Short Convergent Route to Chiral Pyrimidine Analogues of 2′-Deoxy Neplanocin A

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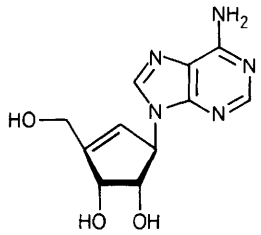
The chiral epoxide (**6**) has been converted in five stages into the thymidine analogue (**14**) of Neplanocin A and into the 6′α-(**8**) and 6′β-(**10**) hydroxy analogues of carbocyclic Thymidine.

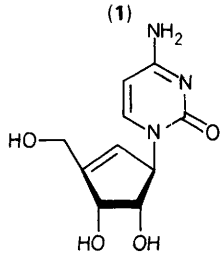
The unusual cyclopentenyl structure and interesting biological properties of the fermentation product Neplanocin A (**1**) have prompted great interest in synthetic approaches to (**1**) and its analogues. These studies have resulted in four total syntheses[1—4] of (**1**), three of them enantioselective,[1—3] and the discovery of antiviral and antitumour activity in the pyrimidine analogue cyclopentenylcytosine (**2**).[5]

The enantioselective syntheses have focused on approaches to either the cyclopentenylamine (**3**), onto which the nucleoside base is constructed,[1,2] or, more directly, to the cyclopentenyl sulphonates (**4**) and (**5**) which allow introduction of the intact nucleoside base.[2,3] The shortest of these routes[2] provides Neplanocin A in eleven stages from D-ribonolactone *via* (**4**) or (**5**). Synthesis of 2′-deoxycyclopentenyl nucleosides requires several more stages to remove the 2′-hydroxy group.[6] In this communication we report a novel convergent approach to pyrimidine analogues of 2′-deoxy Neplanocin A from the chiral epoxide (**6**). Intermediates in this route have also been converted into the 6′α- and 6′β-hydroxy analogues of the antiviral agent carbocyclic Thymidine.[7]

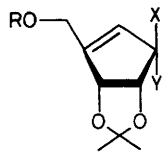
The chiral epoxide (**6**) [enantiomeric excess (e.e.) >98%], available from cyclopentadiene in three stages,[8] has been shown to undergo ring opening in a highly regioselective manner.[9] Thus, with thymine [NaH, dimethylformamide (DMF), 140 °C] the alcohol (**7**) was obtained in 70% yield (Scheme 1). Compound (**7**) was converted in high yield into the novel 2,6′-cyclonucleoside (**9**) [m.p. 188—192°, $\lambda_{max.}$ 230 and 259 nm (EtOH)] with diphenylcarbonate in DMF at 150 °C. This anhydro derivative was found to undergo a facile intramolecular elimination on treatment with potassium



(**1**)



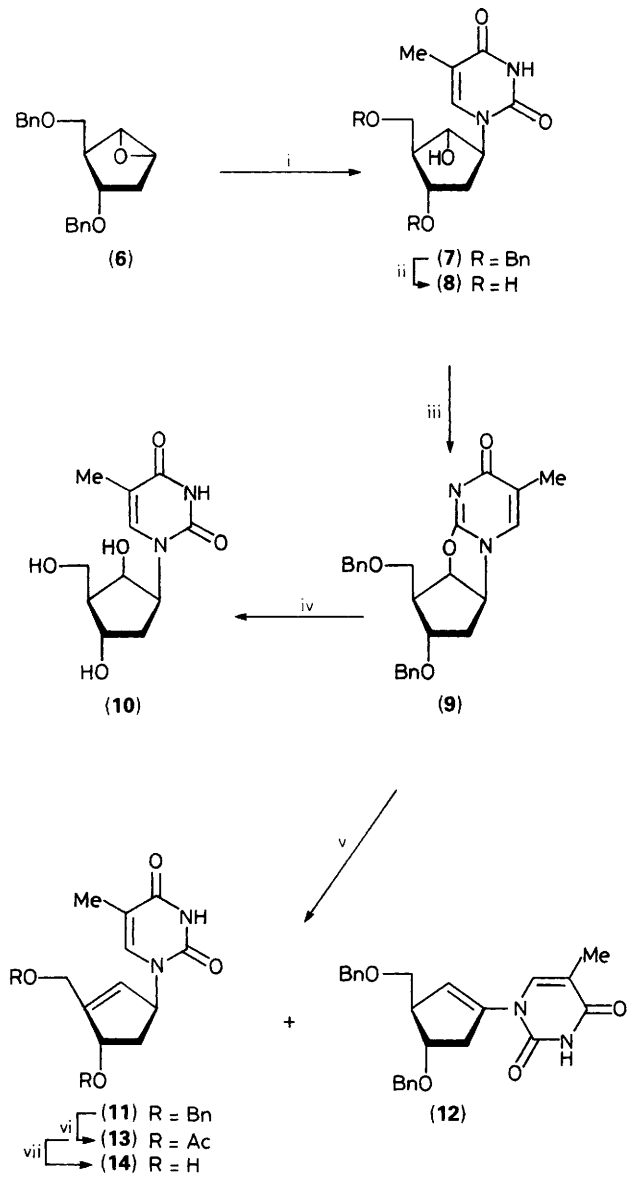
(**2**)



