ORGANIC LETTERS

2011
Vol. 13, No. 14
3670–3673

Concise Total Synthesis of (−)-8-Epigrosheimin

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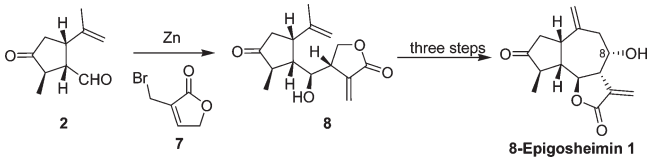
Received May 17, 2011

ABSTRACT



A highly efficient route was developed to synthesize (−)-8-epigrosheimin in four steps from aldehyde 2 based on a substrate-controlled method. The key steps of the synthesis included (1) a stereo- and regioselective allylation addition, (2) an intramolecular translactonization, and (3) an aldehyde-ene cyclization.

Guaianolides, mostly with a *cis*-fused hydroazulene core and a *trans*-annulated γ-butyrolactone motif in the 5, 7, 5-tricyclic carbon skeleton (Figure 1),[1] represent a large subgroup of naturally occurring sesquiterpene lactones.[2] Many of them display a broad biological profile including strong antitumor, antihelmitic, contraceptive, plant growth-regulatory, antiinflammatory, and cytostatic properties,[3] which makes them interesting lead structures for new drugs. While many synthetic approaches have therefore been developed,[4] there are still some challenges in synthesizing this kind of natural lactone. One of them is the efficient assembly of the *trans*-fused γ-butyrolactone ring. Even though there are a variety of methodologies available for the synthesis of substituted γ-butyrolactones,[5] most of the reported methods independently introduce the methyl or methylene group on the lactone unit at a later stage.

In a previous paper, we described a novel strategy for the total synthesis of (−)-8-epigrosheimin (**1**),[6] whose enantiomer was initially isolated as an amoebicidal and antibiotic compound from *Crepis virens* 20 years ago.[7] Recently, we found that the (−)-**1** displayed promising antitumor activities (HepG2: IC_{50} = 6.22 μg/mL; MCF-7: IC_{50} =

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(2) Fraga, B. M. *Nat. Prod. Rep*. **2010**, *27*, 1681–1708 and previous reports in this series.

(3) Ando, M.; Ibayashi, K.; Minami, N.; Nakamura, T.; Isogai, K.; Yoshimura, H. *J. Nat. Prod*. **1994**, *57*, 433–445.

(4) For total synthetic method, see: (a) Zhuzbaev, B. T.; Adekenov, S. M.; Veselovskii, V. V. *Russ. Chem. Rev*. **1995**, *64*, 187–200 and references cited therein. (b) Carret, S.; Deprés, J. P. *Angew. Chem., Int. Ed*. **2007**, *46*, 6870–6873 and references cited therein. (c) Schall, A.; Reiser, O. *Eur. J. Org. Chem*. **2008**, 2353–2364 and references cited therein. (d) Hirose, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem*. **2008**, *73*, 1061–1066. (e) Reboul, I.; Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem*. **2008**, *2008*, 5379–5382. Gone, J. R.; Wallock, N. J.; Lindeman, S.; Donaldson, W. A. *Tetrahedron Lett*. **2009**, *50*, 1023–1025. (g) Elford, T. G.; Hall, D. G. *J. Am. Chem. Soc*. **2010**, *132*, 1488–1489. (h) Navickas, V.; Ushakov, D. B.; Maier, M. E.; Strobele, M.; Meyer, H. J. *Org. Lett*. **2010**, *12*, 3418–3421. For semisynthetic method, see: (i) Banerjee, A. K.; Vera, W. J.; Gonzalez, N. C. *Tetrahedron* **1993**, *49*, 4761–4788 and references cited therein. (j) Yuuya, S.; Hagiwara, H.; Suzuki, T.; Ando, M.; Yamada, A.; Suda, K.; Kataoka, T.; Nagai, K. *J. Nat. Prod*. **1999**, *62*, 22–30 and references cited therein. (k) Bargues, V.; Blay, G.; Cardona, L.; Garcia, B.; Pedro, J. R. *J. Nat. Prod*. **2002**, *65*, 1703–1706 and references cited therein.

