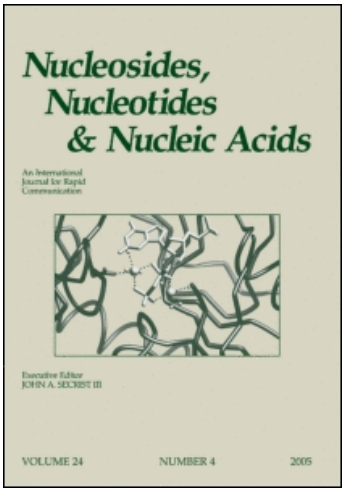

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(D)- AND (L)-CYCLOHEXENYL-G, A NEW CLASS OF ANTIVIRAL AGENTS: SYNTHESIS, CONFORMATIONAL ANALYSIS, MOLECULAR MODELING, AND BIOLOGICAL ACTIVITY

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ABSTRACT

(D)- and (L)-cyclohexeneyl-G were synthesized enantioselectively starting from (*R*)-carvone. Both show potent and selective anti-herpesvirus activity (HSV-1, HSV-2, VZV, CMV). Molecular modeling demonstrates that both isomers are bound in the active site of HSV-1 thymidine kinase in a high-energy conformation with the base moiety orienting in an equatorial position. It is believed that the flexibility of the cyclohexene ring is essential for their antivirial activity.

The development of novel nucleoside analogues as potential antiviral agents continues to attract considerable attention. Better understanding of the structure-activity relationship has provided information and criteria for a more rational design of new drugs. Based on our previous studies, it has been claimed that the conformational behavior of a nucleoside plays an important role in its biological activity. For example, the hexitol nucleosides, which show antiviral activity, in solution as well as in the solid state adopt a 3′-*endo* conformation (northern type) with the base moiety in an axial position. Co-crystallization of an antiviral anhydrohexitol nucleoside with herpes simplex virus (HSV) type 1 thymidine kinase showed a conformational inversion when the nucleoside analogue was bound in the active site (i.e. 2′-*endo*

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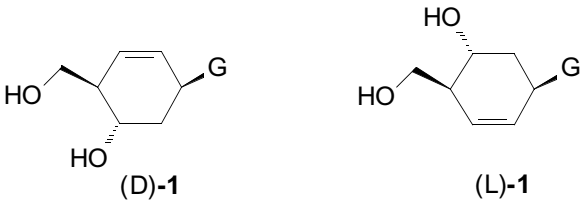

Scheme 1.

conformation with an equatorial base moiety) (1). This suggests that nucleosides can undergo conformational alteration during binding to herpesvirus thymidine kinase. This led us to assume that the conformational flexibility is important for the antiviral activity of a nucleoside.

Cyclohexene nucleosides are a class of six-membered carbocyclic nucleosides in which a double bond replaces the ring oxygen atom of a natural nucleoside. The resulting $\pi \rightarrow \sigma^*_{C1'-N}$ interaction mimics the anomeric effect of a natural nucleoside and considerably reduces the energy difference among the different conformers. These nucleosides are therefore conformationally more flexible to meet different enzymatic requirements.

The enantioselective synthesis of both (D)- and (L)-cyclohexene guanines **1**, using R-(−)-carvone as starting material, is shown in Scheme 1 (2–4). Carvone was converted into intermediate **3a**,**b** according to the reported procedure (5). Depending on the nature of the protection groups R_1–R_4, intermediate **3** allows for the synthesis of both (D)-**1** and (L)-**1**.

For the synthesis of (L)-**1**, the two free hydroxyl groups of **3a** were protected as a benzoate, the TBS group (R_2) was chemoselectively removed by treatment with 1 equiv. of TBAF, and the generated alcohol was converted into mesylate **4**. Removal of the remaining TBS group and eliminative oxidation gave rise to enone **5**. Reduction using $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ afforded the α-enol **6** ready for base moiety introduction. Treatment of **6** with 2-amino-6-chloropurine under Mitsunobu reaction conditions and conversion of the resulting 6-chloropurine compound into the guanine derivative gave (L)-**1**, after final deprotection under basic conditions.

The synthesis of (D)-**1** was carried out in a similar way. Enone **8** was obtained by mesylation of **3b** and deprotection of the Bn group, followed by oxidative elimination. Selective reduction and introduction of the base moiety was carried out according to the same procedure as used for (L)-**1**. Conversion of the 6-chloroguanine into guanine using TFA/H_2O (3:1) resulted in simultaneous deprotection of the two TBS groups, affording directly (D)-**1**.

