STEREOSELECTIVE SYNTHESIS OF *ISO*-CARBOCYCLIC NUCLEOSIDE ANALOGUES AS POTENTIAL ANTIVIRAL DRUGS

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Introduction

Over the last few decades, carbocyclic nucleosides represent an attractive approach for the development of new antiviral drugs. Due to their hydrolytic and enzymatic stability in comparison to the natural nucleosides they show important biological properties.

Carbocyclic nucleoside analogues like carbovir and entecavir were found to be potent inhibitors of **HIV´s reverse transcriptase** and recently the carbocyclic 2'-deoxythymidine analogue *carba*-dT has shown high *in vitro* activity against HIV replication (Figure 1).[1] This compound shows a unique mechanism of inhibition termed delayed chain termination, resulting in the inhibition of DNA synthesis.[2] Moreover, the synthesis of *carba-iso*-dT was reported. This isomer showed a 20-fold decrease of the antiviral activity (EC_{50} = 10 µM) compared to *carba*-dT, but surprisingly without exhibiting any cytotoxicity.[3]

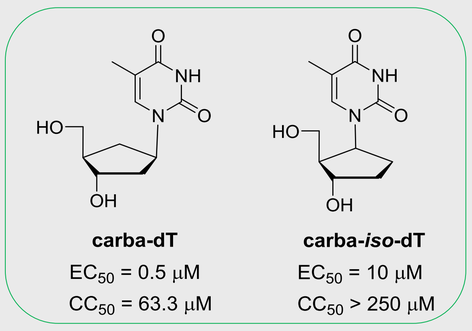
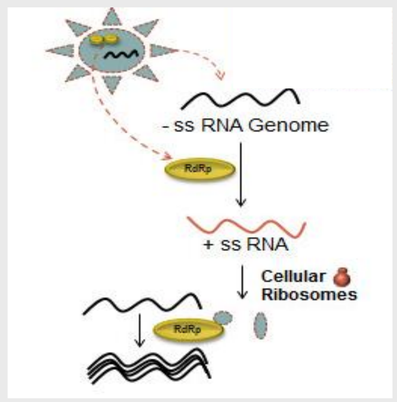
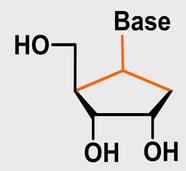


Figure 1. Antiviral activity of *carba*-dT and *carba*-iso-dT.

Objectives

On the basis of these results, the aim of this work is directed to the investigation of new carbocyclic nucleosides against viral infections, e.g. the hepatitis C virus (HCV), a RNA virus that uses a **RNA-dependent RNA-polymerase (RdRp)** for the viral replication. This polymerase is considered to be an essential component in the HCV replication complex and therefore is an ideal target for drug discovery.





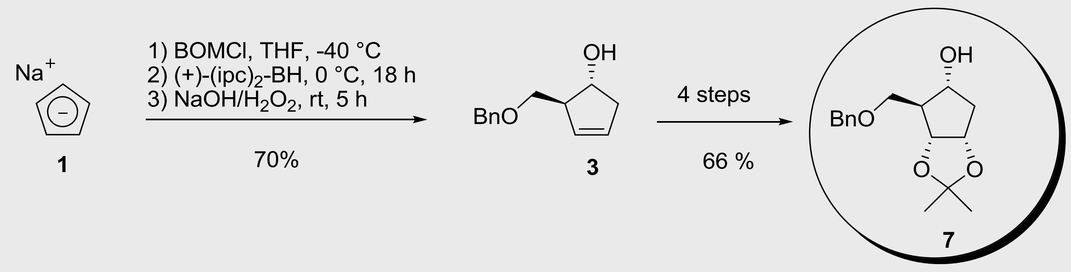
Base = thymine, uracil, adenine

We report on the synthesis of a series of *iso*-carbocyclic nucleoside analogues as potential inhibitors of RdRp.

Chemistry

A convergent approach was used for the synthesis of *iso*-carbocyclic nucleoside analogues **12**, **12a**, **13**, **17** starting from enantiomerically pure (1*R*,2*S*)-2-(benzyloxymethyl)cyclopent-3-enol (**3**), which was used for the preparation of the cyclopentanol derivative **7** (Scheme 1).

