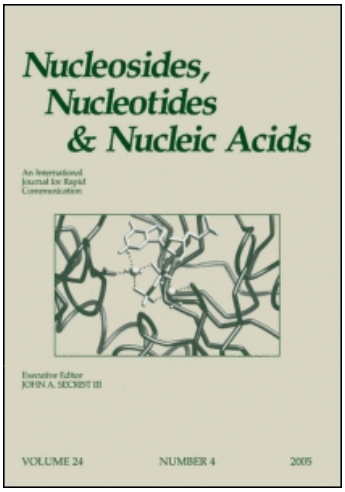

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of Carbocyclic Analogues of Thymidine

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Online publication date: 09 August 2003

To cite this Article Ludek, O. R. and Meier, C.(2003) 'Synthesis of Carbocyclic Analogues of Thymidine', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 683 — 685
To link to this Article: DOI: 10.1081/NCN-120022700
URL: http://dx.doi.org/10.1081/NCN-120022700

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 683–685, 2003

Synthesis of Carbocyclic Analogues of Thymidine

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ABSTRACT

A new route towards an enantiomerically pure carbocyclic 2′-deoxyribonucleoside precursor was developed. After coupling with a nucleobase the product is easily accessible for further modifications at the 3′-hydroxy group.

INTRODUCTION

Nucleoside-based inhibitors of reverse transcriptase (RT) were the first drugs to be used in the chemotherapy of AIDS. After entering the cell, these substances should be activated to their triphosphates by cellular kinases. Thus, for the most extensively used drug, 3′-azido-3′-deoxythymidine (AZT), whereas phosphorylation is facile, the product (AZTMP) is a very poor substrate for the second kinase, thymidylate kinase (TmpK). Due to the steric demand of the azido group in the 3′-position of AZTMP compared to the 3′-hydroxyl group of the natural substrate, 2′-deoxythymidine monophosphate (dTMP), the structure of the enzyme changes, which causes a 200-fold decrease in the rate of phosphorylation.[1] Docking experiments, performed on the basis of molecular modelling, led to the assumption that carbocyclic nucleotide analogues of AZTMP should still bind well to the active

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DOI: 10.1081/NCN-120022700
1525-7770 (Print); 1532-2335 (Online)

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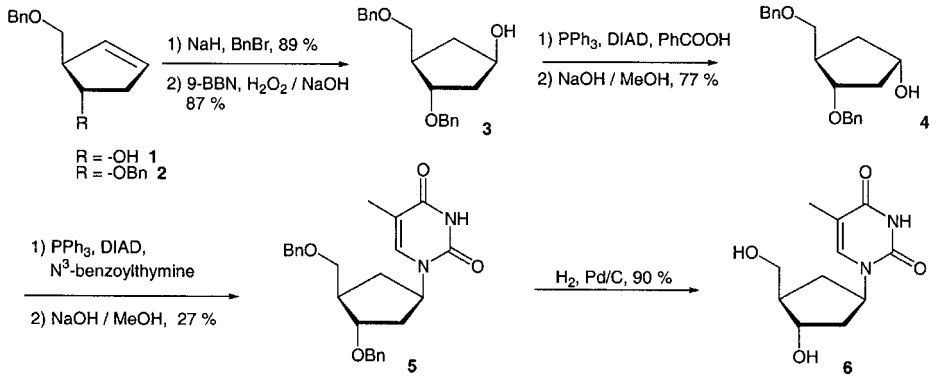
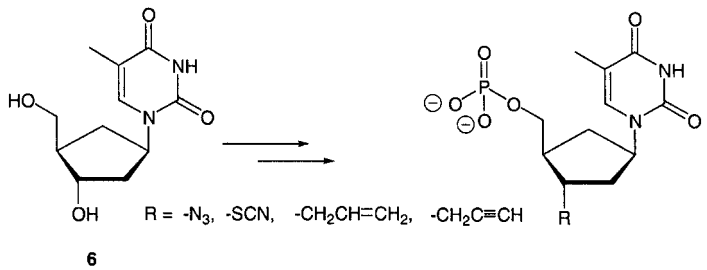
site of TmpK. Due to the increased flexibility these nucleotides should not cause a structural change of the enzyme. Here, we will present the enantioselective synthesis of carbocyclic analogues of thymidine as well as the corresponding monophosphates by using a convergent synthetic strategy. The carbocyclic moiety is coupled to the heterocyclic base to obtain carbocyclic thymidine (*carba*-dT) **6** as a key intermediate for further variations in the 3′-position.

RESULTS



In our search for a short and efficient convergent synthesis towards carbocyclic 2′-deoxythymidine **6,** we were attracted by the simplicity of forming the carbocyclic moiety in two stages using the method of Biggadike et al.[2]. The two stereogenic centers in **1** are introduced by an asymmetric hydroboration of a substituted cyclopentadiene, prepared from cyclopentadiene. After protecting the free hydroxygroup in **1** with the benzyl group, the chiral olefin **2** can be hydroborated regio- and stereoselective using 9-BBN in THF affording the β-alcohol **3** in 87% yield. The β-alcohol **3** can easily be transferred into the desired α-alcohol **4** by a Mitsunobu reaction. The coupling of the carbocyclic precursor **4** and the nucleobase was also achieved by a Mitsunobu reaction, using *N3*-benzoylthymidine as the nucleophile.[3] Removal of the protection groups afforded enantiomerically pure carbocyclic thymidine **6** in 15% overall yield.



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The free hydroxy groups in *carba*-dT **6** can now be replaced by groups isoster to the azido group in order to investigate the sterical and/or electronical influence of the substituent in this position on the substrate properties towards thymidylate kinase.

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