# Stereocontrolled Synthesis of 3′-Isomeric β-Nucleoside by Intramolecular Glycosylation

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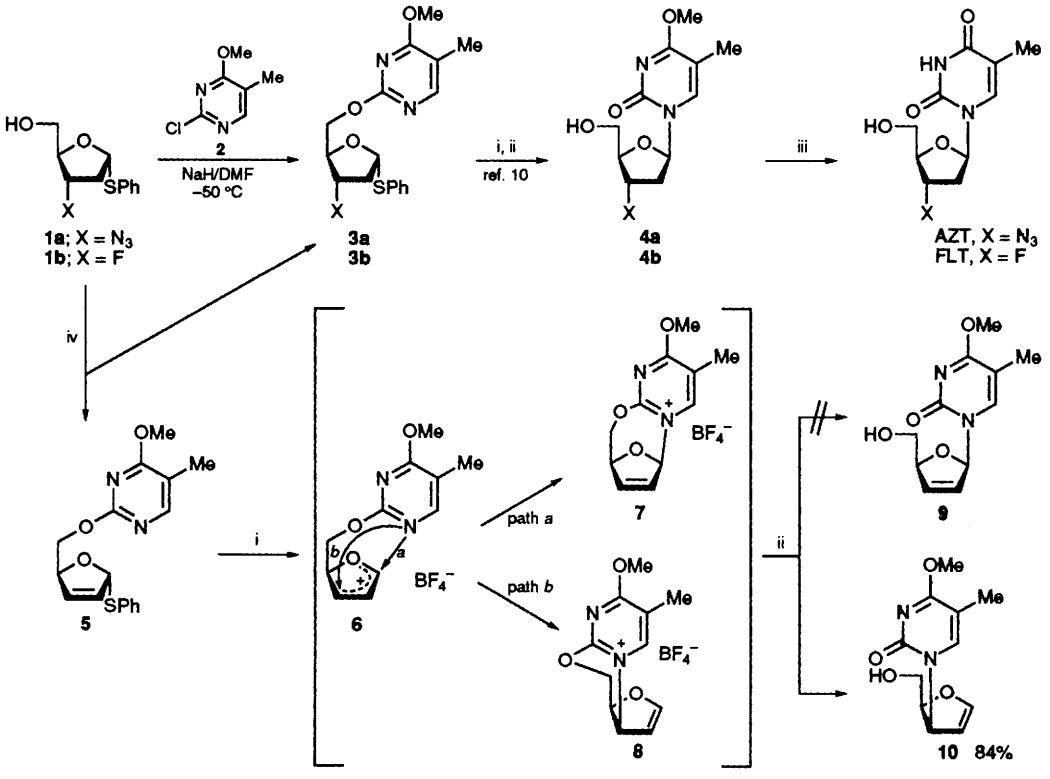
Intramolecular glycosylation of a pyrimidine derivative, which was temporarily connected to a 2,3-unsaturated 1-thiopentofuranoside through an ethereal linkage, led to an unusual 3′-isomeric nucleoside in a stereoselective fashion.

In recent years, there has been considerable interest in regioisomeric nucleosides, in which the heterocyclic base is attached to the C-2 or the C-3 position of the sugar moiety, as potent anti-HIV agents.[1–8] The stereoselective introduction of the heterocyclic base to the desired site on the sugar component is the primary focus during the synthesis of such nucleoside analogues. Recently, we have reported the stereocontrolled synthesis of pyrimidine 2′-deoxy- and 2′,3′-dideoxy-β-nucleosides by intramolecular glycosylation.[9,10] Herein, we report that this strategy is applicable to the stereoselective synthesis of 3′-isomeric nucleoside derivatives.

