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Novel Nucleosides via Intramolecular Functionalization of 2,2'-Anhydrouridine Derivatives

Danny P. C. McGee,[£] David P. Sebesta,*[£] Sarah S. O'Rourke,[£] Rogelio L. Martinez,[£] Michael E. Jung,[∞] and Wolfgang A. Pieken,.[£ 1]

NeXstar Pharmaceuticals Inc., 2860 Wilderness Place, Boulder, Colorado, 80301
and
Department of Chemistry and Biochemistry, University of California, Los Angeles, CA, 90024

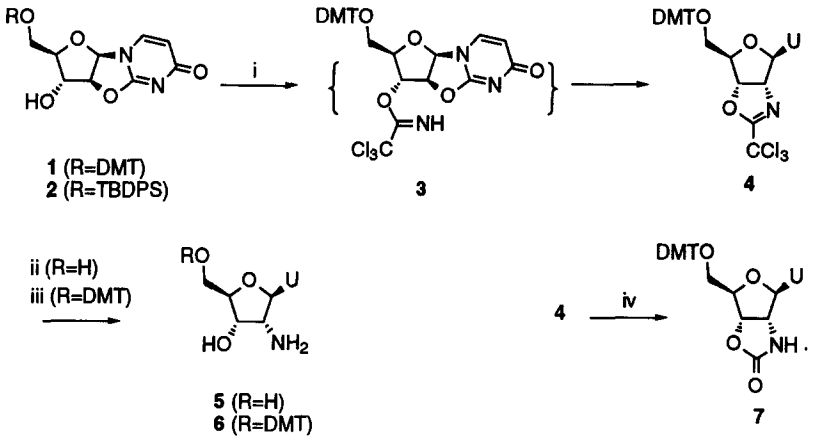
Abstract: The generation of novel ribonucleoside analogues derived from 2,2'-anhydrouridines by a 3'-hydroxyl directed intramolecular nucleophilic substitution of the 2'-position is described. The methodology allows for the efficient, regio- and stereoselective elaboration of the 2'-position, often under exceptionally mild reaction conditions.

Modified nucleosides are of considerable interest as potential therapeutic agents and as precursors to modified oligonucleotides.[2] For example, 2'-modified pyrimidine nucleotides (e.g., 2'-NH_2 or 2'-F uridine and cytidine) have been employed as mechanism-based endonuclease stabilizing elements in ribozymes,[3] while the corresponding nucleotide triphosphates, by virtue of their ability to serve as substrates for T7 RNA polymerase,[4] have been employed in the generation of stabilized oligonucleotide libraries for screening.[5] We report here the generation of novel ribonucleoside analogues derived from 2,2'-anhydrouridines by a 3'-hydroxyl directed intramolecular nucleophilic substitution of the 2'-position. The methodology allows for the efficient, regio- and stereoselective elaboration of the 2'-position, often under exceptionally mild reaction conditions.

Nucleophilic opening of anhydro nucleosides represents a classical technique for elaborating the ribose ring of the nucleoside.[6] For example, the medicinally significant 3'-azido-2',3'-dideoxythymidine (AZT) has been prepared from 2,3'-anhydrothymidine and lithium azide.[7] Likewise, 2'-amino-, 2'-fluoro-, and 2'-phenylseleno-2'-deoxyuridines are derived from nucleophilic openings of 2,2'-anhydrouridine derivatives.[8a-c] Although nucleophilic anhydronucleoside ring opening reactions such as these have found widespread utility, harsh reaction conditions are often required. In addition, competing nucleophilic attack at the 2-position of the pyrimidine base results in the formation of epimeric *arabino*-configured nucleosides as undesired (and often difficult to separate) by-products.[9]

By analogy to the rich spectrum of synthetic approaches to intramolecular and/ or hydroxy-assisted nucleophilic opening of epoxy alcohols,[10] we envisioned the delivery of 3'-hydroxyl tethered nucleophiles to the 2'-position of 2,2'-anhydronucleosides. While examples of intramolecular openings of carbohydrate epoxides have been reported,[10e] this strategy of nucleoside ribose derivatization has, to our knowledge, not been explored[11] and should have the advantage of circumventing the tendency of amine nucleophiles to add at the 2-position.[9b] The present communication delineates some of our initial studies exploiting this approach in the syntheses of the known pyrimidine nucleoside 2'-amino-2'-deoxyuridine, as well as several structurally novel nucleoside analogues including some 5-bromo-2'-deoxyuridine derivatives.

