

## Synthesis of conformationally locked carbocyclic nucleoside phosphonates to probe the active site of HIV-1 RT

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### ABSTRACT

The conformationally locked carbocyclic nucleoside phosphonates **2** and **2'** and key intermediates for the synthesis of **3** and **3'** were prepared from a chiral cyclopentene derivative and epichlorohydrin, respectively. The structure of the nucleoside precursor **6** was confirmed by X-ray crystallography. These carbocyclic nucleoside phosphonates were designed to probe their binding interactions at the active site of HIV-1-RT.

### INTRODUCTION

Nucleoside phosphonates have been recognized as useful prodrugs in the field of antiviral therapy since the 1970's. The advantage of a nucleoside phosphonate resides in its ability to bypass the first phosphorylation step, which is often insufficient and rate limiting during the formation of the key 5'-triphosphate metabolites. An active nucleoside phosphonate can be further phosphorylated by two cellular kinases.<sup>1,2</sup> Recently, Herdewijn et al. reported that deoxy-L-threosyl phosphonate nucleosides were effective anti HIV agents.<sup>3</sup> Significantly, the adenine derivative **1** had excellent anti HIV activity, selective inhibitory activity

against HIV RT, and no cytotoxicity. This finding inspired us to synthesize the conformationally locked, carbocyclic versions of this class of nucleosides. Compound **1** has two extreme conformers: (1) *north-like* with both groups pseudoaxially oriented and (2) *south-like* with both groups pseudoequatorially oriented. Our designed nucleoside phosphonates (**2** and **3**) and the corresponding enantiomers (**2'** and **3'**) are built on a bicyclo[3.1.0]hexane template that is able to mimic both conformers of **1**. It is hoped that these compounds will help us understand the manner in which **1** interacts at the active site of HIV-1 RT.

### RESULTS AND DISCUSSION

For the synthesis of **2**, chiral cyclopentene derivative **4** was cyclopropanated following a previously reported protocol.<sup>4</sup> Subsequently, the hydroxyl group was inverted with pivalic acid via a Mitsunobu reaction<sup>5</sup> and the acetate group was cleaved selectively with K<sub>2</sub>CO<sub>3</sub>/MeOH. 6-Chloropurine was coupled with the corresponding alcohol and after ammonolysis and removal of the pivaloyl group the adenine derivative **6** was obtained. The structure of **6** was confirmed by X-ray crystallography. A phosphonomethyl group was attached to the 3'-hydroxyl group

