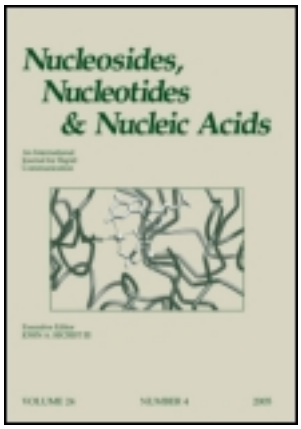


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn20

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

Y. H. Jin [a] & C. K. Chu [a b]

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

[b] College of Pharmacy, University of Georgia, Athens, GA, 30602-2352, USA

Published online: 31 Aug 2006.

To cite this article: Y. H. Jin & C. K. Chu (2003) Practical Synthesis of D-Cyclopent-2-enone, the Key Intermediate of Carbocyclic Nucleosides, Nucleosides, Nucleotides and Nucleic Acids, 22:5-8, 771-773, DOI: 10.1081/NCN-120022631

To link to this article: 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

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 (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

*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.

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

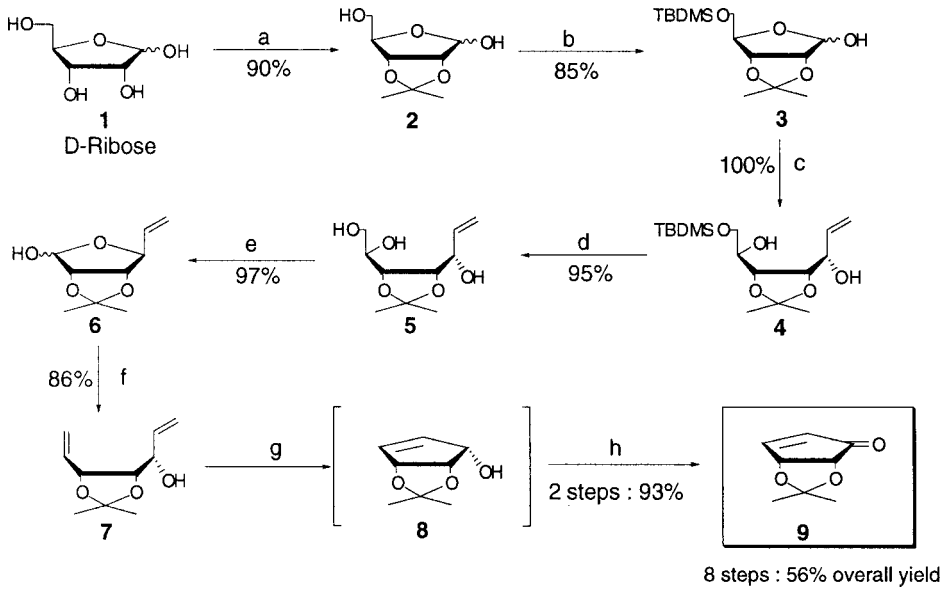
www.dekker.com

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

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.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

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).

REFERENCES

1. (a) Kusaka, T.; Yamamoto, H.; Muroi, M.; Kishi, T.; Mizuno, K. J. Antibiot. **1968**, *21*, 255; (b) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. J. Antibiot. **1981**, *34*, 359.
2. (a) Song, G.Y.; Paul, V.; Choo, H.; Morrey, J.; Sidwell, R.W.; Schinazi, R.F. Chu, C.K. J. Med. Chem. **2001**, *44*, 3958; (b) Wang, P.; Gullen, B.; Newton, M.G.; Cheng, Y.C.; Schinazi, R.F.; Chu, C.K. J. Med. Chem. **1999**, *42*, 3390.
3. (a) Wolfe, M.S.; Anderson, B.L.; Borcherding, D.R.; Borchardt, R.T. J. Org. Chem. **1990**, *55*, 4712; (b) Borcherding, D.R.; Scholtz, S.A.; Borchardt, R.T. J. Org. Chem. **1987**, *52*, 5457.
4. (a) Ali, S.M.; Ramesh, K.; Borchart, R.T. Tetrahedron Lett. **1990**, *31*, 1509; (b) Choi, W.J.; Park, J.G.; Yoo, S.J.; Kim, H.O.; Moon, H.R.; Chun, M.W.; Jung, Y.H.; Jeong, L.S. J. Org. Chem. **2001**, *61*, 6490.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016