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THE FACILE SYNTHESIS OF 2'-AZIDO-2',3'-DIDEOXYADENOSINE. PREPARATIVE APPLICATIONS OF THE DEOXYGENATIVE [1,2]-HYDRIDE SHIFT AND β-ELIMINATION REACTIONS OF SULFONATES WITH $Mg(OMe)_2$-$NaBH_4$

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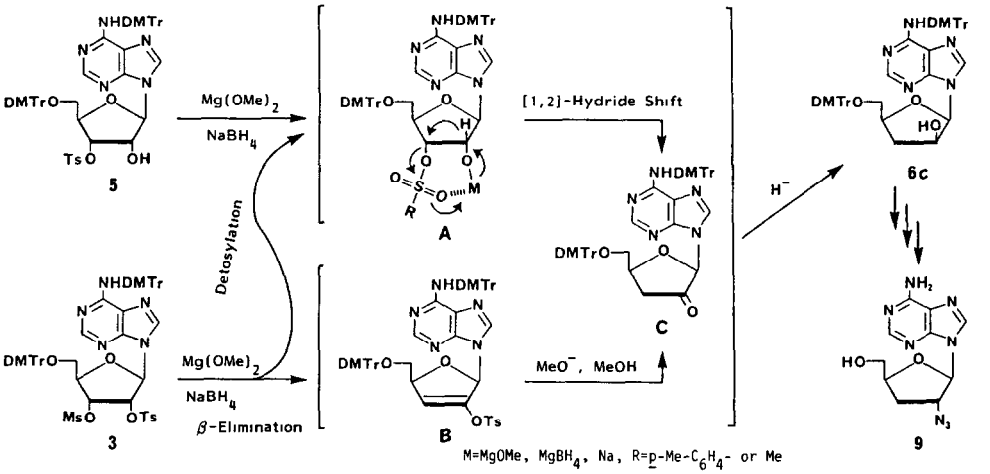
Abstract: The title compound was easily prepared in 37 or 51% overall yield from 2'- or 3'-O-tosyladenosine, respectively, in 5 - 6 steps without isolation of any intermediates. A key intermediate was synthesized by the title reactions in a one-pot procedure.

Recently much attention has been given to the synthesis and biological evaluation of 2',3'-dideoxysugar nucleosides and their azido analogues, because some of these have been shown to possess significant inhibitory activity against AIDS (Acquired Immune Deficiency Syndrome)-associated virus.[1] We wish to report an efficient and practical method for synthesizing the hitherto unknown title compound **9** via a versatile intermediate, N^6,$O^{5'}$-bis(4,4'-dimethoxytrityl)-9-(3-deoxy-β-D-threo-pentofuranosyl)adenine **6c**, which would be useful for the preparation of other deoxy- or dideoxysugar nucleosides. An N^6,$O^{5'}$-bis-monomethoxytritylated derivative **6b** has been known, but this required an 8-step synthesis from adenosine and isolation of the final product from a diastereomeric by-product.[2]

A new route to **6c** involves a 2 or 3-step synthesis in a one-pot procedure. We have found that combined reagents, magnesium methoxide-sodium borohydride [$Mg(OMe)_2$-$NaBH_4$], were extremely effective for the conversion of N^6,$O^{5'}$-bis(4,4'-dimethoxytrityl)-3'-O-tosyladenosine **5** to **6c** through a 2'-keto nucleoside **C**,[3] which was formed by a [1,2]-hydride shift as formulated in **A**.[4,5] The same reagent system was found to be very efficient for preparing **6c** from N^6,$O^{5'}$-bis(4,4'-dimethoxytrityl)-3'-O-mesyl-2'-O-tosyladenosine **3** via an enol sulfonate **B**,[6] which was formed by the β-elimination of **3**.



Starting materials, 2'-O-tosyladenosine **1**[7] and its isomeric 3'-O-tosylate, were readily obtained from adenosine in 2 steps. The latter was isolated as its p-toluenesulfonate **4**[8] (about 10% yield) from a mother liquor for the crystallization of crude **1**. All of the reactions for synthesizing the azido compound **9** proceeded very smoothly; therefore, purification in each step of the reactions was unnecessary.

