

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

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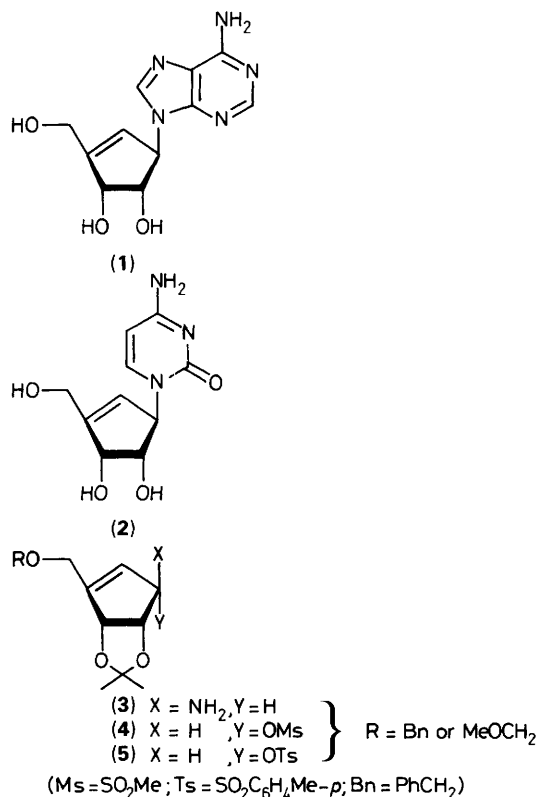
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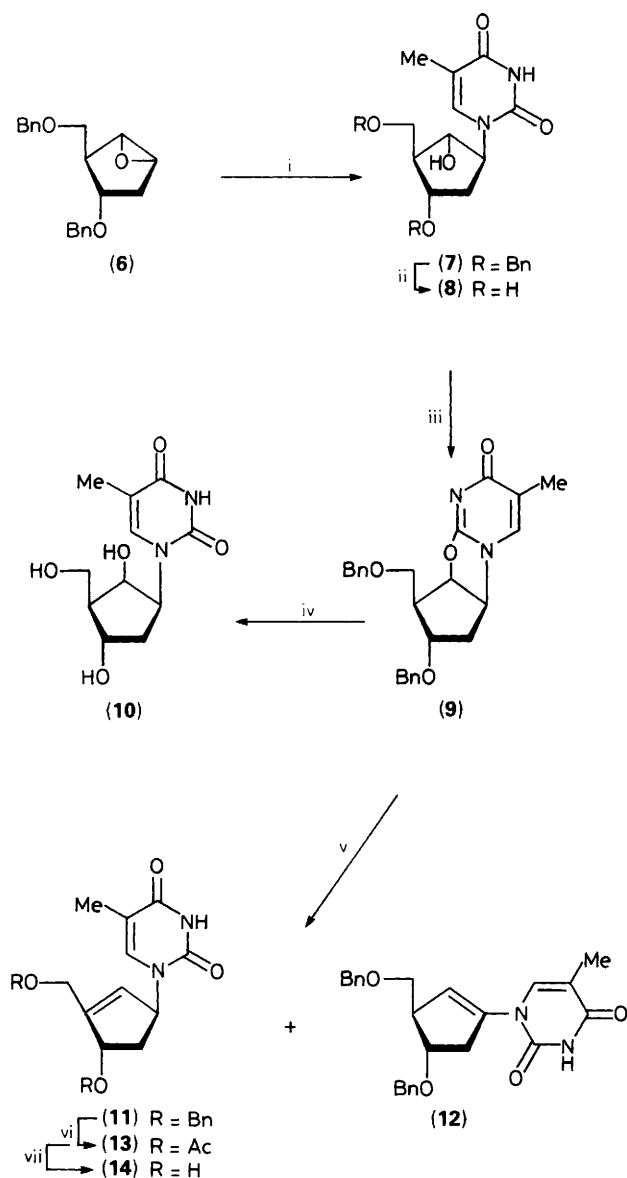
The chiral epoxide (**6**) has been converted in five stages into the thymidine analogue (**14**) of Neplanocin A and into the 6' α -(**8**) and 6' β -(**10**) hydroxy analogues of carbocyclic Thymidine.

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 syntheses¹⁻⁴ 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 routes² 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°, λ_{\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





Scheme 1. Reagents and conditions: i, Thymidine, NaH, DMF, 140°C; ii, H₂, Pd/C; iii, (PhO)₂C=O, DMF, 150°C; iv, NaOH, aqMeOH then H₂, Pd/C; v, KOBu^t, DMF; vi, BF₃, Ac₂O; vii, NH₃, 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/BF₃) followed by methanolysis of the resulting diacetate (**13**), to complete an eight

stage synthesis of the thymidine analogue (**14**),[†] [m.p. 159–163°, [α]_D²⁴ –52° (MeOH)] of Neplanocin A.

Hydrolysis of the anhydro derivative (**9**) (NaOH, H₂O/MeOH, 22°C) followed by hydrogenolytic debenzoylation 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 nucleosides⁹ 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**) ([²H₆]Me₂SO, 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, CH₂) 4.12 (ABq, 2H, CH₂OH), 4.74 (m, 1H, CHOH), 4.90 (t, 1H, CH₂OH), 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 reported⁶ by Ohno *et al.* for material obtained by a multistage chemicoenzymatic synthesis and which displayed [α]_D²⁴ –31° (MeOH). However, the m.p. reported by Ohno (>210°) is surprisingly high when compared to that quoted⁶ for the corresponding 2'-deoxyuridine analogue (m.p. 147–149°).