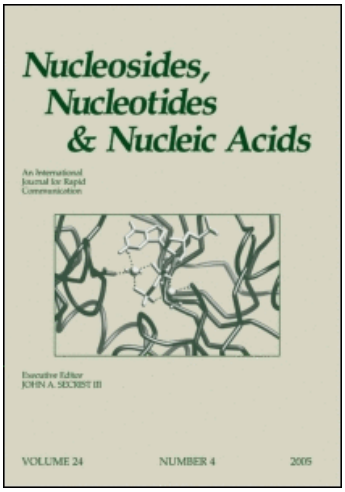

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A Convenient Synthesis of N^4,$O^{3'}$, $O^{5'}$-Triacetyl-2'-Ketocytidine

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A CONVENIENT SYNTHESIS OF $N^4,O^{3'},O^{5'}$-TRIACETYL-2'-KETOCYTIDINE

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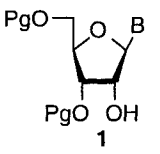
Abstract: A convenient synthesis of the title compound in four steps from cytidine is reported. Key transformations include differentiation of the 2' position as $N^4,O^{3'},O^{5'}$-triacetyl-2,2'-anhydrocytidine, opening to the arabino derivative, and oxidation of the 2' position with the Dess-Martin reagent.

Ketonucleoside derivatives are key intermediates in the synthesis of many potential drugs.[1] The challenge to the formation of ketonucleosides is differentiating the hydroxyl to be oxidized from the others on the sugar. Most existing routes in the literature require chromatographic separation of molecules of types **1** and **2**, which are produced in approximately equal amounts by the protection step.[2] An elegant solution is the use of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (**$TPDSCl_2$**) to selectively make



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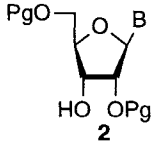

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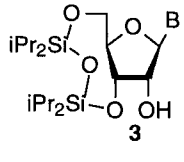
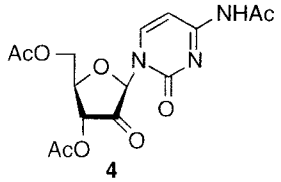


3

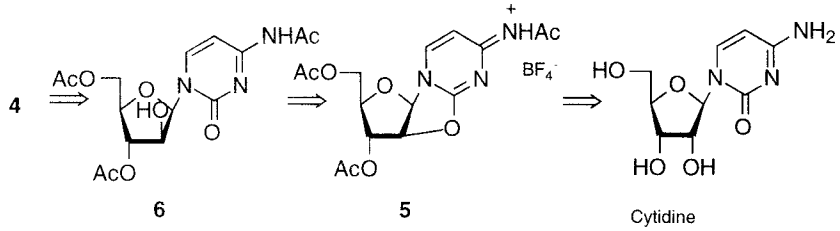
Pg = t-butyldimethylsilyl, Trityl
B = nucleobases

molecules of type **3**.[3] However, this reagent is quite expensive, and the **TPDS** protecting group may not be appropriate for some syntheses. We required significant quantities of a 2'-ketocytidine derivative, and found none of the existing methods suitable. Therefore, we developed a short, regioselective route to the previously unreported N^4,$O^{3'}$,$O^{5'}$-triacetyl-2'-ketocytidine **4**.



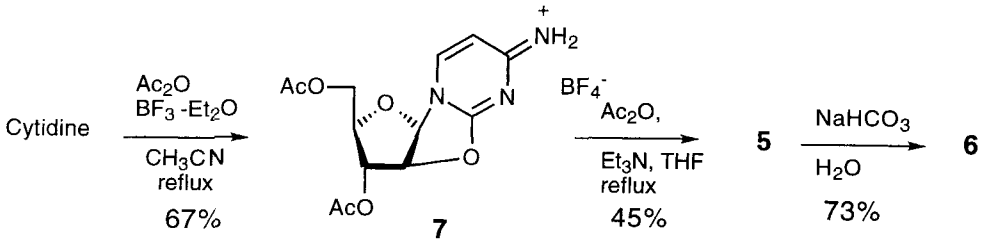
4

We proposed to achieve the key differentiation of the 2'-position via the known N^4,$O^{3'}$,$O^{5'}$-triacetyl-2,2'-anhydrocytidine **5**.[4] Opening of the 2,2' anhydro bond with aqueous $NaHCO_3$ is known to produce the arabino derivative **6**.[4b] The overall yield of arabino **6** by the route of Kondo and Inoue is 22%. While we were unaware of any

