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Collective Enantioselective Total Synthesis of (+)-Sinensilactam A, (+)-Lingzhilactone B and (-)-Lingzhiol: Divergent Reactivity of Styrene

Da-Wei Zhang <sup>a,b</sup>, Hui-Lan Fan <sup>a,b</sup>, Wenzhao Zhang <sup>d</sup>, Cheng-Ji Li <sup>a,b</sup>, Sanzhong Luo <sup>c,d,\*</sup>, Hong-Bo Qin <sup>a\*</sup>

Collective total synthesis of (+)-sinensilactam A, (+)-lingzhilactone B, (+)-lingzhilactone C and (-)-lingzhiol has been accomplished from a common epoxide intermediate 9. Chemoselective epoxy opening with either aryl or alkene moiety of styrene led to different carbon skeletons which can be advanced to divergent and concise total synthesis of four meroterpenoids.

During the past 7 years, Ganoderma meroterpenoids have attracted increasing attentions from phytochemical communities. With meroterpenoids being increasingly identified, such type of molecules has become the third most abundant constituent of Ganoderma. Sinensilactam A, lingzhilactone B and lingzhiol, isolated from the genus Ganoderma by Cheng<sup>1-3</sup>, are reno-protective by inhibition of Smad3 phosphorylation in TGF-B1-induced cellular assays. In 2018, Yang's group reported the first racemic total synthesis of sinensilactam A using a rhodium catalyzed [3+2] cycloaddition as the key step.<sup>4</sup> However, the synthesis required 18 steps involving harsh conditions such as high pressure (14 MPa) and long-time heating (150 °C, 48h). A concise synthetic route under mild conditions is still highly desirable. On the other hand, we and others have previously reported the total syntheses of lingzhiol and lingzhilactone B.5-12 In this communication, we report a distinctive strategy for the collective synthesis of four meroterpernoids, (+)-sinensilactam A, (+)-lingzhilactone B, (+)lingzhilactone C and (-)-lingzhiol. The key step involves a nonmetal promoted selective nucleophilic opening of epoxide by alkene moiety of styrene, which has not been explored in total synthesis, though metal-catalyzed reaction of epoxide with styrene are known.  $^{\rm 13\text{-}15}$ 

Sinensilactam A can be obtained from dimethyl lingzhilactone B **15** by annulation with 5-hydroxy-2-pyrrolidinone. Lingzhilactone B has one more carbon at C8' than lingzhiol, therefore, styrene is a reasonable equivalent of aryl ketone because it can be either oxidatively cleaved into a dicarbonyl compound, or oxidized into aryl ketone (Fig. 1). The retrosynthetic analysis is outlined below. Ketoaldehyde **15** can be obtained by ozonolysis of styrene **12**, which could be synthesized through an epoxy ring opening reaction with the double-bond of styrene **9**. Alternatively, the epoxy ring opening by the aryl moiety would lead to lingzhiol. Styrene **9** could be obtained sequentially by alkylation of ethyl 2-oxocyclopentane carboxylate with aryl acetyl chloride, twice Wittig reaction, regioselective allylic oxidation and epoxidation of allylic alcohol.



We started our total synthesis with the assembly of the chiral intermediate 9 (Scheme 1). Alkylation of 2,5-dimethoxyphenylacetyl chloride 1 with ethyl 2-oxocyclopentanecarboxylate proceeded smoothly to give diketone 2 in 94% yield. A resolution by baker's yeast only recovered the starting material. Therefore, we adopted a detour of a kinetic resolution of the known alkyne ketoester 4. The absolute configuration of the recovered ketone was determined to be R by its transformation

<sup>&</sup>lt;sup>a.</sup> State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences; Yunnan Key Iaboratory of Natural Medicinal Chemistry, Kunming 650201, P. R. China.

<sup>&</sup>lt;sup>b.</sup> University of Chinese Academy of Sciences, Beijing 100049, P. R. China. <sup>c</sup> Center of Basic Molecular Science, Department of Chemistry, Tsinghua University,

Beijing 100084, China <sup>d</sup>. Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190, China.

