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

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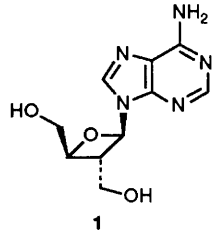
An efficient synthesis of (±)-cycloprop-G from Feist's acid is described.

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 structure–activity relationship of the ring size to the antiviral activity, we have successfully synthesized (±)-cycloprop-G **3**, the cyclopane-ring analogue of cyclobut-G. We report here the synthesis of (±)-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 (H_2O_2–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 azide[7] (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-pyrimidine[8] 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 conditions[9] (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 (±)-cycloprop-G is de-



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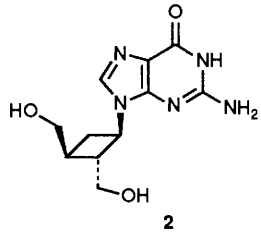

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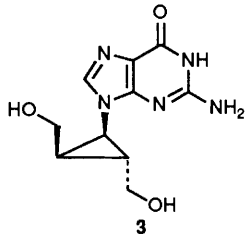

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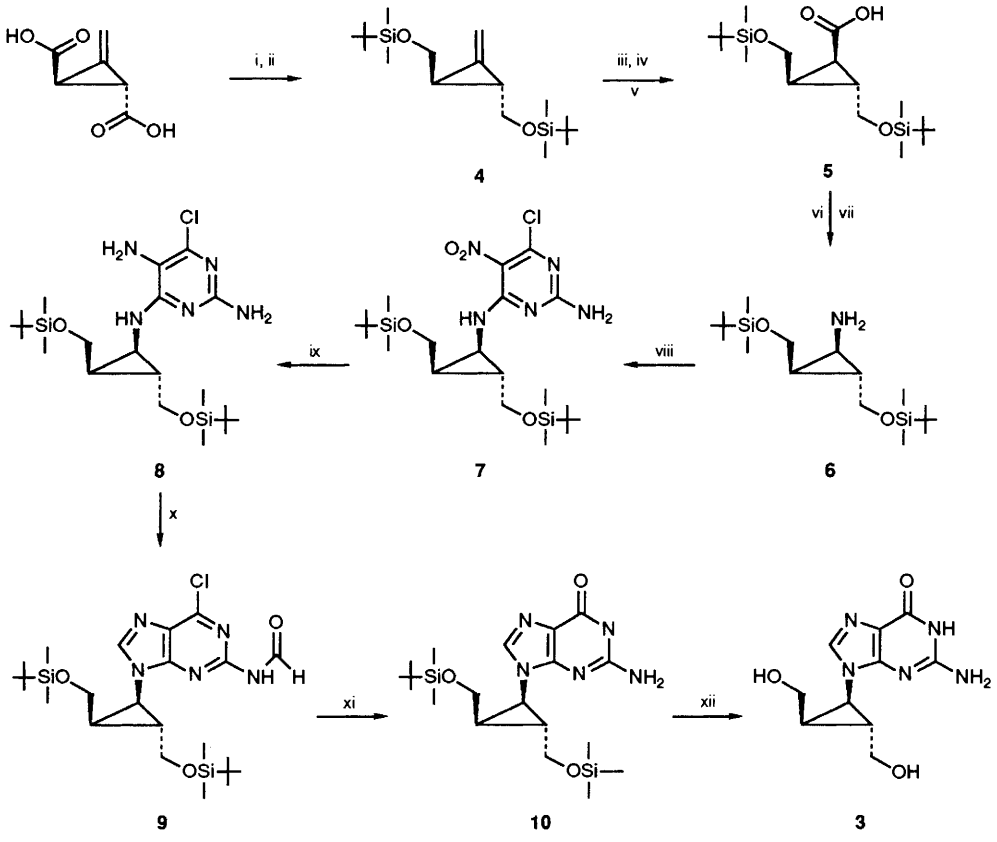

Scheme 1 *Reagents*: i, $LiAlH_4$; ii, Bu^tMe_2SiCl–imidazole; iii, 9-BBN; iv, $(COCl)_2$–Me_2SO; v, $KMnO_4$–Bu^tOH; vi, DPPA–triethylamine–benzyl alcohol; vii, H_2–Pd/C; viii, 2-acetamido-4,6-dichloro-5-nitro-pyrimidine–dimethylformamide; ix, H_2–Raney nickel; x, diethoxymethyl acetate, reflux; xi, mercaptoethanol–NaOMe–MeOH; xii, Me_3SiCl–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 μg ml^{-1}); against HIV-1 in MT-2 and ATH-8 cell (IC_{50} = >100 μg ml^{-1}).

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† All new compounds have satisfactory spectral and elemental analyses.