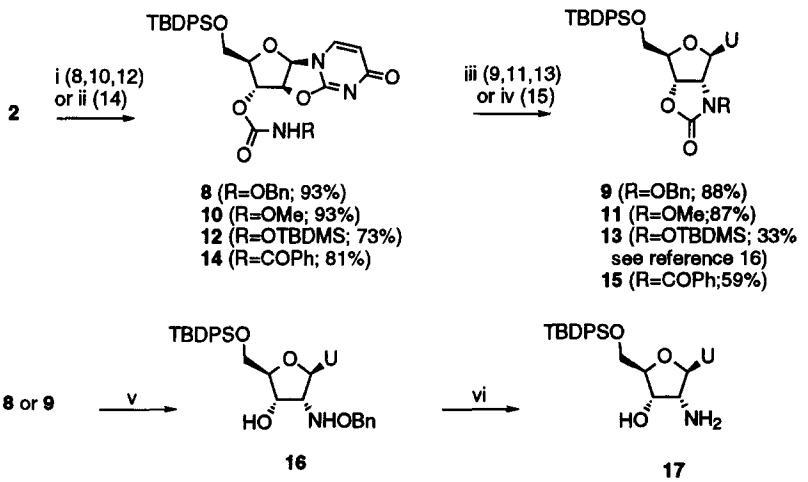
Key starting materials for the present studies are 5'-*O*-DMT and 5'-*O*-TBDPS-2,2'-anhydrouridine derivatives **1** and **2**, respectively, which are readily prepared by known methods.[12] As shown in **Scheme 1**, treatment of the 5'-DMT substrate **1** with trichloroacetonitrile and Et_3N at 90°C provided nucleoside trichloromethyl oxazoline **4** in 80% yield.[13,14] Conversion of **4** to 2'-amino-2'-deoxy uridine **5** was accomplished under acidic conditions, while treatment with aqueous sodium hydroxide in dioxane afforded oxazolidinone **7**. On the other hand, refluxing an ethanol and NaOH solution of **4** facilitated conversion to the 5'-*O*-DMT-2'-aminouridine derivative **6** (79%).[15]



Reagents and Conditions: (i) Et_3N, CCl_3CN, 90°C; 80%, (ii) 80% HOAc; 84% (iii) 6N NaOH/ EtOH, reflux; 79% (iv) Dioxane, NaOH; 58%

Scheme 1

N-Alkoxycarbamate anhydrouridines **8**, **10**, and **12** were prepared in good to excellent yields from **7** by sequential treatment with carbonyldiimidazole and the corresponding hydroxylamine (or hydroxylamine hydrochloride) derivatives in pyridine (**Scheme 2**). Treatment of these intermediates with catalytic DBU in THF effected cyclization to the novel 2'-deoxy-2'-alkoxyamino uridine derivatives **9**, **11**, and **13**. Facile cleavage of the N,O-carbonyl moiety of these derivatives can also be carried out. For example, N-benzyloxyamino nucleoside **16** was prepared in 79% yield by treatment of **9** with Cs_2CO_3 in methanol at 23°C. Alternatively, a tandem cyclization/ deprotection sequence was accomplished in which **8** was treated

