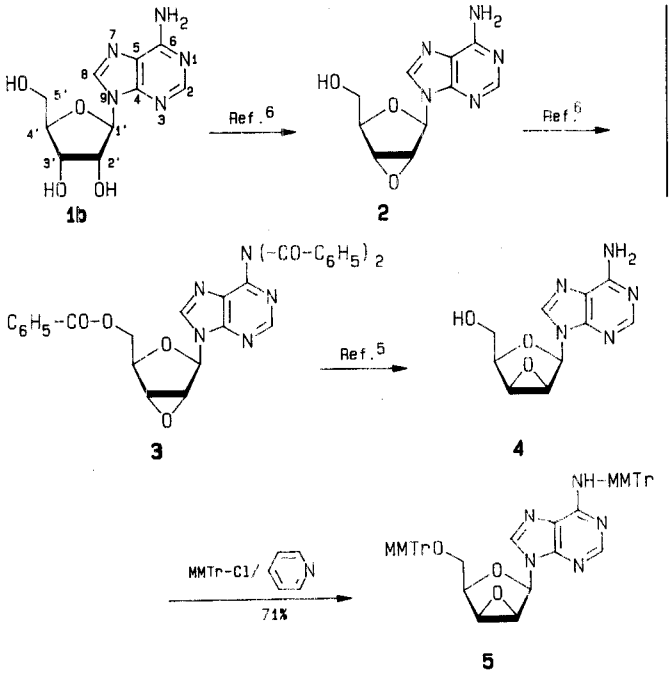
Agrocin 84 is a naturally occurring nucleotide antibiotic[1] whose partial structure only is known. It is an adenosine derivative with a 6-*N*-phosphoramidate linkage to glucofuranose and the ribofuranosyl moiety of adenosine is replaced, as shown in **1a**, by the 3-deoxy-D-*threo*-pentofuranosyl moiety.



