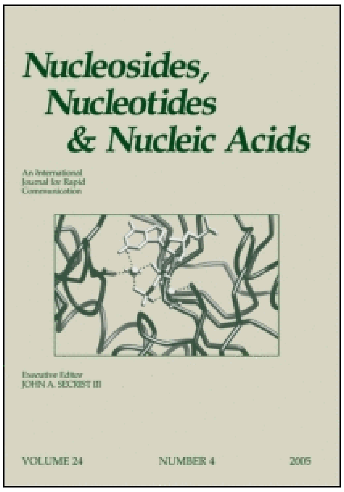

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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

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To cite this Article Jin, Y. H. and Chu, C. K.(2003) 'Practical Synthesis of D-Cyclopent-2-enone, the Key Intermediate of Carbocyclic Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 771 — 773
To link to this Article: DOI: 10.1081/NCN-120022631
URL: http://dx.doi.org/10.1081/NCN-120022631

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 771–773, 2003

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 (4*R*,5*R*)-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.[1] As part of our drug discovery program, recently we have developed the synthesis of enantiomerically pure aristeromycin and neplanocin A analogs.[2] 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.[2] Therefore, additional biological evaluation of these carbocyclic nucleosides as well as the structure-activity relationships studies

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DOI: 10.1081/NCN-120022631
1525-7770 (Print); 1532-2335 (Online)

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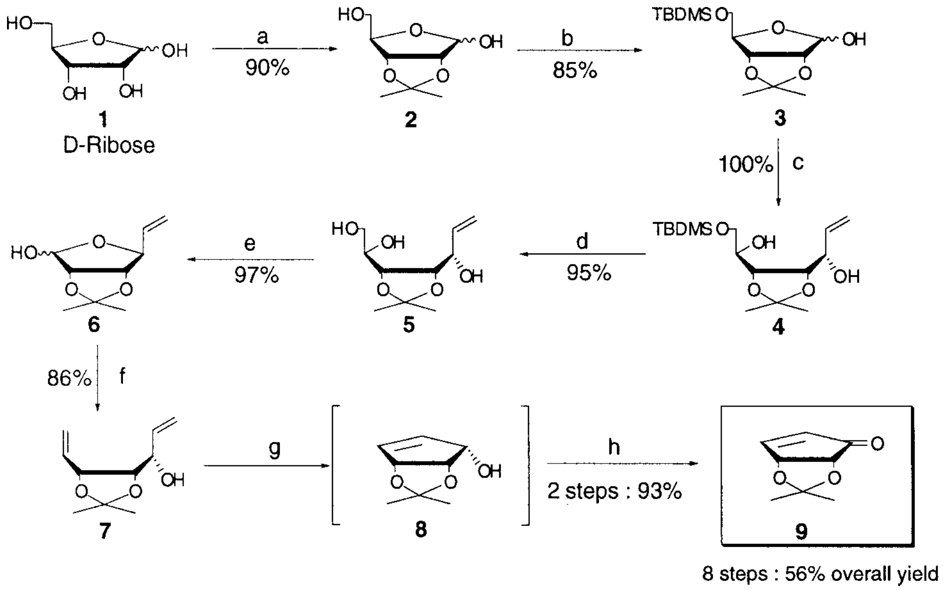
required a large amount of key intermediates. For these carbocyclic nucleosides, D-cyclopent-2-enone serves as a key intermediate.[3] However, the availability of this intermediate has been so far limited due to low and inconsistent yields.[4] Therefore, an efficient synthetic methodology for the key 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 tetrabutylammonium 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°C to rt, 1 h; (b) TBDMSCl, imidazole, CH_2Cl_2, rt, 1 h; (c) Vinylmagnesium bromide, anhydrous THF, −78°C to rt, 1 h; (d) TBAF, THF, rt, 1 h; (e) $NaIO_4$, H_2O, rt 1 h; (f) NaH, DMSO, Methyltriphenylphosphonium bromide, THF, 0°C to reflux, 3 h; (g) Grubbs catalyst, anhydrous CH_2Cl_2, 24°C, 4 h; (h) Pyridinium chlorochromate, 4 Å molecular sieve, AcOH, CH_2Cl_2, 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.

ACKNOWLEDGMENTS

This research was supported by grants of National Institute of Allergy and Infectious Diseases (U01 AI48495 and AI 32351).

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