ORGANIC LETTERS

2008
Vol. 10, No. 11
2111−2113

Studies Directed toward the Total Synthesis of Lancifodilactone G: An Expeditious Route to the ABC Subunit

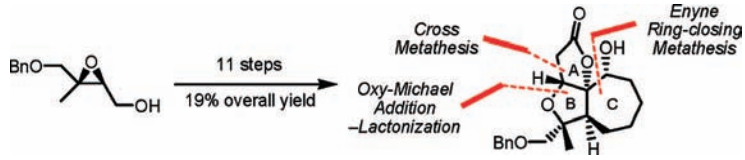
Leo A. Paquette* and Kwong Wah Lai

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

paquette@chemisty.ohio-state.edu

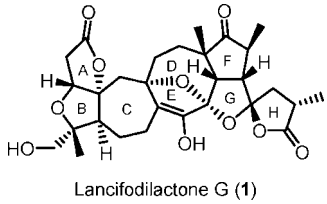
Received February 22, 2008

ABSTRACT



An efficient entry to the ABC network of lancifodilactone G is outlined. The C ring is constructed by way of enyne ring-closing metathesis. The AB component is established via a base-mediated biomimetic oxy-Michael addition−lactonization sequence.

Lancifodilactone G (**1**) is an architecturally novel, highly oxygenated nortriterpenoid isolated from the medicinal plant *Schisandra lancifolia* by Sun and co-workers in 2005 (Figure 1).[1] Its structure and relative stereochemistry were determined



Lancifodilactone G (**1**)

Figure 1. Chemical structure of lancifodilactone G.

on the basis of extensive one- and two-dimensional NMR spectroscopy and mass spectral data, coupled with single-crystal X-ray analysis.[2] Its absolute configuration was recently extrapolated from the biogenetic connectivity to its congener, micrandilactone B.[3] Lancifodilactone G (**1**) exerts minimal cytotoxicity against C8166 cells (CC_{50} > 200 g/mL) while demonstrating anti-HIV activity with an $EC_{50} = 95.47 \pm 14.19$ g/mL and a selectivity index in the range of 1.82−2.46. In addition, its intimidating molecular architecture constitutes a significant challenge for chemical synthesis.

Lancifodilactone G features 8 rings with complicated cyclic connectivity, 12 stereogenic centers, and 10 oxygenated carbons. In addition, the highly congested F ring can be expected to introduce significant complications during construction. Other provocative characteristics of this molecule include the presence of an enol functional group and a sensitive bis-spirocyclic moiety. These structural features serve to make **1** a unique synthetic target. In this paper, we report an expeditious synthesis of the ABC segment of lancifodilactone G (**1**).

Dissection of the ABC framework revealed that the furanyl B ring is exceedingly rich in chirality, including two

(1) For the isolation and biological evaluation of lancifodilactone G, see: (a) Xiao, W.-L.; Zhu, H.-J.; Shen, Y.-H.; Li, R.-T.; Li, S.-H.; Sun, H.-D.; Zheng, Y.-T.; Wang, R.-R.; Lu, Y.; Wang, C.; Zheng, Q. T. *Org. Lett.* **2005**, *7*, 2145.

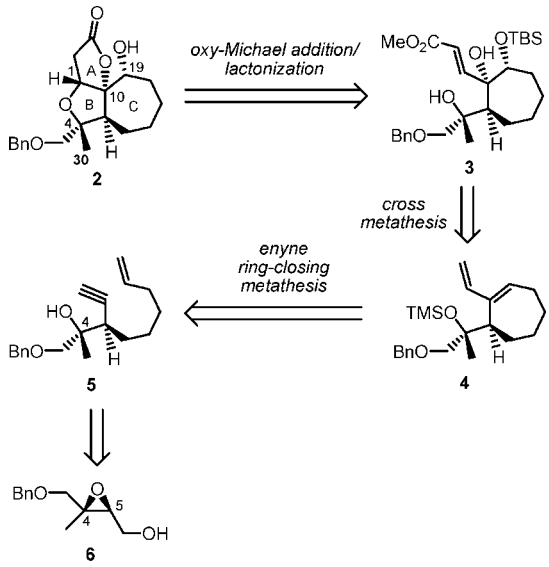
(2) The original structural assignment for lancifodilactone G has been revised, see: (a) Xiao, W.-L.; Zhu, H.-J.; Shen, Y.-H.; Li, R.-T.; Li, S.-H.; Sun, H.-D.; Zheng, Y.-T.; Wang, R.-R.; Lu, Y.; Wang, C.; Zheng, Q. T. *Org. Lett.* **2006**, *8*, 801.

