

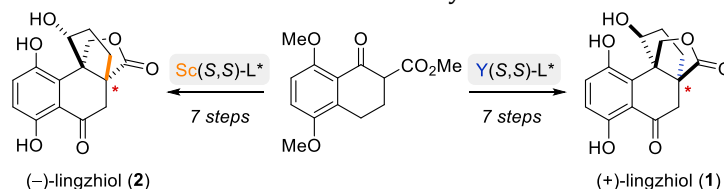
8-Step Enantiodivergent Synthesis of (+)- and (-)-Lingzhiol.

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Supporting Information Placeholder

ABSTRACT: An 8-step enantioselective synthesis of lingzhiol is described herein. The sense of an asymmetric Michael reaction is reversed by the choice of metal source, enabling facile access to both enantiomers. A spontaneous semipinacol ring contraction enables mild construction of the lingzhiol core, and radical-mediated benzylic oxidation proceeds in the presence of an unprotected secondary alcohol. This represents the shortest enantioselective synthesis of lingzhiol to date, and the only enantiodivergent approach to both enantiomers of this meroterpenoid natural product.

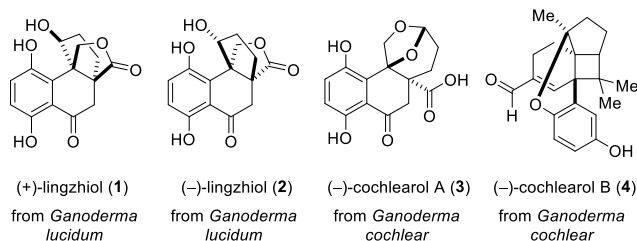


(+)- and (-)-lingzhiol are tetracyclic, rotary-door shaped meroterpenoid natural products isolated as a racemic mixture from *Ganoderma lucidum*, a mushroom commonly used in traditional East Asian medicine for various purposes, including as anti-cancer and antibacterial medicines.¹ Specifically, the respective biological activities are postulated to originate from the terpenoid component of these fungi.² Several additional meroterpenoids have been isolated from this genus that are structurally related to lingzhiol while displaying potent biological activity as renoprotective agents (Fig. 1A).³ Upon isolation of (+)- and (-)-lingzhiol in 2013, Yan and coworkers detailed biological activity studies and identified that both enantiomers inhibit generation of collagen IV, fibronectin, and reactive oxygen species (ROS).⁴ Importantly, lingzhiol was shown to selectively inhibit the Smad3 pathway, which has been implicated in renal fibrosis⁵ and diabetic neuropathy⁶ without inhibiting the renoprotective Smad2 pathway.⁷

Since being isolated in 2013, lingzhiol has attracted substantial synthetic interest. Seven reports detailing total syntheses – including three enantioselective syntheses – have been disclosed.⁸ The earliest, 17-step sequence relied on a rhodium-catalyzed [3+2] cycloaddition to access (-)-lingzhiol.^{8a} Other strategies based on epoxy-arene cyclization^{8b-d}, titanocene-catalyzed radical cyclization^{8e}, and semipinacol ring-contraction^{8f,8g} have also been described.

As both enantiomers of lingzhiol are isolated and display different effectiveness as Smad3 phosphorylation inhibitors (both demonstrate activity but (-)-lingzhiol is more active)⁴, a selective and rapid synthetic approach to both enantiomers is highly desirable. Concurrent studies in our laboratory have revealed that a single enantiomer of bipyridine ligand⁹, when paired with different simple metal triflate Lewis acids, can be employed to enable the synthesis of either enantiomer of lingzhiol in high enantioselectivities and yields (Fig. 1B).

