4'-Modification of Carbocyclic Nucleosides: Synthesis of 4'-α-Fluoro, 4'α-Hydroxy and 4',6'-Unsaturated derivatives of the Antiviral Agent 2'-*ara*-Fluoro Carbocyclic Guanosine

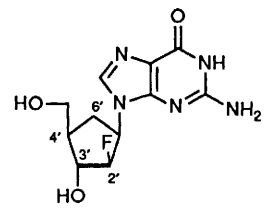
Keith Biggadike* and Alan D. Borthwick

Department of Medicinal Chemistry, Glaxo Group Research Ltd, Greenford, Middlesex UB6 0HE, UK

4'-α-Fluoro **13**, 4'-α-hydroxy **11** and 4',6'-unsaturated **15** derivatives of (±) 2'-*ara*-fluoro carbocyclic guanosine **1** are prepared *via* the 4',5'-alkene **8**.

Carbocyclic nucleosides have been extensively investigated in the search for effective antiviral and antitumour agents.[1] Modification of the cyclopentane ring has concentrated on the 2', 3' and 6' positions with introduction of the small electronegative fluorine substituent being of particular interest.[2–4] Thus, a 2'-*ara*-fluoro substituent has been shown to confer potent antiherpes activity to the purine derivatives **1**[2] and **2**,[3] while fluoro substitution at the 6'-position replaces the furanose oxygen by the interesting isosteric CHF moiety.[4] In contrast, substitution at the 4'-position of carbocyclic nucleosides has been largely ignored[5] despite the presence of a 4'-fluoro substituent in the naturally occurring furanose antibiotic nucleocidin **3**.[6] In this paper we report the methodology for 4'-substitution of intact carbocyclic nucleosides, illustrated by the synthesis of 4'-fluoro and 4'-hydroxy derivatives of compound **1**. 4',6' Unsaturated carbocyclic nucleosides are also of great interest owing to the presence of this functionality in the fermentation product neplanocin A **4**[7] and we now also describe the synthesis of the 4',6'-unsaturated derivative of **1**, the first example of a cyclopentenyl nucleoside bearing the important 2-*ara*-fluoro substituent.

The 2-amino-6-chloro precursor **5**[2] of **1** was first converted in four stages into the suitably protected derivative **6** in 42% overall yield (Scheme 1). Thus, the chloro function of **5** was replaced with the more stable methoxy moiety (70%) and the primary hydroxy group was selectively protected as a t-butyldimethyl silyl ether (87%). The amino and secondary hydroxy functions were then tritylated (82%) and finally the primary hydroxy group was liberated (85%) to give **6**. Reaction of **6** with Rydon's reagent[8] gave the iodide **7** (92%) which on treatment with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in



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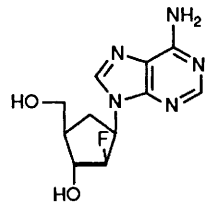

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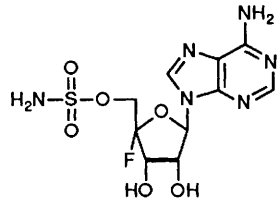

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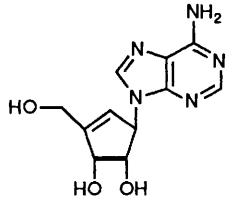

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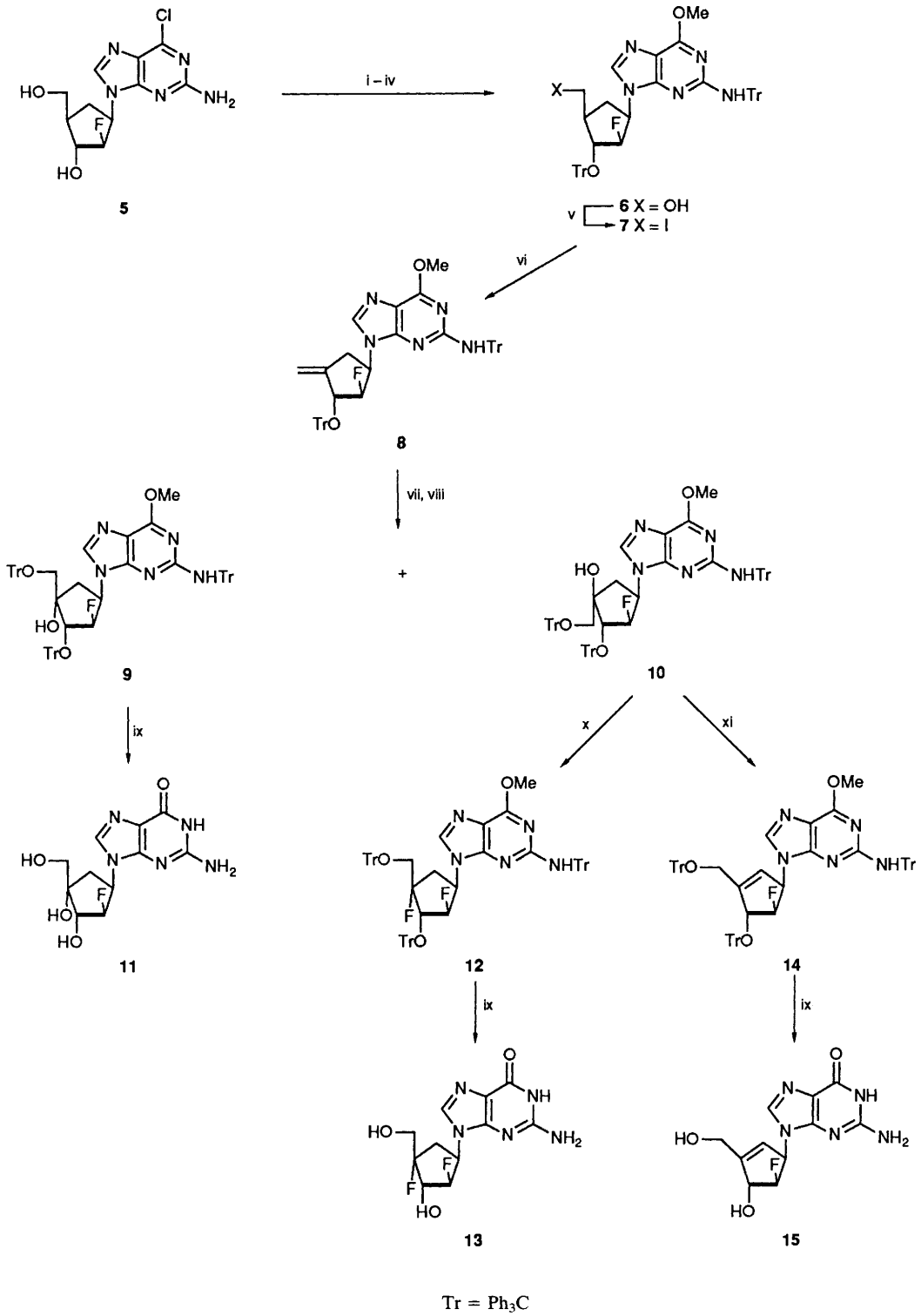