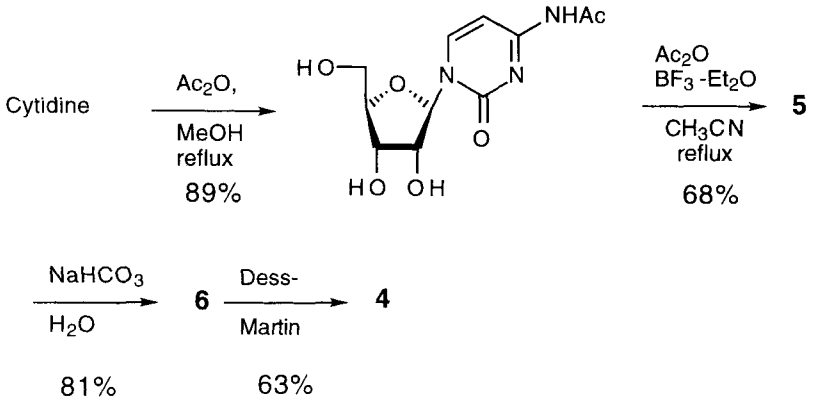


attempts to oxidize arabino sugars to 2'-keto derivatives, we saw no reason for this step to fail.

We also made substantial improvements to the synthesis of **6**. The route of Kondo and Inoue is shown in **Scheme 1**. We found two difficulties with running this route. In our hands the crude (prior to purification by trituration) anhydro intermediate **7** was very gummy and difficult to handle. Also, the yield of **5** from the acetylation of **7** was poor due to instability of the anhydro bond to the acetylation conditions.[4b] We found it advantageous to acetylate the N^4 position[5] prior to ring closure (**Scheme 2**). The opening of the anhydro ring with $NaHCO_3$ produced arabino **6**. By acetylating first, a three-step synthesis of **6** from cytidine was achieved in 49% yield. This more than doubles the yield obtained by acetylating subsequent to ring closure (22% overall). No handling difficulties were encountered with any of the intermediates.

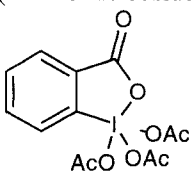


Scheme 1



Scheme 2

Interestingly, while syntheses of **6** are in the literature,[4,6] we are unaware of any attempts to oxidize **6** to the 2'-keto derivative. Oxidation of **6** proved to have difficulties similar to those experienced by Robins when attempting oxidation of TPDS derivatives **3**.[7] As Robins reports for **3**, the Dess-Martin reagent **8** was found to be the most convenient means for the oxidation of **6**. Ketone **4** was isolated in 63% yield after column chromatography to remove residue from the Dess-Martin reagent. Ketone **4** was found to be quite sensitive to water (2'-ketonucleosides have been found to easily form



8

hydrates).[7] Therefore, aqueous workup must be avoided. Ketone **4** can be stored for months in the freezer under nitrogen.

In conclusion, a regioselective four-step synthesis of the N^4,$O^{3'}$,$O^{5'}$-triacetyl-2'-ketocytidine **4** has been achieved. The overall yield of this process is 31%. All intermediates are isolated as solids by filtration. The only chromatography required is in the final step to remove the residue from the Dess-Martin reagent.

Experimental

All commercially available reagents and solvents were reagent grade and used without further purification. The Dess-Martin reagent was prepared by the method of Ireland.[8]

Proton nuclear magnetic resonance spectra and ^{13}C spectra were recorded on Bruker AC300 spectrometers. All chemical shifts are reported as δ values relative to tetramethylsilane. Infrared spectra were recorded on a Nicolet 510P spectrometer. Microanalytical data were obtained on a Control Equipment Corporation 440 Elemental Analyzer .

N^4-Acetylcytidine Cytidine (3.000 g, 12.33 mmol) was placed in a dry, nitrogen-flushed flask equipped with mechanical stirrer and condenser. It was dissolved in methanol (40 mL) and heated to reflux. Acetic anhydride (11.6 mL, 12.6 g, 124 mmol) was added *via* an addition funnel over 2 h. The reaction mixture was refluxed for an additional 1 h. The reaction mixture was then cooled to 0 °C and filtered, affording the acetyl protected product as a colorless crystalline solid (3.114 g, 89 %): mp 206-207 °C, IR (neat) 3473, 3265, 1718, 1643, 1491 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.89 (s, 1H), 8.43 (d, 1H, *J*=7.5Hz), 7.19 (d, 1H, *J*=7.5Hz), 5.78 (d, 1H, *J*=2.6Hz), 5.49 (d, 1H, *J*=4.7Hz), 5.17 (t, 1H, *J*=5.0Hz), 5.06 (d, 1H, *J*=4.7Hz), 3.99 (s, 2H), 3.90 (s, 1H), 3.65 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.1, 162.3, 154.7, 145.4, 95.2, 90.2, 84.2, 74.5, 68.7, 59.9, 24.4. Anal. Calcd for $C_{11}H_{15}N_3O_6$: C, 46.32; H, 5.30; N, 14.73. Found: C, 46.02; H, 5.48; N, 14.56.

