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SYNTHESIS OF SQ-33,054, A NOVEL CYCLOBUTANE NUCLEOSIDE WITH POTENT ANTIVIRAL ACTIVITY

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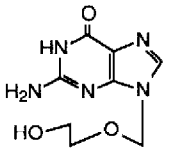
Summary. The racemic, guanine-containing cyclobutane nucleoside SQ-33,054 (**3**) was synthesized in 8 steps from the cyclobutane diester **4**.

Certain nucleosides modified in the carbohydrate portion of the molecule demonstrate selective and potent antiviral activity.[1] Examples include acyclovir (**1**), which is active against various herpes viruses,[2] and the recently isolated natural product, oxetanocin (**2**), which inhibits the *in vitro* replication of the human immunodeficiency virus (HIV).[3] As part of our efforts to synthesize and evaluate new antiviral agents, we prepared the racemic, guanine-containing cyclobutane nucleoside SQ-33,054 (**3**)[4].



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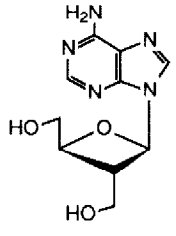

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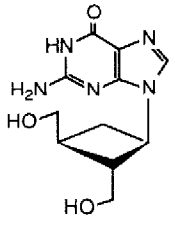
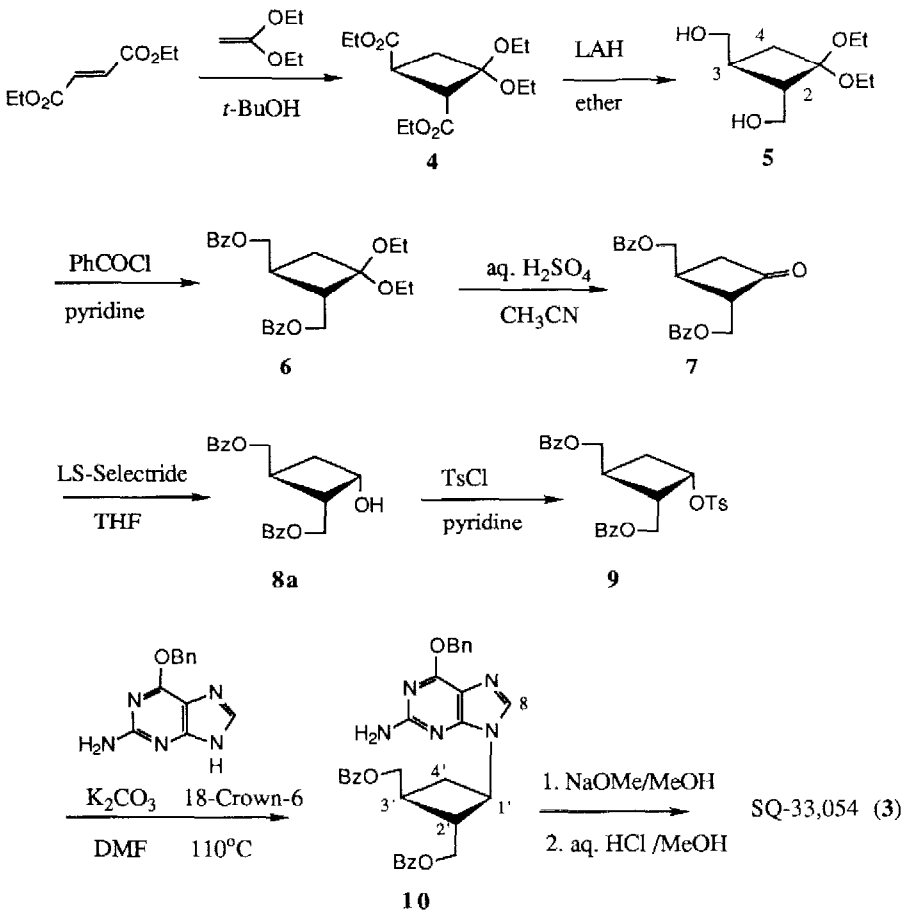


SQ-33,054 (**3**)

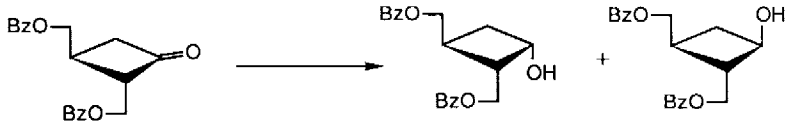
Our synthesis is an efficient, stereospecific conversion of the cyclobutyl diester **4**[5] to the target nucleoside **3** in eight steps (Scheme). Thermal [2+2] cycloaddition of diethyl fumarate with ketene diethylacetal in *t*-butanol at 84°C for 72 hr provided the cyclobutane diester **4**[6] in 53% yield after distillation. This yield for **4** represents a substantial improvement over the 17% yield reported previously for this thermal cycloaddition when carried out in acetonitrile solvent.[5] Reduction of diester **4** with $LiAlH_4$ in ether gave the corresponding diol **5**[7] (86% yield), which was then converted to the dibenzoate **6**[7] (benzoyl chloride, pyridine; 95% yield). Selective hydrolysis of the ketal of **6** was smoothly effected at room temperature with sulfuric acid in water-acetonitrile[9] to afford the cyclobutanone **7**[7] in 83% yield.



