ORGANIC LETTERS

2008
Vol. 10, No. 14
2995−2996

Radical Cyclization of Vinylic Ethers: Expedient Synthesis of (+)-Monocerin

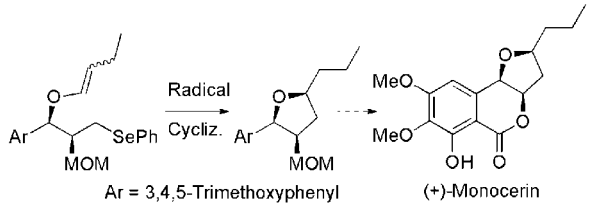
Hyung Kyoo Kwon, Young Eun Lee, and Eun Lee*

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-747, Korea

eunlee@snu.ac.kr

Received May 3, 2008

ABSTRACT

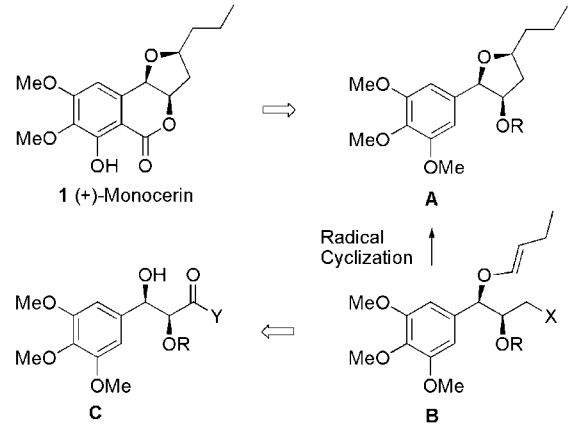


Stereoselective synthesis of (+)-monocerin was accomplished via radical cyclization of a vinylic ether intermediate.

Monocerin is a polyketide natural product isolated from several fungal sources which exhibits antifungal, insecticidal, and plant pathogenic properties.[1] The first total synthesis of monocerin was reported by Mori in 1989,[2] which was followed by a biomimetic synthesis by Simpson and co-workers.[3] More recently, an efficient synthesis was reported by Marsden and co-workers which features stereoselective oxolane synthesis via allylsiloxane aldehyde condensation.[4] In our retrosynthetic analysis, radical cyclization of a vinylic ether intermediate was considered for the stereoselective synthesis of (+)-monocerin (Scheme 1).

Simple vinylic ethers are known to participate in radical cyclization reactions leading to oxacycle synthesis.[5] More recently, a convergent strategy was developed for the assembly of polycyclic ethers via intramolecular acyl radical addition to unactivated enol ethers.[6] Compared to the frequent use of stabilized vinylic ethers (for example, β-alkoxyacrylates[7]) in radical cyclization, the relative paucity of activity in simple vinylic ether radical cyclization is perplexing; it may reflect the difficulty in the preparation of proper enol ether precursors. We were interested for some time in developing vinylic ether radical cyclization for oxacycle synthesis and found that phenyl selenide functionality was compatible with rhodium-catalyzed double-bond

Scheme 1. Retrosynthetic Analysis



(1) (a) Aldridge, D. C.; Turner, W. B. *J. Chem. Soc. C* **1970**, 2598–2600. (b) Grove, J. F.; Pople, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2048–2051. (c) Robeson, D. J.; Strobel, G. A. *Agric. Biol. Chem.* **1982**, *46*, 2681–2683. (d) Cuq, F.; Herrmann-Gorline, S.; Klaebe, A.; Rossignol, M.; Petitprez, M. *Phytochemistry* **1993**, *34*, 1265–1270.

(2) Mori, K.; Takaishi, H. *Tetrahedron* **1989**, *45*, 1639–1646.

(3) Dillon, M. P.; Simpson, T. J.; Sweeney, J. B. *Tetrahedron Lett.* **1992**, *33*, 7569–7572.