(5) (a) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1869–1888 and references cited therein. (b) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377–1395 and references cited therein. (c) Consorti, C. S.; Ebeling, G. Dupont, J. *Tetrahedron Lett*. **2002**, *43*, 753–755. (d) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol*. **2005**, *9*, 285–292 and references cited therein. (e) Ramachandran, P. V.; Pratihar, D. *Org. Lett*. **2007**, *9*, 2087–2090. (f) Ramachandran, P. V.; Garner, G.; Pratihar, D. *Org. Lett*. **2007**, *9*, 4753–4756. (g) Elford, T. G.; Ulaczyk-Lesanko, A.; De Pascale, G.; Wright, G. D.; Hall, D. G. *J. Comb. Chem*. **2009**, *11*, 155–168 and references cited therein. (h) Ramachandran, P. V.; Pratihar, D.; Nair, H. N. G.; Walters, M.; Smith, S.; Yip-Schneider, M. T.; Wu, H. B.; Schmidt, C. M. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 6620–6623. (i) Yanagisawa, A.; Kushihara, N.; Yoshida, K. *Org. Lett*. **2011**, *13*, 1576–1578.

(6) Yang, H.; Qiao, X.; Li, F.; Ma, H.; Xie, L.; Xu, X. *Tetrahedron Lett*. **2009**, *50*, 1110–1112.

(7) Barbetti, P.; Casinovi, C. G.; Santurbano, B.; Longo, R. *Collect. Czech. Chem. Commun*. **1979**, *44*, 3123–3127.

(8) Unpublished results.

(9) The natural enantiomer, (+)-8-epigrosheimin ($[\alpha]^{20}_D$ + 32.4 (*c* 1.0, $CHCl_3$, lit.[7] $[\alpha]^{20}_D$ + 31.5 ± 1 (*c* 0.1, $CHCl_3$)), was also synthesized, and its biological activity is under investigation.

10.1021/ol201322w
Published on Web 06/15/2011

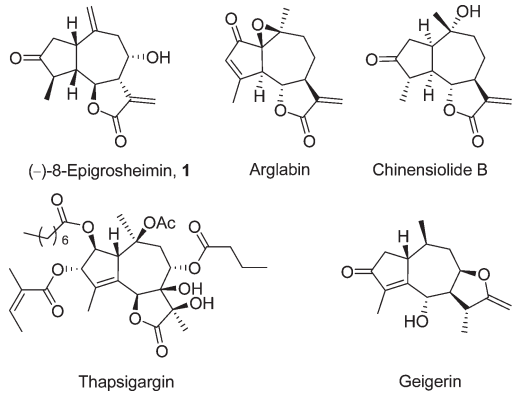


Figure 1. Representative examples of guaianolides.

0.68 μg/mL).[8,9] Encouraged by these results, a much more efficient synthetic route for this compound was developed by taking advantage of a highly diastereoselective synthetic method of α-*exo*-methylene-γ-butyrolactone as a crucial step.

As shown retrosynthetically in Figure 2,[10] one key step should be the introduction of an α-*exo*-methylene-γ-butyrolactone unit via the γ-addition of organozinc **3** to aldehyde **2**. The reason is that there are scarce studies on the allylic addition reactions of this kind with densely functionalized organometallic reagents.[11] Furthermore, this step was expected to form the stereocenters at C6 and C7 and introduce simultaneously the α-*exo*-methylene and carbonyl groups of the 6,12-lactone moiety, and further translactionization would assemble the α-*exo*-methylene-γ-butyrolactone motif and liberate the primary alcohol of C8 for the B-ring construction via aldehyde **4**.

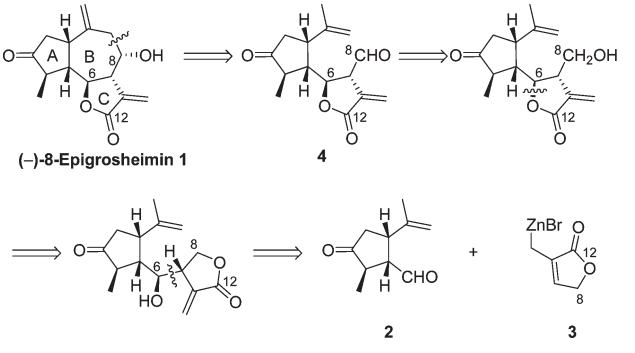
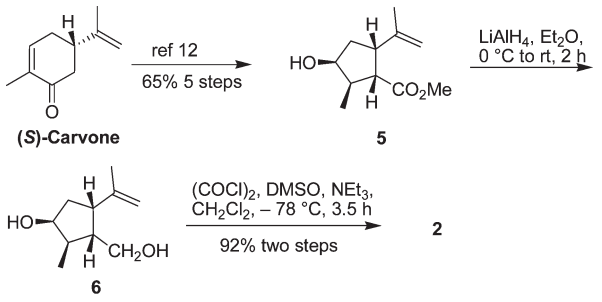


Figure 2. Retrosynthetic analysis of (−)-8-Epigrosheimin.

