ORGANIC LETTERS

2008
Vol. 10, No. 4
665−668

Stereoselective Construction of an Unprecedented 7–8 Fused Ring System in Micrandilactone A by [3,3]-Sigmatropic Rearrangement

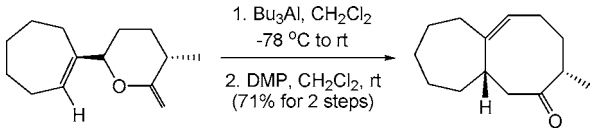
Yan-Dong Zhang, Wei-Wu Ren, Yu Lan, Qing Xiao, Kai Wang, Jie Xu, Jia-Hua Chen,* and Zhen Yang*

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education and Beijing National Laboratory for Molecular Science (BNLMS), College of Chemistry, Laboratory of Chemical Genomics, Shenzhen Graduate School, and State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Science, Peking University, Beijing 100871, China

zyang@pku.edu.cn

Received December 29, 2007

ABSTRACT



The 7–8 bicyclic ring system of micrandilactone A (1) with the required stereochemistry and functional groups was constructed by a Bu_3Al-promoted Claisen rearrangement. Computational studies indicated that the exocyclic vinyl ether undergoes a [3,3] sigmatropic process via a chairlike transition state to afford exclusively the *Z*-double bond in the newly generated 8-membered ring with a high level of chirality transfer.

Micrandilactone A[1] (**1** in Figure 1) is representative of a family of naturally occurring nortriterpenoids **2**−**6**[2] isolated by the research group of Sun in 2003 from *Schisandra micrantha*, a medical plant in China used as a folk medicine for the treatment of rheumatic lumbago and traumatic injury and related diseases.[3] The structure of **1** was confirmed by spectroscopic data in conjunction with a single-crystal X-ray analysis. Micrandilactone A is a densely functionalized polycyclic molecule with 14 stereogenic centers, and its key elements include a highly oxygenated skeleton with a rare, sensitive, and medium size ring[4]-based spiroketal core, and an unprecedented 7-8 fused carbobicyclic ring system.[5]

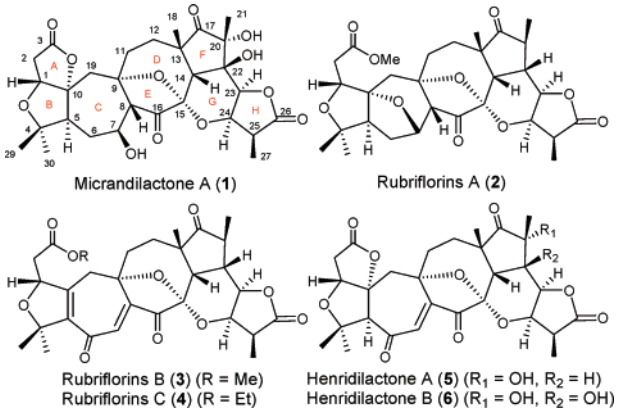


Figure 1. Naturally occurring nortriterpenoids.

(1) Li, R.; Zhao, Q.; Li, S.; Han, Q.; Sun, H.; Lu, Y.; Zhang, L.; Zheng, Q. *Org. Lett.* **2003**, *5*, 1023.

(2) (a) Xiao, W. L.; Yang, L. M.; Gong, N. B.; Wu, L.; Wang, R. R.; Pu, J. X.; Li, X. L.; Huang, S. X.; Zheng, Y. T.; Li, R. T.; Lu, Y.; Zheng, Q. T.; Sun, H. D. *Org. Lett.* **2006**, *8*, 991. (b) Li, R. T.; Shen, Y. H.; Xiang, W.; Sun, H. D. *Eur. J. Org. Chem.* **2004**, 807.