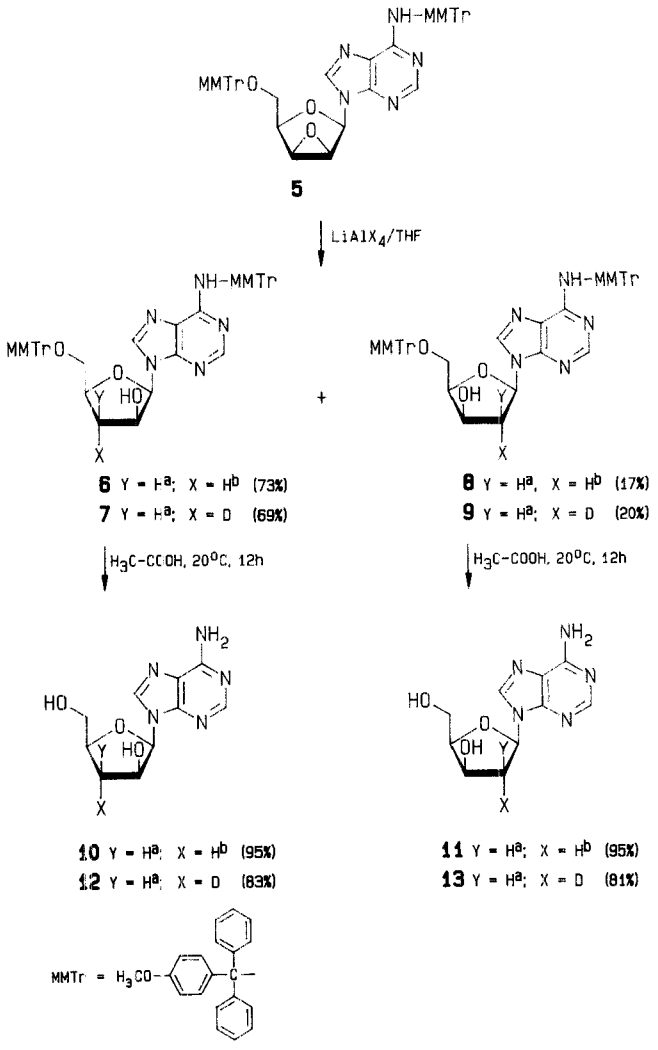
1a

R = unidentified carbohydrate moiety

Such an adenine nucleoside, as in **1a**, has been earlier prepared[2,3,4] through multistep procedures. We report here that reaction of an appropriately protected *lyxo*-epoxide[5] **5** (**1b** → **2** → **3** → **4** → **5**) with an excess of lithium aluminium hydride gives the desired 9-(3′-deoxy-β-D-*threo*-pentofuranosyl)-adenine derivative (**6**) in 73% yield; 9-(2′-deoxy-β-D-*threo*-pentofuranosyl)-adenine (**8**) was also obtained in the same reaction as a by-product in 17% yield. Use of lithium aluminium deuteride resulted in an analogously clean conversion of **5** into the 9-[3′-(*S*)-deuterio-3′-deoxy-β-D-2′-(*S*)-pentofuranosyl]adenine derivative (**7**) in 61% yield and the 9-[3′-(*R*)-2′-deoxy-2′-(*R*)-2′-deuterio-β-D-pentofuranosyl]-adenine derivative (**9**) in 20% yield. Since, this reduction takes place in a S_N2 fashion[7], the epoxide **5** will be opened specifically from the α-face. The latter sequence, therefore, (**5** → **7** + **9**) opens the possibility to incorporate the deuterium labellings at the 3′- and 2′-carbons stereospecifically with 3(*S*) and 2(*R*) configurations, respectively.



1b **2** **3** **4** **5**



Finally, the protecting group [4-methoxytriphenylmethyl-(MMTr)] was cleaved from **6**–**9** by using 80% acetic at 20 °C to give **10**–**13**, respectively, in 80 to 95% yields.

Specific deuterium labellings in **12** and **13** enabled us for the first time to assign all coupling constants of the sugar protons of **10** and **11** respectively (experimental section). It may be added that either the reduction of 9-(3-deoxy-5′-*O*-trityl-β-D-*glycero*-pentofuran-2-ulosyl)-adenine with sodium borodeuteride[3] or the lithium triethylborodeuteride[4] reduction of 3′-*O*-tosyladenosine allow the preparation of 9-(3′-deoxy-2′-deuterio-β-D-*threo*-pentofuranosyl)-adenine; while the reduction of 2′-*O*-tosyladenosine with the latter reagent[4] gives 9-(2′-deoxy-3′-deuterio-β-D-pentofuranosyl)-adenine. Since these reactions[3,4] enable the introduction of deuterium to the hydroxy-bearing carbon, our reaction provides convenient access to the deuterium labelling at the deoxygenated carbon center.

Reactions were monitored by T.L.C. using Merck pre-coated silica gel 60 F_{254} plates using the following solvent systems: (A) 5% ethanol/dichloromethane (v/v); (B) ethyl acetate/cyclohexane (3:2, v/v); (C) 20% methanol/chloroform (v/v). ^{1}H- and ^{13}C-N.M.R. spectra were recorded (tetrametyhlsilane as an internal standard (δ values) using a Jeol FX 90 Q spectrometer. U.V. spectra were recorded in ethanol with a Cary 2200 spectrometer. Specific rotations were measured using a Perkin-Elmer 241 polarimeter.

6-*N*-5′-*O*-Bis[4-methoxytriphenylmethyl]-2′,3′-*lyxo*-anhydroadenosine (5):

