Pergamon

Tetrahedron Letters, Vol. 38, No. 9, pp. 1509-1510, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00142-1

Synthesis of 2',3'-Dideoxy-3'-hydroxymethylcytidine: A Novel Hydroformylation Route

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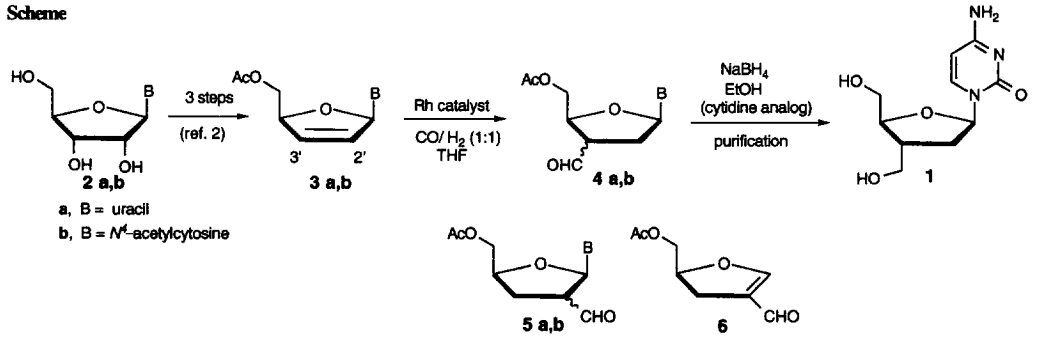
Abstract: 2',3'-Dideoxy-3'-hydroxymethylcytidine (**1**) has been synthesized via stereoselective Rh-catalyzed hydroformylation of 2',3'-didehydro-2',3'-dideoxycytidine **3b**. This synthesis incorporates the first successful hydroformylation of a nucleoside olefin. © 1997 Elsevier Science Ltd. All rights reserved.

2',3'-Dideoxy-3'-hydroxymethylcytidine (**1**), active against HIV, has presented interesting synthetic challenges.[1] In particular, investigators exploring glycosidation-based routes to **1** have contended with the non-stereoselective glycosidation of the pyrimidine base. Only by making special provisions to incorporate temporary functionality to disrupt the pseudo C-2 symmetry of the sugar moiety of **1** could glycosidation be directed effectively to the desired β face. To circumvent glycosidation problems, the use of uridine and cytidine as starting materials was explored. We envisioned an efficient 5 to 7 step route which incorporated a hydrometalation-carbonylation sequence on the readily accessible 2',3'-didehydro-2',3'-dideoxynucleoside (**3**)[2] (Scheme). Herein, we report the Rh-catalyzed hydroformylation of 5'-*O*-N^4-diacetyl-2',3'-dideoxy-2',3'-didehydrocytidine (**3b**) to afford the corresponding 3'-carboxaldehyde **4b** and its transformation to **1**.

Scheme



Hydroformylations of functionalized alkenes using Rh catalysts are well documented.[3] Particularly relevant are hydroformylations of olefinic pyranoses[4] and protected diols of cyclopent-2-ene[5]. Literature precedent, however, does not exist for the hydroformylation of a nucleoside olefin. Our concerns for a hydroformylation strategy were: *a*) the 2' vs. 3' regioselectivity of the hydroformylation,[3b,6] *b*) the tendency for catalyzed olefin migration,[7] and *c*) whether the integrity of the anomeric stereocenter could be preserved under the reaction conditions. By comparison, we inferred that the 3'-α vs.-β stereoselectivity of the hydroformylation could be controlled under kinetic (steric biasing by the 1' and 4' substituents) or thermodynamic conditions.[8]

Hydroformylation of uracil derivative **3a**[2a] using $RhCl(PPh_3)_3$[9] gave products of 2'-regioselectivity, aldehydes **5a** and **6**, in 10% combined yield, along with less than 5 % of the desired 3'-carboxaldehyde **4a**.[10] Presumably, **6** arose from β-elimination of uracil from the 2'-carboxaldehyde **5a**. To bias the product distribution toward 3'-carboxaldehyde **4a**, other Rh catalysts were explored. Use of Rh_2O_3[11] provided a 1:1 ratio of 3' to 2'-hydroformylation products, affording **4a** in 12% yield; while use of $Rh(CO)_2acac$ with PPh_3[12] increased the 3' to 2'-regioselectivity to 3:1, providing **4a** in 27% yield. Application of the latter conditions to cytidine derivative **3b**[2b] afforded **4b**, again with 3:1 regioselectivity, in 32% yield;[13] this resulted in our best

conditions for hydroformylation. The hydroformylation products of **3b** were then carried directly into a $NaBH_4$ reduction. $NaBH_4$ not only reduced the aldehyde to the alcohol, but also cleaved the 5'-*O*-acetyl and N^4-acetyl groups of **4b** to afford **1** in 20% overall isolated yield from **3b**. Reversed-phase HPLC analysis of the crude product **1** from the hydroformylation/ reduction sequence revealed a 94:6-α:β ratio of 3'-C stereoisomers. This α:β ratio was consistent with that obtained upon intentional equilibration of the 5'-*O*-trityl protected analog of **4a** under acid or base catalysis,[8b] thus implying that thermodynamic equilibration of the 3'-C stereoisomers may have occurred prior to reduction.