A. Polycyclic meroterpenoids from *Ganoderma* species.



B. This work: Enantiodivergent synthesis of lingzhiol controlled by choice of metal.

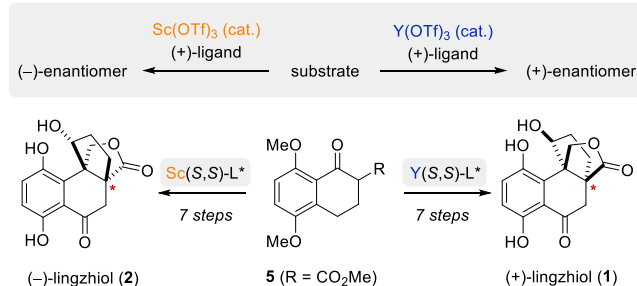


Figure 1. A. Meroterpenoids from *Ganoderma* species, including (+)- and (-)-lingzhiol (1 and 2). **B.** Our approach to both enantiomers of lingzhiol relies on an enantiodivergent conjugate addition mediated by the choice of simple Lewis acid catalyst.

Our retrosynthetic analysis of lingzhiol relied on a one-pot, Et₃Al-mediated¹⁰ semipinacol-reduction-lactonization cascade beginning with oxidized epoxide **9** (Fig. 2). As a Lewis acid, Et₃Al was expected to induce a semipinacol reaction through **8** to afford aldehyde **7**, which can be reduced by hydride transfer from Et₃Al. We anticipated, similarly to Birman^{8f} and Xie^{8g}, that a short series of steps (Robinson annulation, reduction, and epoxidation) would smoothly furnish **9** and enable the facile synthesis of the lingzhiol core structure. To test this retrosynthetic strategy, we prepared model epoxide **10** and treated it with 3 equivalents of Et₃Al

Retrosynthetic Strategy:

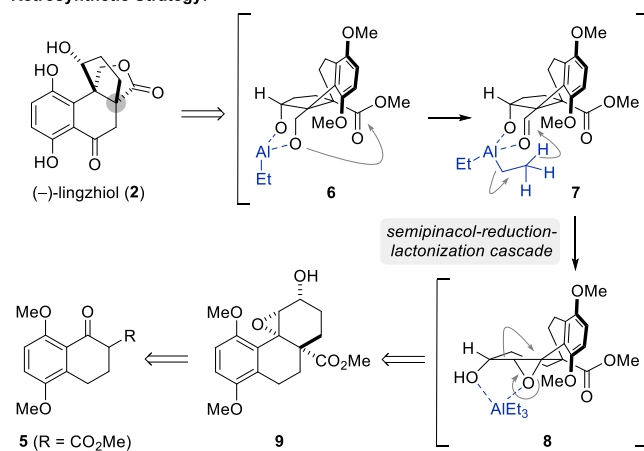


Figure 2. Retrosynthetic strategy towards lingzhiol based on a semipinacol-reduction-lactonization cascade.

(1M in hexane) in THF at ambient temperatures (Fig. 3). Epoxide **10** was fully consumed after reacting overnight and successful isolation of tetracyclic lactone **13** in 30% yield validated this retrosynthetic approach. Having verified our retrosynthetic approach in the model system, we began our efforts to employ this strategy toward the total synthesis of lingzhiol.

To ensure an enantioselective total synthesis, we first sought to apply Kobayashi's conditions¹¹ relying on chiral ligand **14** and Sc(OTf)₃ for the enantioselective Michael addition of methyl vinyl ketone **15** to known¹² β-ketoester **5**. The reported conditions relying on Sc(OTf)₃ and chiral bipyridine **14** afforded **16** within a 4-day reaction time and in modest yield (31%), but successfully furnished product (*S*)-**16** in high ee (90%; Table 1, entry 2). This stands in contrast to a previous report^{8f} describing the formation of (*R*)-**16** as the major enantiomer under identical reaction conditions. Importantly, we were able to verify the formation of (*S*)-**16** by X-ray crystallographic analysis (Table 1). Subsequent investigation of alternative metal triflates as catalysts under these conditions identified Y(OTf)₃ and Dy(OTf)₃ (Table 1, entries 9 and 11) as more efficient catalysts that enable formation of **16** in shorter reaction times (18 and 17 hours, respectively) and higher yields (92% and 88%) while main-

