

The Synthesis of 2',3'-Dideoxycytidine and Its 2'-Azido Analogue.  
Applications of the Deoxygenative [1,2]-Hydride Shift of Sulfonates  
with  $\text{Mg}(\text{OMe})_2\text{-NaBH}_4$

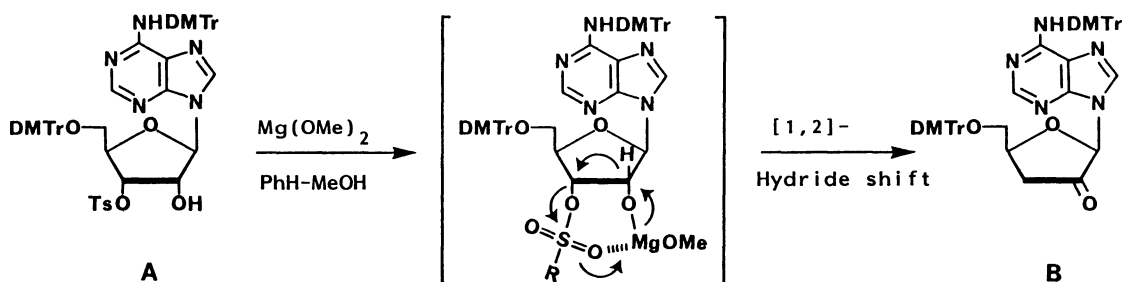
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New synthetic routes to the title compounds from cytidine were developed. Key intermediates were prepared by the deoxygenative reduction of 3'-O-mesylcytidine derivatives with the title reagents in a one-pot procedure.

Since Mitsuya et al.<sup>1)</sup> found that 3'-azido-3'-deoxythymidine and 2',3'-dideoxycytidine **7** showed significant inhibitory activity against Acquired Immune Deficiency Syndrome (AIDS)-associated virus, much attention has been focused on the synthesis and biological evaluation of 2',3'-dideoxynucleosides and their analogues.<sup>2)</sup> Saneyoshi et al.<sup>3)</sup> recently reported that 2'-azido-2',3'-dideoxycytidine **10** strongly inhibited a DNA polymerase (primase) which was purified from cherry salmon testes. We now report new routes to the biologically interesting compounds such as **7** and **10**, starting from cytidine **1**.

The key step for our synthetic approach to these compounds utilized the deoxygenative [1,2]-hydride shift of  $\alpha$ -hydroxysulfonates with organometallic reagents.<sup>4)</sup> We recently found that combined reagents, magnesium methoxide-sodium borohydride [ $\text{Mg}(\text{OMe})_2\text{-NaBH}_4$ ], were effective in the deoxygenative rearrangement of a 3'-O-tosyladenosine derivative **A** and the successive reduction of a 2'-keto compound **B** therefrom in a one-pot procedure.<sup>4d,5)</sup> This method gave us versatile intermediates,  $\text{N}^4$ -(4,4'-dimethoxytrityl)-1-(3-deoxy- $\beta$ -D-threo-pentofuranosyl)-cytosine **4b** and the corresponding  $\text{N}^4, \text{O}^5'$ -dipivaloyl derivative **5a**, which would be useful for the synthesis of other analogues of **1**. The requisite 3'-sulfonate derivative of **1** for our method was prepared according to an efficient procedure for the regioselective acylation of ribonucleosides developed by Ishido et al.<sup>6)</sup>

The syntheses of the key intermediates are as follows. To a cooled suspen-



DMTr: 4,4'-dimethoxytrityl; R: *p*-tolyl; Ts: tosyl.

