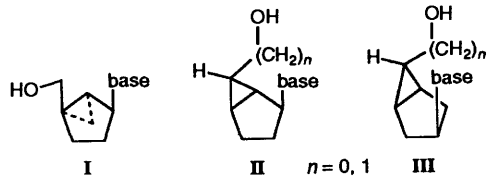
Synthesis of Some Carbocyclic Nucleoside Analogues Based on a Bicyclo[3.1.0]hexane Ring System

H. Gooding,[a] Stanley M. Roberts[a] and Richard Storer[b]
[a] *Department of Chemistry, Exeter University, Exeter, Devon EX4 4QD, UK*
[b] *Medicinal Chemistry, Glaxo Group Research, Greenford, Middlesex UB6 0HE, UK*

The carbocyclic nucleoside analogues **11**, **14** and **17** have been prepared from (*endo*-bicyclo[3.1.0]-hept-2-en-6-yl)methanol.

There is a continuing interest in the synthesis and biological activity of carbocyclic nucleosides.[1] The conformation of the five-membered ring is believed to play a crucial rôle in modulating the antiviral activity of nucleoside analogues and Rodriguez *et al.*,[2] have recently prepared compounds of type **I** to investigate this matter further. We share this interest in the synthesis of conformationally constrained carbocyclic nucleosides, focussing our attention on compounds of type **II** and type **III** which hold the hydroxy group and the base unit relatively close together in space. In this connection it is noteworthy that bicyclo[3.1.0]hexanes of type **III** generally prefer to exist in a boat conformation.[3] We report the preparation of compounds of type **III** (n = 1) in this note.

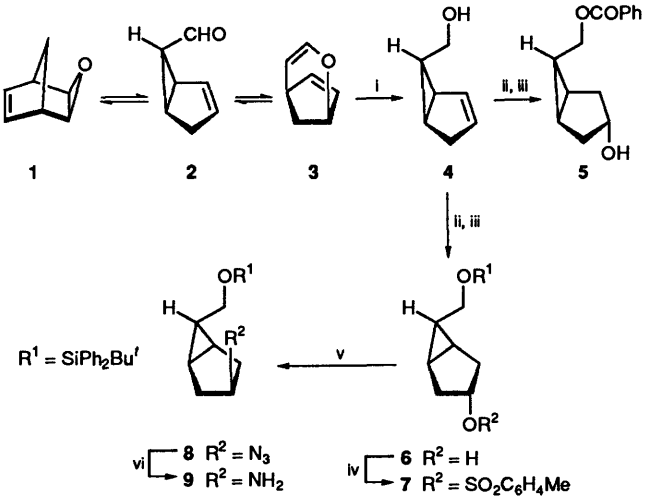


I **II** n = 0, 1 **III**

Peracetic acid oxidation of norbornadiene, in the presence of sodium hydrogen carbonate, afforded the epoxide **1** which exists in equilibrium with the aldehyde **2** and the enol ether **3** (Scheme 1).[4] Sodium borohydride reduction of this mixture provided the primary alcohol **4**. Protection of the hydroxy group was effected using *tert*-butyldiphenylsilyl chloride or benzoyl chloride and base before a standard hydroboration–oxidation sequence furnished the alcohols **5** and **6** exclusively. The simplicity of the ^{1}H and ^{13}C NMR spectra reflected the symmetry of the two compounds **5** and **6**. The exquisite stereoselectivity shown in the functionalisation of the double bond is obviously a result of steric crowding on one face of the molecule coupled with the electronic influence of the cyclopropyl moiety.

The alcohol **6** was converted into the toluene-*p*-sulfonate **7**. Displacement of the toluene-*p*-sulfonate group with azide ion gave compound **8** which was reduced to furnish the amine **9**, a potential precursor to a wide variety of nucleoside analogues.

For the preparation of compounds containing naturally occurring bases we found it simpler to effect direct displacement of the tosyl unit using the requisite pyrimidine or purine, accepting relatively low yields in these reactions owing to the increased bulkiness of the nucleophile and the hindered approach path for the S_N2 displacement. Thus, reaction of the toluene-*p*-sulfonate **7** with thymine in dimethyl sulfoxide (DMSO) containing potassium carbonate and 18-crown-6 gave the required compound **10**, which was deprotected using fluoride ion to give the nucleoside analogue **11** (Scheme 2). The structure of compound **10** was confirmed by ^{1}H NMR spectroscopy including NOE experiments.