Dry 2′,3′-anhydro-*lyxo*-adenosine[5,6,7] (**4**; 0.957 g, 3.8 mmol) is dissolved in dry pyridine (60 ml), 4-methoxytriphenylmethyl chloride (2.96 g, 9.6 mmol) is added, and the mixture is stirred (protected from light) at 60 °C for 20 h. T.L.C. [solvent system (A)] then shows one major spot (R_f = 0.45). Methanol (10 ml) is added, and the mixture is stirred for 2 h, is then poured into saturated aqueous sodium hydrogen carbonate (150 ml), and extracted with dichloromethane (2 × 100 ml). Organic layers are pooled and evaporated in vacuo to give a light brown foam which is dissolved in methanol/tetrahydrofuran (1:1, v/v), and treated with Dowex $OH^{\ominus}$ for 16 h at 20 °C. The supernatant is filtered and concentrated to a foam which is dissolved in dichloromethane/petroleum ether (6:4 v/v), loaded onto a short column of silica gel, and is eluted with ethanol/dichloromethane. Appropriate fractions are pooled and evaporated leaving a white foam which is dissolved in diethyl ether/tetrahydrofuran (30 ml, 8:2 v/v) and precipitated with petroleum ether (100 ml). The supernatant is evaporated and precipitated again using the same solvents; yield: 2.17 g (71%); $[\alpha]_D^{20}$: −37.7° (*c*, 0.54, chloroform); R_f: 0.5 (A), 0.5 (B).

U.V.: λ_{max} = 275 nm (ε = 24900).

M.S. (chemical ionization, NH_3): *m/e* = 794.9 (83%, M^+).

^{1}H-N.M.R. ($CDCl_3$): δ = 8.05 (s, 2H, H-8, H-2); 7.29 (m, 24H, MMTr); 6.29 (s, 1H, H-1′); 4.22 (m, 1H, H-4′); 4.0 (s, 2H, H-2′, -3′); 3.78 (s, 3H), 3.76 (s, 3H), OCH_3); 3.44 ppm (m, 2H, H-5′).

^{13}C-N.M.R. ($CDCl_3$): δ = 86.9 (C-1′); 80.9 (C-4′); 77.0 (C-5′); 57.1 (C-2′); 56.5 ppm (C-3′).

6-*N*-(4-Methoxytriphenylmethyl)-9-(5′-*O*-4-methoxytriphenylmethyl)-3′-deoxy-β-D-*threo*-pentofuranosyl)-adenine (6) and 6-*N*-(4-Methoxytriphenylmethyl)-9-]5′-*O*-(4-methoxytriphenylmethyl)-2′-deoxy-β-D-*threo*-pentofuranosyl]-adenine (8):

Dry 6-*N*-5′-*O*-bis[4-methoxytriphenylmethyl]-2′,3-anhydro-*lyxo*-adenosine (**5**; 2.74 g, 3.44 mmol) in dry tetrahydrofuran (50 ml) is added dropwise over a period of 30 min to a stirred suspension of lithium aluminium hydride (0.81 g, 21.3 mmol) in dry tetrahydrofuran (150 ml; distilled from lithium aluminium hydride before use) under argon at 0 °C. After stirring for 180 min at 20 °C, the mixture is cooled in an ice bath and a mixture of water (10 ml) and tetrahydrofuran (40 ml) is added slowly. A 20% aqueous solution of sodium dihydrogen phosphate (30 ml) is then added followed by water (100 ml). The mixture is poured in a separating funnel and extracted with ethyl acetate (3 × 100 ml). The organic phase is washed with aqueous sodium hydrogen carbonate solution and evaporated in vacuo. The residue is dissolved in dichloromethane (~ 15 ml) and coevaporated with hexane (3 times) to give a white foam. This is dissolved in dichloromethane/petroleum ether (6:4 v/v) and loaded onto a silica gel column which is eluted first with the latter solvent mixture and then with dichloromethane and chloroform. Evaporation of the appropriate fractions gives **6** and **8** which are isolated as amorphous solids.

Compound **6**; yield: 1.99 g (73%); $[\alpha]_D^{20}$: +41° (*c* 0.514, chloroform); R_f: 0.35 (A), 0.37 (B).

U.V.: λ_{max} = 275 nm (ε = 23600).

M.S. (chemical ionization, NH_3): *m/e* = 796.9 (31.6%, M^+).