(3) For the absolute configuration of micrandilactone B, see: (a) Huang, S.-X.; Li, R.-T.; Liu, J.-P.; Lu, Y.; Chang, Y.; Lei, C.; Xiao, W.-L.; Yang, L.-B.; Zheng, Q.-T.; Sun, H.-D *Org. Lett.* **2007**, *9*, 2079. (b) For preliminary synthetic studies aimed at micrandilactone A, consult: Zhang, Y.-D.; Ren, W.-W.; Lan, Y.; Xiao, Q.; Wang, K.; Xu, J.; Chen, J.-H.; Yang, Z. *Org. Lett.* **2008**, *10*, 665.

10.1021/ol800418m CCC: $40.75
Published on Web 05/03/2008

quaternary carbon centers (C4 and C10).[4] Its fusion to the 7-membered C ring and lactonic A ring provides an inviting scaffold for synthesis. A retrosynthetic perspective is depicted in Scheme 1. We conceived that the AB component of

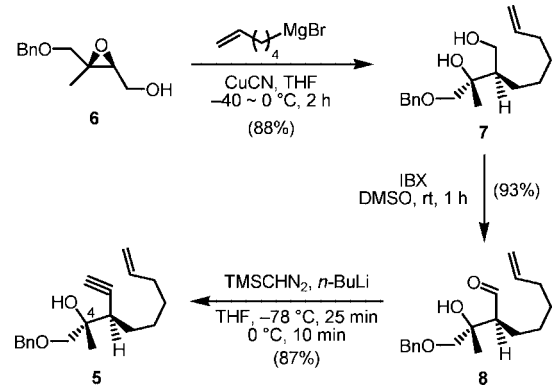
Scheme 1. Retrosynthetic Analysis of Tricycle **2**



tricycle **2** might be established through the base-mediated biomimetic oxy-Michael addition−lactonization of diol **3** in a stereoselective fashion.[5] We anticipated that the Michael acceptor component within **3** could be incorporated into the *endo*-olefin of **4** using cross-metathesis technology.[6] The 7-membered C ring would then be assembled by application of enyne ring-closing metathesis[7] involving **5**, which in turn could be derived from the known epoxy alcohol **6**.[8] It was imperative that the starting material **6** imbed the requisite stereochemistry at C4 and C5 and thus provide a superior starting point to expedite matters.

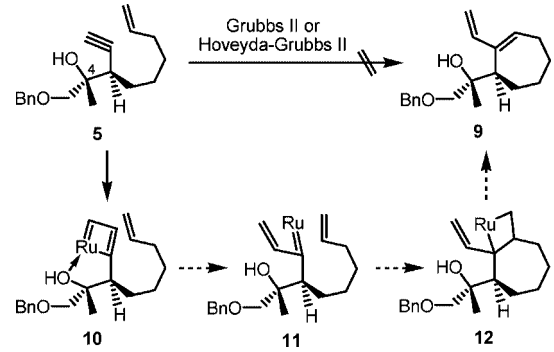
The synthesis commenced with hydroxymethyl-guided epoxide opening of **6**[8] with the organocuprate reagent derived from 5-hexenylmagnesium bromide (Scheme 2).[9] Diol **7** was formed in a regio- and stereoselective manner. IBX oxidation of the

Scheme 2. Preparation of Enyne **5**



primary alcohol functionality in **7** afforded aldehyde **8**.[10] Transformation of the aldehyde **4** to alkyne **5** was best realized by the Miwa protocol using $TMSCHN_2$ in combination with *n*-BuLi.[11] With the key compound **5** in hand, the stage was set to perform the enyne ring-closing metathesis step (Scheme 3).