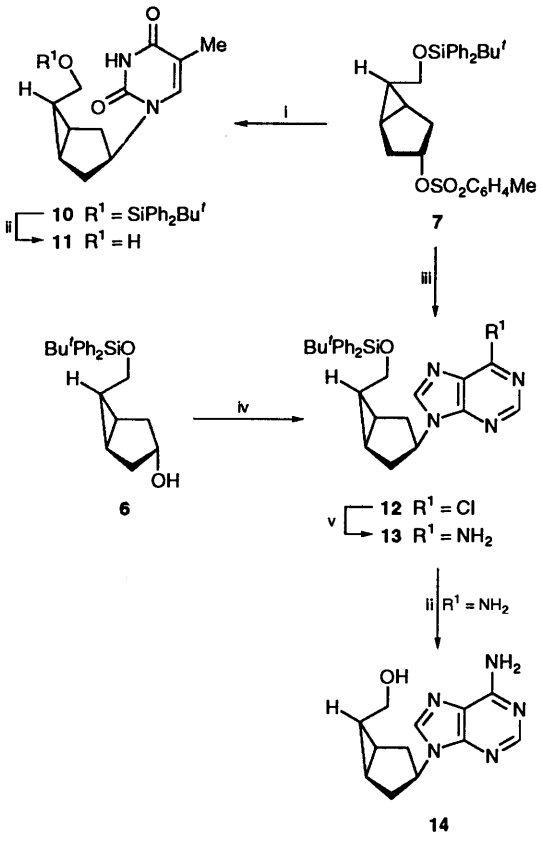
Scheme 1 *Reagents and conditions:* i, $NaBH_4$, CH_2Cl_2–MeOH, 0 °C, 2 h (56%); ii, Bu^tPh_2SiCl, imidazole, DMF 0 °C ⟶ room temp., 14 h (98%) or PhCOCl, pyridine, room temp., 13 h (100 %); iii, BH_3·SMe_2, THF, 0 °C, 2 h then NaOH (aq., 2 mol dm^{-3}), H_2O_2 (94–99%); iv, *p*-$MeC_6H_4SO_2Cl$, pyridine, CH_2Cl_2, 4-dimethylaminopyridine, room temp., 24 h (67%); v, NaN_3, NH_4Cl, DMF, room temp., 12 h (93%); vi, H_2, Lindlar cat., MeOH, room temp., 13 h (75%)

Displacement of the toluene-*p*-sulfonate group from compound **7** using 6-chloropurine gave a poor yield of the compound **12**. A modest improvement in the synthesis was accomplished by treating the alcohol **6** and 6-chloropurine under Mitsunobu conditions (Scheme 2). Conversion of compound **12** into the amine **13** and subsequently into the target compound **14** was accomplished using standard reaction conditions.

Treatment of the toluene-*p*-sulfonate **7** with 2,6-dichloropurine gave no coupled product; similarly, the alcohol **6** did not react with 2,6-dichloropurine under Mitsunobu conditions. However the alcohol **5** did react with 2,6-dichloropurine in tetrahydrofuran (THF) in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine to give the coupled product **15** in 41% yield (Scheme 3).[5] The benzoyl group is ostensibly slightly less bulky than the *tert*-butyldiphenylsilyl group. While controlling the stereochemistry of the hydroboration reaction **4** ⟶ **5**,* the benzoyl group obviously allows the purine access to displace a highly activated hydroxy group.

Treatment of the compound **15** with aqueous sodium

* The corresponding primary acetate undergoes hydroboration on the convex and the concave face of the molecule.