sion of **1** (40 mmol) in dry pyridine (160 ml) was added pivaloyl chloride (160 mmol), and the mixture was stirred at room temperature for 1.5 h.<sup>6)</sup> Mesyl chloride (240 mmol) was then added, and the stirring was continued for another 1 h. The usual work-up and chromatography gave 3'-O-mesyl-N<sup>4</sup>,O<sup>2'</sup>,O<sup>5'</sup>-tripivaloylcytidine **2a**<sup>7)</sup> (yield, 72%),  $[\alpha]_{\text{D}}^{23} +41.0^\circ$  (c 0.3),  $\delta_{\text{H}}$  1.26, 1.27, 1.29 (each s, C(CH<sub>3</sub>)<sub>3</sub> x 3), 3.07 (s, S-CH<sub>3</sub>), and a small amount (9%) of N<sup>4</sup>,O<sup>2'</sup>,O<sup>3'</sup>,O<sup>5'</sup>-tetrapivaloylcytidine. None of the corresponding 2'-mesylate was detected. The crude **2a** could be used, without the chromatographic purification, for next reactions. The position of the mesyl group in **2a** was ascertained by the analysis of the <sup>1</sup>H-NMR spectrum of the corresponding deblocked mesylate **2b**, which was characterized as its hydrochloride salt,  $\delta_{\text{H}}$  (DMSO-d<sub>6</sub>) 4.38 (br t,  $\underline{J}$ =5 Hz, H-2'), 4.98 (t,  $\underline{J}$ =4.4 Hz, H-3'), 5.81 (d,  $\underline{J}$ =5.8 Hz, H-1').

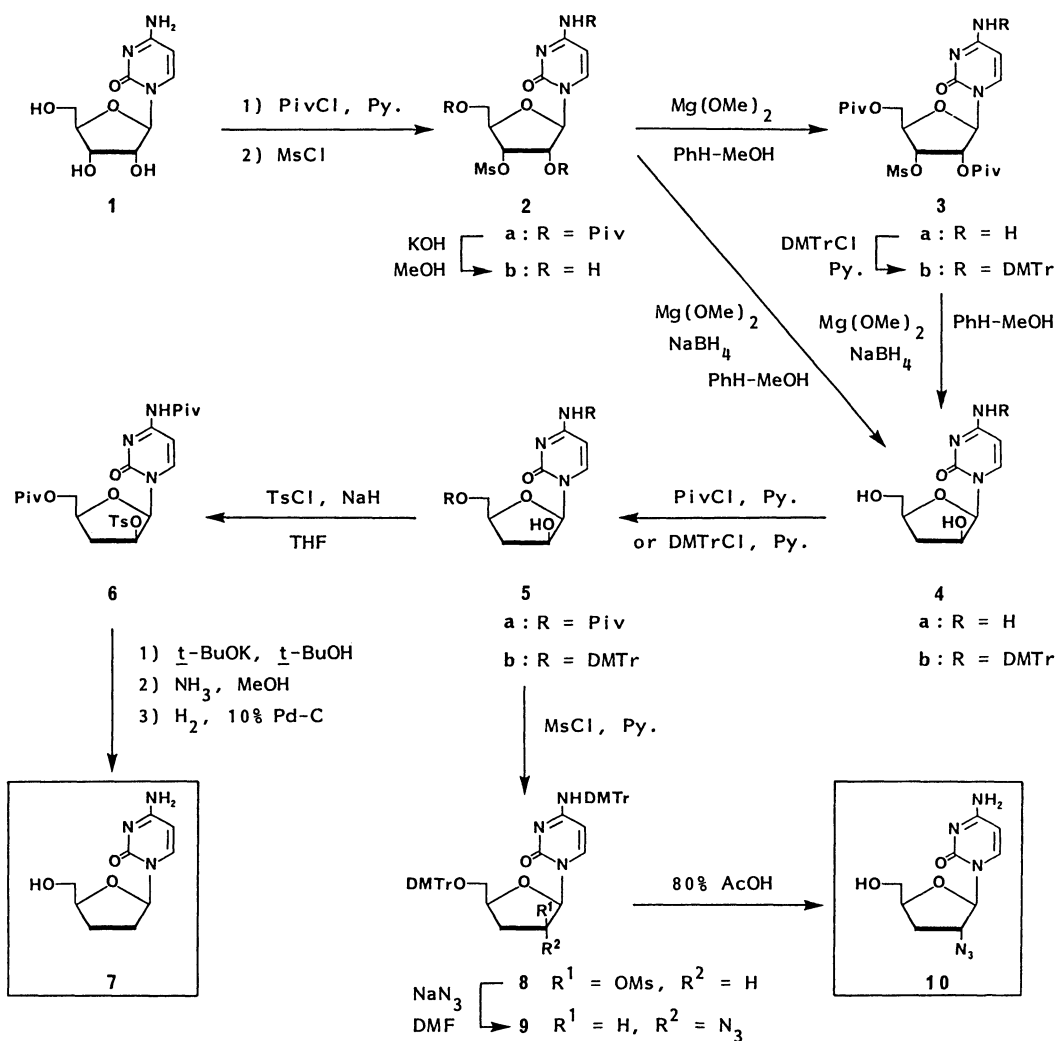
Selective removal of the N<sup>4</sup>-pivaloyl group in **2a** was achieved when **2a** was treated with Mg(OMe)<sub>2</sub> (1.5 equiv.) in a mixture of benzene-methanol at room temperature for 30 min. In this reaction, 3'-O-mesyl-2',5'-di-O-pivaloylcytidine **3a**,  $[\alpha]_{\text{D}}^{20} +41.8^\circ$  (c 0.3),  $\delta$  (DMSO-d<sub>6</sub>) 1.18 (s, C(CH<sub>3</sub>)<sub>3</sub> x 2), 4.24 (dd, H-5'), 4.35-4.38 (m, H-4', H-5''), 5.38 (br t, H-3'), 5.22 (dd, H-2'), 5.75 (d, H-5), 5.79 (d, H-1'), 7.31 (br s, NH<sub>2</sub>), 7.59 (d, H-6), was obtained in 87% yield after silica-gel column chromatography. Treatment of **3a** with 4,4'-dimethoxytrityl chloride (1.2 equiv.) in dry pyridine at room temperature for 3 h provided the corresponding N<sup>4</sup>-dimethoxytrityl derivative **3b**,  $[\alpha]_{\text{D}}^{20} +4.0^\circ$  (c 0.5),  $\delta_{\text{H}}$  5.05 (d, H-5), 7.09 (d, H-6), in 96% yield.

