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# Synthesis of Novel Cyclopropyl Carbocyclic Nucleosides from (−)-(*Z*)-2,3-Methanohomoserine

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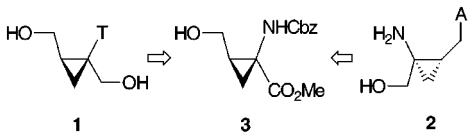
## ABSTRACT




**1** **3** **2**

T = thymine, A = adenine

**The new cyclopropyl carbocyclic nucleosides 1 and 2 have been synthesized by following short and efficient routes starting from conveniently protected (−)-(*Z*)-methanohomoserine derivative 3. Both products 1 and 2 bear a quaternary stereogenic center and have opposite chirality. Moreover, the adenine derivative 2 belongs to a new class of cyclopropyl nucleoside showing an amino alcohol function at C-1 in addition to a methylene spacer between the base and the carbocyclic ring.**

Carbocyclic nucleosides have received great attention since the isolation from natural sources of (−)-aristeromycin[1] and (−)-neplanocine[2] and the verification of their remarkable biologic activities. Among the differently sized carbocyclic nucleosides, the cyclopropane derivatives have focused the interest of chemists and biologists in the past decade due to the potent antiviral properties of some of them. Several structural modifications have been made in order to improve or enhance this activity, the most representative being shown in Figure 1. One of the most usual modifications consists of the incorporation of a second hydroxymethyl group, either in a geminal position at C-1 of the carbocyclic ring (type C) or in a vicinal position at C-2 (type D).[3] Very recently, a new compound bearing a geminal disubstitution at C-3 (type E) has been prepared showing an activity 40 times more potent than acyclovir and better selectivity.[4] The introduction

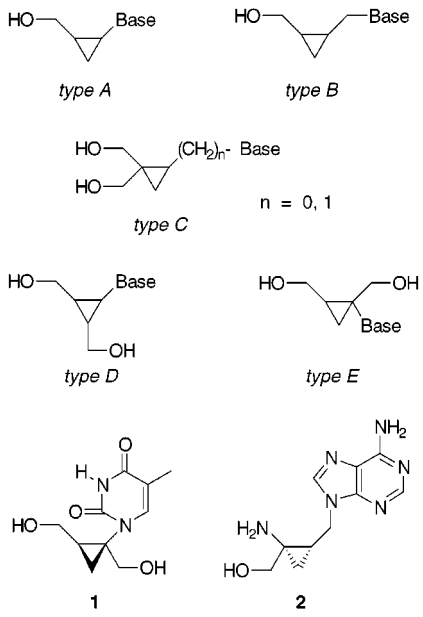



**Figure 1.**

(1) Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255. Yaginuma, S.; Tsujino, M.; Muto, N.; Otani, M.; Hatashi, M.; Ishimura, F.; Fujii, T.; Watanabe, S.; Matsuda, T.; Watanabe, T.; Abe, J. *Curr. Chemother. Infect. Dis., Int. Congr.* **1980**, *2*, 1558.

(2) Yaginuma, S.; Tsujino, M.; Muto, N.; Otani, M.; Hatashi, M.; Ishimura, F.; Fujii, T.; Watanabe, S.; Matsuda, T.; Watanabe, T.; Abe, J. *Curr. Chemother. Infect. Dis., Int. Congr.* **1980**, *2*, 1558.

(3) Maag, H.; Nelson, J. T.; Steiner, J. L. R.; Prisbe, E. J. *J. Med. Chem.* **1994**, *37*, 431.

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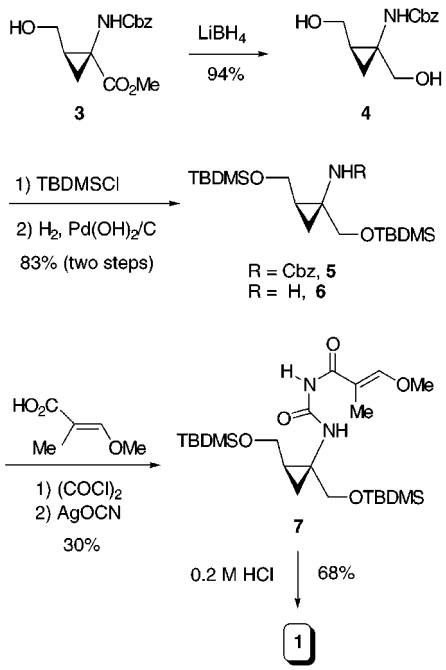
of spacers, i.e., additional methylene groups between the heterocyclic base[5] or the hydroxymethyl group at C-1[6] and the cyclopropane has also been investigated. Spacered cyclopropyl nucleosides of types B and C are more flexible than those of type A, avoiding the high rigidity that seems to be unfavorable either for the interaction with phosphorylating enzymes or for the interaction of the corresponding triphosphate with viral DNA polymerases.[7] Finally, the incorporation of other substituents such as halogen atoms has also been considered.[8]

Therefore, keeping the interest of such products in mind, several synthetic approaches have been reported for the obtention of these different kinds of cyclopropyl nucleosides, as pure enantiomers or as racemates.[3−6,8,9] Nevertheless, the described protocols often involve long synthetic sequences and cyclopropanation methods with rather low stereoselectivity.