In summary, Rh-catalyzed hydroformylations were conducted on 2',3'-nucleoside olefins to provide the corresponding 3'α-aldehydes stereoselectively, albeit in modest yield and with modest regioselectivity. This methodology has been applied as a key step in a concise synthesis of 2',3'-dideoxy-3'-hydroxymethylcytidine.

2',3'-Dideoxy-3'-hydroxymethylcytidine (1). To a 100 mL stainless steel bomb (Parr 4591 Micro Reactor®) was charged 1.0 g of **3b** (3.4 mmol, 1.0 equiv), 50 mg of Rh $(CO)_2$acac (0.19 mmol, 0.056 equiv) and 200 mg of triphenylphosphine (0.76 mmol, 0.22 equiv) under a N_2 atmosphere. The reagents were dissolved in 50 mL of dry THF. The bomb was pressurized to 80 psi with a 1:1 mixture of H_2 and CO and heated to 60 °C. This mixture was stirred at this pressure and temperature for 48 h. Evaporation of the THF under reduced pressure (15 mm Hg, 40 °C) provided a residue, which was triturated with two-30 mL portions of toluene to remove the triphenylphosphine and triphenylphosphine oxide; **4b** was afforded in 32% yield[10]. ^{1}H NMR of unpurified **4b** (300 MHz, THF-d_8) δ 2.05 (s, 3H), 2.13 (s, 3H), 2.37 (m, 1H), 2.81 (m, 1H), 3.12 (m, 1H), 3.90-4.10 (m, 2H) 4.20-4.40 (m, 1H, d, 1H, J = 7.4 Hz), 5.98(m, 1H), 8.07 (d, 1H, J = 7.4 Hz), 9.63 (s, 1H), 10.05 (bs, 1H). The residue was then dissolved into 10 mL of absolute ethanol and the solution cooled to 0 °C; whereupon, 235 mg of $NaBH_4$ (6 mmol) was added. The ice bath was removed and the reaction was allowed to warm to 25 °C and remain at 25 °C for 1 hour with stirring. The reaction was recooled to 0 °C and acetone was added to destroy the excess $NaBH_4$. The reaction was neutralized with 1.0 N HCl until the pH was between 8-9 and then 0.1 N HCl was used to adjust to pH 7. The solvent was evaporated under reduced pressure (15 mm Hg, 40 °C). Toluene was added to remove the final traces of water as the azeotrope. Upon evaporation of the toluene azeotrope 1.46 g of crude residue remained. Isolation of **1** by column chromatography (75 CH_2Cl_2: 25 MeOH: 2 Et_3N to 35 CH_2Cl_2: 15 MeOH: 1 Et_3N) provided 164 mg (20 % yield from **3b**). ^{1}H NMR(300 MHz, D_2O)[1] δ 2.20-2.41 (m, 3H), 3.65 (d, 2H, J = 5.5 Hz), 3.73 (dd, 1H, J = 5.5 Hz, J = 12.5 Hz), 3.89 (dd, 1H, J = 2.8 Hz, J = 12.5 Hz), 4.0 (m, 1H), 6.03, (d, 1H, J = 7.6 Hz), 6.09 (dd, 1H, J = 4.0 Hz, J = 6.5 Hz), 7.91 (d, 1H, J = 7.6 Hz) ^{13}C NMR (125.75 Hz, D_2O)[1] δ 35.6, 40.7, 48.8, 62.5, 63.0, 84.5, 86.8, 96.5, 142.3, 158.3, 168.8; MS [FAB Exact Mass (M + H)] Calculated for $C_{10}H_{15}O_4$ + H: 242.1141; Found: 242.1140.

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10. The yields of **4a** or **4b** and **5a** + **6** or **5b** were determined by ^{1}H NMR analyses using an internal standard. To corroborate the yields obtained by ^{1}H NMR analyses, the hydroformylation products of **3a** were treated with $NaBH_4$ and the resulting alcohols were acetylated to provide the corresponding esters for comparison to an independently synthesized sample. Isolation of 3',5'-*O*-diacetyl derivative of 2',3'-dideoxy-3'-hydroxymethyluridine by column chromatography gave yields that were identical with the yields of the ^{1}H NMR analyses for the hydroformylation product **4a**.
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13. Besides eliminating the uracil to cytocine conversion, another advantage in using **3b** rather than **3a** was that the cytosine moiety exhibited less predisposition toward elimination from **5b**.

(*Received in USA* 12 *November* 1996; *revised* 15 *January* 1997; *accepted* 16 *January* 1997)