Organic LETTERS

Letter

pubs.acs.org/OrgLett

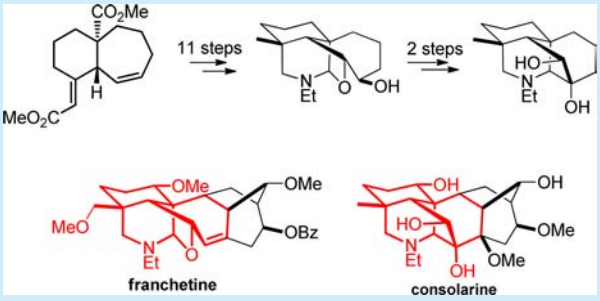
Expedient Construction of the ABEF Azatetracyclic Ring Systems of Lycoctonine-Type and 7,17-*seco*-Type C_{19}-Diterpenoid Alkaloids

Hang Cheng, Fan-Hao Zeng, Ding Ma, Min-Li Jiang, Liang Xu,* and Feng-Peng Wang

Key Laboratory of Drug Targeting and Drug Delivery Systems of the Ministry of Education, Department of Chemistry of Medicinal Natural Products, West China School of Pharmacy, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China

Supporting Information

ABSTRACT: A synthetic strategy for the modeling construction of the highly bridged azatetracyclic ABEF ring system of numerous lycoctonine-type C_{19}-diterpenoid alkaloids bearing a characteristic oxygenated quaternary center at C-7 has been successfully developed. The tetracyclic core was constructed rapidly from a readily prepared 6,7-bicyclic AB ring precursor through a 13-step sequence via an advanced tetracyclic *N*,*O*-acetal intermediate, which belong to another core structure of natural 7,17-*seco*-type alkaloids. The key step involves an SmI_2-promoted intramolecular radical coupling reaction of an *N*,*O*-acetal with a carbonyl group, mimicking a plausible biogenetic transformation.



C_{19}-Diterpenoid alkaloids comprise a large class of structurally complex natural products mainly distributed in plants of the *Aconitium* and *Delphinium* genera, which display a range of biological activities including anti-inflammatory, analgesic, antiarrhythmic, antipyretic, antiepileptic, hypotensive, and bradycardic properties.[1] This large family of natural products (674 at the end of July 2008), characterized by heavily substituted azahexacyclic ring systems, may be subdivided into six types including 13 subtypes and 19 groups on the basis of the carbon skeletons and substituents at the specific positions.[1] The structural complexity and biological significance of the members of this family has led to significant interest from the synthetic community. However, synthesis of C_{19}-diterpenoid alkaloids is a conspicuous challenge due to its intricate structure. So far, only three aconitine-type C_{19}-diterpenoid alkaloids were practically synthesized by Wiesner and co-workers in the 1970s.[2] Very recently, another elegant work was achieved by Gin and co-workers in total synthesis of a C_{18}-diterpenid alkaloid neofinaconitine,[3] which shares a common C_{19}-diterpenoid framework in the absence of carbon C18. Despite numerous other attempts,[4] these remain the only published total syntheses of C_{19}-diterpenoid alkaloids.

Among the vast family of C_{19}-diterpenoid alkaloids, we were particularly intrigued by the lycoctonine-type alkaloids (more than 280 natural compounds), which differ from aconitine-type alkaloids in the substitution pattern at C-7 and possess an extra oxygen-containing functionality at this position (Figure 1). Until now, no chemical preparation of any member of this subtype has been described, presumably due to the increasing challenge for construction of this oxygenated quaternary carbon. Although some partial ring systems have been reported in the synthesis toward a few members of lycoctonine-type alkaloids in the past decades, none of these systems has been

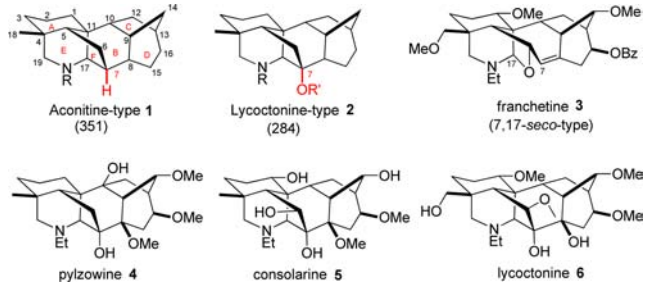


Figure 1. Structures of some members of C_{19}-diterpenoid alkaloids.

