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Practical Synthesis of D-Cyclopent-2-enone, the Key Intermediate of Carbocyclic Nucleosides

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Practical Synthesis of D-Cyclopent-2-enone, the Key Intermediate of Carbocyclic Nucleosides

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ABSTRACT

An efficient and practical method for the synthesis of (4R,5R)-4,5-O-isopropylidene-cyclopent-2-enone was developed from p-ribose by using a ring-closing metathesis reaction.

INTRODUCTION

Carbocyclic nucleosides have been an interesting class of compounds, some of which exhibit potent biological activities. Aristeromycin and neplanocin A were originally isolated from natural sources. As part of our drug discovery program, recently we have developed the synthesis of enantiomerically pure aristeromycin and neplanocin A analogs. We also synthesized enantiomerically pure cytosine and 5-F-cytosine analogs, which exhibit significant anti-HIV, anti-Smallpox Virus and anti-West Nile Virus activities. Therefore, additional biological evaluation of these carbocyclic nucleosides as well as the structure-activity relationships studies

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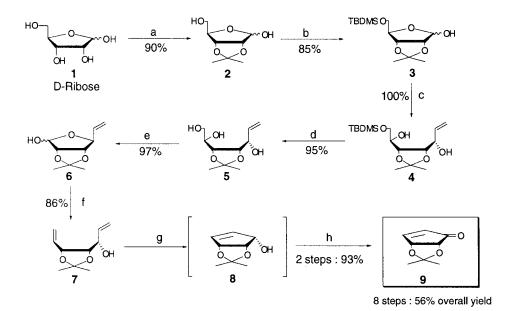
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required a large amount of key intermediates. For these carbocyclic nucleosides, D-cyclopent-2-enone serves as a key intermediate.^[3] However, the availability of this intermediate has been so far limited due to low and inconsistent yields.^[4] Therefore, an efficient synthetic methodology for the key intermediate, D-cyclopent-2-enone, is highly desirable.

CHEMISTRY

The isopropylidene protected derivative **2** (Sch. 1) was obtained from D-ribose with 2,2-dimethoxy propane in the presence of catalytic amount of *p*-toluenesulfonic acid in 90% yield, followed by t-butyldimethylsilane chloride with immidazole to afford the silylated lactol **3** in 85% yield. To introduce an olefin moiety, Grignard reaction was carried out with vinylmagnesium bromide to provide alcohol **4** in 100% yield. The deprotection of the silyl group using 1M solution of tetrabutyl-ammonium fluoride in THF followed by an oxidative cleavage with sodium periodate afforded lactol **6**. Wittig reaction was carried out using NaH and DMSO in THF to give diene **7** in 86% yield which underwent a ring-closing metathesis (RCM) reaction. Several RCM reaction conditions using the Grubbs catalyst from diene **7** to cyclopentenol **8** were investigated, among which 1% Grubbs catalyst at 24°C in anhydrous CH₂Cl₂ provided the best result to obtain cyclopentenol **8**. As the



Scheme 1. Reagents and conditions: (a) 2,2-Dimethoxypropane, *p*-Toluenesulfonic acid, acetone, 0°C to rt, 1 h; (b) TBDMSCl, imidazole, CH₂Cl₂, rt, 1 h; (c) Vinylmagnesium bromide, anhydrous THF, -78°C to rt, 1 h; (d) TBAF, THF, rt, 1 h; (e) NaIO₄, H₂O, rt 1 h; (f) NaH, DMSO, Methyltriphenylphosphonium bromide, THF, 0°C to reflux, 3 h; (g) Grubbs catalyst, anhydrous CH₂Cl₂, 24°C, 4 h; (h) Pyridinium chlorochromate, 4 Å molecular sieve, AcOH, CH₂Cl₂, rt, 12 h.

obtained cyclopentenol **8** was volatile, the desired cyclopentenone **9** was directly obtained in two steps 93% yield from diene **7** by PCC oxidation of cyclopentenol **8** without purification.

In summary, we have developed a significantly improved synthetic method for D-cyclopent-2-enone **9** in a preparative scale, which is a versatile intermediate for the synthesis of carbocyclic nucleosides in 56% overall yield from D-ribose.

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