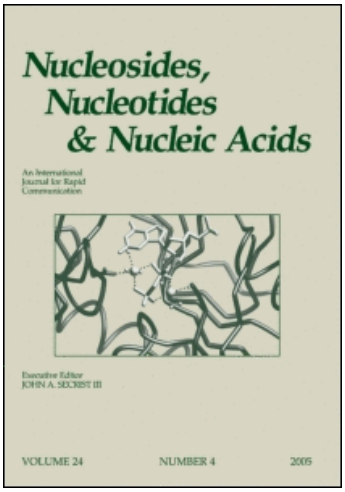



**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# Enantioselective Synthesis and Conformational Analysis of Cyclohexene Carbocyclic Nucleosides

Jing Wang[a]; Piet Herdewijn[a]
[a] Laboratory of Medicinal Chemistry, Rega Institute for Medical Research, K. U. Leuven, Leuven, Belgium

**To cite this Article** Wang, Jing and Herdewijn, Piet(1999) 'Enantioselective Synthesis and Conformational Analysis of Cyclohexene Carbocyclic Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 593 — 594
**To link to this Article: DOI:** 10.1080/15257779908041505
**URL:** http://dx.doi.org/10.1080/15257779908041505

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 593–594 (1999)

# ENANTIOSELECTIVE SYNTHESIS AND CONFORMATIONAL ANALYSIS OF CYCLOHEXENE CARBOCYCLIC NUCLEOSIDES

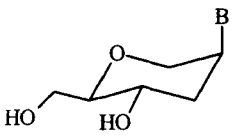
Jing Wang and Piet Herdewijn*

Laboratory of Medicinal Chemistry, Rega Institute for Medical Research, K.U.Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

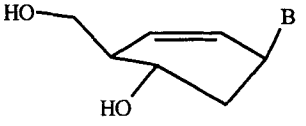
**ABSTRACT**: An enantioselective approach towards the synthesis of optically pure cyclohexene nucleosides **3** has been developed starting from (*R*)-carvone. The key steps are the regio- and stereoselective hydroboration of an exo double bond, the selective reduction of an enone intermediate and introduction of a base moiety by Mitsunobu reaction. Conformational analysis showed that the adenine base adopts predominantly in a pseudo-axial position.



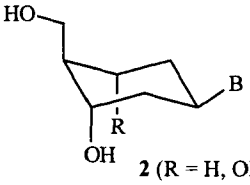
Carbocyclic nucleosides are of broad interest as antiviral agents and as building blocks for oligonucleotides due to their better chemical and enzymatic stabilities, as compared to nucleosides. The difference is due to the replacement of the ring-oxygen atom by a methylene group, hence, to the loss of the anomeric center. In contrast to five-membered ring carbocyclic nucleosides, little is known about the conformational behaviour and biological activity of six-membered ring analogues.




