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SYNTHESIS OF SQ-32,829, A NEW NUCLEOSIDE ANTIVIRAL AGENT

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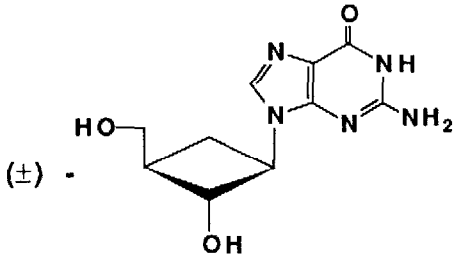
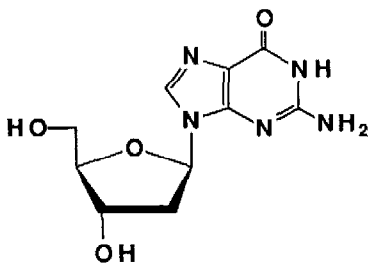
Summary: The guanine-containing cyclobutane nucleoside analog SQ-32,829 (**1**) was synthesized in 8 steps from 1,1-cyclobutanedicarboxylic acid (**3**).

The design of nucleoside analogs that interfere with virus replication but do not interfere with cellular processes has long been a goal in antiviral chemotherapy.[1] Examination of molecular models suggested that a cyclobutane ring might serve as a surrogate for the tetrahydrofuran ring of the natural 2'-deoxynucleosides. These observations led to the synthesis of SQ-32,829 (**1**), an analog of 2'-deoxyguanosine.[2]



SQ-32,829 (1)

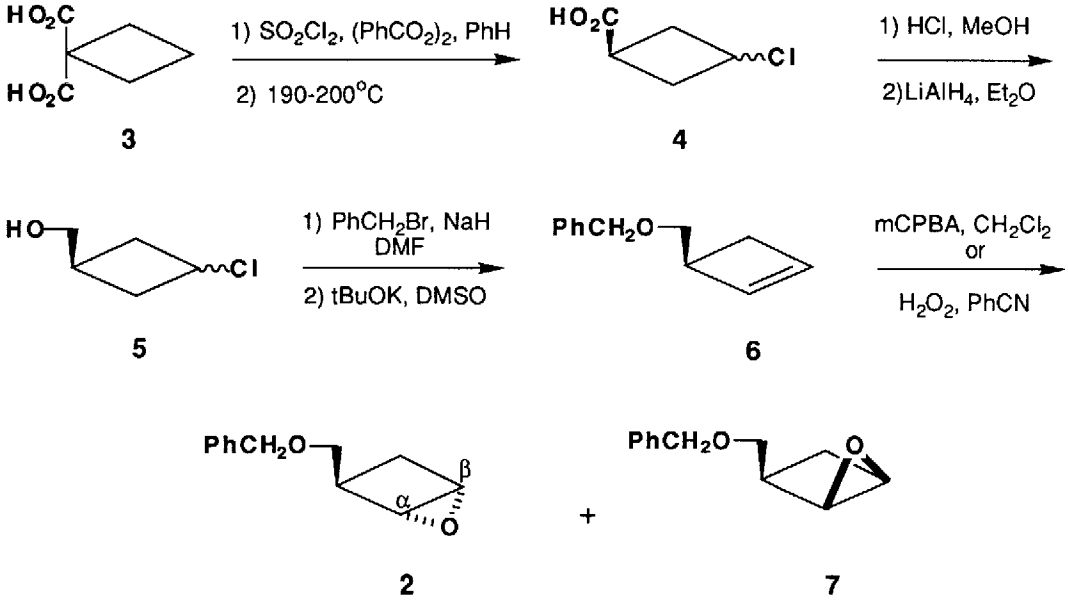


2'-deoxyguanosine

The synthesis of SQ-32,829 centered on a regioselective, nucleophilic ring opening of (±)-*exo*-2-benzyloxy-5-oxabicyclo[2.1.0]pentane (**2**) at the epoxide position *beta* to the benzyloxymethyl substituent (Scheme I). It was anticipated that nucleophilic attack at the α–position would be hindered by steric interaction with the benzyloxymethyl group. Compound **2** was synthesized from 1,1-cyclobutanedicarboxylic acid (**3**) in six steps. Treatment of a benzene solution of **3** with $SO_2Cl_2/(PhCO_2)_2$ and subsequent thermal decarboxylation provided a mixture of *cis*- and *trans*-3-chlorocyclobutanecarboxylic acid (**4**) in 45% yield.[3] Fischer esterification of **4** (CH_3OH/HCl, reflux), followed by reduction of the resulting ester ($LiAlH_4/Et_2O$, 0°C), provided alcohol **5** in 82% yield after distillation.[4] Alcohol **5** was protected as its benzyl ether in 95% yield (NaH/$PhCH_2Br$/DMF, 20°C; chromatography), and elimination to olefin **6** (*t*-BuOK/DMSO, 20°C; chromatography) proceeded in 71% yield.[5] Epoxidation of **6** with m-chloroperoxybenzoic acid in CH_2Cl_2 at 0°C gave a 64% yield of a 1:1 mixture of epoxides **2** and **7**, which were separated by a combination of flash chromatography and preparative HPLC (EtOAc/pentane).[5,6] Treatment of olefin **6** with peroxybenzimidic acid (30% H_2O_2, PhCN, $CH_3OH/CHCl_3$,