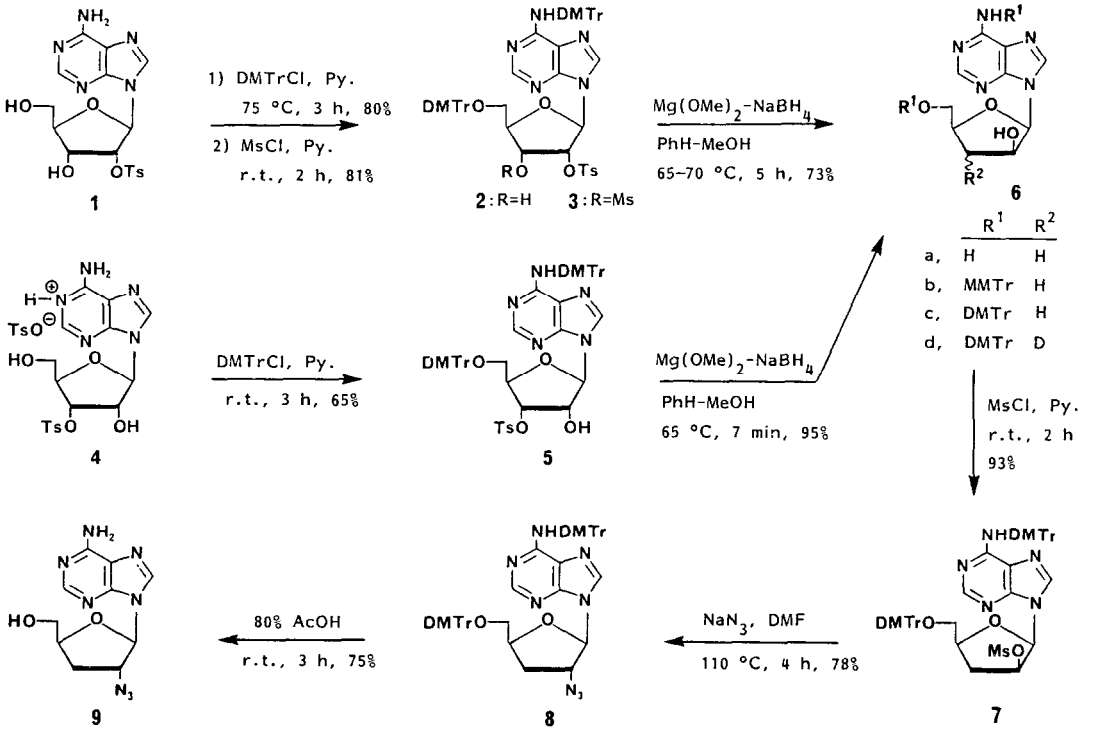
A typical procedure is as follows. To a suspension of **1** (1.68 g, 4 mmol) in dry pyridine (20 ml) was added 4,4'-dimethoxytrityl chloride (DMTrCl; 2.98 g, 8.8 mmol), and the mixture was heated at 75 °C for 2 h, and then cooled to room temperature. Without isolation of the resulting bis-dimethoxytritylated derivative **2**, mesyl chloride (0.62 ml, 8 mmol) was added, and the mixture was stirred at room temperature for 3 h. After the usual work-up, the pyridine was removed by co-evaporation with toluene to give crude **3**, which was dissolved in a mixture of benzene (35 ml) and methanol (35 ml). To this solution there were added $Mg(OMe)_2$ (2.75 g, 32 mmol) and $NaBH_4$ (760 mg, 20 mmol), and the mixture was gently heated at 65—70 °C (bath temperature) under an atmosphere of dry nitrogen for 5 h; hydrogen gas generated during the heating. After cooling, the mixture was extracted with diethyl ether containing a small amount of chloroform, and the organic layer was washed successively with aqueous ammonium chloride and water. The usual work-up gave crude **6c**, which was, without purification, treated with mesyl chloride (0.82 ml, 10.6 mmol) in dry pyridine (20 ml) at room temperature for 2 h to give crude N^6,$O^{5'}$-bis(4,4'-dimethoxytrityl)-9-(3-deoxy-2-O-mesyl-β-D-threo-pentofuranosyl)adenine **7**. A mixture of the total crude **7** and sodium azide (1.3 g, 20 mmol) in dry N,N-dimethylformamide (DMF, 20 ml) was stirred at 110—115 °C (bath temperature) for 4 h. After cooling, the mixture was diluted with diethyl ether and a small amount of chloroform, and the DMF was removed by extraction with water. The organic solution was dried over magnesium sulfate, and concentrated to give crude N^6,$O^{5'}$-bis(4,4'-dimethoxytrityl)-9-[(2R)-2-azido-2,3-dideoxy-β-D-glycero-pentofuranosyl]adenine **8**, which was subjected to the final deprotection reaction. A mixture of the total crude **8** in 80% acetic acid (60 ml) was stirred at room temperature for 3 h, and the acetic acid was co-evaporated with toluene-ethanol to afford a solid, which was triturated with dichloromethane (20 ml). The undissolved materials were collected by filtration and dissolved in refluxing ethanol. On cooling, **9** was spontaneously crystallized: 413 mg (37% overall yield from **1**).

