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Stereoselective synthesis of azanucleosides aza-stavudine (aza-D4T), aza-2′,3′-didehydro-3′-deoxyuridine (aza-D4U), and its hydrogenated analogues from an endocyclic enecarbamate

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Abstract—The stereoselective synthesis of the aza-analogues of nucleosides stavudine (D4T) and dideoxyuridine (DDU) were accomplished in a very concise manner (3–4 step sequences) with high overall yields from a five-membered endocyclic enecarbamate employing phenylselenenyl bromide as an effective promoter.

Azanucleosides show great promise as metabolites capable of interfering with DNA processing enzymes in a controlled manner.[1] Among the key processes in nucleic acid metabolism, the base-excision DNA repair (BER) enzymes play a significant role by repairing damage inflicted to DNA from spontaneous hydrolysis, oxidation and errors in replication. The structural similarity of aza-ribonucleosides to ribonucleosides makes them suitable transition state analogues for fault incorporation into DNA (2-deoxy series) or RNA. A remarkable example of the influence of an azanucleoside incorporated into DNA was recently described by Verdine.[2] The DNA incorporated adenine pyrrolidine homonucleoside (phA) **1** (Fig. 1) was responsible for a strong inhibition of DNA glycolylase MutY. Moreover, azanucleosides such as **2**, containing a C–N glycosidic bond have been shown to stabilize antisense oligonucleotides toward 3′-exonucleases.[3]

Our interest in azanucleosides stemmed from the possibility of creating novel nucleoside analogues from chiral five-membered endocyclic enecarbamates which would be capable of interacting with reverse transcriptase in an inhibitory mode, thus providing new therapeutic leads against HIV viruses. Identification of new agents against drug resistant strains of HIV-1 is a subject of great medical relevance nowadays.[4] Our initial objectives were the synthesis of aza-analogues of stavudine **3** and dideoxyuridine **4** (DDU) (Fig. 1).[5] Stavudine is an anti-retroviral nucleoside drug currently employed as part of a drug cocktail that has been effective in the treatment of the acquired immunodeficiency syndrome (AIDS).

In this communication we present the successful synthesis of these compounds and of their saturated analogues in a straightforward manner with good control of the

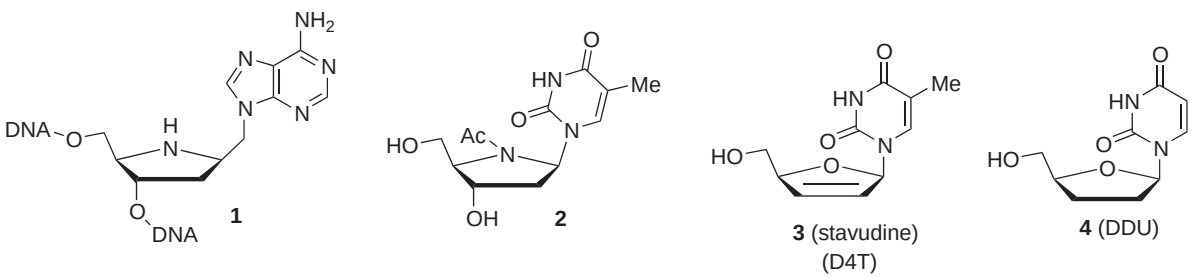

Figure 1.

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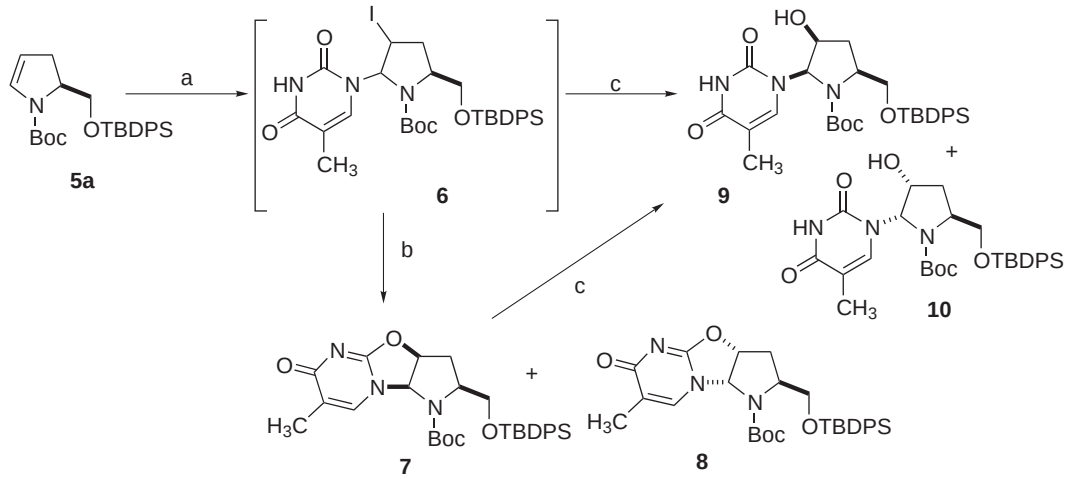
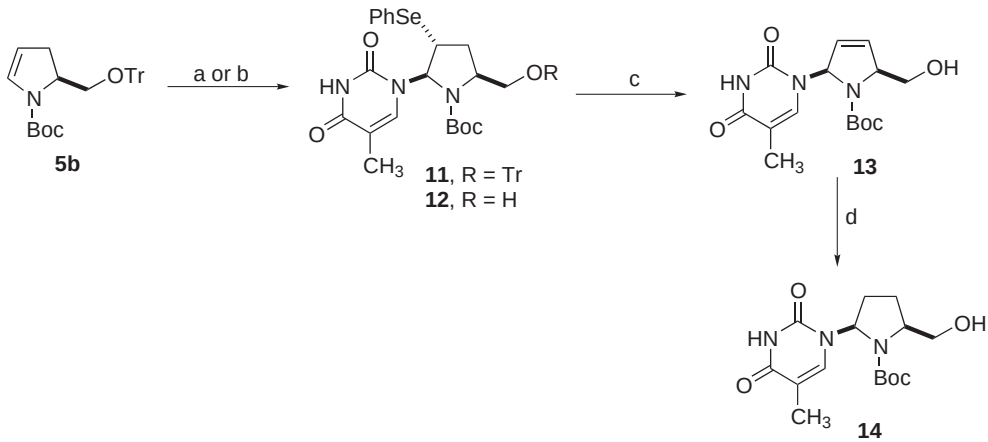