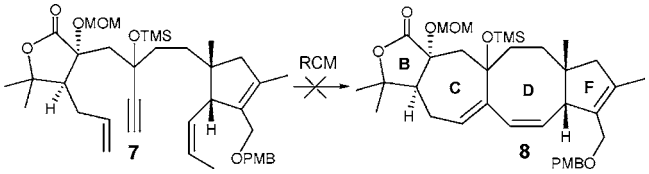
(3) (a) Song, W. Z.; Xiao, P. G. *Chin. Tradit. Herb. Drugs* **1982**, *13*, 40. (b) Kangouri, K.; Miyoshi, T.; Kawashima, A.; Ikeda, A.; Mizutani, T.; Omura, S.; Li, L. N.; Xue, H. *Planta Med.* **1989**, *55*, 297. (c) Li, L. N.; Xue, H.; Ge, D. L.; Kangouri, K.; Miyoshi, T.; Omura, S. *Planta Med.* **1989**, *55*, 300. (d) Sun, H. D.; Qiu, S. X.; Lin, L. Z.; Wang, Z. Y.; Lin, Z. W.; Pengsuparp, T.; Pezzuto, J. M.; Fong, H. *J. Nat. Prod.* **1996**, *59*, 525.

10.1021/ol703126q CCC: $40.75
Published on Web 01/24/2008

We recently reported the syntheses of the ABC fragment[6] by using enyne ring-closing metathesis (RCM) as a key step.[7] In addition, we have synthesized the FGH fragment[8] of micrandilactone A via a Co-thiourea-catalyzed Pauson−Khand reaction[9] and a Pd−thiourea-catalyzed carbonylative reaction[10] developed earlier in our laboratories. With these two key fragments in hand, we set out to identify efficient ways to stereoselectively construct the central ring system, bearing an unusual 7−8 trans-fused carbobicyclic ring skeleton.

Our initial strategy focused on the use of tandem RCM reactions[11] of dienyne **7** for the construction of the central ring system. Despite several attempts with both first- and second-generation Grubbs catalysts, no desired product (**8**) was obtained (Scheme 1). This may be attributed to the

Scheme 1. Attempts to Synthesize **8** via RCM



difficulty associated with the formation of the double bond situated at the ring junction next to a sterically demanding quaternary center.

The difficulties encountered in the RCM approach prompted us to consider that the classical sigmatropic rearrangement processes as an alternative mean to access the 7−8 ring system, because application of the Claisen rearrangement[12] as a powerful and reliable protocol is well documented in the syntheses of complex molecules.[13] Despite impressive progress made during the past several years in the synthesis of 5−8- and 6−8-fused carbocycles through transition-metal-catalyzed cycloadditions,[14] there are no reliable strategies for the construction of fused 7−8 ring systems. In this context, we herein describe our efforts in developing an efficient approach for the stereoselective synthesis of this interesting structure with a Claisen-rearrangement protocol as the key step, which paves the way for the total synthesis of micrandilactone A.

Mechanistically, the Claisen rearrangement could proceed via either a chairlike or a boatlike transition state, with the former being more stable than the latter, in most cases.[15] Paquette and co-workers demonstrated that both chairlike and boatlike transition states could be utilized to account for the stereochemical outcomes in the formation of 5−8 fused carbobicycles generated from 5-membered ring-based endocyclic allyl ethers.[16] Thus, clarification of the transition state in the Claisen reaction of the 7-membered ring-based endocyclic allyl ether **9a** (Scheme 2) is essential before this reaction could be employed in the context of micrandilactone A to deliver the desired stereochemistry.

As illustrated in Scheme 2, the rearrangement could proceed via both chairlike and boatlike transition structures, leading to a cis and a trans bridgehead double bond in the formed 8-membered ring, respectively.

To shed more light on the stereochemical course, we computed the four transition structures and their relative free energies with respect to compound **9a** (see the Supporting Information for computational details and the structures of all stationary points). DFT calculations with the B3LYP/6-31G[17] method indicated that the chairlike transition structure (**12-ts**) is the most favored, whereas another chairlike transition state, **11-ts**, is disfavored by 2.7 kcal/mol. Two boatlike transition structures, **13-ts** and **14-ts**, both require activation energies around 40 kcal/mol, suggesting that these pathways are highly unlikely to occur. The information of **12-ts** and **14-ts** is summarized in Scheme 2.

