Synthesis of (\pm) -Cycloprop-G, the Cyclopropyl Analogue of the Broad Spectrum Antiviral Agent Cyclobut-G

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An efficient synthesis of (±)-cycloprop-G from Feist's acid is described.

Oxetanocin 1, which contains an unprecedented oxetanosyl-N-glycoside linkage,^{1,2} inhibits the *in vitro* replication of human immunodeficiency virus (HIV), the causative agent of AIDS. In an effort to discover novel antiviral agents, we and others have synthesized a variety of oxetanocin analogues.³ One such analogue, cyclobut-G 2, containing a cyclobutane ring linked to a guanine base was found to be a broad spectrum antiviral agent,⁴ effective against HSV-1, HSV-2, VZV, HCMV, EBV and HIV-1. In order to explore the structureactivity relationship of the ring size to the antiviral activity, we have successfully synthesized (\pm)-cycloprop-G 3, the cyclopane-ring analogue of cyclobut-G. We report here the synthesis of (\pm)-cycloprop-G using commercially available Feist's acid as starting material (Scheme 1).

Reduction of Feist's acid (3-methylenecyclopropane-*trans*-1,2-dicarboxylic acid) with diisobutylaluminium hydride provided the corresponding diol which was protected as the *tert*-butyldimethylsilyl ether 4 in 80% overall yield. Hydroboration of the alkene with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by oxidative workup (H₂O₂–NaOH) gave the corresponding primary alcohol which was then oxidized in a stepwise manner: (*i*) Swern oxidation to the aldehyde;⁵ (*ii*) potassium permanganate in *tert*-butyl alcohol,⁶ to provide the cyclopropyl carboxylic acid **5** (85%, 2 steps).

Curtius rearrangement of the acid **5** with diphenylphosphoryl azide⁷ (DPPA) in benzyl alcohol followed by deprotection with H_2 -Pd/C furnished the cyclopropylamine **6** as the key intermediate. Condensation of amine **6** with 2-acetamido-4,6-dichloro-5-nitro-pyrimidine⁸ provided compound **7**. Construction of the masked guanine base in **9** was accomplished by reduction of the nitro group in **7** by hydrogenation using

Raney nickel as catalyst, followed by the reaction of the amino compound **8** with diethoxymethyl acetate. Hydrolysis under basic conditions⁹ (2-mercaptoethanol-sodium methoxide) provided the silyl-protected compound **10**. Finally, removal of the silyl protecting group in **10** using *in situ* generated HCl (chlorotrimethylsilane-methanol) provided analytically pure **3** (m.p. 285–286 °C) after C-18 column chromatography in 65% yield.

In conclusion, an efficient synthesis of the novel 3-membered ring carboxylic nucleoside (\pm) -cycloprop-G is de-





Scheme 1 Reagents: i, LiAlH₄; ii, Bu^tMe₂SiCl-imidazole; iii, 9-BBN; iv, $(COCl)_2$ -Me₂SO; v, KMnO₄-Bu^tOH; vi, DPPA-triethylamine-benzyl alcohol; vii, H₂-Pd/C; viii, 2-acetamido-4,6-dichloro-5-nitro-pyrimidine-dimethylformamide; ix, H₂-Raney nickel; x, diethoxymethyl acetate, reflux; xi, mercaptoethanol-NaOMe-MeOH; xii, Me₃SiCl-MeOH

scribed.[†] The key intermediate amine **6** can provide access to other purine or pyrimidine analogues.¹⁰ The possibility of resolution of Feist's acid also makes the synthesis of chiral cycloprop-G feasible. Compound **3** was tested for activities against HSV-1 and HSV-2 in Vero cells ($IC_{50} = >320 \ \mu g \ ml^{-1}$); against HIV-1 in MT-2 and ATH-8 cell ($IC_{50} = >100 \ \mu g \ ml^{-1}$).

Received, 2nd August 1991; Com. 1/04035I

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 $[\]dagger$ All new compounds have satisfactory spectral and elemental analyses.