Scheme 1. *Reagents and conditions*: (a) $(TMS)_2$-thymine, NIS, CH_2Cl_2, 0°C; (b) DBU, CH_2Cl_2, 0°C; (c) $NaOH/H_2O$/THF, rt, 30 min.



Scheme 2. *Reagents and conditions*: (a) $(TMS)_2$-thymine, PhSeBr, CH_3CN, −23°C (b) i. $(TMS)_2$-thymine, PhSeBr, CH_3CN, −23°C; ii. $ZnBr_2$, MeOH, CH_2Cl_2 (85%); (c) H_2O_2, dioxane, $NaHCO_3$ (96%) (d) H_2, Pd/C, EtOAc (92%).

stereoselectivity of the process and in very good overall yields.

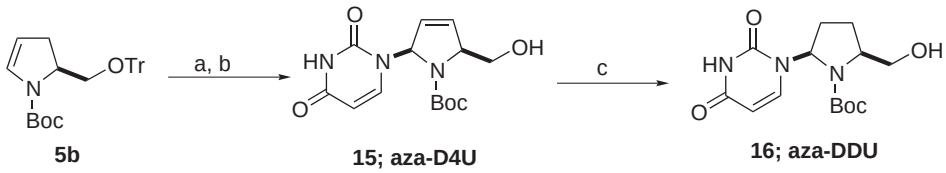
Addition of pyrimidine bases promoted by *N*-iodosuccinimide (NIS)[6a,b]

Addition of bis(trimethylsilyl)thymine to endocyclic enecarbamate **5a** promoted by NIS occurred quickly and cleanly to provide the expected iodonucleoside **6** as a single spot on TLC (Scheme 1).[7] Although compound **6** is stable it was not isolated. Instead, the crude iodonucleoside **6** was directly reacted with DBU to give a 3:1 diastereomeric mixture of the azatricyclic nucleosides **7** and **8** in 75% overall yield demonstrating moderated stereoselectivity for the electrophilic addition process. The diastereomers were separated by column chromatography and analysed spectroscopically (^1H, ^{13}C NMR and COSY spectroscopy) confirming the β anomer as the major reaction product.

Reaction of iodonucleoside **6** with aqueous sodium hydroxide provided the 3′-deoxy azanucleosides **9** and **10** in 87% yield from enecarbamate **5a** as a 3:1 mixture of β and α anomers. This 3:1 stereoselectivity was confirmed by the conversion of azatricyclic nucleoside **7** into the 3′-deoxyazanucleoside **9** in 73% yield. Attempts to perform dehydrohalogenation of iodonucleoside **6** with sodium methoxide resulted only in a mixture of tricyclic products **7** and **8**, together with small quantities of the nucleosides **9** and **10**; the desired unsaturated azanucleoside was not observed in this case. Prompted by these results and by the low stereoselectivity observed for the addition of $(TMS)_2$-thymine to the five-membered endocyclic enecarbamate, we looked for other promoters for the nucleophilic addition of pyrimidine and/or purine bases to the endocyclic enecarbamates.