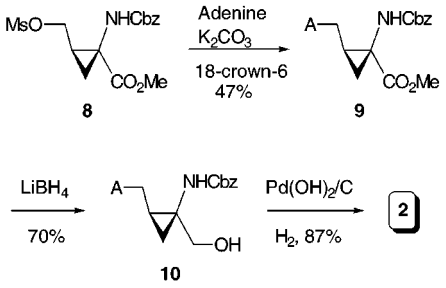
In this Letter, we describe the concise and efficient stereoselective syntheses of the new cyclopropyl carbocyclic nucleosides **1** and **2**. Compound **2** represents a new kind of nucleoside showing a gem-disubstituion, as a $\beta$-amino alcohol function, at C-1 and a methylene spacer between the base and the cyclopropane ring. As additional structural features, the hydroxymethyl group is *trans* with respect to the base-containing chain at C-3, and the quaternary center bears an amino group. On the other hand, nucleoside **1** contains a pyrimidine-family base while nucleoside **2** presents a purine-type one. Both products are enentiomerically pure and have been obtained from conveniently protected (−)-(*Z*)-2,3-methanohomeserine, **3**, as an appropriate precursor which affords the chirality of the cyclopropane stereogenic centers and presents functional groups suitable for the transformations into the target molecules. This homoserine methanolog has been synthesized in our laboratory, in multigramme scale, through the highly stereoselective cyclopropanation of a suitable olefinic substrate, readily available from D-glyceraldehyde, and has successfully been used for the synthesis of other cyclopropane amino acids.[10]

The synthetic routes to **1** and **2** are outlined in Schemes 1 and 2, respectively. The strategies to introduce the heterocyclic base are different for each nucleoside. In the case of **1**, the thymine ring is built from an amino group present in the precursor, following a standard methodology previously described.[11] Adenine, in contrast, is incorporated through nucleophilic displacement of mesylate anion.

**Scheme 1**




**Scheme 2**




Thus, the methyl ester in methanohomoserine derivative **3** was reduced with lithium borohydride to afford, in nearly quantitative yield, diol **4**[12] which was protected as bis(silyl) ether **5**. The amine was deprotected by hydrogenation of benzyl carbamate in the presence of $Pd(OH)_2$ on charcoal as catalyst. Creation of the thymine system to afford compound **7** was accomplished through the reaction between **6** and 3-methoxy-2-methylacryloyl isocyanate. This last reagent was generated in situ from 3-methoxy-2-methylacryloyl chloride and silver isocyanate.

Cyclization of the acryloyl urea to the thymine ring and deprotection of diol was achieved in one single step by treatment of **7** with 0.2 M HCl. In this way, nucleoside **1** was obtained as a solid, mp 180−182 °C and $[\alpha]_D$ −44.0, in 16% overall yield from **3**.

(4) Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. *J. Med. Chem.* **1998**, *41*, 1284.

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(7) Harnden, M. R.; Jarvest, R. L.; Bacon, T. H.; Boyd, M. R. *J. Med. Chem.* **1987**, *30*, 1636.

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(9) (a) Gauvry, N.; Huet, F. *Tetrahedron* **1999**, *55*, 1321. (b) Zhao, Y.; Yang, T.; Lee, M.; Lee, D.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **1995**, *60*, 5236. (b) Lee, G.; Du, J. F.; Chun, M. W.; Chu, C. K. *J. Org. Chem.* **1997**, *62*, 1991.

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(11) (a) Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958**, 153. (b) Shealy, Y. F.; O'Dell, C. A.; Thorpe, M. C. *J. Heterocycl. Chem.* **1981**, *18*, 383. (c) Díaz, M.; Ortuño, R. M. *Tetrahedron: Asymmetry* **1997**, *8*, 3421.

(12) All new products were fully charaterized by their physical constants and spectroscopic data and gave satisfactory microanalysis.

In the second synthetic route, mesylate **8**, obtained from **3** in the usual way,[10] was reacted with adenine in the presence of potassium carbonate and 18-crown-6 at 80 °C for 10 h to give compound **9** in 47% yield.[13] This method afforded better results than the use of NaH as a base even in the presence of a crown ether.[14,15] Intermediate **9** incorporates the heterocyclic base present in the target nucleoside but still retains the amino acid function provided by the precursor. Reduction of the methyl ester to give **10** followed by deprotection of the amino group under catalytic hydrogenation led to the obtention of nucleoside **2** as solid, mp 197−199 °C and $[\alpha]_D$ +22.5 (27% overall yield from **3**).

In conclusion, we have shown the usefulness of (−)-(*Z*)-methanohomoserine as a precursor of different types of cyclopropyl nucleosides. Versatile and straightforward synthetic routes have allowed the obtention of two new compounds whose biological evaluation is in progress.

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(13) In a typical run, a solution of mesylate **8**[10] (286 mg, 0.8 mmol) in anhydrous DMF (5 mL) was added to a mixture of adenine (113 mg, 0.8 mmol), $K_2CO_3$ (121 mg, 0.9 mmol), and 18-crown-6 (211 mg, 0.8 mmol) in DMF (8 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 80 °C for 10 h and then cooled to room temperature. Saturated aqueous NaCl (15 mL) was added, and the solution was extracted with EtOAc (5 × 10 mL). The combined organic extracts were dried over $MgSO_4$, and solvents were removed at reduced pressure. The residue was chromatographed on silica gel (mixtures of $CH_2Cl_2$−methanol as eluent) to afford compound **9** (149 mg, 47% yield).

(14) In the last cases the N-9 alkylated product was produced along with the N-7 regioisomer (85:15 ratio). The structures were assigned by comparison of their $^1$H and $^{13}$C NMR spectroscopic data with those of similar compounds in the literature.[15] Moreover, UV of **2** ($\lambda_{max}$ 256, $\epsilon$ 14000) compares well with that of adenosine ($\lambda_{max}$260, $\epsilon$ 15000), thus discarding the presence of the N-3 regioisomer.

(15) See, for instance: Jung, M. E.; Kiankarimi, M. *J. Org. Chem*. **1998**, *63*, 8133.