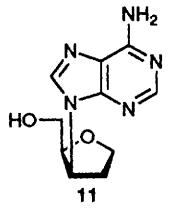
In a previous paper,[10] we reported that 3′-azido-3′-deoxythymidine (AZT) and 3′-deoxy-3′-fluorothymidine (FLT) are synthesised in a stereocontrolled manner by intramolecular glycosylation *via* thioglycosides in which the pyrimidine base is temporarily introduced at the C-5 position through an ethereal linkage, as outlined in Scheme 1. We obtained 3-substituted 5-*O*-(2-pyrimidyl)-1-thiopentofuranosides, **3a** and **3b**, in good yields by the reaction of the sodium salts derived from the thioglycosides, **1a** and **1b**, with 2-chloropyrimidine **2** at −50 °C. However, when a similar reaction was carried out at room temperature, β-elimination of the C-3 substituents occurred to give the 2,3-unsaturated thioglycoside **5**. For instance, when the sodium salt of **1a** was treated with **2** at room temperature for 1 h, **5** was produced in 34% yield, accompanied by a 34% yield of **3a**. If intramolecular glycosylation using **5** proceeds at the C-1 position, the 2,3-unsaturated nucleoside **9**, a precursor of the anti-HIV-active d4T, may be obtained. Usually, 2′,3′-unsaturated nucleosides have been prepared by modifying the sugar moiety of intact nucleosides or their derivatives obtained by the coupling of appropriate sugar components with heterocyclic bases.[11,12] However, there has been no report of the synthesis by direct glycosylation of a heterocyclic base using a 2,3-unsaturated sugar derivative. We therefore attempted the intramolecular glycosylation utilising **5** under similar conditions to those previously reported. Treatment of **5** with $Me_2S(SMe)BF_4$ in MeCN at −20 °C for 5 h, followed by hydrolysis with 1 mol $l^{-1}$ NaOH, however, led to the unexpected 3′-isomeric nucleoside **10**† as a sole product.

A plausible mechanism for the formation of **10** is illustrated in Scheme 1. Activation of **5** with $MeS^+$ will lead to the allylic oxo-carbenium intermediate **6**. Attack by the pyrimidine will exclusively proceed at the C-3 position (path *b*), in preference to C-1 (path *a*), to yield a pyrimidinium intermediate **8**. Hydrolysis of the intermediate **8** will afford the unsaturated 3′-isomeric nucleoside **10**. The exact reason for the regioselective formation of **10** remains unclear at present. Usually, the reaction of 2,3-unsaturated glycosyl donors or glycals with nucleophiles in the presence of a Lewis acid or $Pd^{II}$ has proceeded *via* allylic oxo-carbenium intermediates similar to **6** to give the corresponding 2,3-unsaturated glycosides in which the nucleophiles are introduced at C-1.[13–15] Hence, the present result is, to the best of our knowledge, the first example of incorporation of a nucleophile at the C-3 position of unsaturated sugar components *via* allylic oxo-carbenium ion intermediates.[16]

The synthesis of 3′-isomeric dideoxy adenosine **11** has




**Scheme 1** *Reagents and conditions*: i, $Me_2S(SMe)BF_4$, MeCN, −20 °C, 5 h; ii, 1 mol $l^{-1}$ NaOH aq., 0 °C, 3 h; iii, Dowex 50W ($H^+$), EtOH–$H_2O$; iv, **2**, NaH, DMF, room temp.



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recently been reported by Nuesca and Nair as a novel analogue of anti-HIV-active 2′,3′-dideoxy nucleosides.[8] The present reaction may be an alternative, facile method for the preparation of 3′-isomeric pyrimidine nucleosides. Further investigations of the transformation of **10** into 3′-isomeric dideoxy thymidine and cytidine derivatives as well as the applicability of this method to other substrates such as 2,3-unsaturated 1-thiohexopyranosides are currently under way.

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## Footnote

† Compound **10**: 400 MHz $^1$H NMR ($CDCl_3$) δ 1.95 (s, 3H, Me), 2.99 (dd, 1H, *J* 3.9, 9.1 Hz, OH), 3.53 (ddd, 1H, *J* 3.9, 7.3, 12.2 Hz, H-5′$_a$), 3.70 (ddd, 1H, *J* 4.4, 9.8, 12.2 Hz, H-5′$_b$), 4.01 (s, 3H, OMe), 4.72 (ddd, 1H, *J* 4.4, 7.3, 7.8 Hz, H-4′), 5.11 (t, 1H, *J* 2.9 Hz, H-2′), 5.81 (ddd, 1H, *J* 1.5, 2.9, 8.3 Hz, H-3′), 6.87 (d-like, 1H, *J* 1.5 Hz, H-1′), 7.23 (s, 1H, H-6); $^{13}$C NMR δ 12.33, 54.85, 59.33, 59.40, 85.11, 99.56, 105.03, 141.20, 152.52, 158.10, 170.90.

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