Use of phenylselenenyl bromide as promoter[6c–e]

Addition of silylated thymine to the five-membered endocyclic enecarbamate **5b**[7] promoted by phenylselenenyl bromide at −23°C (Scheme 2) occurred smoothly to give the seleno azanucleoside **11** as a major product. Interestingly, contrary to glycals, no Lewis acid catalyst was necessary to perform the addition of the silylated



Scheme 3. *Reagents and conditions*: (a) i. $(TMS)_2$-uracil, PhSeBr, CH_3CN, −23°C; ii. $ZnBr_2$, MeOH, CH_2Cl_2; (b) H_2O_2, dioxane, $NaHCO_3$; (c) H_2, Pd/C, EtOAc.

base to the enecarbamate.[6c,d] A minor secondary product was identified as the free alcohol **12** resulting from deprotection of the trityl group. Since detritylation was a planned step in the synthesis we decided to remove the Tr group immediately after thymidine addition, without purification. Therefore, the products obtained from addition of $(TMS)_2$-thymine promoted by PhSeBr were treated with $ZnBr_2$[8] to afford a single product by TLC corresponding to the thymidine derivative **12** in 85% isolated yield. Elimination of the phenylselenenyl group to generate the desired olefin was carried out under standard conditions with hydrogen peroxide to give aza-stavudine **13** (aza-2′,3′-didehydro-3′-deoxythymidine; aza-D4T) in 96% yield. The entire process to aza-stavudine from endocyclic enecarbamate comprised only three steps involving two separate operations with an overall yield of 81% yield. The simplicity and high yields associated with these transformations make the process suitable for a considerable increase of scale (we easily prepared batches of 0.5–1.0 g of aza-stavudine **13**). Starting from aza-stavudine preparation of dideoxythymidine **14** (aza-DDT) was straightforward. Catalytic hydrogenation of aza-stavudine **13** cleanly provided aza-DDT **14** in 92% yield. The stereoselectivity of thymine addition employing phenylselenenyl bromide was much higher than that observed for thymine addition promoted by NIS. Aza-stavudine **13**† was obtained as a 9:1 ratio mixture of the β/α anomers as estimated by ^1H NMR analysis at 60°C.[9]

The synthesis of the aza-uridine analogues (aza-DDU) was carried out using the same sequence of reactions depicted above for aza-stavudine and aza-DDT (Scheme 3). Thus, addition of bis(trimethylsilyl)uracil to endocyclic enecarbamate **5b**, followed by deprotection of the uracil adduct with zinc bromide provided the seleno azanucleoside in 73% yield (not shown in Scheme 3). Oxidation of the seleno azanucleoside followed by an easy *syn*-selenoxy elimination provided the aza-D4U **15** in 87% yield (~10:1 diastereomeric ratio by ^1H NMR at 60°C). Catalytic hydrogenation of aza-D4U then provided aza-DDU **16** in 86% yield.

In conclusion, the azanucleosides aza-D4T, aza-DDT, aza-D4U and aza-DDU were prepared in a concise manner and in high overall yields starting from the five-membered endocyclic enecarbamate **5b**. The method employing phenylselenenyl bromide was more stereoselective than that employing NIS as promoter. Moreover, it is pertinent to note that in contrast to similar additions of silylated bases to glycals, no Lewis acid catalysis was necessary to promote addition of the silylated bases to the endocyclic enecarbamate.[6c,d] The methodology described herein to prepare *cis*-azanucleosides complements those available to the synthesis of *trans*-azanucleosides, which make use of *N*-acyliminium intermediates.[10] The methodology is also straightforward and amenable to the synthesis of other azanucleosides of pharmacological and therapeutic interest.

Acknowledgements

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† Selected spectroscopic data: **13** (major isomer). ^1H NMR (300 MHz, $CDCl_3$, 60°C): δ 8.97 (br s, 1H), 7.55 (br s, 1H), 6.89 (br s, 1H), 6.10 (dt, 1H, $J=6.2$, 1.8 Hz), 5.73 (dt, 1H, $J=6.2$, 1.8 Hz), 4.63 (br s, 1H), 4.12 (dd, 1H, $J=11.4$, 2.9 Hz), 3.86 (dd, 1H, $J=11.4$, 4.2 Hz), 1.87 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 154.7, 150.5, 136.0, 132.5, 126.7, 82.4, 73.7, 66.9, 63.9, 28.2, 12.5. **15** (major isomer): ^1H NMR (300 MHz, $CDCl_3$, 55°C) δ 8.92 (br s, 1H), 7.80 (d, 1H, $J=8.1$ Hz), 6.91 (br s, 1H), 6.10 (dt, 1H, $J=6.25$, 1.6 Hz), 5.76 (dt, 1H, $J=6.25$, 2.1 Hz), 5.67 (d, 1H, $J=8.1$ Hz), 4.64 (br s, 1H), 4.15 (dd, 1H, $J=11.4$, 1.8 Hz), 3.84 (dd, 1H, $J=11.4$, 4.0 Hz), 3.02 (br s, 0.6H), 1.76 (br s, 0.4H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6, 154.3, 150.5, 140.6, 132.8, 126.4, 102.3, 82.4, 73.8, 66.7, 63.3, 28.1.

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9. The presence of rotamers greatly complicated NMR analysis, therefore high temperature ^{1}H NMR of compound **13** was necessary to observe the two double triplets at 6.10 ppm corresponding to H-3′. The β anomer of compound **14** also displays a small but significant NOE between H-6 (vinylic hydrogen on the thymine moiety) and H-5′ (hydroxymethylene on the pyrrolidine moiety).
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