SCHEME

When cyclobutanone **7** was reduced with sodium borohydride in ethanol the desired α-hydroxy isomer **8a**[7] was obtained as a mixture with the corresponding β-isomer **8b**[7] in a 22:78 ratio (Table).[10] The use of diborane for this reduction offered no substantial advantage. Although both disiamylborane and L-Selectride® shifted the ratio in favor of the desired isomer, the use of LS-Selectride® ultimately afforded the desired isomer **8a** stereoselectively in 92% yield after chromatography.

Cyclobutanol **8a** was converted to the corresponding α-tosylate **9**[7] (TsCl, pyridine, 60°C, 16 hr; 72% yield after chromatography), and **9** was treated with 2-amino-6-benzyloxypurine in the presence of K_2CO_3/18-crown-6 in DMF (110°C, 16 hr) to afford the coupled product **10**[7] in 40% yield following chromatography. The benzoyl and benzyl protecting groups were sequentially removed by treatment of **10** with catalytic sodium methoxide in methanol at 40°C for 1.5 hr followed by aqueous methanolic HCl at 50°C for 6 hr. Purification by reverse phase chromatography afforded



7 **8a** **8b**

Reducing Agent	Conditions	Ratio **8a**:**8b**	Yield **8a**+**8b**[c]
$NaBH_4$	25°C, EtOH	22:78[a]	80%
BH_3·THF	0°C, THF	35:65[b]	-
L-Selectride®	-78°C, THF	74:26[a]	94%
Disiamylborane	0-5°C, THF	81:19[b]	-
LS-Selectride®	-78°C, THF	>98:2[b]	92%

[a]Ratio based on isolated yields of **8a** and **8b**; [b]Ratio based on quantitative TLC scanning densitometry measurements and/or 270MHz ^{1}HNMR; [c]Isolated yields.

TABLE

nucleoside SQ-33,054 (**3**)[7] in 57% yield from **10**.

In antiviral tests[11] using WI-38 cell monolayer cultures, SQ-33,054 displayed IC_{50} values[12] of 0.08-0.2, 0.04-0.08, 0.2, and 2-4 μM against herpes simplex virus 1 and 2, varicella-zoster virus, and human cytomegalovirus, respectively (cf. acyclovir IC_{50}'s of 0.4, 0.4, 2.2-4.4, and 22-44μM, respectively).

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REFERENCES AND NOTES

1. a). J. L. Kelley, Topics in Medicinal Chemistry, **1988**, 65, 189. b) M. M. Mansuri and J. C. Martin, Annual Reports in Medicinal Chemistry, **1988**, 23, 161. c) M. R. Harnden, A. Parkin and P. G. Wyatt, Tetrahedron Lett. **1988**, 29. 701.

2. a) E. D. Reines and P. A. Gross, Medical Clinics of North America, **1988**, 72, 691. b) J. J. O'Brien and D. M. Campolir, Drugs, **1989**, 37, 233.

3. H. Hoshino, N. Shimizu, N. Shimada, T. Takita and T. Takeuchi, J. Antibiotics, **1987**, 40, 1077.

4. An independent report describing the antiviral properties of compound **3** was very recently communicated: D. Norbeck and H. Mitsuya et. al., "5th International Conference on AIDS," 1989; abstracts M.C.P. 65 and M.C.P. 135.

5. K. C. Brannock, R. D. Burpitt, and J. G. Thweatt, J. Org. Chem., **1964**, 29, 940.

6. **4**: ^{1}HNMR δ(270MHz, $CDCl_3$) ca. 1.2(12H, m, CH_3), 2.24(1H, ddd, J=1.1, 8.8, 12.1Hz, H-4), 2.58(1H, dd, J=11, 12.1Hz, H-4), ca. 3.3-3.8(6H, m) and ca. 4.16(4H, m).