(4) (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res*. **1981**, *14*, 95. (b) For a review, see: Patasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.

(5) For several preliminary reports regarding the formation of 7−8-fused carbobicyclic ring, see: (a) Dowd, P.; Zhang, W. *J. Am. Chem. Soc*. **1991**, *113*, 9875. (b) Molander, G. A.; Cameron, K. O. *J. Org. Chem*. **1993**, *58*, 5931. (c) Bouchard, H.; Pulicani, J.-P.; Vuilhorgne, M.; Bourzat, J.-D.; Commerrcon, A. *Tetrahedron Lett.* **1994**, *35*, 9713. (d) Barluenga, J.; Dieguez, A.; Rodriguez, F.; Florez, J.; Fañanas, F. J. *J. Am. Chem. Soc*. **2002**, *124*, 9056. (e) Kang, H. J.; Kim, S. H.; Pae, A. N.; Koh, H. Y.; Chang, M. H.; Choi, K. I.; Han, S.-Y.; Cho, Y. S. *Synlett* **2004**, 2545. (f) Maiti, S.; Drew, M. G. B.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. K. *Synthesis* **2005**, 3067.

(6) Zhang, Y.; Tang, Y.; Luo, T.; Shen, J.; Chen. J.; Yang, Z. *Org. Lett*. **2006**, *8*, 107.

(7) (a) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* Engl. **1997**, *36*, 2518. (b) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc*. **1997**, *119*, 12388.

(8) (a) Tang, Y.; Zhang, Y.; Dai, M.; Luo, T.; Deng, L.; Chen, J. Yang, Z. *Org. Lett*. **2005**, *7*, 885.

(9) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen. J.; Yang, Z. *Org. Lett*. **2005**, *7*, 593.

(10) Dai, M.; Liang, B.; Wang, C.; Chen, J.; Yang, Z. *Org. Lett*. **2004**, *6*, 221.

(11) (a) Garcia-Fandino, R.; Codesido, E. M.; Sobarzo-Sanchez, E.; Castedo, L.; Granja, J. R. *Org. Lett*. **2004**, *6*, 193. (b) Diver, S. T.; Giessert, A. J. *Chem. Rev*. **2004**, *104*, 1317. (c) Mori, M. *Adv. Synth. Catal*. **2007**, *349*, 121. (d) Boyer, F.-D.; Hanna, I. *Org. Lett*. **2007**, *9*, 2293.

(12) Wipf, P. In *Comprehensive Organic Synthesis:* Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, p 827.

(13) Selected references see: (a) Büchi, G.; *J. Am. Chem. Soc*. **1967**, *89*, 4559. (b) Büchi, G.; Powell, J. E., Jr., *J. Am. Chem. Soc*. **1970**, *92*, 3126. (c) Rhoads, S. J.; Brandenburg, C. F. *J. Am. Chem. Soc*. **1971**, *93*, 5805. (d) Rhoads, S. J.; Watson, J. M. *J. Am. Chem. Soc*. **1971**, *93*, 5813. (e) Ziegler, F. E. *Acc. Chem. Res*. **1977**, *10*, 227. (f) Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *J. Am. Chem. Soc*. **1980**, *102*, 6889. (g) Danishefsky, S.; Tsuzuki, K. *J. Am. Chem. Soc*. **1980**, *102*, 6891. (h) Castro, A. M. M. *Chem. Rev*. **2004**, *104*, 2939.