Scheme 3. Attempted Ring-Closing Metathesis of Enyne **5**



Unfortunately, all trials to effect the cyclization using either the Grubbs II or Hoveyda catalyst system failed, and only recovered starting material **5** was evidenced. To explain this unanticipated failure, we propose a hydroxyl-inhibitory pathway as shown in Scheme 3. This prior complexation of the ruthenium catalyst to the alkyne moiety residing in **5** leads to the presumably stable vinyl alkylidine **10**, which eventually retards the metathesis propagation and recycling steps (via **11** and **12**). Therefore, we reasoned that masking the C4 hydroxyl group in **5** might overcome the inhibitory problem, although added steps would be required.

To our satisfaction, protection of the tertiary alcohol as its TMS ether (**5** → **13**) followed by enyne ring-closing metathesis proceeded smoothly under an ethylene atmosphere in refluxing CH_2Cl_2 to give the 7-membered C ring product **4** in excellent yield (Scheme 4). The next mission was to introduce the

(4) The carbon numbering is assigned according to the system of the parent natural product in ref 1.

(5) For reviews on the biomimetic synthesis of natural products, see: (a) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730. (b) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757.

(6) For reviews on cross-metathesis, see: (a) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3171. (c) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417. (d) Chatter, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3171, and references cited therein.

(7) Reviews on enyne metathesis, see: (a) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Hahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317.

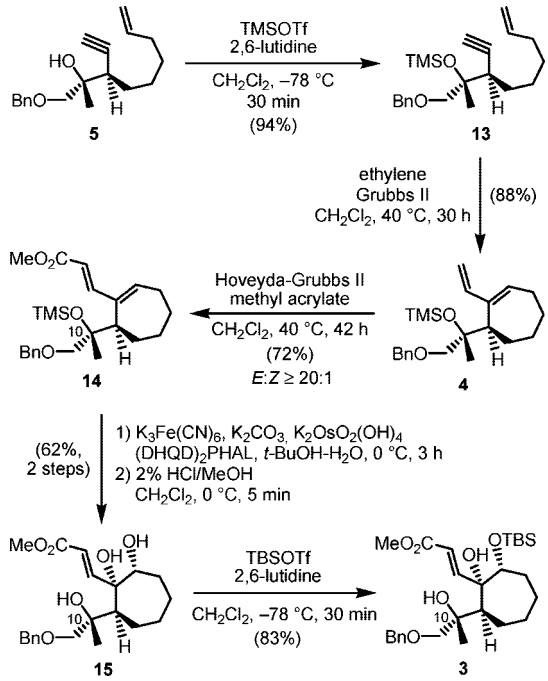
(8) Fontana, A. F.; Messina, R.; Spinella, A.; Cimino, G *Tetrahedron Lett.* **2000**, *41*, 7559. The diastereopurity of **2** was further ascertained by Mosher ester analysis (dr ≥ 20:1)

(9) (a) Juaristi, E.; Jimenez-Vazquez, H. A. *J. Org. Chem.* **1991**, *56*, 1623. (b) Samsel, E. G.; Kochi, J. K. *Inorg. Chem.* **1986**, *25*, 2450.