^{1}H-N.M.R. ($CDCl_3$): δ = 8.2 (s, 1H, H-8); 7.99 (s, 1H, H-2); 7.27 (m, 24H, MMTr); 6.04 (d, 1H, $J_{1',2'}$ = 3.7 Hz, H-1′); 4.53 (m, 1H, H-2′); 4.33 (m, 1H, H-4′); 3.88 (ddd, 2H, $J_{4',5'\text{-}H^a}$ = 2.4 Hz; $J_{4',5'\text{-}H^b}$ = 4 Hz; $J_{5'\text{-}H^a,H^b}$ = 10 Hz, H-5′); 3.77 (s, 6H, OCH_3); 2.3 ppm (m, 2H, H-3′).

^{13}C-N.M.R. ($CDCl_3$): δ = 87.2 (C-1′); 78.4 (C-4′); 71.0 (C-2′); 55.0 (OCH_3); 35.0 ppm (C-3′).

Compound **8**; yield: 0.46 g (17%; $[\alpha]_D^{20}$: −21° (*c*, 0.476, chloroform); R_f: 0.37 (A), 0.25 (B).

U.V.: λ_{max} = 275 nm (ε = 26200).

M.S. (chemical ionization, NH_3): *m/e* = 796.9 (19.4%, M^+).

^{1}H-N.M.R. ($CDCl_3$): δ = 7.92 (s, 1H, H-8); 7.63 (s, 1H, H-2); 7.27 (m, 24H, MMTr); 6.04 (dd, 1H, $J_{1',2'}$ = 8.5 Hz, 9.3 Hz, H-1′); 4.33 (m, 1H, H-3′); 3.99 (m, 1H, H-4′); 3.75 (s, 3H); 3.77 (s, 3H, OCH_3); 3.5 (m, 2H, H-5′); 2.8 (ddd, 1H, $J_{2'\text{-}H^a,H^b}$ = 15.1 Hz, H^b-2′); 2.44 ppm (dd, 1H, H^a-2′).

^{13}C-N.M.R. ($CDCl_3$): δ = 86.7 (C-1′); 84.6 (C-4′); 70.7 (C-3′); 55.0 (OCH_3); 40.7 ppm (C-2′).

6-*N*-(4-Methoxytriphenylmethyl)-9-[5′-*O*-4-methoxytriphenylmethyl-2′-(*S*)-3′-(*S*)-deuterio-3′-deoxy-β-D-pentofuranosyl]-adenine (7) and 6-*N*-(4-Methoxytriphenylmethyl)-9-[5′-*O*-4-methoxytriphenylmethyl-2′-deoxy-2′-(*R*)-deuterio-3′-(*R*)-β-D-pentofuranosyl]-adenine (9):

Compound **5** (1.79 g, 2.25 mmol) in dry tetrahydrofuran is (45 ml) is treated with lithium aluminium deuteride (0.54 g, 98 atom % D) using the same procedure as described above to yield **7** and **9** which also do not crystallize in our hands.

Compound **7**; yield: 1.09 g (61%); $[\alpha]_D^{20}$: +5.28° (*c* 0.492, chloroform); R_f: 0.32 (A), 0.37 (B).

U.V.: λ_{max} = 275 nm (ε = 25000).

M.S. (chemical ionization, NH_3): *m/e* = 797.9 (29.7%, M^+), 796.9 (0.58%).

^{1}H-N.M.R. ($CDCl_3$): δ = 8.2 (s, 1H, H-8); 7.99 (s, 1H, H-2); 7.27 (*m*, 24H), MMTr); 6.04 (d, 1H, $J_{1',2'}$ = 3.18 Hz, H-1′); 4.51 (dd, 1H, $J_{2',3'\text{-}H^a}$ = 4.15 Hz, H-2′); 4.3 (m, 1H, H-4′); 3.76 (s, 6H, OCH_3); 3.39 (ddd, 2H, $J_{4',5'\text{-}H^a}$ = 2.68 Hz, $J_{4',5'\text{-}H^b}$ = 4.15 Hz, $J_{5'\text{-}H^a,H^b}$ = 10.74 Hz, H-5′); 2.10 ppm (dd, 1H, 3′-H^a).

^{13}C-N.M.R. ($CDCl_3$): δ = 87.2 (C-1′); 76.3 (C-4′); 71.2 (C-2′) 65.5 (C-5′), 55.0 (OCH_3), 34.6 ppm (C-3′).