7. The spectral data for all new compounds are in accord with their structures; selected data are as follows: **5** ^{1}HNMR δ($CDCl_3$) 1.186(3H, t, J=7.1Hz, CH_3), 1.190(3H, t, J=7.1Hz, CH_3), 1.73(1H, ddd, J=1.1Hz,

7.7Hz, 12.1Hz, H-4), 2.10(1H, m, H-3), 2.33(2H, m, H-4 and H-2), 3.04(1H, br s, OH), 3.18(1H, br s, OH), ca. 3.47(5H, m) and ca. 3.74(3H, m) [OCH_2]; **6** ^{1}HNMR δ($CDCl_3$) 1.18(3H, t, J=7Hz, CH_3), 1.20(3H, t, J=7Hz, CH_3), 1.98(1H, ddd, J=1.5Hz, 7Hz, 11.6Hz, H-4), 2.38(1H, m, H-3), 2.48(1H, dd, J=9.5Hz, 11.5Hz, H-4), 2.76(1H, ddd, each J=ca. 7Hz, H-2), ca. 3.49(4H, m, $\underline{CH_2}CH_3$), ca. 4.43(3H, m,) and 4.60(1H, dd, J=7Hz, 11.5Hz) [$\underline{CH_2}$OBz], 7.38(4H, m), 7.52(2H, m), and 8.01(4H, m) [OBz]; **7** ^{1}HNMR δ($CDCl_3$) 2.97(1H, m, H-3), 3.05(1H, ddd, J=3.3Hz, 7.1Hz, 17.6Hz, H-4), 3.24(1H, ddd, J=2.2Hz, 9.3Hz, 17.6Hz, H-4), 3.66(1H, m, H-2), 4.57(4H, m, CH_2OBz), 7.42(4H, m), 7.56(2H, m), and 8.00(4H, m) [OBz]; **8a** ^{1}HNMR δ($CDCl_3$) ca. 2.17(2H, m) and ca. 2.72(2H, m) [H-2, H-3, H-4], 3.11(1H, d, J=3.3Hz, OH), 4.35(3H, m,) and 4.83(1H, dd, J=8.8Hz, 11.5Hz) [$\underline{CH_2}$OBz], 4.48(1H, m, H-1), ca. 7.43(4H, m), ca. 7.56(2H, m), and ca. 8.02(4H, m) [OBz]; **8b** ^{1}HNMR δ($CDCl_3$) 1.77(1H, m), ca. 2.16(1H, m), and ca. 2.45(2H, m) [H-2, H-3, H-4], ca. 2.21(1H, OH), 4.13(1H, m, 1-H), ca. 4.43(4H, m, $\underline{CH_2}$OBz), 7.42(4H, m), 7.55(2H, m), and 8.03(4H, m) [OBz]; **9** ^{1}HNMR δ ($CDCl_3$) 2.32(1H, m, H-4)[8], 2.39(3H, s, CH_3), 2.52(1H, m, H-4)[8], 2.76(1H, m, H-3)[8], 2.99(1H, m, H-2)[8], 4.34(2H, m) and 4.51(2H, m) [CH_2OBz], 5.15(1H, m, CHOTs), ca.7.2-8.0(12H, m, OBz and OTs); **10** ^{1}HNMR δ($CDCl_3$) ca. 2.62(3H, m) and 3.34(1H, m) [H-2', H-3', H-4'], 4.52(4H, m, CH_2OBz), 4.68(1H, ddd, each J=ca. 8.8Hz, H-1'), 4.84(2H, s, NH_2), 5.53(2H, s, CH_2OBn), 7.68(1H, s, H-8), ca. 7.26-8.07(15H, m, OBz and OBn); **3** ^{1}HNMR δ(DMSO-d_6) 2.04(2H, m), 2.36(1H, m), and 2.68(1H, m) [H-2', H-3', H-4'], 3.49(4H, m, CH_2O), 4.42(1H, ddd, each J=ca. 8.5Hz, H-1'), 4.57(1H, t, J=5.3Hz, OH), 4.62(1H, t, J=5Hz, OH), 6.36(1H, s, NH_2), 7.82(1H, s, H-8), 10.50(1H, br, NH); ^{13}CNMR δ(DMSO-d_6) 156.85(C-6), 153.28(C-2), 150.91(C-4), 135.71(C-8), 116.76(C-5), 63.46 and 61.41(CH_2O), 47.65, 46.53, 33.05, 29.56; UV λ_{max} (H_2O, pH 7.2, phosphate buffer) 253.3nm (ε11,600).

8. ^{1}HNMR assignments were made by decoupling experiments.

9. A. F. Kluge, D. J. Kertesz, C. O-Yang, and H. Y. Wu, J. Org. Chem. **1987**, 52, 2860.

10. The stereochemistry of **8a** was assigned on the basis of X-ray crystallographic analysis of the corresponding α-tosylate **9**: mp 97-98°C (EtOAc/hexane); a=11.867(1), b=17.777(3), c=6.090(1)Å, α=99.46(2)°, β=104.78(1)°, γ=80.70(1)°, V=1215.7Å^3, D_{obs}=1.34g cm^{-3} space group $P\bar{1}$, Z=2, R=0.064 for 1806 observed intensities.

11. Plaque reduction assay method.

12. Concentration of compound required for 50% inhibition of virus plaque formation.

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