$N^4,O^{3'},O^{5'}$-Triacetyl-2,2'-anhydro-1-(β-D-arabinofuranosyl)cytosine hydrotetraflouroborate (5) N^4-Acetylcytidine (2.92 g, 10.23 mmol) was placed in a dried, nitrogen-flushed flask equipped with condenser, mechanical stirrer, and addition funnel. The substrate was dissolved in acetonitrile (75 mL). Boron trifluoride etherate (3.8 mL, 4.3 g, 31 mmol) was then added. The reaction mixture was heated to reflux and acetic anhydride (2.90 mL, 3.13 g, 30.69 mmol) was added dropwise *via* an addition funnel. After 1 h, the reaction mixture was stripped to an oil and triturated with diethyl ether (75 mL) / isopropyl alcohol (50 mL) to afford the product as a white powder (3.055 g, 68 %): MP 178-180 °C (decomposed), IR (neat) 1747, 1652, 1569, 1469, 1228 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.73 (s, 1H), 9.00 (d, 1H, *J* = 7.3 Hz), 8.14 (d, 1H, *J* = 7.3 Hz), 6.86 (d, 1H, *J* = 6.2 Hz), 5.91 (d, 1H, *J* = 6.2 Hz), 5.48 (d, 1H, *J* = 2.4 Hz), 4.75 (m, 1H), 4.19 (dd, 1H, *J* = 12.6, 5.1 Hz), 3.96 (dd, 1H, *J* = 12.6, 2.9 Hz), 2.25 (s, 3H), 2.12 (s, 3H), 1.82 (s, 3H); ^{13}C NMR δ 172.7, 171.0, 170.9, 166.4, 160.6, 148.3, 106.1, 93.4, 89.8, 85.1, 77.6, 64.6, 26.0, 21.8, 21.3; MS (FAB) *m/z* 352, 309, 155, 152, 135, 119. Anal. Calcd for $C_{15}H_{18}N_3O_7F_4B$: C, 41.03; H, 4.13; N, 9.57. Found C, 40.65; H, 4.18; N, 9.58.

$N^4,O^{3'},O^{5'}$-Triacetyl-1-β-D-arabinofuranosylcytosine (6) The triacetylanhydro-substrate **5** (0.695 g, 1.97 mmol) was placed in a dried, nitrogen-flushed flask and dissolved in an aqueous sodium bicarbonate (0.239 g, 2.9 mmol in 14ml) solution. The reaction was allowed to proceed for 17 h after which it was filtered and washed with water to afford the product as a white powder (0.586 g, 81 %): MP 242-245 (decomposed), IR (neat) 3306, 1722, 1658, 1613, 1493, 1249 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.87 (s, 1H), 7.96 (d, 1H, *J* = 7.5 Hz), 7.21 (d, 1H, *J* = 7.5 Hz), 6.05 (m, 2H), 4.93 (d, 1H, *J* = 1.5 Hz), 4.38 (dd, 1H, *J* = 11.3, 7.3 Hz), 4.22 (m, 3H), 2.09 (s, 6H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 171.4, 170.8, 163.5, 155.5, 147.7, 95.7, 88.4, 81.5, 79.6, 72.7, 64.3, 25.5, 21.8, 21.7; MS (FAB) *m/z* 370 (M+), 309, 155, 135, 119. Anal. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.18; N, 11.38. Found: C, 48.50; H, 5.00; N, 11.23.

N^4,$O^{3'}$,$O^{5'}$- Triacetyl-2'-ketocytidine (4) The 2'-hydroxy-triacetyl substrate **6** (0.325 g, .88 mmol) was placed in a dried nitrogen-flushed flask and dissolved in acetonitrile (5 mL). Dess-Martin reagent (0.560 g, 1.32 mmol) was then added to the rapidly stirred mixture. The reaction was allowed to proceed for 72 h after which it was concentrated *in vacuo* and subjected to flash column chromatography (5% isopropyl alcohol in ethyl acetate) affording the product as a colorless crystalline solid (0.205 g, 63%): IR (neat) cm^{-1} 1742, 1670, 1479, 1325, 1053; ^1H NMR (CD_2Cl_2) δ 9.84 (s, 1H), 7.71 (d, 1H, J = 7.5 Hz), 7.48(d, 1H, J = 7.5 Hz), 5.41 (s, 1H), 5.12 (d, 1H, J = 6 Hz), 4.46 (2H, m), 4.34 (1H, m), 2.21 (3H, s) 2.14 (3H, s), 2.04 (3H, s); ^{13}C NMR δ 200.4, 171.1, 170.9, 170.8, 164.9, 155.1, 149.2, 97.9, 87.5, 79.2, 72.4, 64.7, 25.1, 20.8, 20.4. Anal. Calcd for $C_{15}H_{17}N_3O_8 \cdot H_2O$:[9] C, 46.88; H, 4.97; N, 10.90. Found: C, 46.66; H, 4.77; N, 10.18.

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9 We assume the product formed the hydrate under the conditions of the elemental analysis. All spectra show no evidence of water.

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