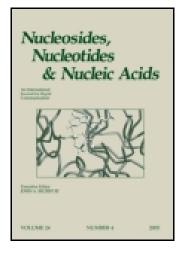
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Nucleosides, Nucleotides and Nucleic Acids

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

STEREOSELECTIVE SYNTHESIS OF 3-HYDROXYMETHYL-D-CYCLOPENTENONE, THE VERSATILE INTERMEDIATE FOR THE SYNTHESIS OF CARBOCYCLIC NUCLEOSIDES

Won Jun Choi^a, Hyung Ryong Moon^b, Hea Ok Kim^a, Young Mi Ko^a, Hye Jin Kim^a, Jeong A. Lee^a, Kang Man Lee^a, Mi Kyung Yun^a, Dae Hong Shin^a, Moon Woo Chun^b, Yhun Y. Sheen^a, Kilhyoun Kim^a & Lak Shin Jeong^a

^a Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul, Korea

^b College of Pharmacy, Pusan National University, Pusan, Korea Published online: 28 Jul 2006.

To cite this article: Won Jun Choi, Hyung Ryong Moon, Hea Ok Kim, Young Mi Ko, Hye Jin Kim, Jeong A. Lee, Kang Man Lee, Mi Kyung Yun, Dae Hong Shin, Moon Woo Chun, Yhun Y. Sheen, Kilhyoun Kim & Lak Shin Jeong (2005) STEREOSELECTIVE SYNTHESIS OF 3-HYDROXYMETHYL-D-CYCLOPENTENONE, THE VERSATILE INTERMEDIATE FOR THE SYNTHESIS OF CARBOCYCLIC NUCLEOSIDES, Nucleosides, Nucleotides and Nucleic Acids, 24:5-7, 611-613, DOI: <u>10.1081/NCN-200061832</u>

To link to this article: <u>http://dx.doi.org/10.1081/NCN-200061832</u>

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STEREOSELECTIVE SYNTHESIS OF 3-HYDROXYMETHYL-D-CYCLO-PENTENONE, THE VERSATILE INTERMEDIATE FOR THE SYNTHESIS OF CARBOCYCLIC NUCLEOSIDES

Won Jun Choi Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul, Korea

Hyung Ryong Moon - College of Pharmacy, Pusan National University, Pusan, Korea

Hea Ok Kim, Young Mi Ko, Hye Jin Kim, Jeong A. Lee, Kang Man Lee, Mi Kyung Yun, and Dae Hong Shin *Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul, Korea*

Moon Woo Chun • College of Pharmacy, Seoul National University, Seoul, Korea

Yhun Y. Sheen, Kilhyoun Kim, and Lak Shin Jeong - Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul, Korea

• The preparative and stereoselective synthesis (45-50% overall yields, >50 g scale) of the key carbasugars $7\mathbf{a}-\mathbf{d}$ was achieved from D-ribose via stereoselective Grignard reaction and oxidative rearrangement as key reactions.

Keywords 3-Hydroxymethyl-D-cyclopentenone, Carbocyclic Nucleosides

INTRODUCTION

Although carbocyclic nucleosides such as neplanocin A^[1] and aristeromycin^[2] exhibited potent biological activity, limited structure-activity relationship (SAR) study of these carbocyclic nucleosides was carried out due to the synthetic difficulties in preparing the D-carbasugars. Thus, modifications have mainly been done on the base moiety,^[3] not on the carbasugars. Many synthetic methods to the carbasugars have so far been reported, but they have drawbacks such as inconsistent and low overall yields, lengthy synthetic routes, racemization, lack of large-scale preparations, and sensitivity to reaction conditions such as temperature

This work was supported by Korea Research Foundation Grant (KRF-2003-005-F00022).