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into the known (-)-lingzhiol. $^1$  A 2,5-dimethoxyphenylboronic acid addition to

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chiral alkyne (R)-4 gave styrene 6 in 80% yield.<sup>16</sup> Wittig reaction of ketone 6 with the ylide generated from *t*-BuOK and triphenyl methyl bromide in THF afforded diene 7 in 81% yield as an optically pure enantiomer.<sup>17</sup> Regioselective allylic oxidation with selenium dioxide and *t*-butyl hydroperoxide converted 7 into allylic alcohol 8 in 69% yield. The regioselectivity can be attributed to the steric hinderance of quaternary carbon and the *cis*-stereoselectivity is possibly arisen from the chelation of selenium with ester group. Next, Sharpless epoxidation<sup>18</sup> produced *cis*-epoxy secondary alcohol 9 regioselectively in 82% yield, which is an advanced intermediate with versatile reactivity.



Scheme 1. Construction of a chiral Common Intermediate 9

We embarked on the first asymmetric synthesis of sinensilactam A and lingzhilactone B because their enantiomers have different bioactivities.<sup>3</sup> To accomplish this, the double bond instead of the aryl ring should preferentially engage in nucleophilic attack (Scheme 2). Similar aryl-epoxide opening has previously been reported, it was found that the aryl attack occurs from the opposite face of epoxide <sup>6, 10</sup>. In our case, the space-demanding cis-geometry of the neighboring hydroxyl group may reinforce this aryl preference. To overturn this preference, we sought for a stereoelectronic approach by oxidizing the cyclopentanol to cyclopentanone. By doing so, the reactivity of the epoxide moiety will be enhanced due to the electron-withdrawing effect, facilitating the less-nucleophilic alkene-attack. In addition, the flattened cyclopentanone ring would disfavor the aryl attack as a result of steric repulsion between the approaching aryl methoxy group and ketone moiety.

To our delight, after oxidation into ketone with DMP, the desired styrene-addition adduct **11** was obtained when treated with  $BF_3$ ·Et<sub>2</sub>O. Lactone **12** was obtained through reduction of ketone with NaBH<sub>4</sub>, followed by lactonization upon treatment

with NaOH in MeOH. The hydroxyl group was transito the lactone due to the directing effect of the adjacent hydroxyl group (Scheme 2, **11**) during reduction. Considering the relative configurations of sinensilactam A and lingzhilactone B, inversion of the configuration of the hydroxyl group is needed. Our extensive examinations of the commonly used Mitsunobu conditions were futile<sup>19-23</sup>, and no inversion occurred. Eventually, when compound **12** was treated with Tf<sub>2</sub>O and pyridine, triflate **13** was converted into *cis* isomer **14** in the presence of NaNO<sub>2</sub> and 18-crown-6<sup>24</sup>. The structure of **13** was unambiguously determined by single-crystal X-ray diffraction analysis.





Scheme 2. Construction of bicyclic styrene 12

From styrene lactone **14**, the total synthesis was achieved following Yang's procedure (Scheme 3). Dihydroxylation and subsequent Pb(OAc)<sub>4</sub>-mediated cleavage of the resulted diol proceeded smoothly to afford the key intermediate **15**, which was then deprotected with BBr<sub>3</sub> to complete the total synthesis of (+)-lingzhilactone B. Further protection of aldehyde into acetal gave (+)-lingzhilactone C. From ketoaldehyde **15**, we tried to utilize 5-ethoxy-2-pyrrolidinone, instead of 5-hydroxy-2-pyrrolidinone, in order to improve the yield. As known, the *insitu* generation of N-acyliminium intermediate from 5-ethoxy-2-pyrrolidinone proceeded much faster at lower temperature (1h v.s. 5h, 0 °C v.s. 40 °C). Unfortunately, we encountered serious issues during purification as its Rf value was the same as product. Finally, total synthesis of (+)-sinensilactam A was achieved by condensation of **15** with 5-hydroxy-2-pyrrolidinone

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(66% yield) and subsequent demethylation with BBr<sub>3</sub> (52% yield). The synthetic samples have rotations of +50.3 (c 0.07, MeOH) [literature value: +35.7 (c 0.11, MeOH)]<sup>3</sup> for (+)sinensilactam A, +154.8 (c 0.08, acetone) for (+)-lingzhilactone B and +114.3 (c 0.06, DMSO) for (+)-lingzhilactone C.



