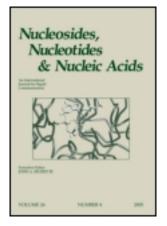
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# Nucleosides, Nucleotides and Nucleic Acids

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

Y. H. Jin<sup>a</sup> & C. K. Chu<sup>a b</sup>

<sup>a</sup> Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, The University of Georgia, Athens, Georgia, USA

<sup>b</sup> College of Pharmacy, University of Georgia, Athens, GA, 30602-2352, USA Published online: 31 Aug 2006.

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

Y. H. Jin and C. K. Chu\*

Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, The University of Georgia, Athens, Georgia, USA

#### ABSTRACT

An efficient and practical method for the synthesis of (4R,5R)-4,5-*O*-isopropylidene-cyclopent-2-enone was developed from D-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.<sup>[1]</sup> As part of our drug discovery program, recently we have developed the synthesis of enantiomerically pure aristeromycin and neplanocin A analogs.<sup>[2]</sup> 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.<sup>[2]</sup> Therefore, additional biological evaluation of these carbocyclic nucleosides as well as the structure-activity relationships studies

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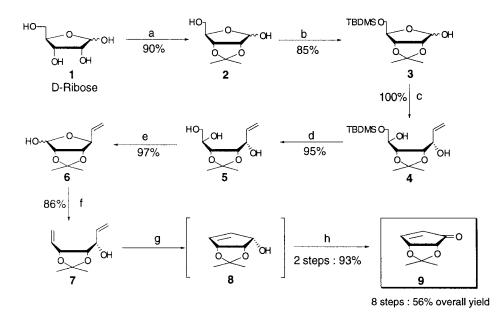
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<sup>\*</sup>Correspondence: C. K. Chu, College of Pharmacy, University of Georgia, Athens, GA 30602-2352, USA; Fax: +1 706 542 5381; E-mail: dchu@rx.uga.edu.

required a large amount of key intermediates. For these carbocyclic nucleosides, p-cyclopent-2-enone serves as a key intermediate.<sup>[3]</sup> However, the availability of this intermediate has been so far limited due to low and inconsistent yields.<sup>[4]</sup> Therefore, an efficient synthetic methodology for the key intermediate, p-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  $CH_2Cl_2$  provided the best result to obtain cyclopentenol 8. As the



Scheme 1. Reagents and conditions: (a) 2,2-Dimethoxypropane, *p*-Toluenesulfonic acid, acetone,  $0^{\circ}$ C to rt, 1 h; (b) TBDMSCl, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; (c) Vinylmagnesium bromide, anhydrous THF,  $-78^{\circ}$ C to rt, 1 h; (d) TBAF, THF, rt, 1 h; (e) NaIO<sub>4</sub>, H<sub>2</sub>O, rt 1 h; (f) NaH, DMSO, Methyltriphenylphosphonium bromide, THF,  $0^{\circ}$ C to reflux, 3 h; (g) Grubbs catalyst, anhydrous CH<sub>2</sub>Cl<sub>2</sub>, 24°C, 4 h; (h) Pyridinium chlorochromate, 4 Å molecular sieve, AcOH, CH<sub>2</sub>Cl<sub>2</sub>, rt, 12 h.

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#### Intermediate for Carbocyclic Nucleoside Synthesis

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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.

#### **ACKNOWLEDGMENTS**

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