Regioselective modification of the sugar moiety in pyrimidine nucleosides *via* a 4′,5′-dehydro-2′,3′-anhydrouridine intermediate

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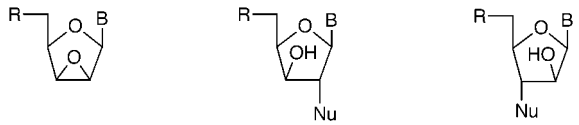
Received (in Cambridge, UK) 12th July 1999, Accepted 9th August 1999

3′-Substituted pyrimidine nucleoside derivatives are obtained in moderate to high yields by the reaction of 1-(2′,3′-anhydro-5′-deoxy-4′,5′-didehydro-α-L-*erythro*-pentofuranosyl)uracil with nucleophiles without the formation of the corresponding 2′-adduct.

Nucleosides modified in the sugar moiety have become important components of both chemotherapeutic agents, as potential antimetabolites,[1] and synthetic oligonucleotide probes.[2] From a synthetic point of view, it is desirable to develop a common key intermediate. 2′,3′-Anhydro-β-D-lyxo-



1 **2** **3**

furanosyl pyrimidine nucleosides **1** first synthesized by Fox *et al.*[3] are versatile building blocks, which through a nucleophilic ring-opening reaction can function as precursors of enantiomerically pure and biologically interesting pyrimidine nucleoside derivatives, and a number of reports for the application of **1** have appeared in the literature.[4] However, it is well known that the nucleophilic addition of **1** gave a mixture of 2′- and 3′-adducts (**2** and **3**) in most cases.

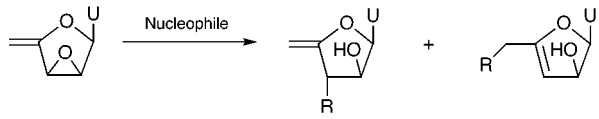
During our studies on the nucleophilic modification of 2′,3′-epoxy derivatives **1** and related compounds, we have discovered that the treatment of 2′,3′-epoxy-5′-iodouridine **4**[3c] with MeONa afforded 4′,5′-dehydro-5′-deoxy-3′-methoxy derivative **5a** in 96% yield as the sole product (Scheme 1). The possible reaction intermediates, 1-(2′,3′-anhydro-5′-deoxy-4′,5′-didehydro-α-L-*erythro*-pentofuranosyl)uracil **6** and 5′-iodo-3′-methoxy derivative **7**, were prepared. The epoxide **6** reacted regioselectively with MeONa to give the corresponding 3′-adduct **5a** in 80% yield *via* regiospecific nucleophilic attack of the methoxide anion at the highly reactive allylic 3′-position of **6**. On the other hand, only 2′,5′-anhydro derivative **8** was accessible from 5′-iodo-3′-methoxy derivative **7** without the formation of **5a** (Scheme 1).

We have now worked out an efficient synthetic method for the epoxide **6**, possessing contiguous enol ether and epoxide moieties in the molecule, which acts as a prominent precursor for a variety of 3′-adducts **5** and that can be incorporated into 3′-modified pyrimidine nucleosides. The synthesis of 2′,3′-anhydrouridine **6** was achieved in 92% yield by the reaction of **4** with LiHMDS (2.2 equiv.) in dry DMF (0 °C, 4 h). The efficiency of **6** as the precursor of the modified sugar moiety was demonstrated in the nucleophilic addition using various nucleophiles (Table 1). With the exception of two examples (Table 1, entries 1 and 2), which needed reflux temperatures for the completion of the reaction, all other additions were achieved at room temperature, and the yields of the 3′-adduct **5** were in the range of 52–81%. In the reaction with NaN_3 or PhSH as a comparatively soft nucleophile, 5′-adduct (**9g** or **9h**)[5] was also formed as a side product (3 or 11% yield) *via* S_N2' addition[6] together with a major product, the 3′-adduct (**5g** or **5h**).

In addition, when Et_2AlCN was used as a nucleophile, isomerized product **11** was obtained in 58% yield due to the activation of 3′-hydrogen of intermediate **10** by the strong electron-withdrawing cyano group (Scheme 2).