**1**



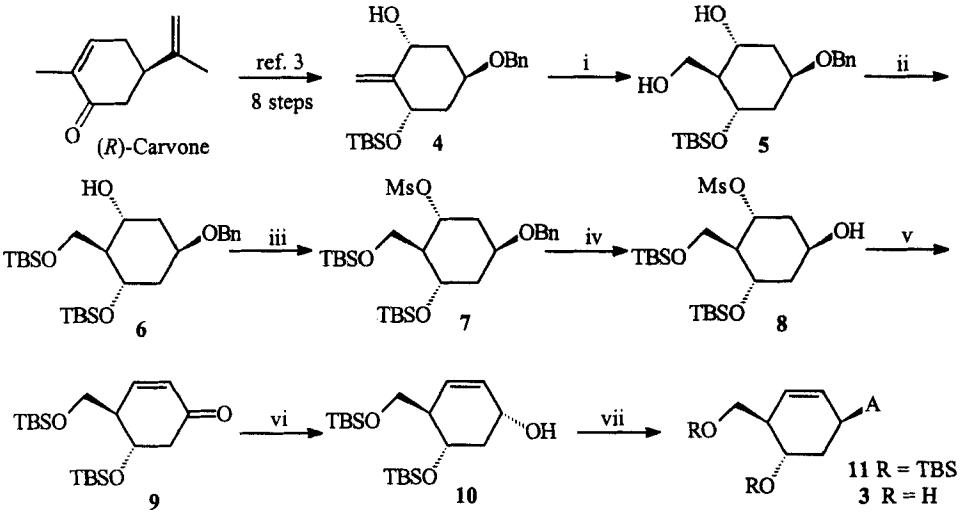

**3**




**2** (R = H, OH)

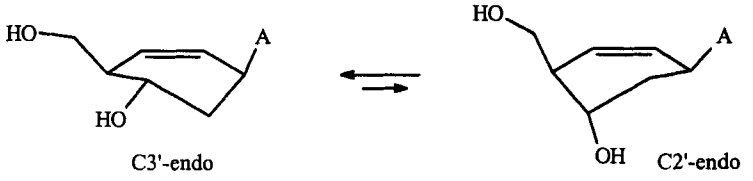
Previous research on six-membered carbohydrate nucleosides such as **1** and their carbocyclic congeners **2** (R = H) has shown that these two series of nucleosides exhibit a striking conformational difference, presumably responsible for their different biological activity. Indeed, the hexitol nucleosides **1**,[1] possessing antiviral activity, exist predominantly in the chair-like C1 conformation with the base moiety in an axial position, mimicking the C3'-endo form of a furanose nucleoside. However, their carbocyclic congeners **2** (R = H),[2] which adopt the opposite 1C chair conformation with

the base moiety in an equatorial position, are devoid of antiviral activity. Introduction of an additional α-oriented hydroxyl group (**2**, R = OH) failed to force the molecule into the desired C1 conformation.[3] In order to facilitate interconversion between conformations in a biological system, which seems to be crucial for biological activity, we synthesized the cyclohexene nucleosides **3** in which a double bond is introduced in the cyclohexyl ring. The energy difference between the two pseudo-chair conformers of **3** is expected to be lower than in the cyclohexane nucleosides **2**. An enantioselective approach to the synthesis of optically pure **3** starting from (*R*)-carvone is presented.




Reagents: i. 9-BBN, THF; ii. TBSCl (1eq), imidazole, DMF; iii. MsCl, $Et_3N$, $CH_2Cl_2$; iv. Pd-C(10%), $HCOONH_4$, MeOH; v. $MnO_2$, $CH_2Cl_2$; vi. $NaBH_4$, $CeCl_3.7H_2O$, MeOH; vii. (a) adenine, $PPh_3$, DEAD, dioxane, r.t., 66% and 17% $N_7$-isomer; (b) TBAF, THF.

According to NMR analysis and molecular modeling, **3** exists predominantly in the C3'-endo conformation, orienting the adenine base in a pseudo-axial position.




## REFERENCES

1. (a) Verheggen, I.; Van Aerschot, A.; Toppet, S.; Snoeck, R.; Janssen, G.; Balzarini, J.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1993**, *36*, 2033-2040; (b) Verheggen, I.; Van Aerschot, A.; Van Meervelt, L.; Rozenski, J.; Wiebe, L.; Snoeck, R.; Andrei, G.; Claes, P.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1995**, *38*, 826-835.
2. Maurinsh, Y.; Schraml, J.; De Winter H.; Blaton, N.; Peeters, O.; Lescrinier, E.; Rozenski, J.; Van Aerschot, A.; De Clercq, E.; Busson, R.; Herdewijn P. *J. Org. Chem.* **1997**, *62*, 2861-2871.
3. Wang, J.; Busson, R.; Blaton, N.; Rozenski, J.; Herdewijn, P. *J. Org. Chem.* **1998**, *63*, 3051-3058.