Organic LETTERS

Letter

pubs.acs.org/OrgLett

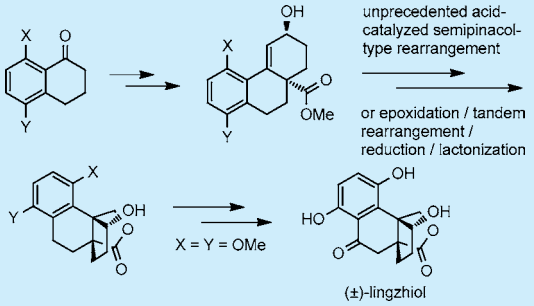
An approach to (±)-Lingzhiol

Xiaoyu Li, Xiaoyu Liu, Xiaozhen Jiao, Hongguang Yang, Yangyang Yao, and Ping Xie*

State Key Laboratory of Bioactive Substance and Function of Natural Medicine, Beijing Key Laboratory of Active Substance Discovery and Drugability Evaluation, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, No. 1 Xiannongtan Street, Beijing 100050, China

Supporting Information

ABSTRACT: (±)-Lingzhiol has been synthesized from commercially available 5,8-dimethoxytetralone in seven steps with an overall yield of 10.3% via an unprecedented acid-catalyzed semipinacol-type rearrangement. In addition, a novel strategy for the construction of the tetracyclic 5/5/6/6 core structure of lingzhiol has been developed via a tandem rearrangement/reduction/lactonization reaction.

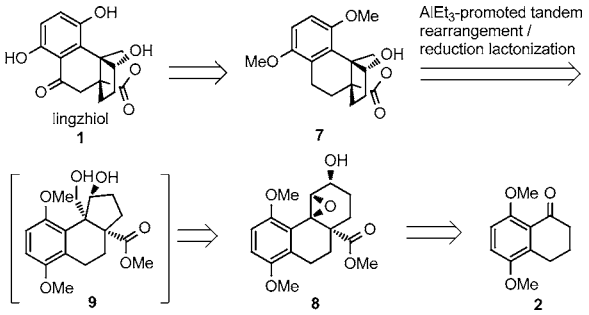


Lingzhiol, a novel meroterpenoid with an unprecedented tetracyclic 5/5/6/6 core structure, was isolated from *Ganoderma lucidum* in its racemic form. Initial biological studies show that (±)-lingzhiol (**1**) has a potent inhibitory effect on the phosphorylation of Smad3, which is implicated in chronic kidney disease, such as diabetic nephropathy, and therefore, it can be considered as a drug lead against chronic kidney disease. Although (±)-lingzhiol (**1**) can be resolved using chiral HPLC, both its enantiomers show similar activity.[1] Its interesting biological activity and unique structure have attracted attention from the organic chemistry community. In 2014, Yang's group[2] completed the first asymmetric synthesis of (−)-lingzhiol in 17 steps. They used a novel Rh-catalyzed [3 + 2] cycloaddition as the key step to efficiently construct the two quaternary carbon centers. Very recently, Qin's group[3] published the total synthesis of (±)-lingzhiol (**1**). They took a different approach and used an epoxyarene cyclization to construct the 5/5/6/6 ring system of (±)-lingzhiol (**1**). Due to the important pharmacological properties of this natural product, a practical and versatile synthetic strategy that is capable of providing an adequate amount of material and its analogues for medicinal studies is urgently needed.

Herein, we describe a highly concise and efficient synthesis of (±)-lingzhiol (**1**). Our retrosynthetic analysis is outlined in Scheme 1.[4] We envisioned that the core structure of tetracyclic 5/5/6/6 lactone **7** might be constructed via an $AlEt_3$-promoted tandem rearrangement/reduction/lactonization of the cyclic 2,3-epoxy alcohol **8**.[5,6] Compound **8**, in turn, could be conveniently prepared from 5,8-dimethoxytetralone **2** via a Robinson annulation, reduction, and epoxidation sequence.

Our synthesis commenced with preparation of the *cis*-*β*-allylic alcohol **5** from commercially available 5,8-dimethoxytetralone **2** (Scheme 2). Treatment of 5,8-dimethoxytetralone **2** with dimethylcarbonate in the presence of NaH gave the known *β*-ketoester **3**.[7,8] Then, a Robinson annulation of *β*-ketoester **3** with

Scheme 1. Retrosynthetic Analysis of (±)-Lingzhiol (1)