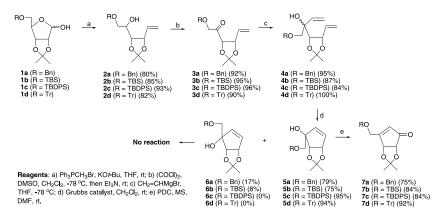
Address correspondence to Lak Shin Jeong, Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea.

and moisture. Therefore, a short and efficient procedure to the D-carbasugars has been highly desirable for the development of carbocyclic nucleosides with new carbasugar templates. In this article, we wish to report the highly efficient synthesis (7 steps and 45–50% overall yields) of the key carbasugar, 3-hydroxymethyl-D-cylcopentenone was accomplished from D-ribose via stereoselective Grignard reaction for the formation of the tertiary β -allylic alcohol and the oxidative rearrangement of the tertiary β -allylic alcohol.

RESULTS AND DISCUSSION

Synthesis of the key carbasugars 7a-d started from 2,3-O-isopropylidene-Dribose (1a-d) with various protecting groups, which were easily prepared from D-ribose, as shown in Scheme 1. Wittig reactions of 1a-d with methyltriphenylphosphonium bromide in the presence of potassium *t*-butoxide in THF gave monovinyl derivatives 2a-d in good yields. Oxidation of 2a-d using oxalyl chloride and DMSO afforded ketone derivatives 3a-d. The introduction of the second vinyl group was achieved using a Grignard reaction. Treatment of 3a-dwith vinylmagnesium bromide produced the inseparable diasteromeric mixture of diene derivatives 4a-d, in which their diastereomeric ratio were found to be greatly affected by the size of the protecting groups, resulting in formation of a single stereoisomer in case of TBDPS and trityl groups.

Exposure of dienes $4\mathbf{a}-\mathbf{d}$ to a Grubbs catalyst^[4] in methylene chloride afforded the separable β -cyclopentenols $5\mathbf{a}-\mathbf{d}$ and α -cyclopentenols $6\mathbf{a}-\mathbf{d}$. The bulkier protecting groups, the more formation of the tertiary β -cyclopentenol was obtained. Oxidative rearrangements of the β -tertiary cyclopentenols $5\mathbf{a}-\mathbf{d}$ to the desired carbasugars $7\mathbf{a}-\mathbf{d}$ were achieved using PDC in DMF, while minor isomers, α -cyclopentenols $6\mathbf{a}-\mathbf{d}$ failed to give the same carbasugars $7\mathbf{a}-\mathbf{d}$ under the various oxidation conditions (PCC, PDC, and CrO₃ in various solvents (CH₂Cl₂, DMSO, ClCH₂CH₂Cl, and DMF). This result clearly indicates that steric



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hindrance by the 2,3-isopropylidene group prevented the conversion of the tertiary chromate ester to the desired product. In summary, we have accomplished the preparative synthesis of the key synthons 7a-d with various protective groups, starting from D-ribose in 7 steps and 45-50% overall yields (>50 g scale). To the best of our knowledge, this synthetic method is regarded as the best procedures from the viewpoint of number of steps, overall yields, large-scale preparation, and mild reaction conditions and has a great potential to be utilized extensively in the SAR study of the carbocyclic nucleosides.

REFERENCES

- Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. Studies on neplanocin A, new antitumor antibiotic. I. Producing organism, isolation and characterization. J. Antibiot. (Tokyo) 1981, 34(4), 359–366.
- Kusaka, T. The mechanism of aristeromycin I. Growth inhibition of xanthomonas oryzae by aristeromycin. J. Antibiot. (Tokyo) 1971, 24(11), 756–760.
- Song, G.Y.; Paul, V.; Choo, H.; Morrey, J.; Sidwell, R.W.; Schinazi, R.F.; Chu, C.K. Enantiomeric synthesis of D- and L-cyclopentenyl nucleosides and their antiviral activity against HIV and West Nile virus. J. Med. Chem. 2001, 44(23), 3985–3993.
- Grubbs, R.H.; Chang, S. Recent advances in olefin metathesis and its application in organic synthesis. Tetrahedron 1988, 54(18), 4413-4450.