Initial Model Studies:

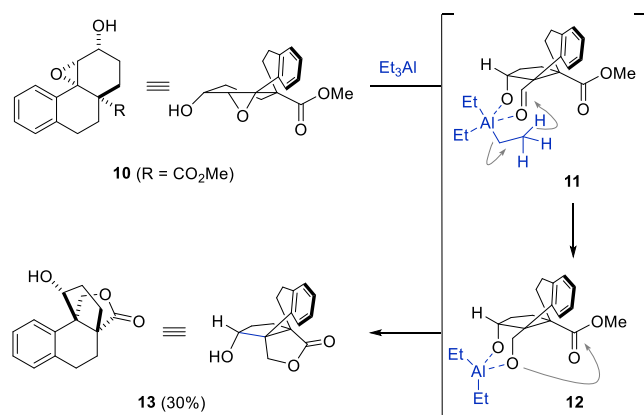
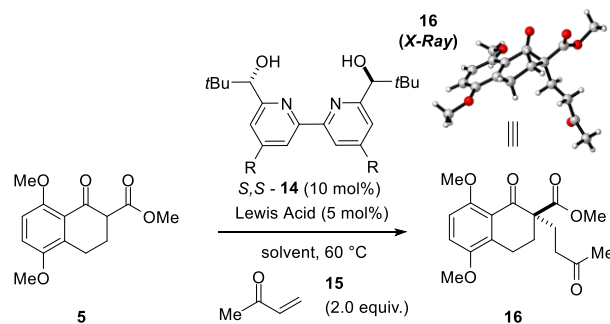


Figure 3. Initial model studies support feasibility of the proposed semipinacol-reduction-lactonization cascade.

taining good enantiomeric excess (71% and 76% ee, respectively). Interestingly, in addition to improving the yield, the reaction catalyzed by Y(OTf)₃ with *S,S*-**14** as ligand afforded the opposite enantiomer of **16** to the reaction catalyzed by Sc(OTf)₃ with *S,S*-**14** ligand. This metal-mediated enantiodivergent conjugate addition represents a rare scenario in metal catalysis¹³ but provides an efficient method enabling access to both enantiomers of lingzhiol.

Additional optimization of reaction parameters identified benzene as a superior solvent, maintaining high yields and improving enantioselectivities (up to 91% ee). In addition to Sc(OTf)₃, Y(OTf)₃ and Dy(OTf)₃, all other available lanthanide(III) triflate sources were evaluated. Lu(OTf)₃ and Yb(OTf)₃ fully consumed the starting material **5** in 42 hours (Table 1, entries 3 and 4) affording high yields (93% and 89%, respectively) and good enantioselectivities (84% ee and 86% ee). Tm(OTf)₃, Er(OTf)₃, and Ho(OTf)₃ reacted more quickly (Table 1, entries 5-7) and furnished product **16** in excellent yields (92%, 95% and 98% respectively) and

