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# Collective enantioselective total synthesis of (+)-sinensilactam A, (+)-lingzhilactone B and (–)-lingzhiol: divergent reactivity of styrene†

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**The 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 an aryl or alkene moiety of styrene led to different carbon skeletons, which can be advanced to a divergent and concise total synthesis of four meroterpenoids.**

During the past 7 years, *Ganoderma* meroterpenoids have attracted increasing attention among the phytochemical community. With meroterpenoids being increasingly identified, this type of molecule 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-β1-induced cellular assays. In 2018, Yang's group reported the first racemic total synthesis of sinensilactam A using 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-term heating (150 °C, 48 h). 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.<sup>5–12,27</sup> In this communication, we have reported a distinctive strategy for the collective synthesis of four meroterpenoids, (+)-sinensilactam A, (+)-lingzhilactone B, (+)-lingzhilactone C and (–)-lingzhiol. The key step involves non-metal promoted selective

nucleophilic opening of epoxide by an alkene moiety of styrene, which has not been explored in total synthesis, though a metal-catalyzed reaction of epoxide with styrene is known.<sup>13–15</sup>

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' compared to 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 the 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 the alkylation of ethyl 2-oxocyclopentanecarboxylate with aryl acetyl chloride, twice Wittig reaction, regio-selective allylic oxidation and the epoxidation of allylic alcohol.

We started our total synthesis with the assembly of the chiral intermediate 9 (Scheme 1). The alkylation of 2,5-dimethoxyphenyl-acetyl 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 alkylne

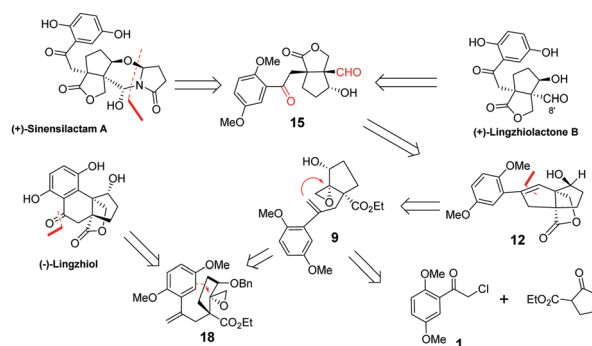


Fig. 1 Structures of several meroterpenoids and retrosynthetic analysis.

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Reaction scheme for the synthesis of **9** from **1**:

**1** (4-methoxy-2-(chloromethyl)benzoic acid derivative) reacts with  $\text{Cs}_2\text{CO}_3$ , KI, DMF (94% yield) to form **2** (4-methoxy-2-(ethoxycarbonylmethyl)benzoic acid derivative).

**2** undergoes baker's yeast resolution to form **3** (4-methoxy-2-(ethoxycarbonylmethyl)benzoic acid derivative, resolved).

**3** is converted to **4** (4-methoxy-2-(ethoxycarbonylmethyl)benzoic acid derivative, resolved).

**4** reacts with baker's yeast,  $\text{HCO}_2\text{NH}_4$ , CuO, 20% aq. sucrose to form **5a** (4-methoxy-2-(ethoxycarbonylmethyl)benzoic acid derivative, resolved).

**5a** is converted to **6** (4-methoxy-2-(ethoxycarbonylmethyl)benzoic acid derivative, resolved).

**6** reacts with  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{HCO}_2\text{H}$ , 1,4-dioxane (80% yield) to form **7** (4-methoxy-2-(ethoxycarbonylmethyl)benzoic acid derivative, resolved).

**7** reacts with  $\text{Ph}_3\text{PCH}_2\text{Br}$ ,  $t\text{-BuOK}$ , THF (81% yield) to form **8** (4-methoxy-2-(ethoxycarbonylmethyl)benzoic acid derivative, resolved).

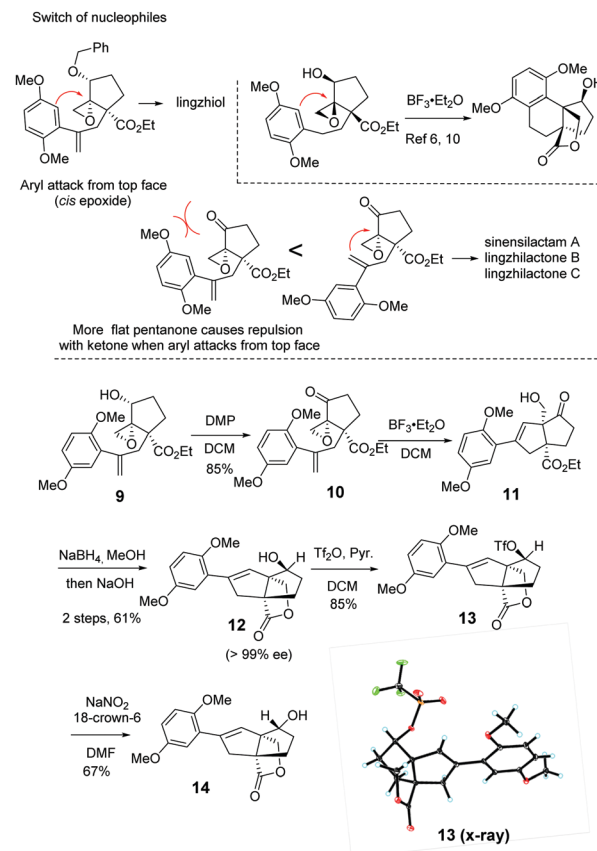
**8** reacts with  $\text{SeO}_2$ , TBHP, DCM (69% yield) to form **9** (4-methoxy-2-(ethoxycarbonylmethyl)benzoic acid derivative, resolved).