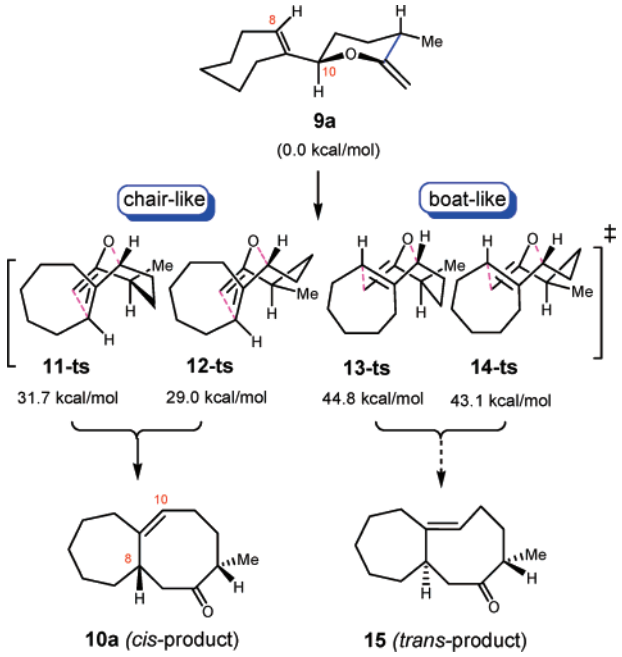
(14) For recent transition-metal-catalyzed cycloadditions in the synthesis of 5−8- and 6−8-fused carbocycles, see: (a) Wang, Y.; Wang. J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P. A.; Yu, Z.-X. *J. Am. Chem. Soc*. **2007**, *129*, 10060. (b) Wender, P. A.; Christy, J. P. *J. Am. Chem. Soc*. **2006**, *128*, 5354. (c) Murakami, M.; Ashida, S. R.; Matsuda, S. *J. Am. Chem. Soc*. **2006**, *128*, 2166. (d) Wegner, H. A.; de Meijere, A.; Wender, P. A. *J. Am. Chem. Soc*. **2005**, *127*, 6530. (e) Evans, P. A.; Baum, E. W.; Fazal, A. N.; Pink, M. *Chem. Commun*. **2005**, 63. (f) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc*. **2002**, *124*, 2876. (g) Gilbertson, S.; DeBoef, B. *J. Am. Chem. Soc*. **2002**, *124*, 8784.

(15) (a) Vittorelli, P.; Winkler, T.; Hansen, J. J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1457. (b) Hansen, H. J.; Schmid, H. *Tetrahedron* **1974**, *30*, 1959. (c) Hill, R. K.; Edwards, A. G. *Tetrahedron Lett.* **1964**, 3239. (d) Hill, R. K.; Synerholm, M. E. *J. Org. Chem*. **1968**, *33*, 925. (e) Hill, R. K.; Soman, R.; Sawada, S. *J. Org. Chem*. **1972**, *37*, 3737.

(16) (a) Paquette, L. A.; Andrews, D. R.; Springer, J. P. *J. Org. Chem.* **1983**, *48*, 1147. (b) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc*. **1984**, *106*, 6868. (c) Paquette, L. A.; Friedrich, D.; Rogers, R. D. *J. Org. Chem.* **1991**, *56*, 3841.

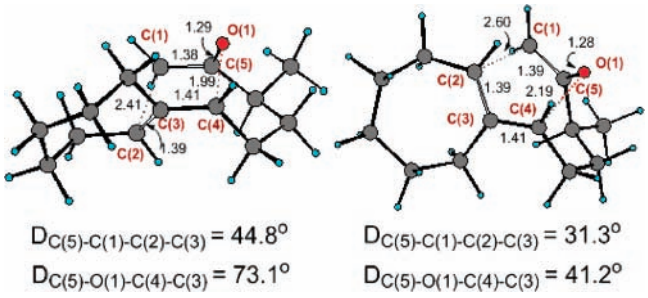
(17) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b). Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785788.

Scheme 2. Results of the DFT Calculations



The energetic preference of **12-ts** over **14-ts** is likely due to steric effects. The dihedral angles C(5)−C(1)−C(2)−C(3) and C(5)−O(1)−C(4)−C(3) in **12-ts** are 44.8° and 73.1°, whereas in **14-ts** they are 31.3° and 41.2° (Table 1). This suggests that the latter suffers from a very staggered conformation, as evident by the short distance between C(3) and C(5). Therefore, DFT calculations predict that the final product of the Claisen-rearrangement would be **10a** (cis configuration) and that the stereochemistry of C10, in substrate **9a**, can be effectively transferred to C8 in the product (**10a**). Thus, the present approach could be utilized to stereoselectively construct the 7−8 bicyclic skeleton of micrandilactone A.