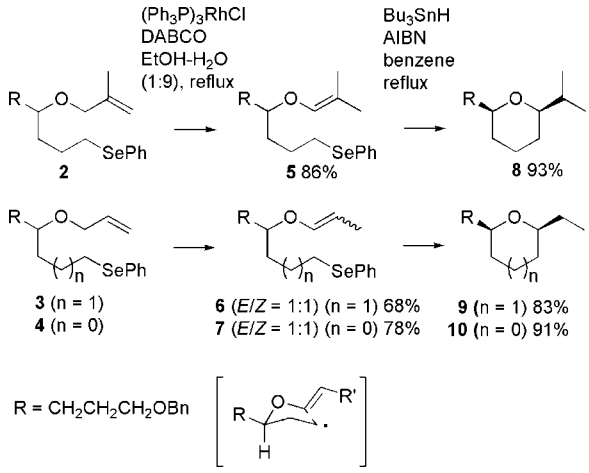
(4) Cassidy, J. H.; Farthing, C. N.; Marsden, S. P.; Pedersen, A.; Slater, M.; Stemp, G. *Org. Biomol. Chem.* **2006**, *4*, 4118–4126.

(5) For a few early examples, see: (a) Tennant, S.; Wege, D. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2089–2093. (b) Gopalsamy, A.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1988**, 28–29. Stereoselection studies at the steady state were carried out for vinyl ether radical cyclization reactions: (c) Andrukiewicz, R.; Cmoch, P.; Gawel, A.; Staliński, K. *J. Org. Chem.* **2004**, *69*, 1844–1848.

10.1021/ol801020w CCC: $40.75
Published on Web 06/13/2008

migration[8] in allylic ethers. This way, allylic ethers **2**, **3**, and **4** were converted into vinylic ethers **5**, **6**, and **7**. Radical cyclization reaction of **5**, **6**, and **7** proceeded efficiently to produce the oxacyclic products **8**, **9**, and **10** (Scheme 2).[9]

Scheme 2. Radical Cyclization of Vinylic Ethers

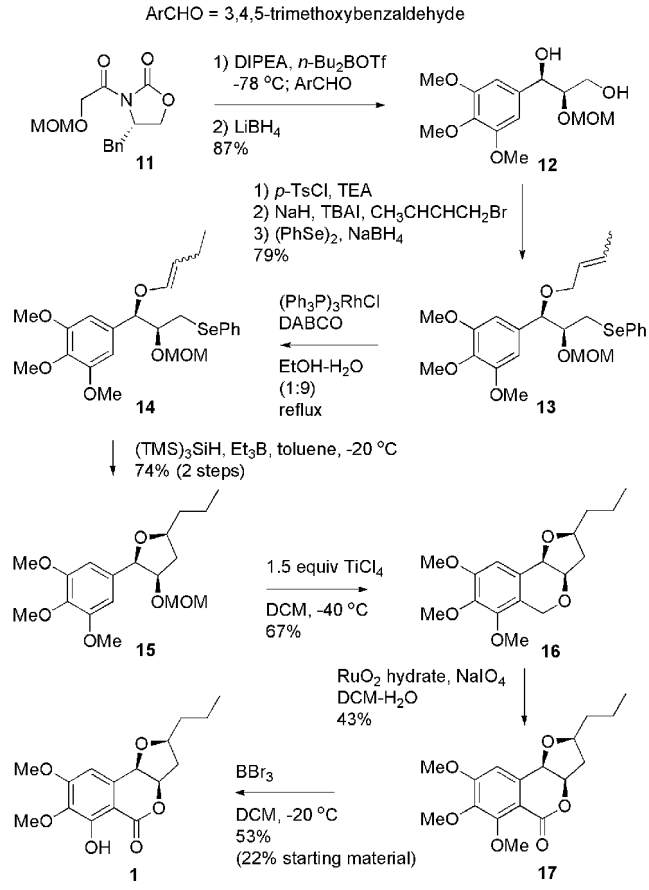


Radical cyclization of both *E*- and *Z*-isomers of **6** and **7** apparently produced only the "2,5- or 2,6-*cis*" products **9** and **10** exhibiting similar stereoselectivity encountered in the reactions of stabilized vinylic ethers.[7]

The synthetic sequence for monocerin started with a stereoselective aldol reaction of the chiral imide **11**[10] and 3,4,5-trimethoxybenzaldehyde, and subsequent reduction with lithium borohydride produced the MOM-protected triol **12** in good yield. Selective tosylation of the primary hydroxyl group, *O*-alkylation with 1-bromo-2-butene, and phenylselenide substitution led to the allylic ether selenide **13**[11] (Scheme 3).