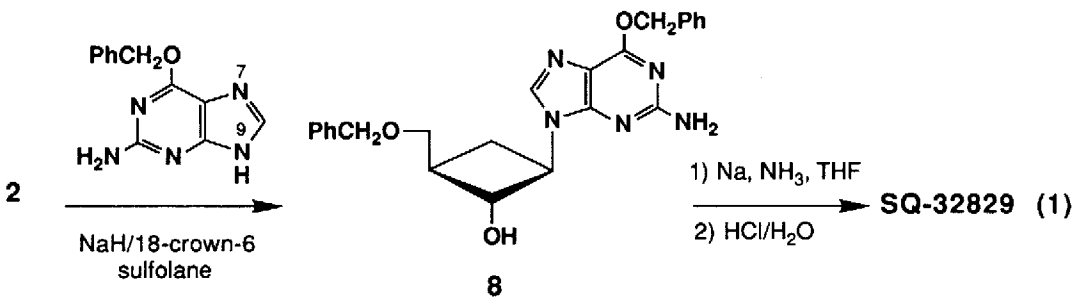
$KHCO_3$, 20°C) was moderately stereoselective, providing a 2.5:1.0 ratio of epoxides **2** and **7**, respectively, in 84% yield.[7,8]

Scheme I



Treatment of a sulfolane solution of epoxide **2** with 2-amino-6-benzyloxypurine in the presence of NaH/18-crown-6 (110°C, 28 hr) resulted in the formation of alcohol **8** in 52% yield (Scheme II).[5,9] A small amount of product resulting from N-9 attack at the epoxide position *alpha* to the benzyloxymethyl group was also isolated in 4.7% yield.[10]

Scheme II



Deprotection of **8** (Na/NH_3/THF, -78°C) and neutralization of an aqueous solution of the crude reaction product gave SQ-32,829 (**1**) as a colorless precipitate in 80% yield.[5,10] In antiviral tests[11] using WI-38 cell monolayer cultures, SQ-32,829 displayed IC_{50} values[12] of 0.8, 0.4, 2-4 and 2-4 μM against herpes simplex virus types 1 and 2, varicella-zoster virus and human cytomegalovirus, respectively (*cf.* acyclovir IC_{50} values of 0.4, 0.4, 2.2-4.4 and 22-44 μM, respectively).

Acknowledgments: We wish to thank Ms. M. F. Malley and Dr. J. Z. Gougoutas for X-ray crystallographic data and Ms. A. V. Tuomari and Dr. A. K. Field for the antiviral assays.

References and Notes

1. a) G. D. Diana, D. Pevear and D. C. Young, *Annu. Rep. Med. Chem.*, **24**, 129 (1989); b) M. F. Jones, *Chem. Br.*, 1122 (1988).

2. Recently, the synthesis and properties of another cyclobutane nucleoside analog have been reported independently (SQ-33,054 or A-69992): a) W. A. Slusarchyk, M. G. Young, G. S. Bisacchi, D. R. Hockstein and R. Zahler, submitted for publication; b) D. Norbeck and H. Mitsuya *et al.*, "5th International Conference on AIDS," abstracts M. C. P. 65 and M. C. P. 135 (1989).

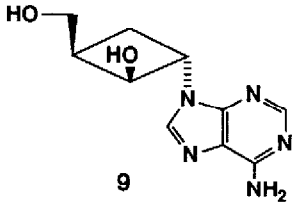
3. G. M. Lampman and J. C. Aumiller, *Org. Synth.*, **51**, 73 (1971).

