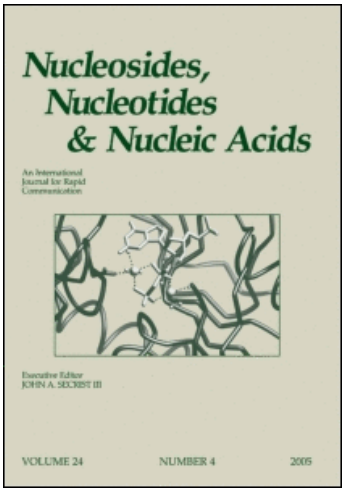

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S. Jessel[a]; E. Hense[a]; C. Meier[a]
[a] Department of Chemistry, Organic Chemistry, Faculty of Science, University of Hamburg, Hamburg, Germany

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CYCLOPENTANE-NUCLEOBASE COUPLING IN THE SYNTHESIS OF CARBOCYCLIC L-NUCLEOSIDES: IS A S_N2-REACTION AN ALTERNATIVE TO THE MITSUNOBU-REACTION?

S. Jessel, E. Hense, and C. Meier □ *Department of Chemistry, Organic Chemistry, Faculty of Science, University of Hamburg, Hamburg, Germany*

□ *Several carbocyclic L-nucleosides have been synthesized by coupling a cyclopentane-system with heterocycles according to a modified Mitsunobu-protocol. This reaction gave two regioisomers, the N1-alkylated product and an unwanted O^2-product. A simple S_N2-reaction has been investigated as an alternative for such couplings.*

Keywords Cyclopentane-nucleobase coupling; carbocyclic nucleosides

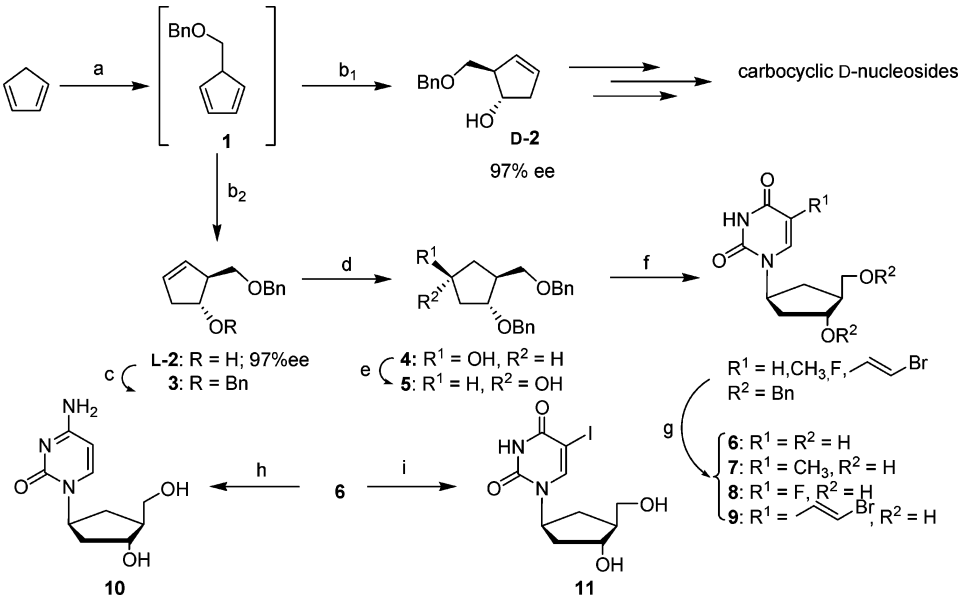
INTRODUCTION

In recent years carbocyclic nucleosides have attracted considerable interest in antitumor and antiviral therapy.[1] The discovered bioactivity of some naturally emerging carbocyclic nucleosides led to a range of modified nucleosides with a cyclopentane system as sugar mimic.[2] These compounds have a reduced toxicity and are stable toward hydrolysis by phosphorylases and, therefore, show an increased biostability.[3]

L-nucleosides, another group of unnatural nucleosides, also have received enhanced interest as antiviral therapeutic agents. Especially for the treatment of hepatitis B the application of L-nucleosides seems to be successful. There is one FDA approved L-nucleosides (lamivudine) and two additional ones are in clinical phase III (telbivudine and clevudine).[4]

Our group is interested in the synthesis and biological evaluation of unnatural nucleosides. The aim is to combine the concepts of carbocyclic and L-nucleosides to yield new potentially bioactive compounds. Carbocyclic nucleosides are synthetically the most demanding class of nucleosides, because they require multiple steps and sophisticated syntheses to build up the stereogenic centers. In the past several synthetic approaches have been

Address correspondence to C. Meier, Department of Chemistry, Faculty of Science, University of Hamburg, Martin Luther King Platz 6, D-20146 Hamburg, Germany. E-mail: chris.meier@chemie.uni-hamburg.de



