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A novel approach to unsaturated acyclic nucleoside analogues and the first synthesis of d4T by ring closure metathesis

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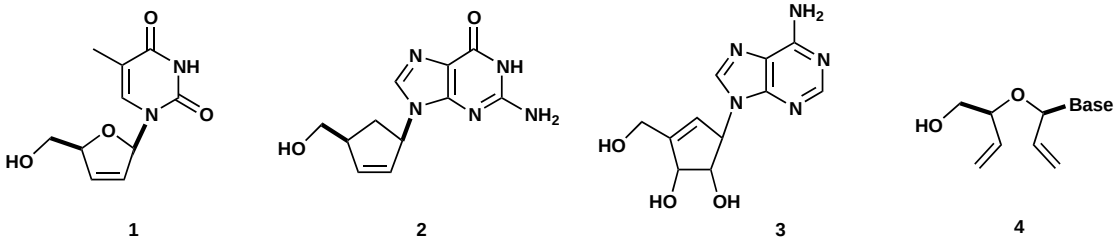
Abstract—Novel unsaturated acyclic nucleoside analogues, 1-{1-[1-(hydroxymethyl)prop-2-enyloxy]prop-2-enyl}uracil, 1-{1-[1-(hydroxymethyl)prop-2-enyloxy]prop-2-enyl}thymine and 1-{1-[1-(hydroxymethyl)prop-2-enyloxy]prop-2-enyl}cytosine have been prepared in good yield from uridine and 5-methyluridine by periodate cleavage followed by a double Wittig reaction which introduces two vinyl groups. The thymine derivative underwent ring closure metathesis to give a novel synthesis of d4T.

Since the discovery that potent inhibition of HIV may be associated with the conversion of the furanose ring of normal nucleosides to the corresponding 2′,3′-didehydro-2′,3′-dideoxy analogue, strong interest has centered round the presence of unsaturation in the sugar moiety of nucleosides. The archetype of this class of compounds is d4T (**1**) which, as its triphosphate, inhibits HIV reverse transcriptase. Although many routes to d4T and analogous 2′,3′-pentenfuranose nucleosides have been found,[1] the concept of unsaturation in the nucleoside glycone has also been extended to many other systems. Recent work includes the formation of nucleoside analogues in which the base is attached to a hexenopyranose ring,[2] a cyclopentenyl ring,[3] a cyclohexenyl ring,[4] a dihydrobenzo[*c*]furan ring[5] and a range of unsaturated acyclic groups.[6] This diverse range of structures includes the anti-HIV agent carbovir (**2**),[7] the antibiotic Neplanocin A (**3**)[8] (Fig. 1) and many other examples of compounds with significant antiviral or antibacterial activity.

We are involved in the search for nucleoside analogues with acyclic glycones which have the potential for a high therapeutic index[9] and we describe here a novel approach to the preparation of enantiomerically pure unsaturated acyclic nucleoside analogues. Our methodology allows the simultaneous creation of two vinyl groups to afford species of type **4**. This in turn leads to a new route to 2′,3′-didehydro-2′,3′-dideoxy nucleosides by ring closure metathesis.

Starting from the readily available nucleoside uridine (**5**) or the 5-methyl analogue (**6**) the primary hydroxyl group was protected by tritylation (Scheme 1) to give compounds **7** and **8**, respectively. Oxidative cleavage of the *cis* vicinal diol grouping was achieved with sodium



1 2 3 4

Figure 1.