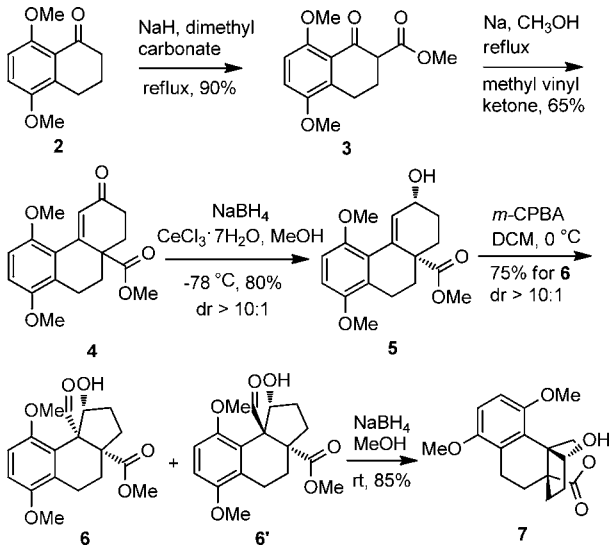


methyl vinyl ketone via heating in the presence of MeONa delivered the *α*,*β*-unsaturated cycloketone **4**. However, during the Luche reduction[9,10] of the *α*,*β*-unsaturated cycloketone **4** at room temperature, only moderate *cis* stereoselectivity was observed. Maintaining the reaction temperature at −78 °C was crucial for attaining a high *cis* stereoselectivity (dr >10:1). The relative stereochemistry of alcohol **5** was clearly confirmed by X-ray crystallography (Figure 1). However, to our surprise, in attempting to prepare the precursor epoxide **8**, we found that treating alcohol **5** with *m*-CPBA in CH_2Cl_2 at room temperature did not result in the expected epoxide but instead gave a 3:1 mixture of ring-contracted aldehydes **6** and **6′**. The structures of aldehydes **6** and **6′** were determined by ^1H NMR, ^{13}C NMR, and 2D NMR spectroscopy, and the configuration of aldehyde **6** was further confirmed by converting into the lactone **7**, the key intermediate in Yang's synthesis of lingzhiol.[2] When aldehyde **6** was subjected to $NaBH_4$ reduction, the tetracyclic lactone **7** was obtained. The ^1H NMR and ^{13}C NMR data of our product **7** were consistent with the data reported in the literature.[2,3]

Received: February 25, 2016
Published: April 4, 2016

DOI: 10.1021/acs.orglett.6b00542
Org. Lett. 2016, 18, 1944−1946

Scheme 2. Synthesis of Lactone 7



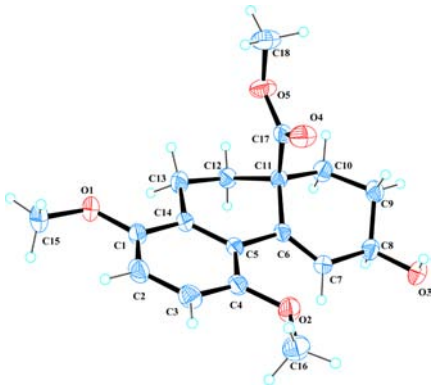
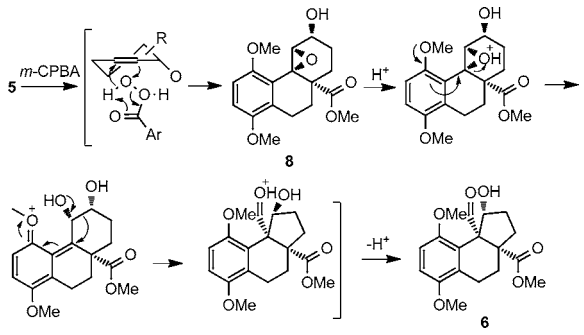


Figure 1. X-ray crystal structure of **5**.

Obviously, an acid-catalyzed semipinacol-type rearrangement of a 2,3-epoxy alcohol mechanism may be used to explain the experimental outcome, as shown in Scheme 3. The Lewis acid

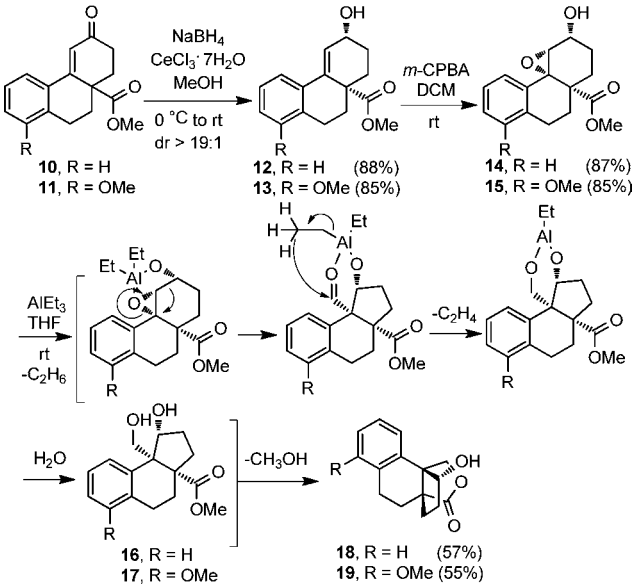
Scheme 3. Possible Mechanism of the Acid-Catalyzed Semipinacol-Type Rearrangement



mediated rearrangement of alcohol-protected 2,3-epoxides has been fully documented,[11] whereas the use of unprotected 2,3-epoxy alcohols is rare.[5,12] It is also worth mentioning that, to our knowledge, this is the first example of a semipinacol-type rearrangement caused by the oxidation of an allylic alcohol using *m*-CPBA. We proposed that the easy rearrangement of the epoxide **8** was attributed to the strong electron-donating (−OMe) substitution present in its ortho-position, which could stabilize the benzylic cation formed in the transition state and facilitated this reaction.