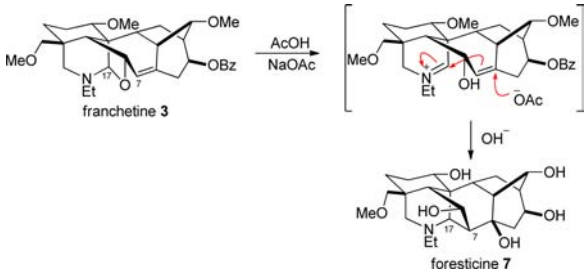
constructed with the featured C-7 oxygenated quaternary center.[5] In view of our long-standing interest toward the total synthesis of C_{19}-diterpenoid alkaloids,[6] we planned to develop a new and efficient methodology for constructing a tetracyclic ABEF ring system, which in combination with our previously accomplished functionalized BCD ring system bearing a key carbonyl group at C-11 on a seven-membered ring B,[6b] would provide a good basis for the total synthesis of some members of lycoctonine-type C_{19}-diterpenoid alkaloids such as pylzowine (**4**), consolarine (**5**), and lycoctonine (**6**).

Herein we present our efforts toward the synthesis of the ABEF azatetracyclic amine **7** of lycoctonine-type alkaloids bearing the key C-7 oxygenated quaternary center. In light of a reported biomimetic transformation from 7,17-*seco*-type C_{19}-diterpenoid alkaloid franchetine **3** to an aconitine-type alkaloid foreticine **7** (Scheme 1),[7] we envisaged that this transformation might be able to allow a plausible cyclization process (**9** → **8**)

Received: March 9, 2014
Published: April 4, 2014

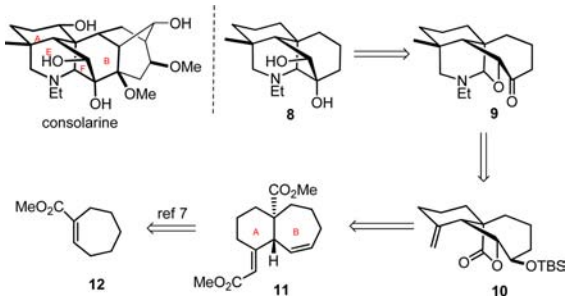
   dx.doi.org/10.1021/ol500726x | *Org. Lett.* 2014, 16, 2299−2301

Scheme 1. Proven Biogenitic Transformation from Franchetine 3 to Aconitine-Type Alkaloid Foreticine 7[7]



through a SmI-promoted biomimetic radical coupling of a *N,O*-acetal with ketone group, culminating in construction of the key oxygenated quaternary center at C-7 (Scheme 2). The unique

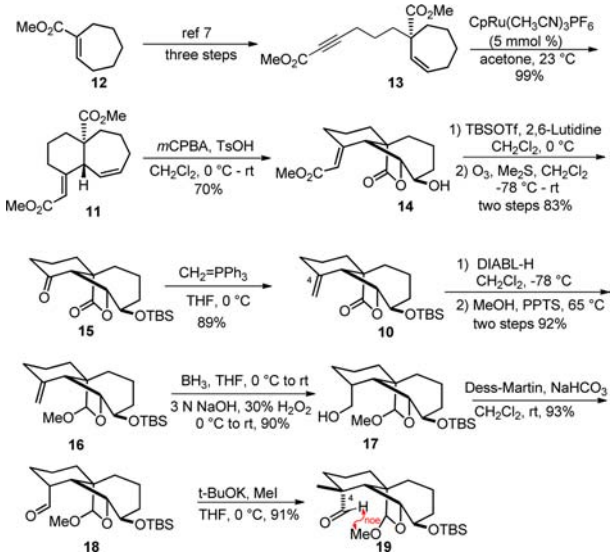
Scheme 2. Retrosynthetic Plan for Synthesis of the ABEF Ring of Lycoctonine-Type C_{19}-Diterpenoid Alkaloid



