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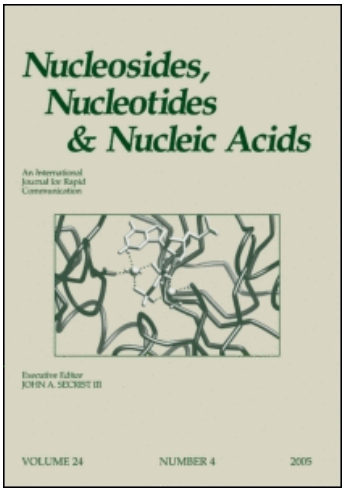

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A Novel and Enantioselective Approach to the Synthesis of Cyclohexane Carbocyclic Nucleosides Starting from (-)-Carvone

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NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 591–592 (1999)

A NOVEL AND ENANTIOSELECTIVE APPROACH TO THE SYNTHESIS OF CYCLOHEXANE CARBOCYCLIC NUCLEOSIDES STARTING FROM (-)-CARVONE†

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ABSTRACT 3,5-dihydroxy-4-(hydroxymethyl)-1-cyclohexanyl adenine has been synthesized starting from (-)-carvone. The adenine base was introduced *via* Mitsunobu reaction. Conformational analysis showed that the base still adopts the equatorial position at the expence of three axial substituents.

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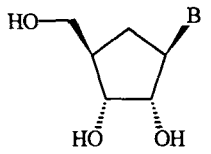
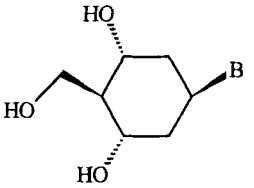
Naturally occurring and synthetic carbocyclic nucleosides like **1** are of interest as broad-spectrum antiviral agents.[1] The therapeutic advantage is attributed to their better chemical and enzymatic stabilities, as compared to natural nucleosides.



1



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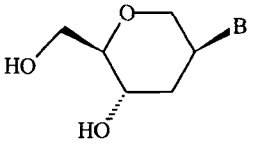

2

The research on nucleosides with a six-membered carbohydrate moiety has shown that hexitol nucleosides of type **2**, likewise, demonstrate antiviral activity.[2] According to conformational analysis, this is due to the chair-like $^4C_1$ conformation of the hexitol nucleoside which orients the base moiety in an axial position, mimicking the C(3')-endo form of a furanose nucleoside. The carbocyclic analogues of **2** in which the O in the ring is replaced by CH_2 group,[3] however, adopt the opposite conformation ($^1C_4$-like) and do

† This work was presented at the International Conference on Nucleic Acids and Related Macromolecules: Synthesis, Structure and Application, Sept. 4-9, 1997, Ulm, Germany.

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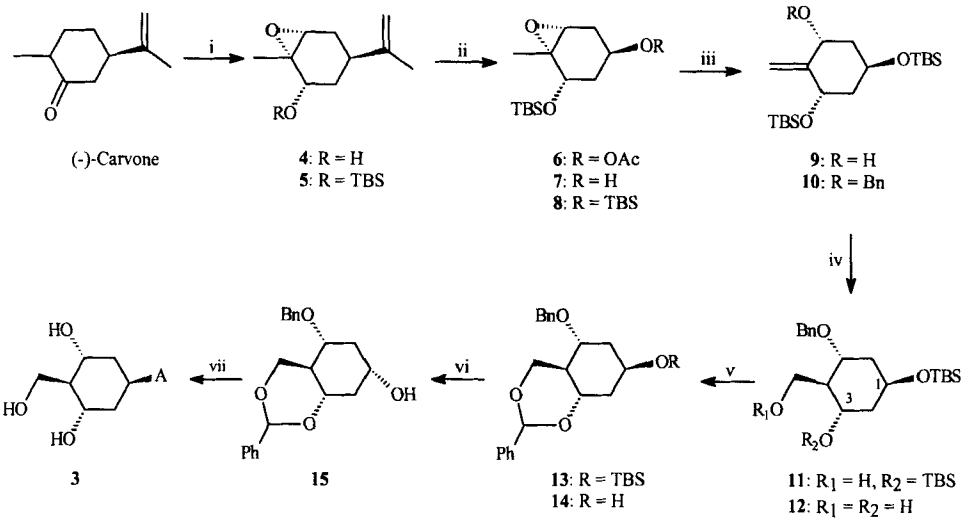
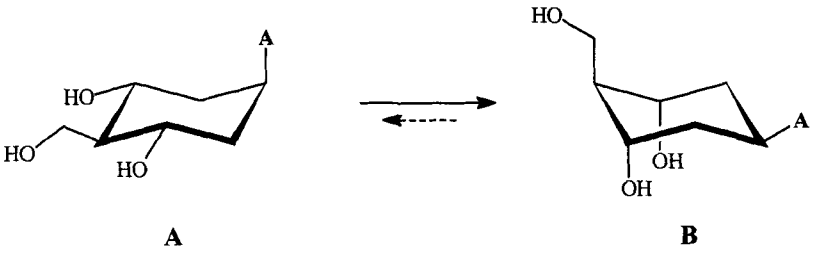


Reagents: i. (a) H_2O_2/NaOH, MeOH; b) L-selectride, THF, -65°C; (c) TBSCl, imidazole; ii. a) OsO_4/KIO_4; MCPBA; (b) K_2CO_3/MeOH; (c) TBSCl, imidazole; iii. (a) LiTMP/Et_2AlCl, benzene; (b) BnBr/NaH, DMF; iv. (a) 9-BBN, THF; (b) TBAF, THF; v. (a) $PhCH(OMe)_2$, PTSA; (b) TBAF, THF; vi. (a) PPh_3, DEAD, PhCOOH; (b) K_2CO_3; vii. (a) PPh_3, DEAD, adenine; (b) $Pd(OH)_2$-C, MeOH.

Scheme 1

not demonstrate antiviral activity. In order to further investigate the structure-activity relationship of nucleosides with a six-membered carbohydrate mimic, we synthesized the 6-membered carbocyclic nucleosides **3** according to Scheme 1 starting from (-)-carvone.

According to NMR analysis, nucleoside **3** surprisingly adopts the **B** chair conformation, orienting the adenine base in equatorial position at the expence of three axial substituents.



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