(**3**) X = NH_2, Y = H
(**4**) X = H, Y = OMs
(**5**) X = H, Y = OTs

} R = Bn or $MeOCH_2$

(Ms = SO_2Me; Ts = $SO_2C_6H_4Me$-*p*; Bn = $PhCH_2$)



Scheme 1. *Reagents and conditions*: i, Thymidine, NaH, DMF, 140 °C; ii, H_2, Pd/C; iii, $(PhO)_2C{=}O$, DMF, 150 °C; iv, NaOH, aqMeOH then H_2, Pd/C; v, KOBu^t, DMF; vi, BF_3, Ac_2O; vii, NH_3, MeOH.

t-butoxide (1.5 equiv.) in DMF at room temperature to give predominantly the 4′,6′-alkene (**11**) (46%) along with a smaller amount of the 1′,6′-alkene (**12**) (23%). Similar eliminations have been used in natural furanose nucleosides to prepare 1′,2′,[10] 2′,3′,[11] 3′,4′,[12] and 4′,5′[13] unsaturated derivatives.

Deprotection of compound (**11**) was accomplished in two stages, acetolysis (acetic anhydride/BF_3) followed by methanolysis of the resulting diacetate (**13**), to complete an eight stage synthesis of the thymidine analogue (**14**),† [m.p. 159—163°, $[\alpha]_D^{24}$ −52° (MeOH)] of Neplanocin A.

Hydrolysis of the anhydro derivative (**9**) (NaOH, H_2O/MeOH, 22 °C) followed by hydrogenolytic debenzylation provided the 6′β-hydroxy derivative (**10**) of the antiviral agent carbocyclic Thymidine. The 6′α-hydroxy derivative (**8**) was also prepared by a similar deprotection of compound (**7**). The biological activity of these derivatives will be reported elsewhere.

These latest applications of the epoxide (**6**), which has been used previously to prepare 2′-deoxycarbocyclic nucleosides[9] and their 6′α- and 6′β-fluoro analogues,[14] demonstrate the versatility of this intermediate in the synthesis of 2′-deoxy carbocyclic derivatives, in optically pure form.

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† ^1H NMR data for (**14**) ([$^2H_6$]Me_2SO, 250 MHz) δ 1.75 (s, 3H, Me) 1.96 (ddd, 1H, *J* 16, 7, 5 Hz) and 2.12 (ddd, 1H, *J* 16, 8, 3 Hz, CH_2), 4.12 (ABq, 2H, CH_2OH), 4.74 (m, 1H, CHOH), 4.90 (t, 1H, CH_2OH), 5.00 (d, 1H, CHOH), 5.53 (narrow m, 1H, −CH=), 5.58 (m, 1H, NCH), 7.08 (s, 1H, NCH=), and 11.24 (s, NH) accorded with that reported[6] by Ohno *et al.* for material obtained by a multistage chemicoenzymatic synthesis and which displayed $[\alpha]_D^{24}$ −31° (MeOH). However, the m.p. reported by Ohno (>210°) is surprisingly high when compared to that quoted[6] for the corresponding 2′-deoxyuridine analogue (m.p. 147—149°).