Short Convergent Route to Homochiral Carbocyclic 2'-Deoxynucleosides and Carbocyclic Ribonucleosides

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The epoxide (**1**) has been converted into the antiviral agents (**5**) and (**7**) while the epoxide (**9**) furnished carbocyclic guanosine (**12**).

There is considerable current interest in the synthesis of carbocyclic nucleosides in our laboratories[1,2] and elsewhere[3] due to the high levels of selective antiviral activity displayed by some members of this group.[4] In stark contrast, the preparation of *optically active* carbocyclic nucleosides has received little attention.[5,6] The recent report by Griengl *et al.* concerning the preparation of homochiral carbocyclic 2'-deoxynucleosides[7] prompts us to report our syntheses of some related optically active antiviral compounds. A key feature of our new method involves the regioselective ring-opening of an epoxide ring system using pyrimidine and purine derivatives.

The protected epoxydiol (**1**) [enantiomeric excess (e.e.) > 98%] is readily prepared from cyclopentadiene in three stages.[2] Ring opening of the epoxide unit in (**1**) by uracil and thymine [NaH, dimethylformamide (DMF), 140 °C] was highly regioselective furnishing the alcohols (**2**) and (**3**) in good yields (63% and 70% respectively). Deoxygenation of compound (**2**) *via* tri-n-butyltin hydride reduction[8] of its 6'-*O*-phenoxythiocarbonyl derivative followed by hydrogenolytic debenzylation afforded optically pure carbocyclic 2'-deoxyuridine (**4**) [54% from (**2**)]. Iodination of compound (**4**) using iodine and nitric acid provided optically active carbocyclic 5-iodo-2'-deoxyuridine (C-IDU) (**5**), {$[\alpha]_D^{22}$ +7°, dimethyl sulphoxide (DMSO)}.

Whilst the ring-opening of epoxide moieties by uracil, thymine, and also adenine is well documented,[6,9,10] the only example cited in the literature involving guanine proceeded in a low yield (27%).[10] In contrast, reaction of 2-amino-6-methoxyethoxypurine with the epoxide (**1**) gave the protected guanine derivative (**6**) in 60% yield. This coupling was best

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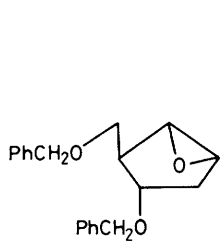
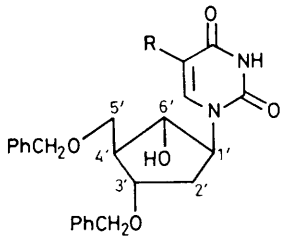


(1)



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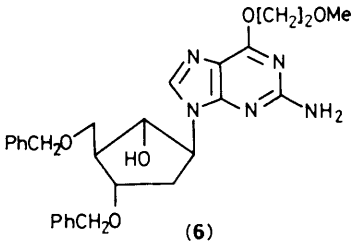
(3) R = Me



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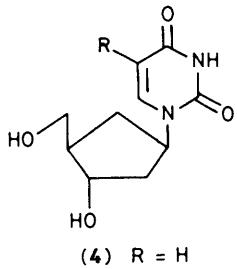
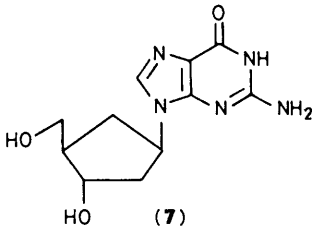


(4) R = H
(5) R = I



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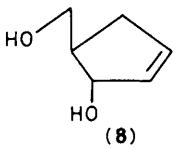

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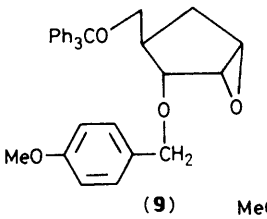

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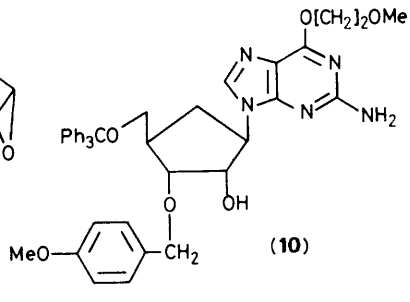

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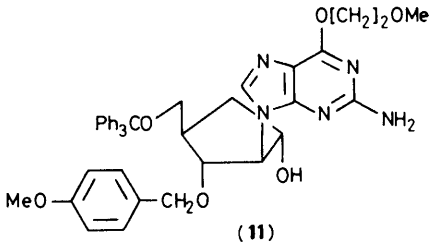
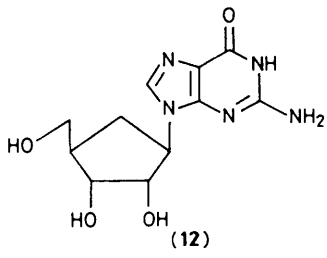


(11)



(12)

effected in DMF at 145 °C using lithium hydride as catalyst. It is noteworthy that the purine was alkylated at N-9 with very high selectivity.[11] Deoxygenation and deprotection (H_2, Pd/C then 3 M HCl, 80 °C) of compound (**6**) furnished optically pure carbocyclic 2′-deoxyguanosine (**7**), {$[\alpha]_D^{22}$ +14° (H_2O)} in 64% yield.

The optically active carbocyclic nucleosides (**5**) and (**7**) were found to be highly active against herpes simplex virus (HSV) *in vitro*, having MIC‡ values of 0.07 and 0.02 μg/ml respectively against HSV-1 infected cells. These values are roughly half the corresponding figures for the racemic compounds indicating the antiviral activity resides largely or entirely with the enantiomer having the absolute configuration corresponding to the natural (deoxy)ribofuranosyl nucleosides.

The improved method for coupling guanine and an oxirane was tested further using the racemic epoxide (**9**) [available in three stages from the known enediol (**8**)].[12] As expected, the ring-opening of the epoxide (**9**) using 2-amino-6-methoxyethoxypurine was less regioselective furnishing the alcohols (**10**) and (**11**) in a ratio of *ca.* 3 : 2. However, the overall yield of the reaction was good (65%) and the purine was again alkylated regiospecifically. Deprotection of compound (**10**) (3 M HCl, heat) gave (±)-carbocyclic guanosine (**12**).[13]

Biological activity data were obtained by Mr. D. J. Knight and Dr. J. A. V. Coates.

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‡ MIC is the minimum inhibitory concentration for observation of antiviral activity.