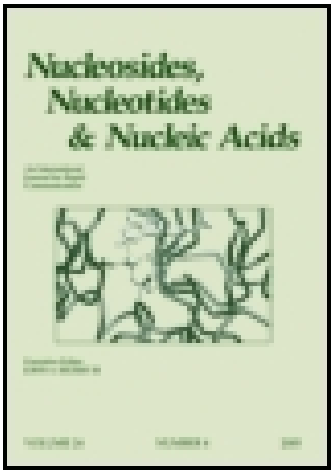

Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn20

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Published online: 10 Dec 2007.

To cite this article: Bastian Reichardt & Chris Meier (2007) A New and Short Convergent Synthetic Strategy to Carbocyclic Nucleosides, Nucleosides, Nucleotides and Nucleic Acids, 26:8-9, 935-937, DOI: 10.1080/15257770701507937

To link to this article: http://dx.doi.org/10.1080/15257770701507937

Nucleosides, Nucleotides, and Nucleic Acids, 26:935–937, 2007

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770701507937

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A NEW AND SHORT CONVERGENT SYNTHETIC STRATEGY TO CARBOCYCLIC NUCLEOSIDES

Bastian Reichardt and Chris Meier □ *Department of Chemistry, Organic Chemistry, Faculty of Science, University of Hamburg, Hamburg, Germany*

□ *An efficient synthesis for racemic cyclopent-3-en-1-yl nucleoside analogues has been developed starting from cyclopentadiene. The key step is the regioselective hydroboration of a mixture of intermediate alkylatede cyclopentadienes to give* one *cyclopentenol.*

Keywords Carbocyclic nucleosides; cyclopentenyl nucleosides; Mitsunobu coupling; purines; pyrimidines

INTRODUCTION

Carbocyclic nucleosides are compounds in which the furan ring has been replaced by a carbocyclic system. These nucleoside analogues have attracted considerable interest due to their important biological activity.[1] Various structural modifications were introduced in both the heterocyclic base and the sugar moiety.[2] Such compounds are stable to hydrolysis by phosphorylases that cleave the glycosidic bond in conventional nucleosides.[3] The bioactivity of the naturally occurring carbocyclic nucleosides (-)-aristeromycin and (-)-neplanocin A led to an interest in this class of compounds, resulting in the generation of a number of antiviral carbocyclic nucleosides. In the past, carbocyclic nucleoside analogues like Abacavir[4] (Ziagen) and Entecavir[5] (Baraclude) showed encouraging in vitro and in vivo activities. Recently, Abacavir was approved as a HIV-drug for clinical application. Moreover, Entecavir was approved by FDA in 2005 for the treatment of chronic HBV infections.

RESULTS AND DISCUSSION

Recently, we published a new procedure for the preparation of racemic cyclopent-3-en-1-yl nucleoside analogues.[7] Cyclopentenol **4** was prepared

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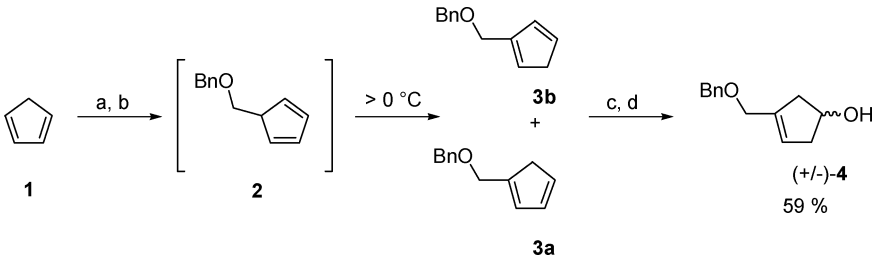
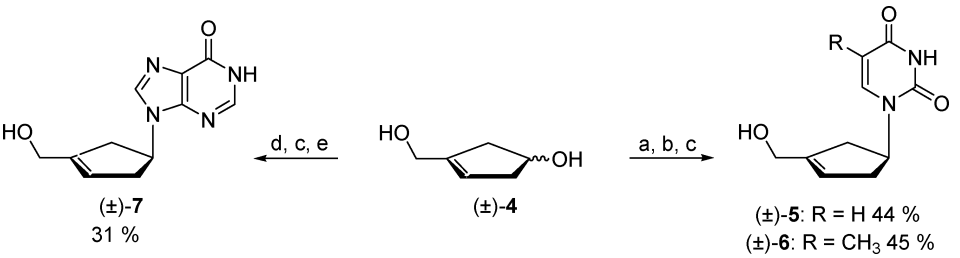
for a convergent approach to carbocyclic nucleosides. This cyclopentenol **4** was developed from cyclopentadiene **1** that was deprotonated and alkylated with benzyloxymethyl chloride to give the diene **2**. This material undergoes isomerization into *two* thermodynamically more stable cyclopentadienes **3a**,**b**. These two dienes were hydroborated with 9-BBN as a sterically demanding hydroboration reagent to (±)-3-[(benzyloxy)methyl]cyclopent-3-en-1-ol **4** in 42% overall yield. Next, the diene mixture was treated with 0.3 equiv. of BH_3 in THF. Surprisingly, also in this case cyclopentenol **4** was isolated as the sole product in 59% overall yield after alkaline work-up. (Scheme 1).



SCHEME 1 a) NaH, 0°C, 0.5 hours, THF; b) benzyloxymenlthyl chloride, −50°C, 2 hours, rt, 12 hours, THF; c) BH_3 *THF, 24 hours, THF; d) $NaOH/H_2O_2$ 12 hours, THF.

