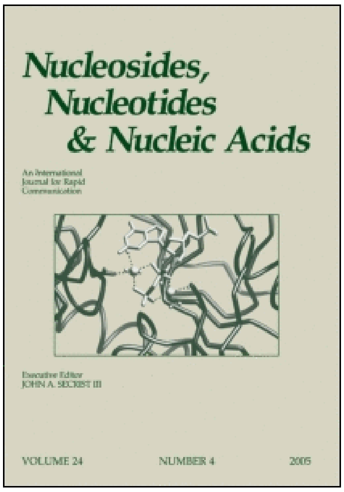

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A NEW AND SHORT CONVERGENT SYNTHETIC STRATEGY TO CARBOCYCLIC NUCLEOSIDES

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□ *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Carbocyclic nucleosides are compounds in which the furan ring has been replaced by a carbocyclic system.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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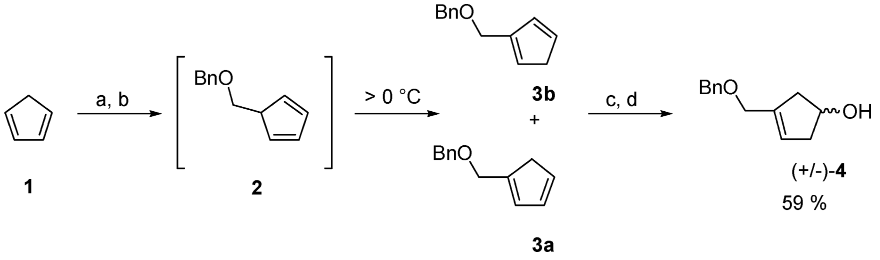
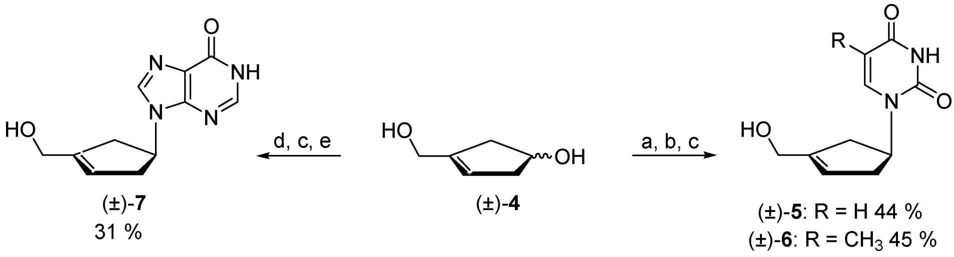
for a convergent approach to carbocyclic nucleosides. This cyclopentenol **4** was developed from cyclopentadiene **1** that was deprotonated and alkylated with benzyloxymethyl chloride to give the diene **2**. This material undergoes isomerization into *two* thermodynamically more stable cyclopentadienes **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 *N*1/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$_2$Cl$_2$; 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.