Another key step should be the intramolecular aldehyde-ene cyclization because of the unstable precursor **4**, whose double bond of the exomethylene group is prone to migrate into the ring and form the stable conjugation aldehyde.

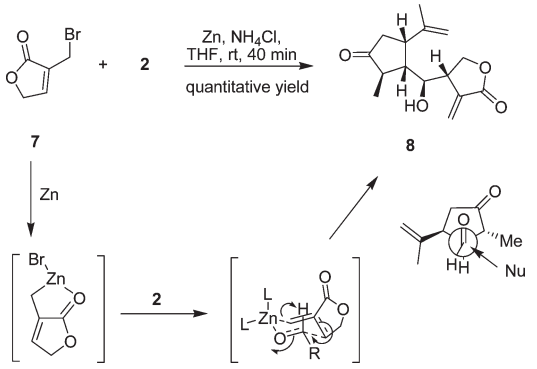
The enantiomer of cyclopentyl carbaldehyde **2** was synthesized from (*S*)-carvone via **5** by Ley's protocol

Scheme 1. Synthesis of Cyclopentyl Aldehyde **2**



(Scheme 1).[12] Reduction of THP-predeprotected **5** could avoid some side reactions[6] and improve the yield of diol **6**.[13]

Scheme 2



To our excitement, we found that mediated by zinc with satd. aq NH_4Cl in THF, 3-(bromomethyl)-2(5*H*)-furan-2-one (**7**),[14] precursor to **3,** reacted smoothly with aldehyde **2** to give the anticipated lactone **8** in quantitative yield (Scheme 2). During this process, the carbonyl group on the cyclopentane ring remained intact. The high regio- and stereoselectivity could be explained by the Felkin−Ahn transition state.[15]

The translactonization of lactone **8** to lactone **9** was realized smoothly in 89% yield by the ring opening of

(10) A related approach using an organoboron reagent was reported during the course of our study.[4g]

(11) Manchanayakage, R.; Handy, S. T. *Tetrahedron Lett.* **2007**, *48*, 3819–3822.

(12) Oliver, S. F.; Hogenauer, K.; Simic, O.; Antonello, A.; Smith, M. D.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5996–6000.

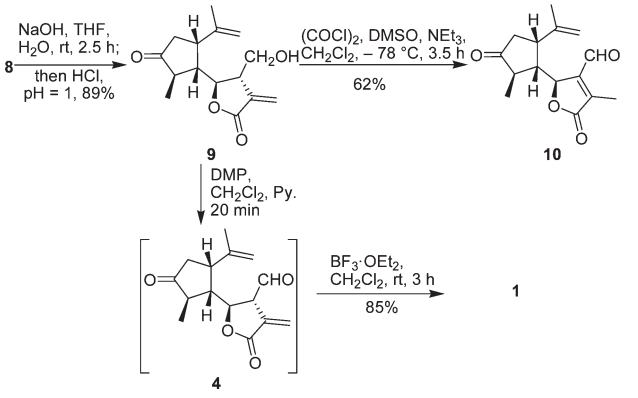
(13) Pogrebnoi, S.; Saraber, F. C. E.; Jansen, B. J. M.; Groot, A. *Tetrahedron* **2006**, *62*, 1743–1748.

(14) In addition to our study on 3-(bromomethyl)-2(5*H*)-furan-2-one, see: (a) Yang, H. S.; Qiao, X. X.; Cui, Q.; Xu, X. H. *Chin. Chem. Lett.* **2009**, *20*, 1023–1024. (b) Xu, X., Yang, H.; Qiao, X.; Xie, L. CN 101481367, 2009; *Chem. Abstr.* **2009**, *151*, 245843. (c) Cui, Q.; Wang, J.; Yang, H. S.; Xie, L. G.; Xu, X. H. *Chin. J. Org. Chem.* **2010**, *30*, 1705–1710. Another research group studied this bromolactone: Hodgson, D. M.; Talbot, E. P. A.; Clark, B. P. *Org. Lett.* **2011**, *13*, 2594–2597.

(15) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151–4157.