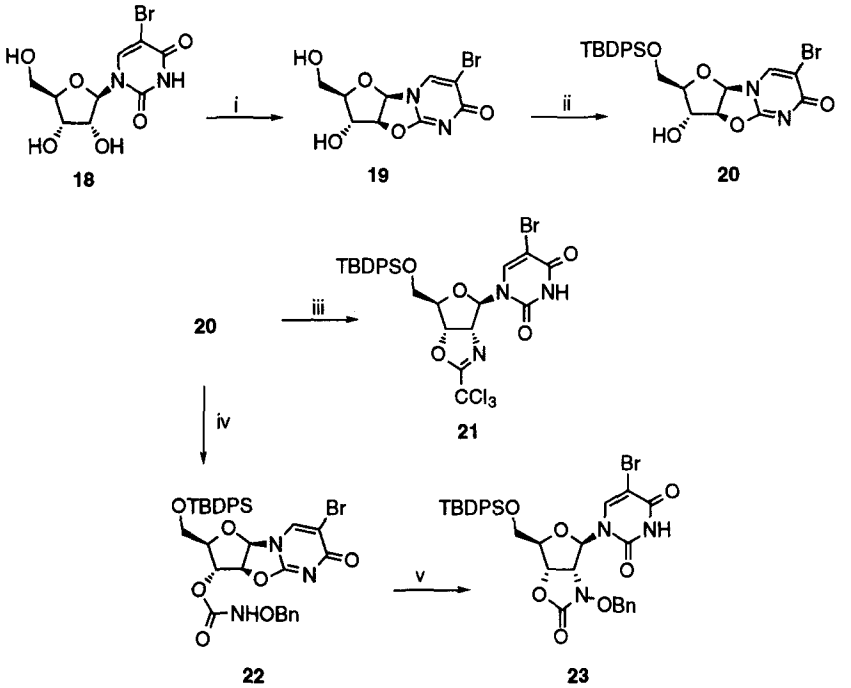


Reagents and Conditions (i) carbonyldiimidazole, pyridine then $RONH_2$ or $RONH_3Cl$, (ii) PhCOCNO, pyridine; 81% (iii)10 mol % DBU, THF. (iv) Cs_2CO_3 (1 equiv), DMF (v) Cs_2CO_3 (2 equiv),methanol; 79% (vi)$Pd(OH)_2$, EtOH, cyclohexene; 60%

Scheme 2

with excess Cs_2CO_3 in methanol to yield **16** directly. Transfer hydrogenolysis of the benzyloxyamine of ring-opened substrate **16** ($Pd(OH)_2$, EtOH, cyclohexene) gave 2'-deoxy-2'-aminouridine derivative **17** in 60% yield.

Additionally, carbamate **14**, the condensation product of **2** and benzoyl isocyanate (pyridine; 81%) afforded, upon treatment with one equivalent of Cs_2CO_3 in DMF, the bicyclic uridine derivative **15** in 66% yield.



Reagents and Conditions (i) $(C_6H_5O)_2CO$, $NaHCO_3$, DMF, 110°C; 79% (ii) TBDPSCl, pyridine; 60% (iii) CCl_3CN, Et_3N, reflux; 79% (iv) CDI, pyridine, then $BnONH_2$ (v)10 mole% DBU, THF; 64%.

Scheme 3

5-Halouridine nucleosides have been established as versatile precursors to modified nucleosides and oligonucleotides via Pd-catalyzed cross coupling with acetylenes,[17] as well as vinyl and aryl stannanes,[18] and we were interested in expanding the scope of our methodology to the preparation of such derivatives. 5-Bromo-2,2'-anhydrouridine **19** (**Scheme 3**) was prepared from 5-bromouridine (**18**; PhO_2CO, $NaHCO_3$, DMF,110°C; 79%).[19] 5'-*O*-Silylation under standard conditions (TBDPSCl, pyridine) gave 5'-O-TBDPS derivative **20** in 60% yield. Conversion of **20** to the trichloromethyloxazoline **21** was observed upon treatment with CCl_3CN and triethylamine at reflux. Similarly, 2'-benzyloxyamine derivative **23** was prepared from compound **20** upon treatment with carbonyldiimidazole and $BnONH_2$, followed by catalytic DBU in THF in 64% overall yield.

In summary, we have demonstrated a useful and flexible synthetic methodology for preparing ribose-modified nucleoside derivatives. The strategy appears general for 2,2'-anhydrouridines and enables the synthesis of novel structures not readily prepared by other approaches.

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19. 5-Iodouridine is unstable under these reaction conditions.

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