Scheme 3. Completion of synthesis of (+)-sinensilactam A

Next, total synthesis of lingzhiol was investigated from epoxy styrene 9 (Scheme 4). The hydroxyl group of 9 was protected as benzyl ether 17 in 75% yield, with a purpose to prevent the undesired semipinacol rearrangement under Lewis acid catalysis.<sup>25</sup> Benzyl ether **17** underwent aryl-epoxide opening reaction to give the expected tetracyclic styrene 18 by TMSOTf catalysis.<sup>6</sup> Initial experiment with BF3 Et2O gave the desired product in 40% isolated yield. After further screening of Lewis acid and temperature, the optimal 51% isolated yield was obtained with 2.5 equiv. TMSOTf in DCM at 0°C. Under the same conditions, BF3 Et2O afforded desired product in 45% yield. No alkene-attack product was observed in these cases. Routine OsO<sub>4</sub>-catalyzed dihydroxylation and subsequent oxidative cleavage of diol with NaIO<sub>4</sub> afforded ketoester **19** in 74% yield. In this way, we took a detour of benzylic oxidation, which was usually not effective. 8 Finally, global deprotection of dimethoxy and benzyloxy group furnished (-)-lingzhiol in 52% yield. Our synthesis took 10 steps and the overall yield is 2.3%.



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Scheme 4 Total synthesis of (-)-lingzhiol

The synthetic strategy is straightforward and the conditions are mild. The synthetic sample has a rotation of -60.7 (c 0.12, MeOH) [literature value: -94.2 (c 0.36, MeOH)].<sup>1</sup> Our NMR data of synthetic samples are all in agreement with those of literature.

To demonstrate the utility of our synthetical strategy, (+)sinensilactam A isomer and (+)-epi-lingzhilactone B, which are C6' epimer of natural products, were also prepared following similar operations (Scheme 5). From styrene 12, similar transformation of double bond afforded 20 in 78% yield. It was then demethylated to give (+)-epi-lingzhilactone B in good yield (81%). When similar operations of pyrrolidionone installation and demethylation were performed, (+)-sinensilactam A isomer was isolated in a comparable yield. The structure of 21 was confirmed by single-crystal X-ray diffraction analysis.



Scheme 5. Synthesis of two isomers

Finally, we sought for an alternative asymmetric synthesis of the key chiral intermediate 3 using the state-of-art enantioselective photocatalytic process. Based on our previously developed chiral primary amine catalyzed photolytic alkylation reaction, <sup>23</sup> the catalytic asymmetric synthesis of the chiral quaternary diketoester 3, which can be readily transformed into 7, was investigated (Scheme 6). Under the optimal conditions,<sup>26a</sup> up to 99% ee was realized with 71% isolate yield at 100 mg scale. It can be transformed into key diene intermediate 7 under similar Wittig reaction condition, possibly shortening the whole synthesis by two steps.



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In summary, we have developed a collective strategy for the concise synthesis of four meroterpenoids based on the divergent reactivity of styrene, which is significantly different from the widely used semipinacol rearrangement strategy in the syntheses of similar meroterpenoids. Regioselective epoxy ring-opening reaction with the double bond of styrene provided the key lactone styrene 12, leading to the total synthesis of (+)-sinensilactam A for the first time in 14 steps and 1.1% overall yield. Starting with the same intermediate, (+)lingzhilactone B was obtained in 13 steps and 2.7% overall yield. On the other hand, the key reaction to (-)-lingzhiol features a one-step construction of a 5/5/6/6 ring system by simultaneous epoxy ring-opening and lactonization promoted by TMSOTf in 10 steps with an overall yield of 2.3%. The current strategy provides a detour from the problematic benzylic oxidation in the total synthesis of this series of natural products. Finally, a

catalytic asymmetric synthesis of this series of natural products. Finally, a catalytic asymmetric synthesis of the key chiral intermediate **3** was also achieved by using the established chiral primary aminocatalytic protocol. It should be noted that the construction of all-carbon quaternary center is quite efficient under rather mild conditions, and may have further application in total synthesis.

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## **Conflicts of interest**

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There are no conflicts to declare.

## Notes and references

Corresponding Author \* E-mail: qinhongbo@mail.kib.ac.cn. ORCID: 0000-0003-2603-9520

\*Email: luosz@tsinghua.edu.cn ORCID: 0000-0001-8714-4047

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