**9** reacts with  $\text{Vo}(\text{acac})_2$ , TBHP, DCM (82% yield) to form **10** (4-methoxy-2-(ethoxycarbonylmethyl)benzoic acid derivative, resolved).

ketoster **4**. The absolute configuration of the recovered ketone was determined to be *R* by its transformation into the known (–)-lingzhiol.<sup>1</sup> The addition of 2,5-dimethoxyphenylboronic acid to chiral alkyne (*R*)-**4** gave styrene **6** in 80% yield.<sup>16</sup> The 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 hindrance of quaternary carbon and the *cis*-stereoselectivity possibly arose from the chelation of selenium with the 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.

We embarked on the first asymmetric synthesis of sinensilactam A and lingzhi lactone 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). A similar aryl-epoxide opening has previously been reported, and 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 a stereoelectronic approach by oxidizing the cyclopentanol to cyclopentanone. By doing so, the reactivity of the epoxide moiety is 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 the ketone moiety.

To our delight, after oxidation into ketone with DMP, the desired styrene-addition adduct **11** was obtained when treated with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ . Lactone **12** was obtained through the reduction of ketone with  $\text{NaBH}_4$ , followed by lactonization upon treatment



with NaOH in MeOH. The hydroxyl group was *trans* to 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, the inversion of the configuration of the hydroxyl group is needed. Our extensive examination of the commonly used Mitsunobu conditions was 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.

From styrene lactone **14**, the total synthesis was achieved following Yang's procedure (Scheme 3). Dihydroxylation and the subsequent  $\text{Pb}(\text{OAc})_4$ -mediated cleavage of the resulting diol proceeded smoothly to afford the key intermediate **15**, which was then deprotected with  $\text{BBr}_3$  to complete the total synthesis of (+)-lingzhilactone B. The 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 is well-known, the *in situ* generation of an *N*-acyliminium intermediate from 5-ethoxy-2-pyrrolidinone proceeded much faster at lower temperature (1 h vs. 5 h, 0 °C vs. 40 °C). Unfortunately, we encountered serious issues during purification as its  $R_f$  value was the same as that of the product. Finally, the total synthesis of (+)-sinensilactam A was achieved by the condensation of **15** with



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

5-hydroxy-2-pyrrolidinone (66% yield) and subsequent demethylation with  $\text{BBr}_3$  (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.

Next, the 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 the purpose of preventing the undesired semipinacol rearrangement under Lewis acid catalysis.<sup>25</sup> Benzyl ether **17** underwent an aryl-epoxide opening reaction to give the expected tetracyclic styrene **18** by TMSOTf catalysis.<sup>6</sup> An initial experiment with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  gave the desired product in 40% isolated yield. After further screening the Lewis acid and temperature, the optimal 51% isolated yield was obtained with 2.5 equiv. TMSOTf in DCM at  $0^\circ\text{C}$ . Under the same conditions,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  afforded the desired product in 45% yield. No alkene-attack product was observed in these cases. Routine  $\text{OsO}_4$ -catalyzed dihydroxylation and subsequent oxidative cleavage of diol with  $\text{NaIO}_4$  afforded ketoester **19** in 74% yield. In this way, we took a detour of benzylic oxidation, which was usually not effective.<sup>8</sup>



Scheme 4 Total synthesis of (-)-lingzhiol.

Finally, the global deprotection of dimethoxy and benzyloxy groups furnished (-)-lingzhiol in 52% yield. Our synthesis took 10 steps and the overall yield was 2.3%.

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 the synthetic samples are all in agreement with those of the literature.

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

Finally, we sought an alternative asymmetric synthesis of the key chiral intermediate **3** using the state-of-the-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>26</sup> up to 99% ee was realized with 71% isolated yield at 100 mg scale. It can be transformed into key diene intermediate **7** under similar Wittig reaction conditions, possibly shortening the whole synthesis by two steps.

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. A 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



Scheme 5 Synthesis of the two isomers.



Scheme 6 Catalytic asymmetric construction of the quaternary stereocenter.

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 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 centers is quite efficient under rather mild conditions, and may have further applications in total synthesis.

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## Conflicts of interest

There are no conflicts to declare.

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