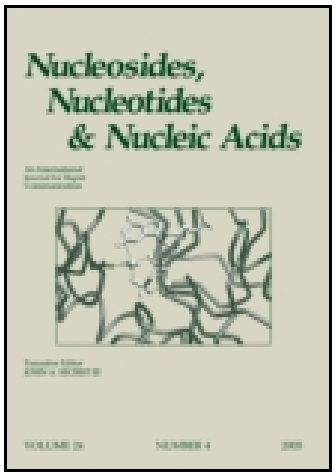

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MODIFIED CYCLOBUTANE CARBONUCLEOSIDES: SYNTHESIS AND EVALUATION OF THEIR ANTIVIRAL ACTIVITY

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ABSTRACT

The synthesis of some 9-(2-cyclobutylethyl)guanine derivatives and analogous carbonucleosides from 1*S*-α-pinene is here presented. None of them showed detectable selectivity when assayed in the performed anti-viral tests.

Carbocyclic nucleosides with a cyclobutane ring linked to a purine base, such as Lubocavir (**1**) (1) and Cyclobut A (2) (2), are known to present interesting antiviral properties. In a search to explore structural variations on the pseudo-sugar moiety which might improve or retain antiviral activity, a series of carbocyclic nucleosides of type **3** (Z=CH, N; X=Cl, OH, NH_2) was studied.

The synthesis of compounds **3** in enantiomerically pure form was carried out starting from easily available 1*S*-α-pinene (**4**). Permanganic oxidation of **4** yielded pinonic acid **5**, which was reduced by $NaBH_4$ mainly to the pinolic acid **6**. Acetylation of **6** by Ac_2O/Pyr was followed by successive treatments with $ClCO_2Et/Et_3N$ and NH_3, to obtain the acetoxy amide **7**. Finally, reduction of **7** by $LiAlH_4$ gave the amino alcohol **8**, in a 26% overall yield.

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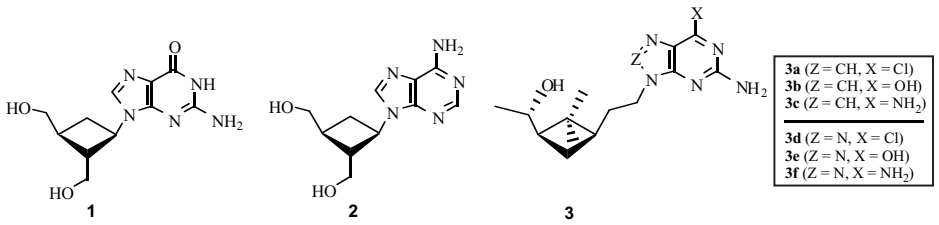
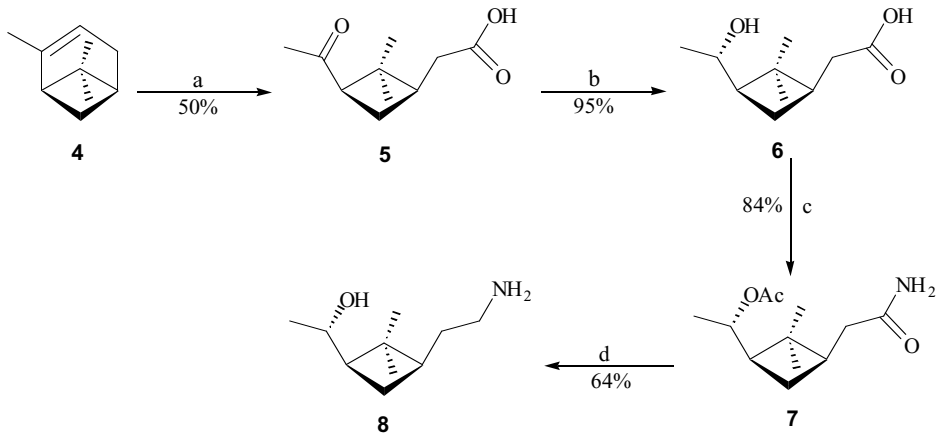
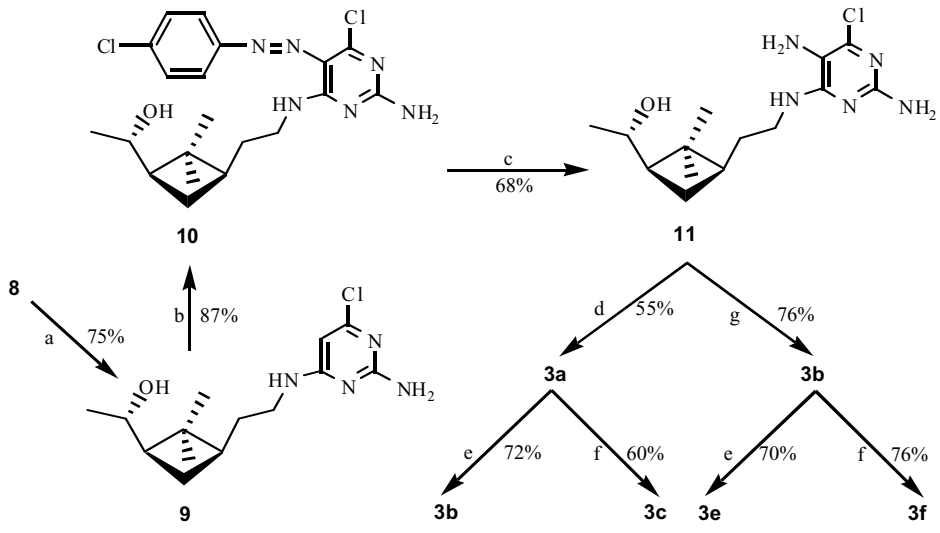


Scheme 1.



Scheme 2. a) $KMnO_4/H_2O$; b) $NaBH_4$/EtOH; c) 1:Ac_2O/Pyr; 2: $ClCO_2Et/Et_3N/NH_3$; d) $LiAlH_4$/THF.



Scheme 3. a) 4,6-Dichloropyrimidin-2-amine/Et_3N/1-butanol; b) 4-$ClC_6H_4N_2/H_2O$; c) Zn/AcOH; d) $CH(OEt)_3$/12N HCl; e) 0.33N NaOH; f) 14M NH_4OH; g) $NaNO_2$/1N HCl; h) 0.33N NaOH; i) 14M NH_4OH.

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Condensation of **8** with 4,6-dichloropyrimidin-2-amine afforded **9**, which was further condensed with 4-chlorophenyldiazonium chloride to give the 5-azopyrimidine derivative **10**. The hydrogenation of the azo group of **10** with Zn/AcOH yielded the 2,5-diaminopyrimidine derivative **11**. This key intermediate was then used to construct the guanine or 8-azaguanine derivatives using well stablished procedures (3).

Compounds **3(a–f)** were assayed against a variety of viruses, including HIV-1 and HIV-2, cytomegalovirus, TK^+ and TK^- varicella zoster virus, influenza [H2N2 A2 Japan/305/57, H3N2 (X31) and B Hong Kong/51/72] virus, herpes simplex virus type 1 and type 2, vaccinia virus, vesicular stomatitis virus, reovirus-1, sindbis virus and Punta Toro virus. No antiviral activity at concentrations $\geq$ 5-fold below the corresponding cytotoxicity thresholds could be discerned with any of the compounds against any of the viruses evaluated.

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