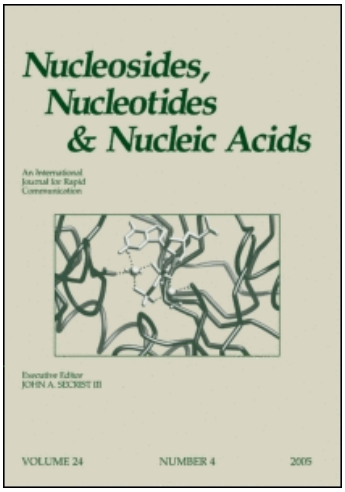

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The Synthesis of the Carbocyclic Derivative of *lin*-Benzo-Separated 2',3'-Dideoxyinosine

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THE SYNTHESIS OF THE CARBOCYCLIC DERIVATIVE OF *lin*-BENZO-SEPARATED 2',3'-DIDEOXYINOSINE

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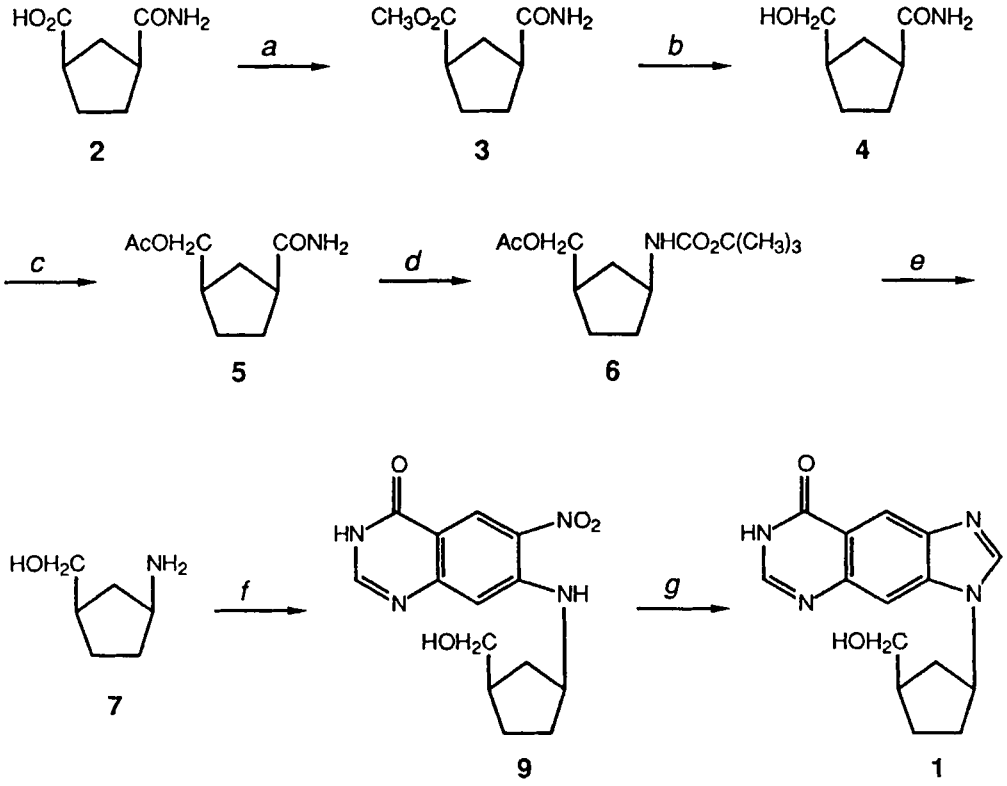
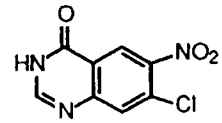
Abstract: The synthesis of the carbocyclic derivative of *lin*-benzo-2',3'-dideoxyinosine has been accomplished as an example of a benzo-separated carbocyclic purine analogue.

In an extension of a program on benzo-separated purines,[1] this laboratory is pursuing the synthesis of the benzo-separated analogs of the 2',3'-dideoxynucleosides that are known to be effective agents in the treatment of human immunodeficiency virus.[2] In this direction, this paper reports the synthesis of the carbocyclic derivative of *lin*-benzo-separated 2',3'-dideoxyinosine (**1**).

Synthesis of the carbocyclic portion of **1** began with esterification of the racemic acid **2**[3] with diazomethane in ether. The resultant **3** (92% , white plates, mp 118-120 °C)[4] was easily reduced to the alcohol **4** with cold lithium aluminum hydride in tetrahydrofuran (59%, white needles, mp 121-122 °C). Compound **4** was acetylated with acetic anhydride in pyridine to give **5** (82%, white plates, mp 100-101 °C). Hofmann degradation of the amide functionality of **5** with bromine and base met with limited success; therefore, lead tetraacetate was utilized to effect conversion to the intermediate isocyanate, which was readily converted to the corresponding carbamate **6** with t-butyl alcohol (70%, pale yellow oil). Treatment with methanolic HCl gave (±) cis-3- hydroxymethyl-1-aminocyclopentane (**7**, 91%, yellow oil).[5]

To complete the synthesis of **1**, a mixture of **7** and 7-chloro-6-nitroquinazolin-4(3*H*)-one (**8**)[6] in 1-butanol was heated with triethylamine for 3 days and, after chromatographic purification, **9** (30%, orange solid, mp 191-193 °C (decomp.)) was obtained . Reduction of the nitro group by hydrogenation over palladium-carbon followed by cyclization of the resulting product with formic acid gave the desired carbocyclic *lin*-benzo-2',3'-dideoxyinosine (**1**)(32%, tan solid, mp 183-186 °C (decomp.)).



Reagents: *a*) CH_2N_2 in Et_2O; *b*) $LiAlH_4$ (cold) in THF; *c*) Ac_2O, pyridine; *d*) $Pb(OAc)_4$ in tBuOH; *e*) HCl, MeOH; *f*)NEt_3,  in nBuOH; *g*) H_2/ 10% Pd-C in HCO_2H

8

Scheme

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(3) Berger, H.; Paul, H.; Hilgetag, G. *Chem. Ber.*, **1968**, *101*, 1525.
(4) All new compounds reported herein gave satisfactory IR, ^1H NMR and ^{13}C NMR spectral data. Yields refer to isolated product after purification by recrystallization and/or silica gel chromatography.
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