4. A. G. Davies, D. Griller, K. U. Ingold, D. A. Lindsay and J. C. Walton, *J. Chem. Soc. Perkin II*, 633 (1981).

5. The spectral data for all compounds are in accord with their structures. Selected data are as follows: **6** ^{1}H NMR δ (270 MHz, $CDCl_3$) 2.20 (1H, dd, J=1.0, 13.7 Hz), 2.68 (1H, dd, J=4.0, 13.7 Hz), 3.13 (1H, m), 3.53 (2H, m), 4.53 (2H, s), 6.09 (2H, s), 7.24-7.36 (5H, m); **2** ^{1}H NMR (400 MHz, CD_2Cl_2) 1.68 (1H, ddd, J=1.1, 3.5, 12.0 Hz), 1.88 (1H, ddd, J=2.9, 5.4, 12.0 Hz), 2.34 (1H, m), 3.55 (1H, dd, J=8.6, 9.7 Hz), 3.67 (1H, dd, J=5.7, 9.7 Hz), 3.79 (1H, m), 3.84 (1H, m), 4.50 (1H, d, J=11.7 Hz), 4.55 (1H, d, J=11.7 Hz), 7.28-7.39 (5H, m); **7** ^{1}H NMR (400 MHz, CD_2Cl_2) 1.40 (1H, ddd, J=2.9, 3.7, 12.1 Hz), 2.15 (1H, ddd, J=1.1, 9.2, 12.1 Hz), 2.65 (1H, m), 3.25 (1H, dd, J=6.6, 9.2 Hz), 3.55 (1H, dd, J=8.4, 9.2 Hz), 3.75 (1H, m), 3.80 (1H, m), 4.44 (1H,d, J=11.9 Hz), 4.47 (1H, d, J=11.9 Hz), 7.27-7.37 (5H, m); **8** ^{1}H NMR (270 MHz, DMSO-d_6) 1.75 (1H, ddd, each J=*ca.*9.8 Hz), 2.17 (1H, m), 2.29 (1H, ddd, each J=*ca.*8.8 Hz), 3.63 (2H, m), 4.27 (1H, ddd, each J=*ca.*7.2 Hz), 4.42 (1H, ddd, each J=*ca.*8.4 Hz), 4.52 (2H, s), 5.50 (2H, s), 5.64 (1H, d, J=6.3 Hz), 6.39 (2H, br s), 7.26-7.51 (10H, m), 8.00 (1H, s); ^{13}C NMR δ (67.94 MHz, DMSO-d_6) 24.2, 54.2, 66.8, 71.3, 71.9, 73.4, 113.9, 127.3, 127.4, 127.9, 128.2, 128.3, 136.7, 138.3, 138.6, 154.4, 159.5, 160.0 (the ^{13}C-NMR in $CDCl_3$ also has an aliphatic absorption at δ 38.4 which is obscured in DMSO-d_6); **1** ^{1}H NMR (270 MHz, DMSO-d_6) 1.66 (1H, ddd, each J=*ca.*10.0 Hz), 1.99 (1H, m), 2.20 (1H, ddd, each J=*ca.*9.1 Hz), 3.56 (2H, m), 4.18 (1H, ddd, each J=*ca.*7.0 Hz), 4.30 (1H, ddd, each J=*ca.*8.4 Hz), 4.54 (1H, t,

J=5.3 Hz), 5.52 (1H, d, J=6.3 Hz), 6.41 (2H, br s), 7.79 (1H, s); ^{13}C NMR (67.94 MHz, DMSO-d_6) 23.6, 40.9, 53.9, 61.6, 72.6, 116.6, 135.5, 151.0, 153.3, 156.8; UV λ_{max} (H_2O, pH 7.2) 253 nm (11,900), 274 nm (sh, 8,500); MS (FAB) M+H=252.

6. The stereochemistry of epoxides **2** and **7** was assigned on the basis of X-ray crystallographic analysis of adenine adduct **9**: crystallized from H_2O; a=7.848(7), b=9.19(1), c=16.18(1)Å, β=91.64(4)°, V=1167(4)Å^3, D_{calc}=1.44g cm^{-3}, Z=4 for $C_{10}H_{13}N_5O_2 \cdot H_2O$, space group $P2_1/c$, R=0.062, R_w=0.069 for 967 observed intensities.



9

Compound **9** was synthesized by regioselective opening of epoxide **7** with adenine (K_2CO_3/DMF, 110°C; 40%) and subsequent deprotection ($Pd(OH)_2$ on carbon/cyclohexene/EtOH, 80°C; 41%).

7. a) G. B. Payne, P. H. Deming, and P. H. Williams, *J. Org. Chem.*, **26**, 659 (1961); b) Y. Ogata and Y. Sawaki, *Tetrahedron*, **20**, 2065 (1964); c) R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **32**, 1363 (1967).

8. These conditions were convenient for the epoxidation of *ca* 0.5g of olefin **6**; however, the reaction could not be brought to completion upon increasing the scale ten-fold.

9. The thermal stability of epoxides **2** and **7** under the coupling conditions was surprising in view of the reported instability of some 5-oxabicyclo[2.1.0]pentanes: J.-L. Ripoll and J.-M. Conia, *Tetrahedron Lett.*, 979 (1965).

10. Assignment of N-9 (*vs.* N-7) purine alkylation is based on the ^{13}C-chemical shifts of purine carbons-5 and -8: J. Kjellberg and N. G. Johansson, *Tetrahedron*, **42**, 6541 (1986).

11. Plaque reduction assay method.

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

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