Compound **9**; yield: 0.36 g (20%); $[\alpha]_D^{20}$: −24° (*c* 0.5, chloroform); R_f: 0.37 (A), 0.26 (B)

U.V.: λ_{max} = 275 nm (ε = 24100).

M.S. (chemical ionization, NH_3): *m/e* = 797.9 (28.9%, M^+), 796.9 (0.54%).

^{1}H-N.M.R. ($CDCl_3$): δ = 7.89 (s, 2H, H-8, H-2); 7.27 (m, 24H, MMTr); 6.02 (d, 1H, $J_{1',2'}$ = 2.1 Hz, H-1′); 4.33 (d, 1H, $J_{2',3'}$ = 3.2 Hz, H-3′); 3.97 (m, 1H, H-4′); 3.54 (m, 2H, H-5′); 2.44 ppm (d, 1H, 2′-H^a).

^{13}C-N.M.R. ($CDCl_3$): δ = 84.5 (C-1′); 83.9 (C-4′); 70.6 (C-3′); 62.6 (C-5′); 40.4 ppm (C-2′).

Deprotection of Compounds 6,7,8, and 9; General Procedure:

A stirred suspension of the protected substrate **6**, **7**, **8**, or **9** in a mixture of acetic acid/water (100 ml, 8:2 v/v) is kept at 20 °C for 12 h. After evaporation in vacuo the residue is coevaporated several

times with toluene. The residue is taken up in water (150 ml) and washed with diethyl ether (3 × 10 ml). The aqueous layer is lyophylized to give either **10**, **11**, **12**, or **13**.

Compound **10**; yield: 0.226 g (95%); m.p. 194–195°C (Ref.[2], m.p. 195–196°C); $[\alpha]_D^{20}$: +20.9° (*c* 0.516, methanol); R_f: 0.33 (C).

M.S. (chemical ionization, NH_3): *m/e* = 252.2 (79.4%, M^+).

^{1}H-N.M.R. (DMSO-d_6): δ = 8.29 (s, 1 H, H-8); 8.13 (s, 1 H, H-2); 7.2 (br. s, 2 H, NH_2); 6.14 (d, 1 H, $J_{1',2'}$ = 5.4 Hz, H-1'); 4.5 (dd, 1 H, $J_{2',3'}$ = 6.9 Hz, H-2'); 4.09 (m, 1 H, H-4'); 3.61 (m, 2 H, H-5'); 2.17 ppm (ddd, $J_{2'\text{-H}^a,\text{H}^b}$ = 13.2 Hz, H-3').

^{13}C-N.M.R. (DMSO-d_6): δ = 155.8; 152.3; 149.5; 142.2; 140.3; 118.3; 84.7 (d, J_{CH} = 174.0 Hz, C-1'); 78.0 (d, J_{CH} = 144.9 Hz, C-4'); 70.2 (d, J_{CH} = 150.5 Hz, C-2'); 33.8 ppm (t, J_{CH} = 131.4 Hz, C-3').

Compound **11**; yield: 0.205 g (95%); m.p. 197–198°C; $[\alpha]_D^{20}$: +27.2° (*c* 0.492, water); R_f: 0.27 (c).

$C_{10}DH_{12}N_5O_3$	calc.	C 47.62	H/D 5.59	N 27.76
(252.25)	found	47.51	5.69	27.93

U.V.: λ_{max} = 259 nm (ε = 13600).

M.S. (chemical ionization, NH_3): *m/e* = 253.2 (68.9%, M^+), 252.2 (1.28%).

^{1}H-N.M.R. (DMSO-d_6): δ = 8.29 (s, 1 H, H-8); 8.13 (s, 1 H, H-2); 7.21 (br. s, 2 H, NH_2); 6.16 (d, 1 H, $J_{1',2'}$ = 5.1 Hz, H-1'); 4.5 (dd, 1 H, $J_{2',3'}$ = 7.1 Hz, H-2'); 4.09 (dd, $J_{3',4'}$ = 7.6 Hz; $J_{4',5'}$ = 3.7 Hz, H-4'); 3.62 (m, 2 H, H-5'); 2.0 ppm (dd, 1 H, H-3).