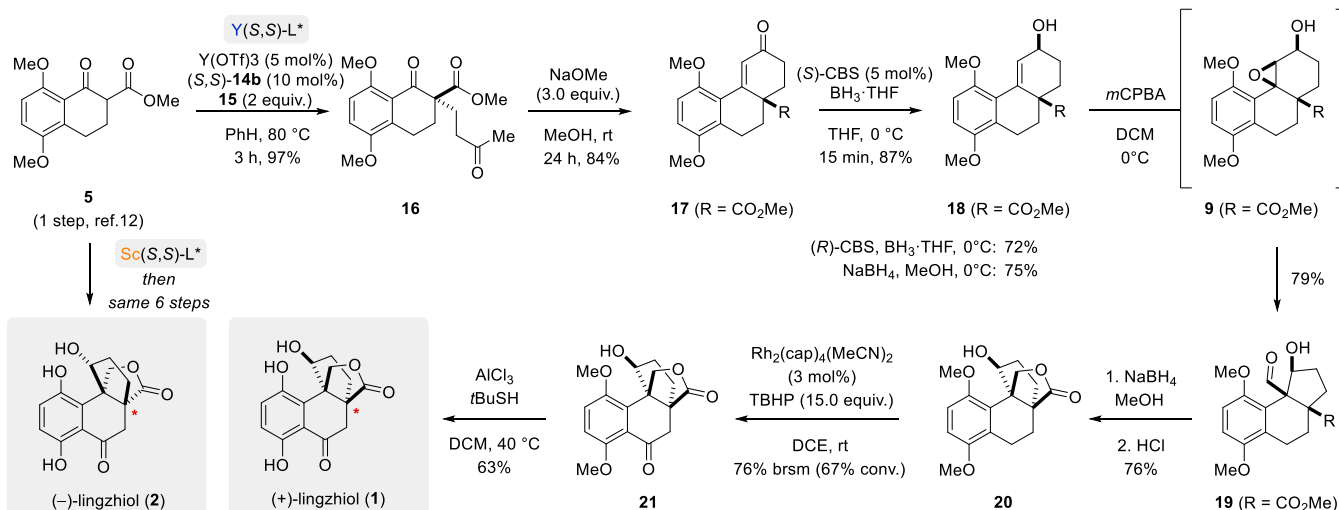
Table 1. Optimization of the enantioselective conjugate addition.



entry	Lewis acid	solvent	time (h)	yield 16 (%)	ee (%)
1	Sc(OTf) ₃	benzene	96	0	-
2	Sc(OTf) ₃	DCE	96	31	-90
3	Lu(OTf) ₃	benzene	42	93	82
4	Yb(OTf) ₃	benzene	42	89	84
5	Tm(OTf) ₃	benzene	22	92	86
6	Er(OTf) ₃	benzene	18	95	89
7	Ho(OTf) ₃	benzene	18	98	89
8	Y(OTf) ₃	benzene	18	91	91
9	Y(OTf) ₃	DCE	18	92	71
10	Dy(OTf) ₃	benzene	17	83	90
11	Dy(OTf) ₃	DCE	17	88	76
12	Tb(OTf) ₃	benzene	17	98	90
13	Gd(OTf) ₃	benzene	17	97	87
14	Eu(OTf) ₃	benzene	17	99	83
15	Sm(OTf) ₃	benzene	17	96	74
16	Nd(OTf) ₃	benzene	17	96	13
17	Pr(OTf) ₃	benzene	17	94	-23
18	Ce(OTf) ₃	benzene	17	81	-42
19	La(OTf) ₃	benzene	17	97	-43
20 ^a	Y(OTf) ₃	benzene	14	99	94
21 ^b	Sc(OTf) ₃	DCE	96	58	-91
22 ^c	Y(OTf) ₃	benzene	4	97	91

Conditions: 10 mol% **14** and 5 mol% M(OTf)₃ were pre-stirred at 60 °C (1 h). Reactions were performed on 0.15 mmol scale in the listed solvent (0.02 M) at 60 °C for the listed time. Entries 1-20 employed *S,S*-**14** (R = H) as ligand. ^aReaction performed at 80 °C and 0.04 M ^bIdentical reaction conditions to entry 2 using *S,S*-**14** (R = OMe) ^cIdentical reaction conditions to entry 8 using *S,S*-**14** (R = OMe). X-Ray crystallographic analysis confirmed the stereochemical assignment of **16** resulting from the conditions described in entry 22.