Scheme 1 *Reagents and conditions*: i, NaOMe (3 equiv.), MeOH, 50 °C; ii, Bu^tMe_2SiCl (1.1 equiv.), imidazole (4 equiv.), dimethylformamide, 20 °C; iii, Ph_3CCl (4 equiv.), powdered molecular sieves, CH_2Cl_2, reflux, 3 days; iv, Bu_4NF, tetrahydrofuran, 20 °C; v, $(PhO)_3PMeI$ (1.5 equiv.), tetrahydrofuran, −65 to 0 °C; vi, DBN (1.5 equiv.), pyridine, 60 °C; vii, OsO_4 (1 equiv.), pyridine, 20 °C; viii, Ph_3CCl (1.25 equiv.), powdered molecular sieves, CH_2Cl_2, 20 °C; ix, aq. AcOH, 80 °C, then 2 M HCl, 80 °C; x, DAST (2 equiv.), CH_2Cl_2, 0 °C

pyridine at 60 °C afforded the key intermediate 4′,5′-alkene **8**† (m.p. 267–268 °C) in 78% yield.

Osmylation of the alkene **8** afforded a mixture of diols which were more readily separated after tritylation of the primary hydroxy group. Osmium addition occurred predominantly from the opposite face to the allylic trityl ether moiety in accordance with Kishi's rule.[9] The isomers **9** and **10** were thereby obtained in a ratio of *ca.* 1:3 and in a combined yield of 75% from **8**. The minor isomer **9** was deprotected in a stepwise fashion: detritylation (aq. AcOH, 80 °C) followed by hydrolysis of the methoxy function (2 M HCl, 80 °C), to afford the 4′-α-hydroxy derivative **11** (m.p. 229–232 °C) of compound **1** in 63% yield.

Reaction of the major 4′-β-hydroxy isomer **10** with diethylaminosulphur trifluoride (DAST) in dichloromethane at 0 °C introduced fluorine with an inversion of configuration to give **12** in 35% yield. This inversion of configuration in the reaction of a tertiary alcohol with DAST parallels the situation with secondary alcohols, which, in the absence of participating neighbouring groups, give inverted secondary fluorides with DAST.[10] Deprotection of **12** gave the 4′-α-fluoro derivative **13** [m.p. 228–230 °C, ^{19}F NMR (CD_3SOCD_3) δ- 196.4 (2′-F) and −172.3 (4′-F)] of **1** in 49% yield. A minor product in the reaction of **10** with DAST was identified as the 4′,6′-alkene **14**. This product was deliberately prepared in high yield (88%) by treatment of **10** with phosphoryl chloride (2 equiv.) and DMAP (10 equiv.) (CH_2Cl_2, 0 °C). Deprotection of **14** then provided the 4′,6′-unsaturated 2′-*ara*-fluoro-carbocyclic guanosine **15** (m.p. 178–180 °C) in 69% yield.

The 4′-α-fluoro **13** and 4′-α-hydroxy **11** derivatives displayed potent activity against herpes simplex viruses types 1 and 2 (HSV 1 and 2). Compound **13** was *ca.* 30× and compound **11** *ca.* 4× more effective than Acyclovir against HSV2 in the mouse protection test after subcutaneous dosing. The cyclopentenyl derivative **15** was approximately equipotent to Acyclovir in the same test. These results have demonstrated that the 4′-position is a fruitful site for modification of antiviral carbocyclic nucleosides.[11]

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† All new compounds gave satisfactory analytical and spectral data.

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