Double-bond migration was catalyzed by the Wilkinson catalyst, and the product vinylic ether **14**, which was obtained as a ~2:3 mixture of *E*- and *Z*-isomer, was treated with

Scheme 3. Total Synthesis of (+)-Monocerin



tris(trimethylsilyl)silane in the presence of triethylborane. This way, oxolane **15** was obtained in 74% yield from **13**. Formation of other stereoisomeric products was not noticed.

The MOM protecting group participated in the next reaction as dioxatricycle **16** was obtained from **15** via treatment with titanium(IV) chloride. Ruthenium-catalyzed oxidation[12] of **16** led to lactone **17**, which was converted into (+)-monocerin (**1**)[13] upon partial demethylation[2] with boron tribromide.[14]

The vinylic ether radical cyclization strategy described in this communication provides a direct and stereoselective route to (+)-monocerin. The scheme may be adapted for synthesis of a large number of oxacyclic natural products, which will be the focus of future studies.

Acknowledgment. This research was supported by a grant from the Marine Biotechnology Program funded by the Ministry of Land, Transport and Maritime Affairs, Republic of Korea, and a grant from the Korea Research Foundation (MOEHRD) (KRF-2005-070-C00073). Brain Korea 21 graduate fellowship grants to Y.E.L. and H.K.K. are gratefully acknowledged.

Supporting Information Available: Experimental procedures and ^{1}H NMR and ^{13}C NMR spectra of the intermediates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801020W

(6) (a) Inoue, M.; Ishihara, Y.; Yamashita, S.; Hirama, M. *Org. Lett.* **2006**, *8*, 5801–5804. (b) Inoue, M.; Yamashita, S.; Ishihara, Y.; Hirama, M. *Org. Lett.* **2006**, *8*, 5805–5808. (c) Inoue, M.; Saito, F.; Iwatsu, M.; Ishihara, Y.; Hirama, M. *Tetrahedron Lett.* **2007**, *48*, 2171–2175.

(7) For a few recent examples, see: (a) Kwon, M. S.; Woo, S. K.; Na, S. W.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 1733–1735. (b) Kim, W. H.; Hong, S. K.; Lim, S. M.; Ju, M.-A.; Jung, S. K.; Kim, Y. W.; Jung, J. H.; Kwon, M. S.; Lee, E. *Tetrahedron* **2007**, *63*, 9784–9801. For more examples on vinyl ether radical cyclization, read the following review: (c) Lee, E. In *Radicals in Organic Synthesis, Vol. 2: Applications*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; pp 303−333.

(8) Corey, E. J.; Suggs, W. J. *J. Org. Chem.* **1973**, *38*, 3224.

(9) Lee, Y. E. Radical Cyclization Strategy for Oxacyclic Natural Product Synthesis. M. S. Dissertation, Seoul National University, Seoul, Korea, 2002.

(10) Owen, R. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 3941–3944.

(11) Use of commercially available 1-bromo-2-butene led to the formation of a mixture (*E*:*Z* = ~4:1) of the allylic ether **4**.

(12) Martin, O. R.; Hendricks, C. A. V.; Deshpande, P. P.; Cutler, A. B.; Kane, S. A.; Rao, S. P. *Carbohydr. Res.* **1990**, *196*, 41–58.

(13) The synthetic sample exhibited identical spectroscopic properties as reported for the natural sample.

(14) The overall yield of (+)-**1** from **11** was 7.8% in 10 steps. In Mori synthesis, (+)-**1** was prepared from ethyl (*S*)-3-hydrxyhexanoate in 14 steps in 6.6% overall yield. In Marsden synthesis, (±)-**1** was synthesized from (±)-1-hepten-4-ol in 8 steps in 6.5% overall yield.