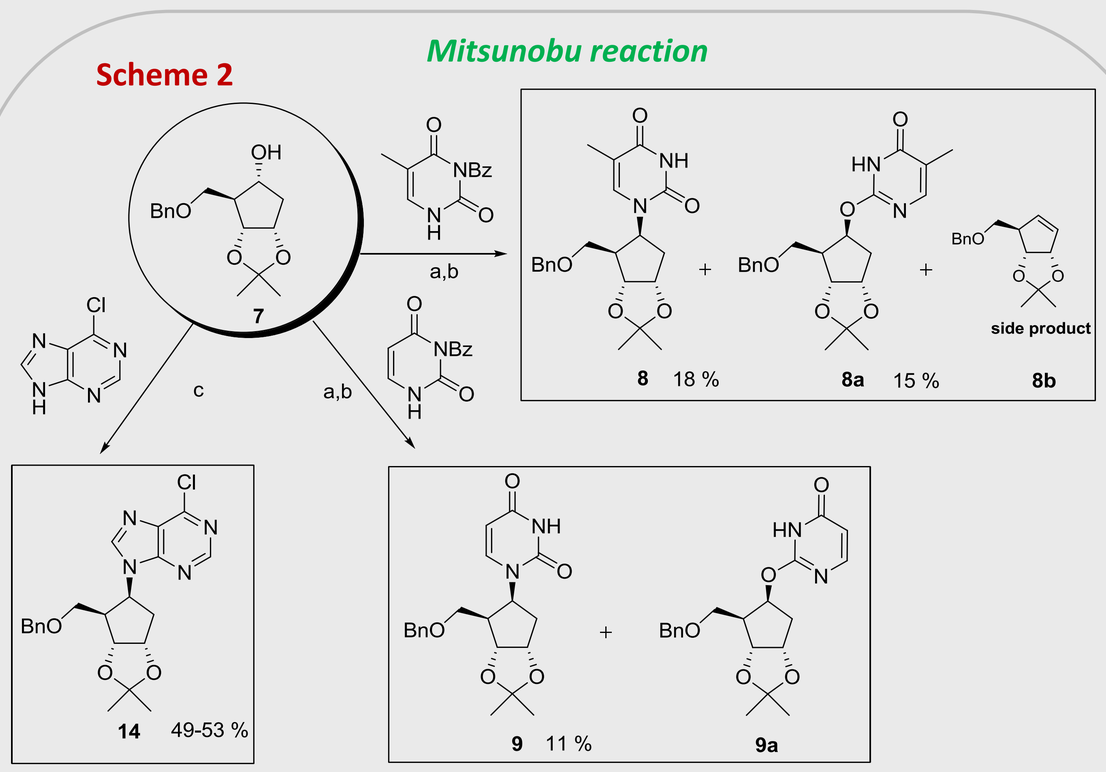
Scheme 1



The coupling with *N*3-protected pyrimidine nucleobases presented a critical step (Scheme 2) [4]. The nucleobases react as ambident nucleophiles, leading to a mixture of *N*1- and O^2-isomers (Table 1) and the product of elimination **8b** occurred as major side reaction. First the standard Mitsunobu conditions reported by Ludek [3] and then the microwave assisted conditions were used with comparable results. The coupling with the 6-chloro purine showed higher yield (**14**, 49-53 %).

Scheme 2

Mitsunobu reaction



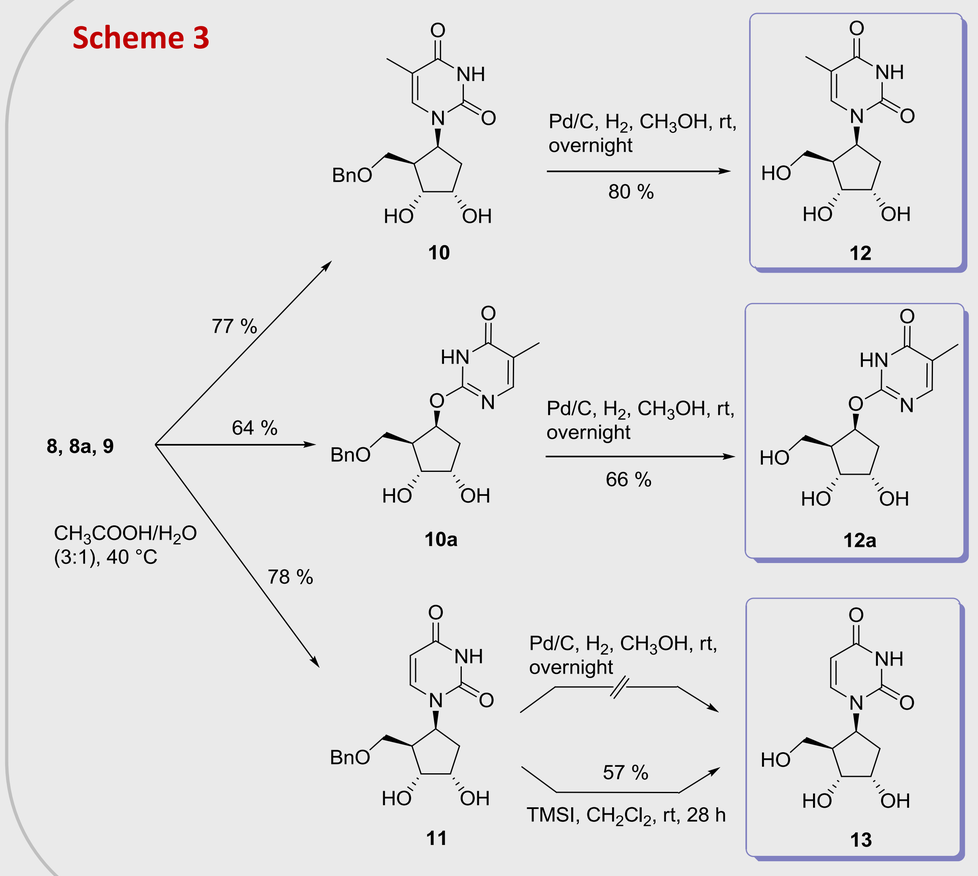
Reagents and conditions: a) Ph_3P, DIAD, *N*3-protected nucleobase, CH_3CN, 100MW, 50 °C, 15 min; (b) 1% NaOH in CH_3OH, rt, 16 h; (c) Ph_3P, DIAD, 6-Cl-purine, CH_3CN, 100MW, 50 °C, 15 min.