Figure 4. Enantiodivergent total synthesis of (+)- and (-)-lingzhiol in 7 overall steps starting from β -ketoester **5**.



high enantioselectivities (86% ee, 89% ee and 89% ee). $\text{Tb}(\text{OTf})_3$, $\text{Gd}(\text{OTf})_3$ and $\text{Eu}(\text{OTf})_3$ (Table 1, entries 12-14) provided nearly quantitative yields (97-99%) and good to excellent enantioselectivities (83-90% ee). $\text{Sm}(\text{OTf})_3$ (Table 1, entry 15) maintained high yield of 96%, but enantiomeric excess was eroded (74% ee). $\text{Nd}(\text{OTf})_3$ (Table 1, entry 16) was similarly high yielding, but the enantioselectivity was very low (13% ee). When employing $\text{Pr}(\text{OTf})_3$, $\text{Ce}(\text{OTf})_3$, and $\text{La}(\text{OTf})_3$ (Table 1, entries 17-19) as catalysts, we again observed high yield (81% - 97%) and low enantioselectivities of -23% ee, -42% ee, and -43 ee, respectively. Interestingly, the major enantiomer in these cases was opposite to the major enantiomer with all other metal triflates evaluated except $\text{Sc}(\text{OTf})_3$. We attribute the variability in enantiomeric excess to the wide range of ionic radii of the M^{3+} centers leading to differential binding of the substrate to the metal-ligand complex.¹⁴

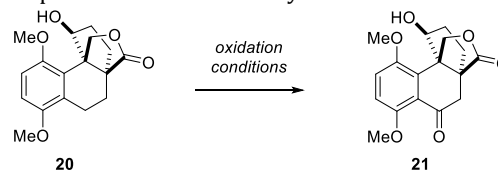
The optimal yield (99%) and enantiomeric excess (95%) were achieved using $\text{Y}(\text{OTf})_3$ at 80 °C in benzene (0.04 M; Table 1, entry 20). Based on the proposed mechanism of this transformation proceeding through a metal enolate¹¹, we hypothesized that a more electron-rich metal-ligand complex would accelerate the rate of reaction and improve the yield, particularly in the scandium-catalyzed system. By employing methoxy-substituted S,S -**14**, we found that this strategy proved effective. This resulted in almost double the yield (58%) for the $\text{Sc}(\text{OTf})_3$ -catalyzed reaction with no loss of enantioselectivity (91% ee, Table 1, entry 21), dramatically improving the synthetic utility of this reaction. Similarly, the $\text{Y}(\text{OTf})_3$ -catalyzed reaction is accelerated, reducing the reaction time from 14 hours to 4 hours (Table 1, entry 22).

We next turned our attention to elaborating **16** to lingzhiol (**1** and **2**, Fig. 4). NaOMe-mediated aldol condensation afforded tricyclic enone **17** in 65% yield. Reduction of the ketone with NaBH_4 furnished allylic alcohol **18** in 75% yield, and this yield could be improved to 84% by using (*S*)-CBS catalyst and BH_3 as the stoichiometric reductant. The corresponding (*R*)-CBS catalyst resulted in the lowest isolated yield of **18**, which we attribute to increased yield of the minor diastereomer (See Supporting Information for details). Treatment with *m*CPBA was expected to lead to epoxide **9**

and set the stage for the Et_3Al -mediated cascade semipinacol-reduction-lactonization reaction, but we instead isolated aldehyde **19** resulting from a spontaneous, *in situ* semipinacol rearrangement.^{8f,8g} In comparison, the less electronically activated analogous epoxide **10** is readily isolated under identical conditions, indicating that the instability of **9** is due to the highly electron-rich aromatic substituent lowering the transition state energy for a semipinacol reaction.

Aldehyde **19** is readily reduced and lactonized with NaBH_4 and acidic workup to afford the lingzhiol core **20** in 76% yield. Elaboration of **20** to lingzhiol (**2**) requires installation of the benzylic ketone and bis-demethylation of the phenolic ethers. We sought to selectively carry out benzylic oxidation of **20**, which contains an unprotected secondary alcohol. A two-step protocol relying on aqueous NBS followed by treatment with MnO_2 did not afford the desired product **21** (Table 2, entry 1).¹⁵ We then evaluated various other conditions aimed at the installation of the benzylic ketone without protection of the secondary alcohol moiety, including catalytic RuCl_3 ¹⁶, $\text{Co}(\text{OAc})_2/\text{NHPI}$ ¹⁷, and $\text{Pd}(\text{OH})_2$ ¹⁸, (Ta-

Table 2. Optimization for the benzylic oxidation of alcohol **20**.