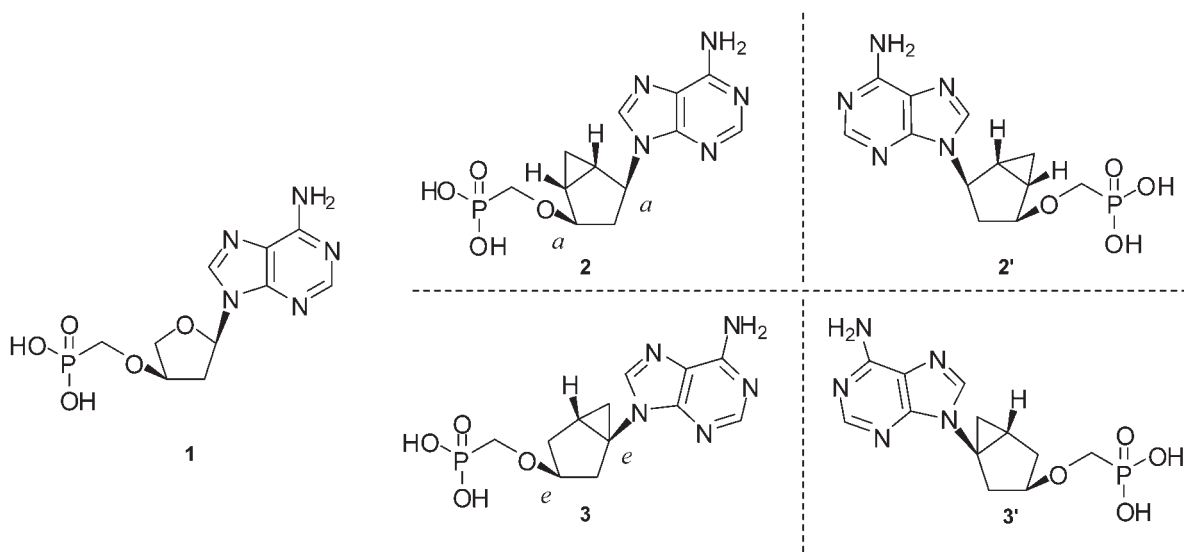
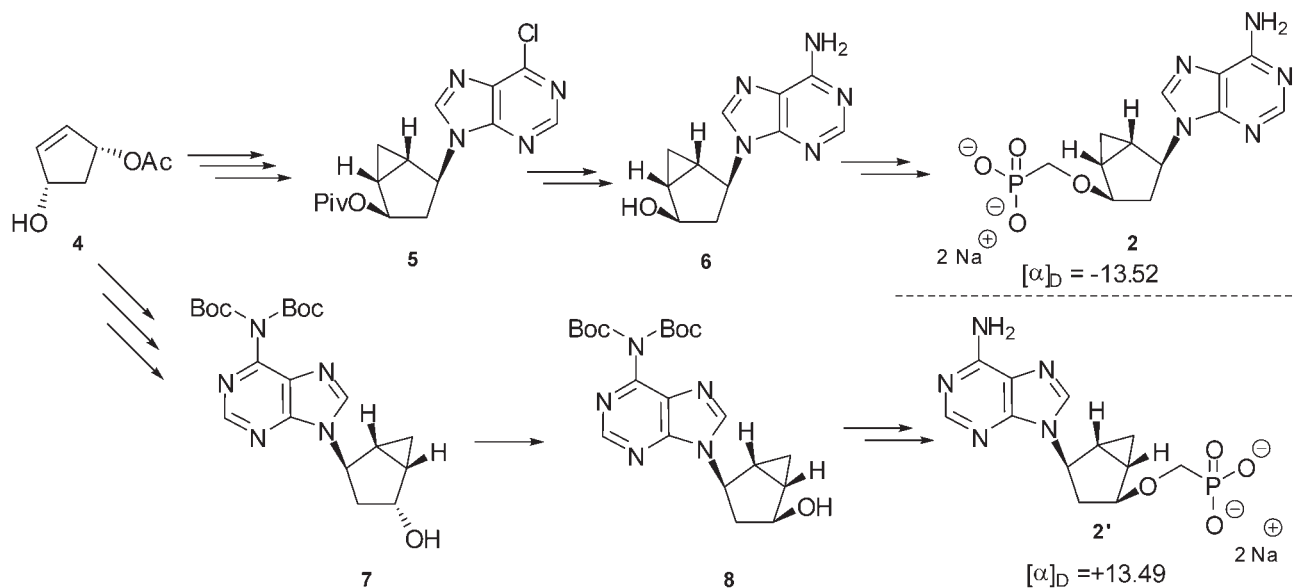


Fig. 1 Chemical structure of **1** and related locked carbocyclic nucleoside phosphonates **2**, **2'**, **3**, **3'** (*a* = axial; *e* = equatorial).



**Scheme 1** Synthesis of **2** and **2'**

(nucleoside numbering) using the triflate of diethyl phosphonomethanol and LHMDS as a base. This operation required protection of the 6-aminopurine with the DMTr group. Finally, the ethyl groups of the phosphonate and the DMTr were removed simultaneously with TMSBr.

The synthesis of **2'** required the same starting material (**4**). Compound **7** was synthesized after several steps and then the 3'-hydroxyl group (nucleoside numbering) was inverted via a tandem oxidation-reduction methodology. The hydroxyl group of **8** was phosphonomethylated and the protecting groups on the phosphonate and adenine moieties were removed in a similar manner as before to give **2'** as the sodium salt. The optical rotation values of compounds **2** and **2'** showed that they are perfect enantiomers. In vivo preliminary results indicated that **2** had no anti-HIV activity. Molecular docking of the diphosphate of **2** (triphosphate congener) at the active site of HIV RT shows a severe steric clash between the bulk of the bicyclo[3.1.0]hexane moiety and M184. This clash is avoided by compound **2'**, which is under evaluation.

We have already started the synthesis of antipodes **3** and **3'**. The key step is the construction of a bicyclo[3.1.0]-hexylamine derivative, which was accomplished by a titanium-mediated reductive intramolecular cyclization.<sup>6-8</sup> These compounds will be converted to the corresponding nucleoside phosphonates in a similar manner.

## CONCLUSION

In this study, two conformationally locked carbocyclic nucleoside phosphonates, designed as mimics of anti-HIV active deoxy-L-threosyl phosphonate nucleosides, were synthesized to probe their binding interactions at the active site of HIV1-RT.

## ACKNOWLEDGMENTS

This research was supported by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.

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