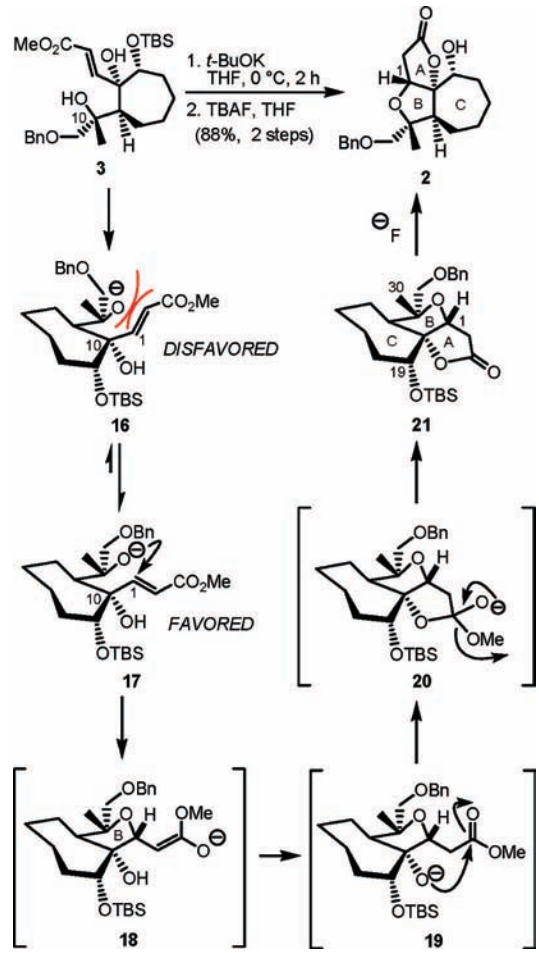
(10) For IBX oxidation, see: (a) Frigerio, N.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.

(11) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107.

Scheme 4. Preparation of Diol **14**



Scheme 5. Biomimetic Synthesis of ABC ring **15**



Michael acceptor by cross-metathesis technology involving the Hoveyda catalyst and methyl acrylate. Indeed, the desired **14** was formed with reasonable efficiency and an impressive *E*−*Z* selectivity of 20:1. At this point, we proceeded to set up the oxidation level in **14** by means of regio- and diastereoselective single-site dihydroxylation in the presence of $(DHQD)_2PHAL$ as the accelerating ligand,[12] followed by discharge of the acid-sensitive TMS protecting group with a mixture of HCl in methanol. This reaction sequence restored the hydroxyl functionality at C10 and delivered the triol **15** in ca. 60% yield over two steps. Chemoselective protection of the secondary alcohol within **15** gave rise to the desired TBS ether **3**.

With the key intermediate **3** in hand, we proceeded to trigger the biomimetic cascade illustrated in Scheme 5 which consisted of an intramolecular oxy-Michael addition initiated by potassium *tert*-butoxide for closing up the 5-membered B ring as in **18**, followed by lactonization to build the remaining A ring and cleanly afford the tricyclic **21**. Particularly compelling is the formation of a single diastereoisomer in this reaction. The inherent selectivity of this process can be rationalized in terms of a preference for forming conformer **17** in which the acrylate side chain occupies a pseudoequatorial position, with attack by the alkoxide occurring on the double bond (C1 position). In contrast, conformer **16** is disfavored because of steric compression and poor alignment of the acrylate moiety. These considerations also explain why the C-1 position of final product **21** possesses the *R* configuration.[13] The crude product **21** was directly treated with TBAF to induce desilylation and produce the ABC tricycle **2** in 88% yield over two steps.

In summary, we have developed an efficacious access route to the ABC segment of lancifodilactone G. The entire sequence involves 11 steps and proceeds in 19% overall yield. The prominent steps involved enyne ring-closing metathesis, cross-metathesis, and a base-mediated biomimetic oxy-Michael addition−lactonization sequence. In addition, we uncovered a hydroxyl-inhibitory problem in the ring-closing metathesis reaction. Progress toward completion of the total synthesis of lancifodilactone G (**1**) is currently underway in our laboratory.

Acknowledgment. We thank The Ohio State University for partial financial support and Robert Dura (The Ohio State University) for assistance with the NOE and 2D NMR experiments.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800418M

(12) Under ligandless conditions, OsO_4 led to a low reaction rate and poor chemical yield. For chiral dihydroxylation catalysts in enantioselective synthesis, see: (a) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B *Chem. Rev.* **1994**, *94*, 2483. The stereochemistry of **15** was determined by spectral comparison with the advanced compound **21.**

(13) Diagnostic NOE enhancements between H-1 and H-19 and H-1 and H-30 were observed.