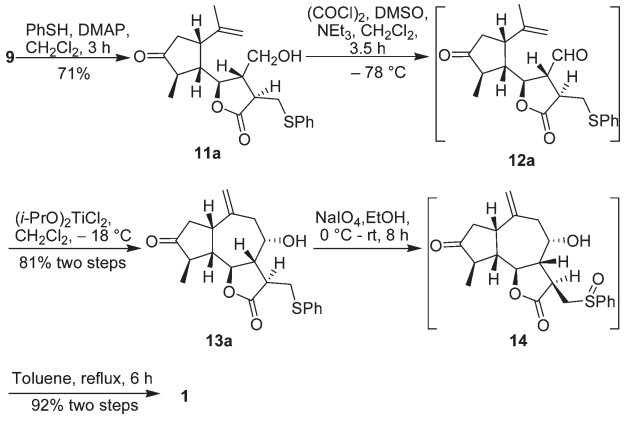
the lactone with NaOH, followed by careful acidification to pH 1 with HCl (Scheme 3). However, subsequent Swern oxidation of alcohol **9** gave rise to aldehyde **10** in 62% yield, in which the *exo*-methylene double bond had concurrently migrated into conjugation with the aldehyde and lactone carbonyl groups. A series of oxidation reagents and conditions (PCC, IBX, DMP) was attempted. It was found that the reaction was clean with DMP as the oxidation reagent and pyridine as the cosolvent. The obtained crude aldehyde **4** underwent ene cyclization to give the desired (−)-8-epigrosheimin (**1**) in 85% yield under catalysis with $BF_3 \cdot OEt_2$ at rt in 3 h.

Scheme 3



Alternatively, the double bond of the α-exomethylene butyrolactone of **9** could be protected first by thiophenol via Michael addition to produce thiother **11a** in 71% yield (Scheme 4). Following a similar procedure developed by us,[14] Swern oxidation of the primary alcohols **11a** and intramolecular aldehyde-ene cyclization under $(i\text{-PrO})_2TiCl_2$ catalysis generated guaianolides **13a** in 81% in two steps. The absolute configuration of **13a** was confirmed unambiguously by X-ray crystallographic analysis. The target molecule **1** was produced from thioether **13a** in 92% yield

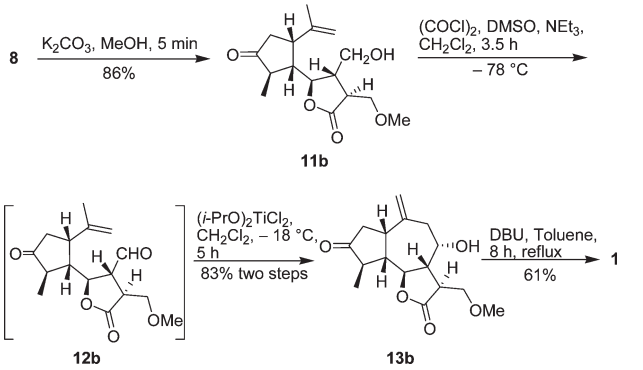
Scheme 4



via the pyrolytic elimination of the sulfoxide **14**, which was obtained readily by oxidizing thioether **13a** with $NaIO_4$ in ethanol at room temperature.

Moreover, when the lactone **8** was treated with K_2CO_3 in methanol, not only translactonization but also Michael addition occurred to give the methyl ether **11b** in 86% yield (Scheme 5). Swern oxidation and aldehyde-ene reaction gave the cyclized **13b** in 83% yield in two steps. The β-elimination of **13b** with DBU in refluxing toluene afforded **1** in 61% yield.

Scheme 5



In summary, a highly diastereoselective and efficient total synthesis of (−)-8-epigrosheimin (**1**) was achieved from commercially available (*S*)-carvone in 11 steps with 45% overall yield. This synthesis featured an efficient installation of the *trans*-fused α-*exo*-methylene-γ-butyrolactone unit via a highly regio- and diastereoselective Barbier reaction. The key assembly of the framework of the natural product was the sequential allylation, intramolecular translactonization, and intramolecular aldehyde-ene cyclization. This sequence could serve as a general total synthetic route for guaianolides,[16] especially for 8-oxygenated guaianolides,[17] which could not be hydroxylated easily from α-santonin[18] or C8-deoxygenated guaianolide. Furthermore, total synthesis of the closely related pseudoguaianolides[2] could utilize this approach as an alternative

(16) The hydroxyl group at C8 could be eliminated readily; see: Kalidindi, S.; Jeong, W. B.; Schall, A.; Bandichhor, R.; Nosse, B.; Reiser, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 6361–6363.

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(18) (a) Blay, G.; Luz Cardona, M.; Garcia, B.; Pedro, J. R. *J. Org. Chem.* **1991**, *56*, 6172–6175. Ramachandran, P. V.; Garner, G.; Pratihar, D. *Org. Lett.* **2007**, *9*, 4753–4756.

protocol. Studies along these lines are ongoing in this laboratory.

Acknowledgment. We thank the National Science Foundation of China (Grant Nos. 20572055 and 20421202) for financial support.

Supporting Information Available. Experimental procedures; spectroscopic data of compounds **2**, **4**, **8**–**10**, **11a**, **11b**, **13a**, and **13b**; and crystallographic information file (CIF) for compound **13a**. This material is available free of charge via the Internet at http://pubs.acs.org.