CHEMISTRY LETTERS, pp. 2419-2422, 1987.

The Synthesis of 2',3'-Dideoxycytidine and Its 2'-Azido Analogue. Applications of the Deoxygenative [1,2]-Hydride Shift of Sulfonates with $Mg(OMe)_2$-$NaBH_4$

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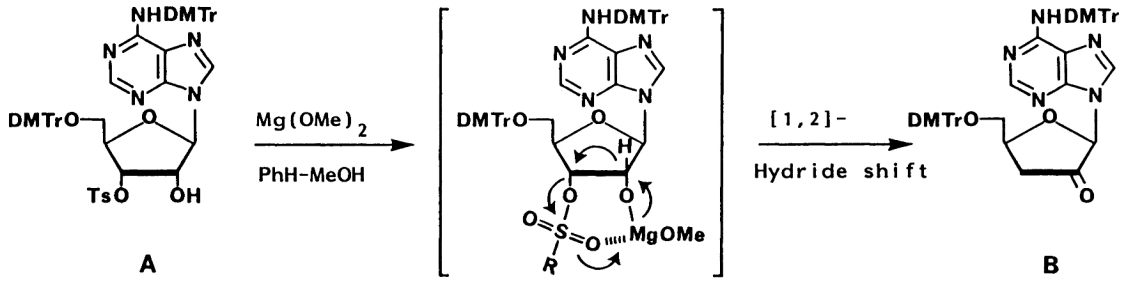
New synthetic routes to the title compounds from cytidine were developed. Key intermediates were prepared by the deoxygenative reduction of 3'-O-mesylcytidine derivatives with the title reagents in a one-pot procedure.

Since Mitsuya et al.[1] 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.[2] Saneyoshi et al.[3] 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 α-hydroxysulfonates with organometallic reagents.[4] We recently found that combined reagents, magnesium methoxide-sodium borohydride [$Mg(OMe)_2$-$NaBH_4$], 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.[4d,5] This method gave us versatile intermediates, N^4-(4,4'-dimethoxytrityl)-1-(3-deoxy-β-D-threo-pentofuranosyl)-cytosine **4b** and the corresponding N^4,$O^{5'}$-dipivaloyl derivative **5a**, which would be usuful 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.[6]

The syntheses of the key intermediates are as followes. 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.[6] 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^4,$O^{2'}$,$O^{5'}$-tripivaloylcytidine **2a**[7] (yield, 72%), $[\alpha]_D^{23}$ +41.0° (c 0.3), δ_H 1.26, 1.27, 1.29 (each s, $C(CH_3)_3$ x 3), 3.07 (s, S-CH_3), and a small amount (9%) of N^4,$O^{2'}$,$O^{3'}$,$O^{5'}$-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 ^{1}H-NMR spectrum of the corresponding deblocked mesylate **2b**, which was characterized as its hydrochloride salt, δ_H (DMSO-d_6) 4.38 (br t, J=5 Hz, H-2'), 4.98 (t, J=4.4 Hz, H-3'), 5.81 (d, J=5.8 Hz, H-1').