Next, we examined the hydroboration reaction of **5a**, aiming to convert it into the 5′-hydroxy derivatives **12** and **13**. When **5a** was refluxed with 18 equiv. of BH_3–THF in dry THF and then subsequently treated with H_2O_2–NaOH, the α-isomer **12** was obtained as the major product (53%) together with the β-isomer

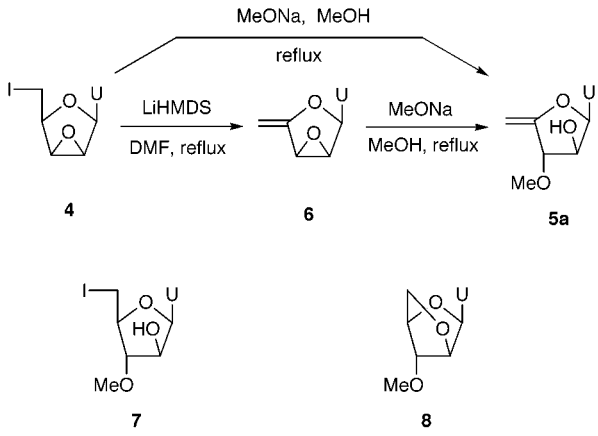
Table 1 Nucleophilic addition to **6**



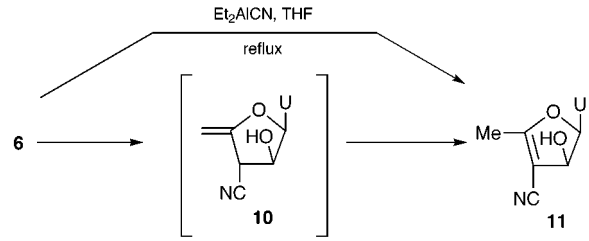
6 **5** **9**

Entry	Nucleophile	Solvent[a]	*t*/h	R	Product	Yield (%)[b] **5**	**9**
1	MeONa	MeOH[c]	2	OMe	**a**	80	ND[d]
2	Me_3Al	CH_2Cl_2[c]	12	Me	**b**	81	ND[d]
3	$BnNH_2$	CH_2Cl_2	24	NHBn	**c**	81	ND[d]
4	$NaCH(CO_2Me)_2$	MeOH	12	$CH(CO_2Me)_2$	**d**	69	ND[d]
5	BzOH[e]	CH_2Cl_2	1	OBz	**e**	61	ND[d]
6	BzSH[e]	CH_2Cl_2	48	SBz	**f**	52	ND[d]
7	NaN_3	DMF	3	N_3	**g**	63	3
8	PhSH	Et_3N	1	SPh	**h**	80	11

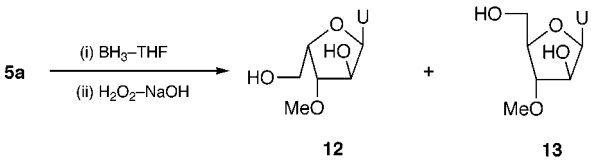
[a] Unless otherwise noted, the reactions were carried out at room temperature. [b] Isolated yields after chromatographic separation; all the reaction products were fully characterized by elemental analysis and spectroscopic data. [c] The reactions were carried out under reflux conditions. [d] Not detectable. [e] Reactions were performed in the presence of Et_3N as base.



Scheme 1



Scheme 2



Scheme 3

13 as a minor product (17%) (Scheme 3). This isomer ratio may be interpreted by invoking the steric hindrance effects of the methoxy group at the 3′-position.

In conclusion, we have developed a regioselective method for the synthesis of 3′-substituted pyrimidine nucleoside derivatives **5**, **11**, **12** and **13** using 1-(2′,3′-anhydro-5′-deoxy-4′,5′-didehydro-α-L-*erythro*-pentofuranosyl)uracil **6** as a key intermediate without the formation of the corresponding 2′-adduct. The results presented herein provide a novel entry into a variety of sugar-modified pyrimidine nucleosides.

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Communication 9/05608D