To prove the assumed mechanism of rearrangement and provide structural analogues to probe biological activity, similar cyclic allylic alcohols **12** with no substituent and **13** with a −OMe group in the meta-position, which were obtained with a high stereoselectivity (dr >19:1) based on our previous work (Scheme 2), were selected as test substrates (Scheme 4). As expected,

Scheme 4. Synthesis of Lactones 18 and 19



when the cyclic allylic alcohol **12** or **13** was treated with *m*-CPBA, only the epoxide product **14** or **15** was isolated (Scheme 4). In addition, to our delight, when compound **14** or **15** was treated with $AlEt_3$ in THF using Tu's procedure,[5,6] the desired tetracyclic lactone **18** or **19**, which bears the core structure of lingzhiol, could be obtained in a one-step procedure with a reasonable yield of 57 and 55%, respectively (Scheme 4). The relative stereochemistry of lactone **18** was unambiguously determined by X-ray crystallography (Figure 2).

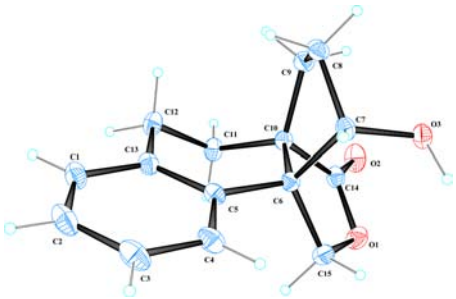
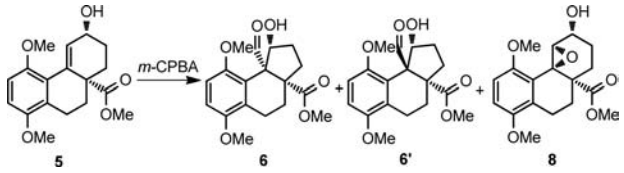


Figure 2. X-ray crystal structure of **18**.

With rapid construction of key intermediate **7** through our unexpected acid-catalyzed semipinacol-type rearrangement, our attention then turned to improve the *cis* stereoselectivity in the preparation of aldehyde **6**, where different reaction conditions were tested (Table 1). It was found that the solvent and temperature have a substantial effect on the reaction. The reaction performed in an apolar solvent (CH_2Cl_2 or toluene) at

DOI: 10.1021/acs.orglett.6b00542
Org. Lett. 2016, 18, 1944−1946

Table 1. Optimization of the 6/6′ Ratio Using Different Solvents and Reaction Conditions



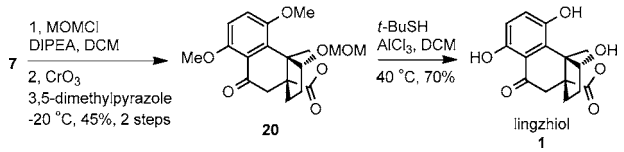
entry	solvent	condition	time (h)	ratio[a] (6/6′)
1	THF	rt	24	*b*
2	EtOAc	rt	24	*b*
3	CH_3CN	rt	24	3:1
4	toluene	0 °C	3	5:1
5	CH_2Cl_2	rt	1	3:1
6	CH_2Cl_2	0 °C	3	10:1
7	CH_2Cl_2	−20 °C	3	*b*

[a]Determined by ^{1}H NMR spectroscopy. [b]Major product was epoxide **8**.

room temperature or 0 °C was fast with no detectable trace of the expected epoxide **8**,[13] but decreasing the temperature to −20 °C or using a polar solvent (THF or ethyl acetate) led to a much slower reaction and resulted in the formation of epoxide **8** and only trace amounts of **6** and **6′** (Table 1). Furthermore, the **6**/**6′** ratios, which were determined by ^{1}H NMR spectroscopy, could be improved to 10:1 by using CH_2Cl_2 as the solvent and simply altering the reaction temperature from 25 to 0 °C. Under the optimized condition, aldehyde **6** was easily obtained by treating alcohol **5** with 1.1 equiv of *m*-CPBA, and without separation, the resultant mixture of aldehydes **6** and **6′** was subsequently reduced using $NaBH_4$ in a one-pot procedure to afford lactone **7** in 70% isolated yield after column chromatography.