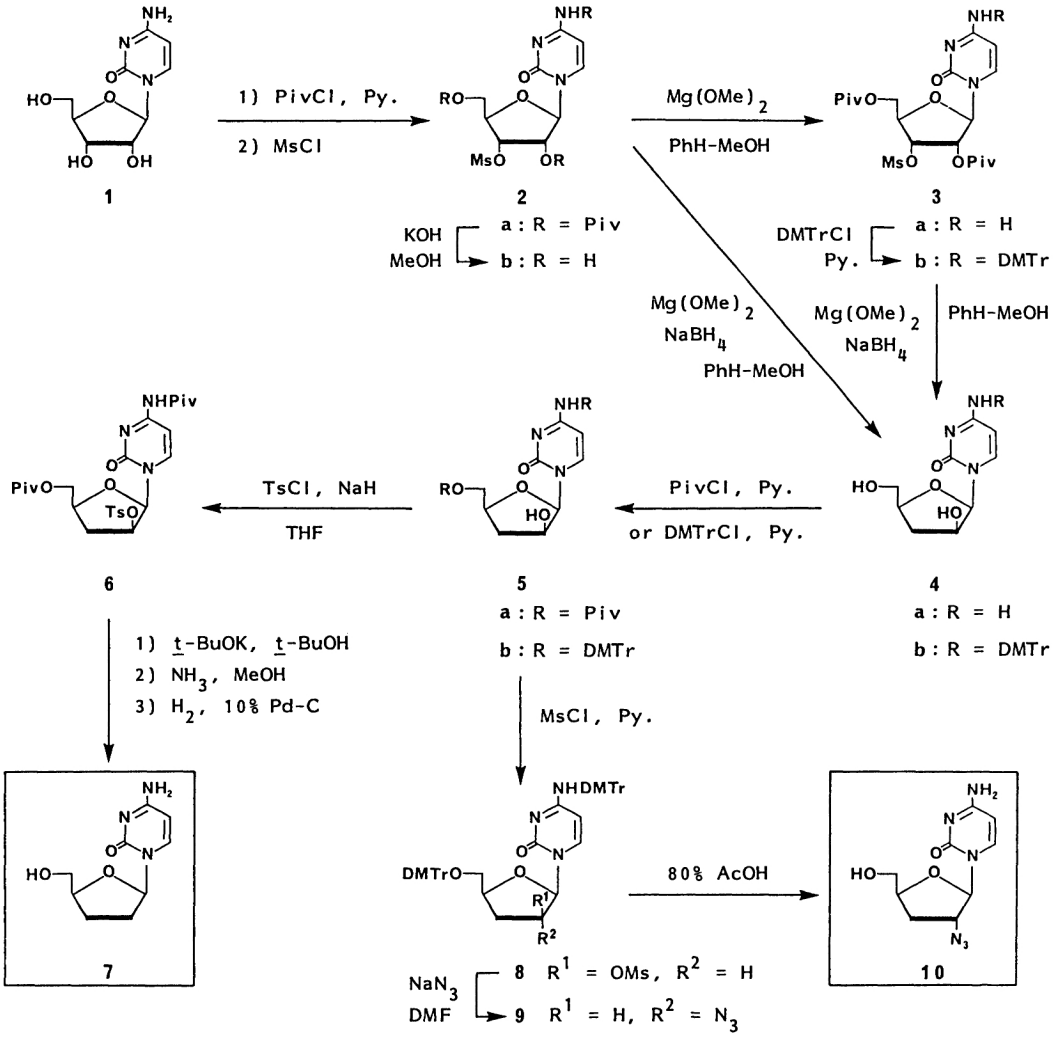
Selective removal of the N^4-pivaloyl group in **2a** was achieved when **2a** was treated with $Mg(OMe)_2$ (1.5 equiv.) in a mixture of benzene-methanol at room temperature for 30 min. In this reaction, 3'-O-mesyl-2',5'-di-O-pivaloylcytidine **3a**, $[\alpha]_D^{20}$ +41.8° (c 0.3), δ (DMSO-d_6) 1.18 (s, $C(CH_3)_3$ 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_2), 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^4-dimethoxytrityl derivative **3b**, $[\alpha]_D^{20}$ +4.0° (c 0.5), δ_H 5.05 (d, H-5), 7.09 (d, H-6), in 96% yield.

The compound **3b**, thus obtaied, 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 $Mg(OMe)_2$ (5 mmol) and $NaBH_4$ (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%), $[\alpha]_D^{26}$ +27.0° (c 0.6), δ_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, 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 $Mg(OMe)_2$ 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 ^{1}H-NMR spectrum of methyl glycosides derived by the methanolysis of **4b** were identical with those for specimens from the known analogue of adenosine.[5,8]

On the other hand, an N^4-amino free compound **4a**[9] 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, $[\alpha]_D^{26}$ +151° (c 0.5, H_2O), δ_H (DMSO-d_6) 1.76 (m, H-3'), 2.26 (m, H-3''), 5.90 (d, 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^4 and $O^{5'}$ 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, $[\alpha]_D^{24}$ +134° (c 0.5), δ_H 1.26, 1.29 (each s, $C(CH_3)_3$ 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° (c 0.5), δ_H 3.73, 3.74, 3.75 (each s, O-CH_3 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° (c 0.6), δ_H 2.42 (s, C-CH_3), 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° (c 1.0), δ_H 2.88 (s, S-CH_3), 5.31 (m, H-2'), 6.11 (d, J=4.6 Hz, H-1'), was obtained in 79% yield.



DMTr: 4,4'-dimethoxytrityl; Ms: mesyl; Piv: pivaloyl; Ts: tosyl.

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,[10] which was hydrogenated over 10% palladium-carbon to produce **7** in 50% overall yield from **6**. The physical properties (mp, $[\alpha]_D$, and ^{1}H-NMR) of **7** were in excellent agreement with those for a specimen reported in the literature.[2a,10]

For the synthesis of **10**, **8** was treated with sodium azide (5 equiv.) in N,N-dimethylformamide (DMF) at 115 °C to give N^4,$O^{5'}$-bis(4,4'-dimethoxytrityl)-1-[(2R)-2-azido-2,3-dideoxy-β-D-glycero-pentofuranosyl]cytosine **9** (93%), $[\alpha]_D^{25}$ -31.0° (c 0.9), δ_H 4.27 (d, H-2'), 5.89 (br s, H-1'), ν_{max}^{KBr} 2110 cm^{-1} (N_3). The configuration of the azido group in **9** was assigned on the basis of the stereochemical course of an S_N2 reaction, together with the expected value of $J_{1',2'}$ (≈0 Hz) in its ^{1}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° (c 0.3, DMF), λ_{max}^{MeOH} 271 nm (ε 8900), ν_{max}^{KBr} 2130 cm^{-1} (N_3), δ_H (DMSO-d_6) 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[4d,5] by the present method are currently being undertaken in this laboratory.

The authors wish to thank Professor Yoshiharu Ishido, Tokyo Institute of Technology, for his valuable comments and suggestions. This work was supported, in part, by a Research Grant for Life Science promoted by this Institute.

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(Received September 19, 1987)