^{13}C-N.M.R. (DMSO-d_6): δ = 155.8; 152.3; 149.5; 140.2; 118.3; 84.6 (d, J_{CH} = 162.8 Hz, C-1'); 77.8 (d, J_{CH} = 144.9 Hz, C-4'); 70.1 (d, J_{CH} = 148.3 Hz, C-2'); 62.7 (t, J_{CH} = 146.0 Hz, C-5'); 33.6 ppm (t, J_{CH} = 17.9 Hz, C-3').

Compound **12**; yield: 0.12 g (83%); m.p. 217–218.5°C (Ref.[2], m.p. 218.9–219.5°C); $[\alpha]_D^{20}$: −26.7° (*c* 0.43, water); R_f: 0.29 (c).

U.V.: λ_{max} = 259 nm (ε = 14000).

M.S. (chemical ionization, NH_3): *m/e* = 252.2 (73.5%, M^+).

^{1}H-N.M.R. (DMSO-d_6): δ = 8.41 (s, 1 H, H-8); 8.21 (s, 1 H, H-2); 7.31 (br. s, 2 H, NH_2); 6.32 (dd, 1 H, $J_{1',2'\text{-H}^a}$ = 2.2 Hz; $J_{1',2'\text{-H}^b}$ = 5.1 Hz, H-1'); 5.96 (d, $J_{3',OH}$ = 5.6 Hz, 3'-OH); 4.68 (t, 1 H, $J_{5',OH}$ = 4.7 g, H-5'); 4.33 (m, 1 H, H-3'); 3.87 (m, 1 H, H-4'); 3.7 (m, 2 H, H-5'); 2.76 (ddd, 1 H, $J_{3',2'\text{-H}^b}$ = 5.86 Hz, 2'-H^b); 2.24 ppm (dd, $J_{2'\text{-H}^a,\text{H}^b}$ = 14.1 Hz, 2'-H^a).

^{13}C-N.M.R. (DMSO-d_6 + CD_3OD; 7:3 v/v): δ = 156.3; 152.6; 148.8; 140.8; 119.4; 88.5 (d, J_{CH} = 148.3 Hz, C-4'); 83.4 (d, J_{CH} = 165.1 Hz, C-1'); 69.8 (d, J_{CH} = 152.8 Hz, C-3'); 60.4 (t, J_{CH} = 138.2 Hz, C-5'); 41.0 ppm (t, J_{CH} = 134.1 Hz, C-2').

Compound **13**; yield: 0.09 g (81%); m.p. 219–220°C; $[\alpha]_D^{20}$: −18.5°C (*c* 0.4, water); R_f: 0.25 (c).

$C_{10}DH_{12}N_5O_3$	calc.	C 47.62	H/D 5.59	N 27.78
(252.25)	found	47.43	5.78	27.78

U.V.: λ_{max} = 259 nm (ε = 13000).

M.S. (chemical ionization, NH_3): *m/e* = 253.2 (71.4%, M^+); 252.2 (1.38%).

^{1}H-N.M.R. (DMSO-d_6): δ = 8.37 (s, 1 H, H-8); 8.16 (s, 1 H, H-2); 6.26 (d, 1 H, $J_{1',2'\text{-H}^a}$ = 2.4 Hz, H-1'); 4.33 (d, 1 H, $J_{3',4'}$ = 2.0 Hz, H-3'); 3.91 (m, 1 H, H-4'); 3.7 (m, 2 H, H-5'); 2.25 ppm (d, 1 H, 2'-H^a).

^{13}C-N.M.R. (DMSO-d_6): δ = 85.0 (d, J_{CH} = 153.8 Hz, C-4'); 84.3 (d, J_{CH} = 170.8 Hz, C-1'); 69.0 (d, J_{CH} = 144.9 Hz, C-3'); 59.8 ppm (t, J_{CH} = 140.4 Hz, C-5'); C-2' absorption was not detectable.

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