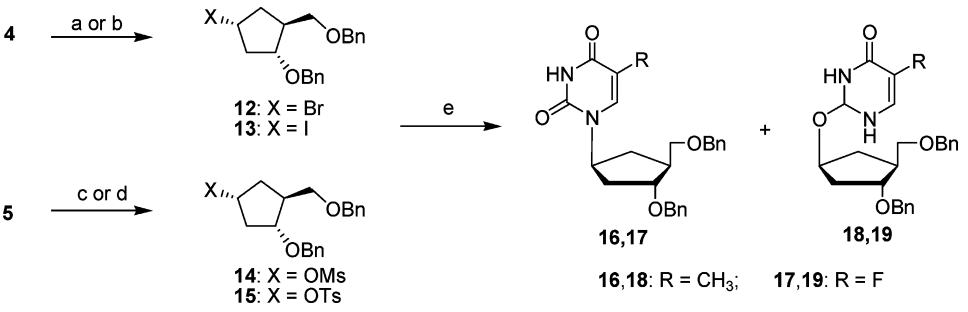
SCHEME 1 a) NaH, BOMCl, THF, −60°C, 3 hours; b) (+)-ipc$_2$BH (1) or (−)-ipc$_2$BH (2), −60°C to r.t., 15 hours 45%; c) NaH, BnBr, TBAI, THF, r.t., 12 hours, 91%; d) 9-BBN, THF, r.t., 12 hours, 3N NaOH, 30% H_2O_2, 0°C, 79%; e) PPh_3, DIAD, benzoic acid 0°C to r.t., 96%; f) PPh_3, DIAD, *N*3-benzoylphyrimidines, CH_3CN, −40°C to r.t., 15 hours, 1% NaOH in CH_3OH, r.t., 4 hours; g) Pd/C, H_2, EtOH; h) triazole, $POCl_3$, Et_3N, CH_3CN, 0°C, 24 hours, NH_3/H_2O, CH_3CN, r.t., 48 hours; i) I_2, dioxane, 100°C, 1.5 hours, 62%.

reported.[3a] Recently we reported a route, that allows the preparation of stereochemically pure carbocyclic nucleosides in gram quantities.[5] This convergent strategy was optimized for the synthesis of D-*carba*-dT. The same strategy was also used to synthesize further pyrimidine analogues in good yields, for example, D-*carba*-dC or D-*carba*-dU.

The key step is the stereoselective synthesis of the cyclopentane system **2**. Starting from cyclopentadiene an alkylation with BOMCl followed by a stereoselective hydroboration introduces the 3′-hydroxy group of the needed nucleoside sugar moiety (Scheme 1).

This step allows the subsequent synthesis of L- or D-nucleosides using (+)-di*iso*pinocampheylborane or (−)-(ipc)$_2$-borane, respectively. Following this method several carbocyclic L-nucleosides were synthesized, e.g. L-*carba*-dU **6**, L-*carba*-dT **7**, L-*carba*-FdU **8** and L-*carba*-BVDU **9** and L-*carba*-dC **10** (Scheme 1).

Another important step in this convergent strategy is the coupling of a heterocycle to the cyclopentane system **5**. It enables a high flexibility in yielding different carbocyclic nucleosides by using a wide range of pyrimidines or purines. This step was achieved by using a modified Mitsunobu-protocol. However, after introduction of the *N*3-protected heterocycles varying ratios



SCHEME 2 a) PPh_3, CBr_4, CH_2Cl_2, −75°C to r.t., 3 hours, 84%; b) PPh_3, NIS, CH_2Cl_2 0°C, 1 hour, r.t., 3 hours, 84%; c) MsCl, THF, Et_3N, 0°C, 10 minutes, 99%; d) NaH, THF, 0°C, 30 minutes, TsCl, r.t., 3 hours, 68%; e) K_2CO_3, *N*3-Bz-pyrimidine, DMF, r.t., 30 minutes, 150°C, 3 hours yields: see Table 1.

of *N*1/O^2-alkylation were found, for example, 3:1 for **16** and 1:1 for **17**. The ratio depends on several factors like the solvent, the *N*3-protecting group, the temperature or the heterocycle.[6] The challenge of this method is the separation of the *N*1-alkylated product from the undesired O^2-alkylated side product and the converted Mitsunobu reagents. Especially **17** cannot be separated from ist O^2-alkylated sideproduct. An alternative to the Mitsunobu-method may be a simple S_N2-reaction. Here, eventually an improved alkylation ratio and/or less side products may be possible. To prove this strategy the hydroxyl group in **5** was replaced by several leaving groups like bromide, iodide, mesylate or tosylate. The halogenation was accomplished by redox condensation according to Mukaiyama in good chemical yields.[7] Thus, the bromo derivative **12** was obtained by reacting **4** with triphenylphosphine (PPh_3) and CBr_4. Analogously, cyclopentanol **4** was treated with PPh_3 and NIS to give the iodo derivative **13**. The mesylate and tosylate were introduced by reaction of the corresponding acid chlorides and compound **5** (Scheme 2).

The precursors for the S_N2-displacement were reacted with deprotonated *N*3-benzoylthymine and *N*3-benzoyl-5-fluorouracil. The reaction with the leaving groups bromide and mesylate led in fact to an exclusive formation of the *N*1-alkylated product (Table 1). However, the yields of 22% (Br) and 18% (OMs) for **16** and 18% (Br) and 15% (OMs) for the **17** were not satisfying. In contrast, the yield increased about threefold with the better leaving groups iodide or tosylate. Interestingly, now the O^2-alkylated side product also was formed. The S_N2-coupling generates mostly the *N*1-product but there is always a noticeable fraction of elimination products like **L-2** causing the poor yields. In summary, under certain circumstances, the S_N2-reaction can be used as a useful alternative to the Mitsunobu-protocol, especially when there are problems in the purification and isolation of the alkylation products like in the case of **17**.

TABLE 1 Coupling of cyclopentane derivatives with pyrimidines

Leaving group X	Nucleobase	*N*1-/O^2-ratio	Yield of *N*1-product
Br	3-benzoyl-thymine	100/0	22%
I	3-benzoyl-thymine	75/25	56%
OMs	3-benzoyl-thymine	100/0	15%
OTs	3-benzoyl-thymine	70/30	43%
Br	3-benzoyl-5-fluoro-uracil	100/0	15%
I	3-benzoyl-5-fluoro-uracil	60/40	44%
OMs	3-benzoyl-5-fluoro-uracil	100/0	14%
OTs	3-benzoyl-5-fluoro-uracil	50/50	38%

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