Keywords: unsaturated acyclic nucleosides; ring closure metathesis; d4T.
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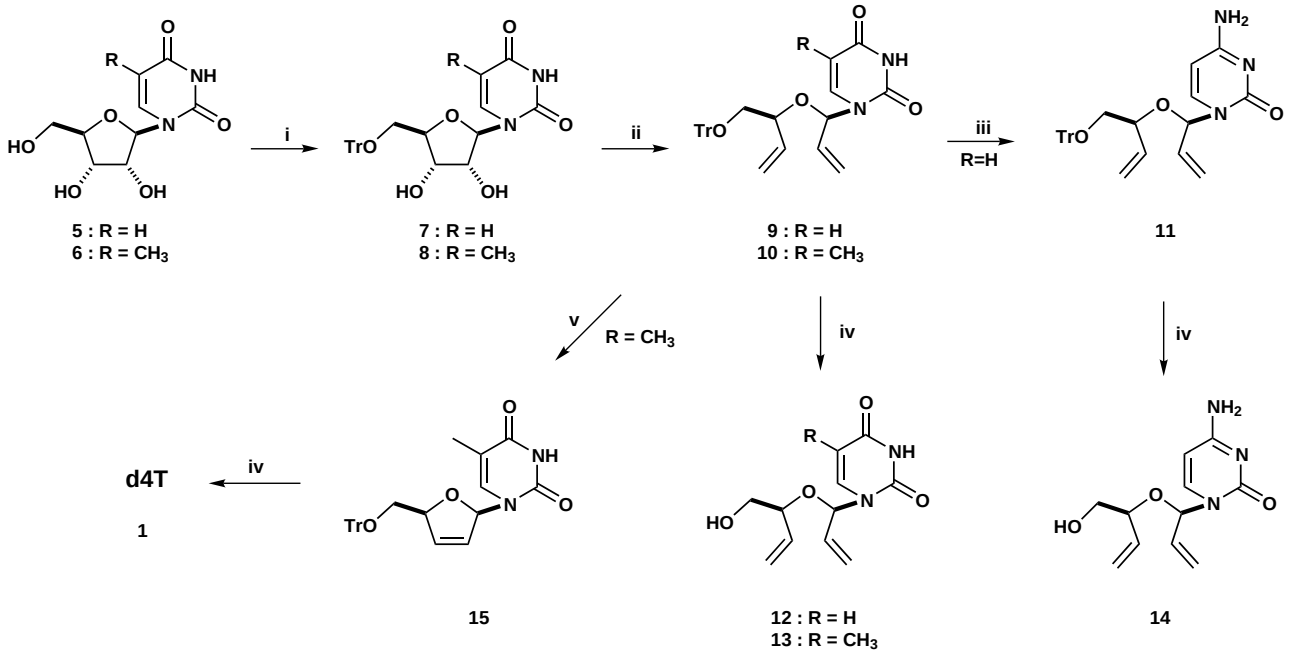

Scheme 1. (i) TrCl, pyr.; (ii) (a) $NaIO_4$, $EtOH/H_2O$, (b) Ph_3PCH_3Br, *t*-BuOK, toluene; (iii) (a) 1,2,4-triazole, $POCl_3$, CH_3CN, Et_3N, (b) aq. 30% NH_3 in 1,4-dioxane; (iv) AcOH 80%; (v) Grubbs reagent, CH_2Cl_2.

periodate in ethanol/water to give the corresponding dialdehydes. These compounds were not stable and hence, after isolation, they were subjected directly to a double Wittig olefination with methyltriphenylphosphonium bromide to afford the novel bis alkenes 1-{1-[1-(trityloxymethyl)prop-2-enyloxy]prop-2-enyl}uracil (**9**) and 1-{1-[1-(trityloxymethyl)prop-2-enyloxy]prop-2-enyl}thymine (**10**). It was found that the yield in this olefination step was strongly dependent on the base used, *t*-BuOK in toluene being much more effective (50% yield) that BuLi in tetrahydofuran (25% yield). Standard nucleoside methodology was used to convert the uracil compound **9** to the cytosine analogue **11** in 89% yield.[10] The three bis alkene nucleoside analogues were easily deprotected in very high yield (>88%) to give compounds **12**, **13**[11] and **14**, respectively. These interesting compounds are clearly capable of further elaboration by epoxidation or dihydroxylation and may lead to novel polyhydroxy nucleoside analogues with therapeutic potential.

The discovery of convenient catalysts has greatly increased interest in ring closure metathesis.[12] Treatment of the 5-methyluracil derivative **10** with Grubbs reagent in dichloromethane resulted in clean ring closure to form the protected d4T species **15**. To our knowledge this is the first example of the formation of the 2,5-dihydrofuran ring by metathesis. Compound **15** had identical physical data to that reported by Cosford[13] and was easily deprotected to afford d4T (**1**).

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