The compound **3b**, thus obtained, was subjected to the deoxygenative reduction. To a solution of **3b** (1 mmol) in a mixture of benzene (7 ml) and methanol (7 ml) were added Mg(OMe)<sub>2</sub> (5 mmol) and NaBH<sub>4</sub> (3 mmol), and the mixture was stirred at 65 °C for 1.5 h under an atmosphere of dry nitrogen. An excess of the reducing agent was decomposed with acetone, and the products were extracted with chloroform. After the usual work-up, the residue was chromatographed on a silica-gel column with chloroform-methanol (98:2) to give **4b** (56%),  $[\alpha]_{\text{D}}^{26} +27.0^\circ$  (c 0.6),  $\delta_{\text{H}}$  1.99 (ddd, H-3'), 2.39 (m, H-3''), 3.64 (dd, H-5'), 3.90 (dd, H-5''), 4.57 (br s, H-2'), 5.07 (d, H-5), 5.90 (d,  $\underline{J}$ =3.7 Hz, H-1'), 7.54 (d, H-6), and its crude erythro isomer (4%). It was later found that potassium hydroxide instead of Mg(OMe)<sub>2</sub> was also effective in this reaction. The 2'-up OH configuration in **4b** was determined on the basis of the fact that the thin-layer chromatographic behavior and <sup>1</sup>H-NMR spectrum of methyl glycosides derived by the methanolysis of **4b** were identical with those for specimens from the known analogue of adenosine.<sup>5,8)</sup>

On the other hand, an N<sup>4</sup>-amino free compound **4a**<sup>9)</sup> was obtained directly from **2a** under conditions similar to those for the preparation of **4b**; the hygroscopic product **4a** was characterized as its crystalline hydrochloride salt, mp 183.5-184.5 °C,  $[\alpha]_{\text{D}}^{26} +151^\circ$  (c 0.5, H<sub>2</sub>O),  $\delta_{\text{H}}$  (DMSO-d<sub>6</sub>) 1.76 (m, H-3'), 2.26 (m, H-3''), 5.90 (d,  $\underline{J}$ =4.4 Hz, H-1'). The stereoselectivity (threo vs. erythro) of this reaction (**2a** → **4a**) was 88 : 12.