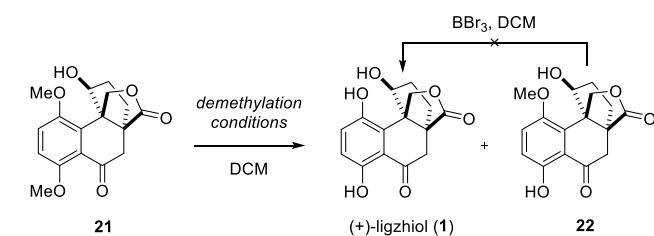


entry	conditions	solvent	yield 21 (%)
1	NBS/ H_2O then MnO_2	CCl_4	0
2	RuCl_3 , TBHP	cyclohexane	0
3	$\text{Co}(\text{OAc})_2$, NHPI, O_2	acetone	0
4	$\text{Pd}(\text{OH})_2$, K_2CO_3 , TBHP	DCM	0
5	oxone, KBr, hv	DCM/ H_2O	0
6	Rh_2cap_4 , T-HYDRO	DCE	6
7	Rh_2cap_4 , TBHP	DCE	38 (76% brsm)

Conditions: Reactions performed on 0.13 or 0.065 mmol scale using the reagents described. cap = ϵ -caprolactam. TBHP = *tert*-butyl hydroperoxide. See Supporting Information for additional experimental details.

ble 2, entries 2-4). These conditions, in addition to stoichiometric oxone/KBr¹⁹ (Table 2, entry 5) all failed to provide the desired product **21**. However, by employing conditions reported by Doyle and coworkers²⁰ for benzylic C-H oxidations relying on Rh₂cap₄ (Table 2, entry 7), we were able to successfully isolate benzyl ketone **21** in 38% yield (76% brsm). Modified conditions²¹ relying on aqueous TBHP (T-HYDRO) as oxidant afforded only small amounts of product (6%, Table 2, entry 6).

To reveal the hydroquinone moiety and complete the total synthesis, we subjected **21** to standard conditions for BBr₃-mediated phenol demethylation and isolated only the singly demethylated product **22** in 82% yield (Table 3, entry 1). Resubjecting this compound to BBr₃ failed to show any conversion to lingzhiol. Similarly, BCl₃/TBAI-mediated demethylation provided **22** in 69% yield (Table 3, entry 2). Completion of the synthesis was ultimately achieved by employ-



entry	reagent	temperature	time (h)	yield 1 (%)	yield 22 (%)
1	BBr ₃	0°C	2	0	82
2	BCl ₃ , Bu ₄ NI	-78°C to rt	11	0	69
3	AlCl ₃ , <i>t</i> BuSH	40°C	16	59	0

Conditions: Reactions were performed on ~0.04 mmol scale in DCM (0.02 M) at the temperature listed. See Supporting Information for additional details.

ing previously reported^{8a} conditions for bis-demethylation of **21** relying on AlCl₃ with *t*BuSH at elevated temperatures (Table 3, entry 3).

Herein, we have described an 8-step synthesis of either enantiomer of lingzhiol relying on an enantiodivergent Michael addition, spontaneous semipinacol rearrangement, and selective radical benzylic oxidation. The discovery of a metal-controlled switch in enantioselectivity for the addition of **5** to methyl vinyl ketone not only provides efficient access to both enantiomers of lingzhiol but also represents a remarkable observation in enantioselective catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectral data, HPLC chromatographs and optical rotations; (PDF)

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Notes

The authors declare no competing financial interest.

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