tetracylic *N,O*-acetal **9**, also as the subunit of natural 7,17-*seco*-type alkaloid, could arise from the bridged tricycle lactone **10** by stereoselective construction of a quaternary center at C-4 followed by installation of nitrogen-containing ring E. In turn, the bridged lactone **10** would result from an acid-promoted epoxidation of a known 6,7-bicycle ene ester **11**,[8] which could serve as the precursor of trans-fused ring AB.

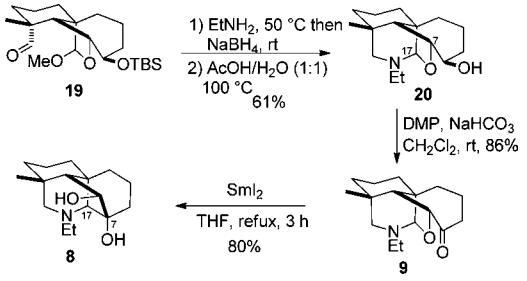
We commenced our synthesis from the known trans-fused 6,7-bicycle **11**, prepared from the methyl cyclohept-1-enecarboxylate **12** by a convergent four-step process involving a ruthenium-catalyzed diastereoselective enyne cycloisomerization reaction (**13** → **11**), which was developed by Trost et al. in 2008.[8] Subsequently, installation of the bridged lactone moiety on ring B was accomplished by direct treatment of the compound **11** with *m*-CPBA in dichloromethane in the presence of catalytic TsOH, delivering lactone **14** as a single positional isomer in 70% yield. This reaction proceeded, in fact, with concomitant stereoseletive epoxidation and ring-opening of the resulting epoxy by the intramolecular attack of ester group. After a simple TBS protection on the C-7 hydroxyl group of **14**, ozonolysis of the conjugated enoate provided ketone **15** in 92% yield. With the requisite ketone in hand, construction of the C-4 quaternary center was next addressed. For this purpose, homologation and subsequent alkylation at the C-4 position were undertaken. Our initial attempt by direct treatment of ketone **15** with (methoxymethylene)-triphenylphosphine to give homologous aldehyde was totally unsuccessful. Nevertheless, Wittig reaction of ketone **15** with more active methylenetriphenylphosphine preceded smoothly, affording alkene **10** in 89% yield. Considering the plausible instability of the lactone moiety under basic reaction conditions at late stage, the lactone **10** was converted to relatively more stable methyl acetal in advance via a two-step sequence. First, lactone **10** was reduced to the corresponding lactol (DIBAL-H, CH_2Cl_2, −78 °C), which was heated in MeOH in the presence of catalytic PPTS to provide the methyl ether **16**, surprisingly, as a single diastereomer in excellent yield. Then, sequential hydroboration−oxidation[9] of terminal olefin **16** and Dess−Martin oxidation of the resulting primary alcohol **17** were effected, exclusively delivering the formyl group to the *α*-face to give aldehyde **18** in 93% yield. The following alkylation at C-4 was carried out according to the conventional method using methyl iodide and potassium *tert*-butoxide in THF. It has been shown that such an alkylation reaction is highly sensitive to steric hindrance of axial hydrogens and axial substituents in a cyclohexane ring and produces equatorially alkylated product predominantly.[10] Accordingly, a high stereoselectivity of this alkylation was expected. In fact, methylation of our acetal aldehyde **18** produced only one isomer **19** with the desired configuration in 91% yield (Scheme 3). The axial configuration of the formyl group of the product **19** was proved unequivocally on the basis of NOE and further cyclization to a piperidine compound (vide infra).