In order to prepare the 2'-O-monosulfonylated derivatives of **4a** and **4b**, both N<sup>4</sup> and O<sup>5'</sup> positions of these compounds were protected. Thus crude **4a** was treated with pivaloyl chloride (2.3 equiv.) in dry pyridine at room temperature to give **5a** (87%), mp 150-151 °C,  $[\alpha]_{\text{D}}^{24} +134^\circ$  (c 0.5),  $\delta_{\text{H}}$  1.26, 1.29 (each s, C(CH<sub>3</sub>)<sub>3</sub> x 2),

5.97 (d,  $J=3.6$  Hz, H-1'), after silica-gel column chromatography, while **4b** was converted into the corresponding  $N^4, O^5'$ -bis(4,4'-dimethoxytrityl) derivative **5b** (71%),  $[\alpha]_D^{24} +17.7^\circ$  (c 0.5),  $\delta_H$  3.73, 3.74, 3.75 (each s, O-CH<sub>3</sub> x 4), 5.98 (d,  $J=5.1$  Hz, H-1'), with 4,4'-dimethoxytrityl chloride (1.2 equiv.) by the conventional method. Tosylation of **5a** with tosyl chloride (2 equiv.)-sodium hydride (2 equiv.) in dry oxolane at room temperature afforded 2'-tosylate **6** (95%), mp 175-176 °C,  $[\alpha]_D^{24} +109^\circ$  (c 0.6),  $\delta_H$  2.42 (s, C-CH<sub>3</sub>), 5.24 (ddd, H-2'), 5.99 (d,  $J=3.4$  Hz, H-1'). On treatment of **5b** with mesyl chloride (3 equiv.) in the usual way, 2'-mesylate **8**,  $[\alpha]_D^{25} +27.6^\circ$  (c 1.0),  $\delta_H$  2.88 (s, S-CH<sub>3</sub>), 5.31 (m, H-2'), 6.11 (d,  $J=4.6$  Hz, H-1'), was obtained in 79% yield.



The synthesis of **7**, one of the final products, was accomplished in a three-step reaction starting from **6**. Treatment of **6** with potassium *t*-butoxide (5 equiv.) in *t*-butyl alcohol at room temperature, followed by the deprotection with methanolic ammonia gave crude 2',3'-didehydro-2',3'-dideoxycytidine,<sup>10)</sup> which was hydrogenated over 10% palladium-carbon to produce **7** in 50% overall yield from **6**. The physical properties (mp,  $[\alpha]_D$ , and <sup>1</sup>H-NMR) of **7** were in excellent agreement with those for a specimen reported in the literature.<sup>2a,10)</sup>

For the synthesis of **10**, **8** was treated with sodium azide (5 equiv.) in *N,N*-dimethylformamide (DMF) at 115 °C to give *N*<sup>4</sup>,*O*<sup>5'</sup>-bis(4,4'-dimethoxytrityl)-1-[(2*R*)-2-azido-2,3-dideoxy-β-*D*-glycero-pentofuranosyl]cytosine **9** (93%),  $[\alpha]_D^{25} -31.0^\circ$  (c 0.9),  $\delta_H$  4.27 (d, H-2'), 5.89 (br s, H-1'),  $\nu_{\max}^{\text{KBr}}$  2110  $\text{cm}^{-1}$  ( $\text{N}_3$ ). The configuration of the azido group in **9** was assigned on the basis of the stereochemical course of an  $\text{S}_{\text{N}}2$  reaction, together with the expected value of  $J_{1',2'}$  ( $\approx 0$  Hz) in its  $^1\text{H}$ -NMR spectrum. Finally deprotection of **9** with 80% acetic acid at 50 °C easily produced **10** (84%), mp 171-172 °C (dec.),  $[\alpha]_D^{25} -42.6^\circ$  (c 0.3, DMF),  $\lambda_{\max}^{\text{MeOH}}$  271 nm ( $\epsilon$  8900),  $\nu_{\max}^{\text{KBr}}$  2130  $\text{cm}^{-1}$  ( $\text{N}_3$ ),  $\delta_H$  (DMSO-*d*<sub>6</sub>) 4.32 (br d, H-2'), 5.72 (d,  $J=1.2$  Hz, H-1').

Experiments directed toward synthesizing other modified nucleosides from the 2'- or 3'-*O*-sulfonylated ribonucleosides<sup>4d,5)</sup> by the present method are currently being undertaken in this laboratory.

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