Table 1. Relative Energies of All of the Structures (the Unit of All Values Is kcal/mol) and the Dihedral Angles of **12-ts** and **14-ts**

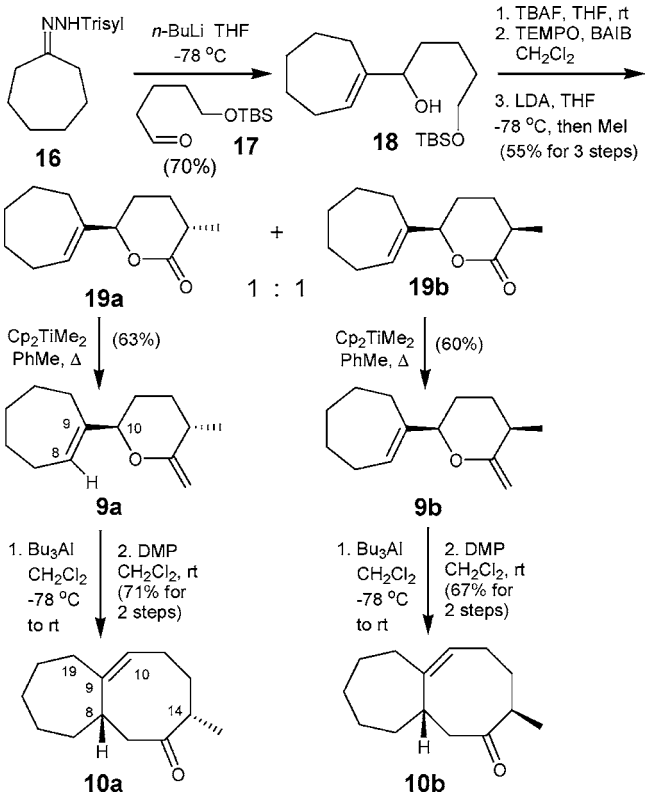


	structure						
	9a	**11-ts**	**12-ts**	**13-ts**	**14-ts**	**10a**	**15**
*E**	0.0	31.6	29.2	45.5	44.3	−15.5	−4.4
*G***	0.0	31.7	29.0	44.8	43.1	−22.5	−12.9

[a] *E** is the relative single point energy in gas phase. *G*** is the relative Gibbs free energy in gas phase.

To verify these computational modeling results, we then synthesized substrates **9a** and **9b** and evaluated them in the Claisen-rearrangement reaction for the formation of **10a** and **10b**, respectively. The synthetic sequence is briefly outlined in Scheme 3. The treatment of hydrazone **16** with *n*-BuLi at −78 °C[18] provided the 7-membered ring-based vinyl species **18** which was reacted with aldehyde **17** to give allylic alcohol **18** in 70% yield. After removal of the silyl ether in allylic alcohol **18**, the diol was oxidized in the presence of TEMPO/BIAB[19] and was immediately methylated by a sequential LDA−MeI treatment to give **19a** and **19b** (1:1) in 55% isolated yield over three steps. The relative stereochemistries of **19a** and **19b** were determined by NOE measurements (see the Supporting Information for details). Compounds **19a** and **19b** were then treated with Petasis reagent[20] to afford the desired products **9a** and **9b** in 63% and 60% yields, respectively.

