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MODIFIED CYCLOBUTANE CARBONUCLEOSIDES: SYNTHESIS AND EVALUATION OF THEIR ANTIVIRAL ACTIVITY

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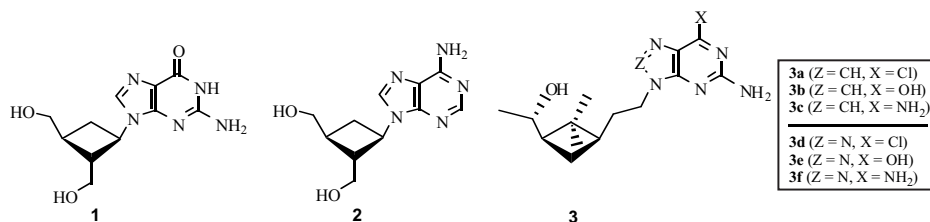
ABSTRACT

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.

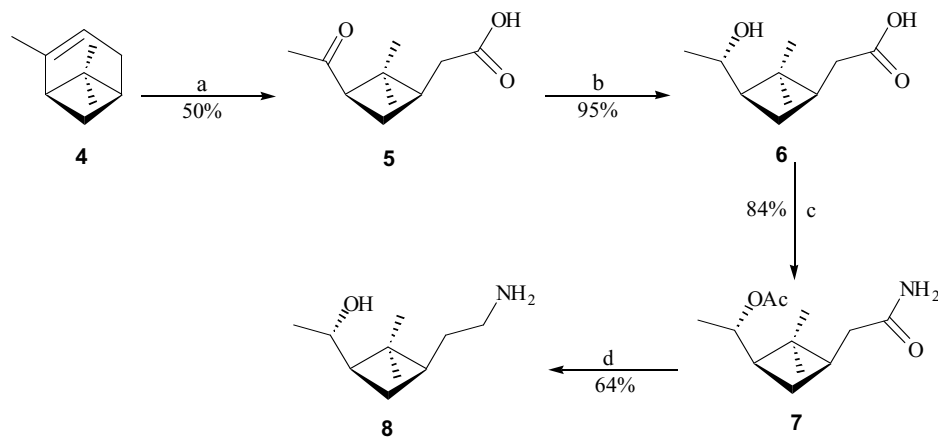
Carbocyclic nucleosides with a cyclobutane ring linked to a purine base, such as Lubocavir (**1**) (1) and Cyclobut A (**2**) (2), are known to present interesting antiviral properties. In a search to explore structural variations on the pseudo-sugar moiety which might improve or retain antiviral activity, a series of carbocyclic nucleosides of type **3** (Z=CH, N; X=Cl, OH, NH₂) 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 NaBH₄ mainly to the pinolic acid **6**. Acetylation of **6** by Ac₂O/Pyr was followed by successive treatments with ClCO₂Et/Et₃N and NH₃, to obtain the acetoxo amide **7**. Finally, reduction of **7** by LiAlH₄ gave the amino alcohol **8**, in a 26% overall yield.

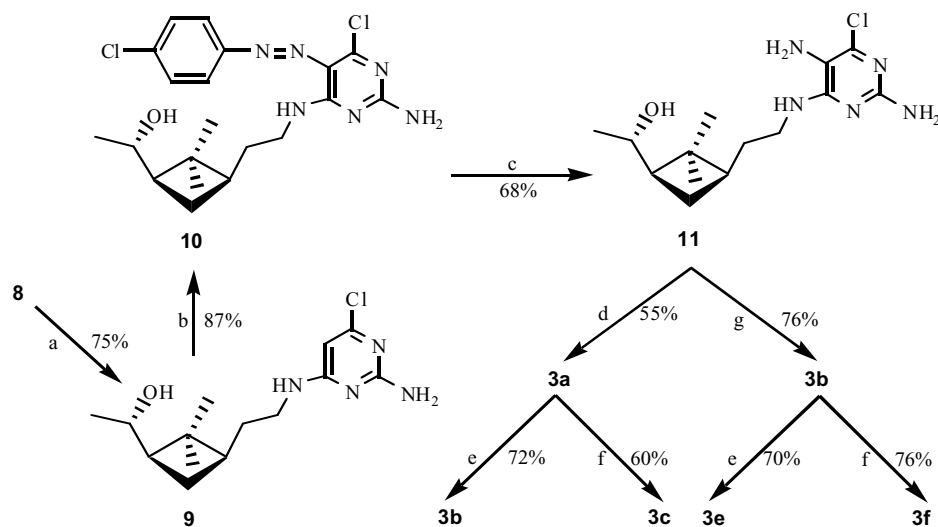
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Scheme 1.



Scheme 2. a) KMnO₄/H₂O; b) NaBH₄/EtOH; c) 1:Ac₂O/Pyr; 2: ClCO₂Et/Et₃N/NH₃; d) LiAlH₄/THF.



Scheme 3. a) 4,6-Dichloropyrimidin-2-amine/Et₃N/1-butanol; b) 4-ClC₆H₄N₂/H₂O; c) Zn/AcOH; d) CH(OEt)₃/12N HCl; e) 0.33N NaOH; f) 14M NH₄OH; g) NaNO₂/1N HCl; h) 0.33N NaOH; i) 14M NH₄OH.



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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 established 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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