Alternative way to get **9** was easier than the previous one. A mixture of **4** (2.39 g, 4 mmol) and DMTrCl (2.85 g, 8.4 mmol) in dry pyridine (20 ml) was stirred at room temperature for 3 h. After the usual work-up and removal of the pyridine, the resulting crude N^6,$O^{5'}$-bis-(4,4'-dimethoxytrityl)-3'-O-tosyladenosine **5** was treated with $Mg(OMe)_2$ (2.75 g, 32 mmol) and $NaBH_4$ (380 mg, 10 mmol) in a mixture of benzene (35 ml) and methanol (35 ml) at 65 °C for 10 min under an atmosphere of dry nitrogen to yield crude **6c**, which was converted to **9** (560 mg, 51% overall yield from **4**) in a manner similar to that for the preparation starting from **1**.

Each reaction was carried out independently by the use of the pure corresponding starting materials, and the analytically pure products, **2**, **3**, and **5** ~ **8** were fully characterized.[8] In the deoxygenative reductions, no epimer of **6c** was detected by means of ^1H NMR spectroscopy. The configuration of a 2'-up OH group in **6c** was ascertained by the conversion of **6c** into the known 9-(3-deoxy-β-D-threo-pentofuranosyl)adenine **6a**.[2] The R configuration at the 2'-position of **8** was deduced on the basis of the stereochemical course of a S_N2 reaction at the C-2' of **7**.

The combined reagents, $Mg(OMe)_2$-$NaBH_4$, in methanol are considered to produce sodium methoxide in situ according to the HSAB principle.[9] It seems likely that the strongly basic methoxide ion attacked not only the H-2' of **3** for the β-elimination, but also its tosyl sulfur to form **A** (R=Me). It has been known that 2'-O-acyl[10a], benzyl[10b], and tosyl[10c] groups in nucleosides were removed under basic conditions. The incorporation of a deuterium atom at the C-3' of **6c** in the path **B** → **C** was examined by the use of methanol-d_1 instead of methanol. The ^1H NMR spectrum of the product from **3** showed that the content of the deuterium at this position (**6d**) was 37.5%. This suggested that about 75% of the reaction proceeded through **B**, while most of the remainder underwent via **A**.

These procedures are presently being applied to the modification of other ribonucleosides to the corresponding 3'-deoxy or 2',3'-dideoxy analogues.



DMTr=4,4'-dimethoxytrityl; MMTr=4-monomethoxytrityl; Ms=mesyl; Ts=tosyl.