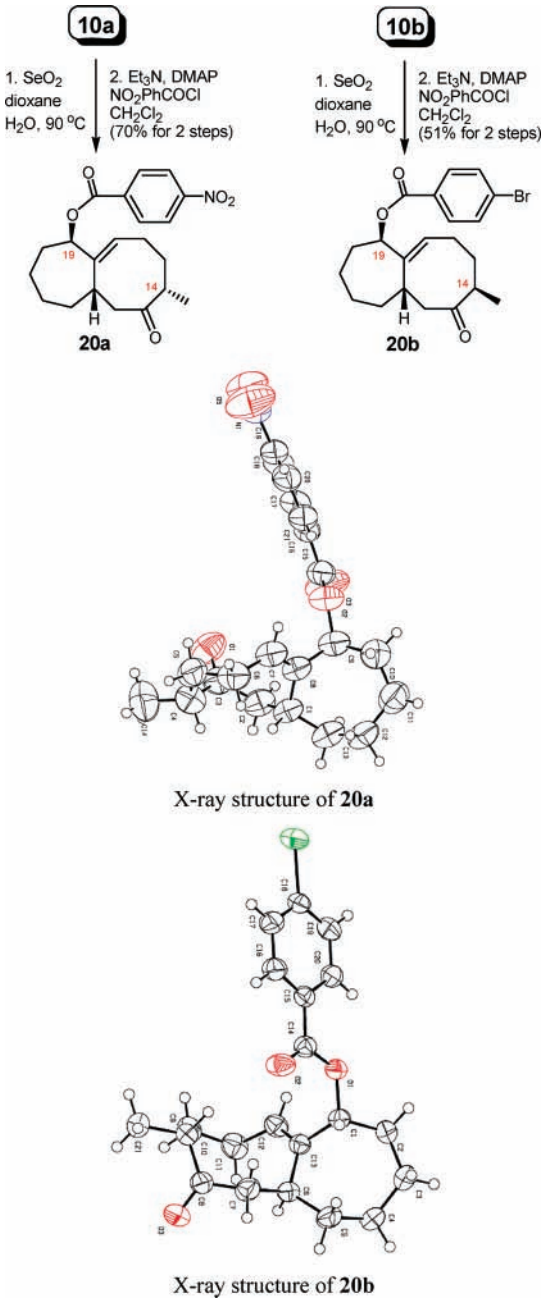
Scheme 3. Syntheses of **10a** and **10b**



Considering the relative instability of the 7-membered ring-derived endocyclic allyl ethers **9a** and **9b** due to their

(18) Corey, E. J.; Estreicher, H. *Tetrahedron Lett.* **1980**, *21*, 1113.
(19) (a) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57. (b) Thunuguntla, S. S. R.; Nyavanandi, V. K.; Nanduri, S. *Tetrahedron Lett.* **2004**, *45*, 9357.
(20) (a) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141. (b) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

Scheme 4. Syntheses of Esters **20a** and **20b**, and Their X-ray Crystallography



pronounced tendency to isomerize their vinyl double bond into the tetrahydropyran ring, the freshly made **9a** and **9b** were treated with Lewis acid Bu_3Al[16c] in CH_2Cl_2 to initiate the proposed Claisen rearrangement.

Delightfully, as expected, the desired products **10a** and **10b** were obtained smoothly in 67% and 71%, respectively, after oxidation of the resultant alcohols by DMP. The stereochemical identity of 7−8 bicyclic rings in **10a** and **10b** was unambiguously established through X-ray crystallography of the corresponding *p*-nitrobenzoyl ester from **10a** (**20a**) and *p*-bromobenzoyl ester from **10b** (**20b**), which were both derived from a SeO_2 allylic oxidation−acylation sequence (Scheme 4).

Several features of this Claisen rearrangement to generate the 7−8 ring system of micrandilactone A are worth noting. First, as predicted in the computational modeling, the double bond geometry in the newly formed 8-membered ring is cis, which supports the proposed chairlike transition state. Second, in both cases, the chirality transfer from the concerted process is excellent, thus securing a key stereochemical control. Third, the stereochemistry of C14 methyl group did not impose a bias on the newly generated C8 stereocenter, which is extremely important, as it would offer the freedom to preassemble the FGH ring system of the micrandilactones, without jeopardizing the stereochemical course of the subsequent Claisen rearrangement.

In summary, we have developed a concise and efficient approach for stereoselective synthesis of the central 7−8 fused bicyclic core of micrandilactone A, which endows the D-ring with the suitable functionality for further structural elaboration toward the full skeleton of micrandilactone A. Further integration of this robust protocol in assembling the CDEFGH ring system of micrandilactone A is currently underway in our laboratories and will be reported in due course.

Acknowledgment. We gratefully acknowledge financial support by the National Science Foundation of China (Grant Nos. 20672004 and 20521202).

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

OL703126Q