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

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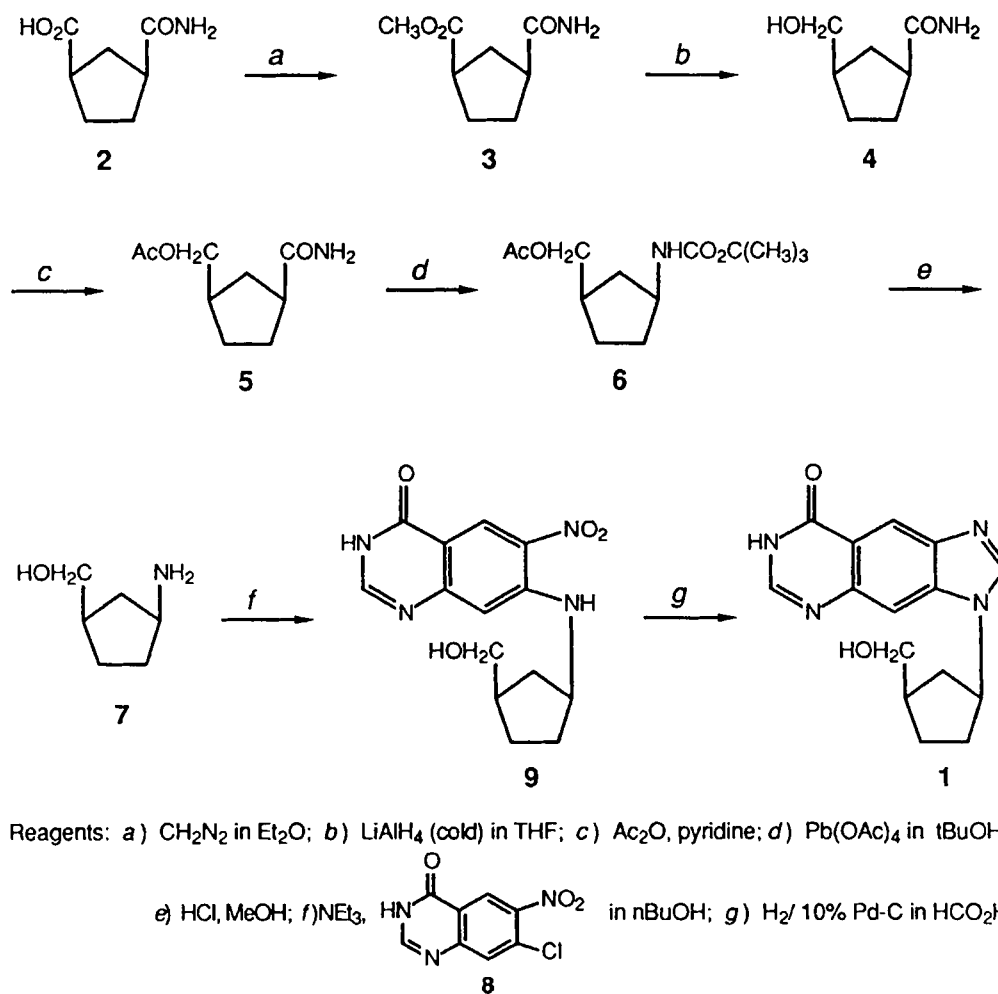
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Abstract: The synthesis of the carbocyclic derivative of *lin*-benzo-2',3'-dideoxyinosine has been accomplished as an example of a benzo-separated carbocyclic purine analogue.

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 2³ 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.)).



Scheme

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