To prove the suitability of cyclopentenol to act as starting material for the synthesis of carbocyclic nucleosides, pyrimidine heterocycles were introduced using the modified Mitsunobu reaction conditions as reported previously.[8,11] Thus, *N*3-benzoylthymine and *N*3-benzoyluracil were condensed successfully with cyclopentenol **4**. Alkaline treatment of the crude reaction product led to *O*-benzylcyclopentenyl nucleosides. In the case of 3-benzoylthymine the $N1/O^2$-regioselectivity was found to be 5:1 while a 9:1-regioselectivity was found for 3-benzoyluracil. Debenzylation of the nucleosides proceeded in 76–82% yield using BCl_3 at –78°C to give cyclopentenyl nucleoside analogues, respectively.[12] Mitsunobu coupling of precursors (±)-**4** with 6-chloropurine led to the formation of the protected purine nucleosides in 54% yield, respectively.[7] The *N*9/*N*7-regioselectivity was 9:1 and the two isomers were separated by column chromatography. Finally, removal of the *O*-benzyl group of the nucleoside proceeded in 82% yield using BCl_3 at –78°C to give cyclopentenyl nucleoside analogues **5**,**6**. In addition, the purine analogue was converted to the inosine nucleoside analogue (±)-**7** by treatment of the chloropurine derivative with sodium methanolate and 2-mercaptoethanol in 68% yield (Scheme 2).

In summary, we have elaborated an interesting new pathway towards the synthesis of carbocyclic pyrimidine and hypoxanthine nucleoside analogues. The method starts from cheap cyclopentadiene and is a powerful addition



SCHEME 2 a) DIAD, PPh_3, N3-^{Bz}Ura/N3-^{Bz}Thy, −40°C, 2 hours, CH^3 CN; b) NaOH/CH_3 OH 1%, 12 hours; c) BCl_3 5 hours, −78°C, CH_2Cl_2; d) DIAD, PPh_3, 6-chloropurine, 24 hours, THF; e)2-mercaptoethanol, NaOMe, MeOH, 60°C, 4 hours.

to our previously reported methodology. The biological evaluation of the compounds is under investigation.

REFERENCES

1. a) Balzarini, J. Metabolism and mechanism of antiretroviral action of purine and pyrimidine derivatives. *Pharm. World Sci.* **1994**, 16, 113–126; b) De Clercq, E. Strategies in the design of antiviral drugs. *Nat. Rev. Drug Discovery* **2002**, 1, 13–25.
2. Herdewijn, P.; Balzarini, J.; De Clercq, E. 2′,3′-Dideoxynucleoside analogs as anti-HIV agents. In *Advances in Antiviral Drug Design*, ed. De Clercq, JAI Press Inc., Greenwich, CT; 1993, vol. 1, pp. 233–318.
3. a) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S.R.; Earl, R.A.; Guedj, R. Synthesis of carbocyclic nucleosides. *Tetrahedron* **1994**, 50, 10611–10670; b) Crimmins, M.T. New developments in the enantioselective synthesis of cyclopentyl carbocyclic nucleosides. *Tetrahedron* **1998**; 54, 9229–9272.
4. Daluge, S.M.; Martin, M.T.; Sickles, B.R.; Livingston, D.A. 2000. An efficient, scalable synthesis of the HIV reverse transcriptase inhibitor Ziagen, *Nucleosides, Nucleotides & Nucleic Acids*. 19, 297–327.
5. Bisacchi, G.S.; Chao, S.T.; Bachard, C.; Daris, J.P.; Innaimo, S.; Jacobs, G.A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyk, W.A.; Sundeen, J.E.; Young, M.G.; Colonno, R.; Zahler, R. BMS-200475, a novel carbocyclic 2′-deoxyguanosine analog with potent and selective anti-hepatitis B virus activity in vitro. *Bioorgan. Med. Chem. Lett.* **1997** 7, 127–132.
6. Wyatt, P.G.; Anslow, A.S.; Coomber, B.A.; Cousins, R.P.C.; Evans, D.N.; Gilbert, V.S.; Humber, D.C.; Paternoster, I.L.; Sollis, S.L.; Tapolczay, D.J.; Weingarten, G.G. A short high yielding synthesis of the potent anti-VZV carbocyclic nucleoside analog carba-BVDU. *Nucleosides Nucleotides*, **1995**, 14, 2039–2049.
7. Reichardt, B.; Ludek, O.R.; Meier, C. New and efficient synthesis of racemic cyclopent-3-en-1-yl nucleoside analogues and their derivatives. *Collect. Czech. Chem. C.* **2006**, 71 (7), 1011–1028.
8. Ludek, O.R.; Meier, C. New convergent synthesis of carbocyclic nucleoside analogues. *Synthesis*, **2003**, 13, 2101–2109.
9. Ludek, O.R.; Meier, C. Synthesis of carbocyclic pyrimidine nucleosides using the Mitsunobu reaction - part I: influence of the alcohol on N1- versus O2-alkylation. *Synlett*, **2005**, 20, 3145–3147.
10. Ludek, O.R.; Meier, C. Synthesis of carbocyclic pyrimidine nucleosides using the Mitsunobu reaction—part II: influence of the solvent on N1—versus O2-alkylation, *Synlett* **2006** 2, 324–326.
11. Ludek, O.R.; Krämer, T.; Balzarini, J.; Meier, C. Divergent synthesis and biological evaluation of carbocyclic α -, iso- and 3′-epi-nucleosides and their lipophilic nucleotide prodrugs. *Synthesis* **2006**, 8, 1313–1324.
12. O'Dell, C.A.; Shealy, Y.F. Carbocyclic analogs of 3′,4′-didehydro-2′-deoxyribofuranosyl-2,4(1H,3H)-pyrimidinediones. *Nucleosides, Nucleotides* **1994**, 13, 1929–1937.