References and Notes

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8) Satisfactory elemental analyses were obtained for all new compounds, and their spectral data are as follows [mp; specific rotations ($CHCl_3$); UV, λ_{max}^{MeOH} (ε); ^1H NMR (400 MHz, $CDCl_3$); IR, ν_{max}^{KBr}]. **2**: amorphous; $[\alpha]_D^{24}$ -39.2° (c 0.5); 274 nm (26100); δ 2.29 (3H, s, C-CH_3), 3.31 (1H, dd, H-5'), 3.44 (1H, dd, H-5"), 3.77 (12H, s, O-CH_3), 4.19 (1H, m, H-4'), 4.65 (1H, m, H-3'), 5.73 (1H, t, H-2'), 6.07 (1H, d, J=6.1 Hz, H-1'), 7.73 (1H, s, H-2 or 8), 7.81 (1H, s, H-8 or 2). **3**: amorphous; $[\alpha]_D^{20}$ -34.1° (c 0.6); 273 nm (27900); δ 2.28 (3H, s, Ts-CH_3), 3.11 (3H, s, Ms-CH_3), 3.45 (1H, dd, H-5'), 3.54 (1H, dd, H-5"), 3.78 (12H, s, O-CH_3), 4.45 (1H, q, H-4'), 5.44 (1H, dd, H-3'), 5.89 (1H, dd, H-2'), 6.08 (1H, d, J=6.6 Hz, H-1'), 7.69 (1H, s, H-2 or 8), 7.78 (1H, s, H-8 or 2). **4**: 195—196 °C (dec.); $[\alpha]_D^{27}$ -23.0° (c 0.94, DMSO); 259 nm (16200); δ (DMSO-d_6 - D_2O) 2.30 (3H, s, CH_3), 2.43 (3H, s, CH_3), 3.42 (1H, dd, H-5'), 3.58 (1H, dd, H-5"), 4.14 (1H, m, H-4'), 4.82 (1H, dd, H-2'), 5.03 (1H, dd, H-3'), 5.96 (1H, d, J=7.0 Hz, H-1'), 7.15 (2H, d,), 7.51 (4H, m,), 7.88 (2H, m,), 8.46 (1H, s, H-2), 8.64 (1H, s, H-8). **5**: 130 (sintered)—142 °C; $[\alpha]_D^{22}$ +4.8° (c 0.57); 274 nm (24200); δ 2.40 (3H, s, C-CH_3), 3.07 (1H, dd, H-5'), 3.39 (1H, dd, H-5"), 3.76 and 3.77 (12H, each s, O-CH_3), 4.42 (1H, m, H=4'), 5.02 (1H, q, H-2'), 5.08 (1H, dd, H-3'), 5.15 (1H, d, OH), 5.88 (1H, d, J=6.1 Hz, H-1'), 7.97 (2H, s, H-2 and 8). **6c**: amorphous; $[\alpha]_D^{22}$ +9.2° (c 0.9); 274 nm (30000); δ 2.15 (1H, m, H-3'), 2.47 (1H, m, H-3"), 3.19 (1H, dd, H-5'), 3.56 (1H, dd, H-5"), 3.78 (12H, s, O-CH_3), 4.34 (1H, m, H-4'), 4.53 (2H, br s, H-2' and OH), 6.06 (1H, d, J=2.9 Hz, H-1'), 8.02 (1H, s, H-2), 8.24 (1H, s, H-8). **7**: amorphous; $[\alpha]_D^{22}$ +8.2° (c 0.9); 274 nm (29400); δ 2.47 (1H, m, H-3'), 2.62 (1H, m, H-3"), 2.52 (3H, s, C-CH_3), 3.38 (1H, dd, H-5'), 3.44 (1H, dd, H-5"), 3.78 and 3.79 (12H, each s, O-CH_3), 4.34 (1H, m, H-4'), 5.32 (1H, m, H-2'), 6.34 (1H, d, J=4.6 Hz, H-1'), 8.00 (1H, s, H-2 or 8), 8.02 (1H, s, H-8 or 2). **8**: amorphous; $[\alpha]_D^{20}$ -37.5° (c 0.4); 274 nm (28900); δ 2.13 (1H, ddd, H-3'), 2.41 (1H, m, H-3"), 3.33 (1H, dd, H-5'), 3.41 (1H, dd, H-5"), 3.77 (12H, s, O-CH_3), 4.53 (1H, m, H-4'), 4.82 (1H, m, H-2'), 5.98 (1H, d, J=2.2 Hz, H-1'), 7.94 (1H, s, H-2 or 8), 8.03 (1H, s, H-8 or 2); 2110 cm^{-1} (N_3). **9**: 203—204 °C (dec.); $[\alpha]_D^{22}$ -66.0° (c 0.6, DMF); 258 nm (15000); δ (DMSO-d_6) 2.14 (1H, m, H-3'), 2.46 (1H, m, H-3"), 3.54 (1H, m, H-5'), 3.72 (1H, m, H-5"), 4.32 (1H, m, H-4'), 4.85 (1H, m, H-2'), 5.25 (1H, t, OH), 6.01 (1H, d, J=3.2 Hz, H-1'), 7.36 (2H, br s, NH_2), 8.16 (1H, s, H-2 or 8), 8.40 (1H, s, H-8 or 2); 2120 cm^{-1} (N_3).

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