Table 1. Coupling of *N*3-protected pyrimidine with cyclopentanol **7**.

Nucleobase	N1/O^2 ratio	Yield % (*N*1- isomer)
*N*3-benzoylthymine	1.2 : 1	18 %
*N*3-benzoyluracil	1 : 1	11 %

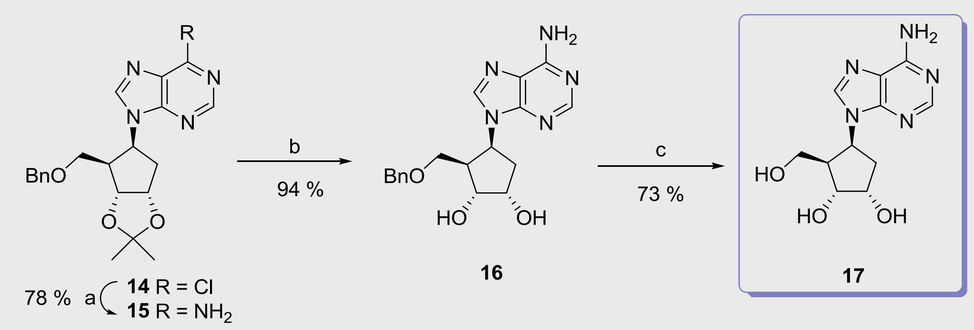
The *iso*-carbocyclic nucleosides **8**, **8a**, and **9** were isopropyliden-deprotected by using a mixture of acetic acid/H_2O (3:1) to obtain the compounds **10**, **10a**, **11** (Scheme 3) that were subsequently deprotected by hydrogenolysis on Pd/C in methanol. The uracil compound **11** was debenzylated by the treatment with trimethylsilyl iodide in CH_2Cl_2 .

Scheme 3



The adenine compound **14** was aminated by the treatment with ammonia in methanol, under microwave assisted conditions, to give the adenine carbocyclic nucleoside **15** (Scheme 4). This compound was isopropyliden-deprotected and subsequently debenzylated, with the same procedure used for compounds **10**, **10a**, to give the final compound **17**.

Scheme 4



Reagents and conditions: a) NH_3 7M in CH_3OH, 50 MW, 80 °C, 1 h; b) CH_3COOH/H_2O (3:1), 40 °C, 16 h; c) Pd/C, H_2, CH_3OH, rt, overnight

References

[1] Mahler, M., Reichardt, B., Hartjen, P., van Lunzen, J., Meier, C. *Chem. Eur. J.* **2012**, 18, 11046-11062.
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[3] Ludek, O.L., Krämer, T., Balzarini, J., Meier, C. *Synthesis* **2006**, *8*, 1313-1324.
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Conclusion

✓ A series of new *iso*-carbocyclic nucleoside analogues were synthesized using a convergent approach.
✓ The low yields of the coupling Mitsunobu reaction may be explained by the production of *N*1- and O^2-isomers and by the formation of cyclopentene **8b** due to the steric hindrance of the benzyloxymethyl group in the cyclopentanol **7** that prevents the approach of the nucleophile group.
✓ The final compound **12**, **12a**, **13** and **17** will be tested as potential antiviral drugs.