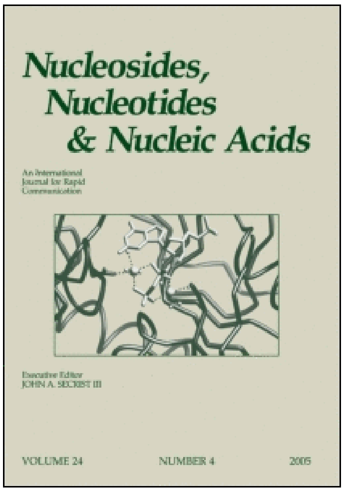

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REARRANGING THE BICYCLO[3.1.0]HEXANE TEMPLATE OF CARBOCYCLIC NUCLEOSIDES TO IMPROVE BINDING RECOGNITION BY KINASES

Victor E. Marquez and Maria J. Comin □ *Laboratory of Medicinal Chemistry, Center for Cancer Research, National Cancer Institute at Frederick, Frederick, Maryland, USA*

□ *A novel bicyclo[3.1.0]hexane carbocyclic nucleoside (**4**) with a south-like conformation amenable to interact with the herpes thymidine kinase (HSV-tk) was synthesized with an endo-hydroxyl group positioned at the tip of the bicyclo[3.1.0]hexane ring system opposite to the tip of the fused cyclopropane ring. The introduction of the hydroxymethyl chain through a Baylis-Hillman type reaction and the regioselective opening of a cyclic sulfite intermediate to introduce the nitrogen functionality at the correct position are highlighted.*

Keywords Carbocyclic nucleosides; bicyclo[3.1.0]hexane; herpes thymidine kinase

INTRODUCTION

Carbocyclic nucleosides built on a bicyclo[3.1.0]hexane template have provided important clues to differentiate the contrasting conformational preferences between kinases and polymerases.[1–3] Albeit the binding preference of the various polymerases examined to date is consistent for a north rigid template, the kinases' preference for the antipodal south conformation is sensitive to additional conformational restrictions imposed by the bicyclo[3.1.0]hexane system, such as a higher *syn* $\leftrightarrows$ *anti* energy barrier, which in the case of pyrimidine nucleosides forces the disposition of the base into the *syn* range. Also, the critical presence and the stereochemistry of the 3′-OH (nucleoside numbering) on the pseudoribose ring are important structural elements for recognition by kinases.

In the case of the south thymidine analogue (**1**), the preference for the *syn* conformation diminishes its substrate affinity for the first phosphorylation step catalyzed by the herpes thymidine kinase (HSV-tk).[2]

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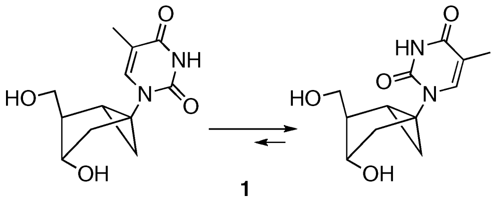
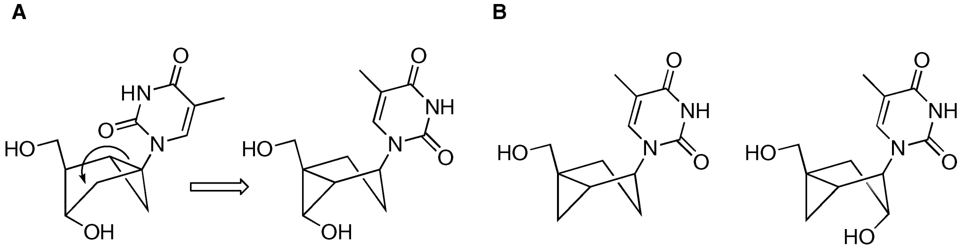


1

Because the fusion of the cyclopropane ring adjacent to the nucleobase is responsible for the *syn* preference, we sought to alleviate this problem by repositioning the fused cyclopropane ring in **1** to the other end of the molecule generating a new compound (**2**) that still maintained an intact south-like conformation but with the thymine ring in the *anti* disposition (Scheme 1A).



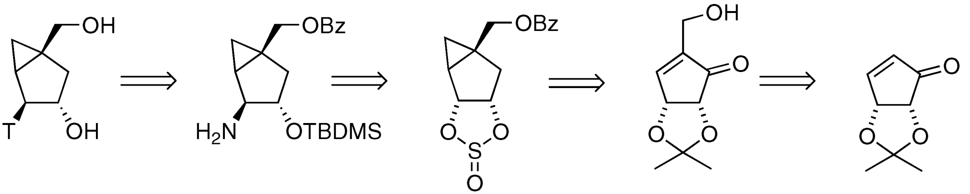
1 **2** **3** **4**

SCHEME 1

Because compound **2** was prone to undergo ring opening at room temperature via a retro aldol reaction, compound **3** was synthesized instead (Scheme 1B). A crystal structure of compound **3** indeed confirmed that the conformation of the nucleobase was *anti*, and the phosphorylation efficiency for the first step catalyzed by HSV-tk more than doubled relative to compound **1**.[3] Unfortunately, the removal of the critical 3′-OH proved to be fatal for the second phosphorylation step, also catalyzed by HSV-tk. This result prompted us to remedy the lack of recognition by HSV-tk resulting from the absence of the 3′-OH by relocating this critical group in a similar endo disposition but from the opposite end of the pseudoboat ring (compare **2** versus **4**, Scheme 1) where it could engage in H-bonding in a manner akin to that of **1**. Molecular docking with HSV-tk confirmed that this was possible and the synthesis of **4** is described herein.