Scheme 3. Synthesis of Methyl Acetal Intermediate 19



With the requisite AB-ring functionality in place, we next focused our attention to the installation of the piperidine ring E and subsequent construction of tetracyclic ABEF ring system (Scheme 4). First, a straightforward introduction of nitrogen atom was achieved by reductive amination of the aldehyde **19** with ethylamine. Without purification, the resulting amine was

Scheme 4. Construction of Tetracyclic Amines 8 and 9



dx.doi.org/10.1021/ol500726x | *Org. Lett.* 2014, 16, 2299−2301

directly heated at 100 °C in AcOH/H_2O (1:1) to induce formation of the C17-*N* bond with simultaneous removal of TBS protecting group to furnish the tetracyclic *N*,*O*-acetal compound **20** in good yield. After oxidation of **20** with Dess−Martin periodinane, the resulting ketone **9** was subjected to SmI_2-promoted intramolecular reductive radical cyclization[11] between *N*,*O*-acetal and the carbonyl group to form a C7−C17 bond, mimicking the plausible biogenetic transformation. The initial attempts under the conventional reaction conditions (SmI_2/HMPA/*t*-BuOH, SmI_2/HMPA, or SmI_2/MeOH, −78 to 0 °C) all failed to give the desired cyclization product, and only some unidentified deoxygenated products were isolated.[12] After carefully screening various reaction conditions, we were pleased to discover that by adding the ketone **9** to a solution of SmI_2 in THF at reflux in the absence of any additives[13] the desired reductive coupling product **8** could be isolated in 80% yield, together with a small amount of carbonyl group directly reduced product. The whole stereochemical structure of **8** was unequivocally confirmed based on the interpretation of its 2D NMR spectra (see the Supporting Information). To the best of our knowledge, it was the first time that the *N*,*O*-acetal group without any radical stabilized substitutes was used as reaction component to undergo a facile SmI_2-induced reductive coupling with ketone.[14]

In conclusion, the synthesis of highly bridged azatetracyclic amine **8** with a key oxygenated quaternary carbon at C-7, modeling the ABEF ring system of lycoctonine-type C_{19}-diterpenoid alkaloids, has been successfully accomplished via an advanced *N*,*O*-acetal tetracyclic intermediate **9**, which belong to another core structure of natural 7, 17-*seco*-type C_{19}-diterpenoid alkaloids. The synthesis features a known Trost's ruthenium-catalyzed enyne cycloisomerization to stereoselectively construct trans-fused AB ring precursor and an unprecedented SmI_2-promoted biomimetic ketone *N*,*O*-acetal reductive coupling to form C7−C17 bond as the key steps. This strategy for construction of a model ABEF ring system, combined with our previously developed synthetic strategy for the BCD ring system,[6b] should thus provide a solid basis for the total synthesis of 7,17-*seco*-type C_{19}-diterpenoid alkaloid and lycoctonine-type C_{19}-diterpenoid alkaloid such as francetine, consolarine, and lycoctonine.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and procedures, compound characterization data, copies of ^1H and ^{13}C NMR spectra for new compounds, 2D NMR spectra and their interpretations for compound **8**, and the NOE difference spectrum for compound **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liangxu@scu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by the National Natural Science Foundation of China (Grant Nos. 30873147 and 21272163).

■ REFERENCES

(1) Wang, F. P.; Chen, Q. H. *Alkaloids* **2010**, *69*, 1−577.

(2) (a) Wiesner, K.; Tsai, T. Y. R.; Huber, K.; Bolton, S. E.; Vlahov, R. *J. Am. Chem. Soc.* **1974**, *96*, 4990−4992. (b) Wiesner, K.; Tsai, T. Y. R.; Nambiar, K. P. *Can. J. Chem.* **1978**, *56*, 1451−1454. (c) Wiesner, K. *Pure Appl. Chem.* **1979**, *51*, 689−703.

(3) Shi, Y.; Wilmot, J. T.; Nordstrom, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313−14320.

(4) For a review, see: Goodall, K. J.; Barker, D.; Brimble, M. A. *Synlet.* **2005**, *12*, 1809−1827.