Finally, with tetracyclic lactone **7** in hand, Yang's protocol[2] could be employed to complete the total synthesis of (±)-lingzhiol. Alternatively, introduction of the benzylic carbonyl functionality could also be achieved via oxidation with freshly preprared CrO_3/3.5-dimethylpyrazole[14] after intermediate **7** was protected with MOMCl (Scheme 5). Then, the methoxymethyl

Scheme 5. Synthesis of (±)-Lingzhiol (1)



group and two methoxyl groups of ketone **20** could be simultaneously removed to deliver (±)-lingzhiol (**1**) using $AlCl_3$ and *t*-BuSH in CH_2Cl_2.[2] The spectroscopic data of our synthesized (±)-lingzhiol (**1**) were in excellent agreement with the data reported in the literature.[1−3]

In summary, a novel strategy for the rapid construction of the core structure of lingzhiol (**1**) has been developed. The strategy was based on an unprecedented acid-catalyzed semipinacol-type rearrangement of a bicyclic allylic alcohol and a tandem rearrangement/reduction/lactonization of a bicyclic 2,3-epoxy alcohol. This strategy was not only applied in the concise synthesis of (±)-lingzhiol (**1**) but also proved to be suitable for straightforward construction of its structural analogues.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00542.

Experimental procedures, product characterizations, and NMR spectra for all new compounds (PDF)
X-ray crystal structure data for **5**, CCDC 1442840(CIF)
X-ray crystal structure data for **18**, CCDC 1442869 (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xp@imm.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Major Scientific and Technological Special Project (No. 2012ZX09301002001004) for financial support.

■ REFERENCES

(1) Yan, Y. M.; Ai, J.; Zhou, L. L.; Chung, A. C. K.; Li, R.; Nie, J.; Fang, P.; Wang, X. L.; Luo, J.; Hu, Q.; Hou, F. F.; Cheng, Y. X. *Org. Lett.* **2013**, *15*, 5488.
(2) Long, R.; Huang, J.; Shao, W.; Liu, S.; Lan, Y.; Gong, J. X.; Yang, Z. *Nat. Commun.* **2014**, *5*, 5707.
(3) Chen, D.; Liu, H. M.; Li, M. M.; Yan, Y. M.; Xu, W. D.; Li, X. N.; Cheng, Y. X.; Qin, H. B. *Chem. Commun.* **2015**, *51*, 14594.
(4) After the submission of our manuscript, a biogenetically inspired synthesis of lingzhiol using a similar strategy was recently published by another group: Gautam, K. S.; Birman, V. B. *Org. Lett.* **2016**, 1499.
(5) Li, X.; Wu, B.; Zhao, X. Z.; Jia, Y. X.; Tu, Y. Q.; Li, D. R. *Synlett* **2003**, *5*, 623.
(6) Li, D. R.; Xia, W. J.; Tu, Y. Q.; Zhang, F. M.; Shi, L. *Chem. Commun.* **2003**, 798.
(7) Justribó, V.; Pellegrinet, S. C.; Colombo, M. I. *J. Org. Chem.* **2007**, *72*, 3702.
(8) Johnson, D. W.; Mander, L. N. *Aust. J. Chem.* **1978**, *31*, 1561.
(9) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(10) Jung, M. E.; Piizzi, G. *Org. Lett.* **2003**, *5*, 137.
(11) (a) Yamamoto, H.; Nozaki, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 169. (b) Maruoka, K.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 5001. (c) Maruoka, K.; Sato, J.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 3749. (d) Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983. (e) Maruoka, K.; Hasegawa, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 3827. (f) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G.-I. *Tetrahedron Lett.* **1987**, *28*, 5891. (g) Suda, K.; Nakajima, S.-I.; Satoh, Y.; Takanami, T. *Chem. Commun.* **2009**, 1255. (h) Neef, G.; Baesler, S.; Depke, G.; Vierhufe, H. *Tetrahedron Lett.* **1999**, *40*, 7969.
(12) (a) Zhao, X. Z.; Jia, Y. X.; Tu, Y. Q. *J. Chem. Res., Miniprint* **2002**, 210. (b) Kita, Y.; Matsuda, S.; Inoguchi, R.; Ganesh, J. K.; Fujioka, H. *J. Org. Chem.* **2006**, *71*, 5191.
(13) Epoxide **8** was unstable; quenching the mixture upon addition of a solution of aqueous $NaHCO_3$ prior to workup and then attempting chromatographic purification of epoxide **8** on silica gel led to partial decomposition.
(14) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

■ NOTE ADDED AFTER ASAP PUBLICATION

The Supporting Information (pdf) file was corrected on April 7, 2016.

DOI: 10.1021/acs.orglett.6b00542
Org. Lett. 2016, 18, 1944−1946