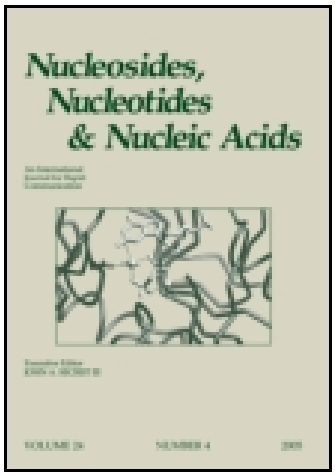

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STEREOSELECTIVE SYNTHESIS OF 3-HYDROXYMETHYL-D-CYCLOPENTENONE, THE VERSATILE INTERMEDIATE FOR THE SYNTHESIS OF CARBOCYCLIC NUCLEOSIDES

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▫ *The preparative and stereoselective synthesis (45–50% overall yields, >50 g scale) of the key carbasugars* **7a–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

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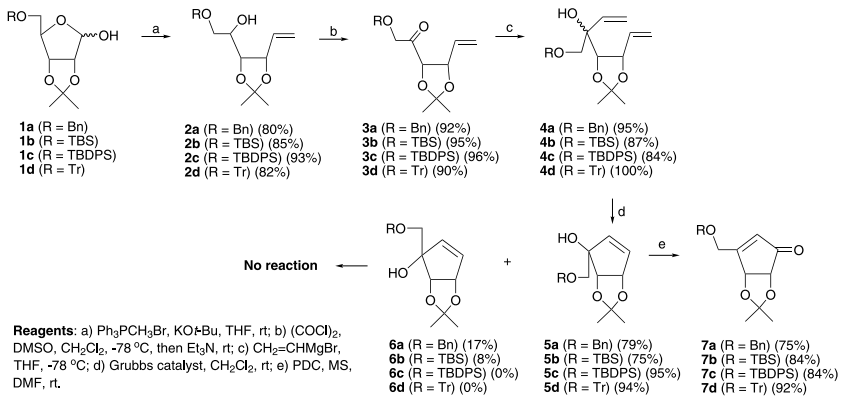
and moisture. Therefore, a short and efficient procedure to the D-carbasugars has been highly desirable for the development of carbocyclic nucleosides with new carbasugar templates. In this article, we wish to report the highly efficient synthesis (7 steps and 45–50% overall yields) of the key carbasugar, 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-D-ribose (**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–d** with 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 **4a–d** to a Grubbs catalyst[4] in methylene chloride afforded the separable β-cyclopentenols **5a–d** and α-cyclopentenols **6a–d**. The bulkier protecting groups, the more formation of the tertiary β-cyclopentenol was obtained. Oxidative rearrangements of the β-tertiary cyclopentenols **5a–d** to the desired carbasugars **7a–d** were achieved using PDC in DMF, while minor isomers, α-cyclopentenols **6a–d** failed to give the same carbasugars **7a–d** under the various oxidation conditions (PCC, PDC, and CrO_3 in various solvents (CH_2Cl_2, DMSO, $ClCH_2CH_2Cl$, and DMF). This result clearly indicates that steric



SCHEME 1

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.

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