(5) For construction of AE rings, see: (a) Ismail, K. A.; Bergmeier, S. C. *Eur. J. Med. Chem.* **2002**, *37*, 469−474. (b) Goodall, K. J.; Brimble, M. A.; Barker, D. *Tetrahedron* **2012**, *68*, 5759−5778. (c) Grangier, G.; Trigg, W. J.; Lewis, T.; Rowan, M. G.; Potter, B. V. L; Blagbrough, I. S. *Tetrahedron Lett.* **1998**, *39*, 889−892. (d) Callis, D. J.; Thomas, N. F.; Pearson, D. P. J.; Potter, B. V. L *J. Org. Chem.* **1996**, *61*, 4634−4640. (e) Coates, P. A.; Blagbrough, I. S.; Rowan, M. G.; Pearson, D. P. J.; Lewis, T.; Potter, B. V. L *J. Pharm. Pharmacol.* **1996**, *48*, 210−213. (f) Barker, D.; McLeod, M. D.; Brimble, M. A.; Savage, G. P. *Tetrahedron Lett.* **2002**, *43*, 6019−6022. (g) Kraus, G. A.; Andersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* **1993**, *34*, 1741−1744. For construction of the AEF ring, see: (h) Baillie, L. C.; Bearder, J. R.; Li, W. S.; Sherringham, J. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4047−4055. For construction of the ABEF ring, see: (i) Kraus, G. A.; Kesavan, S. *Tetrahedron Lett.* **2005**, *46*, 1111−1113.

(6) (a) Liu, Z. G.; Xu, L.; Chen, Q. H.; Wang, F. P. *Tetrahedron* **2012**, *68*, 159−165. (b) Cheng, H.; Xu, L.; Chen, D. L.; Chen, Q. H.; Wang, F. P. *Tetrahedron* **2012**, *68*, 1171−1176. (c) Liu, Z. G.; Cheng, H.; Ge, M. J.; Xu, L.; Wang, F. P. *Tetrahedron* **2013**, *69*, 5431−5437.

(7) Wang, F. P.; Li, Z. B.; Dai, X. P.; Peng, C. S. *Phytochemistry* **1997**, *45*, 1539−1542.

(8) (a) Trost, B. M.; Ferreira, E. M.; Gutierrez, A. C. *J. Am. Chem. Soc.* **2008**, *130*, 16176−16177. (b) Trost, B. M.; Gutierrez, A. C.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 9206−9218.

(9) Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1956**, *78*, 5694−5695.

(10) (a) Nagata, W.; Sugasawa, T.; Narisada, M.; Wakabayashi, T.; Hayase, Y. *J. Am. Chem. Soc.* **1967**, *89*, 1483−1499. (b) Johnson, W. S.; Allen, D. S.; Hindersinn, R. R.; Sausen, G. N.; Pappo, R. *J. Am. Chem. Soc.* **1962**, *84*, 2181−2196.

(11) For selected reviews of the use of SmI_2 in organic synthesis, see: (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68. (b) Molander, G. A. *Org. React.* **1994**, *46*, 211−367. (c) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. (d) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321−3354. (e) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351−10372. (f) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3372−3404. (g) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140−7165.

(12) For reductive cleavage of α-oxygenated ketone by SmI_2, see: Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135−1138.

(13) For examples of SmI_2-promoted cyclization without additives, see: (a) Hoffmann, H. M. R.; Munnich, I.; Nowitzki, O.; Stucke, H.; Williams, D. J. *Tetrahedron* **1996**, *52*, 11783−11789. (b) Nowitzki, O.; Munnich, I.; Stucke, H.; Hoffmann, H. M. R. *Tetrahedron* **1996**, *52*, 11799−11810. (c) Zi, W.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 5887−5890.

(14) For sparse examples of SmI_2-promoted radical cyclization of *N*,*O*-acetal bearing a radical-stabilized ester group, see: (a) Ricci, M.; Blakskjær, P.; Skrydstrup, T. *J. Am. Chem. Soc.* **2000**, *122*, 12413−12421. (b) Jacobsen, M. F.; Turks, M.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2002**, *67*, 2411−2417.