Both enantiomers show potent and selective anti-herpesvirus activity (HSV-1, HSV-2, VZV, CMV) (3). The activity spectrum of both compounds is very similar. They display the same activity against HSV-1 and HSV-2. Against VZV and CMV the potency of (L)-**1** is two-fold lower than that of (D)-**1**. They are as active as acyclovir and brivudin against HSV-1 and their activity is similar to that of

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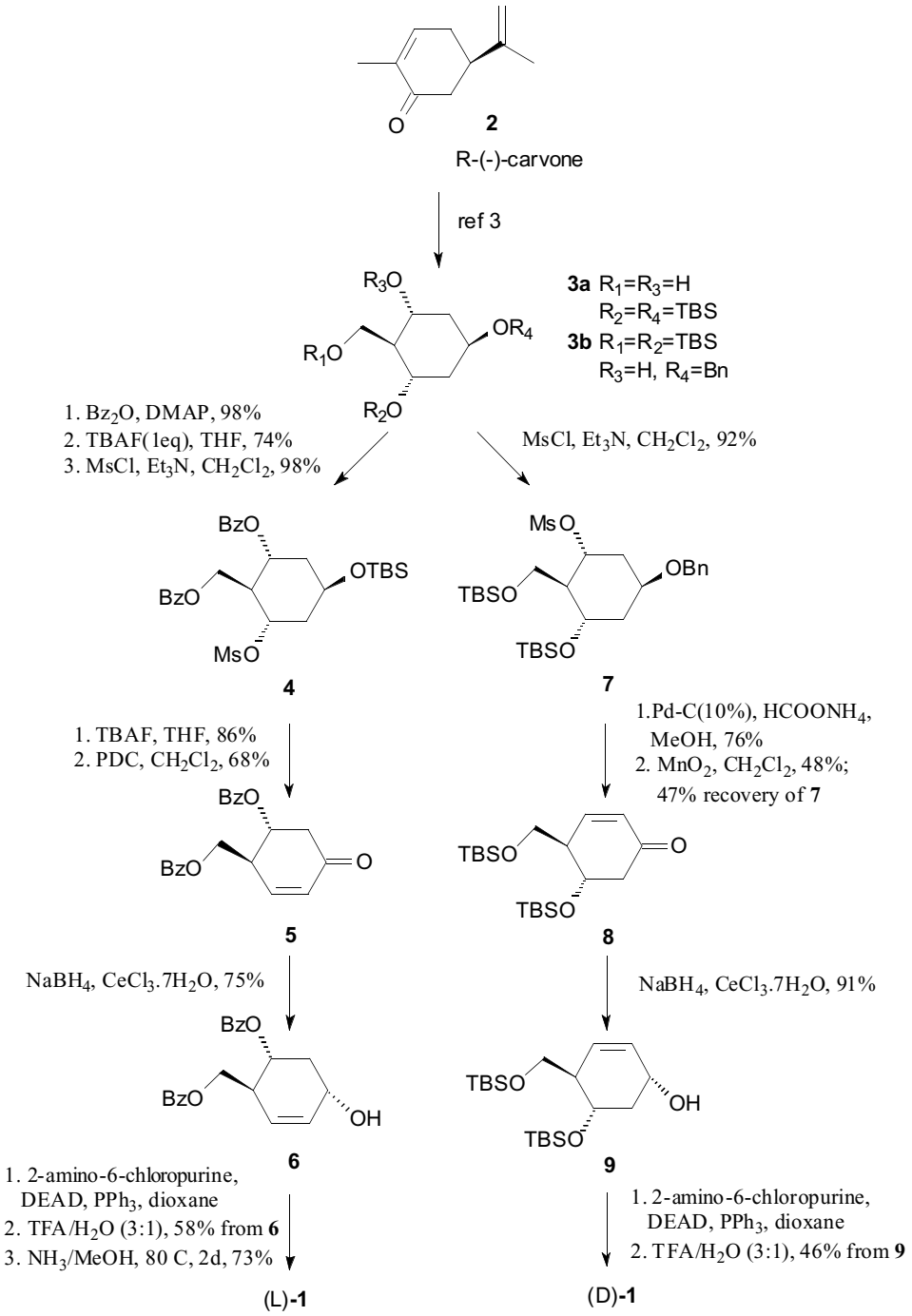

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acyclovir against HSV-2. (D)-**1** shows the same potency against CMV as ganciclovir. (D)-**1** as well as (L)-**1** didn't show toxicity in four different cell lines (HeLa, Vero, E_6Sm, HEL).

Both compounds showed a reduced antiviral activity when evaluated against TK^- strains of HSV-1. This suggests that intracellular phosphorylation in the virus-infected cells is an important step for the enzymatic activation of these two nucleosides. Molecular modeling of (D)-**1** and (L)-**1** in complex with HSV-1 thymidine kinase showed that both compounds were bound in the active site in a high-energy conformation ($^2H_3$ with pseudo-equatorial orientation of the base moiety in the syn conformation). This is in agreement with our previous observation that HSV-1 thymidine kinase may induce a conformational change of the nucleoside upon binding. The amino acids involved in binding of both isomers are the same, but their interaction energy is slightly different, mainly due to the hydrogen bonding interaction difference between the secondary hydroxyl group of the nucleosides with Glu-225. This energy difference might be relevant to their different biological activity.

Structural analysis demonstrates that the cyclohexene system is very flexible. This flexibility may be an important conformational characteristic explaining the potent antiviral activity of these cyclohexenyl nucleosides.

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