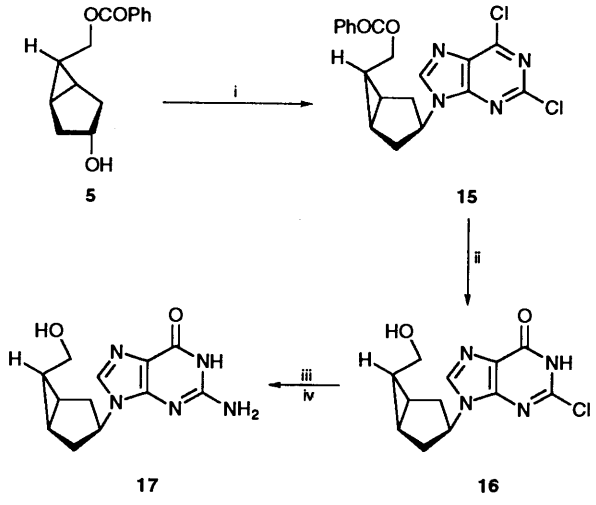
Scheme 2 *Reagents and conditions:* i, thymine, K_2CO_3, 18-crown-6, DMSO, room temp., 64 h (23%); ii, TBAF, THF, room temp., 16 h (70–93%); iii, 6-chloropurine, K_2CO_3, 18-crown-6, DMSO, room temp., 64 h (13%); iv, 6-chloropurine, Ph_3P, DEAD, THF, room temp., 16 h (30%); v, NH_3(l), 100 psi (1 psi ≈ 6.89 × 10^{-3} Pa), room temp., 16 h (50%)

hydroxide gave the alcohol **16** which was treated with azide ion and then reduced to give the guanine derivative **17**.

The nucleoside analogues **11**, **14** and **17** hve been synthesized from the alcohol **4** in a small number of steps. The key reactions, involving the coupling of the appropriate base to the bicyclic system, take place in modest yield (13–41%). The biological activity of the above compounds will be reported elsewhere.

Experimental

Preparation of 9-(6′-endo-*Benzoyloxymethylbicyclo*[3.1.0]-*hexan*-3′-endo-*yl*)-2,6-*dichloropurine* **15**.—Diethyl azodicarboxylate (0.75 g) was added dropwise to a solution of compound **5** (0.67 g), triphenylphosphine (1.6 g) and 2,6-dichloropurine (0.83 g) in dry tetrahydrofuran (20 cm^3). After being stirred for 24 h at room temperature the solution was concentrated under reduced pressure and chromatographed over silica using cyclohexane and acetone (3 : 1) as eluent to give the *title compound* **15** (0.47 g) m.p. 155 °C (light petroleum–acetate, 3 : 1) (Found C,



Scheme 3 *Reactions and conditions:* i, 2,6-dichloropurine, DEAD, PPh_3, THF, room temp., 24 h (41%); ii, NaOH (aq., 2 mol dm^{-3}), heat, 2 h, then neutralize with HCl (10 mol dm^{-3}); iii, NaN_3, NH_4HCO_3, $NaO_2CC_6H_5$, DMF, 100 °C, 2 h; iv, H_2, Lindlar cat., MeOH, room temp., 13 h

56.2; H, 4.0; N, 13.9%; M^+, 403.0722. $C_{19}H_{16}Cl_2N_4O_2$ requires C, 56.6; H, 4.0; N, 13.9%; M^+, 403.0728); λ_{max}(EtOH)/nm 217 (ε dm^3 mol^{-1} dm^{-1} 28 000) 236 (12 100) and 274 (10 100); ν_{max}-(Nujol)/cm^{-1} 1710, 1598 and 1450; δ_H(250 MHz; $CDCl_3$; *J*/Hz) 8.32 (1 H, s, 8-H), 8.08 (2 H, d, *J* 5.0, Ar-H), 7.56 (1 H, d, *J* 5.5, Ar-H), 7.44 (2 H, dd, *J* 5.5, 5.0, Ar-H), 5.27 (1 H, m, 3′-H), 4.82 (2 H, d, *J* 6.5, CH_2), 2.61 (2 H, m, 1-H, 5′-H), 2.12 (2 H, m, 2′-H *exo*, 4′-H *exo*) and 1.63 (3 H, m, 2′-H *endo*, 4′-H *endo*, 6′-H); δ_C(62.9 MHz; CD_3OD) 166.9 (C), 152.8 (C), 152.6 (C), 151.7 (C), 144.8 (CH), 133.1 (CH), 130.2 (CH), 129.8 (CH), 128.3 (CH), 62.9 (CH), 60.9 (CH_2), 29.8 (CH_2), 24.5 (CH) and 20.4 (CH).

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Paper 4/02008A
Received 5*th April* 1994
Accepted 20*th May* 1994