SYNTHESIS

Thymidine analog **4** was synthesized through a linear approach in excellent yield from the carbocyclic amine **5**. The pseudosugar ring was prepared from known cyclopentenone **8**[4] employing two key steps: (1) a



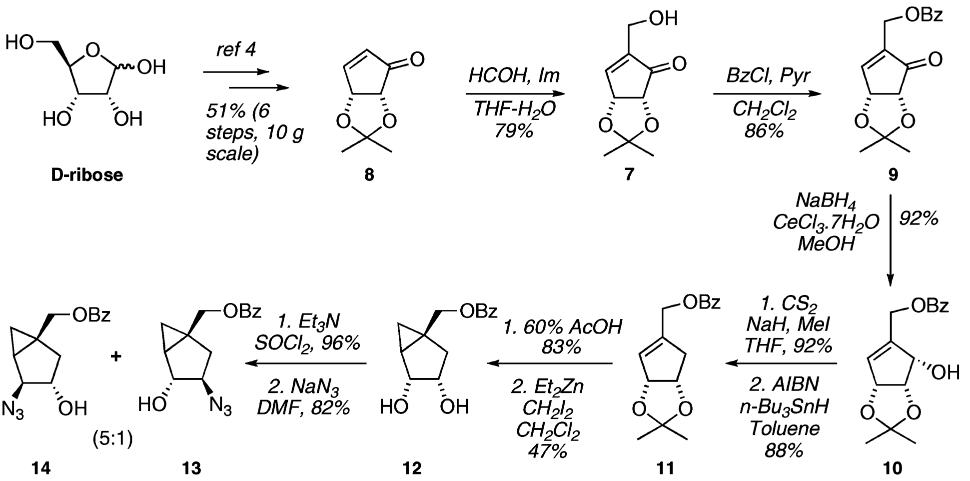
4 **5** **6** **7** **8**

SCHEME 2

Baylis-Hillman reaction[5] to assemble the 5′-hydroxymethyl side chain, and (2) a regioselective opening of cyclic sulfite **6** to introduce the nitrogen substituent at the correct position[6] (Scheme 2).

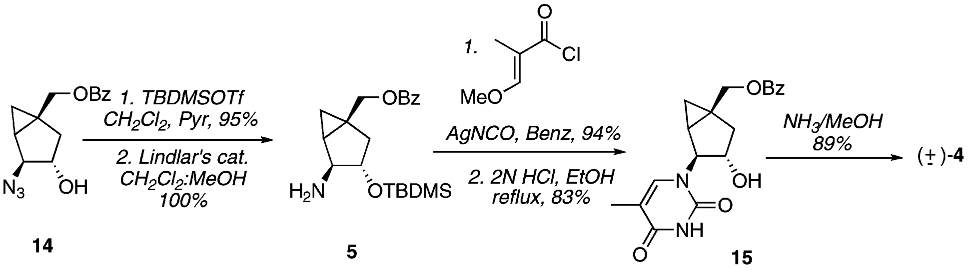
Therefore, treatment of cyclopentenone **8** with formaldehyde in the presence of imidazole in aqueous media gave the desired hydroxymethyl cyclopentenone **7** in high yield (Scheme 3).[7]

After protection of the primary hydroxyl group as a benzoyl ester, the ketone functionality was diastereoselectively reduced by treatment with sodium borohydride in the presence of cerium salts in quantitative yield. Radical deoxygenation of the corresponding xanthate under Barton conditions[8] gave the desired compound **11**. Racemization was observed during this step. This result can be rationalized in terms of the two resonance structures of the intermediate radical, which happen to be energetically equivalent and enantiomeric. In order to further test our synthetic approach, we decided to continue the synthesis with racemic compound **11**. Thus, after cleavage of the ketal ring, the corresponding diol was cyclopropanated and then converted to the sulfite derivative that reacted with sodium azide in dimethylformamide to yield a 5 to 1 diastereomeric mixture



SCHEME 3

of azide-alcohols favoring the desired isomer **14** in 82% yield. With intermediate **14** at hand, synthesis of the final racemic nucleoside was straightforward as shown in Scheme 4.



SCHEME 4

A slightly different approach in order to avoid racemization during the radical deoxygenation is currently underway. The new synthetic approach and the biological studies will be published in due course.

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